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PRACTICAL, PEER-REVIEWED PERSPECTIVES

# ONCOLOGY®

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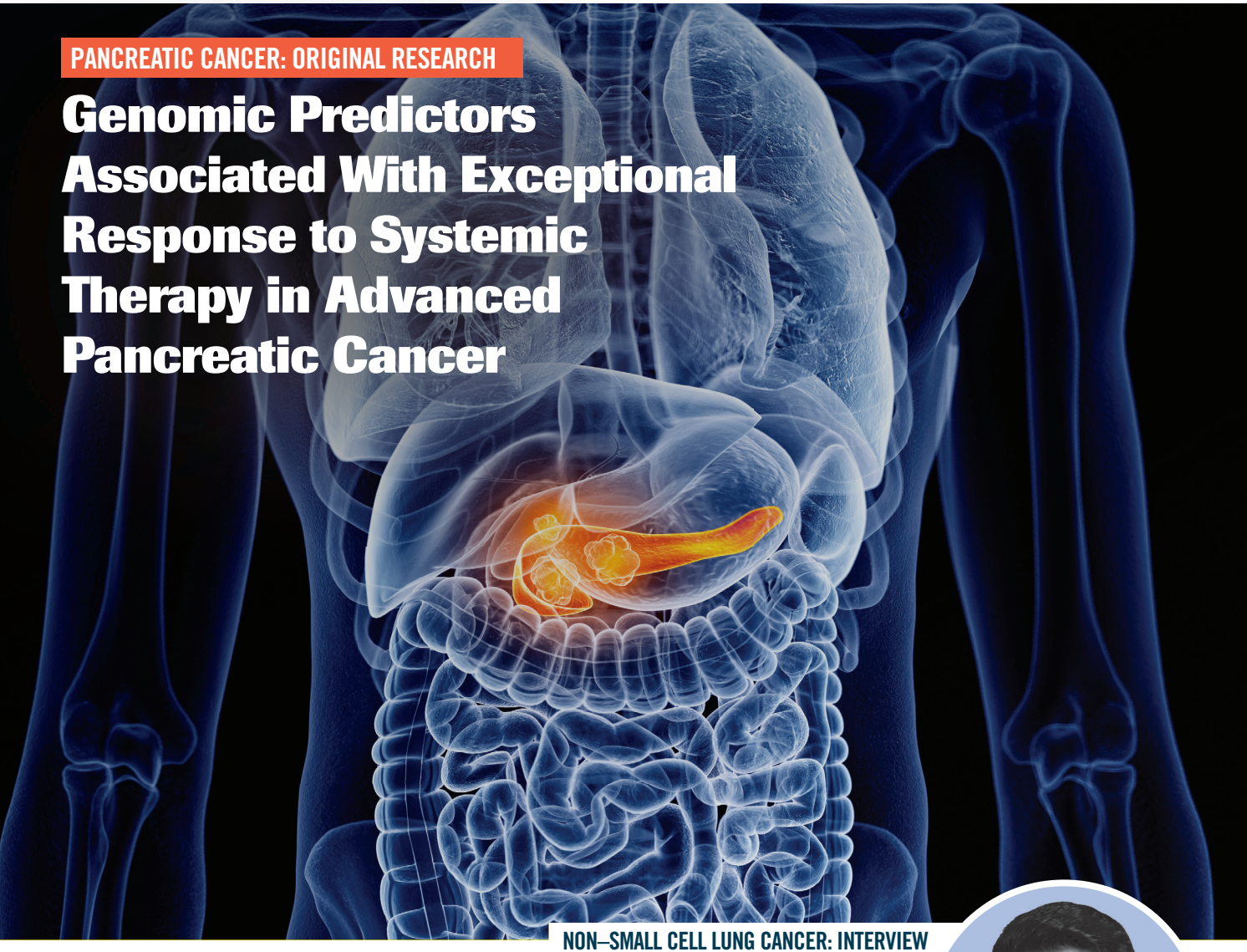

PANCREATIC CANCER: ORIGINAL RESEARCH

## Genomic Predictors Associated With Exceptional Response to Systemic Therapy in Advanced Pancreatic Cancer

NON–SMALL CELL LUNG CANCER: INTERVIEW

## Sandip P. Patel, MD

Impact of Sotorasib and Adagrasib in *KRAS* G12C–Mutated NSCLC



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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

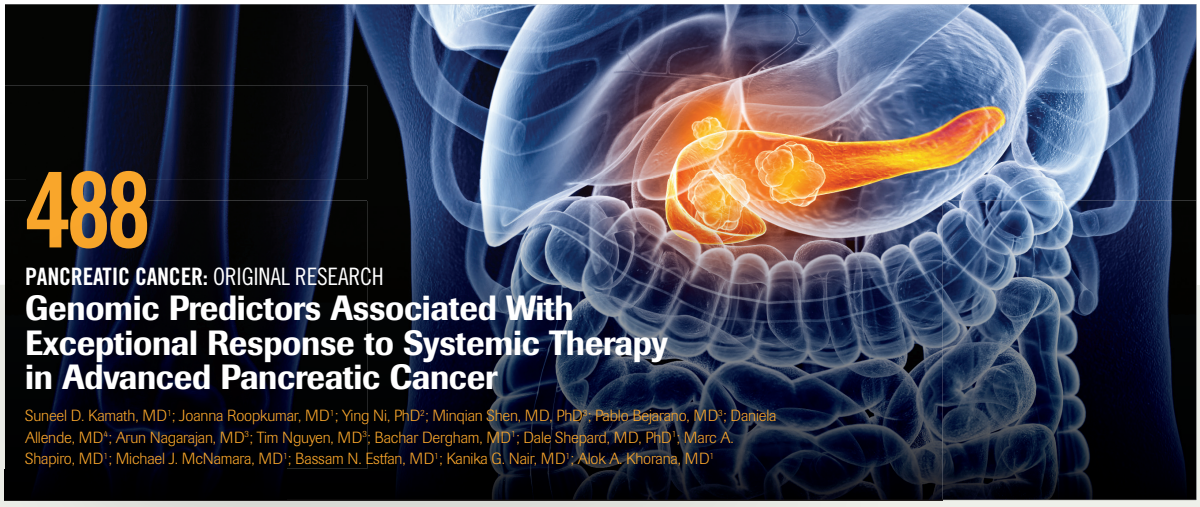
Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose *[see Use in Specific Populations]*.

Product of Ireland

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



cp-213278v1



PRACTICAL, PEER-REVIEWED PERSPECTIVES
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***ONCOLOGY* would like to thank all of those who served as a reviewer for our publication this year. Your thorough work and dedication are greatly appreciated.**

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# 2023 Year in Review: Topics in Hematology/Oncology

The year 2023 has been an important one, with many discoveries of new therapies for diverse types of malignancies. There are also some big-picture topics in hematology/oncology that have some important implications for our patients, the practice of hematology/oncology, or the general population. Examples of topics for further discussion include the following:

### 1. Drug Shortages

Although this has been an issue for many years off and on, it seems that shortages are happening more frequently and with more agents as the number of companies that make these older agents decreases and the profitability goes down. We all need to work with the FDA and other involved industries to keep the pipeline of these older agents flowing for our patients.

### 2. Hematology/Oncology Training

During the past 3 years, COVID-19 affected not only public health, our patients, and health care workers, but also on hematology/oncology trainees. In the early days of the pandemic, many patients with suppressed immune systems became critically ill with COVID-19, and it became a challenge for trainees to fulfill the standard hematology/oncology educational and clinical requirements needed for complete training during this time. Hopefully, as we come out of the pandemic, training programs can catch up and be updated to become more flexible.

### 3. Artificial Intelligence

This topic will be in the news for many years. This technology can be an immensely powerful tool for analytical data analysis, patient profile screening for early diagnosis, genomic screening and analytics, and machine learning such as analyzing radiographs in areas where imaging expertise is not available. The applications are endless when used in a positive fashion to help both our patients and the science of hematology/oncology care.

### 4. Precision Oncology

Molecular characterization of specific tumor types has led to an increase in treatments using "personalized targeting" of the patient's malignancy. This method is now used in most malignancies to improve the outcome of the patient's therapy while trying to reduce the use of toxic agents that are not predicted to benefit the patient. This is an ongoing area of research in almost all malignancies.

### 5. Liquid Biopsies

Once a pipe dream, the technology to perform testing for molecular aberrations in the blood is becoming a reality. These tests identify changes in circulating tumor DNA derived from unknown tumor cells, which could potentially signal cancer or minimal residual disease (MRD) following cancer therapy. There are many applications still being tested, but some already in use include testing for MRD in the blood following standard therapies, which may lead to further evaluation for the disease or further treatments for the patient. Other applications include the use of these tests for asymptomatic patients without known cancer for early detection of disease. This testing could have the potential to reduce cancer morbidity and mortality. Over the next year, we will likely see further approvals and applications for this testing.

### 6. Immunotherapy

No single area of cancer therapy has exploded more than the use of immunotherapy. This broad area includes such agents as monoclonal antibodies, bispecific antibodies, chimeric antigen receptor T cells, and immune checkpoint inhibitors. Over the next few years, this area of research and oncology care will continue to expand to treat more types of malignancies and be applied earlier in the course of malignancy treatment.

Hopefully, 2024 will continue to bring new discoveries, treatments, and cures for our patients with all types of malignancies. Happy holidays and happy New Year to all *ONCOLOGY* readers. ■

# Early Access to Electronic Health Records May Influence the Patient Experience

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With the advent of the internet, people are accustomed to being able to access data on demand. For example, to check their latest financial details, they log into their bank's website; to get information about their school-aged children's needs, they can routinely access a portal developed by their school; and so on. Implemented on April 5, 2021, the 21st Century Cures Act, known as the "Cures Rule," requires health care providers to allow patients access to all the health information in their electronic health records (EHRs). In a way, this has led to a disruptive innovation for health care organizations: the development of patient portals. Now, patients can take an active role in their care by having nearly instant access to their own medical records. However, the advantages of accessing EHRs by patient portals should be weighed against the disadvantages of this novelty.

## Disadvantages of Patient Portal Access

EHR accessibility may pose harm due to a lack of security during information dissemination. This has been a major concern for industries such as finance, defense, and health. The fundamental security goals for all these industries, including EHRs, are confidentiality, integrity, and availability.[1] Promoting patients' access to their own EHRs could have an impact on activities, such as health information disclosures on job applications or applying for life insurance.[2]

Defined as the ability to acquire and understand medical information to follow treatment and make health decisions, health literacy has been reported in only 53% of adults. If a user does not understand the medical terms within the patient portal, early access to results will more likely cause confusion and anxiety than any help.[3]

One study found that abnormal test results caused confusion, anxiety, and concerns for 56% of patients, including 21% of patients who had normal results. Even if a test result is not recognizably negative, a patient portal presentation of an uninterpreted report can be unpleasant to patients and certainly unproductive. Nearly two-thirds of patients who obtained test results via a portal received no explanatory information about the findings, and half ended up conducting online searches or calling their doctors.[4]

Medical professionals should be aware of how to choose the right clinical terms and when to enter major diagnostic information. Seeing previously undisclosed information, derogatory language, or inconsistencies in notes may cause annoyance and concern in patients.[5] Most laboratory test results are not created with the patients in mind; they are often complicated and not easily understandable by nonmedical professionals.

Specifically, pathology reports may be challenging to comprehend in light of a cancer diagnosis. Miscommunication may happen between a patient and their clinician after a pathology report has been uploaded to the patient portal, and the patient in turn reaches out to their provider for clarification. Individual providers may feel challenged in the unfamiliar realm of properly interpreting a cancer diagnosis without an opportunity for the health care team to discuss it in the setting of a multidisciplinary tumor board approach.

Although it is intended to promote patient empowerment, instant access to results through patient portals can be a mixed blessing. A challenge occurs when abnormal results are uploaded


and providers are not instantly available to properly interpret these results for patients. Unnecessary anxiety may occur due to an out-of-reference value for a nonfasting glucose level, red blood cell distribution width, mean platelet volume, or stable elevated liver enzyme levels from fatty liver disease, which are not clinically relevant or significant. For a patient to properly understand the significance of these results, a health care provider will have to be available to interpret for them. Having patients call about test results or ask questions may create more demand on the already strained health care providers' time. A study by Han et al suggests an increase in consultation times if patients have access to their own EHRs via patient portals.[6]

Some patients would prefer to remain uninformed and leave all clinical decisions to their providers to share and explain during their visit. Receiving copious emails and texts can create a need for them to check these results. Patients with long-term conditions with greater needs to trace their disease trajectories and those experiencing recent incident health events are more likely to benefit from accessing their EHRs, which might work better in the primary care settings as opposed to cancer care. Patients who are 60 years or older use the greater proportion of health care, are more likely to have cancer, and are less likely to adopt EHR portals. Reasons for this include having less access to and experience with technology, less education, and low health literacy and numeracy skills.[7-9] Alienation between patients and clinicians can occur for those who do not or cannot use these tools. Of note, with early access to results, patients may discover a cancer diagnosis prior to meeting with the clinician, which can cause a longer patient-clinician interaction when the appointment occurs.[10,11]

Finally, studies have shown promoting EHR access to minors can also be a challenge. Although the patient might welcome such access, it could raise concerns among parents, caregivers, and guardians regarding the level of details visible to the patient.[12,13]

## Advantages of Patient Portal Access

In recent years, the addition of preappointment paperwork to EHRs has lessened the administrative burden on medical offices. Administrative staff, who used to spend a great deal of time copying medical records and updating the audit trail, can now simply direct the patient to their portal so they can update the information electronically.

In addition to instant access to medical records, patient portals can provide appointment scheduling, telehealth features, and educational content to help patients better understand their health conditions. The benefits can range from increased awareness and medication adherence, reduced anxiety, and reassurance to better doctor-patient relationships and a positive impact on consultations. In patients with chronic conditions, improvements in outcomes have been observed in various areas, including medication adherence, blood pressure, glucose level control, improved functional status, and reduced high-cost health care utilization.[14-20]

The ability to access EHRs may also help patients to actively participate and reduce any inaccuracies within their EHR, which in turn may lead to more reliable health records and enhanced patient-provider communication.[21,22] Patient access to EHRs can also help patients to be better prepared and well informed about their medical issues prior to their doctor visits.[22] Moreover, the ability of the patients to provide a reliable medical history to a provider by referencing their own EHR through the mobile phone in an emergency department or urgent care setting can significantly improve the quality of care.

Finally, for both patients and health care professionals, not only having access to EHRs for test results but also having the ability to book appointments and order prescriptions online holds valuable benefits.[10,23,25] Better health outcomes seem to result from patient empowerment through health care information exchange to aid self-care, informed decision-making, enhanced medical adherence, and improved trust between patients and medical professionals.

Like in anything else, continued long-term awareness, familiarity with its use, and education on how best to use this tool will help EHRs evolve into a more efficient and appropriate usage level in time, proving its value with more pros than cons. ■

**For references visit**
cancernetwork.com/12.23_EHR

MEET OUR EXPERT

**Sandip P. Patel, MD**
Professor in the Department of Medicine at the University of California, San Diego

# Impact of Sotorasib and Adagrasib in *KRAS* G12C–Mutated NSCLC

*"KRAS is probably the most exciting area in clinical trials right now, not only in thoracic oncology but also pancreatic and colorectal cancer, where we've seen a lot of combination therapies. My view is the small molecule inhibitors are the base, not the ceiling."*

Regarding the use of sotorasib (Lumakras) and adagrasib (Krazati), for patients with *KRAS* G12C–mutated non–small cell lung cancer (NSCLC), Sandip P. Patel, MD, emphasized that these treatments for the second-line setting can be impactful after treatment with chemoimmunotherapy in the first line.

Patel, a professor in the Department of Medicine at the University of California, San Diego, also spoke about important trials in the space and where he hopes to see research efforts headed in the future.

**Q: Can you give a brief overview of the treatment landscape for *KRAS* G12C–mutated NSCLC?**

**PATEL:** There's probably no space in oncology that's had as dramatic an era of drug development as *KRAS*-mutated [NSCLC, with] targeted therapies and with the development of small molecule inhibitors for KRAS G12C, the 2 FDA-approved agents being sotorasib and adagrasib. Currently, in NSCLC these mutations are also seen in colorectal cancer and pancreatic cancer. One key concept is at the current time, these agents are for second-line use after progression, optimally after chemoimmunotherapy because many patients with KRAS G12C inhibitors will have reasonable and durable responses with immunotherapeutic approaches in the frontline setting. When we think about *KRAS* G12C, treating [patients] in the second-line setting with the small molecule inhibitors, whether it's sotorasib or adagrasib, is a very reasonable treatment strategy. Recent data may have tempered some of the enthusiasm around some of the overall survival data compared with docetaxel. The flip side is that in many of those studies, there is differential loss of patients on the control arm, for example. We need to look further in terms of the details.

It's clear that the tolerability of the small molecule inhibitors is far superior to that of docetaxel, especially when you think about some of the [adverse] effects [AEs] like alopecia and neutropenia. Other AEs that we don't see with the small molecule inhibitors typically have AEs related to mild liver dysfunction, which we can manage. The first and most important concept is we did test these patients with metastatic NSCLC, with multiplex sequencing, most commonly next-generation sequencing, for all the mutations of which *KRAS* G12C is a driver that we can target now. However, it's a driver that we target in the second-line setting optimally, and in my clinic, it still means my preferred choice in the second-line setting with chemotherapy is reasonable. The AE profile and central nervous system [CNS] activity of drugs like sotorasib and adagrasib are reasons I still would favor the oral agent over intravenous [IV], but reasonable [clinicians] can have a discussion on what makes sense for their practice setting.

**Q: Is there a specific trial involving this patient population that would be pertinent to discuss?**

**PATEL:** There have been several studies in the *KRAS* G12C space that have been illustrative of efficacy; one is the phase 3 CodeBreak 200 trial [NCT04303780] for sotorasib, and we [reference] the phase 1/2 KRYSTAL-1 study [NCT03785249] for adagrasib.[1,2] When we're talking NSCLC, part of the interest is that historically, KRAS has been thought to be an undruggable target. This is the first generation with multiple novel KRAS inhibitors, including pan-KRAS inhibitors in clinical trials. When we're thinking about the data, especially because [they are] a subset, it's reasonable to look at the data and the totality [of them all]. However, the only randomized control comparison we have in the second-line setting of sotorasib vs docetaxel did not show a substantial survival advantage. It's not unreasonable to give chemotherapy to these patients by any means, especially for patients with brain metastases and whose tolerability for IV infusion may be an issue or who may have concerns about the AEs of chemotherapy. In my clinic, the general preference may be for the oral small molecule inhibitor, though I think reasonable [clinicians] can think about the best opportunity for their patients and a way to sequence them in a way that maximizes their quality and quantity of life. ■

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# Danazol for the Treatment of Myelodysplastic Syndromes: A Systematic Review

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## ABSTRACT

### Purpose

To study the potential utility of danazol for treating patients with myelodysplastic syndromes, with a focus on efficacy and adverse effects (AEs).

### Methods

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus were searched for relevant publications from inception June 1, 1950, until June 28, 2022. The studies were screened by title and abstract, followed by full-text screening. The quality of the included studies was assessed via a prespecified set of questionnaires. Data on the efficacy measures and adverse outcomes were extracted and included in a descriptive summary.

### Results

Nine studies consisting of 246 participants were included in our review. The overall quality of the included studies was fair. The age of the participants ranged from 61 to 78 years. In all 9 studies, more male patients had been enrolled than female patients. Overall, a proportion of patients in all the studies reported a desired major response to a danazol dose of 400 to 800 mg/day. Few studies did not observe any improvement in the platelet count. Elevated liver enzyme levels, weight gain, headache, dermatitis, and weakness were the most common AEs observed. One study reported a fatal intracerebral hemorrhage in 1 participant.

### Conclusions

Danazol has been effective in increasing platelet count and hemoglobin level. Despite a few AEs, danazol is a safe drug for the treatment of patients with myelodysplastic syndromes.

Myelodysplastic syndromes (MDS) are a group of clonal hematological illnesses defined by inefficient hematopoiesis, varying degrees of peripheral cytopenia, and a propensity to develop acute myeloid leukemia (AML).[1-3] There is no pharmacologic treatment to cure MDS. Allogeneic stem cell transplant (ASCT) offers a potential cure rate of 30% to 50%,[4] but less than 5% of patients are ideal candidates for it. Patients who are not eligible for ASCT have few treatment options.

While a cure for MDS has not yet been found, there have been effective treatments identified to help the population. Azacitidine and decitabine, 2 hypomethylating drugs, have been the first-line therapies advised by the German MDS group for patients with high-risk MDS since 2009.[5,6] Comparing the use of azacitidine to best supportive care of erythropoietin has shown that the agent reduces the need for transfusions, lessens the risk of developing AML, and ultimately increases survival.[5] In addition, lenalidomide, a microenvironment-modulating drug, has recently been shown to be a successful treatment, especially for patients with low-risk MDS and deletion 5q.[6] However, the majority of uninsured patients in low- to middle-income nations are unable to afford these new agents due to their high cost.[7] In young patients, high-dose chemotherapy may result in complete remission and a notable improvement.[7]

For patients with MDS who are older and have poorer performance status and medical comorbidities, supportive care remains the primary treatment.[8] Other patient subgroups may respond to growth factors or immunosuppressive medications in varying degrees.[9]

Danazol is a synthetic androgen with progestational and glucocorticoid properties that inhibits the production of tumor necrosis factor α and IL-1.[10,11] Additionally, danazol has proven useful in immunological cytopenias; its androgenic features, which promote healthy hematopoiesis and decrease neoplastic cell clones, are thought to be responsible for its efficacy.[11-13] One study noted a 5-year overall survival rate of approximately 60% for patients with aplastic anemia treated with danazol.[14]

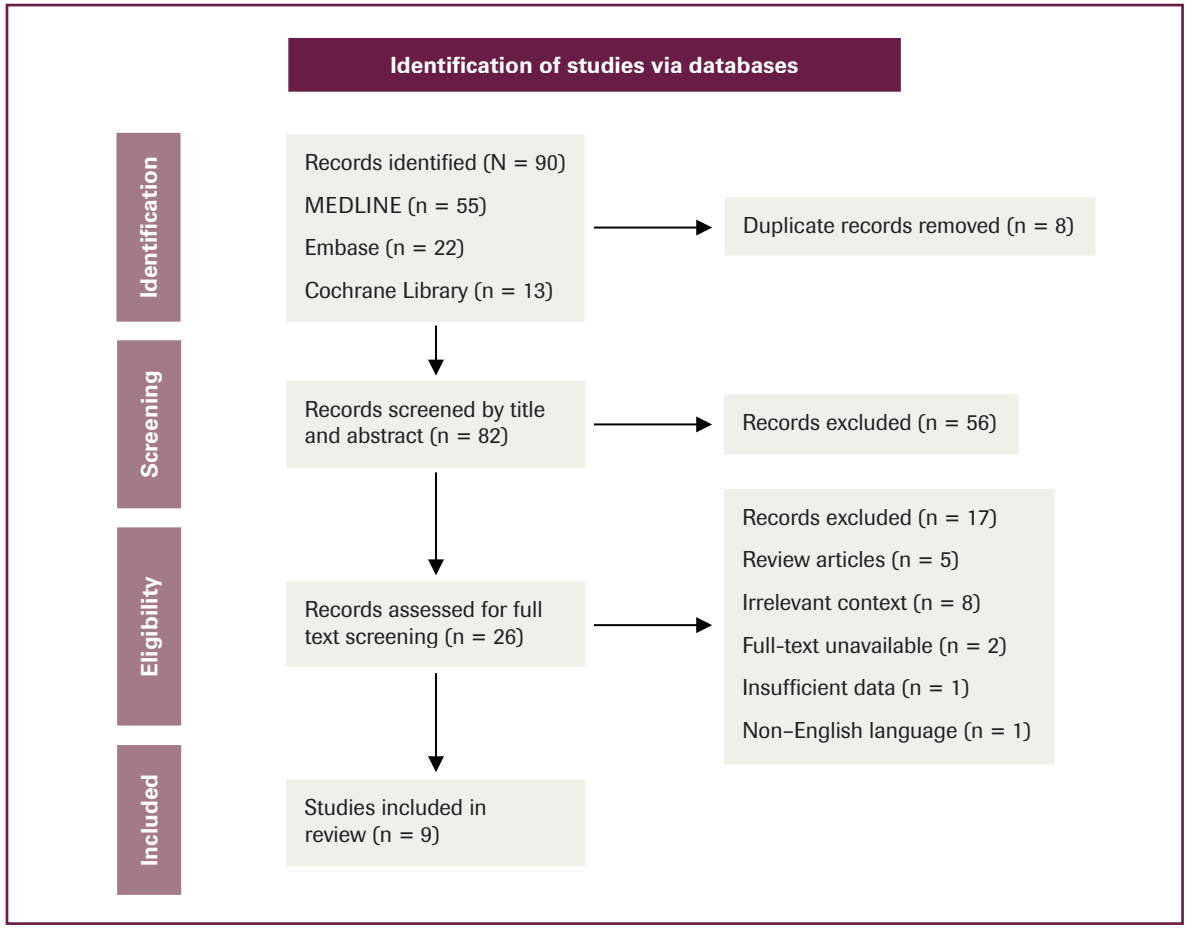
There is, however, conflicting evidence that androgens may be helpful in MDS. Some studies suggest patient benefit, whereas others have demonstrated a lack of efficacy.[2,8,9,15,16,18-21] Telomere dysfunction as a pathogenic mechanism in various hematological disorders, particularly in bone marrow failure syndromes, has drawn more attention recently.[22,23] Telomeres are noncoding repeating sequences at the end of each DNA chromosome that help maintain chromosomal stability and prevent chromosomal abnormalities.[24]

The use of danazol is still a desirable option in a facility with limited access to novel therapeutic alternatives for patients with MDS, such as hypomethylating drugs and lenalidomide, because of its low cost, local availability, and favorable safety profile. Herein, we systematically review the clinical outcomes of patients diagnosed with MDS and treated with danazol as first-line therapy.

## Methods

This study's protocol was created in advance. The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and its protocol has not been registered in PROSPERO, the international prospective register of systematic reviews.[25]

FIGURE. **PRISMA Study Selection**




PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

TABLE 1. **Quality Assessment of the Included Studies**[2,11,17-20,24-26]

| Study | Clarity of study objectives | Study period stated clearly | Criteria for patient selection | Study conducted in multiple centers | Danazol treatment method and dosage mentioned | Baseline equivalence groups clearly considered |
|---|---|---|---|---|---|---|
| Jaime-Pérez et al[17] | 1 | 1 | 1 | 1 | 1 | 0 |
| Letendre et al[18] | 1 | 1 | 1 | 1 | 1 | 1 |
| Chan et al[11] | 1 | 1 | 1 | 1 | 1 | 1 |
| Catalano et al[26] | 1 | 1 | 1 | 1 | 1 | 0 |
| Viniou et al[2] | 1 | 1 | 1 | 1 | 1 | 1 |
| Stadtmauer et al[25] | 1 | 1 | 1 | 1 | 1 | 1 |
| Wattel et al[24] | 1 | 1 | 1 | 1 | 1 | 1 |
| Doll et al[19] | 1 | 1 | 1 | 1 | 1 | 1 |
| Buzaid et al[20] | 1 | 1 | 1 | 1 | 1 | 1 |

MR, major response; mr, minor response; PC, platelet count.

## Data Sources and Search Strategies

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus were all thoroughly searched electronically for relevant pieces of literature published from inception June 1, 1950, until June 28, 2022. The 2 study authors independently planned and carried out the search method. The appendix contains a full description of the search strategy (**Supplemental File 1**).

## Study Selection

Each article's eligibility was evaluated by 2 separate authors (SS and RY) based on predetermined standards after carefully reading all the titles and abstracts. We retrieved the pertinent references' entire texts and uploaded them for full-text evaluation in accordance with the qualifying requirements. Conflicts were settled by consensus and with the help of a third reviewer (KG).

## Eligibility Criteria

In this systematic review, we incorporated randomized controlled trials, original papers (cohort, prospective study), and studies that examined the use of danazol to treat patients with MDS. Studies had to report at least 1 of the following outcomes:

- Major response
- Minor response
- Platelet count

According to the study procedures, major response, minor response, increase in platelet count, and hematologic parameters were all defined.

Case reports, editorials, reviews, and articles written in a language other than English were excluded.

## Data Extraction

Two reviewers (SS and RY) utilized Microsoft Excel, 2013 version, to create standardized, pilot-tested forms and independently extracted data (2013). Discussions between the 2 reviewers helped settle disagreements. Study characteristics, participant descriptions, intervention information, and important outcomes were retrieved from each study. A number of relevant patient outcomes

TABLE 1. Continued

| Definition of primary outcome (MR, mr, or PC) defined prior to the study | Adequate follow-up period | Adverse effects stated | Limitations of each study were considered | Total score |
|---|---|---|---|---|
| 1 | 1 | 1 | 1 | 9 |
| 1 | 1 | 1 | 1 | 10 |
| 1 | 1 | 1 | 1 | 10 |
| 1 | 1 | 0 | 1 | 8 |
| 1 | 1 | 0 | 1 | 9 |
| 1 | 1 | 1 | 1 | 10 |
| 1 | 1 | 1 | 1 | 10 |
| 1 | 1 | 1 | 1 | 10 |
| 1 | 1 | 1 | 1 | 10 |

MR, major response; mr, minor response; PC, platelet count.

were extracted, and we gathered information on the results at the longest follow-up period mentioned in the study.

## Quality Assessment

The quality assessment of the included studies was performed by the authors (AB and SS) in accordance with the following items: (1) clarity of the study objectives; (2) study period stated clearly; (3) criteria for patient selection; (4) study conducted in multiple centers; (5) danazol treatment method and dosage mentioned; (6) baseline equivalence groups clearly considered; (7) definition of the primary outcome (major response, minor response, or platelet count defined prior to the study; (8) adequate follow-up period; (9) adverse effects (AEs) stated; and (10) the limitations of each study were considered. We did not use quality assessment as an exclusion criterion. Individual study questions were answered with *yes* or *no*, with 1 point awarded for *yes* and 0 points for *no*. Total score was calculated for each study. The quality of the included studies was judged to be *fair* (total score, 8-10), *average* (5-7), and *low* (0-4). Consensus with the reviewer (RY) was used to resolve any disputes.

## Synthesis of Results

The narrative synopsis with summary tables for attributes covered all identified studies. Additionally, descriptive statistics were used to summarize the data. For dichotomous variables, we used frequencies and percentages, whereas we used mean or median for continuous variables.

## Outcome of Interest

### Efficacy Measures

The following were used to examine patients' functional outcomes:

1. **Major response was defined as:**
   - a more than 2-g/dL increase in hemoglobin level for patients with a pretreatment hemoglobin level of less than 11 g/dL;
   - transfusion independence for patients who were red blood cell (RBC) transfusion dependent;
   - an absolute increase of $30 \times 10^9$/L or more for patients with a pretreatment platelet count of less than $100 \times 10^9$/L;
   - stabilization of platelet count and platelet transfusion independence for patients who were platelet transfusion dependent; or
   - a 100% increase or an absolute neutrophil count (ANC) increase of more than $0.5 \times 10^9$/L for patients with a pretreatment ANC of less than $1.5 \times 10^9$/L.

2. **Minor response was defined as:**
   - an increase of 1 to 2 g/dL in hemoglobin level for patients with a pretreatment hemoglobin level of less than 11 g/dL;
   - a 50% decrease in transfusion requirements for patients who were RBC transfusion dependent;
   - a 50% or more increase in platelet count with a net increase greater than $10 \times 10^9$/L but less than $30 \times 10^9$/L; or
   - an ANC increase of at least 100% but an ANC increase of less than $0.5 \times 10^9$/L.[26] Response was required to last at least 2 months.

3. **Increase in platelet count: Response was defined as a platelet count increase of at least $30 \times 10^9$/L.**

TABLE 2. **Descriptive Characteristics of the Included Studies**[2,11,17-20,24-26,a]

| Study number | Lead author, study year | Sample size | Study design | Country of study | Age (median or mean) | Gender ratio (male: female) | Danazol dose | Efficacy measures | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Jaime-Pérez et al, 2017[17] | 42 | Retrospective | Mexico | 61* | NR | 400 mg | ▪MR<br>▪mr | Gastrointestinal symptoms, weight gain |
| 2 | Letendre et al, 1995[18] | 46 | Prospective | United States | 70* | 32:14 | 800 mg | ▪MR | Dermatitis, exfoliative dermatitis |
| 3 | Chan et al, 2002[11] | 33 | Retrospective | United States | 68** | 20:13 | 600 mg,<br>400 mg,<br>200 mg | ▪Increase in PC | Mild headaches, nausea, weight gain |
| 4 | Catalano et al, 1993[26] | 47 | NR | Italy | NR | NR | 400-600 mg | ▪Increase in PC | NR |
| 5 | Viniou et al, 200[22] | 17 | Prospective | Greece | 68** | 10:7 | 600 mg | ▪Increase in PC | NR |
| 6 | Stadtmauer et al, 1991[25] | 22 | Prospective | United States | 65* | 14:6 | 600-800 mg | ▪Increase in PC | Maculopapular rash, increased serum transaminase level |
| 7 | Wattel et al, 1994[24] | 13 | Prospective | France | 61** | 8:5 | 600 mg | ▪Increase in PC | Weight gain, moderate asthenia, mild liver function test abnormalities |
| 8 | Doll et al, 1987[19] | 6 | Prospective | United States | 72** | 5:1 | 800 mg | ▪Increase in PC | Suspected exacerbation of thrombocytopenia due to secondary to danazol |
| 9 | Buzaid et al, 1987[20] | 20 | Prospective | United States | 68* | 4:1 | 800 mg | ▪Increase in PC | Headache, mild water retention, transient elevation of liver enzyme levels |

MR, molecular response; mr, minimal response; NR, not reported; PC, platelet count.

*median; **mean.

[a]This table includes only the patients we defined in the MR and mr criteria section of this article, so these data may be different from the conclusions published for the individual studies because the response criteria might have been different from ours. We analyzed the charts published with the individual studies to find the data best suited to match our response criteria.

## Results

### Literature Search and Study Selection

The literature search resulted in the retrieval of 90 studies. After the complete screening process of titles, abstracts, and full texts, 81 studies did not meet the eligibility criteria. Nine articles with various study designs that met the criteria were included in the review. A description of study selection is shown in the PRISMA flow diagram in the **Figure.**

### Quality Assessment Among the Included Studies

The result of the quality assessment of the included studies is displayed in **Table 1.**[2,11,17-20,24-26] We included and critically analyzed a total of 9 studies, among which 6 scored 10 of 10, 2 scored 9 of 10, and 1 scored 8 of 10. Based on our judgments, all studies scored between 8 and 10 and were therefore deemed *fair* quality. The average score was 9.55, making the overall quality of the included studies *fair*.

TABLE 3. **Efficacy Results of the Included Studies**[2,11,17-20,24-26]

| Study number | Lead author, study year | Efficacy measure(s) | Outcomes |
|---|---|---|---|
| 1 | Jaime-Pérez et al, 2017[17] | 1. MR | Sixty percent of patients experienced any response. MR for patients with anemia was 23.8%. MR for ANC was 36.8% and for platelet count was 60%. Median increase in hemoglobin level was 1.1 g/dL (95% CI, 0.7-1.5), in ANC was 0.6 × $10^9$/L (95% CI, 0.3-1.1 × $10^9$/L), and in platelet count was 42 × $10^9$/L (95% CI, 16-83 × $10^9$/L). |
| | | 2. Time to initial response | Time to initial response was 2 months; time to best response was 3 months. Median DOR was 6 months. Responders were significantly older than nonresponders (median age 70 vs 52 years, respectively) and had a higher baseline hemoglobin level (9.7 g/dL vs 7.7 g/dL) ($P$ = .025 and $P$ = .009). |
| | | 3. Transfusion independence | Thirteen of 23 patients dependent on transfusion support (57%) became platelet transfusion independent, and 8 of 23 patients dependent on PRBC transfusion support (35%) became independent. |
| 2 | Letendre et al, 1995[18] | MR | One patient improved after danazol treatment, 1 patient had a partial response, and 9 patients had no response (1 nonresponder with an initial neutrophil count of .7 × $10^9$/L did experience a 1-month increase in ANC to 1.5 × $10^9$/L; another had an increased hemoglobin level of 1 g/dL). Crossover to high dose showed no improvement. |
| 3 | Chan et al, 2002[11] | Increase in platelet count | The mean platelet count of participants after 6 weeks of therapy rose to 60 × $10^9$/L (9-223 × $10^9$/L; $P$ < .015); 76% of participants had an increase in platelet count (1-181 × $10^9$/L), with 36% of them experiencing a platelet count increase of more than 50%. |
| 4 | Catalano et al, 1993[26] | Increase in platelet count | A response was evident in 6 patients who had platelet count increase > 40 × $10^9$/L (in 1 case with an increased WBC count and in 2 cases with discontinuation of the transfusion requirement). |
| 5 | Viniou et al, 2002[2] | Increase in platelet count | Platelet antibodies were detected in 70.6% of patients with MDS. Seven patients (41.2%) responded to treatment and achieved a significant increase in platelet count (median value increased from 40 × $10^9$/L to 122 × $10^9$/L). |
| 6 | Stadtmauer et al, 1991[25] | Increase in platelet count | Eleven of 22 evaluable patients taking danazol showed improvement of peripheral counts. |
| 7 | Wattel et al, 1994[24] | Increase in platelet count | Eight of 13 evaluable patients taking danazol showed improvement of peripheral counts. |
| 8 | Doll et al, 1987[19] | Increase in platelet count | No patient had a response to therapy as determined by an increase in either the hemoglobin level or platelet count, and none of the patients had a prolongation of their transfusion interval. |
| 9 | Buzaid et al, 1987[20] | Increase in platelet count | Three patients (15%) responded to the treatment; all responders had an increase in platelet count only. |

ANC, absolute neutrophil count; DOR, duration of response; MDS, myelodysplastic syndromes; MR, major response; PRBC, packed red blood cells; WBC, white blood cell.

## Descriptive Characteristics of the Included Studies

Nine studies consisting of 246 participants were included in our review. Six were prospective observation studies, and the remaining 4 studies were retrospective. Six studies were performed in North America (5 of which in the United States), and 3 studies were conducted in Europe. The age of the participants ranged from 61 to 72 years, and all 9 studies enrolled more male than female patients. All the studies reported the dose of danazol administered and at least 1 of the efficacy measures (major response, minor response, or increased platelet count). Seven studies reported the AEs of danazol observed in the patients. The descriptive characteristics of the 9 included studies are detailed in **Table 2.**[2,11,17-20,24-26]

## Efficacy Measures

Overall, the participants (with MDS subtypes refractory anemia [RA], RA with ringed sideroblasts [RARS], RA with excess of blasts [RAEB], RAEB in transformation [RAEB-T], or chronic myelomonocytic leukemia [CMML]) in all 9 studies experienced the desired response, and their hemoglobin level and platelet count increased. In studies from which we could derive data, 41.37% of

patients in the RA group, 40% in the CMML group, 35.4% in the RAEB group, 10% in the RAEB-T group, and 4% in RARS group responded with either a major or a minor response. All studies except Buzaid et al followed the participants for 3 months.[20]

In Catalano et al, 6 of 47 patients who received 400 to 600 mg of daily danazol showed a major response in platelet count and 1 of 47 and 2 of 47 patients showed a major response in ANC and hemoglobin level, respectively.[26] Similar results were demonstrated by Chan et al—10 of 33 patients administered 200 to 600 mg of daily danazol showed a major response in platelet count.[11] Major responses were satisfactorily obtained in all studies that mentioned it. In the study done by Jaime-Pérez et al, more than half of the participants experienced an increased platelet count.[14] In the study performed by Buzaid et al, all the participants who did not improve had RAEB.[20] Stadtmauer et al and Letendre et al both reported an elevated hemoglobin level as the minor response achieved.[18,25] However, the findings were contrary in Doll et al.[19] None of the participants showed an increased platelet count at a dose of 800 mg/day of danazol. **Table 3**[2,11,17-20,24-26] details the outcomes of each study.

## Adverse Effects

Elevated liver enzyme levels, weight gain, headache, dermatitis, and weakness were the most common AEs observed among the participants treated with danazol. In Buzaid et al, 2 patients discontinued the drug before 4 weeks, 1 due to a fatal intracerebral hemorrhage and 1 due to intractable headache, which improved after discontinuation of the drug.[20] Doll et al[19] reported thrombocytopenia in the participants, but the etiology was not determined and attributed to exacerbation secondary to danazol administration. The AEs experienced by participants in the included studies are shown in **Table 2**.

## Discussion

Different drugs have been developed to treat patients with MDS, but stem cell transplantation is the only potential cure available; however, there is no cure for the vast majority of patients with MDS.[27] As a result, treatment for patients with MDS aims to delay the onset of AML in high-risk patients and reduce cytopenia-related problems in low-risk patients.[28]

MDS has been treated with corticosteroids, 13-cis-retinoic acid, and androgens with varying degrees of success.[10,29,30] Hypomethylating drugs have recently been found to improve hematological outcomes in 25% to 50% of patients with high-risk MDS, achieve a full response in 10% to 20% of patients, and enhance survival compared with best supportive therapy.[31] Despite these hopeful outcomes, 40% to 50% of patients will not benefit from the hypomethylating drugs.[31] Due to its effectiveness in treating immunological cytopenia, danazol has drawn particular attention. Additionally, it has recently been demonstrated that the agent can lengthen telomeres, resulting in a hematological response in patients with telomere illness.[32] However, earlier research on danazol as a treatment for MDS had conflicting outcomes.[32]

Since the 1960s, androgens such as danazol have been used to treat MDS and AML.[19] Because clonal myeloid disorders like MDS, AML, and aplastic anemia share anomalies of the *TERC/TERT* partners of telomerase activity, one hypothesis for the positive effect of androgens such as danazol on telomerase may explain why norethandrolone has recently been shown to be effective in treating AML.[33]

Danazol's mode of action in patients with MDS is still unknown. Many of our patients' responses took longer than expected, which raises the possibility that the mechanism of action may be immune mediated rather than involving direct stimulation of megakaryocytes. People with idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia respond well to danazol therapy.[34] Danazol also has been shown to lower the antiplatelet IgG level in patients with ITP who are responding.[35,36] A decrease in the quantity of platelet-associated IgG may not be the only mechanism through which the response to danazol is mediated.[37] Numerous immunological problems, such as the development of autoantibodies and autoimmune diseases, are linked to MDS,[38] and immunosuppressive therapy is effective in certain patients with MDS.[39] The delay in platelet response in certain patients after 12 weeks of danazol therapy suggests an immune-mediated impact that may necessitate a prolonged course of treatment, even though danazol's mechanism of action in MDS and immune-mediated illnesses is unknown.

## Limitations

Our review had several limitations. First, neither a worse prognosis nor clinical signs were used to choose individuals for the majority of the research. Danazol was used concurrently with other medications, which also affected the results. The efficacy end points that were utilized to measure effectiveness might be unreliable for a variety of MDS. Additionally, the functional scale used to evaluate efficacy varied between studies. The included research also had tiny sample numbers, and the study's time frame was likewise brief. Finally, most of the trials were single center, open label, and nonrandomized.

## Conclusions

Our systematic review included a total

of 246 patients; 57 (23.17%) of these patients showed a major response in platelet count, 18 (7.32%) had a major response in ANC, and 15 (6.10%) experienced a major response in hemoglobin level. Two patients showed a minor response in ANC, and 1 patient had a minor response in hemoglobin level. Danazol has been effective in increasing platelet count and hemoglobin level. Despite a few AEs, danazol is a safe treatment option for patients with MDS. ■

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# Genomic Predictors Associated With Exceptional Response to Systemic Therapy in Advanced Pancreatic Cancer

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## ABSTRACT

**Introduction:** Exceptional response to therapy is rare in patients with advanced pancreatic cancer. This study explored potential genomic differences between typical and exceptional responses that could confer more favorable biology.

**Methods:** We included exceptional responders and controls with advanced pancreatic cancer from Cleveland Clinic from April 2013 to August 2017. Exceptional responders were defined as patients with an overall survival of more than 18 months for metastatic disease and more than 24 months for locally advanced disease. Clinical data were obtained, and next-generation sequencing was performed. Statistical analyses comparing the 2 groups were performed using descriptive statistics, the Kaplan-Meier method, and the log-rank test.

**Results:** The study comprised 4 exceptional responders and 6 controls. Both groups were well balanced in age, sex, race, and treatment regimens. Exceptional responders had significantly fewer nonsynonymous mutations than controls (2.25 vs 5.17; $P = .014$). A mutation count of less than 3 was associated with significantly better progression-free survival (17.2 vs 2.3 months; $P = .002$) and overall survival (29.4 vs 4.6 months; $P = .013$). Tumor mutational burden did not differ between exceptional responders and controls (4.88 vs 5.70 mut/Mb; $P = .39$).

**Conclusion:** A lower number of nonsynonymous mutations may correlate with exceptional outcomes in patients with pancreatic cancer. These findings should encourage future studies into genomic signatures of exceptional response.

## Introduction

Pancreatic cancer is associated with poor outcomes at any stage. However, a very small number of patients—approximately 3% of those with metastatic disease—experience long-term survival through 5 years and durable responses to systemic therapy.[1] The biological mechanisms that underlie the benefits observed with these *exceptional responders* are not completely understood. It is possible that certain tumor molecular features, including somatic mutations or tumor mutation burden, affect the tumor microenvironment and lead to more indolent biology or increased sensitivity to specific therapies.

Because exceptional responders are rare, the molecular underpinnings of exceptional response also may be rare and thus difficult to study and characterize. In pancreatic cancer, this challenge is further compounded by a high proportion of small tissue specimens obtained via fine needle aspiration (FNA) that are often insufficient for comprehensive genomic profiling.

The ongoing National Cancer Institute (NCI) Exceptional Responders Initiative provides the most robust molecular data thus far; it includes 111 patients who are exceptional responders to date. For 26 patients (23.4%), likely genomic mechanisms for exceptional response

TABLE 1. **Baseline Characteristics of the Study Population Divided Into Exceptional Responders and Matched Controls**

| | Exceptional responders (n = 4) n (%) | Matched controls (n = 6) n (%) |
|---|---|---|
| **Median Age (years)** | **69 (range, 65-82)** | **67.5 (range, 57-71)** |
| **Sex** | | |
| Female | 1 (25%) | 2 (33%) |
| Male | 3 (75%) | 4 (67%) |
| **Ethnicity** | | |
| Latino or Hispanic | 0 (0%) | 1 (17%) |
| Not Latino or Hispanic | 4 (100%) | 5 (83%) |
| **Race** | | |
| White | 3 (75%) | 4 (67%) |
| Black | 1 (25%) | 2 (33%) |
| Asian | 0 (0%) | 0 (0%) |
| **Stage at diagnosis** | | |
| I | 0 (0%) | 0 (0%) |
| II | 2 (50%) | 1 (17%) |
| III | 0 (0%) | 0 (0%) |
| IV | 2 (50%) | 5 (83%) |
| **Primary pancreatic tumor site** | | |
| Head | 2 (50%) | 4 (67%) |
| Neck | 0 (0%) | 0 (0%) |
| Body | 0 (0%) | 2 (33%) |
| Tail | 2 (50%) | 0 (0%) |
| **Treatment regimens** | | |
| **Adjuvant** | 2 (50%, gem [1], gem + nab-pac [1]) | 0 (0%) |
| **First line** | **(n = 4)** | **(n = 6)** |
| FOLFOX | 2 (50%) | 0 (0%) |
| FOLFIRINOX | 2 (50%) | 2 (33%) |
| Gem + nab-pac | 0 (0%) | 4 (67%) |
| **Second line** | **(n = 4)** | **(n = 3)** |
| 5-FU | 1 (25%) | 0 (0%) |
| FOLFOX | 1 (25%) | 2 (67%) |
| Gem + nab-pac | 2 (50%) | 1 (33%) |
| **Third line** | **(n = 2)** | **(n = 0)** |
| 5-FU + lipo irinotecan | 1 (50%) | 0 (0%) |
| FOLFOX | 1 (50%) | 0 (0%) |
| **Fourth line** | **(n = 1)** | **(n = 0)** |
| 5-FU + lipo irinotecan | 1 (100%) | 0 (0%) |

5-FU, 5-fluorouracil; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; gem, gemcitabine; lipo, liposomal; nab-pac, nab-paclitaxel.

were found, predominantly in DNA damage response, intracellular signaling, and immunologic engagement pathways.[2] However, only 1 patient had pancreatic adenocarcinoma, and for 76.6% of patients, no discernible genomic cause for exceptional response was found. Another series that performed comprehensive genomic profiling of tumors from 16 exceptional responders showed similar alterations in DNA damage repair pathways and immune cell infiltration mechanisms.[3] However, none of these patients had pancreatic adenocarcinoma.

Given the relative lack of data on exceptional responders with pancreatic adenocarcinoma, this study aimed to identify potential molecular signatures of exceptional response, which could influence prognostic modeling or identify novel predictive biomarkers for future therapies.

## Methods

The study population comprised consecutive exceptional responders and matched controls with locally advanced or metastatic pancreatic cancer from Cleveland Clinic Ohio and Cleveland Clinic Florida from April 2013 to August 2017. Exceptional responders were defined as patients with overall survival (OS) greater than 18 months for metastatic disease and greater than 24 months for locally advanced disease. Matched controls were defined as patients with OS less than 9 months for metastatic disease and less than 12 months for locally advanced disease. They were selected among the patients in our tumor registry who were diagnosed between April 2013 and August 2017 and were matched based on age, sex, disease stage, and type of chemotherapy. The study was approved by the Institutional Review Board of Cleveland Clinic Taussig Cancer Institute.

Clinical data including patient demographics, comorbidities, disease

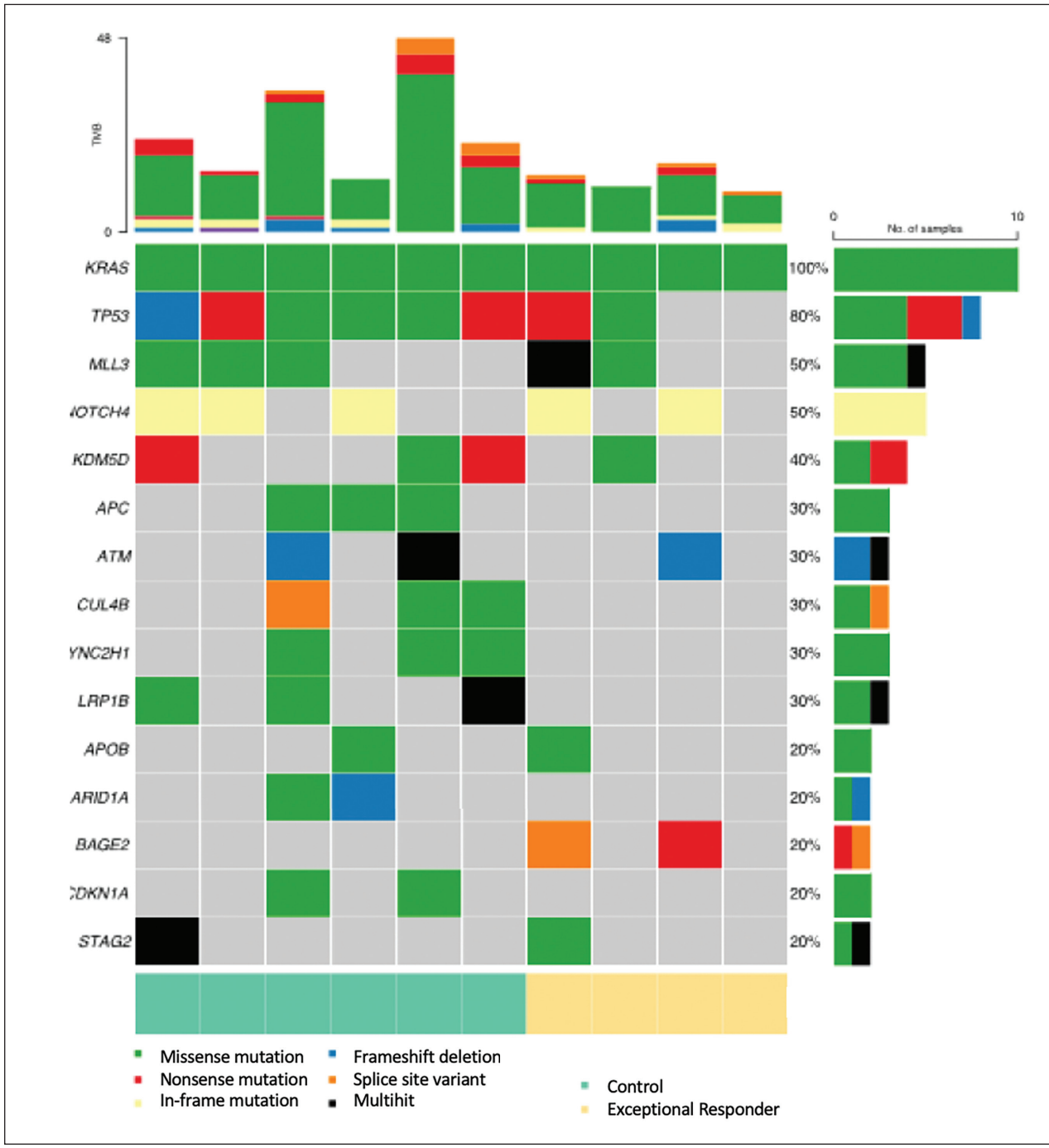
TABLE 2. **Summary of Individual Patient-Level Data on Baseline Characteristics, Cancer Stage, Treatment History, and Outcomes**

| Patient number | Age (years) | Sex | Stage at diagnosis | Treatments | Treatment duration (months) | Best response | Overall survival (months) |
|---|---|---|---|---|---|---|---|
| **Exceptional responders** | | | | | | | |
| 1 | 65 | Male | IIB | Surgery | NA | NA | 51.5 |
| | | | | Adjuvant gemcitabine | 6 | NA | |
| | | | | FOLFOX | 6.5 | SD | |
| | | | | 5-FU | 30 | SD | |
| | | | | FOLFOX | 2.5 | PD | |
| | | | | 5-FU + liposomal irinotecan | 0.25 | PD | |
| 2 | 71 | Female | IV | FOLFIRINOX | 11.5 | PR | 23 |
| | | | | Gemcitabine + nab-paclitaxel | 4.5 | PD | |
| | | | | 5-FU + liposomal irinotecan | 0.5 | PD | |
| 3 | 67 | Male | IV | FOLFIRINOX | 16.5 | SD | 36 |
| | | | | Gemcitabine + nab-paclitaxel | 9 | SD | |
| 4 | 82 | Male | IIB | Surgery | NA | NA | 29.5 |
| | | | | Gemcitabine + nab-paclitaxel | 5 | PD | |
| | | | | FOLFOX | 4.5 | SD | |
| | | | | 5-FU + liposomal irinotecan | 1 | PD | |
| **Matched controls** | | | | | | | |
| 5 | 70 | Female | IV | FOLFIRINOX | 1.5 | PD | 7 |
| | | | | Gemcitabine + nab-paclitaxel | 2 | PD | |
| 6 | 61 | Female | IV | Gemcitabine + nab-paclitaxel | 4 | PD | 4.5 |
| 7 | 69 | Male | IIA | Gemcitabine + nab-paclitaxel | 3 | SD | 8 |
| | | | | FOLFOX | 1 | PD | |
| 8 | 71 | Male | IV | Gemcitabine + nab-paclitaxel | 0.5 | PD | 1.5 |
| 9 | 57 | Male | IV | FOLFIRINOX | 2.5 | PD | 3.5 |
| 10 | 66 | Male | IV | Gemcitabine + nab-paclitaxel | 3 | PD | 7 |
| | | | | FOLFOX | 0.5 | PD | |

5-FU, 5-fluorouracil; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.

characteristics, and treatment history were collected. In addition, DNA next-generation sequencing (NGS) was performed for 648 genes, microsatellite instability, and tumor mutation burden (TMB) using the Tempus xT platform. Briefly, this panel uses formalin-fixed, paraffin-embedded tissue from the tumor and a matched normal specimen from peripheral blood or saliva to detect single nucleotide variants, insertions and deletions, and copy number variants in 648 genes and for genomic rearrangements in 23 genes. Genes are sequenced to an average on-target depth of 500 times using the Illumina HiSeq 4000.[4] Due to insufficient tissue, additional comprehensive genomic profiling,

FIGURE 1. **Number of Functional, Nonsynonymous Genomic Alterations Divided by Exceptional Responders and Matched Controls**

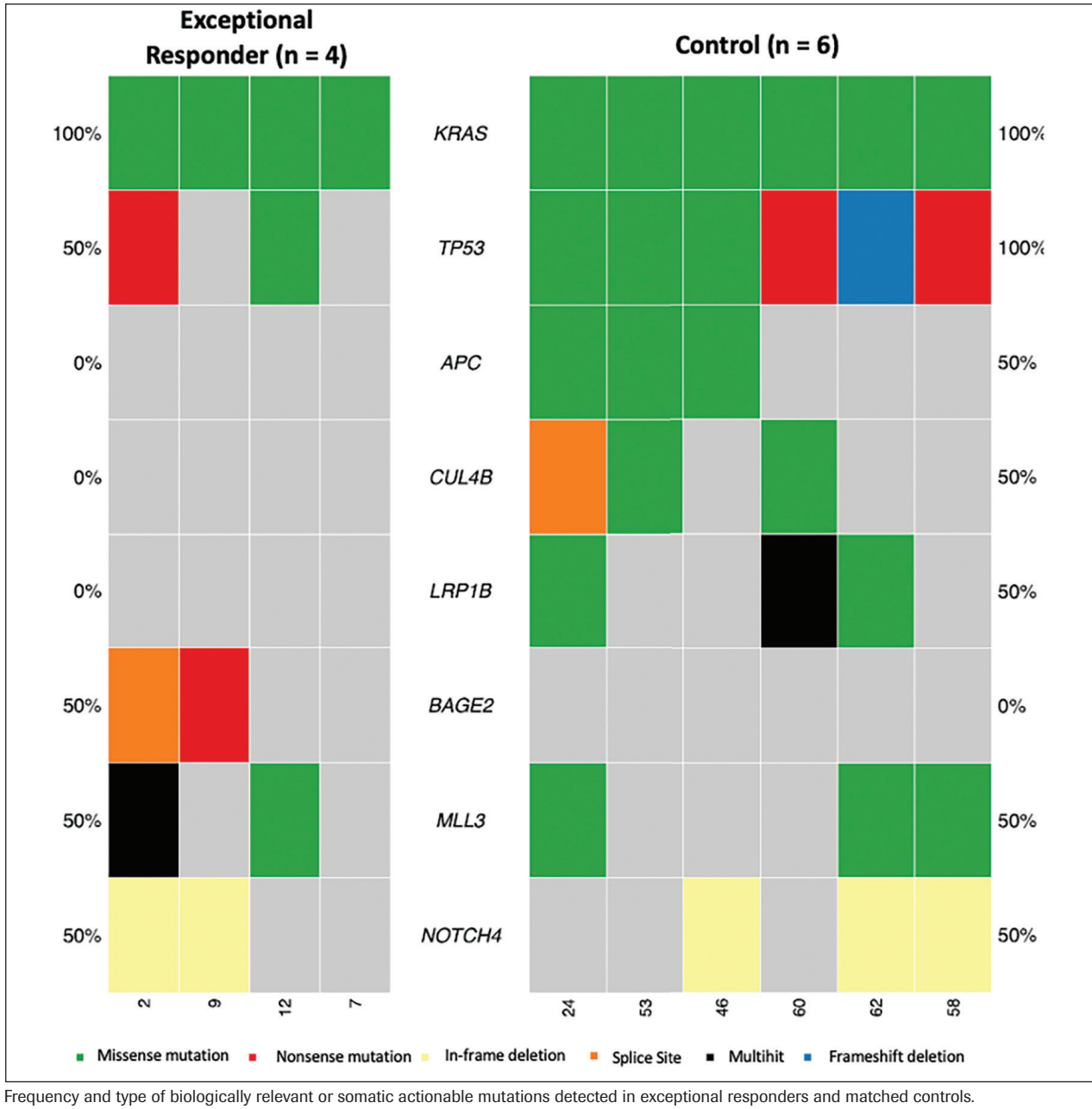



Frequency and type of all functional, nonsynonymous variants detected in exceptional responders and matched controls.

including whole exome sequencing and RNA sequencing, was not performed.

Statistical analyses comparing differences in clinical characteristics or genomic alterations between exceptional responders and matched controls were performed using descriptive statistics. Differences in the total number of functional, nonsynonymous mutations or TMB between exceptional responders and matched controls were analyzed using the log-rank test. Progression-free survival (PFS) and OS were estimated using the Kaplan-Meier method, and differences in survival outcomes based on the number of functional, nonsynonymous mutations or TMB were assessed using the log-rank test.

FIGURE 2. **Number of Somatic Actionable Mutations Divided by Exceptional Responders and Matched Controls**




Frequency and type of biologically relevant or somatic actionable mutations detected in exceptional responders and matched controls.

## Results

The study population initially comprised 14 exceptional responders and 42 matched controls. However, due to insufficient tissue for comprehensive genomic profiling, only 4 exceptional responders and 6 matched controls were included for analysis.

Both groups were well balanced in terms of age, sex, race, and first-line chemotherapy regimen. The median ages for exceptional responders and matched controls were 69.0 and 67.5 years, respectively. Both exceptional responders and matched controls were predominantly men (75% vs 67%, respectively) and predominantly White (75% vs 67%, respectively). Half of the exceptional responders had pancreatic tail primary tumors, compared with none of the matched controls. These data are summarized in **Table 1**.

Exceptional responders were labeled as patients 1 to 4, and matched controls

were labeled as patients 5 to 10. Patient 1 had the longest OS (51.5 months) and during one period experienced prolonged stable disease for 30 months on 5-fluorouracil (5-FU) alone. Patient 2 experienced a partial response to first-line FOLFIRINOX (leucovorin calcium, 5-FU, irinotecan hydrochloride, and oxaliplatin) and did not have progression of disease for 11.5 months. Patient 3 experienced relatively prolonged stable disease on first-line FOLFIRINOX and second-line gemcitabine plus nab-paclitaxel (16.5 months and 9.0 months, respectively). These data and others for each exceptional responder and matched control are summarized in **Table 2**.

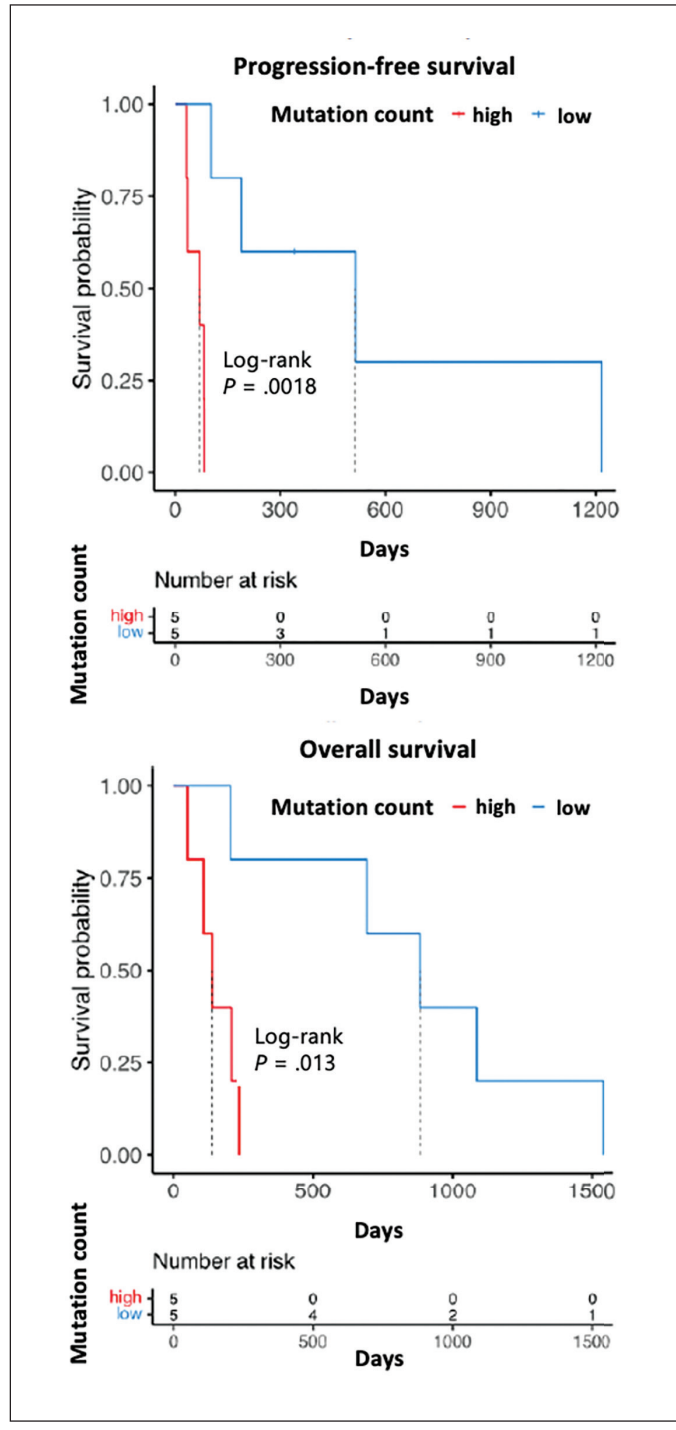
A total of 208 functional, nonsynonymous variants were detected in the study population, 52 in the exceptional responders and 156 in the matched controls. The genes with alterations and the types of variants detected are shown in **Figure 1**. Focusing on biologically relevant or somatic actionable mutations, 40 mutations were detected in the study population: 9 in the exceptional responders and 31 in the matched controls. Missense mutations in *KRAS* were present in 100% of exceptional responders and matched controls. Of the exceptional responders, 50% had alterations in *BAGE2* vs 0% of the matched controls. Conversely, 50% of the matched controls had alterations in *LRP1B*, *CUL4B*, or *APC* vs 0% of the exceptional responders. These data are summarized in **Figure 2**.

Exceptional responders had significantly fewer functional, nonsynonymous mutations compared with matched controls (2.25 vs 5.17, $P = .014$). Mutation count of less than 3 was associated with significantly better PFS (17.2 vs 2.3 months, $P = .002$) and OS (29.4 vs 4.6 months, $P = .013$). Kaplan-Meier curves illustrating these data are shown in **Figure 3**. TMB did not differ between exceptional responders and matched controls (4.88 vs 5.70 Mut/Mb, $P = .39$).

## Discussion

We found that patients with advanced pancreatic cancer with exceptional response to systemic therapy had tumors that were associated with fewer functional, nonsynonymous mutations. There are several possible explanations for the correlation between the number of functional, nonsynonymous mutations and exceptional response. One possibility

FIGURE 3. **Outcomes for Patients With High Vs Low Number of Genomic Mutations**




Progression-free survival and overall survival curves as estimated by the Kaplan-Meier method. The mutation count cut point used was less than or equal to 3 (low) vs greater than 3 (high). Time was measured in days.

is that exceptional responders are more driven by oncogenic addiction. Oncogenic addiction is defined as the presence of a genetic alteration within the tumor cell that causes it to be highly dependent on the downstream proteins and pathways of that individual gene. This could render these tumors more sensitive to standard cytotoxic chemotherapy, leading to exceptional responses. For example, the NCI Exceptional Responders Cohort included 1 patient with pancreatic adenocarcinoma and a germline *BRCA1* mutation who had a complete response to FOLFOX (5-FU, leucovorin, oxaliplatin), suggesting exquisite platinum sensitivity due to impaired DNA damage response (DDR) caused by the *BRCA1* mutation.[2] This cohort and multiple others have highlighted the importance of DDR pathway defects in exceptional responders.[2,3,5]

In another series of 18 patients with advanced pancreatic cancer who were treated with genomically targeted therapies, those who received therapies with higher matching scores based on tumor genomic profile experienced higher response and clinical benefit rates, including 1 patient with *KRAS* and *CDKN2A/CDKN2B*-mutated pancreatic cancer who had a durable response for 18 months with trametinib, palbociclib, and bevacizumab.[6] Because the matching score is derived from the number of genomic alterations with matched targeted therapies divided by the total of genomic alterations identified, it is possible that having fewer genomic alterations could lead to improved outcomes with targeted therapies.[7] Although our study did not identify specific genes that could engender oncogenic addiction, these genes may exist but remain undiscovered.

Our results contrast with a prior analysis that performed targeted genomic sequencing on 16 exceptional responder patients and found high frequencies of *EPHA5* mutations and *NF1* splicing mutation (88% and 69%, respectively).[3] However, none of the patients in this prior study had pancreatic adenocarcinoma, and it is likely that molecular drivers of exceptional response will differ across tumor types. From a cancer immunology perspective, prior work examining neoantigen quality and editing in pancreatic adenocarcinoma has shown that exceptional responders have primary tumors with approximately 12 times as many activated CD8+ T cells predicted to target immunogenic neoantigens and more clonal T-cell expansion compared with average responders. These findings were associated with fewer genomic mutations and fewer neoantigens.[8,9] It is possible that having fewer genomic alterations in an immunologically *cold* tumor such as pancreatic adenocarcinoma allows for improved T-cell identification of the resultant neoantigens and clonal expansion. Because our study could not adequately investigate mechanisms by which a lower number of functional, nonsynonymous mutations could potentiate exceptional responses, more work is needed to understand the significance of this correlation.

We found that a numerically higher proportion of exceptional responders had *BAGE2* alterations compared with the matched controls. Given the small sample size, our study cannot establish a correlation between *BAGE2* alterations and exceptional response, but this could be an interesting area for future research. *BAGE2* is a member of the family of genes located in the juxtacentromeric regions of chromosomes 13 and 21 that encode tumor antigens that can be recognized by cytotoxic T cells.[10] *BAGE2* alterations are well described in melanoma, but little is known about their significance in pancreatic adenocarcinoma.[10,11] One study evaluating distinct molecular subtypes in pancreatic cancer that included 178 patients from The Cancer Genome Atlas found only 2 patients with *BAGE2* deletions, which showed no correlation with exceptional response or favorable outcomes.[12]

Our study highlights the importance of searching for biomarkers of response to identify smaller subsets of patients who experience exceptional responses not observed in the broader population. For example, the original trials of EGFR inhibitors in lung adenocarcinoma with no biomarker selection showed only modest activity, but once EGFR was identified as a predictive biomarker in a subset of patients, the true activity of these drugs became apparent.[13-15] Similarly, EGFR inhibition in advanced colorectal cancer initially appeared ineffective, but improved biomarker prediction has shown this drug class is effective in those with *RAS/RAF* wild-type, HER2-negative, and left-sided primary tumors.[16,17]

Our study was limited by our inability to obtain complete RNA and DNA sequencing because of insufficient tissue for the majority of patients, which limited the strength of our results. Due to the anatomic location, pancreatic mass biopsies are often FNAs obtained via endoscopic ultrasound (EUS), which yield insufficient tissue for NGS. The hallmark features of pancreatic adenocarcinoma—low tumor cellularity and high stromal content—also diminish the yield for NGS for many patients. This highlights the importance of obtaining core biopsies from metastatic sites or referring to advanced endoscopists who are experienced in obtaining fine needle biopsies via EUS rather than FNA. NGS panels that can be performed successfully on more limited tissue specimens should be utilized in cases with insufficient tissue with the understanding

that they are less comprehensive for DNA and RNA sequencing and have reduced depth and breadth of coverage.[18,19] Because this is not dependent upon having sufficient tissue or tissue-based NGS testing, obtaining plasma circulating tumor DNA NGS at the time of diagnosis also can mitigate this issue.

Because of the limitations of this study from the small sample size and limited genomic sequencing due to insufficient tissue for most patients, these results should be viewed as hypothesis generating. Our study did not look at differences in tumor immune microenvironment, microbiome, metabolome, or other factors that may influence underlying tumor biology and response to therapy. We used a survival-based definition for exceptional response, whereas most prior studies in the literature have defined exceptional response by prolonged response duration, which may limit the generalizability of our findings. However, we chose our definition because survival outcomes are far more clinically meaningful than response outcomes and the previous definitions were not systematically validated enough to be considered accepted standards. Although outcomes for many malignancies have improved in the past decade, progress has been slower and more modest in pancreatic cancer. This suggests that survival cutoffs of 18 months and 24 months for metastatic and locally advanced disease, respectively, are relevant, especially for patients who received a diagnosis in 2016 or earlier.

## Conclusion

Exceptional responders are rare in pancreatic cancer, but they do occur. Having fewer functional, nonsynonymous mutations may be associated with exceptional response and improved survival outcomes in patients with advanced pancreatic cancer receiving systemic therapy. Although these data are inadequate to inform clinical practice, if they were confirmed in a larger cohort, there may be an opportunity to use maintenance therapy or brief treatment suspension more frequently in select cases of exceptional response. More work is needed in a larger population to confirm these findings and to elucidate potential mechanisms mediating the relationship between the number of functional, nonsynonymous mutations and exceptional response. ■

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***AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST***

SDK: Consulting/advisory role: Exelixis, Foundation Medicine, Guardant Health, Seagen, Tempus. Speaking: Merck, Seagen

DS:Consulting or speaking: Sanofi S.A.

AAK: Honoraria: Bayer; Halozyme; Janssen; Medscape; Nektar Therapeutics; Pfizer Consulting or advisory role: Bayer; Halozyme; Janssen; Pfizer; Pharmacyclics; PharmaCyte Biotech; Seagen

JR, YN, MS PB, DA, AN, TN, BD, MS, MJM, BEN, KGN: No relevant conflicts of interest to disclose

***AUTHOR CONTRIBUTIONS***

SDK: Conception/design, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript

JR: Conception/design, collection and/or assembly of data, data analysis and interpretation, final approval of manuscript

YN: Conception/design, collection and/or assembly of data, data analysis and interpretation, final approval of manuscript

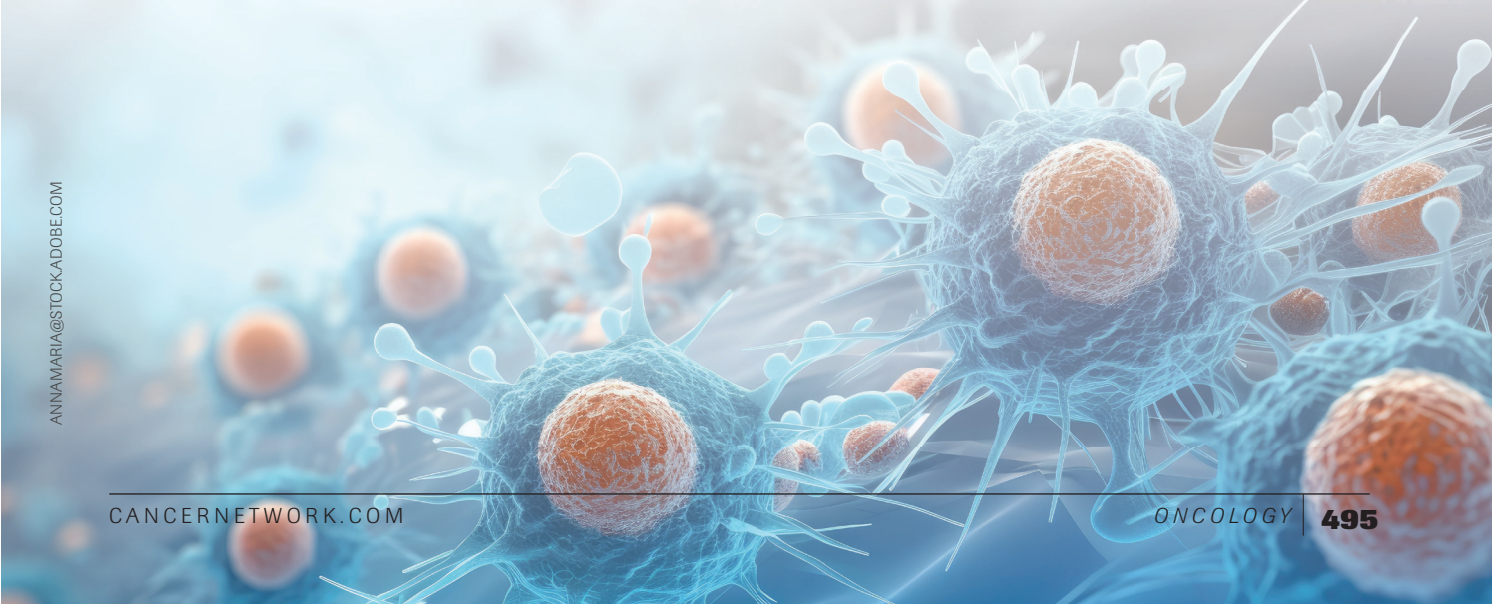
MS, PB, DA, AN, TN, BD, DS, MS, MJM, BNE, KGN: Provision of study material or patients, final approval of manuscript

AAK: Conception/Design, Provision of study material or patients, data analysis and interpretation, final approval of manuscript

***DATA AVAILABILITY STATEMENT***

Authors SDK and AAK had full access to all the data in the study. We take full responsibility for the integrity of the data. The data that support the findings of this study are available from the corresponding author on request.

**For references visit**
cancernetwork.com/12.23_Pancreatic



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# CONTINUING MEDICAL EDUCATION (CME)

# Emerging Treatments and Evolving Paradigms in HER2-Low Breast Cancer


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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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## LEARNING OBJECTIVES

*Upon successful completion of this activity, you should be better prepared to:*

- Identify patients with HER2-low breast cancer by utilizing guideline-based recommendations to differentiate between HER2-negative and HER2-low breast cancer
- Discuss the rationale for and clinical relevance of recent clinical trials utilizing HER2-targeting strategies for the management of patients with HER2-low breast cancer
- Determine strategies to integrate evolving evidence into treatment planning for patients with HER2-low breast cancer


**RELEASE DATE:** DECEMBER 1, 2023
**EXPIRATION DATE:** DECEMBER 1, 2024


## INSTRUCTIONS FOR PARTICIPATION AND HOW TO RECEIVE CREDIT

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2. Go to **https://gotoper.com/etep23her2-breastcancer** to access and complete the posttest.
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HER2-low metastatic breast cancer (mBC) represents a recently established subset of HER2-negative (HER2–) BC, defined by a HER2 immunohistochemical (IHC) score of 1+ or 2+ and in situ hybridization (ISH) negative phenotype.[1] Recent clinical trial data have shown clinical and survival benefit with novel, HER2-targeting antibody-drug conjugates (ADCs). Specifically, fam-trastuzumab deruxtecan-nxki (T-DXd) is the first FDA-approved targeted therapy for HER2-low BC based on the phase 3 DESTINY-Breast04 trial.[2]

It is estimated that approximately 45% to 55% of patients with BC are classified as HER2-low; however, HER2 scoring criteria varies.[1] Interestingly, HER2-low status is more common in patients with hormone receptor–positive (HR+) BC than in those with triple-negative breast cancer (TNBC).

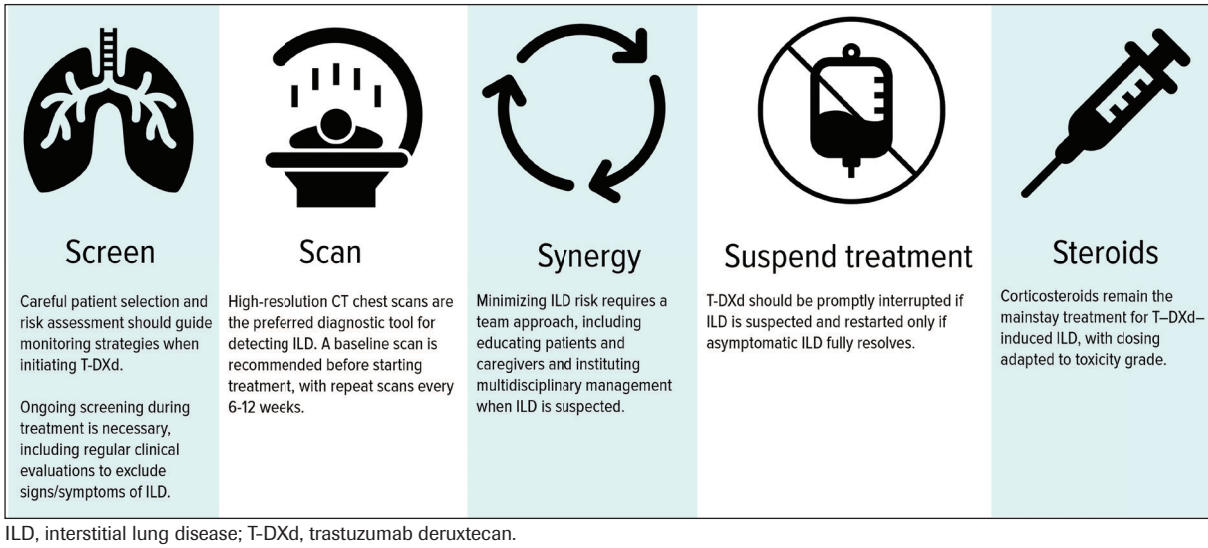
In this article, Paolo Tarantino, MD, advanced research fellow at the Breast Oncology Center at Dana-Farber Cancer Institute and Harvard Medical School in Boston, Massachusetts, discusses biologic insights, the current treatment landscape, and relevant data updates for HER2-low BC.

**Q: Which HER2-targeted therapies have shown efficacy in HER2-low BC? How do novel anti–HER2 therapies challenge the HER2 binary paradigm?**

**TARANTINO:** This is a very interesting question. It began with the idea that we may be able to expand the reach of HER2-targeted treatments beyond the 15% to 20% of patients who have HER2+ disease to the larger population with HER2-low BC (at least IHC 1+).[3] The largest trial that tested this hypothesis was NSABP B-47, a phase 3 study examining whether adding trastuzumab to adjuvant chemotherapy improves outcomes in the curative setting for patients with early-stage HER2-low BC.[4] This study was negative in terms of disease-free and overall survival (OS), demonstrating that blocking HER2 with a naked antibody does not benefit patients with HER2-low BC.[5] Years after the presentation of these results, linking agents to antibodies such as chemotherapy with ADCs, was found to provide relevant antitumor activity in both HER2+ and HER2-low BC.[6]

This was not seen with trastuzumab emtansine (T-DM1), likely because it has few chemotherapy molecules per antibody (drug to antibody ratio).[7] The drug to antibody ratio of T-DM1 is 3.5, whereas novel ADCs have up to 8 molecules of chemotherapy attached and utilize cleavable linkers and novel mechanisms like topoisomerase inhibitors.[8] Several novel ADCs have shown activity in HER2-low disease. The only approved ADC is trastuzumab deruxtecan (T-DXd), but others (like trastuzumab duocarmazine) have also demonstrated activity.[9] Most notably, a compound from China called SHR-A1811 had response rates above 50% in metastatic HER2+ and HER2-low BC.[10] We expect these and

FIGURE 1. **Management of ILD With T-DXd With the *5 S Rules*[13]**




ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

TABLE 1. **Key Survival Results From the Updated DESTINY-Breast04 Trial[16]**

| Agent | OS, mo | 24-mo OS | 36-mo OS | PFS, mo |
|---|---|---|---|---|
| T-DXd (n=331) | 23.9 | 49.0 | 26.5 | 9.6 |
| TPC (n=163) | 17.6 (HR, 0.69) | 35.1 | 16.9 | 4.2 |

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice

TABLE 2. **The Phase 2 TRUDI Trial[17]**

| Patient population | Study design | Treatment arms | End points |
|---|---|---|---|
| ▪ Stage III<br>▪ HER2+ *or* HER2-low<br>▪ Treatment naive | ▪ N=63<br>▪ Phase 2<br>▪ Open label<br>▪ Parallel assignment | Cohort 1 (HER2+): Durvalumab + T-DXd<br><br>Cohort 2 (HER-low): Durvalumab + T-DXd | ▪ pCR<br>▪ RCB<br>▪ EFS<br>▪ DDFS |

DDFS, distant disease-free survival; EFS, event-free survival; pCR, pathologic complete response; RCB, residual cancer burden; T-DXd, trastuzumab deruxtecan.

other conjugates may be active in HER2-low disease, but, to date, ADCs have shown the most promise while naked antibodies and tyrosine kinase inhibitors have had insufficient activity.

**Q: How has the approval of T-DXd changed the way you treat HER2-low BC? How has this approval affected patient outcomes?**

**TARANTINO:** The approval of T-DXd for patients with HER2-low BC occurred very rapidly, just 2 months after the data were presented at the 2022 American Society of Clinical Oncology Annual Meeting.[2] This approval has greatly impacted how we treat these patients since few drugs provide an OS advantage in HER2– mBC, which progresses after endocrine therapy and chemotherapy. With a 50% response rate and significant benefits in progression-free survival (PFS) and OS, we can be confident that this drug will help patients in the clinic, which is why it has been widely adopted as a preferred second-line agent for HER2-low metastatic disease.[11] I have seen prolonged responses, and we hope to present real-world data soon. The impact of T-DXd is huge, not only due to its activity, but also because of the ability to treat a large population. HER2-low cancers account for over half of all breast cancers.[1]

**Q: Interstitial lung disease (ILD)/pneumonitis is an adverse event of interest with T-DXd. How do you manage ILD in patients undergoing treatment with T-DXd therapy?**

**TARANTINO:** It is extremely important to be aware of the ILD risk with T-DXd. Approximately 10% to 15% of patients receiving the drug are expected to develop some degree of ILD or pneumonitis, although, in most cases, it is only grade 1 or 2.[12] Grade 1 refers to radiographic findings only, while grade 2 includes mild symptoms. In most T-DXd trials, there were also some fatal cases, usually 1% or less of patients, which reminds us of the severity of this adverse effect. Importantly, risk does not appear cumulative, but is highest within the first year of treatment. The median onset of ILD is about 4 to 5 months after starting T-DXd.

A helpful framework is the *5 S Rules* to monitor and manage ILD: (1) screening to understand patient risk factors (eg, comorbidities, frailties, or vulnerabilities); (2) scanning with serial chest CTs at 6 to 12 weeks for lower-risk patients and preferably at 6 to 9 weeks for high-risk patients; (3) synergy in discussing cases with radiologists and pulmonologists to establish multidisciplinary care; (4) suspension of treatment with any suspicion of ILD or permanent discontinuation of treatment with T-DXd if the ILD is symptomatic; and (5) steroids for treatment (**Figure 1**).[13] Steroids are the mainstay of treatment, and patients require access to oral or intravenous (IV) steroids to manage ILD. With this approach, fatal cases decreased from 2.7% in the DESTINY-Breast01 trial to 0% in the DESTINY-Breast03 trial.[14,15] Management is getting better, but there are still some cases of ILD in certain clinical trials, as well as in clinical practice.

**Q: Can you please comment on the updated survival data from the DESTINY-Breast04 trial presented at the European Society for Medical Oncology Congress 2023?**

**TARANTINO:** It was nice to see the update of the DESTINY-Breast04 trial. The results confirmed what we already knew: T-DXd works much better than chemotherapy, in terms of PFS and OS, with medians of survival quite

TABLE 3. **Primary Results From the TROPION-Breast01 Trial[21]**

| Agent | PFS, mo | 9-mo PFS, % | ORR, % | Grade ≥ 3 TRAEs |
|---|---|---|---|---|
| Dato-DXd (n=365) | 6.9 | 37.5 | 36.4 | 20.8 |
| ICC (n=367) | 4.9 (HR, 0.63; $P < .0001$) | 18.7 | 22.9 | 44.7 |

Dato-DXd, datopotamab deruxtecan; ICC, investigator's choice chemotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.

consistent with those observed at the prior presentation of the data. T-DXd, compared with chemotherapy, roughly doubled PFS and achieved an OS benefit of about 6 months (**Table 1**).[16]

**Q: Are there any other treatment approaches being evaluated in patients with HER2-low BC?**

**TARANTINO:** After seeing the impact of T-DXd in the metastatic setting, we want to explore the potential in the curative setting. Can T-DXd cure more patients with early-stage or locally advanced HER2+ or HER2-low BC? Can T-DXd prevent metastatic recurrence? This led to testing T-DXd with durvalumab as neoadjuvant treatment for inflammatory breast cancer with HER2 expression in the phase 2 TRUDI trial (**Table 2**).[17] I helped design this trial with Filipa Lynce, MD, at Dana-Farber; the trial is open and accruing patients at Dana-Farber and The University of Texas MD Anderson Cancer Center. We hope to see a high pathologic complete response rate with this combination in HER2+ and HER2-low disease, where there is major unmet need. We hope to have data within the next few years.

Additional trials in the curative setting are ongoing, like DESTINY-Breast05 and DESTINY-Breast11 in HER2+ settings, and the TRIO-US B-12 TALENT trial in HER2-low settings, which reported early activity at San Antonio Breast Cancer Symposium 2022 last year.[18-20] Many more trials are ongoing, so there are opportunities to leverage this potent drug.

We are also considering drugs like datopotamab deruxtecan (Dato-DXd), which is a similar ADC that uses the deruxtecan payload but targets TROP2 instead of HER2.[21] Primary data presented at ESMO 2023 showed positive survival outcomes compared with chemotherapy in the TROPION-Breast01 trial in patients with HR+/HER2– BC (**Table 3**).[21] Dato-DXd could be FDA approved next year; this would raise sequencing challenges but provide more treatment options. Since ADCs have distinct adverse effects, it is good to adapt treatment strategy, activity, and toxicities to patient preferences and profiles. In the future, we may have multiple ADCs to select from based on a multiplicity of patient- and disease-related factors.

**Q: How do you test for HER2 in your practice?**

**TARANTINO:** We test for HER2 in the classical way according to the ASCO/College of American Pathologists (CAP) guidelines, which is the authority for HER2 testing and interpretation on all samples with IHC and ISH/fluorescence in situ hybridization (FISH).[22] These allow us to determine if a tumor is HER2-positive or negative, with *negative* meaning no amplification or overexpression, not complete absence. IHC can also identify HER2-low tumors with 1+ or 2+ staining without amplification.

Some institutions do not perform IHC and perform only ISH/FISH, which misses HER2-low status. The 2023 ASCO/CAP guideline update specified adding a footnote that some ADCs can be used in HER2-low BC.[22] In general, following ASCO/CAP guidelines and performing IHC and FISH testing on tissue is the most comprehensive. We may have novel assays in the future, including blood-based tests to determine HER2 status from plasma, but we're not there yet.

**Q: What genetic differences exist between HER2-low and HER2-zero tumors?**

**TARANTINO:** When the HER2-low subgroup was defined and established in practice, a key question was whether it is a distinct molecular subtype of BC or just a clinical entity without molecular basis. Several groups studied this by comparing the genomic profiles of HER2-low and HER2-zero tumors. We presented one of the largest datasets on this at SABCS 2022, comparing gene mutations, amplifications, and copy number variations in more than 1000 patients with mBC.[23] We found no significant differences after multiple testing corrections.

The only difference was the average *ERBB2* allele copy number, which was higher in HER2-low tumors and which may potentially have therapeutic repercussions.[23] Single-copy *ERBB2* deletions were more common in HER2-zero than in HER2-low BC. This was the only major difference; HER2-low and HER2-zero are not considered distinct molecular entities, but they exist as part of a spectrum. We are now trying to dissect this spectrum with quantitative mRNA and proteomic assays.

**Q: Which biopsy should be used to define a tumor as HER2-low?**

**TARANTINO:** This is a major clinical dilemma in treating these patients, because we tend to trust the most recent biopsy as reflecting the current biology of the tumor. But, with HER2-low, this is tricky due to the high discordance rate between primary and recurrent tumors, and between subsequent biopsies over time. About 30% of tumors change from HER2-zero to HER2-low or vice versa at each time point.[24] Given this variability and heterogeneity, results of a Dutch autopsy study found different liver lesions in the same patient range from HER2-low to HER2-zero to HER2–ultra-low, depending on the biopsy site.[25,26]

The biopsy result dictates treatment and it is not always consistent. Given this and the OS benefit of T-DXd, we have become pragmatic on how we treat patients. The ESMO expert consensus on HER2-low breast cancer had over 90% agreement on using any biopsy in the patient's history for T-DXd consideration.[27] Even if only 1 of many is HER2-low, even if it is the primary or an old biopsy, it may predict T-DXd benefit over chemotherapy.

A DESTINY-Breast04 subgroup analysis examined whether primary tumor status predicted the benefit of T-DXd in the metastatic setting and whether an older biopsy predicted benefit as well as a recent one.[28] The answer was yes in both cases. The benefit of T-DXd over chemotherapy was consistent regardless of the tissue used for enrollment. Currently, we favor using any biopsy to consider T-DXd eligibility. We will present data on HER2-low evolution and T-DXd activity, so these assumptions may evolve as we learn more about their relationship over time.

**Q: The J101, DESTINY-Breast01, and BEGONIA trials excluded patients with HER2-zero tumors. How does the phase 2 DAISY trial differ and what is the key takeaway from that trial?**

**TARANTINO:** It was bold to design large trials like DESTINY-Breast04 that treated historically HER2– disease with an ADC. Designing for HER2 1+ and 2+/ISH-negative disease led to an effective treatment for these patients. The same occurred in the phase 1 J101 trial, BEGONIA, and most trials utilizing T-DXd in patients with HER2– and HER2-low expression.[29,30]

The phase 2 DAISY trial included cohorts for HER2+, HER2-low, and HER2-zero disease treated with T-DXd.[31] This showed encouraging activity not just in HER2+ and HER2-low disease, but in HER2-zero disease as well, demonstrated by a 30% objective response rate in patients with HER2-zero and disease progression on chemotherapy. It also showed PFS was dependent upon HER2 expression; the longest PFS was in HER2+ patients, intermediate PFS was seen in HER2-low, and the shortest PFS was in patients with HER2-zero disease.

This makes sense, because chemotherapy can detach from the antibody and circulate in the body like traditional chemotherapy, meaning that T-DXd likely has some activity irrespective of HER2 expression. This may explain activity in metastatic HER2-zero disease. If HER2 is expressed or overexpressed, there is additional, more durable activity of T-DXd. Overall, the DAISY trial expanded the horizon beyond what we consider HER2-expressing BC, and patients with HER2-zero disease may potentially benefit from T-DXd.

**Q: How does the trial design of the phase 3 DESTINY-Breast06 trial differ from that of the DESTINY-Breast04 trial? What are the implications of these data and how can we use these data moving forward?**

**TARANTINO:** DESTINY-Breast04 was a second-line trial for HR+/HER2– BC progressing on endocrine treatment and at least 1 line of chemotherapy.[16] This trial demonstrated superior outcomes with T-DXd compared with chemotherapy. The phase 3 DESTINY-Breast06 trial was initiated to evaluate T-DXd vs taxanes or capecitabine among patients with HR+ metastatic disease progressing on endocrine therapy without prior chemotherapy.[32]

There are 2 additional key differences from DESTINY-Breast04. First, about 10% of patients in DESTINY-Breast04 had triple-negative disease, whereas DESTINY-Breast06 investigators limited eligibility to HR+ disease.[32,33] Second, DESTINY-Breast04 included only HER2-low patients, while DESTINY-Breast06 also included those with HER2–ultra-low disease (IHC 0 with < 10% HER2 expression). If the data are positive, DESTINY-Breast06 could expand the use of T-DXd to the first-line setting following endocrine therapy failure and to patients with HER2–ultra-low expression. The results of this important trial may substantially broaden the use of T-DXd.

**Q: In your opinion, what does the future hold with respect to the evolution of HER2-low therapies? What is on the horizon that is shaping the treatment paradigm and the future of care in this space?**

**TARANTINO:** An important part of the future will be determined by biomarkers, because IHC is not ideal for

assessing HER2-low disease. IHC identifies HER2+ amplified/overexpressed cancer well, but, in the HER2-low realm, T-DXd had equal activity in IHC 1+/2+ and ISH-negative disease in DESTINY-Breast04.[33] IHC does not predict T-DXd activity, and we need better assays. Immunofluorescence, mass spectrometry, mRNA analysis, liquid biopsy, and more are being tested. Finding a biomarker to predict T-DXd activity in HER2-low disease will help to optimize treatment.

Other ADCs beyond T-DXd are being tested in this space. Disitamab vedotin is an ADC with a microtubule inhibitor payload.[34] Another ADC with a topoisomerase I inhibitor payload, SHR-A1811, has shown promising activity in preliminary trials.[10] In general, many ADCs may fill this space, leading to sequencing challenges to determine optimal treatment strategies. A major question is whether ADCs like T-DXd could replace anthracyclines and taxanes for early-stage treatment. Ongoing and planned trials will help answer if T-DXd and other ADCs can provide better cures for early BC, which is a huge innovation opportunity, because we need better curative treatments for these patients.

**Q: In your opinion, what is one of the biggest unmet needs in breast oncology?**

**TARANTINO:** One of the biggest unmet needs in breast oncology is effective treatment for brain metastases. It has been encouraging to see novel ADCs achieve high intracranial response rates and efficacy in this population. Recent data at ESMO 2023 showed a pooled analysis of DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03 trials that demonstrated response rates of over 40% in patients with HER2+ disease and untreated or active brain metastases.[35] PFS reached 1 year with stable brain metastases and 18.5 months with active brain metastases.

In general, promising data indicate that we are moving in the right direction to better treat patients with brain metastases. We still lack data on T-DXd for HER2-low brain metastases. The DEBBRAH trial had very few of these patients so more data are needed.[36]

We know that HER2+ BC has a high brain metastasis incidence; 30% to 50% of patients develop brain metastasis.[37] Brain metastasis is less frequent in HER2– disease, but because most breast cancers are HER2–, in absolute terms, most brain metastasis patients we see clinically have HER2– disease.[38]

We have yet to see much benefit for these patients with traditional chemotherapy, but ADCs are moving the needle. At Dana-Farber Cancer Institute, we will open a phase 2 trial of Dato-DXd for patients with brain metastases (DATO-BASE trial), with either HR+ or triple-negative disease and even leptomeningeal disease, which has a very poor prognosis.[39] Even in this setting, we can see responses with T-DXd and other ADCs, so it is important to study ADCs in this population. We hope to see activity for these difficult-to-treat patients.

Taken together, several emerging agents are shaping the evolving treatment landscape in defining and treating HER2-low mBC. ■

**Key References**

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