RARE CANCERS

SPECIAL REPORT

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RARE CANCERS

SPECIAL REPORT

Laura Nikolaides

EDITOR'S NOTE

Rare cancers, though individually rare by definition, represent almost a quarter of the total adult cancer burden when grouped together. Few traditional trials exist for these patients, many physicians know little about such tumors, and approved therapies are limited or nonexistent. However, a drop in genome sequencing cost, a new generation of genomically-driven clinical trials, development of immunotherapies, and the power of social media for recruiting patients are all contributing to a new era for the treatment of rare tumors. In this *Rare Cancers Special Report* we bring you the latest information on the sea change through interviews with those leading the charge, such as Razelle Kurzrock, MD, director of the Center of Personalized Cancer Therapy at the University of California, San Diego, and co-founder of the UCSD Rare Tumor Clinic, Keith Flaherty, MD, the ECOG-ACRIN study chair for the ongoing National Cancer Institute's Molecular Analysis for Therapy Choice (NCI-MATCH) trial, and Corrie Painter, PhD, a former rare tumor patient herself and currently researcher and director of the Angiosarcoma Project, a nationwide, patient-researcher collaboration to map the genomic landscape of the disease.

In this *Rare Cancers Special Report* we bring you reports on NCI-MATCH, which allotted 25% of slots for patients with rare tumors, and the SWOG-managed Dual Anti-CTLA-4 & Anti-PD-1 Blockade in Rare Tumors (DART) trial, as well as the latest reports on pediatric tumors. Also find resources for you and your patients provided by the National Institutes of Health and by the National Organization for Rare Disorders. I hope you enjoy the issue.

—Laura Nikolaides, Editor, Oncology Practice

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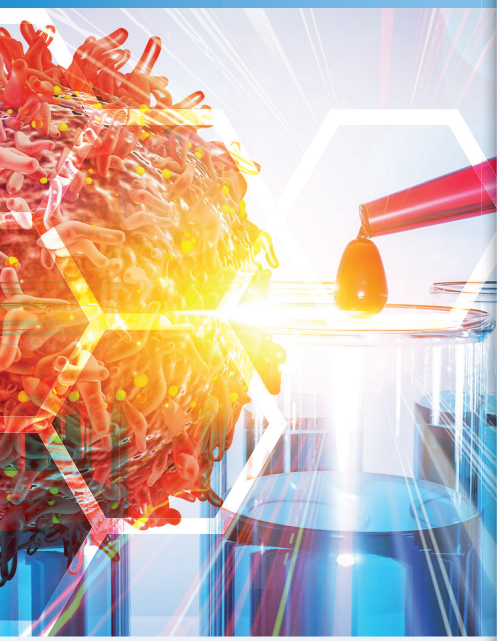

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A NOTE FROM NORD

Rallying Public Support for Awareness of Rare Cancers

This issue of *Rare Cancers Special Report* from *Hematology News* comes at a critical time in the history of rare cancer communities: For the first time ever, a national coalition of rare cancer organizations came together to coordinate a unified "Rare Cancer Day" on October 1. This new campaign endeavors to engage and inform the public about rare cancers at a time of increased attention from researchers, regulators, academicians, industry, and patient advocates—on both a national and global scale.

The National Organization for Rare Disorders© (NORD) announced October 1 as a day devoted to raising awareness about rare cancers. Spearheaded by the NORD Rare Cancer Coalition, which is comprised of 24 rare cancer-specific Member Organizations, Rare Cancer Day highlighted the challenges that researchers and people living with rare cancers face and the importance of early diagnosis. The coalition raises the fact that separately, we are rare, but when we come together, we raise our collective voices—for research, support and hope.

Those living with rare cancers deal with a lack of available information and effective treatment options, in addition to the isolation, fear, frustration and other overwhelming feelings that can accompany a more common cancer diagnosis. The goal of #RareCancerDay is to raise critical awareness of rare cancers and the need for greater research funding and patient support. Hundreds of thousands of people on Facebook, Twitter, LinkedIn, and on NORD's website, www.RareDiseases.org, saw infographics and messages of support for the community.

We are excited to grow with each year, and continue to shed light on how rare cancers can be isolating, are difficult to diagnose, and suffer from a lack of research and treatments. But that's not all the Rare Cancer Coalition does. We work collaboratively to build each other up through networking, capacity-building and sharing resources. We work through NORD for complimentary access to exhibiting at major conferences like ASCO and NORD's Rare Diseases and Orphan Products Breakthrough Summit.

This new *Rare Cancers Special Report* is part of this larger effort to continue to educate and promote awareness. We welcome anyone involved in rare cancer patient organizations to join our coalition for activities like Rare Cancer Day and other opportunities to bring rare cancer to the forefront of research, education, and awareness.

Jim Palma
Executive Director,
TargetCancer Foundation
Rare Cancer Coalition Co-Chair

John Hopper
President,
The Fibrolamellar Cancer Foundation
Rare Cancer Coalition Co-Chair

Genomically driven approaches gain steam for treating rare tumors

By Sharon Worcester

A "breathtakingly precipitous" drop in genome sequencing costs, a related surge in testing access and data generation, and an "almost unimaginable" rush of technological and treatment advances have converged to bring rare tumors to the precision medicine table.

It's a welcome development, Razelle Kurzrock, MD, director of the Center for Personalized Cancer Therapy and chief of the division of hematology-oncology in the department of medicine at the University of California, San Diego (UCSD) said of the increasing attention to genomically matched treatment for rare tumors.

"Rare tumors are individually rare by definition, but when you put them all together they represent almost a quarter of the total adult cancer burden—it's an enormous unmet need," she explained in an interview, noting that few trials exist for patients with rare tumors, many physicians know little about such tumors, and approved therapies are limited or nonexistent.

However, the factors bringing these tumors into greater focus, along with initiatives like the UCSD Rare Tumor Clinic[1], cofounded and directed by Dr. Kurzrock and the ongoing National Cancer Institute's Molecular Analysis for Therapy Choice (NCI-MATCH)[2] trial, are making headway.

Lower cost accounts for much of the recent attention

The U.S. portion of the Human Genome Project totaled about $2.7 billion, according to a National Human Genome Research Institute estimate—and that's in 1991 dollars and excludes contributions made to the project by other countries. The first human genome sequence completed in 2003 as part of that project cost an estimated $500 million to $1 billion.

Once the infrastructure was in place, the NHGRI estimated[3] the hypothetical 2003 cost to generate a second reference sequence at about $50 million.

Taking into account the refinement of processes, revolutionary new technologies, and a shift toward sequencing individuals' personal genomes over the years, the cost in 2006 was estimated at $20-$25 million for a completed sequence.


Razelle Kurzrock, MD

The complex and evolving landscape of genome sequencing makes direct cost comparison difficult, but thanks in part to the emergence of commercial genome-sequencing enterprises—and competition among them—it's clear that the cost, which is typically less than $1,500 for a draft genome sequence, has plummeted.

With costs down, the Centers for Medicare & Medicaid Services announced[4] in 2018 that it would begin covering next-generation sequencing (NGS) for Medicare beneficiaries with advanced cancer, noting that "NGS as a diagnostic laboratory test is reasonable and necessary and covered nationally," as long as it meets prespecified criteria, is performed in a Clinical Laboratory Improvement Amendments (CLIA)–certified lab, and is ordered by a treating physician.

That means more access to testing, a related amassing of data that can help make that testing more meaningful for individual patients, and ultimately more progress toward improved outcomes for patients with cancer—including for those with rare tumors, Dr. Kurzrock said, adding that "sequencing genomes or important parts of genomes is now in the realm of something that's affordable ... it's still not cheap, but the price has fallen so precipitously that it's really quite breathtaking."

Access and data have been a particularly important factor for patient accrual to the ongoing 1,100-site, 39-arm NCI-MATCH trial, which allotted 25% of slots for patients with rare tumors, according to Alice Chen, MD, a medical oncologist at

the NCI, head of the early clinical trials development program there, and NCI study chair for the overall NCI-MATCH trial.

As genomic testing became more accessible and data more plentiful, it became apparent that those data would be helpful for identifying patients with extremely rare mutations to help bolster enrollment in relevant trial arms, she said in an interview, noting that even after screening 6,000 patients for the trial, enrollment for those arms—each evaluating a specific treatment for a specific mutation—remained a challenge.

"We have worked with academic as well as commercial labs so that if they find these mutations they can refer patients to the NCI-MATCH," she said, explaining that if a physician orders sequencing for a patient through a lab participating in the trial and the lab finds an actionable mutation being studied in one of the trial's arms, the lab notifies the physician that the patient is eligible for participation.

It's an approach, like that of the ongoing NCI- and SWOG-sponsored 800-site Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART)[5] trial, that has successfully brought treatment for rare tumors practically to patients' doorsteps.

The rapidity with which the data come into the system is accelerating and will continue to drive progress, not just in selecting the right therapies, but in helping drugmakers develop effective new ones based on their enhanced understanding of tumor biology, Dr. Kurzrock said.

Treatment advances and technology

As she described the progress that has been made thus far, Dr. Kurzrock highlighted three particular advances related to genomics and personalized therapy.

"Probably the first big success was [with] chronic myelogenous leukemia (CML)," she said.

The discovery of the role of the BCR-ABL chimeric oncogene and tyrosine kinase in CML pathogenesis led to effective treatment with the first-generation tyrosine kinase inhibitor (TKI) imatinib[6]– and to a disease-free survival rate that is currently in the 20-year range. Before that, most patients died within 4 years of diagnosis, which occurs at a mean age of 63 years, she said.

"Today, the drugs that specifically target [BCR-ABL] work so well that there's probably a normal life expectancy," she added.

The enormity of such advances was underscored recently when two of her fellows—young physicians who never experienced the CML carnage before the days of imatinib (Gleevec)—told her that "CML isn't really a cancer, because it's so easy to treat."

More recent breakthroughs involve neurotrophic receptor tyrosine kinase (NTRK) gene fusions and immunotherapy, she said.

NTRK gene fusions are a molecular abnormality found in 0.3% of patients with varying cancer histologies, and based on data[7] showing marked and durable antitumor activity in NTRK fusion-positive cancers, the Food and Drug Administration in 2018 granted accelerated approval[8] of the highly selective TRK inhibitor larotrectinib for the treatment of certain solid tumors.

"[NTRK gene fusions] can be found in any disease, and the approval was across diseases; it didn't matter if the disease came from the lung or the breast or the colon—it just mattered that you had this abnormality," Dr. Kurzrock said, noting that investigator-assessed response rates with larotrectinib (Vitrakvi) were about 80% and durable, which in cancer is "really phenomenal."

"This is another example of how you have to individualize; you have something that is very uncommon, but you have to recognize it because the other treatments for these patients don't work, and this works extremely well," she explained.

Of note, the tissue-agnostic larotrectinib approval marks the FDA's second such approval; the first was the 2017 accelerated approval[9] of the immune checkpoint inhibitor pembrolizumab for certain microsatellite instability–high (MSI-H) solid tumors.

MSI-H, an immune biomarker often associated with DNA mismatch repair gene deficiency and a high mutational burden because of a "broken DNA repair gene," affects about 2%-3% of tumors.

"That was a disaster for patients before immunotherapy came along," Dr. Kurzrock said. "But with immunotherapy, about 50% of them will have really beautiful responses."

She described a patient who presented to the Rare Tumor Clinic in 2015 with a basal cell carcinoma—not a rare tumor in itself, but the tumor had metastasized, which is uncommon and presages an aggressive and potentially lethal course.

The patient had brain and liver metastases, and neither chemotherapy nor the two drugs approved for such tumors —vismodegib (Erivedge) and sonidegib (Odomzo), selective antagonists of the hedgehog pathway that is often altered in these patients—had been effective.

"He came to us and we did genomics on him, and what we found sort of answered why he hadn't responded to these single drugs that target a pathway that's activated: He had a very high mutational burden," she said, explaining that emerging data at the time suggested immunotherapy might be helpful in cases involving such "messed up, chaotic tumors."

"We gave this patient [the checkpoint inhibitor] nivolumab [Opdivo], and long story short, it's 4 years later and he's still in complete remission and doing great."

The excitement regarding immunotherapy relates to these dramatic responses in the "small but real subset" of patients

who go from being near death to having no evidence of disease, she said adding: "As an oncologist I'm hesitant to use the word cured, but they sure look cured. We have really never seen that before."

The DART trial is further evaluating combined immunotherapy with the anti-CTLA-4 agent ipilimumab (Yervoy) and the anti-PD-1 agent nivolumab in patients with any of 40 different rare tumors to assess which subgroups respond, she noted.

"We're doing genomics on these patients—we're doing blood genomics, we're doing immune markers," she said. "This is going to be a huge resource for understanding the biology of these tumors."

However, there's still much to learn.

"We don't know exactly which drugs are best for which alterations," she said, noting that the evidence levels vary widely. "Sometimes it's just guessing based on what signaling pathways are activated."

Enhanced computer power and the increasing ability to catalog real-world data should help change that, she said, noting that until very recently, the mere idea that such advances would occur—let alone at lightning speed—was "almost unimaginable."

The Rare Tumor Clinic

At the UCSD Rare Tumor Clinic that Dr. Kurzrock helped launch in 2017, clinicians work in conjunction with the Center for Personalized Cancer Therapy[10] there to harness—and build on—those advances to provide comprehensive care for patients with rare tumor types. They emphasize genomically targeted treatments and immunotherapy.

"With the new way that we're doing things with precision medicine and genomic typing, [the clinic] really gives us a way to bring these tumors to the forefront, do genomics on them and treat them based on their genomic anomalies, " Dr. Kurzrock said.

"We've probably seen about 100 different types of rare tumors," she said.

Among them are certain types of sarcomas, thymomas, and diseases like ameloblastoma—an ultrarare tumor type.

"I've seen it twice now in the Rare Tumor Clinic; I hadn't even heard of it before," she said of the disorder involving the jaw and surrounding structures.

Clinic patients undergo genomic testing and immune marker analyses to determine "what is driving the tumor," and a multispecialty molecular tumor board of experts uses the best available evidence—be it anecdotal experience, trial data, or preclinical findings—to develop a treatment plan.

"Usually that involves a customized combination of therapies," Dr. Kurzrock said.

The testing itself is performed by one of a number of companies or universities "that do very-high-quality clinical-grade sequencing."

"We allow our physicians to choose the sequencing ... based on what they feel is best for the patients, with the caveat that it has to be CLIA approved, it has to be clinical grade, and it has to be approved through California as well."

They may want blood sequencing—which is "something that might have been just about unimaginable about 6 or 7 years ago," or germline sequencing, or immune marker detection, so companies are selected based on their "menu of offerings."

The point is to recognize that every tumor is different and that it's important to understand the individual patient.

"I don't actually care about what another hundred patients have—I care about what is wrong in the tumor of that patient sitting in front of me," she said. "I don't need to have a study that tells me that this rare tumor that this patient has responded to this or that; I now have the tools—that's what the biomarkers are—to understand what is wrong with that tumor."

Outcomes related to the clinic's approach are encouraging

In a paper[11] published in April in Nature Medicine, Dr. Kurzrock and colleagues reported results from the cross-institutional I-PREDICT study, which showed that individualized combination therapy regimens based on tumor DNA sequencing was feasible, with 49% of consented subjects receiving treatment.

Targeting of a larger proportion of identified molecular alterations correlated with significantly improved disease control rates and longer PFS and OS, compared with the targeting of fewer somatic alterations. This suggests that the current clinical trial paradigm for precision oncology—pairing one driver mutation with one drug—could be optimized by treating molecularly complex and heterogeneous cancers with customized treatment combinations, they concluded.

In 2018, she and her colleagues reported[12] on the preliminary experience with the clinic's first 40 patients, more than half of whom attained either complete response, partial response, or stable disease for at least 6 months after receiving genomically driven matched therapy. Those findings also underscored the feasibility of performing genomics and protein analyses in patients with rare cancers.

To date, more than 300 patients have been seen in the clinic.

"We have extensive biomarker testing, genomic testing on all of these patients and I think [these are] very valuable data," Dr. Kurzrock said, noting that she is preparing a follow-up report of those initial 40 patients

"It's a small number of patients, but from seeing these patients, we're observing what I think are some very gratifying

responses," she said. "I'm optimistic about what the data will look like, but we'll have to wait until we do the analysis."

NCI-MATCH

If the findings reported to date from NCI-MATCH are any indication, that optimism is warranted.

The trial, which is codirected by NCI and the ECOG-ACRIN Cancer Research Group,[13] is one of few large-scale studies currently using genomic testing to match patients with therapies, and enrollment of patients with uncommon histologies—tumors other than those of the breast, colon, prostate, or lung—surpassed expectations, Dr. Chen, the NCI study chair said.

Other ongoing trials are already looking at genomic testing and treatment options for those "common" tumors, so it was important to begin to look at more rare tumor types, she explained.

"We are very happy that over 60% of [participants] are patients who fall outside of those four particular histologies," she said, noting the paucity of data regarding genomic testing for rare tumor types like sarcomas and cholangiocarcinomas, and the lack of trials looking specifically at rare tumor types—and more specifically at mutations among those tumor types. "This gives us an opportunity to look at those patients, to be able to collect some information in a broad fashion to ... see if there are any specific mutations of interest."

And it provides patients with an opportunity to receive treatment in their own communities with drugs they may not have been able to access otherwise, she said.

The intent of the NCI-MATCH trial at its launch in 2015 was to chart the genomic landscape of patients with either solid tumors, lymphoma, or myeloma, most of whom were previously treated, and to identify actionable mutations to target with specific drugs, she said, explaining that while the intent evolved over time with the emergence of new data and treatment strategies—involving immunotherapy, for example, the goal of using the network of NCI investigators to provide widespread access to patients across the United States has been achieved.

An initial plan to enroll 3,000 patients expanded to 6,000 as genomic testing became "kind of a common practice" in the wake of Medicare's decision to start paying for it, she said.

Participants are screened by biopsy and an NCI assay developed for the trial, and those with actionable mutations for which there is a treatment arm are assigned accordingly.

Of 11 trial arms with outcomes data available and reported at various conferences to date, 3 arms have had positive results, but NCI-MATCH is a "signal-finding" trial, so even when findings are negative because they don't show the anticipated response, any signal is exciting and highlights areas for further study, Dr. Chen said.

The latest findings from the study came from Arm H looking at combination treatment with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib for tumors with certain BRAF gene mutations.

Three of four patients with cholangiocarcinoma harboring the BRAF gene variant V600E experienced a confirmed partial response. The fourth patient with the rare bile duct cancer experienced a significant reduction in target lesions.

Additionally, five of six patients with gynecologic tumors—including five with rare low-grade papillary serous adenocarcinoma of the ovary—also had a partial response, and the sixth had stable disease.

The findings, along with those for 23 other heavily pretreated patients with distinct tumor types harboring the same BRAF mutation, were reported[14] in June at the annual meeting of the American Society of Clinical Oncology.

Arm H met its primary endpoint of partial response in 11 patients for an overall objective response rate of 33.3%, April K.S. Salama, MD, of Duke University, Durham, N.C., said at that meeting.

Median progression-free survival was 11.4 months, median overall survival was 28.8 months, and median duration of response was 12 months, but varied histologies—including histiocytic sarcoma, cholangiocarcinoma, mixed adenoneuroendocrine carcinoma of unknown primary, and others—had longer duration of response, Dr. Salama noted.

Challenges and future direction

"There are initial hints that this is a great way to treat cancer," Dr. Chen said. "We're now trying in this large study to validate that you can look for specific mutations, that there are treatments specific to those mutations, and that histology may not be important.

"What we're really trying to address is if we can be tissue agnostic," she explained, adding that further success toward that goal requires effective communication and data sharing to promote knowledge and understanding of actionable mutations.

More effective communication, relevant data sharing, and continued progress require that physicians become better versed in precision medicine, which requires better medical school training on the topic and a concerted effort on the part of practicing physicians to get up to speed on this "complicated field that is moving extremely quickly," Dr. Kurzrock said.

"New physicians need to be native speakers, and older doctors will have to adopt it as a new language," she added.

REFERENCES

1. Cancer Services: Rare Tumor Clinic. UC San Diego Health. https://health.ucsd.edu/specialties/cancer/programs/personalized-therapy/Pages/rare-tumor.aspx. Accessed October 15, 2019.

2. NCI-MATCH Trial (Molecular Analysis for Therapy Choice). National Cancer Institute. https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match. Updated September 5, 2019. Accessed October 15, 2019.
3. The cost of sequencing a human genome. National Human Genome Research Institute. https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost Updated July 10, 2019. Accessed October 15, 2019.
4. Decision memo for next-generation sequencing (NGS) for Medicare beneficiaries with advanced cancer (CAG-00450N). Centers for Medicare & Medicaid Services. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx. Updated March 16, 2019. Accessed October 15, 2019.
5. DART trial: Dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors. SWOG Cancer Research Network. https://www.swog.org/clinical-trials/s1609. Accessed October 15, 2019.
6. Targeted therapies for chronic myeloid leukemia. American Cancer Society. https://www.cancer.org/cancer/chronic-myeloid-leukemia/treating/targeted-therapies.html. Updated June 19, 2018. Accessed October 15, 2019.
7. Rosen EY, Schram AM, Young RJ, et al. Larotrectinib demonstrates CNS efficacy in TRK fusion-positive solid tumors. *JCO Precis Oncol*. 2019;3:1-5.
8. FDA approves larotrectinib for solid tumors with NTRK gene fusions. US Food and Drug Administration. December 14, 2018. https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0. Accessed October 15, 2019.
9. FDA approves first cancer treatment for any solid tumor with a specific genetic feature. US Food and Drug Administration. March 23, 2017. https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature. Accessed October 15, 2019.
10. Center for Personalized Cancer Therapy. UC San Diego Health. https://health.ucsd.edu/specialties/cancer/programs/personalized-therapy/Pages/default.aspx. Accessed October 15, 2019.
11. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combina-tion therapy: the I-PREDICT study. *Nat Med*. 2019;25(5):744-750.
12. Kato S, Kurasaki K, Ikeda S, Kurzrock R. Rare Tumor Clinic: The University of California San Diego Moores Cancer Center experience with a precision therapy approach. *Oncologist*. 2018;23(2):171-178.
13. NCI-MATCH/EAY131. ECOG-ACRIN Cancer Research Group. https://ecog-acrin.org/trials/nci-match-eay131. Accessed October 15, 2019.
14. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and trametinib in patients with tumors with BRAFV600E/K mutations: Results from the molecular analysis for therapy choice (MATCH) Arm H. *J Clin Oncol*. 2019;37:15(suppl):3002.

Angiosarcoma Project brings data on rare cancer to light

By Neil Osterweil

At the age of 36, Corrie Painter, a mother of 2 young children, was about to graduate with a PhD in biochemistry from the University of Massachusetts Medical School in Worcester, Mass., when she discovered a lump in her breast.

It took several months, 11 core needle biopsies, and a lumpectomy to nail down the diagnosis: not breast cancer, but angiosarcoma, a malignancy of the epithelial lining of blood and lymphatic vessels. Only 300 or so cases of angiosarcoma are diagnosed in the United States annually.

"When they did identify what it was, they couldn't tell if it was localized or metastatic, and they didn't think I would be alive for much longer than about 6 months. My kids were 2 and 4 at that time, and it was really quite devastating, as you can imagine," she said in an interview.

As with many other rare forms of cancer, there were precious few data about how to treat it, and no standard of care.

"I was prepared to die and was getting my affairs in order, but then I didn't die," she said.

Instead, Dr. Painter went on to earn her doctorate, cofounded an angiosarcoma support group, got a position in a cancer immunology lab, and today, 9 years after her diagnosis, she is the associate director of operations and scientific outreach in the cancer program at the Broad Institute of the Massachusetts Institute of Technology and Harvard University in Cambridge, Mass.

And fittingly, given her scientific training and medical history, she is also the leader of the Angiosarcoma Project,[1] a nationwide, patient-researcher partnership in which current angiosarcoma patients and survivors, their loved ones, physicians, pathologists, and other clinicians collaborate to map the genomic landscape of the disease and create a public resource for researchers, clinicians, and others.

Free public database


Corrie Painter, PhD

The Angiosarcoma Project is part of the Count Me In program,[2] a partnership between Emerson Collective, a California-based social change organization; the Broad Institute of MIT and Harvard; the Biden Cancer Initiative, an independent nonprofit organization that builds on the federal government's Cancer Moonshot; and the Dana-Farber Cancer Institute.

At the American Society of Clinical Oncology (ASCO) 2019 annual meeting, Dr. Painter gave a presentation about the Count Me In initiative and the rationale underpinning it.

"We wanted to ask, what if we could generate a massive, publicly available database of clinical, genomic, molecular, and patient-reported data in cancer, to enable researchers to find patterns in the data and help accelerate discoveries in the development of novel treatment strategies?" she said.

"Another way to put this is we wanted to combine information that we could find from the genomics of the tumor with information that a patient could tell us, with real-world information that was gleaned from their medical records, aggregate that data, and make it freely available for everybody, so people could just dip in and take what they wanted from it, without having to build out that infrastructure or spend money on building up their own cohorts, and also without having to silo it off," she added.

Each Count Me In project involves direct communication with patients through support groups, social media, and clinical contacts. The patients are asked if they would volunteer to share their medical information, tumor samples, and experiences with researchers.

For those patients who grant permission, project staff contact physicians and hospitals to obtain copies of medical records and a portion of stored tumor samples. The patients also receive a saliva kit that will be sequenced and used as a comparison of the DNA germline with tumor DNA. The contributed tumor samples undergo whole exome sequencing, and the results, as noted before, are published[3] online without restrictions (apart from removal of any potentially identifying data).

Since the Angiosarcoma Project was launched in March 2017, as many as 418 women and men with angiosarcoma have joined, and more than 125 others have submitted information on behalf of a loved one who died from angiosarcoma.

"We had a large initial spike because patients knew this was coming [through social media]. And so in the first couple of days after launch, we had 63 people sign up for the project. But we have this consistent trailing line of about 6-10 new patients that sign up every month. And for a cancer that gets about 300 people per year, this is a really remarkable number of people" that have signed up, she said at ASCO 2019.

Molecular data, clinical insights

Although angiosarcomas can arise or metastasize virtually anywhere in the body, approximately 60% occur in elderly white people above the clavicle. These tumors are often grouped as lesions of the head, face, neck, or scalp (HFNS).

To further explore this, the project's computational biologist ran a signature analysis of tumor DNA from patients across the entire cohort. The analysis found a distinct UVA signature in the DNA of patients with HFNS lesions, suggesting that the cancer could be triggered by sun exposure. The same patients also had high tumor mutational burden, which has been established as a marker for response to immune checkpoint inhibitor therapy.

"So we went through our cohort and identified patients who had been put on compassionate care with checkpoint inhibitors and found a couple of patients who had metastatic head, face, neck, and scalp angiosarcoma who went into complete and durable remissions after being put on checkpoint inhibitors, and that response has endured to this day, even though they were both brought off the therapy [for toxicities] back in 2016," Dr. Painter said.

In addition to the HFNS findings, the data point to noncanonical mutations in PIK3CA, the gene encoding for the phosphatidylinositol 3-kinase (PI3K), all of which were mapped to patients with breast angiosarcoma.

Looking at the structure of the mutations, Dr. Painter saw evidence suggesting that the mutation may affect the adherence of p53 (a tumor suppressor gene commonly mutated in many cancers) to the cellular membrane.

"It's pretty interesting that you can see site-specific alterations that are targetable because these are also predicted to be actionable—I mean, activated—mutations," she told her ASCO audience.

A friendly reminder

Dr. Painter emphasized that, in addition to patients, advocates, and loved ones, clinicians can play an important role in recruiting patients to the Angiosarcoma Project and other Count Me In initiatives. In particular, she likes to quote this tweet from George Demetri, MD, director of the Sarcoma Center at Dana-Farber: "Tell your friends, friends' friends, and friends of friend's friends. Friends don't let friends' angiosarcoma go unstudied for progress."

REFERENCES

1. Angiosarcoma Project. https://ascproject.org/. Accessed October 15, 2019.
2. Count Me In. https://joincountmein.org/. Accessed October 15, 2019.
3. The Angiosarcoma Project – Count Me In (Provisional, September 2018). cBioPortal for Cancer Genomics. http://www.cbioportal.org/study/summary?id=angs_project_painter_2018#summary. Accessed October 15, 2019.

Immunotherapy emerges as important tool in rare tumor arsenal

By Sharon Worcester

Immunotherapy is taking aim at rare tumors, and genomics is bringing those tumors into sharper focus in the crosshairs.

Consider, for example, the pancreatic cancer patient in her late 40s who presented at the Moores Cancer Center at the University of California, San Diego (UCSD) and was found to have a PBRM1 gene alteration.

Pancreatic cancer is known to be unresponsive to immunotherapy with checkpoint inhibitors, but for reasons that aren't yet entirely clear, PBRM1 inactivating mutations have been shown in certain types of kidney cancer to be associated with response to immunotherapy, prompting interest in whether the same might be true in other tumor types, according to Razelle Kurzrock, MD, director of the Center for Personalized Cancer Therapy at Moores Cancer Center and chief of the Division of Hematology-Oncology in the Department of Medicine at UCSD.

A study[1] presented in 2018 at the annual meeting of the American Society of Clinical Oncology, for example, found that while the overall rate of PRBM1 alterations in more than 3,600 tumors was 2.6%, the rate in clear cell renal cell carcinomas was 45%. Certain other tumors, including rare tumors like cholangiocarcinomas and chordomas, also harbored PBRM1 alterations at higher rates (12% and 11%, respectively vs. less than 3% among highly prevalent tumors like melanomas and cancers of the lung, breast, colon, and prostate).

"So, we treated [the pancreatic cancer patient] with immunotherapy," said Dr. Kurzrock,[2] who also co-founded and directs the Rare Tumor Clinic at UCSD.[3] "Her home doctor said, 'why are you doing this—immunotherapy doesn't work in pancreatic cancer, and I said, 'yeah, I know, but this patient has an unusual alteration and we want to treat everybody as individuals.'

"I want to be cautious, but she's about 9 months in and close to complete remission. We'll see if this lasts; I hope it does—she feels great."


Razelle Kurzrock, MD

The idea of using genomics in this setting is to look at individual markers that help determine, patient-by-patient, the likelihood of response to immunotherapy, Dr. Kurzrock explained, noting that studies looking at the significance of PBRM1 alterations in cancer other than kidney cancer are underway.

"Again, the question is: 'Are you more likely to respond to immunotherapy if you have this abnormality?'" she said. "While we're not quite ready to publish our impression, it's definitely yes."

The DART trial

The deeper dive into genomics-driven immunotherapy is an extension of more general efforts to look at immunotherapy in rare tumors. The ongoing SWOG-managed Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors (DART) trial,[4] for example, is looking at combined immune checkpoint inhibition with the anti-CTLA-4 agent ipilimumab, and the anti-programmed death-1 (PD-1) agent nivolumab in 37 cohorts of patients, each with a different rare tumor type.

That treatment combination is approved and has been successful for the treatment of melanoma, explained Dr. Kurzrock, who is chair of the SWOG Early Therapeutics and Rare Cancers Committee, and a DART senior study chair.

The National Cancer Institute (NCI)-sponsored, 800-site phase 2 basket trial "draws on the design and takes advantage

The DART study is funded by the National Institutes of Health through National Cancer Institute grant awards and in part by Bristol-Myers Squibb.

Dr. Patel reported receiving grants from Bristol-Myers Squibb and personal fees from Bristol-Myers Squibb during the conduct of the study, as well as grants from Eli Lilly, Incyte, AstraZeneca/MedImmune, Merck, Pfizer, Roche/Genentech, Xcovery, Fate Therapeutics, Genocea, and Iovance; and personal fees from AstraZeneca, Illumina, Tempus, and Novartis.

of the scale of another landmark trial offered through the NCI's National Clinical Trials Network–the NCI-Molecular Analysis for Therapy Choice, or NCI-MATCH,[5] a precision medicine trial open at more than 1,000 clinical sites," according to SWOG.

NCI-MATCH, which is co-led by the ECOG-ACRIN Cancer Study Group,[6] also uses genomic testing to match patients with any solid tumor, as well as patients with lymphoma and myeloma, to targeted treatments and immunotherapy. Patients with rare tumors—defined for the DART trial as disease with an incidence of less than 6 in 100,000 per year—who are registered to NCI-MATCH and either don't respond to NCI-MATCH therapy or have no treatment option available, are eligible for DART trial enrollment.

"As immunotherapy was coming on board, we felt there was a particular role that organizations like SWOG could play that is a little different than an academic center like UCSD," Dr. Kurzrock said. "Even though there were a lot of immunotherapy trials in the country, the vast majority didn't allow rare cancers, so patients who really wanted to get on trials—who wanted trial access—for many, if not most, there wasn't even a clinical trial available."

SWOG was a perfect organization to open an immunotherapy trial using ipilimumab and nivolumab, she said, noting that one of the things she likes most about the trial is the access it gives patients who wouldn't otherwise get appropriate treatment.

Patients don't have to travel and leave their families and incur the expenses associated with that, "which is huge," she said.

The rapid accrual—more than 500 patients in the first 18 months—underscored the need for such access among patients with rare tumors, and the first results reported from the trial underscore the potential of immunotherapy for rare tumors.

DART: Neuroendocrine tumor findings

In a DART trial arm looking exclusively at neuroendocrine tumors, the ipilimumab and nivolumab combination therapy was well tolerated in 32 patients, and demonstrated particular efficacy in high-grade tumors, DART principal investigator Sandip Praven Patel, MD,[7] reported in April at the annual meeting of American Association for Cancer Research.[8]

In patients with high-grade tumors, which tend to be aggressive, the response rate was 44%, whereas those with low- or intermediate-grade tumors had a 0% response rate, but a suggestion of improved 6-month progression-free survival and median overall survival in the entire study arm requires further evaluation, said Dr. Patel, a medical oncologist at the UCSD Moores Cancer Center.

Dr. Patel said the findings, which may be related to a higher tumor mutational burden in high-grade tumors, are exciting for this patient population given that current treatment options are generally limited to aggressive chemotherapy regimens.

The most common tumor sites among patients in the neuroendocrine tumor arm were non-pancreatic gastrointestinal (about 50%) and lung (about 20%), but also included pulmonary and gynecologic primary sites. The effects of treatment did not appear to differ based on primary site, Dr. Patel said, noting that pancreatic neuroendocrine tumors are being studied in a separate DART trial arm that is currently accruing patients.

An effort is underway to verify the results specifically in a new cohort of patients with high-grade neuroendocrine tumors, he said.

The initial results have been submitted for publication.

"DART has already yielded results that may impact the standard of care, once we publish [these results] in paper form," Dr. Kurzrock said, adding that analyses of other cohorts are also underway.

"We've treated a lot of patients and there are going to be other interesting results, but I can't go beyond that at this time," she said.

NCI-MATCH

Results are also emerging from NCI-MATCH.

"As of ASCO 2019, we have presented results for 11 subprotocols," Keith Flaherty, MD,[9] the ECOG-ACRIN study chair for the overall NCI-MATCH trial, said in an interview. "Not surprisingly, the arms for which we have presented data are those that were seeking the most prevalent biomarker-defined populations; those arms accrued most quickly."

Additional arms for which the prevalence rates are lower remain open for patient enrollment, said Dr. Flaherty, a professor of medicine at Harvard Medical School, and director of clinical research and the Henri and Belinda Termeer Center for Targeted Therapy at the Cancer Center, Massachusetts General Hospital, Boston.


Keith Flaherty, MD

"We are excited about the prospect of these upcoming arms to shed new light on responsive tumor types, as there is far less data available in such populations from previously conducted trials," he said.

NCI-MATCH was launched in 2015, and a priority for the 39-arm precision medicine trial, which is now open at more than 1,000 sites, was to enroll patients with rare tumors.

"Dedicated clinical trials in such populations are rarely done and we reasoned that a particularly important role that the trial could play in the development of therapies under study was

to understand their therapeutic potential in rare tumor populations," Dr. Flaherty said, noting that the plan for at least 25% of the first 6,000 screened participants to have rare tumors—tumor types other than breast, colorectal, non-small lung or prostate—was easily surpassed.

The initial design of NCI-MATCH focused on targeted therapies "simply because there was so much more available data at the time regarding the ability to use next generation sequencing (NGS) to identify patients for these molecularly targeted drugs," but the trial design evolved over time as new data emerged, such as findings regarding molecular markers predictive of immune checkpoint antibody response; new trial arms were added accordingly.

An example includes findings regarding the efficacy of nivolumab in patients with microsatellite instability high (MSI-H) cancers; NCI-MATCH now has an arm looking specifically at nivolumab in patients with MSI-high tumors.

"We have seen responses across a broad range of tumor types, including ones in which responses have not been previously described for a given molecular feature paired with a MATCH agent," Dr. Flaherty said, noting that "follow-on studies are ongoing outside of NCI-MATCH to further pursue these signals."

Immunotherapy-related outcomes reported to date from NCI-MATCH include preliminary findings from trial arm Z1D showing a confirmed overall response rate of 24% in the first 35 patients treated with nivolumab for mismatch repair-deficient noncolorectal cancers, which have a frequency of about 1.5%.

An additional 27% of patients had stable disease, Nilofer Azad, MD, of Johns Hopkins University, Baltimore, reported at the 2017 meeting of the Society of Immunotherapy for Cancer.[10]

A manuscript on thse findings is pending.

Another trial arm currently in development (Z1M) will look at combination nivolumab and relatlimab in mismatch repair-deficient tumors with LAG-3 expression, which also have a frequency of about 1.5%.

"The challenge we now face is completing accrual to as many MATCH arms as possible," Dr. Flaherty said. "Many of the arms for which we are still seeking patients are ones for which the molecular feature is known to be very rare; even with the large lab network collaborating with us, it is still taking a long time to find these patients."

Still, the approach used in NCI-MATCH and the DART trial holds promise for meeting the needs of patients across the country with rare tumors, including in community settings, he noted.

"Dedicated clinical trials are rarely launched for patients with rare tumors, and the feasibility of conducting such trials with individual therapeutic regimens per trial is further limited if a molecular feature is required for inclusion," he explained, noting that "running multiple such treatment arms in parallel as we did in NCI-MATCH is vastly more efficient."

"At the practice level, this means that a single trial can provide a vastly higher likelihood of finding eligible patients than any one trial."

Alice Chen, MD,[11] a medical oncologist at the NCI, head of the NCI's Early Clinical Trials Development Program, and NCI study chair for the overall NCI-MATCH trial, further noted that genomic testing and immunotherapy are important tools for the treatment of tumors, including rare tumors.

"Do I think that this will ultimately be the way to cure cancer? I'm probably not ready to go that far," she said. "Immunotherapy is another weapon in the search for a cure, but ultimately it's going to take using a lot of different tools; treatment for cancer has become much more sophisticated over time, but I'm not sure one thing is going to take care of it all."

REFERENCES

1. PBRM1 mutation and immunotherapy efficacy: A comprehensive genomic profiling (CGP) assessment. *J Clin Onc*. 2018;36(suppl 15):12091.
2. Razelle Kurzrock, MD. UC San Diego Health. https://providers.ucsd.edu/Details/22465. Accessed October 15, 2019.
3. Cancer Services: Rare Tumor Clinic. UC San Diego Health. https://health.ucsd.edu/specialties/cancer/programs/personalized-therapy/Pages/rare-tumor.aspx. Accessed October 15, 2019.
4. DART trial: Dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors. SWOG Cancer Research Network. https://www.swog.org/clinical-trials/s1609. Accessed October 15, 2019.
5. NCI-MATCH Trial (Molecular Analysis for Therapy Choice). National Cancer Institute. https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match. Updated September 5, 2019. Accessed October 15, 2019.
6. NCI-MATCH/EAY131. ECOG-ACRIN Cancer Research Group. https://ecog-acrin.org/trials/nci-match-eay131. Accessed October 15, 2019.
7. Patel SP. https://providers.ucsd.edu/details/22420/sandip-patel-cancer-la_jolla. Accessed October 15, 2019.
8. Immune checkpoint inhibitor combination efficacious for patients with high-grade neuroendocrine carcinoma. American Association for Cancer Research. https://www.aacr.org/Newsroom/Pages/News-Release-Detail.aspx. March 31, 2019. Accessed October 15, 2019.
9. Keith T. Flaherty, MD. Dana-Farber/Harvard Cancer Center. https://www.dfhcc.harvard.edu/insider/member-detail/member/keith-t-flaherty-md/. Accessed October 15, 2019.
10. 32nd annual meeting and pre-conference programs of the Society for Immunotherapy of Cancer (SITC 2017): Late-breaking abstracts. *Journal for ImmunoTherapy of Cancer*. 2017;5(suppl 3).
11. AP Chen, MD. National Cancer Institute. https://ctep.cancer.gov/branches/idb/bios/chen_alice.htm. Updated January 6, 2014. Accessed October 15, 2019.

The promise and setback of gene therapy with CRISPR/Cas9 technology

By Nicholas Munafo and Ronald DeBellis, PharmD

With every advancement in technology comes the potential for setbacks. That's the case with CRISPR/Cas9 (the abbreviated name for clustered regularly interspaced short palindromic repeats and associated protein 9), a group of gene-editing technologies propelled to the front line of genetic engineering, where they are being considered as therapeutic tools to target diseases such as cancer, Huntington's disease, cystic fibrosis, human immunodeficiency virus infection, and hemoglobinopathies. Focus on CRISPR/Cas9 technology has been intense, with great hope and promise.

Yet, with the novel mechanisms of gene editing, it appears that the potential for side effects is raising concerns that have led to temporary scientific challenges in bringing this tool to clinical use. In this article, we describe how and why setbacks with CRISPR/Cas9 have occurred, what the potential solutions are to address those problems, and what the full potential of CRISPR/Cas9 might be to treat heritable disorders.

The promise of great utility

Gene therapy has been pursued aggressively since it first appeared in the early 2000s. Over the past 5 years, it has held out promise as a new avenue for treating (and potentially curing) complex genetic diseases. The potential of gene therapy is huge: Approximately 80% of rare diseases are genetically linked.[1] Through the impact of the Orphan Drug Act of 1983, a biological target-rich market has emerged for scientists, genomic engineers, and drug developers.[2]

Scientific advances in the understanding and treatment of rare diseases, cancer, and other areas of precision medicine have outpaced advances in health insurance, regulation, and education in this area.[3] Even more exciting are the potential therapeutic options for rare-disease patients, who are a minority in the US health care population. Gene editing using CRISPR/Cas9 has yielded promising results and risen to the top of many gene-therapy discussions, particularly of late.[4]

Most recently, the application of CRISPR/Cas9 to human embryonic stem cells, induced pluripotent stem cells, and non-transformed human retinal pigmented epithelial cells has been under fire after implications of tumor protein p53 (hereafter p53) suppression and the potential to induce malignancy.[4]

The problem of potential complications

After *Nature Medicine* published 2 articles in June 2018 on the tumor-seeding implications of editing the *TP53* gene that produces p53 using CRISPR/Cas9, the stock of 3 major gene therapy companies dropped significantly, causing a total loss of $300 million in share value. Another article published in July 2018 in *Nature Biotechnology* contributed to this loss by suggesting that CRISPR/Cas9 caused malignancy from lack of specificity and downstream gene alteration.[4]

Taken together, these 3 articles might have been the most pivotal news in gene therapy failure since 2003, when a study of gene therapy for X-linked severe combined immunodeficiency disorder was halted by French authorities when treated patients developed leukemia. This catastrophic adverse effect was thought to be a result of insertional mutagenesis, striking a blow against gene therapy.[5]

What do the findings of the *Nature Medicine* and *Nature Biotechnology* reports last year mean for gene editing? Can these researchers' observations be generalized to gene therapies across the board? To look further into this matter, we first need

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to delve into the process of CRISPR/Cas9 and how and where p53 comes into play in this technology.

How does CRISPR/Cas9 work?

CRISPR/Cas9 first identifies specific target nucleotide regions using a guide strand of RNA. Once a corresponding region is identified, CRISPR/Cas9 unwinds the DNA utilizing an enzyme helicase. Once the DNA is unwound, a nuclease-cutting enzyme (Cas9) induces a double-strand break (DSB) in the DNA at the target site.

The cell then repairs the DSB through 1 of 2 possible mechanisms: nonhomologous end joining (NHEJ) or homology-directed repair (HDR).

Nonhomologous end joining brings the 2 cleaved DNA strands together, re-ligating them without a template strand. This process is prone to error and often causes insertion/deletion mutations within DNA that disrupt target genes and induce what are known as reading-frame shifts.

Nonhomologous end joining can be utilized for gene "knock-out" or gene deletion. Gene knock-out occurs when the ligated DNA causes a frame shift and knocks out the targeted gene. Using gene knock-out therapeutically appears particularly promising in Huntington's disease, in which a mutation in the huntingtin gene gives rise to a toxic protein. Taking advantage of NHEJ, scientists attempt to knock out the mutant allele.

Gene deletion is achieved by utilizing two DSBs in the target DNA, which leads to genomic deletions of several megabases. In Duchenne muscular dystrophy, it is believed that gene deletion can correct the reading frame to a truncated version, rendering a partially functional protein.[6]

Homology-directed repair. In contrast to NHEJ repair, HDR uses DNA donor templates to repair the DSB. HDR can introduce site-specific gene changes by transferring donor DNA into the desired target cell, allowing for specific edits or changes in genes. Rather than just knocking out or deleting genes, HDR is capable of writing in the desired gene to repair the DNA break.[7]

The HDR process, which requires upwards of 800 base pairs on each end of the strand to refuse the strands, has been the target of many new gene-therapy advances. One roadblock, however, is that NHEJ is used preferentially by the cell to change or alter genes and does not require a large number of base pairs to splice the genetic material back together. This complicates gene editing because once the DSB is made, NHEJ brings the 2 strands together at the point of break. This occurs whether or not base pairs match and since it biologically preferred, it takes precedence.

Nonhomologous end joining often results in base pairs that fall off, which makes its effects unpredictable, even when they are on-target for a particular gene. To harness the specificity of HDR and improve efficacy, scientists are studying NHEJ inhibitors to determine whether they can increase HDR efficiency.[6]

The role of p53 Is key

The tumor-suppressor gene *TP53* encodes p53, which produces cell-cycle arrest and apoptosis in cells with damaged DNA. Cells that lack this gene are prone to mutation and unable to regulate damaged cells. (This function is the source of many cancers reported on by news media.[8])

Researchers have noted high levels of transient cell-cycle arrest and cellular toxicity with CRISPR/Cas9 and sought the mechanism of this problem. They hypothesized that when DSBs occur in DNA as a result of the action of CRISPR/Cas9, p53 recognizes DNA damage and initiates cell-cycle arrest. Increased specificity in genome editing comes from utilizing the HDR process. Thus, p53 suppression should increase the efficacy of genome editing, as the DSB would not induce cellular toxicity.

However, p53 suppression poses a potential problem, because the cell is now vulnerable to tumor-inducing mutations and chromosomal rearrangement. Just as scientists hypothesized, cells that survive the process are deficient in or completely missing p53.[9, 10] These findings could have positive and negative implications. We now know that to maximize the efficiency of HDR, p53 needs to be either temporarily or permanently suppressed. But suppressing p53 could potentiate subsequent mutagenesis.

In the July 2018 *Nature Biotechnology* paper, implications for downstream mutagenesis also raised concern. This study concluded that there were significant on- and off-target mutations occurring in the gene. Based on this activity, the authors urged that there be additional genomic analysis to identify normal cell lines before insertion in humans.[11] Results of the article could suggest similar poor outcomes like the one seen in the 2003 French trial discussed above.[5] Although there was a sufficient on-target effect, these changes to the genome were within the vicinity of oncogenes that became activated.

This raises a crucial question: Why did these same mutations go unnoticed with earlier forms of gene therapy, such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs)? All 3 processes require DSBs that activate p53 to respond to damage to the genome. A possible answer is that scientists simply were not looking for the specific adverse mutational changes in the genome. These adverse mutational changes were largely unforeseen from the beginning and never explored.[4]

Getting around issues with p53 and mutation

Despite recent concerns with CRISPR/Cas9 technology-based gene therapy, there are promising ways around the inefficient

repair from NHEJ and the potentially devastating effects of p53 suppression. An example: NHEJ suppression could lead to preferential repair via HDR. This technique would provide cells the opportunity to enable DNA repair more specifically with donor templates.[10]

More promising is base editing, which is being studied to target and change base pairs within a specific location on a gene, without causing DSBs. Utilizing cytidine deaminase base editors, researchers are looking at the possibility of changing single base pairs. This would catalyze the conversion of cytosine to uracil and create C-to-T point mutations.

Similarly, adenine deaminase-based DNA base editors—which do not occur in nature—are also in development. This process would allow converting A-G or A-T to GC. These processes are particularly appealing because they do not require DSBs and provide a way around p53 activation and the potential for cancer to surface.[12]

Following the June 2018 report of a "minor malfunction" in gene therapy, *Nature Medicine* published an article in October 2018 on base-editing applications in a mouse model. Scientists engineered a CRISPR/Cas9 cytidine deaminase base editor to correct phenylketonuria, a gene-linked inborn error of metabolism. Mice in the experiment had a loss of function in enzymes essential for hepatic metabolism. At the completion of the experiment, researchers found that enzyme function was fully restored in several mice. In addition, researchers looked at downstream effects of base editing and failed to note any significant DNA damage or cell proliferation. These results are positive and show the feasibility of in vivo application and the potential for near-future therapeutic development.[13]

Last, ADAR2-based RNA base editors are worth mentioning and have emerged as the most recent technology in base-pair editing. ADAR2, an adenosine deaminase enzyme, can be used to edit mRNA sequences. This method would be advantageous because it does not cause permanent changes to the genome.

These various approaches to base editing are revolutionary: They reduce or eliminate insertion/deletion mutations on- and off-target, and provide a means of efficiently editing the genome without suppressing p53 function. Base editing is in development infancy, but it is worth noting the positive direction in which gene editing is advancing.[12]

Don't throw in the towel!

CRISPR/Cas9 is particularly exciting because it has the ability to affect not just one disease, but a multitude of disorders. Tailoring therapy to individual genetic mutations provides personalized outcomes for patients who do not have many options in the rare-disease space.[1] While pharmaceutical companies seek expedited medical approval through the Orphan Drug Act, there are more than 7,000 rare diseases known and approximately 600 treatments for approximately 450 rare diseases.[3]

As with any therapy, risk and reward need to be considered. Gene editing is being looked at only for severe and life-threatening diseases; for many patients and clinicians, gene editing is a last resort. Therefore, looking at the risk of mutagenesis weighs differently in the decision-making of people who do not have other options.

Researchers are continually advancing gene therapy. Eventually and inevitably, a temporary roadblock emerges: Stay tuned for instructions about a detour!

REFERENCES

1. National Organization for Rare Disorders (NORD). Danbury, CT: NORD. Data on file.
2. Electronic Code of Federal Regulations (e-CFR). Orphan drugs. Washington, DC: US Government Publishing Office; December 20, 2018. www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=0e737d105ef9a1632b19a1e713b93cc4&mc=true&n=pt21.5.316&r=PART&ty=HTML. Accessed January 12, 2019.
3. Aitken M, Kleinrock M. Orphan drugs in the United States: providing context for use and cost. Parsippany, NJ: Quintiles/IMS Institute; October 2017. www.iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states.pdf?&_=1547428106461. Accessed January 12, 2019.
4. Begley S. CRISPR causes significantly greater DNA damage than previously thought, study finds. PBS News Hour. www.pbs.org/newshour/health/crispr-causes-significantly-greater-dna-damage-than-previously-thought-study-finds. July 18, 2018. Accessed January 12, 2019.
5. Hacein-Bey-Abina S, von Kalle CV, Schmidt M, et al. A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. *N Engl J Med*. 2003;348(3):255-256.
6. Savić N, Schwank G. Advances in therapeutic CRISPR/Cas9 genome editing. *Transl Res*. 2016;168:15-21.
7. Maeder ML, Gersbach CA. Genome-editing technologies for gene and cell therapy. *Mol Ther*. 2016;24(3):430-446.
8. Brady CA, Attardi LD. p53 at a glance. *J Cell Sci*. 2010;123:2527-2532.
9. Haapaniemi E, Botla S, Persson J, Schmierer B, Taipale J. CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response. *Nat Med*. 2018;24(7):927-930.
10. Ihry RJ, Worringer KA, Salick MR, et al. p53 inhibits CRISPR–Cas9 engineering in human pluripotent stem cells. *Nat Med*. 2018;24(7):939-946.
11. Kosicki M, Tomberg K, Bradley A. Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements. *Nat Biotechnol*. 2018;36(8):765-771.
12. Eid A, Alshareef S, Mahfouz MM. CRISPR base editors: genome editing without double-stranded breaks. *Biochem J*. 2018;475(11):1955-1964.
13. Villiger L, Grisch-Chan HM, Lindsay H, et al. Treatment of a metabolic liver disease by in vivo genome base editing in adult mice. *Nat Med*. 2018;24(10):1519-1525.

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Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Major hemorrhage (≥Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA® in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. In IMBRUVICA® clinical trials, 3.1% of patients taking IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

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Monitor and evaluate patients for fever and infections and treat appropriately.

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Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

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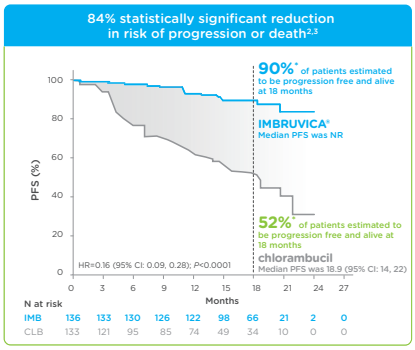
RESONATE™-2: A multicenter, randomized, open-label, phase 3 trial evaluating ibrutinib vs chlorambucil in treatment-naïve patients 65 yrs or older with CLL/SLL (patients with del 17p were excluded) (N=269).[3]

Primary analysis: Superior PFS by IRC assessment with IMBRUVICA® with a median follow-up of 18 months[1,3]



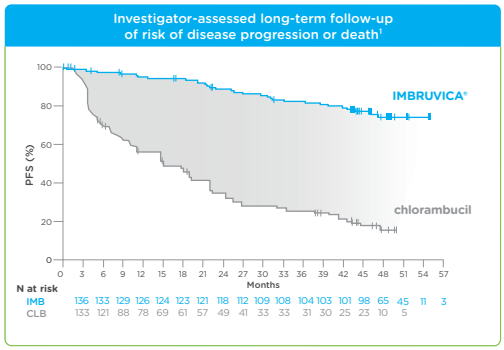
*Estimated PFS at 18 months.

Secondary endpoint: OS with IMBRUVICA® vs chlorambucil[1,3]

Based on a median follow-up of 28 months, IMBRUVICA® resulted in a 56% statistically significant reduction in the risk of death vs chlorambucil (HR=0.44 [95% CI: 0.21, 0.92])[2]

- The estimated survival rate at 24 months was 95% with IMBRUVICA® (95% CI: 89, 97) vs 84% with chlorambucil (95% CI: 77, 90)
- 41% of chlorambucil-treated patients crossed over to IMBRUVICA® upon disease progression

Long-term follow-up: Investigator-assessed median PFS was not reached with IMBRUVICA® with an overall follow-up of 55 months[1,2]



Median PFS was not reached with IMBRUVICA® with an overall follow-up of 55 months[1,2]:

- Median time on study was 48 months (0.1 - 55 months)
- 74% of patients estimated to be progression free and alive at 4 years in the IMBRUVICA® arm (95% CI: 65, 81)
- 16% of patients estimated to be progression free and alive at 4 years in the chlorambucil arm (95% CI: 9, 24)

Complete long-term follow-up results are not included in the Prescribing Information for IMBRUVICA®. The timing for long-term follow-up was not prespecified and the analysis was descriptive in nature.

Approved for use in combination with obinutuzumab for frontline treatment of adult patients with CLL/SLL based on the iLLUMINATE™ trial

CI=confidence interval, HR=hazard ratio, IRC=Independent Review Committee, NR=not reached, OS=overall survival, PFS=progression-free survival.

Hypertension: Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions.

Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%)*, diarrhea (41%), anemia (38%)*, neutropenia (35%)*, musculoskeletal pain (32%), rash (32%), bruising (31%), nausea (26%), fatigue (26%), hemorrhage (24%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (18%)*, thrombocytopenia (16%)*, and pneumonia (14%).

Approximately 7% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%)*, muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%)*, and pneumonia (21%).

The most common Grade 3 or higher adverse reactions (≥5%) reported in patients with cGVHD were pneumonia (14%), fatigue (12%), diarrhea (10%), neutropenia (10%)*, sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

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(ibrutinib)
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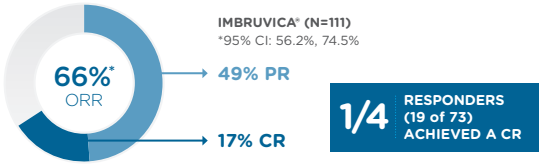
2L+ MCL

Phase 2, multicenter, open-label, single-arm trial in previously treated adult patients (N=111)[1]

Primary Endpoint: Overall Response Rate[1]



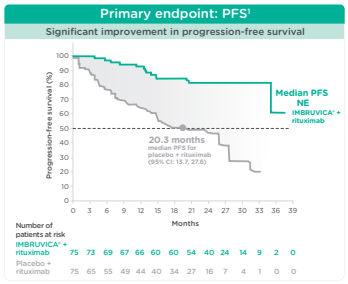
1/4 RESPONDERS (19 of 73) ACHIEVED A CR

IMBRUVICA® delivered responses in a population including heavily pretreated patients[1]

Responses were assessed by investigators according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma criteria.[1]

WM

Phase 3, randomized, double-blind, placebo-controlled trial of ibrutinib or placebo in combination with rituximab in treatment-naïve or previously treated adult patients (N=150)[1]



80%
statistically significant reduction in risk of progression or death with IMBRUVICA® + rituximab vs rituximab monotherapy[1] HR=0.20 (95% CI: 0.11, 0.38); *P*<0.0001†

82%
of patients estimated to be progression-free at 30 months with IMBRUVICA® + rituximab vs 28% with rituximab monotherapy[4]

- Median follow-up was 26.5 months[1]

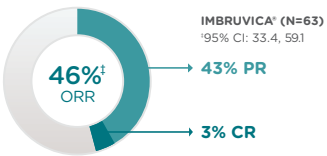
The responses were assessed by an IRC using criteria adopted from the International Workshop of Waldenström's Macroglobulinemia.

†*P* value is from log-rank test stratified by WM IPSS (low, medium, high) and a number of prior systemic treatment regimens (0, ≥1).

2L+ MZL

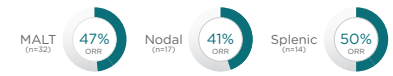
Phase 2, open-label, multicenter, single-arm trial in adult patients who received at least 1 prior anti-CD20-based therapy (N=63)[1]

Primary Endpoint: Overall Response Rate[1]



The median time to response was 4.5 months (range, 2.3 to 16.4 months)

RESPONSES ACROSS ALL 3 MZL SUB-TYPES[1]

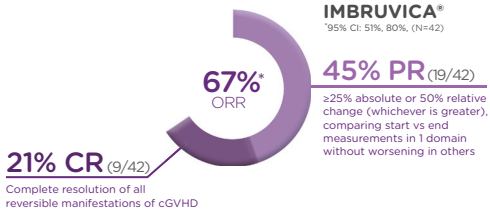


The responses were assessed by an IRC using criteria adopted from the International Working Group criteria for malignant lymphoma.[1]

2L+ cGVHD

Phase 1b/2, open-label, multicenter, single-arm trial in adult patients after failure of first-line corticosteroid therapy (N=42)[1]

Primary Endpoint: Overall Response Rate[1,5]



2 out of 3 patients achieved a PR (19/42) or CR (9/42)[1]

The responses were assessed by investigators using the 2005 National Institutes of Health (NIH) Consensus Panel Response Criteria with two modifications to align with the updated 2014 NIH Consensus Panel Response Criteria.[1]

CI=confidence interval, CR=complete response, HR=hazard ratio, IRC=Independent Review Committee, NE=not evaluable, PFS=progression-free survival, ORR=overall response rate, PR=partial response, WM IPSS=International Prognostic Scoring System for Waldenström's Macroglobulinemia.

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

*Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS

CYP3A Inhibitors: Modify IMBRUVICA® dose as described in USPI sections 2.4 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA® dose.

References: 1. IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC. **2.** Data on file. Pharmacyclics LLC. **3.** Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437. **4.** Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. *N Engl J Med*. 2018;378(25):2399-2410. **5.** Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. *Biol Blood Marrow Transplant*. 2006;12(3):252-266.

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10/19 PRC-05241a

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imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)
IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, for oral use

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial *[see Clinical Studies (14.1) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

Marginal Zone Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (14.4) in Full Prescribing Information].* Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Chronic Graft versus Host Disease: IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. In IMBRUVICA clinical trials, 3.1% of patients taking IMBRUVICA without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14) in Full Prescribing Information].*

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA in clinical trials *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. See Additional Important Adverse Reactions.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information].*

Hypertension: Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Cardiac Arrhythmias *[see Warnings and Precautions]*
- Hypertension *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	8†
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	5†
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

† Includes one event with a fatal outcome.

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Treatment-emergent Grade 4 thrombocytopenia (6%) and neutropenia (13%) occurred in patients.

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and four randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS, and iLLUMINATE) in patients with CLL/SLL (n=1,506 total and n=781 patients exposed to IMBRUVICA). Patients with creatinine clearance (CrCl) ≤ 30 mL/min, AST or ALT ≥ 2.5 x ULN (upper limit of normal), or total bilirubin ≥ 1.5x ULN (unless of non-hepatic origin) were excluded from these trials. Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 386 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 267 randomized patients with treatment naïve-CLL or SLL who were 65 years or older and received single agent IMBRUVICA or chlorambucil, HELIOS included 574 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab, and iLLUMINATE included 228 randomized patients with treatment naïve CLL who were 65 years or older or with coexisting medical conditions and received IMBRUVICA in combination with obinutuzumab or chlorambucil in combination with obinutuzumab.

The most commonly occurring adverse reactions in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, rash, musculoskeletal pain, bruising, nausea, fatigue, pyrexia, hemorrhage, and cough.

Four to 10 percent of patients with CLL/SLL receiving IMBRUVICA discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia. Adverse reactions leading to dose reduction occurred in approximately 7% of patients.

Study 1102: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

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Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies	10	2†
Vascular disorders	Hypertension	16	8

†One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

Treatment-emergent Grade 4 thrombocytopenia (8%) and neutropenia (12%) occurred in patients.

RESONATE: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Pyrexia	24	2	15	2†

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE (continued)

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Infections and infestations				
Upper respiratory tract infection	16	1	11	2†
Pneumonia*	15	12†	13	10†
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given adverse reaction (ADR) term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

Treatment-emergent Grade 4 thrombocytopenia (2% in the IMBRUVICA arm vs 3% in the ofatumumab arm) and neutropenia (8% in the IMBRUVICA arm vs 8% in the ofatumumab arm) occurred in patients.

RESONATE-2: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0

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Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2 (continued)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Eye disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular disorders				
Hypertension*	14	4	1	0
Nervous system disorders				
Headache	12	1	10	2

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

HELIOS: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	56†
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular disorders				
Hemorrhage*	19	2†	9	1
Hypertension*	11	5	5	2

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS (continued)

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%
† Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm and 1 event of neutropenia with a fatal outcome in the placebo + BR arm.

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo +BR.

iLLUMINATE: Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

Table 9: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE

Body System Adverse Reaction§	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia*	48	39	64	48
Thrombocytopenia*	36	19	28	11
Anemia	17	4	25	8
Skin and subcutaneous tissue disorders				
Rash*	36	3	11	0
Bruising*	32	3	3	0
Gastrointestinal Disorders				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Nausea	12	0	30	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	27	1	12	0
Injury, Poisoning and Procedural Complications				
Infusion related reaction	25	2	58	8
Vascular disorders				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3
Infections and Infestations				
Pneumonia*	16	9	9	4†
Upper Respiratory Tract Infection	14	1	6	0
Skin infection*	13	1	3	0
Urinary tract infection	12	3	7	1
Nasopharyngitis	12	0	3	0
Conjunctivitis	11	0	2	0

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Table 9: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE (continued)

Body System Adverse Reaction§	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Metabolism and Nutrition Disorders				
Hyperuricemia	13	1	0	0
Cardiac Disorders				
Atrial Fibrillation	12	5	0	0
General Disorders and Administration Site Conditions				
Pyrexia	19	2	26	1
Fatigue	18	0	17	2
Peripheral edema	12	0	7	0
Psychiatric disorders				
Insomnia	12	0	4	0

§ The data are not an adequate basis for comparison of ADR rates between treatment arms.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† Includes one event with a fatal outcome.

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in three single-arm open-label clinical trials (Study 1118, Study 1121, and INNOVATE monotherapy arm) and one randomized controlled trial (INNOVATE) in patients with WM or MZL, including a total n=307 patients overall and n=232 patients exposed to IMBRUVICA. Study 1118 included 63 patients with previously treated WM who received single agent IMBRUVICA. Study 1121 included 63 patients with previously treated MZL who received single agent IMBRUVICA. INNOVATE included 150 patients with treatment naïve or previously treated WM who received IMBRUVICA or placebo in combination with rituximab. The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received IMBRUVICA.

The most commonly occurring adverse reactions in Studies 1118, 1121, and INNOVATE (≥ 20%) were thrombocytopenia, diarrhea, bruising, neutropenia, musculoskeletal pain, hemorrhage, anemia, rash, fatigue, and nausea.

Seven percent of patients receiving IMBRUVICA across Studies 1118, 1121, and INNOVATE discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were atrial fibrillation, interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 13% of patients.

Study 1118 and INNOVATE Monotherapy Arm: Adverse reactions and laboratory abnormalities described below in Tables 10 and 11 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118 and 33 months in the INNOVATE Monotherapy Arm.

Table 10: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	38	2
	Nausea	21	0
	Stomatitis*	15	0
	Constipation	12	1
	Gastroesophageal reflux disease	12	0
Skin and subcutaneous tissue disorders	Bruising*	28	1
	Rash*	21	1
Vascular disorders	Hemorrhage*	28	0
	Hypertension*	14	4
General disorders and administrative site conditions	Fatigue	18	2
	Pyrexia	12	2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	21	0
	Muscle spasms	19	0

Table 10: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Infections and infestations	Upper respiratory tract infection	19	0
	Skin infection*	18	3
	Sinusitis*	16	0
	Pneumonia*	13	5
Nervous system disorders	Headache	14	0
	Dizziness	13	0
Respiratory, thoracic and mediastinal disorders	Cough	13	0

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 11: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

	Percent of Patients (N=94)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	38	11
Neutrophils Decreased	43	16
Hemoglobin Decreased	21	6

Treatment-emergent Grade 4 thrombocytopenia (4%) and neutropenia (7%) occurred in patients.

INNOVATE: Adverse reactions described below in Table 12 reflect exposure to IMBRUVICA + R with a median duration of 25.8 months and exposure to placebo + R with a median duration of 15.5 months in patients with treatment naïve or previously treated WM in INNOVATE.

Table 12: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Skin and subcutaneous tissue disorders				
Bruising*	37	1	5	0
Rash*	24	1	11	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	35	4	21	3
Arthralgia	24	3	11	1
Muscle spasms	17	0	12	1
Vascular disorders				
Hemorrhage*	32	3	17	4†
Hypertension*	20	13	5	4
Gastrointestinal disorders				
Diarrhea	28	0	15	1
Nausea	21	0	12	0
Dyspepsia	16	0	1	0
Constipation	13	1	11	1
Infections and infestations				
Pneumonia*	19	13	5	3
Skin infection*	17	3	3	0
Urinary tract infection	13	0	0	0
Bronchitis	12	3	7	0
Influenza	12	0	7	1
Viral upper respiratory tract infection	11	0	7	0
General disorders and administration site conditions				
Peripheral edema	17	0	12	1
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	11	0

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Table 12: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE (continued)

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and Lymphatic System Disorders				
Neutropenia*	16	12	11	4
Cardiac Disorders				
Atrial fibrillation	15	12	3	1
Nervous system disorders				
Dizziness	11	0	7	0
Psychiatric disorders				
Insomnia	11	0	4	0
Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes one event with a fatal outcome.

Grade 3 or 4 infusion related reactions were observed in 1% of patients treated with IMBRUVICA + R.

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising*	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular disorders	Hemorrhage*	30	2†
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes one event with a fatal outcome.

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

Treatment-emergent Grade 4 thrombocytopenia (3%) and neutropenia (6%) occurred in patients.

Chronic Graft versus Host Disease: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 15 and 16 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 15: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	14†
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Metabolism and nutrition disorders	Hypokalemia	12	7

The system organ class and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

† Includes 2 events with a fatal outcome.

Table 16: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	33	0
Neutrophils Decreased	10	10
Hemoglobin Decreased	24	2

Treatment-emergent Grade 4 neutropenia occurred in 2% of patients.

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Additional Important Adverse Reactions: *Cardiac Arrhythmias:* In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.5% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 9% versus 1.4% and for Grade 3 or greater was 4.1% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea: In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), diarrhea of any grade occurred at a rate of 39% of patients treated with IMBRUVICA compared to 18% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range, 0 to 708) versus 46 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 655) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively. Less than 1% of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Visual Disturbance: In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (10% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (6% Grade 1 and <1% Grade 2 and 3). The median time to first onset was 91 days (range, 0 to 617) versus 100 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

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

- Hepatobiliary disorders: hepatic failure including acute and/or fatal events, hepatic cirrhosis
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasis, panniculitis
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy

DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities *(see Data)*. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

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

Data: Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: *Pregnancy Testing:* Conduct pregnancy testing in females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception: Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥ 65 years of age, while 23% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

Hepatic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

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PATIENT COUNSELING INFORMATION

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

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions]*.
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions]*.
- *Cardiac Arrhythmias:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions]*.
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions]*.
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions]*.
- *Tumor lysis syndrome:* Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions]*.
- *Embryo-fetal toxicity:* Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions]*.
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information]*.
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose *[see Dosage and Administration (2.6) in Full Prescribing Information]*.
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions]*. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION .
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions]*.
- Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration *[see Adverse Reactions]*.

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Genomic sequencing sheds light on development of pediatric cancer

By Bianca Nogrady

Genome sequencing technologies are providing a valuable new window into the development and progression of pediatric cancers, according to the authors of a review.

In contrast to adult cancers, which are frequently driven by oncogenic mutations, many pediatric cancers have a low burden of somatic mutations, wrote E. Alejandro Sweet-Cordero, MD, from the University of California, San Francisco, and Jaclyn A. Biegel, MD, from the University of Southern California in Science. Instead, large-scale sequencing studies have found that childhood cancers have a much higher likelihood of being caused by germline mutations in genes that predispose development of cancer.

"Particularly surprising was the observation that even high-risk, highly aggressive cancers in many cases had no identifiable driver gene or pathway," the authors wrote.

Some pediatric cancers do have identified driver genes, but even these are often different to those seen in adult cancers. The authors gave the example of one study of 1,699 patients and six types of cancer: This study identified 142 likely oncogenes, but only 45% of these matched those seen in the adult cancers.

Many pediatric cancers also have unique genetic features, such as the age-dependent gene fusion events, in which two genes join to form an oncogenic hybrid, and focal areas of gene deletion, which are often seen in pediatric acute myeloid leukemia but less so in adult forms of this cancer.

"In some instances, the fusion events involve genes that are known to be cancer drivers; this raises the intriguing possibility that some pediatric cancers are driven by 'private' oncogenic fusions," the authors wrote, pointing out that this has daunting implications for the development of precision medicine. However they also noted that the presence of common gene fusion events could hold significance for choice of therapies; for example, central nervous system gliomas with the common BRAFV600E mutation may respond to specific BRAF inhibitors.

The authors drew particular attention to the role that genomic analysis could play in studying cancer during treatment and relapse, but they said few studies have explored this in pediatric patients.

"Such studies are critical given what we have learned from adult cancers, which show a capacity to evolve rapidly and acquire new driver mutations," they wrote. One study found that only one-third of tumors with a potentially targetable genetic mutation had retained that target when analyzed at a later time.

On the issue of targeted therapy, the authors noted that no prospective study has yet looked at the use of sequencing approaches to define new therapies for pediatric cancer. However, they did refer to the Pediatric MATCH clinical trial, which is currently evaluating targeted therapies for relapsed solid tumors in children.

They also identified a need for research on predictors of treatment response in pediatric cancer.

"As the genetic variants that are associated with drug response are, by nature and design, variants present in the normal population, they are typically not included in DNA sequencing panels and are filtered out in WES [whole-exome sequencing] or WGS [whole-genome sequencing] bioinformatics pipelines," they wrote.

They addressed the question of when to do germline testing in pediatric cancer, saying that, for most pediatric cancer patients, germline testing was indicated by the presence of a pathogenic genetic alternative affecting a gene known to be associated with a predisposition for germline cancer.

The authors suggested that data sharing was important to advancing genomic analysis in pediatric cancers because most of the studies so far had been relatively small. However, they highlighted emerging resources for large-scale analysis of pediatric cancer data, such as public portals for investigating discovery genomic data sets and data repositories of clinical-grade sequencing data.

REFERENCE

Sweet-Cordero A et al. *Science.* 2019;363:1170-5.

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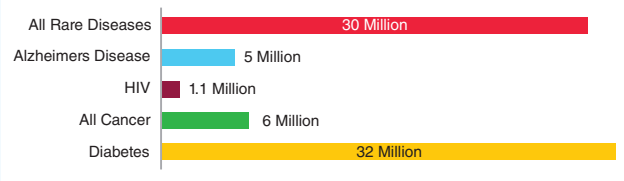
Rare diseases aren't as rare as you might think: Look to the NIH's many resources for help


By Tiina K. Urv, PhD, and
Anne R. Pariser, MD

Rare diseases aren't rare. That statement might sound contradictory: After all, a rare disease is defined (in the United States) as a disease or condition of fewer than 200,000 affected persons living in the United States. Collectively, however, there are approximately 7,000 different rare diseases, with about 250 newly identified conditions added to the list each year. That equates to approximately 30 million Americans who are affected by a rare disease—more than the number of people who have cancer, human immunodeficiency virus infection, and Alzheimer's disease combined, and nearly as many as the number who have diabetes (Figure 1).

More than one-half of the 30 million people affected by a rare disease in the United States are children. Most rare diseases are serious and can involve chronic illness, disability, and, often, premature death. Rare diseases are complex, and treatments exist for fewer than 5% of these conditions. It is important, therefore, to recognize that rare diseases are a significant public health issue. And since 350 million people are affected by rare diseases worldwide, it is not just a national problem, but a global problem.

FIGURE 1: Estimated prevalence of rare and other selected diseases



One of the greatest challenges facing people who have a rare disease is getting an accurate and timely diagnosis. The average time from onset of symptoms to diagnosis is 4.8 years (range, 0-20 years), during which time these people visit approximately 7 physicians, on average.[1] It is understandable why this process is often referred to as the diagnostic odyssey.

Since 1 in 10 Americans is affected with a rare disease, it is highly likely that during the course of any given day, a physician will encounter a patient with a rare disease in the examining room. This situation raises a question: How could a single physician be expected to have knowledge of more than 7,000 disorders that he has never encountered? During training, medical students have historically been taught that when you are working up a patient to make a diagnosis and you hear hoofbeats (i.e., see symptoms), you should look for horses, not for zebras—meaning that a common diagnosis is much more likely than an unusual one.

Many providers and researchers in the rare disease community have adopted the zebra as their mascot: They are the uncommon cause of hoofbeats in the medical field. Physicians, in this age of rapidly advancing science, might find themselves contend-

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This article reflects the views of the authors and should not be construed to represent the views or policies of NCATS or NIH.

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ing with not 1, but a herd of zebras, and it can be challenging to know where to turn for reliable information about rare diseases.

One good place to turn

The National Institutes of Health (NIH) (www.nih.gov), part of the US Department of Health and Human Services, is the nation's medical research agency. Among many other services, the NIH conducts and supports research related to rare diseases—from the most basic bench research to translational, clinical, and broad overall public health research.

The NIH comprises 27 institutes and centers (https://www.nih.gov/about-nih/what-we-do/nih-almanac/nih-organization), many of which conduct rare disease research. It can be daunting to know where within such a large institution to find information related to rare diseases. The answer? Within the National Center for Advancing Translational Science (NCATS) (https://ncats.nih.gov) of the NIH resides the Office of Rare Diseases Research (ORDR) (https://ncats.nih.gov/about/center/org/ordr).

The ORDR was established at the NIH in 1985 (originally as the Office of Rare Diseases). The ORDR supports programs that help accelerate scientific discovery and offers patients and their health care providers information on identifying, diagnosing, treating, and living with a rare disease. The office does so by facilitating coordination among multiple stakeholders in the rare disease community, including scientists, clinicians, patients, and patient groups.

> Since 1 in 10 Americans is affected by a rare disease, it is highly likely that during the course of any given day, a physician will encounter a patient with a rare disease in the examining room.

In 2002, Congress and President George W. Bush further established the ORDR and its responsibilities in a statute by enacting the Rare Diseases Act of 2002. The ORDR has established numerous resources for researchers, patients, and clinicians, which we catalogue and describe in this article.

NCATS ORDR programs for rare diseases

Genetic and Rare Diseases Information Center (GARD)

https://rarediseases.info.nih.gov

GARD is a collaboration of the National Human Genome Research Institute and NCATS/ORDR to provide comprehensive information about rare and genetic disease to patients, their families, health care providers, researchers, and the public. Use of the GARD website and Contact Center is broad and has continued to grow (Figure 2).

The GARD website and database provide comprehensive, reliable, plain-language information on rare or genetic diseases that is freely accessible to the public and available in English and Spanish. Videos, brochures, publications, and links to disease-related organizations are also available. A contact center staffed by information specialists with expertise in genetic counseling provides free, individualized responses by telephone or email to support patients with a rare disease.

Rare Diseases Clinical Research Network (RDCRN)

https://www.rarediseasesnetwork.org

The RDCRN was established by the Rare Diseases Act of 2002 as the Rare Diseases Clinical Research Centers of Excellence. The RDCRN comprises a number of consortia, each studying at least 3 disorders and partnering closely with patient advocacy groups and NIH program staff (Table 1). The goal of the network, through its consortia, is to advance the diagnosis, management, and treatment of rare diseases. Each consortium promotes highly collaborative, multisite, patient-centric translational and clinical research. The individual consortia and the RDCRN are supported by a data management and coordinating center.

The network was first funded in 2003 and has been funded continuously since that time, with a recompetition every 5 years. To date, the program has successfully supported 31 individual consortia that have conducted research on 238 disorders, involving more than 40,000 participants, all leading to a greater understanding of rare diseases.

The aims of the upcoming program are to specifically address, through clinical research, 5 challenges to bringing effective treatment to more people living with rare diseases.

FIGURE 2: Genetic and Rare Diseases Information Center (GARD) utilization in recent years

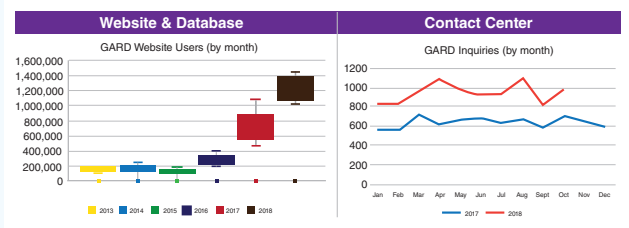


TABLE 1. Rare Diseases Clinical Research Network Consortia

Advancing Research and Treatment for Frontotemporal Lobar Degeneration Consortium (ARTFL) https://rdcrn.org/artfl	Lysosomal Disease Network (LDN) https://rdcrn.org/ldn
Autonomic Disorders Consortium (ADC) https://rdcrn.org/adc	NEPTUNE: Nephrotic Syndrome Study Network https://rdcrn.org/neptune
Brain Vascular Malformation Consortium (BVMC) https://rdcrn.org/bvmc	North American Mitochondrial Disease Consortium (NAMDC) https://rdcrn.org/namdc
Brittle Bone Disorders (BBD) https://rdcrn.org/bbd	Porphyrias Consortium (PC) https://rdcrn.org/porphyrias
Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) https://rdcrn.org/cegir	Primary Immune Deficiency Treatment Consortium (PIDTC) https://rdcrn.org/pidtc
CReATe: Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium https://rdcrn.org/create	Rare Kidney Stone Consortium (RKSC) https://rdcrn.org/rksc
Developmental Synaptopathies Consortium (DSC) https://rdcrn.org/dsc	Rare Lung Diseases Consortium (RLDC) https://rdcrn.org/rld
Dystonia Coalition https://rdcrn.org/dystonia	Rett Syndrome, MECP2 Duplication, & Rett-Related Disorders Consortium (RTT) https://rdcrn.org/rett
Genetic Disorders of Mucociliary Clearance Consortium (GDMCC) https://rdcrn.org/gdmcc	STAIR: Sterol and Isoprenoid Research Consortium https://rdcrn.org/stair
Inherited Neuropathies Consortium (INC) https://rdcrn.org/inc	Urea Cycle Disorders Consortium (UCDC) https://rdcrn.org/ucdc
	Vasculitis Clinical Research Consortium (VCRC) https://rdcrn.org/vcrc

Making a diagnosis can be challenging. Many patients experience a diagnostic odyssey of many months, even years, because of limited knowledge of the range of disease manifestations and of genotype–phenotype studies.

Often, there are no high-quality natural history data sets documenting how a disease affects patients' functioning and how it progresses over time.

Often, there are no adequate clinical or biological markers to support the clinical development of new therapeutics.

The number of patients and clinicians caring for them is relatively small, leading to challenges in the design and implementation of clinical trials.

Resources for developing therapeutics are limited, making it critical to find frameworks for leveraging partnerships among patient groups, industry, academic investigators, and federal funding agencies. In addition, the global burden associated with rare diseases necessitates international coordination and collaboration.

The RDCRN is a partnership of multiple NIH Institutes and Centers, including NCATS; the National Cancer Institute; the National Heart, Lung, and Blood Institute; the National Institute of Allergy and Infectious Diseases; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; the Eunice Kennedy Shriver National Institute of Child Health and Human Development; the National Institute of Dental and Craniofacial Research; the National Institute of Diabetes and Digestive and Kidney Diseases; and the National Institute of Neurological Disorders and Stroke.

An important component of the RDCRN is the Coalition of Patient Advocacy Groups (CPAG). This collective representation of patient groups is affiliated with the consortia within the RDCRN. The mission of CPAG is to promote collaboration between rare disease advocacy organizations and the RDCRN to facilitate better access to and earlier benefit from research conducted on rare diseases. As the patient advocacy arm of the RDCRN, CPAG members use their posi-

tion to advance rare disease research and improve patient outcomes through the network. There are 151 active member patient organizations participating in the CPAG.

NCATS Toolkit for Patient-Focused Therapy Development

https://rarediseases.info.nih.gov/toolkit

The toolkit was developed by ORDR in collaboration with patient groups and is intended to provide patient groups with the tools needed to help advance their research agenda. It provides a single site that draws accessible, practical, action-centered information from many groups across the Internet. The goal of the program is to ensure that patients are engaged as essential partners from beginning to end of research and development. This is a living site to which tools are continually being added for and by patient groups in concert with their academic, government, industry, and advocacy partners. An example of a tool within the kit is a description of how a new therapy for a disorder is developed (https://rarediseases.info.nih.gov/toolkit/getting-started).

Rare Diseases Registry Program (RaDaR)

https://rarediseases.info.nih.gov/radar

The Rare Diseases Registry Program (RaDaR) is a component of the toolkit that is under development and expected to be released in 2019. This program is not a registry, but a tool to develop a registry. Registries and natural history studies are the foundations of any drug development program, especially for rare diseases. They provide information about the rare disease, establish a link to patients, aid in the identification and development of outcome measures, contribute to the interpretability of clinical studies, and serve as a comparator group in trials. Information collected in a registry has to meet specific needs to be used in research.

The intent of RaDaR is to be a "registry in a box." It will connect researchers and patient groups to tools with training and instruction on key decisions, tasks, and challenges needed for creating and managing a registry. When complete, RaDaR will provide step-by-step directions for creating high-quality registries to support clinical trials and therapy development. It will provide templates and tools to incorporate best practices and standards for registries, along with strategies for maintaining, promoting, using, and expanding registries.

NIH resources beyond the ORDR

The Undiagnosed Diseases Network

https://undiagnosed.hms.harvard.edu

The Undiagnosed Diseases Network (UDN) was established to meet the needs of the hundreds of men, women, and children who face uncertainty when their providers are unable to discover the cause of their symptoms. The UDN provides information for patients and families affected by mysterious conditions and helps them learn more about common diseases. The goals of the network are the following:

- **improve the level of diagnosis and care** for patients with undiagnosed diseases, through development of common protocols designed by a large community of investigators.
- **facilitate research into the etiology of undiagnosed diseases** by collecting and sharing standardized, high-quality clinical and laboratory data, including genotyping, phenotyping, and documentation of environmental exposures.
- **create an integrated and collaborative community** across multiple clinical sites and among laboratory and clinical investigators prepared to investigate the pathophysiology of these new and rare diseases.

The program consists of clinical sites across the United States (Table 2) and supporting cores related to DNA sequencing, metabolomics, and model organisms. Because of the complex nature of the human body and the diseases being investigated, the UDN cannot accept all applicants into the study. However, all applications receive full review. To date, 2,939 applications have been submitted; 1,215 have been accepted into the program; 952 participants have been evaluated; and 249 have been given a diagnosis.

This program is funded by the NIH Common Fund (https://commonfund.nih.gov). Physicians and patients can refer themselves; however, a study recommendation letter is needed from a licensed primary health care provider. To be eligible for the UDN program, a participant must:

- have a condition that remains undiagnosed despite thorough evaluation by a provider
- have at least 1 objective finding
- agree to the storage and sharing of information and biomaterials in an identified fashion amongst the UDN centers, and in a deidentified fashion to research sites beyond the network (https://undiagnosed.hms.harvard.edu/apply).

Educational Materials About Genetics and Genomics

https://www.genome.gov/education

Approximately 80% of rare diseases adhere to Mendelian laws of inheritance, and genomic science and technology are fast-moving. To continually educate the public and health care professionals, the National Human Genome Research Institute has developed extensive materials and online genetic education resources, as well as online courses related to genomics and genetics.

TABLE 2. Clinical sites of the Undiagnosed Diseases Network (UDN)

Bethesda, Maryland (National Institutes of Health)
Boston, Massachusetts (Brigham and Women's Hospital, Boston Children's Hospital, and Massachusetts General Hospital)
Durham, North Carolina (Duke University and Columbia University)
Houston, Texas (Baylor College of Medicine)
Los Angeles, California (University of California, Los Angeles)
Miami, Florida (University of Miami School of Medicine)
Nashville, Tennessee (Vanderbilt University Medical Center)
Philadelphia, Pennsylvania (Children's Hospital of Philadelphia and University of Pennsylvania)
Salt Lake City, Utah (University of Utah)
Seattle, Washington (University of Washington School of Medicine and Seattle Children's Hospital)
Stanford, California (Stanford Medicine)
St. Louis, Missouri (Washington University in St. Louis)

Clinicaltrials.gov

https://clinicaltrials.gov/ct2/home

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. This web-based resource, provided by the National Library of Medicine, provides patients and their family members, health care professionals, researchers, and the public with easy access to information on clinical trials on a range of diseases and conditions. The site allows users to find and view clinical studies, learn more about clinical research, manage study records, and use site tools and data.

Research Portfolio Online Reporting Tools (RePORT)

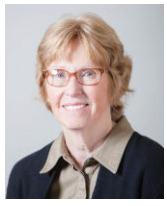
https://report.nih.gov/index.aspx

The Research Portfolio Online Reporting Tool provides a central point of access to reports, data, and analyses of NIH research activities, including expenditures and results of NIH-supported research. A tool that is exceptionally valuable in finding information about specific rare diseases is the NIH RePORTER tool (https://projectreporter.nih.gov/reporter.cfm), which allows members of the public to search for research related to any disease or disorder. Using a simple, web-based query, information regarding ongoing research projects, publications, patents, and clinical studies can be accessed, along with data visualization and the NIH institute that is funding the research.

REFERENCE

1. Engel PA, Bagal S, Broback M, Boice N. Physician and patient perceptions regarding physician training in rare diseases: The need for stronger educational initiatives for physicians. *J Rare Dis*. 2013;1:1-15.

NORD offers resources to benefit health care providers, patients, and caregivers



Mary Dunkle

The National Organization for Rare Disorders (NORD) (https://rarediseases.org) has been providing resources for health care providers since 1983. As the primary nonprofit organization representing patients and families affected by rare diseases in the United States, NORD considers support for health care providers to be an essential part of its mission.

An informed and supported medical care team is one of the most important assets that patients and caregivers coping with a rare disease can have. As a result, NORD sees outreach to health care providers as one of the foundations of its services for patients and caregivers.

NORD resources for health care providers can be found within each of the 4 pillars of NORD programs and services: education, advocacy, patient and family services, and research.

1. Education

NORD's **Rare Disease Database** (https://rarediseases.org/for-patients-and-families/information-resources/rare-disease-information/) is a unique and widely cited resource that encompasses expert-reviewed, disease-specific reports providing overviews of approximately 1,200 rare diseases.[1] These reports include general descriptions, synonyms and subdivisions, signs and symptoms, causes, affected populations, related disorders, standard therapies, investigational therapies, resources (including disease-specific patient organizations), and references.

Of the approximately 1 million visits to NORD's website each month, 85% first go to the Rare Disease Database. Medical experts assist NORD in developing the reports and serve as reviewers to ensure accuracy. In many cases, the reviewers are the physicians for whom the diseases are named, or who serve as the world's leading experts on their topic. These medical experts volunteer their time and support because of the value of the database in educating other providers and students, as well as affected patients and caregivers.

NORD recently obtained permission from the National Institutes of Health (NIH) to display information from the NIH **Genetic and Rare Diseases Information Center (GARD)** (https://rarediseases.info.nih.gov/) alongside NORD's disease information on the NORD website. These combined resources cover all 7,000-plus known rare diseases.

In addition to the database of disease reports, NORD maintains a database of more than **1,000 patient organizations** (https://rarediseases.org/for-patients-and-families/connect-others/find-patient-organization/) that provide services for people affected by rare diseases. This database can be searched by disease or organization name. Many patient organizations in this database provide services helpful to providers, including information about genetic testing, centers of excellence, and consultation and telemedicine services.

NORD's **Rare Disease Video Library** (https://rarediseases.org/video-topic/medical-education/) includes short (approximately 4-minute) animated videos that provide overviews of rare diseases. These videos cover information similar to what is in the Rare Disease Database reports, but in an engaging format for providers as well as students, patients and caregivers. Categories include advocacy, medical education, patient and caregiver resources, and research and science. The videos are available on the NORD website.

The monthly **NORD eNews** digital newsletter reaches a broad audience, including many health care providers. It covers upcoming conferences and events, funding opportunities, advocacy initiatives, news from NIH and the Food and Drug Administration (FDA), including recently approved drugs for rare disorders, and other topics of interest to providers caring for patients who have rare diseases.

In 2019, NORD launched a **Continuing Medical Education (CME) program** that includes a mix of live events and online access-on-demand resources. NORD hosted its

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first CME event in 2017 and has been building on that experience to develop an expanded program to meet the needs of community physicians, RNs, PAs, and others serving as members of the health care team for patients affected by rare diseases.

The annual **NORD Rare Diseases and Orphan Products Breakthrough Summit (www.nordsummit.org/)** takes place each October in Washington, DC, and addresses cutting-edge topics related to rare diseases. The 2019 Summit was the largest to date, with more than 950 participants, including NIH and FDA staff, clinicians, researchers, patient organization leaders, and industry representatives. With a mix of general and breakout sessions, topics in 2019 included drug pricing, gene therapy, social determinants of health, and patient registries.

NORD also hosts conferences for patients, caregivers, students, and providers at locations around the United States. The 2020 **Living Rare, Living Stronger Forum** will be held in Cleveland, Ohio in May.

NORD provides **educational resources for patients and caregivers** about current topics related to rare diseases that can be helpful to members of the care team. NORD hosts a webinar series for patients and caregivers on topics such as genetic testing and insurance access; generic drugs and biosimilars; specialty pharmacies; self-advocacy/care coordination; and gene therapy.

In its **Patient/Caregiver Resource Center**, (https://rarediseases.org/for-patients-and-families/information-resources/patient-and-caregiver-resource-center/) NORD provides links to videos and free downloadable resources. A recently created video, "Patient/Caregiver Questions About Gene Therapy," has been widely viewed and circulated among patients, caregivers, and providers. Another video provides an overview of resources for patients whose rare disease is newly diagnosed.

For **Rare Disease Day** (www.rarediseaseday.us), observed globally on the last day of February each year, NORD provides special resources and news about events of interest to providers, patients, and caregivers.

2. Advocacy

Through its office in Washington, DC, and a network of state and local volunteers known as the **Rare Action Network®** (https://rareaction.org/), NORD leads advocacy on state and federal public policy issues that affect the rare disease community. These initiatives include advocating for:

- funding for medical research
- patient access to affordable health insurance
- coverage for medical foods and newborn screening
- patient protections around the use of step therapy and related practices.

Over the years, NORD has played a major role in advocacy to encourage development of diagnostics and treatments for people with rare diseases, to end discrimination against those with pre-existing medical conditions, and to support expanded funding for rare disease research at the NIH.

3. Patient and family services

Since 1987, NORD has provided assistance programs (https://rarediseases.org/for-patients-and-families/help-access-medications/patient-assistance-programs-2/) to help patients obtain life-saving and life-sustaining medical and other resources that they could not otherwise afford. These programs provide medication, financial assistance with insurance premiums and co-pays, diagnostic testing assistance, and travel assistance for clinical trials or consultation with disease specialists.

NORD's **Patient Services** staff provides white-glove service to patients and caregivers, working closely with physicians and physicians' office staff to ensure that patients have access to the medical care their providers believe is best for them.

NORD's **Rare Disease Video Library**, mentioned above, also includes patient and caregiver resources, including videos on pediatric movement disorders, gene therapy, newly diagnosed patients, and rare disease facts. NORD also received 2 additional grants from the FDA. Also in partnership with the Critical Path Institute, FDA's Center for Drug Evaluation and Research (CDER) funded a 1-year project to develop and operationalize a Rare Disease Clinical Outcomes Assessment Consortium. FDA's Center for Biologics Evaluation and Research awarded for a 1.5-year project to develop and implement a registry with mobile app and medical record.

4. Research

NORD and Critical Path Institute launched the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP) through funding from the FDA. The Platform is an integrated database and analytics hub that is designed to be used in building novel tools to accelerate drug development across rare diseases by pulling in patient-level data from diverse sources, including clinical trials, longitudinal observational studies, patient registries and real-world data (eg, electronic health records) across a multitude of rare diseases.

This year marks the 30th anniversary of NORD's **Research Grants Program** (https://rarediseases.org/for-clinicians-and-researchers/research-opportunities/research-grant-program/), which provides grants—typically $30,000 to $50,000, sometimes greater—for the study of rare diseases. The intent is to advance

understanding of specific rare diseases and provide funding for studies that might lead to new diagnostic tools or treatments for patients.

In at least 2 cases, research that was initially funded by a NORD seed grant led to a product approved by the FDA:

• The so-called titanium rib, approved in 2004 through FDA's Humanitarian Use Device pathway, was developed by researchers at Santa Rosa Children's Hospital, San Antonio, Texas, for children affected with any of several rare disorders resulting in thoracic insufficiency syndrome (https://news.uthscsa.edu/titanium-rib-becomes-1st-new-fda-approved-spine-deformity-treatment-in-40-years/). This medical device has been credited with saving the lives of hundreds of children over the years.

As the primary nonprofit organization representing patients and families affected by rare diseases in the United States, NORD considers support for health care providers to be an essential part of its mission.

• A drug for neurogenic orthostatic hypotension, approved by FDA in 2014, resulted from research that began with a grant from the NORD Research Grants Program (https://www.drugs.com/history/northera.html).

NORD grants are competitive and international. The intent is to support the most promising research that has the greatest likelihood of improving the lives of patients. Each year, funding opportunities are posted on the NORD website, usually in late winter or early spring.

Letters of intent and final proposals are reviewed by the NORD Medical Advisory Committee, whose members are rare disease experts at teaching hospitals and medical schools across the United States. Members of this committee volunteer their time to make it possible for NORD to offer this program.

Grants are funded by donations from patients, family and friends of patients, patient organizations, foundations, and other sources. Anyone can make a donation to NORD for this purpose, and if no fund exists for a specific disease, a new one can be started. Typically, NORD has active funds for more than 200 rare diseases. When a fund reaches the required minimal amount, a Request for Proposals (https://rarediseases.org/for-clinicians-and-researchers/research-opportunities/requests-proposals/) will be generated.

Program guidelines and policies are available on the NORD website. When new requests for proposals are posted, NORD advertises them through its eNews, on its website, and through disease-specific patient organizations. The intent is to cast the broadest possible net to get the best possible proposals.

In recent years, NORD has also launched a **platform for patient registries and natural history studies** to advance understanding of rare diseases and support research. NORD works with disease-specific patient organizations to develop global registries that are tailored to the needs of each patient community.

NORD is currently hosting or developing 29 registries, working with organizations such as the Foundation for Prader-Willi Research, the OMSLife (Opsoclonus Myoclonus Syndrome) Foundation, the Fibrous Dysplasia Foundation, and the Platelet Disorder Support Association. These organizations are encouraged to interact with medical researchers and look for opportunities to collaborate for the benefit of the patient community.

Resources of NORD member organizations

In addition to NORD's own resources, those developed by its **nearly 300 member organizations** (https://rarediseases.org/for-patient-organizations/membership-profiles/member-list/) are also often featured on the NORD website or through its communications media.

For example, **CureSMA**, which represents families affected by spinal muscular atrophy (SMA), recently launched a new **SMArt Moves** microsite (http://events.curesma.org/site/PageNavigator/SmartMoves/SmartMoves.html) and campaign to help parents and providers recognize early signs and symptoms of SMA. Early identification of infants affected by SMA is extremely important because treatment is available that, begun early, can greatly improve quality of life and, for some patients, slow the advance of this progressive condition.

NORD helps its member organizations promote awareness of these types of resources to educate patients and providers about specific rare diseases.

REFERENCE

1. Mullen L. NORD expands and enhances its Rare Disease Database, a primary resource for millions of people affected by rare diseases. January 3, 2018. Press release. https://rarediseases.org/nord-expands-and-enhances-its-rare-disease-database-a-primary-resource-for-millions-of-people-affected-by-rare-diseases. Accessed January 6, 2018.

NORD® RARE CANCER COALITION

UNITING RARE CANCER ADVOCATES TO LEARN, SHARE AND RAISE AWARENESS.

Created in 2017, **NORD's Rare Cancer Coalition** (RCC) aims to unite NORD Member Organizations working in rare cancers to collaborate on issues facing the greater rare cancer community. The coalition strengthens its individual members through capacity building, networking and peer-to-peer mentoring.

NORD'S RCC executive leadership and coalition member organizations have served on multiple panels on the global stage, such as attending the World Orphan Drug Congress - USA to speak about rare cancers. RCC also launched a day specifically devoted to raising awareness about rare cancers. #RareCancerDay is observed on October 1 to highlight the challenges people living with rare cancers face and to unify individuals living with rare cancers for awareness and early diagnosis.

With more than 35 years of experience as an umbrella organization in the rare disease space, NORD provides our coalition members with a proven support system and an unmatched depth of resources to advance the fight against rare cancers efficiently and effectively.

FOR MORE INFORMATION CONTACT RCC CO-CHAIRS:

- ***Jim Palma,*** *Executive Director of the TargetCancer Foundation, at jim@targetcancerfoundation.org*
- ***John Hopper,*** *President of the Fibrolamellar Cancer Foundation, at jhopper@fibrofoundation.org or email membership@rarediseases.org*

SEE OUR ACHIEVEMENTS AND LEARN MORE AT:

rarediseases.org/get-involved/rarecancercoalition/

NORD Rare Cancer Coalition Partners

Alone we are rare.
Together we are strong.®

NORD: Fighting for the rare community every day for more than 35 years.
NORD is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and patient support services. NORD Headquarters: 55 Kenosia Avenue, Danbury, CT 06810 Tel: 203.744.0100 Fax: 203.263.9938

NORD® National Organization for Rare Disorders

rarediseases.org