ASSOCIATION OF COMMUNITY CANCER CENTERS

TESTING AND TREATING ALK+ NON-SMALL CELL LUNG CANCER

ACCC
Association of Community Cancer Centers

The anaplastic lymphoma kinase (ALK) gene rearrangement is a genetic alteration that may lead to the development of lung cancer in certain individuals.[1] Over the last decade, advances in molecular diagnostics and treatments for lung cancer have led to the development of multiple targeted therapies for patients with non-small cell lung cancer (NSCLC). Patients with ALK+ NSCLC may be appropriate candidates for such targeted therapy, but this lung cancer subtype is rare. Only approximately 5 percent of patients with lung adenocarcinoma are ALK+, so molecular biomarker testing is a critical step to identifying those patients who may be appropriate for targeted therapy.[2]

Testing and Treating ALK+ Non-Small Cell Lung Cancer Education Project

ACCC launched the "Testing and Treating ALK+ Non-Small Cell Lung Cancer" project in 2016 to support community-based cancer programs and practices in the use of precision medicine and molecular testing in caring for patients with ALK+ NSCLC. The project's primary goal is to provide examples of effective practices for utilizing appropriate molecular testing when treating patients with ALK+ NSCLC. In 2016 this project explored barriers and issues related to testing and treating patients with ALK+ NSCLC through an environmental scan that was also informed by the insights of the project's expert Advisory Committee (a summary of the scan is available on the ACCC website at: accc-cancer.org/projects/alk-positive-lung-cancer/overview). In 2017 ACCC conducted focus groups to further understanding of the landscape of testing and treating patients with ALK+ NSCLC. In 2018 ACCC performed site visits at five ACCC member programs to explore how they are effectively diagnosing and managing patients with ALK+ NSCLC:

1. The Center for Cancer Prevention and Treatment at St. Joseph Hospital, Orange, Calif.
2. Cone Health Cancer Center, Greensboro, N.C.
3. Tennessee Oncology in Nashville, Tenn.
4. Baptist Cancer Center in Memphis, Tenn.
5. Sanford Cancer Center in Sioux Falls, S.D.

Major Themes

Through this project, ACCC discovered several key issues related to testing and treating patients with ALK+ NSCLC:

- ***Molecular testing.*** There are many ways to perform molecular testing on lung cancer biopsy samples. While many cancer programs are using a series of single-gene tests for EGFR, ALK, and ROS1, others may be using next-generation sequencing to perform broad genomic profiling, even when samples are small. Many centers are also testing for the PD-L1 biomarker. In 2018 the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) released updated molecular testing guidelines that provide additional guidance regarding optimal testing samples and methods.[3]
- ***Evolving treatment guidelines.*** The first ALK inhibitor was approved in 2011 and subsequent agents were approved between 2014 and 2017 (see Table 1, page 2). Currently, three ALK inhibitors are approved for first-line therapy and three are approved for second-line therapy. All the agents are listed in the National Comprehensive Cancer Network (NCCN) Guidelines for NSCLC (Version 3.2018).[4] ACCC member programs participating in this project reported that they had been using crizotinib in the first-line setting until 2017. Then, they switched to using alectinib in the first-line setting after

Table 1. ALK Inhibitors

Generic Name	Brand Name	First-Line Therapy for ALK+ NSCLC	Second-Line Therapy for ALK+ NSCLC
crizotinib	Xalkori®	FDA approval 2011	
ceritinib	Zykadia®	FDA approval 2017	FDA approval 2014
alectinib	Alecensa®	FDA approval 2017	FDA approval 2015
brigatinib	Alunbrig®		FDA approval 2017
lorlatinib			FDA breakthrough therapy designation 2017

hearing the results from the J-ALEX study.[5] There seemed to be no established consensus on how ALK inhibitors should be sequenced in the second-line setting. Given that tumors treated with ALK inhibitors may acquire additional mutations, disease progression remains an ongoing challenge in patients with ALK+ NSCLC.[6]

- ***Low patient volume and limited clinical experience.*** On average, medical oncologists in the community may only treat one to three patients with ALK+ NSCLC each year. Due to this low patient volume, these providers often have limited experience using different ALK inhibitors. Some of the ACCC member programs participating in this project reported that they have dedicated medical oncologists who focus their practice on the management of lung cancer and who also lead their institutional thoracic oncology program.
- ***Treatment monitoring.*** Through this program, ACCC heard about several different ways to educate and monitor patients who are started on oral ALK inhibitors. Some cancer programs have their own oncology pharmacist educate and follow patients, others primarily rely on their nurses for these responsibilities. Other cancer centers use a dual-team approach where the oncology nurse and pharmacist both educate the patient and reinforce key messages at different times.

The Center for Cancer Prevention and Treatment at St. Joseph Hospital in Orange, California

The Center for Cancer Prevention and Treatment at St. Joseph Hospital is a member of St. Joseph Health, an integrated Catholic healthcare delivery system. In 2016 Providence Health & Services merged with St. Joseph Health to form Providence St. Joseph Health. Annual newly diagnosed lung cancer patients: 150+.

The Center for Cancer Prevention and Treatment at St. Joseph Hospital in Orange, Calif., has a dedicated multidisciplinary thoracic oncology team, led by Program director John Maurice, MD. The team meets weekly to review and discuss all newly diagnosed lung cancer patients. While there are three private medical oncology groups that manage patients with lung cancer at St. Joseph's, the multidisciplinary thoracic oncology team establishes institutional processes and procedures to ensure a uniform approach to patient care.

Prioritizing Molecular Testing in Lung Cancer

The thoracic oncology team has been working for several years to optimize molecular testing processes to ensure that patients are receiving the right tests in a timely fashion. Patients with advanced NSCLC receive EGFR, ALK, ROS1, and PD-L1 testing, and results are usually available within 10 business days. Occasionally, next-generation sequencing may be ordered if patients are being considered for clinical trials, but St Joseph's does not have a formal policy governing the use of next-generation sequencing testing for patients with lung cancer. Since lung needle biopsies are mostly performed by radiologists using core biopsy needles, their pathologists almost always obtain adequate tissue for molecular testing. Most recently, the thoracic oncology team began evaluating a revised lung cancer molecular testing order form. This new form requires medical oncologists to select and prioritize specific molecular tests so that pathology can assess how to allocate small biopsy samples for testing.

Molecular Tumor Board

Given recent advances in cancer genetics and genomics, St. Joseph's cancer care team launched a new molecular tumor board program in 2018. This program is led by Cancer Genetics Program Manager Sandra Brown, MS, LCGC. (The Cancer Genetics Program provides cancer risk assessment, genetic counseling, and plans to assist in early detection, prevention and improved cancer management.) With this new molecular tumor board program, the goal is to discuss specific patient cases, review the latest scientific and clinical evidence, and educate members of the broader cancer care team about the practical utility of genomic and genetic testing to inform treatment decisions in patients with cancer. The cancer care team has reviewed patients with ALK+ NSCLC and identified several topics that could be discussed pertaining to molecular testing interpretation and clinical trial matching. In the first year, the team plans to hold quarterly meetings with all the members of the cancer care team. In the second year, their intent is to incorporate molecular tumor board discussions into all site-specific cancer programs.

Active Clinical Research

St. Joseph's has a very active clinical research program led by Lavinia Dobrea, RN, MS, OCN. The Thoracic Oncology Program navigator, Enza Nguyen, RN, MS, ANP-BC, works closely with the research team to identify patients with ALK+ NSCLC who may be eligible for clinical trials. The research team uses a visual tool to facilitate the process of identifying patients with NSCLC for clinical trials. View this tool online at accc-cancer.org/projects/alk-positive-lung-cancer/overview.

Cone Health Cancer Center in Greensboro, North Carolina

Cone Health is an integrated not-for-profit network of health care providers serving patients in North Carolina. Cone Health Cancer Center provides comprehensive cancer care at five locations. Annual newly diagnosed lung cancer patients: 450+.

Cone Health Cancer Center at Wesley Long in Greensboro, North Carolina, is the main location for lung cancer care. Within the Cone Health medical oncology group of 18 medical oncologists, Mohamed Mohamed, MD, primarily focuses his practice on lung cancer and leads the thoracic cancer program across the entire Cone Health system. Under his leadership, Cone Health has established organizational policies to guide the clinical care of patients with advanced lung cancer. Cone Health launched an oncology clinical pathway program in July 2017 that is integrated with its electronic health record (EHR). The pathway program allows providers to review and evaluate their use of ALK inhibitors in both the first-line and second-line settings.

Initiating Molecular Testing Early

The thoracic multidisciplinary team meets weekly to discuss every newly diagnosed patient who is presented by pathology. By discussing patients before they are seen by a medical oncologist, the team can evaluate whether biopsy samples are adequate for molecular testing and start the ordering process. Since it may take up to 14 days to receive next-generation sequencing test results, the team initiates the process as early as possible. A thoracic cancer nurse navigator, Dana Herndon, RN, follows up with pathology to confirm that tests have been ordered and to review the status of pending test results. Direct access to the testing portal allows the nurse navigator to immediately see when results are available and share this information with the treating oncologist. The multidisciplinary approach of discussing patients before they are seen has also allowed the team to identify instances where the biopsies appear to be inadequate for molecular testing. In those circumstances, the team discusses the feasibility of performing a second biopsy vs. ordering a liquid biopsy test (circulating tumor DNA).

Oral Chemotherapy Navigation

Cone Health has a specialty pharmacy and a dedicated oncology pharmacist, Jesse Mack, PharmD, BCPS, BCOP, who serves as an oral chemotherapy navigator. This pharmacist navigator meets directly with the patient to provide comprehensive patient education and assists with the necessary paperwork to facilitate patient access to medications. The navigator also makes follow-up phone calls to ensure that the patient has received the medication, to assess for side effects, and to track treatment adherence. If patients are hospitalized at a Cone Health hospital, the inpatient team notifies the oral chemotherapy navigator and reviews a set of established hold criteria parameters to assess whether the patient should continue receiving the oral oncolytic agent while hospitalized.

Studying Molecular Testing Accuracy

The thoracic oncology team at Cone Health has researched the accuracy of different molecular testing methods. In the past, they had utilized several molecular testing companies and had noted some discordance in results. This led the team to participate in a research study that revealed how next-generation sequencing testing may discover more positive mutations than are identified by standard molecular testing methods.[7] This type of rigorous research enabled the thoracic oncology team to gain trust and approval from their administration to support the broader use of next-generation sequencing testing for patients with advanced lung cancer.

Tennessee Oncology in Nashville, Tennessee

Tennessee Oncology, established in 1976, is an independent group with multiple locations throughout the state. With 80 medical oncology providers, Tennessee Oncology treats 14,000 new cancers each year. Annual newly diagnosed lung cancer patients: 1,000+

Tennessee Oncology Nashville-Centennial Clinic is one of the largest of the 20-plus practice locations throughout the state. In 1993 Tennessee Oncology initiated the first community-based cancer research program in Tennessee offering clinical trials, including phase I research studies, outside of an academic setting. In 2004, the research program was officially named the Sarah Cannon Research Institute. The institute's mission was to make clinical trials accessible to patients close to their home communities, thus eliminating the need for extensive travel to and from academic centers. In 2012, Sarah Cannon Research Institute became the Cancer Institute of HCA Healthcare.

As the clinical management of ALK+ NSCLC continues to evolve, ACCC remains committed to providing practical insights that can inform the application of precision medicine.

Robust Clinical Research

Tennessee Oncology and Sarah Cannon remain closely integrated and share the same building and clinical spaces. Patients have convenient access to a wide range of clinical research opportunities, including phase I clinical trials. Patients with ALK+ NSCLC who are treated at Tennessee Oncology may enroll in a clinical trial and receive lorlatinib, an ALK inhibitor that received breakthrough therapy designation by the FDA in 2017. Tennessee Oncology physicians Melissa L. Johnson, MD, and Todd Bauer, MD, among others, have been studying this agent for several years and have presented their phase I/II research findings at recent ASCO conferences.[8]

Multidisciplinary Treatment Plans

Tennessee Oncology Nashville-Centennial Clinic is located next to Tristar Centennial Medical Center. Every week, clinicians participate in site-specific tumor boards where they discuss molecular test results, review clinical evidence, and collaborate to personalize treatment plans for patients. Some of their discussions pertaining to ALK+ NSCLC have led to different treatment approaches by the Tennessee Oncology radiation oncologists, including James Gray, MD. After discussing how the presence of an ALK mutation may confer better long-term prognosis if patients are treated with effective targeted agents, this information is altering how radiation oncologists treat patients with ALK+ NSCLC who have brain metastases. Instead of using whole-brain radiotherapy, radiation oncologists now try to use stereotactic radiosurgery to better preserve long-term cognitive function in patients with ALK+ NSCLC.

Investing in Technology to Improve Care

In 2017 Tennessee Oncology made the investment to switch to a more robust oncology-focused EHR and implemented clinical pathways across the entire organization. That same year, Sarah Cannon acquired Genospace, a company that provides molecular pathology reporting, analytics, clinical trial matching, patient portals, and other cloud-based services. The investment in technology reflects the belief that these platforms will enable their oncology providers to deliver more consistent care across all their locations, as well as help their team identify eligible patients for clinical trials.

Baptist Cancer Center in Memphis, Tennessee

Baptist Memorial Health Care created the Baptist Cancer Center, an integrated cancer program serving patients living in north Mississippi, west Tennessee, and eastern Arkansas. Annual newly diagnosed lung cancer patients: 1,000+.

The Baptist Cancer Center in Memphis, Tennessee, is the main campus that offers cancer treatment, research, support services, community education, and genetic counseling and testing. Out of a 28-medical oncologist provider group, 1 clinician primarily focuses his practice on the management of lung cancer. He also serves as the director of the Baptist Cancer Center Multidisciplinary Thoracic Oncology Program. His team oversees lung cancer screening and provides nurse navigation for patients with lung cancer. To maximize the molecular testing yield from small biopsy samples, Baptist Cancer Center sends most lung cancer biopsies for next-generation sequencing testing and it usually receives results within 10 business days. In 2015 the cancer center's pathology department worked with radiology and pulmonology to develop specific criteria to help ensure that needle biopsy samples were adequate for molecular testing.

Patient Education Led by Nurse/Pharmacist Team

To optimize patient education and care coordination, the thoracic oncology team uses a comprehensive approach that is co-led by an oncology nurse and an oncology pharmacist at the Baptist Cancer Center specialty pharmacy. The oncology nurse begins the patient education process by reviewing the items outlined in

the treatment consent form. The patient learns about the ALK inhibitor, the medication's side effects, safe handling instructions, etc. The next day, the patient typically receives a follow-up phone call from the oncology pharmacist who reinforces key messages about medication adherence and toxicity management. The nurse/pharmacist team also routinely print and distribute patient educational materials provided by the Bonnie J. Addario Lung Cancer Foundation and the drug manufacturer websites. Patients are instructed to call the clinic nurse directly if they experience side effects and they are followed closely by the nurse/pharmacist team who have access to the same EHR to coordinate care.

Processing Orders for ALK Inhibitors

When the medical oncology providers enter an order for an ALK inhibitor, the Baptist Specialty Pharmacy receives and reviews every order. The specialty pharmacy is staffed by an oncology pharmacist, a pharmacy technician, and a rotating PGY2 pharmacy resident. The oncology pharmacist will check for drug-drug interactions, fill out the required prior authorization paperwork, and identify potential patient assistance programs that may reduce the cost of treatment. When required, the Baptist Specialty Pharmacy sends prescriptions to other in-network specialty pharmacies based on the patient's health insurance.

Overcoming Health Disparities

Baptist Cancer Center is one of the National Cancer Institute (NCI) Community Oncology Research Program (NCORP) sites focusing on minority and underserved patients. The cancer center also has a dedicated thoracic clinical research team that actively recruits patients for these studies. In 2016 the Baptist Cancer Center thoracic research team published their findings on coordinating and delivering care in a National Cancer Institute and American Society of Clinical Oncology (NCI-ASCO) "Teams in Cancer Care Delivery" project that used team science principles to improve lung cancer care delivery.[9]

Sanford Cancer Center in Sioux Falls, South Dakota

Sanford Health is an integrated health system headquartered in the Dakotas. It is the largest rural, not-for-profit healthcare system in the nation with 45 hospitals and 289 clinics in 9 states and 3 countries. Annual newly diagnosed lung cancer patients: 200+.

Sanford Cancer Center in Sioux Falls, South Dakota, the southern regional referral hub of Sanford Health, is staffed with a team of more than 50 physicians and advanced practice providers. At its weekly multidisciplinary tumor boards, members of the cancer team present and discuss every newly diagnosed patient. Sanford also holds separate molecular tumor boards twice each week to review and discuss the results of broad genomic profiling (next-generation sequencing) tests performed on patients with advanced cancers. Sanford uses videoconferencing to engage and educate Sanford Health oncology providers who are located across the region in their molecular tumor boards.

Standardizing Molecular Testing Processes

At Sanford, ALK testing is performed in-house by their team of pathologists. Some lung cancer biopsies are also sent out for next-generation sequencing testing to identify patients who may be eligible for clinical trials. The oncology nurses work closely with the medical oncologists to submit the molecular testing orders and to follow-up with the pathology team to obtain timely results that can inform care decisions. Over the years, the team has gained significant experience working with multiple next-generation sequencing testing vendors and they are currently in the process of standardizing their processes for next-generation sequencing testing in advanced NSCLC.

Sequencing ALK Inhibitors

The team at Sanford has built electronic order sets and treatment plans for each ALK inhibitor. Their medical oncologists typically start patients who have advanced ALK+ NSCLC on either alectinib or crizotinib in the first-line setting. If patients begin to progress on treatment, they may then be switched from alectinib to ceritinib or vice versa. The Sanford specialty pharmacy processes all the orders for ALK inhibitors, handles prior authorization requirements, and provides extensive patient education and counseling to ensure that patients fully understand the importance of proper medication adherence. Medication monitoring is accomplished through a combination of face-to-face visits and phone calls. The specialty pharmacy team is also tasked with finding applicable patient assistance programs to ensure that patients always have access to the therapies they need.

Leveraging Telemedicine to Improve Access

In the southern part of South Dakota, many patients live in rural areas and may have limited access to cancer providers. Sanford has been leveraging telemedicine for the past three years to bridge these gaps, and the team in Sioux Falls currently remotely treats and manages patients in partnership with eight different telemedicine sites throughout the region. These sites include hospitals and clinics that have the equipment and staff to provide cancer therapies including infusion services. Some patients with ALK+ NSCLC who are treated with oral oncolytic agents may start their initial treatment in Sioux Falls but then receive ongoing monitoring at a clinic sites equipped for telemedicine closer to their home. Sanford also provides genetic counseling services using video technology and is in the process of expanding access to oncology palliative care services via telemedicine.

Closing Thoughts

As the clinical management of ALK+ NSCLC continues to evolve, ACCC remains committed to providing practical insights that can inform the application of precision medicine. Molecular testing processes are an ongoing topic of discussion at many cancer programs. Clinicians recognize that next-generation sequencing may be appealing because it provides multiple results from a single biopsy sample.[10] However, the turnaround time for getting next-generation sequencing testing results may be longer, and the oncology community needs more clarification on how the Centers for Medicare & Medicaid Services will be reimbursing for this type of testing in patients with advanced cancers. The use of liquid biopsy (circulating tumor DNA) is a growing option when patients are unable to undergo a repeat biopsy.[11] However, clinicians also recognize that a negative liquid biopsy result may necessitate molecular testing on tissue samples. ACCC thanks members of the project advisory committee and all the staff who provided valuable insights during the site visit discussions. More information about this project can be found on the ACCC website at: accc-cancer.org/projects/alk-positive-lung-cancer/overview.

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A CMS Update on Next Generation Sequencing (NGS)

On March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) announced its final National Coverage Determination (NCD) for diagnostic laboratory tests using NGS for patients with advanced cancer. According to the CMS press release:

"CMS finalized a National Coverage Determination that covers diagnostic laboratory tests using Next Generation Sequencing (NGS) for patients with advanced cancer (i.e., recurrent, metastatic, relapsed, refractory, or stages III or IV cancer). CMS believes when these tests are used as a companion diagnostic to identify patients with certain genetic mutations that may benefit from U.S. Food and Drug Administration (FDA)-approved treatments, these tests can assist patients and their oncologists in making more informed treatment decisions. Additionally, when a known cancer mutation cannot be matched to a treatment then results from the diagnostic lab test using NGS can help determine a patient's candidacy for cancer clinical trials… this final decision expanded coverage to patients with relapsed, refractory or stage III cancers. The final decision also extends coverage to repeat testing when the patient has a new primary diagnosis of cancer."

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