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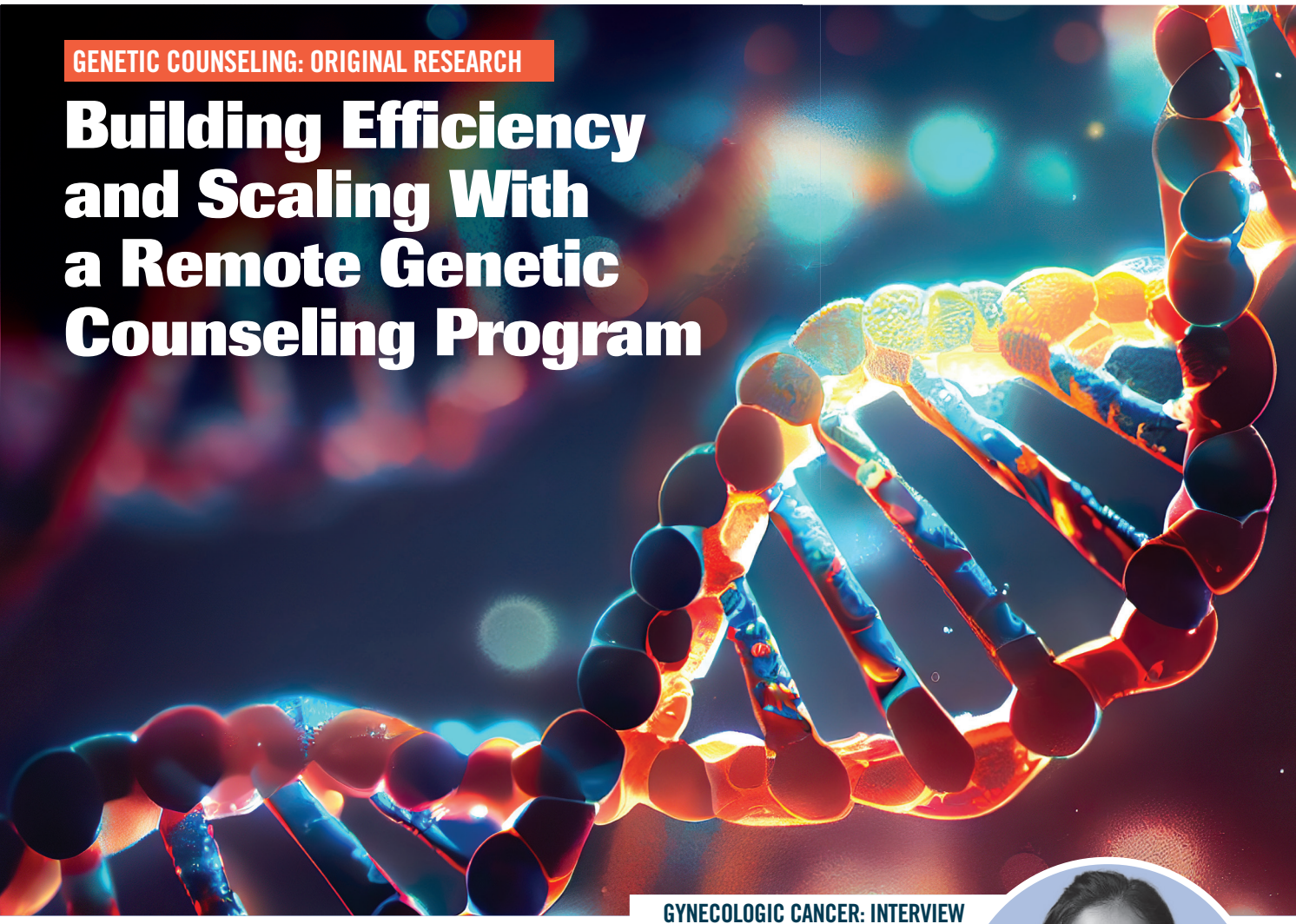
PRACTICAL, PEER-REVIEWED PERSPECTIVES

ONCOLOGY®

JANUARY 2024 | Vol 38 • No 1



GENETIC COUNSELING: ORIGINAL RESEARCH

Building Efficiency and Scaling With a Remote Genetic Counseling Program

GYNECOLOGIC CANCER: INTERVIEW

Ritu Salani, MD, MBA

Tiragolumab Plus Atezolizumab Will Not Be Pursued in Further Cervical Cancer Management

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RYBREVANT®
(amivantamab-vmjw)
Injection for IV Use | 350 mg/7 mL (50 mg/mL)

ENGINEERED FOR A CHALLENGING LANDSCAPE

In the world of *EGFR*+ mNSCLC, few challenges have been tougher to navigate than *EGFR* exon 20 insertion mutations.[1-10]

Until RYBREVANT®—the first and only bispecific antibody built for the treatment of adult patients with locally advanced or mNSCLC with ***EGFR* exon 20 insertion mutations,** as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.[11]

INDICATION

RYBREVANT® (amivantamab-vmjw) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT® can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT® due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity.

Interstitial Lung Disease/Pneumonitis

RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Adverse Reactions

RYBREVANT® can cause rash (including dermatitis acneiform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT®. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.

In a multicenter, open-label, multicohort study[11]*

Results for tough-to-treat disease

- 3.7% of patients achieved a CR
- 36% of patients achieved a PR

- Efficacy was evaluated by ORR† and DOR[11]

MEDIAN DOR WAS 11.1 MONTHS[11]‡
(95% CI: 6.9, NE)[11]

*CHRYSALIS was a multicenter, open-label, multicohort study conducted to assess the safety (n=129) and efficacy (n=81) of RYBREVANT® in adult patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 patients with locally advanced or metastatic NSCLC who had *EGFR* exon 20 insertion mutations as determined by prospective local testing, whose disease had progressed on or after platinum-based chemotherapy. RYBREVANT® was administered intravenously at 1050 mg for patients <80 kg or 1400 mg for patients ≥80 kg once weekly for 4 weeks, then every 2 weeks thereafter, starting at Week 5, until disease progression or unacceptable toxicity.[11]

†According to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR).[11]

‡Based on Kaplan-Meier estimates.[11]

The safety of RYBREVANT® was evaluated in the CHRYSALIS* study (n=129)[11]:

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity[11]
- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%)[11]
- The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%)[11]
- IRRs occurred in 66% of patients treated with RYBREVANT®, the majority of which may occur with the first infusion[11§]

§Based on the safety population, N=302.

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CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; mNSCLC, metastatic non-small cell lung cancer; NE, not estimable; ORR, overall response rate; PR, partial response.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Ocular Toxicity

RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT®. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT®.

Adverse Reactions

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

Please see Brief Summary of full Prescribing Information for RYBREVANT® on subsequent pages.

References: 1. Clinical Test Report: Oncomine™ Dx Target Test US. Thermo Fisher Scientific. Accessed October 13, 2021. https://tools.thermofisher.com/content/sfs/brochures/oncomine-dx-target-test-sample-report.pdf **2.** Chiang AC. *BMC Cancer*. 2020;20(1):356. **3.** Robichaux JP. *Nat Med*. 2018;24(5):638-646. **4.** Riess JW. *J Thorac Oncol*. 2018;13(10):1560-1568. **5.** FoundationOne®CDx. Technical specifications. Foundation Medicine. Accessed October 13, 2021. https://assets.ctfassets.net/w98cd481qyp0YqqKHaqQmFeqc5ueQk48w/0a34fcdaa3a71dbe460cdcb01cebe8ad/F1CDx_Technical_Specifications_072020.pdf **6.** Arcila ME. *Mol Cancer Ther*. 2013;12(2):220-229. **7.** Oxnard GR. *J Thorac Oncol*. 2013;8(2):179-184. **8.** Naidoo J. *Cancer*. 2015;121(18):3212-3220. **9.** Chen D. *Onco Targets Ther*. 2016;9:4181-4186. **10.** Girard N. Presented at: IASLC 2020 World Conference on Lung Cancer; January 28-31, 2021; Singapore. **11.** RYBREVANT® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

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cp-213274v2

RYBREVANT (amivantamab-vmjw) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

RYBREVANT is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1) in Full Prescribing Information]*, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population *[see Adverse Reactions]*, IRR occurred in 66% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT as recommended *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Administer RYBREVANT via a peripheral line on Week 1 and Week 2 *[see Dosage and Administration (2.6) in Full Prescribing Information]*.

Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Interstitial Lung Disease/Pneumonitis

RYBREVANT can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population *[see Adverse Reactions]*, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Dermatologic Adverse Reactions

RYBREVANT can cause rash (including dermatitis acneiform), pruritus and dry skin. Based on the safety population *[see Adverse Reactions]*, rash occurred in 74% of patients treated with RYBREVANT, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT was permanently discontinued due to rash in 0.7% of patients *[see Adverse Reactions]*.

Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBREVANT.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Ocular Toxicity

RYBREVANT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population *[see Adverse Reactions]*, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT. *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions *[see Warnings and Precautions]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions]*
- Dermatologic Adverse Reactions *[see Warnings and Precautions]*
- Ocular Toxicity *[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.

The safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT as a single agent in the CHRYSALIS study in 302 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYBREVANT, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (≥ 20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased phosphate, decreased albumin, increased glucose, increased gamma glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase.

The data described below reflect exposure to RYBREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

The median age was 62 years (range: 36 to 84 years); 61% were female; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had baseline body weight <80 kg.

Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥ 2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in ≥ 2% of patients included rash and paronychia.

The most common adverse reactions (≥ 20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.

Table 1 summarizes the adverse reactions in CHRYSALIS.

Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBREVANT in CHRYSALIS

Adverse Reactions	RYBREVANT (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Rash[a]	84	3.9
Pruritus	18	0
Dry skin	14	0
General disorders and administration site conditions		
Infusion related reaction	64	3.1
Fatigue[b]	33	2.3
Edema[c]	27	0.8
Pyrexia	13	0
Infections and infestations		
Paronychia	50	3.1
Pneumonia[d]	10	0.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[e]	47	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[f]	37	2.3
Cough[g]	25	0
Gastrointestinal disorders		
Nausea	36	0
Stomatitis[h]	26	0.8
Constipation	23	0
Vomiting	22	0
Diarrhea	16	3.1
Abdominal Pain[i]	11	0.8
Vascular disorders		
Hemorrhage[j]	19	0
Metabolism and nutrition disorders		
Decreased appetite	15	0
Nervous system disorders		
Peripheral neuropathy[k]	13	0
Dizziness	12	0.8
Headache[l]	10	0.8

[a] Rash: acne, dermatitis, dermatitis acneiform, eczema, eczema asteatotic, palmar-plantar erythrodysesthesia syndrome, perineal rash, rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrolysis

[b] Fatigue: asthenia, fatigue

[c] Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling

[d] Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis

[e] Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain

[f] Dyspnea: dyspnea, dyspnea exertional

[g] Cough: cough, productive cough, upper airway cough syndrome

[h] Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis

[i] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort

[j] Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage

[k] Peripheral neuropathy: hypoesthesia, neuralgia, paresthesia, peripheral sensory neuropathy

[l] Headache: headache, migraine

Clinically relevant adverse reactions in <10% of patients who received RYBREVANT included ocular toxicity, ILD/pneumonitis, and toxic epidermal necrolysis (TEN).

RYBREVANT™ (amivantamab-vmjw) injection

Table 2 summarizes the laboratory abnormalities in CHRYSALIS.

Table 2: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSALIS

Laboratory Abnormality	RYBREVANT+ (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Chemistry		
Decreased albumin	79	8
Increased glucose	56	4
Increased alkaline phosphatase	53	4.8
Increased creatinine	46	0
Increased alanine aminotransferase	38	1.6
Decreased phosphate	33	8
Increased aspartate aminotransferase	33	0
Decreased magnesium	27	0
Increased gamma-glutamyl transferase	27	4
Decreased sodium	27	4
Decreased potassium	26	6
Hematology		
Decreased lymphocytes	36	8

[+] The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other amivantamab products may be misleading.

In CHRYSALIS, 3 of the 286 (1%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab-vmjw antibodies (one at 27 days, one at 59 days and one at 168 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBREVANT.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryolethality, malformations, and post-natal death in animals *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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.

Data

Animal Data

No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in

multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmjw has the potential to be transmitted from the mother to the developing fetus.

Lactation

Risk Summary

There are no data on the presence of amivantamab-vmjw in human milk on milk production, or its effects on the breastfed child. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the final dose.

Females and Males of Reproductive Potential

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

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT.

Pediatric Use

The safety and efficacy of RYBREVANT have not been established in pediatric patients.

Geriatric Use

Of the 129 patients treated with RYBREVANT, 41% were 65 years of age or older, and 9% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions *[see Warnings and Precautions]*.

Interstitial Lung Disease/Pneumonitis

Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms *[see Warnings and Precautions]*.

Dermatologic Adverse Reactions

Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT *[see Warnings and Precautions]*. Advise patients to apply alcohol free emollient cream to dry skin.

Ocular Toxicity

Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated *[see Warnings and Precautions]*.

Paronychia

Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia *[see Adverse Reactions]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy. *[see Warnings and Precautions, Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose *[see Use in Specific Populations]*.

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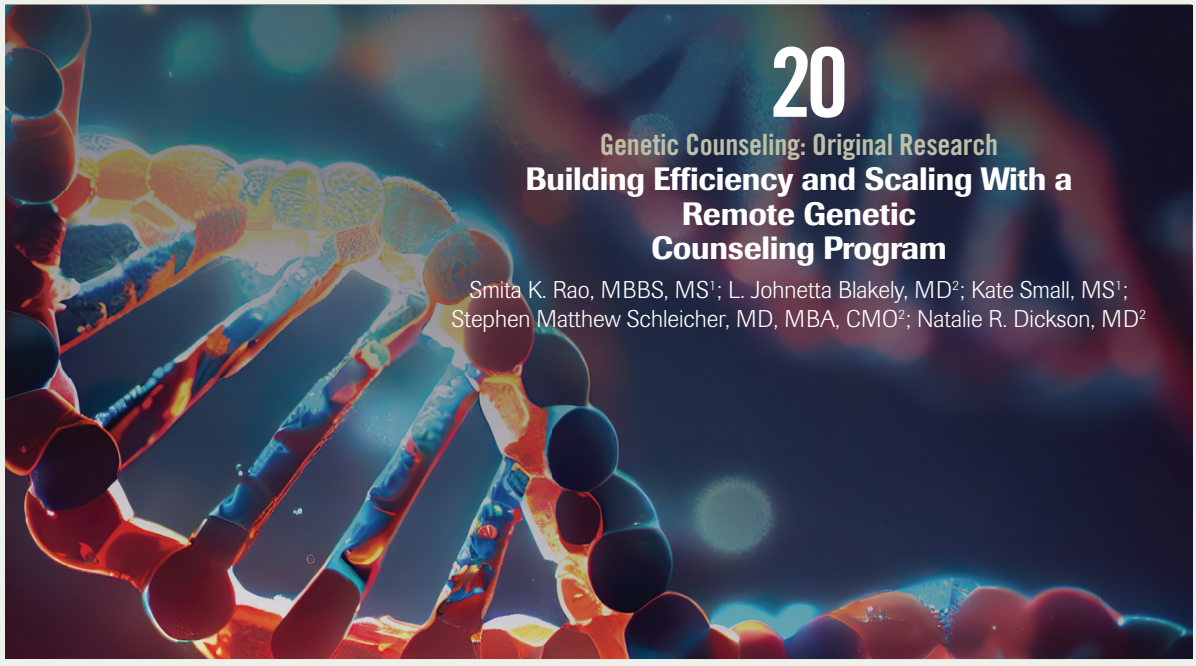
cp-213278v1



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PUBLISHER'S NOTE

As we usher in 2024, *ONCOLOGY* is proud to announce that Neil M. Iyengar, MD, will be the new co–editor-in-chief for our solid tumors manuscripts. Julie M. Vose, MD, MBA, will return as our other co–editor-in-chief, specializing in hematologic malignancies.

Iyengar, is a breast oncologist at Memorial Sloan Kettering Cancer Center with a focus in exercise oncology. Throughout his career, Iyengar has been involved in numerous clinical trials, including, most recently, "Obesity Promotes Breast Epithelium DNA Damage in Women Carrying a Germline Mutation in BRCA1 or BRCA2", and "Incidence, Risk Factors, and Management of Alpelisib-Associated Hyperglycemia in Metastatic Breast Cancer".

He has also received several awards, including Chemotherapy Foundation Symposium Oncology Hero Award, Physicians Education Resource (2023); Career Development Award, Conquer Cancer the ASCO Foundation; and Breast Cancer Achievement Award, Lynn Sage Breast Cancer Symposium.

The entire *ONCOLOGY* team welcomes Ieynagr, and we are very excited to work with him. ■

CALL FOR REVIEWERS AND PAPERS

ONCOLOGY is seeking to expand its list of ad hoc reviewers to provide constructive feedback on manuscripts that have received initial editorial approval. Comments and criticisms are a necessary and invaluable part of the journal's process, and our need for more willing experts grows in step with the journal.

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JANUARY 2024 ▪ VOL. 38 ▪ NO. 1

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Co–Editor-in-Chief Introduction: Priorities and New Directions

As the new co–editor-in-chief of *ONCOLOGY,* I am delighted to introduce myself to you, and highlight key priorities and new directions. I am a physician-scientist who clinically subspecializes in breast cancer treatment with a research program aimed at uncovering and harnessing the oncogenic impact of metabolic health in globally diverse populations. In an era of rapid scientific advances, my primary goal in this new role is to elevate the voices of clinicians, researchers, and advocates to provide a go-to platform for knowledge dissemination and discussion. I am excited to join my esteemed colleague, Julie M. Vose, MD, MBA, at the helm of *ONCOLOGY* to continue to expand our impact on the field and, ultimately, equip our readers to improve the lives of those affected by cancer.

To the readership, I submit 3 priorities for the coming years: First, we will continue to prioritize the submission of original research across all areas of interest within oncology. I encourage my colleagues engaged in discovery, clinical, and health services research to consider *ONCOLOGY* as a venue for data dissemination. As part of this priority, we encourage submissions from new and established researchers with works ranging from pilot to definitive studies. A second priority is to contextualize recently reported data for knowledge advancement, clinical implementation, and/or future study. We invite submissions of meta-analyses, literature reviews, editorials, and perspectives that help synthesize and integrate new findings with current knowledge. A third priority is to promote discussion of clinical controversies and conundrums that identify current knowledge gaps and stimulate future investigation. We invite submissions of commentaries and letters that address current or new clinical controversies generated by recently reported findings. Through this platform of iterative discussion, we aim to further propel scientific and clinical advances. Finally, a critical objective that encompasses all 3 priorities is the promotion of research and strategies to improve knowledge, care quality, access, and tailored approaches for underrepresented and underserved populations across a diversity of racial/ethnic, gender, socioeconomic, sexual orientation, and geographic groups. Only by improving the care of our most vulnerable populations will we be able to elevate public health on a global scale.

I also am excited to highlight several new directions that build upon the original mission of *ONCOLOGY*. First, we aim to expand the journal's reach throughout the oncology community by providing an attractive platform for manuscript submission and by addressing topics of interest identified by the readership. We will address these goals by using an increasingly efficient peer review process that provides fair and constructive feedback. We will also solicit topics of interest from readers by having a continued presence at major scientific and professional society meetings. We aim to increase these efforts by timing the publication of manuscripts with related seminal data releases and by targeting subspecialty meetings and complementary disciplines to provide a rich extent of topics for our readers.

In this regard, another new direction is to expand our scope to include a range of multidisciplinary topics in oncology. As a translational researcher, I will take this opportunity to highlight the study of host metabolism intersections with cancer as an example of a nascent topic for expansion. A growing body of evidence indicates that cancer risk and outcomes may be improved through the optimization of metabolic health via lifestyle interventions and/or pharmacologic approaches with cardiometabolic targets. Obesity is a classic example of metabolic dysfunction that promotes at least 13 different cancers and is globally prevalent at epidemic proportions. By combining strategies such as diet, exercise, and weight-loss medications with oncologic interventions, we may be able to lessen the global burden of obesity-related cancers.

Similarly, further development of lifestyle interventions, including structured exercise and plant-forward diets, may lead to improvements in cancer outcomes in addition to improving quality of life. Indeed, current guidelines recommend regular physical activity and a diet rich in minimally processed, whole-food vegetable and fruit sources. Unfortunately, the involvement of registered dietitians and/or exercise physiologists as part of the oncology care team is limited by the lack of insurance coverage for these services. The generation of further data supporting the benefits and health care cost savings associated with lifestyle interventions could propel third-party reimbursement and ultimately improve the quality of care and cancer outcomes on a much larger scale. We will strive to provide a platform for the publication of data from multidisciplinary fields, such as exercise oncology, that could be adopted in clinical practice at the systems, provider, and/or patient level.

The pace of scientific discovery is accelerating at an unprecedented rate, and it is an exciting time to be a clinician and researcher in oncology and its related fields. Vose, the *ONCOLOGY* staff, and I are committed to providing a reliable and consistent resource to disseminate new advances and share how these advances can be integrated into clinical practice. I hope to hear from you, our readers, as we continue in this partnership to improve the lives of all those affected by cancer. ■

MEET OUR EXPERT

Ritu Salani, MD, MBA
Gynecologic Oncology Fellowship Director UCLA Health
Los Angeles, CA

Tiragolumab Plus Atezolizumab Will Not Be Pursued in Further Cervical Cancer Management

"In this patient population, the addition of a TIGIT [inhibitor] and a PD-L1 or PD-1 inhibitor probably does not have any path forward in that combination alone."

Ritu Salani, MD, MBA, highlighted the results from the phase 2 SKYSCRAPER-04 trial (NCT04300647), which combined tiragolumab with atezolizumab (Tecentriq) for patients with PD-L1–positive recurrent cervical cancer.[1]

Across the total patient population, the primary end point of objective response rate (ORR) was 19% in patients who received tiragolumab plus atezolizumab compared with 15.6% in those treated with atezolizumab alone. Among 105 patients with PD-L1–high tumors, the ORR was 25% and 20.7% among those who received combination therapy and monotherapy, respectively. Of 66 patients with PD-L1–low tumors, a response was observed in 10% of patients who received combination therapy and 6.3% of those who received monotherapy. However, although a response was seen, it did not match statistical significance for historical reference. Salani, gynecologic oncology fellowship director at UCLA Health in Los Angeles, California, and gynecologic editorial board member for ONCOLOGY, touched on why future research efforts will not be pursued with this combination and upcoming treatment options for patients with cervical cancer.

Q: What was the rationale behind the phase 2 SKYSCRAPER-04 study?

SALANI: In recurrent cervical cancer, we've seen that the addition of checkpoint inhibitors has benefited patients with ORR and duration of responses. Unlike what we've seen with chemotherapy, even though [checkpoint inhibitors] leave a lot to be desired, this was a huge advantage for these patients. The rationale behind the phase 2 SKYSCRAPER-04 trial was to see whether we could continue to leverage the immune system by adding a TIGIT inhibitor to a checkpoint inhibitor to see whether we could avoid immune system exhaustion and continue to capitalize on the benefit of the immunotherapy.

Q: The trial showed an improvement in the ORR, but the impact of the ORR did not reach statistical significance based on historical reference. Can you address these results?

SALANI: There are 2 points to this study. One, this was the first study using a single-agent checkpoint inhibitor in this controlled fashion, so in a phase 2 study. We were able to show that a PD-L1 inhibitor was comparable to what we see historically with PD-1 inhibitors. That was an important takeaway. Unfortunately, the addition of the TIGIT inhibitor wasn't able to overcome that immune exhaustion. Although we did see numerical improvement, we weren't able to show that this was statistically significant. The addition of a TIGIT inhibitor to a checkpoint inhibitor, in this case atezolizumab, didn't provide the improvement that we were hoping to see.

Q: Are there any adverse effects (AEs) clinicians should be aware of based on the study?

SALANI: One important message is that the checkpoint inhibitor therapy was safely administered. There were no new safety signals. This has been used across other disease sites [as well]. This [study] continues to add to that experience. Even with the addition of the TIGIT inhibitor, [there was a] minimal increase in AEs. They were slightly higher, but no grade 5 AEs and very few grade 3 or 4 AEs [were observed]. It is a safe combination; it just wasn't as effective as we were hoping.

Q: Are there any next steps in researching the tiragolumab/atezolizumab combination in this patient population?

SALANI: In this patient population, the addition of a TIGIT [inhibitor] and a PD-L1 or PD-1 inhibitor probably does not have any path forward in that combination alone. [In future

studies, clinicians should] consider adding it to bevacizumab or other agents that might have some viability, but this is probably the end of a TIGIT PD-1/PD-L1 combination.

Q: Are you currently working on any research you'd like to highlight?

SALANI: Continuing to exploit the immune system is important in cervical cancer. This is a patient population who has not gotten a lot of attention. With the advent of immunotherapy in the setting, we've found some avenues of treatment. One thing I'm excited about that I'm working on is this [phase 2 VB-C-02 trial] looking at the human papillomavirus type 16 [HPV-16] target, and it's a vaccine targeting HPV-16 in combination with immunotherapy in patients who have been previously exposed to immunotherapy.[2] This is not an immunotherapy-naive population; it's one who's seen it. This is a population [with] high-risk [disease], but for HPV-16 cervical cancers, we can see whether we can capitalize on targeting the HPV-16, complementing it with immunotherapy, and continuing to see whether we can get that benefit from the immune system. It makes sense because cervical cancer is infection related, so using the immune system is a logical target. We just have to find that right combination. Knowing that we have some benefit with immunotherapy [and are] seeing it move to earlier settings [such as] the frontline setting, there may be some potential for it to be moved even with chemoradiation. Understanding the sequencing of these therapies but also understanding that immune therapy may play a role even after a prior checkpoint inhibitor therapy and continuing to explore those avenues is exciting. That's what I'm most excited about.

Q: Is there anything else you'd like to add?

SALANI: Cervical cancer is an area that's being studied aggressively right now. We have approval with tisotumab vedotin-tftv [Tivdak], which [had an] accelerated approval.[3] We just saw the confirmatory phase 3 data that were positive. That will hopefully be another avenue of treatment for our patients. Looking at other targets, there were some compelling data. Although it's not the most common biomarker, HER2 positivity may be another avenue for patients with cervical cancer, particularly adenocarcinoma. Then there's some interest in looking at TROP2 inhibitors and cervical cancer. We cannot rest on the gains we have had. They're modest, and we can do better. This is an exciting area of study. Encouraging patients to go on trials, making sure patients get access to these trials, and giving these patients access to the best therapies are going to be critical areas of study. ■

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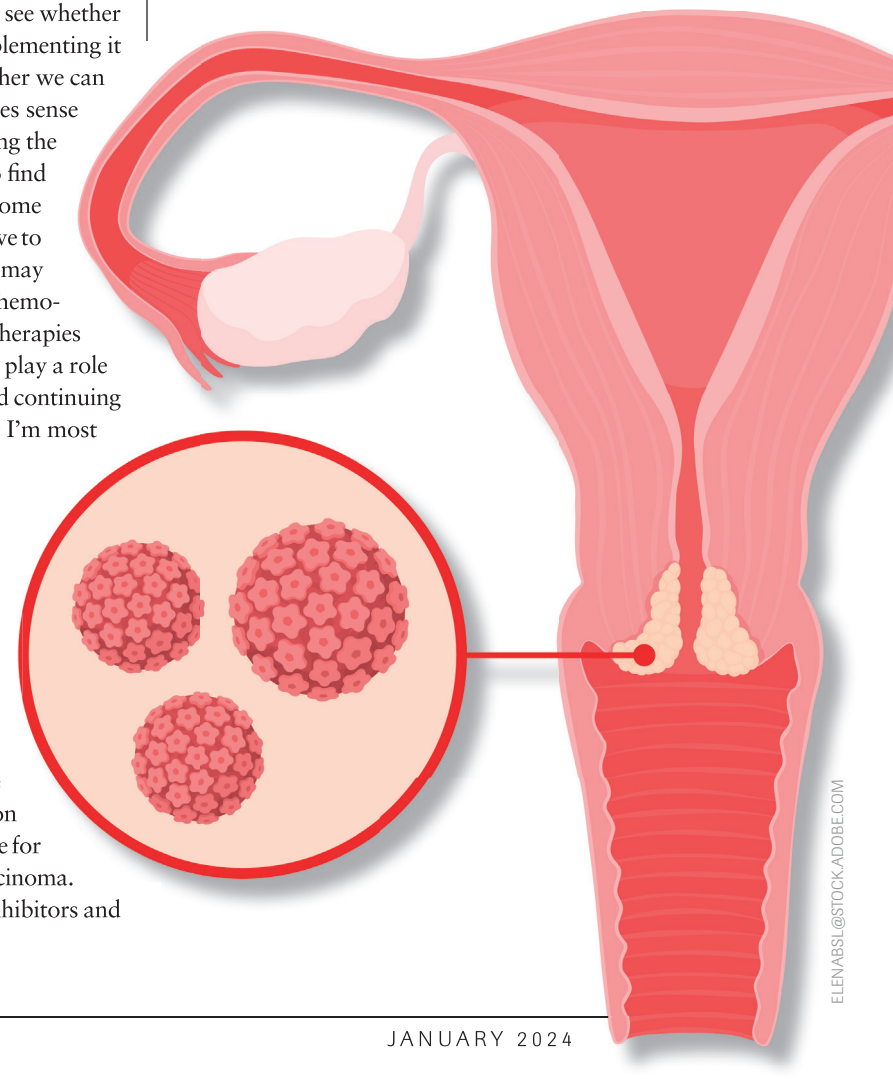

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Life Experience of Survivors of Gynecologic Cancers: A Survey Conducted in Italy

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ABSTRACT

Background: The study of health-related quality of life in survivors of gynecologic cancers is becoming increasingly important as 1.5 million survivors of gynecologic cancer in the United States and more are expected due to advances in diagnosis and treatment. This project investigated the perceived needs and lived experiences of survivors of gynecological cancer to help design supportive activities to be implemented in clinical practice.

Methods: Patients were recruited in hospitals or through social media and responded to an online survey that was addressed to patients in Italy, specifically in Sicily, Puglia, and Campania. Patients with ovarian, endometrium, or cervix cancer were recruited among women attending Cannizzaro Hospital and Alleanza Contro il Tumore Ovarico (Alliance Against Ovarian Cancer) members.

Results: Body image perception was changed in 82.3% of respondents, whereas familial relationships were described as changed by 27.5% of women. In 69.6% of patients, sexual habits were hindered by changes in the body, depression, pain, and awkwardness. Physicians informed patients about sexuality changes related to cancer extensively in 16.7% of cases and briefly in 19.6% of cases. The advice of a clinical sexologist was considered potentially helpful by 31.4% of patients and not potentially helpful by 47.1%, whereas 21.6% of patients had no opinion.

Conclusions: Although sexual habits are often changed by cancer, women surviving gynecological cancer rarely seek medical advice in this area. Physicians should be trained to inform patients and to promote referrals to sexologists.

Keywords: Gynecological cancer, quality of life, sexual activity

Gynecologic cancers, including ovarian, cervical, endometrial, and vaginal cancers, have a growing incidence worldwide.[1] Accordingly, the number of survivors is growing, being second only to survivors of breast cancer, and women may live for many years after receiving a diagnosis.[2,3] The study of health-related quality of life in survivors of gynecological cancers is becoming increasingly important and is considered a relevant patient-reported outcome, in addition to overall or disease-free survival.[4] Assessment of pre- and posttreatment health-related quality of life is a predictive factor for postoperative complications and a prognostic factor for overall survival and progression-free survival in patients with gynecological cancers.[5] Quality of life after gynecologic cancer also has been found to be related to cancer-related cognitive impairment.[6]

Quality of life for an individual is defined by the CDC as "physical and mental health perceptions and their correlates, including health risks and conditions, functional status, social support, and socioeconomic status."[4] This broad definition includes all areas of everyday life, such as relationships, work, communication, and self-care. Among other components, the deterioration of sexual health has been repeatedly described in survivors of gynecological cancer.[7-11] Indeed, the treatment of cancers

TABLE. **Health-Related Quality of Life Questionnaire**

Questions	Answers	Respondents (%)
What kind of help or support could make cures easier?	▪ Psychologic ▪ Social (individual accompanying to therapy, caregiver at home, help for family members) ▪ Economic ▪ Working	▪ 52.0 ▪ 32.4 ▪ 8.8 ▪ 6.9
Which area of your life was most impacted by the disease?	▪ Work ▪ Family ▪ Personal (care of yourself, identity)	▪ 12.7 ▪ 27.5 ▪ 59.8
How much did your body image change?	▪ Not at all ▪ Quite a bit ▪ Very much	▪ 17.6 ▪ 53.9 ▪ 28.4
Do you feel different?	▪ Not at all ▪ Quite ▪ Very much	▪ 13.7 ▪ 54.9 ▪ 31.4
Can you recognize your own image in a mirror?	▪ Not at all ▪ Quite ▪ Very much	▪ 29.4 ▪ 62.7 ▪ 7.8
Your mood is…	▪ Good ▪ Quite good ▪ Depressed	▪ 26.5 ▪ 57.8 ▪ 15.7
Who supports you most?	▪ Parents and family ▪ Husband/partner ▪ Friend ▪ Other (please specify)	▪ 21.6 ▪ 47.1 ▪ 8.8 ▪ 22.5
What changed most in your life?	▪ Nothing ▪ I can no longer plan ▪ Everyday life ▪ Working life	▪ 9.7 ▪ 31.0 ▪ 45.1 ▪ 14.2
Do you feel different?	▪ No ▪ A little ▪ Very much	▪ 13.7 ▪ 54.9 ▪ 31.4
Communication with your physician is…	▪ Very poor ▪ Fairly good ▪ Good ▪ Very good	▪ 2.0 ▪ 23.5 ▪ 35.3 ▪ 39.2
Which is the main emotion related to the disease?	▪ Anger ▪ Disbelief ▪ Acceptance ▪ Other (specify)	▪ 23.4 ▪ 22.4 ▪ 45.8 ▪ 8.4
Do you easily talk about the disease with your family?	▪ Yes ▪ No ▪ Sometimes	▪ 80.4 ▪ 6.9 ▪ 12.7
Are children in your family are aware of your disease?	▪ Yes ▪ No ▪ Partially	▪ 49.0 ▪ 23.5 ▪ 27.5
Are you afraid that anyone in your family may develop the disease?	▪ Yes ▪ No ▪ A little	▪ 59.8 ▪ 19.6 ▪ 20.6

Do you think a group of patients could support you?	▪ Yes ▪ No ▪ I do not know	▪ 40.2 ▪ 14.7 ▪ 45.1
Which one of the following could support you better?	▪ Talking with a friend ▪ Physical activity ▪ Cooking ▪ Other (specify)	▪ 40.2 ▪ 11.8 ▪ 17.6 ▪ 30.4
Has the attitude of the people closest to you changed?	▪ Yes, it is improved. ▪ Yes, it is worse. ▪ No, it is unchanged.	▪ 38.8 ▪ 6.8 ▪ 54.4
Did your nutrition change?	▪ Yes ▪ No	▪ 61.8 ▪ 38.2
Do you want to improve your nutrition?	▪ Yes ▪ No	▪ 66.7 ▪ 33.3
Do you think that support by a nutritionist with expertise in oncology could help you?	▪ Yes ▪ No	▪ 71.6 ▪ 28.4
Did you practice sports before the disease?	▪ Yes ▪ If yes, which sport? ▪ No	▪ 31.5 ▪ 25.4 ▪ 43.1
Do you practice sports now (even if a mild one)?	▪ Yes ▪ If yes, which sport? ▪ No	▪ 24.1 ▪ 16.4 ▪ 59.5
Did sexual habits with your partner change?	▪ Yes ▪ No ▪ Partially	▪ 44.1 ▪ 30.4 ▪ 25.5
What prevents normal sexual habits?	▪ Nothing ▪ Changes in the body ▪ Depression ▪ Pain ▪ Awkwardness ▪ Inadequate information ▪ Sense of guilt	▪ 30.1 ▪ 25.2 ▪ 21.1 ▪ 15.4 ▪ 6.5 ▪ 0.8 ▪ 0.8
Did your physician give you information about changes in sexual habits?	▪ Yes ▪ No ▪ A little	▪ 16.7 ▪ 63.7 ▪ 19.6
Is your partner sympathetic about distress in sexual health and dysfunction?	▪ Yes ▪ No	▪ 75.5 ▪ 24.5
Do you think a clinical sexologist could help you?	▪ No ▪ Yes ▪ I do not know	▪ 47.1 ▪ 31.4 ▪ 21.6
More than 1 answer is allowed for each question		

originating in sexual organs inevitably has short- and long-term effects that can interfere with normal sexual function, body image, and sexuality.[7,12] These effects include premature menopause, pain, depression, anxiety, fatigue, sleep disruption, an increase or decrease in weight, scars, loss of skin sensation, loss of bowel and bladder function (formation of ostomies), lymphoedema, and social isolation.[12]

High frequencies of sexual problems in this population have been reported: 40% to 100% of patients reported dyspareunia or pain, 60% to 87% reported vaginal dryness, 25% to 61% reported loss of libido or low arousal, and 45% reported low/lack of orgasm.[13-15]

Support for difficulties in life is currently considered important for facilitating survivors' quality of life. Adequate services need to be provided with perspectives tailored to patients' needs and clinical management of cancer. To design supportive activities to be implemented in the clinical practice, perceived needs and the lived experiences of survivors of gynecological cancer should be queried, taking into account cultural properties. To this aim, the life experience of survivors of gynecological cancers was investigated by an online survey created by the investigators to address doubts arising from their clinical practice and addressed to patients in Sicily, Puglia and Campania, Italy.

Patients and Methods

Participant Selection

The survey was addressed to adult women affected by gynecological cancer, at any stage and in any phase of the disease, and inhabitants of a socially homogeneous area in Sicily, Puglia and Campania. Patients were included if they lived in Sicily, Puglia, and Campania; and in Sicily, specifically, they were included if they were patients at Cannizzaro Hospital, where the Alleanza Contro il Tumore Ovarico (ACTO; Alliance Against Ovarian Cancer) was founded. Patients in the aforementioned populations who were ACTO members were invited to participate in the survey. Patients could partake in the survey either during control visits or follow-up in Sicily or through social media groups for ACTO Puglia and ACTO Campania.

Methods

The authors developed a questionnaire from the perspectives of specialized physicians and patients. It contained 27 questions investigating the following areas: changes in everyday life; perception of body image; subjective psychological and physical well-being, including sexuality; patient-physician communication; and nutrition. The questionnaire, arranged via the Survio software, was delivered online and in paper form.[16]

Open and closed (multiple choice, with either single or multiple permitted answers) questions were included. Survey results were anonymous. Data were analyzed by descriptive statistics and are presented as absolute numbers or percentages.

Results

Overall, 102 women answered the survey, of whom 88 were outpatients of Cannizzaro Hospital and 14 were members of ACTO Puglia and ACTO Campania. The respondents' ages ranged from 32 to 80 years.

The **Table** reports the frequency of answers to the questionnaire. Main changes in everyday life after the diagnosis of gynecological cancer were reported about mostly personal areas (care of oneself, identity, body image). This area was of concern for 59.8% of patients, the family area for 27.5%, and the work area for 12.7%. The patients reported that their disease was known to family members and could be mentioned freely by 80.4%, rarely by 12.7%, and not at all by 6.9%. Children were aware of the mother's disease in 49.0% of cases, not fully aware in 27.5%, and not at all in 23.5%.

Perception of body image was of concern for 99.9% of patients; that it had changed very much was reported in 28.4%, changed quite a bit by 53.9%, and was unchanged by 17.6%. Specifically, 31.4% of patients perceived themselves as very transformed, 54.9% as a little transformed, and 13.7% as not transformed. One's image in a mirror could be completely recognizable by 7.8% of women, quite recognizable by 62.7%, and not at all recognizable by 29.4%.

Mood changes seemed not to be a common concern. The mood was described as depressed by 15.7% of subjects, quite good by 57.8%, and good by 26.5%. The emotion mainly related to the disease was acceptance for 45.8%, anger for 23.4%, disbelief for 22.4%, and other for 8.4%.

Answers about sexual habits showed relevant changes following cancer diagnosis and treatment and some difficulties in addressing them. Sexual habits were noted as changed for 44.1% of patients, partially changed for 25.5%, and unchanged for 30.4%. Factors impacting sexuality were a sense of guilt in 0.8% of cases, limited information in 0.8%, awkwardness in 6.5%, pain in 15.4%, depression in 21.1%, and body changes in 25.2%. No impacting factor was reported by 30.15% of patients. Partners were reported as sympathetic to the sexual distress of patients in 75.5% of cases.

Communication with the referring physician, either an oncologist or a gynecologist, was judged as very good by 39.2%, good by 35.3%, quite good by 23.5%, and bad by 2%. Physicians informed patients about sexuality changes related to cancer in 16.7% of cases; 19.6% of patients received limited information in this area, and 63.7% were not informed. The advice of a clinical sexologist was considered helpful by 31.4% of subjects and not helpful by 47.1%, whereas 21.6% of women had no opinion on this point.

Nutrition was changed after cancer diagnosis in 61.8% of cases. An improvement in nutrition was desired by 66.7% of patients and was not desired by 33.3%. Support by a nutritionist with expertise in the nutrition of patients with cancer was considered helpful by 71.6% and not helpful by 28.4%.

Discussion

Results showed that perception of changes in oneself was a main concern in patients, more frequent than social relationship impairments. Changes in

family and work were considered a secondary problem to personal changes. Body image perception was changed by cancer experience in approximately 80% of patients, whereas family relationships were described as changed in less than 30% of women.

Notwithstanding this fairly good evaluation of family life, sexual habits with one's partner were changed for 69.6% of patients. Many patients didn't appear to understand what caused this change. For example, 21% of patients answered that sexual changes were due to depression, but only 16% had reported depressed moods. More commonly, body changes were the reported cause of sexual impairment. The partner's disposition toward sexual habits changes was considered sympathetic by 75.5% of survey participants. Indeed, only 31% considered advice from a clinical sexologist as potentially useful. Although the relationship with physicians was reported as good by the majority of patients, the physicians only rarely discussed sexual impairment associated with gynecological cancer.

Overall, the results of this survey showed that women are mainly concerned with changes in one's person, whereas family and work relationships are less concerned in the experience of cancer. For the survey participants, sexual habits were often changed and seemed to be associated with physical problems or mood disorders. Medical advice in this area seemed to be little desired. It is also possible, conversely, that women do not want to share this problem with professionals for lack of confidentiality or confidence in possible effectual help. Finally, sexual changes may be accepted as events without consequences in a couple's relationship. Based on the authors' clinical experience with these patients, they can confirm that even when a strong alliance is established, sexual problems are seldom mentioned by women during the follow-up. Medical advice meant to improve treatment efficiency is mainly dismissed, whereas women seem to be ashamed or to feel guilty in addressing a secondary priority need.

Such results suggest that patients would need professional aid to communicate their distress in resuming sexual activity after the diagnosis of gynecologic cancer and to face such problems. Physicians who follow up with these patients should be trained to promote confidentiality and to provide assistance in the sexuality area, specifically by referring patients to a sexual health therapist. The opportunity to seek a sexual health therapist's assistance should be actively explained and encouraged.

This study has some limitations, such as the moderate number of participants and their residence in a select part of Italy. A limitation of our study could be that validated instruments for the measurement of quality of life, such as the European Organisation for Research and Treatment of Cancer Quality of Life-C30, PROMIS-29, FACT-G, and QOL-CS, were not used; indeed, we aimed at identifying different areas of discomfort. For this reason, no direct comparison may be made with studies assessing quality of life.[5,6]

After the survey, a focus group was organized with 10 patients to better understand their attitudes toward sexuality and to shape a support group responding to their needs. The results of this intervention will be the subject of a future article.

In conclusion, although this survey confirmed that gynecologic cancer impacts sexual health and dysfunction, further investigation is necessary to identify a possible approach to organizing support services for cancer survivors in the south of Italy. ■

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Building Efficiency and Scaling With a Remote Genetic Counseling Program

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ABSTRACT

Purpose

A third-party telemedicine (TM) genetic counseling program was initiated at a large community oncology practice spanning 35 clinical sites with 110 clinicians and 97 advanced practice providers throughout Tennessee and Georgia.

Patients and Methods

Appropriate patients were referred through the electronic health record (EHR) based on current National Comprehensive Cancer Network guidelines. A combination of TM and genetic counseling assistants enhanced convenience, broadened access, and decreased no-show rates. Physician education for mutation-positive screening recommendations was provided through deep integration of dedicated genetic counseling notes in the EHR.

Results

From 2019 to 2022, the program expanded from 1 to 20 clinics with referrals growing from 195 to 885. An average of 82% of patients completed genetic counseling consultations over TM with more than 70% completing genetic testing. The average was 4 to 6 days from referral to consultation. The no-show rate was maintained at less than 7%. In 2023, this model supported all 35 clinics across the state.

Conclusion

Our program illustrates how remote genetic counseling programs are an effective choice for scaling genetics care across a large community oncology practice. Deep integration of TM genetic counseling within the EHR helps identify patients who are high risk and improves test adoption, patient keep rate, and turnaround time, helping to achieve better patient outcomes.

Background

Genetic counseling started as a specialty service in prenatal and pediatric patient populations in the 1970s and expanded to cancer care in the 1990s. Initially, it was used only to identify hereditary cancer syndromes in affected patients and define the risk for unaffected family members. Now the utility of genetic testing and therefore the scope for cancer genetic counseling have expanded to determining treatment options through surgical interventions and genetic profiling to direct appropriate chemotherapy options. These advancements have forced genetic counseling to become integral in comprehensive cancer care, with genetic testing offered earlier in the diagnostic process to facilitate clinical decision-making.[1]

Through this evolution, the field of cancer genetic counseling faced multiple challenges. First there was a supply-side workforce shortage. Prior studies have reported approximately 1 genetic counselor (GC) for every 300,000 Americans and equated it to 8 GCs for 1 million individuals in the United States population.[2,3] In 2017, the Genetic Counselor Workforce Working Group, conferred under the National Society of Genetic Counselors (NSGC), projected that the demand for the genetic workforce to have 1 GC for every 100,000 Americans would be met in 2023 to 2024, which is said to have been attained.[4] Further increase in demand to 1 GC for every 75,000 Americans might not be met until 2029 to 2030,

but given the recent growth in genetic counseling training programs it could be anticipated by 2026.[5]

The second challenge was in the ever-expanding National Comprehensive Cancer Network (NCCN) guidelines testing criteria. NCCN Clinical Practice Guidelines in Oncology for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic per source[6] and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal[7] provide evolving clinical guidance to identify patients who should be offered a hereditary genetic panel test. To determine how much in demand GCs were, an independent objective assessment by a study from Greenberg et al found that 21.6% of patients with cancer met NCCN guidelines at the time of the study in 2019, and that proportion increased to 62.9% when family history was taken into account.[8] Other publications that same year reported that even though NCCN guidelines were considered one of the standard tools to help identify individuals eligible for germline genetic testing, these criteria continue to fail to identify women with breast cancer who carry *BRCA1* and *BRCA2* mutations.[9,10] Since then, NCCN guidelines have continued to be more inclusive for patients affected by cancer and those who do need germline genetic testing. A study done by Yadav et al in 2020 found that the NCCN criteria had an 87% sensitivity rate and 53% specificity rate to help identify *BRCA1* and *BRCA2* mutation carriers among 3907 women with breast cancer. They suggest that further expanding the NCCN criteria to test all women 65 years and older at breast cancer diagnosis would improve the sensitivity such that women carrying pathogenic mutations would not be missed.[11]

The third challenge was in the traditionally entrenched service delivery model. Innovation was a key need as multiple studies cited long wait times and lack of access to genetic counseling.[12,13] The customary 1-hour pretest appointments gave way to alternate models: some GC directed, such as group counseling or TM counseling, and some non–GC directed, where education and informed consent are provided by prerecorded video, web-based education, chatbots, or interactive relation agents.[1]

Although TM (audiovisual or audio only) has been used for genetic counseling for over a decade, its implementation has increased drastically since 2019 for various reasons. According to a Professional Status Survey (PSS) on access and service delivery by the NSGC, the completion of counseling visits over the phone rose from 36% in 2019 to 74% in 2021. Similarly, 28% of GCs reported using audiovisual TM in 2019 compared with 82% in 2021.[14] Studies have shown that these alternate service

FIGURE 1. **Depiction of GC Calls and Coverage Provided**

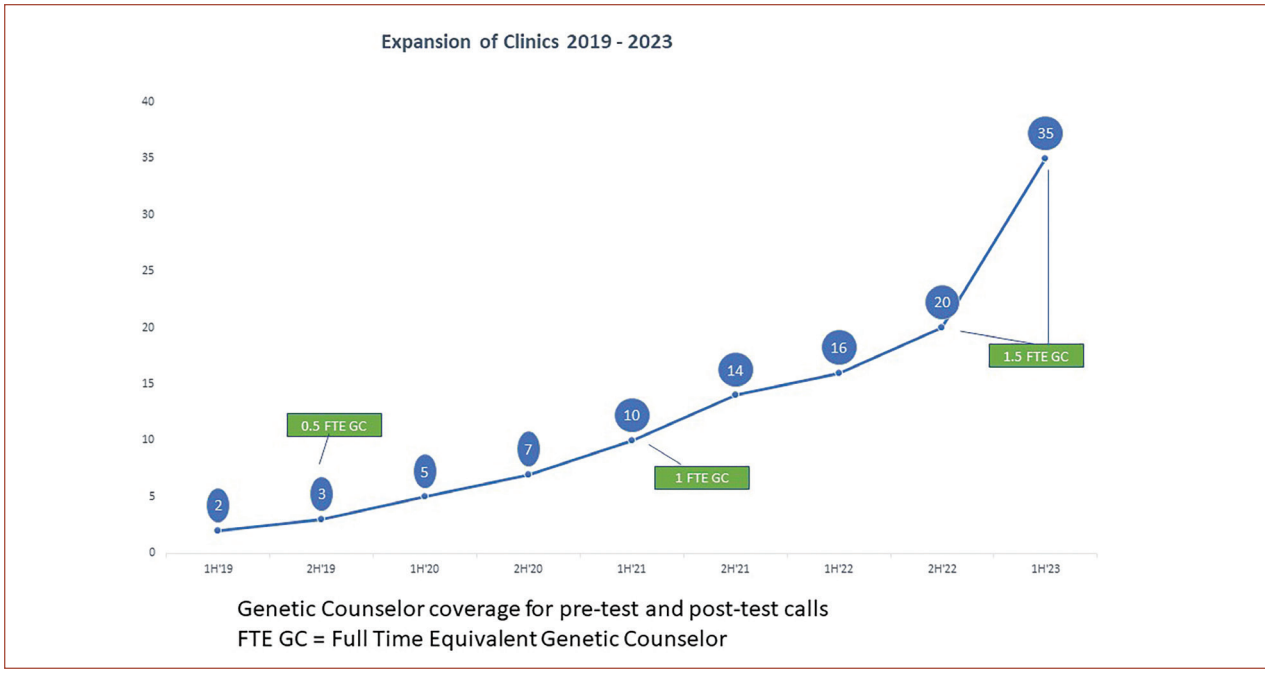
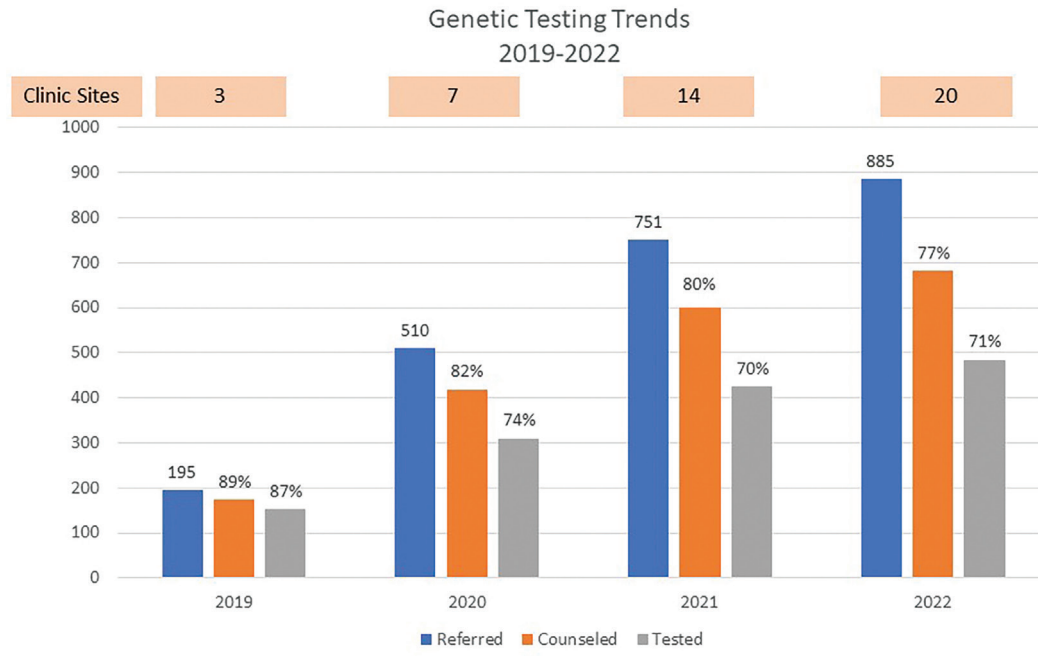


FIGURE 2. **Trends in GC 2019-2022**



delivery models increase patient convenience by mitigating travel and wait time–related barriers, improve patient satisfaction, and are ultimately successful in meeting the growing demand for genetics services.[15]

The advent of genetic counseling assistants (GCAs) also helps meet the growing demand for services. Previous literature shows that certified GCs with GCA support can see an average increase of 60% in patient volume compared with GCs alone, thereby expanding access to the genetic counseling services.[16] Another study demonstrated that GCAs assist GCs in focusing on the direct patient care for which they are specifically trained by significantly reducing the time taken to prepare for a patient appointment, and significantly increase the total number of patients seen per week (7.9 vs 11.4 after using GCA support).[17]

Here, we report on an efficient service delivery model for GC that incorporates a third-party TM-based genetic services vendor with deep integration into the electronic health records (EHRs) to scale the implementation of genetic counseling services in a community-based oncology setting across 35 clinics. The significance of this model is in the efficiency built into the patient engagement where GC consults do not add time to the genetic testing process.

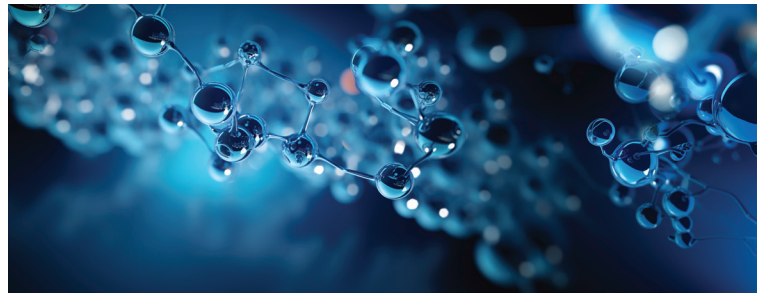
Methods

A TM genetic counseling program using a third-party genetics vendor was initiated in 2019 at Tennessee Oncology (TO), a large community oncology practice spanning 35 hematology/oncology clinical sites with 110 doctors and 97 advanced practice providers (APPs) throughout Tennessee and North Georgia. TO's core expertise is in onsite chemotherapy treatments, so patients may receive the necessary care without the strain of long-distance travel. TO, one of the nation's largest, community-based cancer care specialists, is home to one of the leading clinical trial networks in the country. Over the years it has been consistent with its mission statement to provide high-quality cancer care and the expertise of clinical research for all patients at convenient locations within their community and close to their home.[18] Therefore, incorporating a TM-based genetic counseling and testing program fits well with TO's mission and long-term vision.

In initiating the first genetics program at this practice, a total of 3 to 4 months was spent in discovery, infrastructure development, and establishing process flow to support the genetics team. In the discovery phase, an in-depth study of patient intake documents for new patient charts and existing lab processes was undertaken. Members of the genetics team shadowed physicians and

advanced practice nurses to understand the clinic flow in terms of clinic appointments, lab orders, and front desk scheduling activities. During the infrastructure development phase, family history elements were added to the new patient intake paperwork, and specific lab orders were built for germline genetic tests. Custom genetics fields were set up within the EHR for exclusive use by the genetics team for consultation notes and clinic templates for scheduling. In the third and final phase of establishing a process that could be duplicated at every clinic site, a project management workflow was created in partnership with the operations team at TO. Front office, clinical, and billing workflows were created. Incorporating genetic services at various clinics began with the training of lab and front desk staff on the new service line, simultaneously with educational touch points for physicians and APPs on current NCCN guidelines. Decision aids were also built into the EHR to help appropriately capture patients who might meet these guidelines, but they were quickly abandoned due to technical challenges. All referrals were entered through the EHR to promote tracking for genetic counseling and testing.

GCAs were assigned to support front office staff at TO for scheduling all GC consults over TM. Protocols were created to triage scheduling for urgent referrals within 1 to 3 business days, and nonurgent referrals to not exceed 4 to 6 business days of wait time for patients. Particular attention was allocated to patients with pancreatic cancer, metastatic prostate cancer, or metastatic breast cancer diagnoses to assess eligibility for PARP inhibitor chemotherapy. Other urgent appointments were categorized as newly diagnosed patients with breast cancer undergoing surgical planning and patients carrying Cigna insurances with a requirement for genetic counseling services to precede the genetic test orders.[19] Referrals meeting these urgent criteria were invited from all 35 clinic sites practice-wide right from the onset. For nonurgent referral types (defined as patients affected by cancer meeting other NCCN criteria), the program was introduced 1 clinic site at a time as detailed in **Figure 1**.



All GC appointments were scheduled as TM audio and visual visits, which were switched to audio only (phone) if requested by the patient. TM calls were held either over Zoom or Doxy.me to the patient's home or workplace, usually outside clinic hours, and therefore considered asynchronous to their in-person oncologist's appointment. Additionally, genetic counseling sessions and notes were completed independently of the oncologist.

By the end of 2022, the GC team at TO had 1.5 full-time equivalent (FTE) of genetic counselor time and 1 FTE of GCA time. As there was not an established genetics service at TO prior to initiating this program, the performance metrics of this new service delivery model for GC are compared against the national averages for genetic counseling services published in 2023 by NSGC in its PSS document.[11]

Results

In the first year, the service was piloted at 1 TO clinic site for 3 months, (January-March 2019) with 5 clinicians and 4 APPs using all the functionality of the program. Prepilot data from 2018 showed a total of 7 patients consented to genetic testing at that particular initial clinical site. During the pilot phase, 34 patients were referred for genetic counseling and 30 completed genetic tests. This result demonstrated a 5-fold increase in identifying and appropriately testing patients and was published as an abstract at the 2019 American Society of Clinical Oncology Annual Meeting.[20]

Based on the success of the pilot, the TM-based genetic counseling service progressively rolled out to more clinics across the state of Tennessee. Starting with 3 clinics in the first year, the incorporation of clinical sites into the program progressed to 7 sites at the end of 2020, 14 sites at the end of 2021, and 20 sites at the end of 2022. In 2023, with the beginning of year 5, the program had expanded to all 35 clinics across the practice (Figure 1).

Breakdown of the referral volume indicates the largest growth in referral numbers for genetics in year 2 by 160%. Although tapered now to a 20% year-over-year increase for 2022, the cumulative growth for genetic counseling referrals over the past 4 years (2019-2022) was 350% (**Figure 2**).

As shown in Figure 2, consistently over 77% of patients completed genetic counseling consultations over the years, with a high of 89% in 2019. Of the completed consultations, over 70% of patients completed genetic testing with a high of 87% seen in 2019 (Figure 2). The no-show rate is consistently less than

TABLE. **Building Efficiency in GC Clinic Workflow[14]**

For 1.5 FTE GCs	National average*	TO efficiency model for GC
Weekly patient visits	21	33
No-show rates	10%-30%	< 7%
STAT appts	1-3 days	1-3 days
Wait times	3 days to 2 weeks	4-6 days

FTE, full-time equivalent; GC, genetic counselor; STAT, Specific Timely Appointments for Triage; TO, Tennessee Oncology.
*Based on National Society of Genetic Counselors, Professional Status Survey 2023

7% for the program (**Table 1**).

Comparing results against national averages, for a staff of 1.5 FTE GCs and 1 GCA, this efficient service delivery model for genetic counseling offers a higher number of available slots per week for counseling appointments (33 vs 21), a lower no-show rate (< 7% vs 10%-30%), and comparable wait times for urgent (1-3 days) and nonurgent (4-6 business days) referrals (Table 1).

Discussion

A third-party genetics team of TM-based GCs was brought on in 2019 to facilitate appropriate genetic test ordering and offer comprehensive cancer care for patients at TO. In the genetic counseling profession, amid discussions about a dearth of genetics professionals, we describe a fully scaled genetic counseling and testing program offered over TM with deep integration of the EHR at 35 clinical sites in a community-based setting.

The efficient service delivery model for GCs deployed at TO facilitates a clinic workflow wherein the third-party GCs and GCAs are in direct EHR-based communication with the oncologist and their clinical team, which, in turn, promotes higher adoption of the service. The effectiveness of this model is seen in higher patient engagement with genetic counseling services due to the convenience of TM conducted asynchronously to the oncologist's in-person appointment.

After initially proving the success of the pilot program,[20] the next challenge was to scale this service across all clinical sites. With this efficient service delivery for the genetic counseling model, the scalability of genetic counseling services persisted through years 2, 3, and 4 as the program was rolled out at more than half of the existing clinics over TM by the end of 2022 (Figure 1). Currently, in year 5, the TM-based GC team supports all 35 clinics with no increased wait times or no-show rates. This scalability is powered by the effective use of TM in combination with the deep integration of GC's and GCA's into the hospital EHR as a service modality.

TM genetic counseling appointments at the patient's home or workplace enhance access, decrease no-show rates, and promote patient engagement. Built on the proven efficacy of TM,[15] this genetics service was established as a remote program before the COVID-19 pandemic years. Expansion of services showed consistent growth through 2022. The consistency of completed genetic counseling appointments and genetic test uptake by patients demonstrates the seamless use of this service modality for scaling genetic counseling (**Figure 2**). Although not measured yet, based on anecdotal patient engagement, patient satisfaction with the TM service is not hindered. This quality improvement enhancement is planned for the next phase of maintaining the relevance of the service.

Performance metrics for the program, described above, indicate that this integrated genetic counseling program is more efficient in available consult slots than national averages for GCs. The program maintained a 4 to 6 business-day wait time even with a significant uptick in the referrals in year 2 when a decision support aid was in use in the EHR to help physicians talk about genetics with their patients and update family history information during the clinic visit. This aid was disabled at the end of year 2 and deferred for future use after completing program integration across all 35 clinical sites. We plan to make further attempts at building a decision support tool in the EHR in 2023.

Per standard recommendations in the field, incorporating 1 GCA of FTE support has been key in improving the efficiency of our GC team.[13] The GCAs schedule TM patient appointments for genetic counseling for each TO clinical site. They function as the point of contact in the clinic and liaise with lab personnel and operations managers to help coordinate dispatching and tracking tests and uploading genetic reports. GCAs also assist in care coordination by being the conduit with the genetic testing labs, overseeing specimen processing and timely retrieval of reports. The overall impact of a GCA is greater than the sum of their role. They are the first to educate patients on the need for genetic counseling. They also shepherd clinic personnel on how to navigate the genetic testing process.

The appropriate implementation of a combination of TM with the use of GCAs coupled with EHR integration helps alleviate the administrative

and operational burden of adding genetic services to an already busy community-based oncology service. With the addition of GCAs, GCs work at the top of their license to interpret results, conduct variant assessments, and dictate medical care plans for patients who are mutation positive per the current standard-of-care guidelines in the industry. This model proves the management of clinical efficiency and scalability for genetic counseling to be on the front line in multiple clinics. The genetic counseling consults are completed within 4 to 6 business days and do not delay the genetic testing. Rapid turnaround times support quality medical care as complete and verified genetic results are made available to providers promptly in the EHR.

The ultimate success of the program is in the deep integration of this remote service into the EHR. All notes and pedigrees are uploaded as unique fields in the EHR and not as scanned documents. Communications with clinic staff and physicians are conducted through an EHR messaging system and completed notes in the patient charts to extend transparency into the workings of the remote team.

Initiatives for this program in the coming year include electronic decision support tools, additional provider education, and the development of management algorithms for patients who are mutation positive. We also plan to incorporate patient engagement tools to further expedite the process and deploy patient satisfaction surveys to offer superior patient care. For a large, community-based oncology center that is focused on high-quality comprehensive cancer care for all its patients, this efficient service delivery model for genetic counseling scales to fit all its clinical site needs and has bandwidth to incorporate additional referrals and clinics as it expands. We encourage genetic counseling programs to incorporate the described service delivery model to build efficiency and promote quality genetics care for patients.

Conclusion

As germline genetic testing integrates further into oncology care, GCs will increasingly partner with community-based cancer centers. Our program illustrates how remote genetic counseling programs can build efficiency and are an effective choice for scaling genetics care. Building efficient teams includes collaborating with the clinic site to integrate workflow without disruption. Deep integration of TM-based genetic counseling within the EHR helps identify patients who are high risk and improves test adoption, patient keep rate, and turnaround time, therefore helping to achieve better patient outcomes. Maintaining an open channel of communication with the clinic staff and oncologists through an EHR-based messaging system helps build transparency and trust. This efficient service delivery model for genetic counseling and testing programs is an important, successful part of comprehensive cancer care. ■

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RAPID REPORTER

ONCOLOGY Reviews Key Presentations From the
2023 Annual Global Meeting of the International Gynecologic Cancer Society

Trastuzumab Deruxtecan Showcases Clinical Efficacy in HER2+ Gynecological Cancers

Fam-trastuzumab deruxtecan-nxki (Enhertu) demonstrated clinically meaningful benefit in patients with heavily pretreated endometrial, cervical, or ovarian cancer across varying HER2 immunohistochemistry (IHC) levels, according to findings from the phase 2 DESTINY-PanTumor02 trial (NCT04482309).

In patients with endometrial cancer, the investigator-assessed objective response rate (ORR) was 57.5% compared with 50.0% in those with cervical cancer and 45.0% in patients with ovarian cancer. The median duration of response (DOR) was not reached (NR; 95% CI, 9.9-not estimable [NE]) in the endometrial cancer cohort, 14.2 months (95% CI, 4.1-NE) in the cervical cancer group, and 11.3 months (95% CI, 4.1-22.1) in the ovarian cancer cohort.

Response rates were also evaluated by HER2 status, and data showed that responses were highest in those with IHC 3+ tumors. For example, in the endometrial cancer cohort (n = 40), patients with IHC 3+ had an ORR of 84.6%, IHC 2+ was 47.1%, IHC 1+ was 25.0%, and IHC 0 was 60.0%; the median DORs were NR (95% CI, 9.6-NE), 18.2 months (95% CI, 3.0-NE), NR (95% CI, not available), and 9.9 months (95% CI, 2.8-NE), respectively.

In those with cervical cancer (n = 40), the ORRs were 75%, 40%, 50%, and 50% in the IHC 3+, 2+, 1+, and 0 groups, respectively; the median DORs were NR (95% CI, 9.3-NE), 3.8 months (95% CI, 2.8-NE), 14.2 months (95% CI, 8.3-NE), and NR (95% CI, 6.8-NE), respectively.

Finally, in the ovarian cancer cohort (n = 40), the ORRs were 63.6%, 36.8%, 20.0%, and 60.0%, respectively. Here, the median DORs were 22.1 months (95% CI, 4.2-NE), 11.3 months (95% CI, 2.8-NE), 8.3 months (95% CI, not available), and 4.5 months (95% CI, 2.6-NE) in the IHC 3+, 2+, 1+, and 0 groups, respectively.

→ **For the full article, visit** CancerNetwork.com/PanTumor02_IGCS

Induction Chemotherapy/CRT Improves Efficacy in Advanced Cervical Cancer

Induction chemotherapy with weekly paclitaxel and carboplatin before chemoradiotherapy improved progression-free survival (PFS) and overall survival (OS) for patients with locally advanced cervical cancer, according to results from the phase 3 GCIG INTERLACE trial (NCT01566240).

At a median follow-up of 64 months, there were 146 PFS events (HR, 0.65; 95% CI, 0.46-0.91; $P = .013$). In the induction chemotherapy plus chemoradiotherapy arm or the combination arm, the 3-year PFS rate was 75% and at 5 years it was 73%. For the chemoradiotherapy alone arm, the 3-year PFS rate was 72%, and at 5 years it was 64%.

OS was also analyzed, with investigators reporting 109 deaths in the overall study population (HR, 0.61; 95% CI, 0.40-0.91; $P = .04$). In the combination arm the 3-year OS rate was 86%, and at 5 years it was 80% compared with 80% and 72%, respectively, in the chemoradiotherapy arm.

A total of 500 patients were randomly assigned 1:1 to either the combination chemotherapy or the chemoradiotherapy arms. In the combination chemotherapy arm, carboplatin was given at an area under the curve of 2 along with paclitaxel at 80 mg/m^2 weekly for 6 weeks.

In the standard chemoradiotherapy arm, patients were given cisplatin at 40 mg/m^2 weekly for 5 weeks, external beam radiation therapy at 40 to 50 Gy in 20 to 28 fractions, and beam therapy at minimum equivalent total doses of 78 Gy to point A. A 3D image-guided brachytherapy was recommended. The

overall treatment time was 50 days or less and all centers had radiotherapy quality assurance. The follow-up was every 3 months for 2 years, then every 6 months for 5 years.

→ **For the full article, visit** CancerNetwork.com/INTERLACE_IGCS

Dostarlimab Combo Significantly Improves PFS in Advanced Endometrial Cancer

Treatment with dostarlimab-gxly (Jemperli) and chemotherapy followed by dostarlimab maintenance resulted in significant progression-free survival (PFS) benefit compared with chemotherapy alone among patients with advanced or recurrent endometrial cancer, according to the findings from the phase 3 RUBY/ENGOT-EN6/GOG3031/NSGO trial (NCT03981796).

Data from the trial indicated that at a median follow-up of 25.4 months across the overall population, treatment with dostarlimab plus chemotherapy reduced the risk of disease progression or death compared with placebo plus chemotherapy (HR, 0.64; 95% CI, 0.507-0.800; *P* <.0001). In the dostarlimab and placebo arms, respectively, the PFS rate was 48.2% vs 29.0% at 12 months and 36.1% vs 18.1% at 24 months.

After a median follow-up of 24.8 months among patients with mismatch repair deficient (dMMR) or microsatellite instability–high (MSI-H) disease, the dostarlimab regimen produced a reduction in the risk of progression or death (HR, 0.28; 95% CI, 0.162-0.495; *P* <.0001). The 12-month and 24-month PFS rates in each respective arm were 63.5% vs 24.4% and 61.4% vs 15.7%.

With respect to overall survival (OS) in the overall population, dostarlimab plus chemotherapy reduced the risk of death (HR, 0.64; 95% CI, 0.464-0.870; *P* = .0021). In the dostarlimab and placebo arms, respectively, the OS rates were 84.6% vs 81.3% at 12 months and 71.3% vs 56.0% at 24 months.

OS data in the dMMR/MSI-H cohort indicated that there was a reduction in the risk of death with the dostarlimab regimen (HR, 0.30; 95% CI, 0.127-0.699). Among patients who received dostarlimab and those treated with placebo in this population, respectively, the 12-month OS rates were 90.1% vs 79.6% and the 24-month OS rates were 83.3% vs 58.7%.

→ **For the full article, visit** CancerNetwork.com/RUBY_IGCS

Radical Hysterectomies Show Sexual Toxicity in Early-Stage Cervical Cancer

Radical hysterectomy is associated with significantly higher levels of sexual toxicity compared with simple hysterectomy in patients with low-risk, early-stage cervical cancer, according to results from the phase SHAPE trial (NCT01658930).

As previously reported, the primary end point of pelvic recurrence rate (PRR) at 3 years was 2.52% for simple hysterectomy and 2.17% for radical hysterectomy (95% CI, 2.32%-4.00%). Investigators could conclude that hysterectomy was noninferior compared with radical hysterectomy with respect to PRR. The use of adjuvant radiation was less than 10% in both treatment arms.

Results from the sexual health assessment (SHA) showed that patients who received a radical hysterectomy experienced worse sexual vaginal functioning (*P* <.001-.02) for up to 24 months, worse desire (*P* = .001) and arousal (*P* <.0001) at 3 months, and worse lubrication (*P* = .003-.18) and sexual pain (*P* <.001-.01) for up to 12 months. Radical hysterectomies also produced sexual dysfunction in the clinical range for up to 6 months (*P* < .001-.02) and more sexual distress (*P* = .018) at 3 months compared with simple hysterectomy. There was no change in orgasm or satisfaction.

Sexual toxicity symptoms seemed to recover over time, allowing for opportunities for early sexual intervention in patients who required radical hysterectomies.

Secondary end points included patient-reported sexual health and quality of life, which were based on validated questionnaires completed at baseline and 3, 6, 12, 24, and 36 months following surgery and before recurrence. The SHA included 485 patients with a median age of 42 years (range, 24-72) and consisted of the female sexual functioning index and the revised female sexual distress scale. A total of 85% of patients completed the SHA at baseline and 65% completed it at 36 months.

→ **For the full article, visit** CancerNetwork.com/SHAPE_IGCS ■

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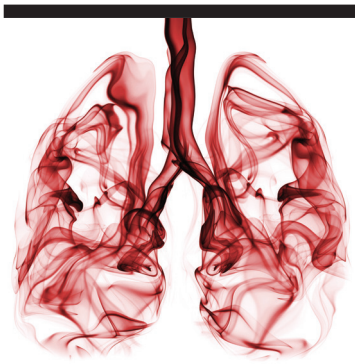
Frontline FORUM

Defining a Space for *NRG1* Fusion–Positive Tumors in Lung and GI Cancers



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A group of lung and gastrointestinal (GI) cancer experts gathered during a Frontline Forum event to discuss treatment options for *NRG1* fusion–positive tumors. The panel covered how to best detect this gene through different assays using DNA or RNA, and updates in the therapeutic space.

The panel was led by **Alexander I. Spira, MD, PhD, FACP**, codirector of the Virginia Cancer Specialists Research Institute and director of the Thoracic and Phase I Program in Fairfax. He was joined by **Teresa Macarulla, MD, PhD, a** physician in the Medical Oncology Department at Vall d'Hebron University Hospital in Barcelona, Spain; **Cindy Neuzillet, MD, PhD, HDR,** head of the Gastrointestinal Oncology Unit and professor in the Department of Medical Oncology at the Curie Institute in Saint-Cloud, France; **Joshua K. Sabari, MD**, assistant professor of medicine and director of high reliability organization initiatives at NYU :angone Health in New York, New York; **Alison Schram, MD**, assistant attending physician at Memorial Sloan Kettering Cancer Center (MSKCC) in New York, New York; and **Eric Van Cutsem, MD, PhD,** full professor at the University of Leuven and division head of Digestive Oncology at University Hospitals Gasthuisberg in Leuven, Belgium.

A Brief Overview of *NRG1* Gene Fusions

To begin the conversation, the panel first discussed what *NRG1* gene fusions were and how they applied to the lung and GI cancer space, respectively. The most common *NRG1* fusion partner is *CD74*. It was noted that *SLC3A2*, *VAMP2*, *RBPMS*, *WNR*, and *SDC4* may retain a membrane-bound EGF-like domain, which can retain the wild-type *NRG1* III-β3 form. The oncogenic potential of *CD74-NRG1* can be maintained by the other fusions listed.[1,2]

When looking into the background of *NRG1* gene fusions, most notably the fusions occur in 0.5% of patients with cholangiocarcinoma and pancreatic ductal adenocarcinoma, respectively. For patients with non–small cell lung cancer, they occur in 0.3%. A total of 51% of women who are nonsmokers receive a diagnosis of mucinous subtype adenocarcinoma each year.

The panel agreed that they rarely see patients with *NRG1* gene fusions. However, Schram from MSKCC said her institution is a referral center and has seen an uptick in these patients. Van Cutsem has stopped specifically screening for this and instead does a broad next-generation sequencing (NGS) panel.

Neuzillet said she does not do molecular screening regularly for

TABLE 1. **Current Assays to Detect *NRG1* Gene Fusion**[3-6]

Assay	Input
Fluorescence in situ hybridization	DNA
Anchored multiplex polymerase chain reactions for targeted RNA sequencing	RNA
NGS of DNA (MSK-IMPACT)	DNA
Targeted RNA sequencing (MSK Solid Fusion Assay) (Archer FusionPlex)	RNA
Immunohistochemistry	Proteins (antigens)

NGS, next-generation sequencing

those in the GI space. Her institution limits screening to *KRAS* and microsatellite instability testing. Spira said the difference between the United States and European countries regarding testing is that the United States may be more willing to include additional testing due to having fewer budget constraints, which is why more RNA testing is ordered.

"It's a question of reimbursement. In the majority of countries in Europe, it's not reimbursed through the NGS analysis in pancreatic cancer. For example, in our country, in Spain, we are doing it only in referral centers in which it's paid by the center but not by the government," said Macarulla.

In the United States when NGS testing gets billed, Sabari said it never gets sent to the patient. At NYU Langone, the institution's internal assay is utilized, which helps to cut down on the costs. In France, Neuzillet said, it is not reimbursed at all, so it is hard to initiate that practice change of testing for specific genes.

Current Standard of Care

Next the panel focused on assays used to detect *NRG1* gene fusions (**Table 1**).[3-6] Spira began with fluorescence in situ hybridization for DNA input. This is something that clinicians widely use, and it can be completed quickly with no restrictions on fusion partners. The multiplex polymerase chain reaction assay can be utilized to find fusion partners. It is a very sensitive and specific assay.

Schram highlighted the MSK-IMPACT test, which was developed to "detect exons in over 500 cancers associated with genes in DNA specifically." This assay focuses on introns and genes that are known to have fusions so it can be more comprehensive. Assays that focus on RNA input look for the transcriptome and can detect *NRG1* gene fusions more frequently because they do not rely on tiling introns.

"In our institution, because we know that MSK-IMPACT has that limitation, we do reflex RNA testing in all cases, where you don't find a driver. For example, in pancreatic cancer, we're not doing RNA [testing] in all our patients, but in any patient with *KRAS* wild-type pancreatic cancer, they do get RNA [testing] and you'll find *NRG1* fusions and *FGFR* fusions and other alterations, like *ALK*, etc. That also goes for lung cancer; if we don't find a driver using DNA, we go to RNA. That's the way that we improve our sensitivity," said Schram.

Macarulla has found that it is more difficult to obtain RNA samples. More tissue is asked for in patients with pancreatic cancer because it is difficult to obtain these results. In Van Cutsem's practice, the initial biopsy for pancreatic cancer is often cytology or a fine needle aspiration through endoscopic ultrasonography.

The immunohistochemistry assay is widely available, can be done quickly, and does not cost much money. These assays are used in different scenarios, but Spira asked his colleagues how ordering these tests differed between the United States and Europe.

TABLE 2. **Efficacy Response of the Phase 1/2 eNRGy Trial**[7]

Outcome	Zenocutuzumab in PDAC	Zenocutuzumab in *NRG1* fusion–positive solid tumors
ORR	42.4% (95% CI, 25.5%-60.8%)	37.2% (95% CI, 26.5%-48.9%)
CBR	N/A	61.5% (95% CI, 49.8%-72.3%)
Median DOR	9.1 months (95% CI, 5.5-12.0)	14.9 months (95% CI, 7.4-20.4)

CBR, clinical benefit rate; DOR, duration of response; ORR, overall response rate; N/A, not applicable; PDAC, pancreatic ductal adenocarcinoma.

As Schram works at MSKCC, she typically sticks with the MSK-IMPACT assay because she finds it covers all her needs and she has access to the raw data. When needing an assay for RNA, she goes with the Archer FusionPlex assay, even if it is not comprehensive. Sabari's experience has included a wait time of 4 to 6 weeks if the tissue sample needs genome testing. To keep the sequencing in house, he orders FusionSeeker to help save some time.

In Spain, Macarulla uses the panel in

TABLE 3. **Efficacy Results of the eNRGy1 Global Multicenter Registry[8]**

Outcome	Afatinib vs platinum doublet chemotherapy in *NRG1* fusion–positive lung cancer
Median PFS	2.8 months (95% CI, 1.9-4.3) vs 5.8 months (95% CI, 2.2-9.8)
Median OS	10.5 months (95% CI, 3.2-undefined) vs 53.8 months (95% CI, 14.2-undefined)

OS, overall survival; PFS, progression-free survival.

her hospital for both DNA and RNA testing. In France, Neuzillet said they use an internal panel. She did bring to light that there is a program in France to give access to NGS testing to all patients, but currently it is only for frozen materials, which are not needed for fusion detection.

Treatment Options for the Population

The panel discussed 2 potential therapy options: zenocutuzumab and afatinib. They are currently novel therapeutic options that can help aid with *NRG1* fusion–positive tumors in lung or GI cancers. The experts discussed efficacy rates from the phase 1/2 eNRGy trial (NCT02912949) and the eNRGy1 Global Multicenter Registry when deciding between different treatment options, with the data shown in **Tables 2**[7] and **3**.[8]

Schram presented these data at the 2023 European Society for Medical Oncology meeting, which included all different histologies for patients with *NRG1* fusion–positive tumors. "One of the questions that we had is whether zenocutuzumab could be effective in patients who had been previously treated with afatinib. If you look at the response rates, [they're] comparable to [those of] the overall population so we don't think that there's much of a difference if you've had prior afatinib," she said.

When looking at these data, Schram noted that the results are often compared with those of patients who have *ALK*, *ROS*, or *EGFR* mutations, but *NRG1* is not comparable with those. By itself, this is a good option because there are no targeted therapies for this population, and it holds up well compared with chemotherapy.

"I think this [can be approved] in the frontline setting based on these data; it depends on how the FDA feels on this. This is a very small subset of patients with a very small population, and overall, whether you'll get a broad agnostic approval across different diseases [or not], it'll be interesting," said Sabari. ■

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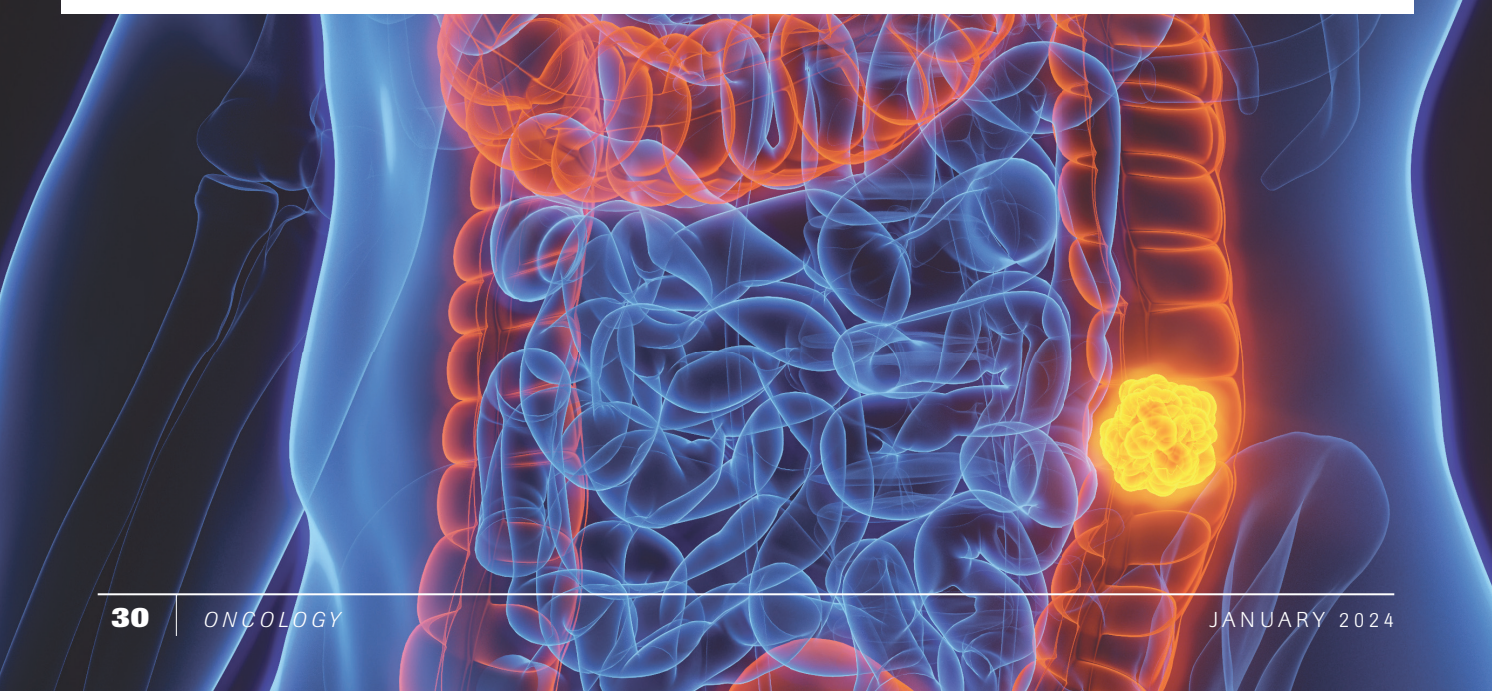

CONTINUING MEDICAL EDUCATION (CME)

Toward Personalized Treatment Approaches in Soft Tissue Sarcomas

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This activity was written by PER® editorial staff under faculty guidance and review. The Q&A portion of the activity was transcribed from a recorded interview with the faculty and edited by faculty and PER® editorial staff for clarity.

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- Identify remaining unmet needs in soft tissue sarcomas.

RELEASE DATE: JANUARY 1, 2024
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Soft tissue sarcomas (STS) are a rare, heterogeneous collection of tumors with more than 100 histological tumor subtypes, some of which are associated with chromosomal translocations. Treatment for several cancer types follows a trend toward personalized therapy based on tumor molecular profiling. Only a small percentage of sarcoma subtypes, including perivascular epithelioid cell tumors (PEComas) and gastrointestinal stromal tumors (GISTs), currently have identified actionable driver alterations. Immune checkpoint blockade has recently been approved for a specific sarcoma subtype. In this article, **Ciara Kelly, MBBCh, BAO**, explores recent advancements toward personalized treatment in sarcoma.

Q: What steps are being taken to reduce the average time to diagnosis of sarcomas?

KELLY: The rarity of sarcomas poses significant diagnostic and management challenges, particularly to providers who do not see them frequently. The most important aspect of optimizing diagnosis and management is ensuring that patients are seen in a Sarcoma Center of Excellence. Sarcomas are complex tumors that require expert opinion and integration of molecular diagnostics with histomorphologic features for an accurate diagnosis. At expert sarcoma centers, incorporating molecular diagnostics into the pathology assessment of sarcomas has been shown to improve diagnostic accuracy in up to 14% of cases.[1]

Q: What progress has been made to identify and use diagnostic biomarkers?

KELLY: Significant progress has been made, and we see this with the increasing use of molecular diagnostics, including RNA sequencing, looking particularly for translocation-associated tumor subtypes. The increasing role of next-generation sequencing (NGS) is also evident. A recent study examined NGS in 7500 sarcomas, identifying recurrent and subtype-specific alterations.[2] In that study, 10.5% of cases had refinement or reassignment of their sarcoma diagnosis. A further 31.7% had actionable alterations, which may have led to potential treatment options.

Several studies showed that it is feasible to detect circulating tumor DNA (ctDNA) in sarcoma cases.[3] However, the sensitivity and specificity vary based on the sarcoma subtype. A study presented at 2023 American Society of Clinical Oncology Annual Meeting (ASCO 2023) examined ctDNA as a marker of minimal residual disease (MRD) at diagnosis and postoperatively in patients with large, high-grade sarcomas who underwent neoadjuvant treatment, surgery, and follow-up.[4] The study showed 80% of patients had detectable ctDNA at baseline, and 94% became MRD negative after surgery. Also, patients who were ctDNA positive during surveillance had an 18-fold higher chance of recurrence than ctDNA-negative patients. This study showed the potential of ctDNA, but more work is needed before this will become integrated into the management of sarcoma patients as a standard of care. There have been more GIST-specific studies that included sequenced ctDNA as a correlative assessment. The phase 3 INTRIGUE trial examined sunitinib vs ripretinib in the advanced GIST second-line setting. Ripretinib was not found to be superior to sunitinib in terms of progression-free survival (PFS). In an exploratory analysis of sequenced ctDNA obtained at baseline, patients with *KIT* exon 11–mutant GIST harboring secondary *KIT* exon 17 and/or 18 mutations derived a significant PFS benefit with ripretinib compared with sunitinib. Currently the INSIGHT randomized, phase 3 clinical trial will evaluate the efficacy of ripretinib vs sunitinib in patients with advanced GIST who have progressed on imatinib and harbor *KIT* exon 11 mutations co-occurring with resistance mutation in *KIT* exon 17 and/or 18 confirmed via sequencing.[5]

Q: How well do sarcomas respond to chemotherapy?

KELLY: Chemotherapy remains the standard-of-care treatment for advanced soft tissue sarcoma. However, objective response rates to doxorubicin-based or gemcitabine and docetaxel regimens are approximately 20%.[6] Response rates are lower in the second- and third-line settings. For example, pazopanib was approved based on an improvement in median PFS in the PALETTE trial in soft tissue sarcomas, excluding liposarcoma, where they demonstrated an objective response rate of 6%.[7] Another example is trabectedin, which is approved for use in leiomyosarcoma, where the response rate was in the order of 10%.[8] Despite very low response rates, our standard-of-care chemotherapy options can lead to stabilization of disease. But, on the whole, activity and objective responses to treatments are low and this underpins the importance of developing new treatment options for patients with sarcoma.

Q: How is molecular profiling used to guide treatment decisions in patients with STS?

KELLY: We are using molecular information to guide selection of targeted therapies. For example, PEComa is a malignant perivascular epithelioid cell tumor that had no approved treatment until the FDA approved nab-sirolimus in November 2021 based

on the results of a phase 2 single-arm study that demonstrated an objective response rate of 39%. Also, 89% of patients with a *TSC2* mutation achieved a confirmed response; 13% of patients without a *TSC2* mutation also had a response.[9]

Another recent approval was tazemetostat, an EZH2 inhibitor approved for epithelioid sarcoma with *INI1/SMARCB1* loss, based on a 15% response rate in an open-label phase 2 basket study in the epithelioid sarcoma cohort of 62 patients.[10]

GIST is a poster child for the utility of molecular profiling in sarcoma. GIST is one of the most common sarcomas of the GI tract, and up to 75% harbor mutations in *KIT* and approximately 10% to 15% of patients may have mutations in the *PDGFRA* gene.[11] Another 10% to 15% will have other rare, molecularly defined GIST subtypes. With advances in molecular diagnostics and their increased use in GIST, the proportion of true wild-type GIST has been reduced. Several tyrosine kinase inhibitors targeting KIT have been approved for the management of advanced GIST including imatinib, sunitinib, and regorafenib.[12-14] Ripretinib was recently approved in the fourth-line setting for patients with advanced GIST based on a median PFS of 6.3 months for the ripretinib arm compared with 1 month for placebo.[15]

Avapritinib was approved in January 2020 based on results from the NAVIGATOR trial, which showed that in patients with *PDGFRA* D842V–mutant GIST—a very rare subtype of GIST for which there was previously no effective treatment—there was an objective response rate of 91% and a clinical benefit rate of 98%. All these studies emphasize the utility of molecular information to appropriately select patients for treatment.[16]

How can we convert that immune-desert tumor into an immune-stimulated microenvironment?

Q: Atezolizumab was recently approved in alveolar soft part sarcoma (ASPS). Is there an opportunity for immunotherapy to make a positive impact in other STS types?

KELLY: Atezolizumab was FDA approved in December 2022 based on a phase 2 study examining adult and pediatric patients with advanced ASPS—a translocation-associated sarcoma subtype.[17] The study demonstrated an objective response rate of 37% in 52 patients, including 1 complete responder and 18 partial responders with a median time to response of 3.6 months and a median duration of response of 24.7 months. Currently, we do not understand exactly why we are seeing response to immune checkpoint blockade in this subtype, but it does clearly signify the merit of evaluating immunotherapy in sarcoma.

The SARC028 study looked at pembrolizumab monotherapy in both soft tissue and bone sarcomas, demonstrating an objective response rate of 18% in soft tissue sarcoma and 5% in bone sarcoma.[18] In the Alliance study 091401, efficacy of nivolumab was evaluated alone or in combination with ipilimumab in patients with soft tissue sarcoma.[19] The response rate for the nivolumab arm was 5%. For the combination, it was 16%. These results led to an expansion phase in specific subtypes where a response rate of 27% was observed in undifferentiated pleomorphic sarcoma (UPS).

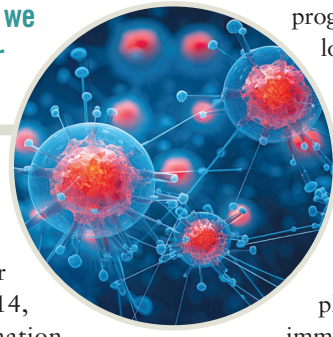
UPS, myxofibrosarcoma (MFS), and angiosarcoma are subtypes where we have consistently seen responders with respect to immune checkpoint inhibition. The DART trial evaluated nivolumab and ipilimumab in angiosarcoma and demonstrated a response rate of 25%. Notably, 3 out of the 4 responders had cutaneous angiosarcoma of the head and neck region.[20] A study presented at ASCO 2023 explored nivolumab and cabozantinib in patients who have previously progressed on taxane-based treatment and an overall response rate of 62% was observed.[21] In the population of patients with cutaneous angiosarcoma, an objective response rate of 58% was observed. In the population of patients with noncutaneous angiosarcoma, the response rate was 67%. Cutaneous angiosarcomas have a high tumor mutational burden, which lends itself to being sensitive to immune checkpoint inhibition, so there is merit in evaluating immunotherapy in this space. There are some sarcoma subtypes that may benefit from immune checkpoint inhibition, such as UPS/MFS, ASPS, and angiosarcoma. But for the majority of sarcomas that have immune cold signatures, more novel combination approaches incorporating immunotherapy in addition to novel immunotherapeutics, chemotherapy, targeted therapies, or radiation warrant further evaluation. How can we convert that immune-desert tumor into an immune-stimulated microenvironment?

Q: What progress is being made to identify biomarkers for immunotherapy in STS?

KELLY: There have been several

correlative-based studies that have been conducted in the sarcoma community. The SARC028 study suggested that PD-L1 expression on tumor-infiltrating lymphocytes, but not on tumor cells, was associated with response to pembrolizumab.[18] However, another study looking at NKTR-214, an IL-2 agonist, in combination with nivolumab did not demonstrate this.[22] In both of these studies, it was suggested that tumor-infiltrating lymphocytes were more common in responders, but were not necessary or sufficient to generate response. There are also data looking at the role of gene expression profiling and developing an immune signature for sarcoma subtypes. Petitprez et al looked at gene expression profiling in 600 sarcomas and identified 5 distinct immune microenvironments representing a spectrum of immune infiltration.[23] The immune-desert cohort had the worst prognosis and no responses to immune checkpoint blockade. The immune-high groups had a better prognosis and more responders to immune checkpoint inhibition. PD-L1 and CD8 T-cell expression were not prognostic here. However, investigators did suggest that tertiary lymphoid structures and expression of B-cell lineage genes were prognostic for outcomes and may be predictive of response to immune checkpoint blockade. There is difficulty in identifying 1 specific biomarker. It may be the interaction of several biomarkers and biomarkers outside the tumor itself—looking at hematopoiesis within the bone marrow and myeloid cell makeup, for example—that is important.

We have not reached a point where we can provide personalized therapy for all patients with sarcoma, but we are doing this successfully for some patients.



Q: How close are we to personalized therapy in sarcomas?

KELLY: We are making some progress, but we have a lot more work to do. Many of the FDA approvals for sarcoma have been focused on more personalized therapy. One example of personalized immunotherapy is the evaluation of the safety and activity of autologous T cells expressing NY-ESO.[24] Response rates in patients with synovial sarcoma have been in the order of 50%. Circulating NY-ESO T cells were present post infusion in all patients and persisted for at least 6 months. Unfortunately, we have not reached a point where we can provide personalized therapy for all patients with sarcoma, but we are doing this successfully for some patients.

Afamitresgene autoleucel (afami-cel) is another form of adoptive T-cell therapy being developed to treat HLA-A*02–restricted patients with advanced synovial sarcoma that is positive for the cancer/testis antigen melanoma-associated antigen A4.[25] The long-term outcomes in patients with advanced synovial sarcoma treated with afami-cel in SPEARHEAD-1, a phase 2, open-label, 2-cohort trial, were recently presented at the Connective Tissue Oncology Society annual meeting in 2023. Among 44 heavily pretreated patients, 17 had a RECIST response by independent review. Responsive patients experienced promising survival probabilities; the 12-month overall survival [OS] probability was 90%, and the 24-month OS probability was 70%.

Q: What is on the horizon for personalized treatment in STS?

KELLY: Novel combination strategies — be that chemotherapy, immunotherapy, or targeted therapy— are on the horizon. On the chemotherapy side of things, an interesting study is currently ongoing to evaluate lurbinectedin and doxorubicin in patients with leiomyosarcoma.[26] Phase 1 data that had a number of responders in leiomyosarcoma were presented at ASCO 2023. And now a larger trial is ongoing in leiomyosarcoma, specifically.

I am interested to see if novel immunotherapeutics and combination immunotherapy strategies under evaluation can stimulate the immune microenvironment in immune-desert tumors. Other notable research efforts on the horizon are looking at treatment in the neoadjuvant sarcoma setting. Can neoadjuvant therapeutic strategies help to reduce the risk of recurrence and improve survival following optimal local control for localized sarcoma with high-risk features? Research in this area continues to evolve, and the neoadjuvant setting in sarcoma lends itself nicely to intratumor-administered therapeutic approaches.■

Key References

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