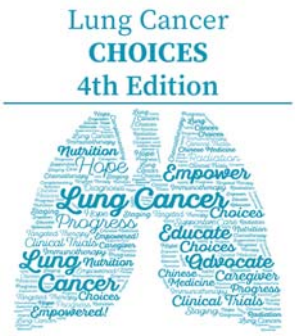

Chapter 6

Clinical Trials and Emerging Therapies for Lung Cancer

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Introduction

Clinical research continues to identify and develop novel treatment options for lung cancer patients. Multiple new treatments have been made commercially available over the past few years, while others still in the developmental pipeline remain available only to patients who participate in clinical trials. There are several different classes of systemic therapy used to treat lung cancer, including chemotherapy, targeted therapy, and immunotherapy. Although traditional chemotherapy remains an important tool for lung cancer treatment, both targeted therapies and immunotherapies are playing an increasingly important role in treatment, particularly for patients diagnosed with advanced stages of the disease.

Instead of attacking all rapidly dividing cells the way chemotherapy does, targeted therapies concentrate on specific genetic abnormalities unique to some tumors, often resulting in fewer side effects and the potential for improved cancer control. Targeted therapies can pinpoint specific DNA mutations in the tumor and utilize them to prevent cancer cells from growing and dividing out of control. Targeted therapies may be used alone or in combination with other treatments to improve overall survival. The drawback to targeted therapies is that they can only be utilized by a select group of patients who have tumors with unique DNA mutations. As a result, these therapies are not indicated for all patients.

Immunotherapy is a newer type of targeted therapy that is appropriate for many lung cancer patients.

Immunotherapy is a newer type of targeted therapy that is appropriate for many lung cancer patients. Immunotherapy medications interact with certain receptors on tumor cells and immune cells to change the way the body reacts to a tumor, often allowing the immune system to recognize and attack tumors. In some cases, turning on the immune system with the help of immunotherapy can even cause the body to completely eliminate

the tumor. Immunotherapies are showing great promise in lung cancer as well as in many other types of advanced malignancies.

While many of the recently approved therapies appear to be very promising, chemotherapy remains an important part of the treatment plan for many lung cancer patients, and researchers continue to evaluate the effect of combining chemotherapy with immunotherapies and targeted therapies in an effort to further improve outcomes for patients diagnosed with lung cancer. Other areas of research include the utilization of targeted agents and chemotherapy for lung cancer maintenance therapy (prevention of relapse) and medications to prevent lung cancer (chemoprevention) in patients at high risk for developing this disease. The recently approved targeted and immunotherapies are already improving progression-free and overall survival rates for lung cancer patients, but there is more work to be done. Research and clinical trials continue to evaluate the best use of novel therapeutic agents in an effort to improve the quality of life and longevity of patients with lung cancer.

Clinical Trials

Drug development begins with the identification of new substances that show anti-cancer activity in research laboratories. Following extensive laboratory testing, clinical trials are done to establish whether these substances are safe and effective at fighting cancer in people. The purpose of clinical trials is to identify new agents that can improve survival or quality of life compared to currently available treatments.

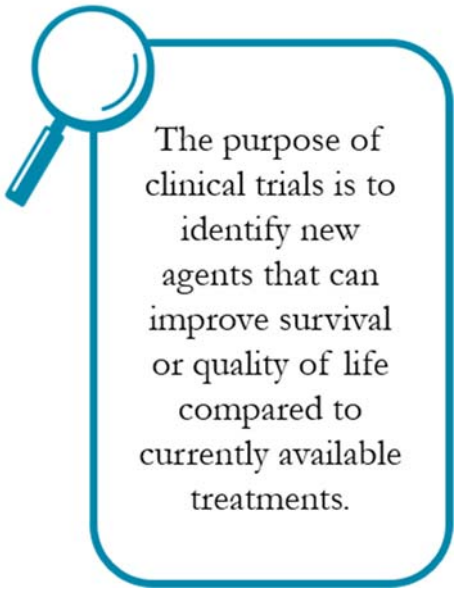
Clinical trials of new drugs are done in a series of phases, each with a specific purpose. If the drug is safe and provides benefit in an early phase trial, it is further tested in subsequent phases:

Phase 1: the drug is tested for the first time in people to establish safety, tolerability, dosage, and treatment schedule for subsequent studies.

Phase 2: the drug is tested in a larger group of people to continue to evaluate efficacy and safety, and to identify the range and severity of side effects.

Phase 3: the drug is tested in an even larger group of people to determine whether or not the new drug is more effective than existing treatments. Side effects and safety also are monitored. FDA approval for drugs is typically based on the results of Phase 3 trial data.

Phase 4: after approval by the United States Food and Drug Administration (FDA), the drug is available for use in the general population and further monitored for safety, efficacy, and long-term side effects.

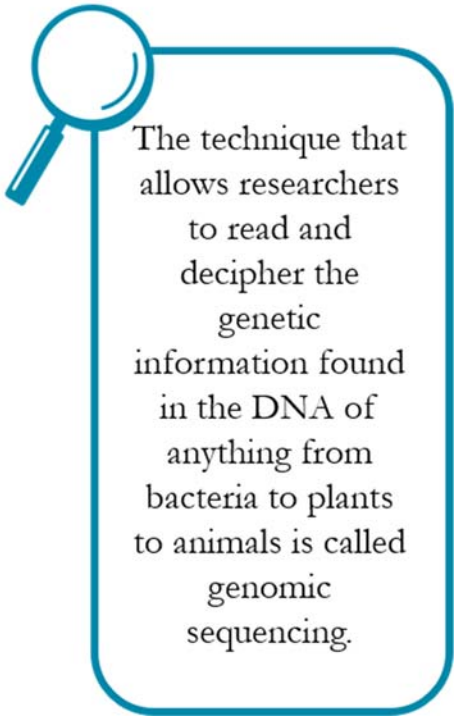


During Phases 1 to 3, the drugs are available only to patients who participate in the clinical trial. In phase 4, the drugs are commercially available through drug stores and specialty pharmacies. Clinical trials have historically been available only at major medical centers but are increasingly becoming available at smaller community medical centers due to the expansion of hospital networks. A list of all clinical trials available for lung cancer patients is provided on the Internet site of the National Cancer Institute (http://www.cancer.gov/clinicaltrials/search). The treating oncologist may recommend trials that are available locally, as well as at regional medical centers.

Sometimes new drugs that demonstrate a major increase in efficacy compared with older therapies are granted FDA Breakthrough Therapy or Fast Track status. The status expedites the development and FDA review process with the goal of making these exciting new treatments available to patients in the shortest possible time while still preserving the research process and maintaining patient safety. Drugs with Fast Track Status or Breakthrough Therapy designation are initially available only in clinical trials, but typically move through the clinical trial process and become widely available through commercial dispensing pharmacies much more quickly than if they had followed traditional approval pathways. Certain targeted therapies have shown such improvement in efficacy and tolerability compared to standard therapies that they have moved from Phase 1 "first in human trials" to FDA approval in under four years. Shortening the timeline for moving novel drugs from the laboratory into the clinic for patient use has clear benefit for improving patient outcomes, particularly in lung cancer where for many years, there has been a clearly documented need for new and improved treatments.

Targeted Therapy

Chemotherapy drugs work by killing cancer cells that multiply rapidly. However, many normal cells also multiply rapidly, such as cells of the digestive tract, hair follicles, and blood. When these normal cells are affected by chemotherapy drugs, undesirable side effects occur. Targeted therapy includes newer drugs that interfere with specific aspects of cancer cells, minimizing damage to normal cells. Targeted therapy consists of either monoclonal antibodies (drug names ending in "-ab") that target the outside surface of the cancer cell or small molecules (drug names ending in "-ib") that target the inside of the cancer cell.



As genetic research advances, great strides are being taken to better understand the molecular make-up of tumors, and to determine the mechanisms which drive tumor development, growth, and spread to other organs (metastasis). The wider availability of full genome sequencing of tumor DNA is opening up the opportunity for truly personalized medicine, in which therapies are

targeted to the specific genetic make-up of an individuals' tumor. Genome sequencing offers the opportunity to identify rare mutations and then design a treatment plan to block the exact mechanism that is making the cancer grow. Examples of well-studied mutations that are common in lung cancer are EGFR mutations, EML4-ALK gene rearrangements, and KRAS mutations. Newer targets being researched in lung cancer include ROS1, BRAF, HER2, MET, PIK3CA, RET, MEK, and NTRK. Several drugs used to target these mutations have been approved by the FDA for either lung cancer or other types of cancer, while many of the novel agents listed below are available only through clinical trials.

Monoclonal Antibodies

Monoclonal antibodies are one type of signaling molecule that binds to receptors on the cell surface. When these signaling molecules stimulate cell surface receptors, they initiate a cascade of messages inside the cell that promotes cellular growth and development. The normal cellular controls for this process are absent in malignant cells, and cellular replication proceeds uncontrolled. Antibodies are produced by the immune system to fight infections caused by bacteria or viruses, and the body produces specific antibodies for each type of infectious agent (antigen) to which the body is exposed. Identification of tumor-specific antigens allows novel drugs to use the immune response to recognize and fight cancer cells. This class of drugs, known as monoclonal antibodies, are produced in a laboratory and are designed to bind with a very specific target, such as a cell surface receptor or other defects unique to cancer cells.

Monoclonal antibodies fight cancer cells through several mechanisms, including:

- Blocking cell surface receptors to turn off the downstream cell signaling cascade.
- Targeting specific defects in the cancer cells or labeling the cancer cells, making them more vulnerable to destruction by the body's immune system.
- Delivering other drugs or substances directly to the cancer cells.

It should be noted that many of the recently approved immunotherapies used in treating lung cancer patients are monoclonal antibodies. See Chapter 3: *Systemic Therapy for Non-Small Cell Lung Cancer*

Trastuzumab is a monoclonal antibody that targets HER2 overexpression. It has been used in HER2 positive breast cancer (received FDA approval for this application in 1998) and is now being evaluated in lung cancers with the same mutation. Common side effects include nausea, vomiting, loss of appetite, fatigue and muscle or joint aches.[1] Cardiac toxicity can be a serious complication, and warrants close monitoring.[2] Allergic reactions may occur during the infusion of this drug. If used in combination with chemotherapy, it may contribute to decreased white blood cell count and increased risk of infection.

JNJ-61186372 (JNJ-372) is an antibody with activity against EGFR and cMet mutations. It is currently being evaluated in Phase 1 clinical trials for patients who have progressed on first-line EGFR directed therapy. Side effects included dermatologic toxicities such as rash, paronychia, and

pruritus, as well as diarrhea, shortness of breath, leg swelling, and infusion reactions. The response rate was 28% in the evaluable patient population. Further testing in an expansion cohort is ongoing.[3]

Telisotuzumab Vedotin (ABBV-399) is a c-Met–targeted antibody-drug conjugate. Results of the Phase 1b study of telisotuzumab vedotin in combination with erlotinib in patients with lung cancer harboring an EGFR mutation and c-Met amplification showed a response rate of up to 35%. Side effects included rash, diarrhea, nausea, vomiting, fatigue, neuropathy, and loss of appetite. An increased risk of blood clots was seen as well.[4]

Small Molecules

Small molecule drugs are a large class of medications that work by entering the cell and blocking the sequence of reactions that cause cellular proliferation. By blocking this sequence of reactions in cancer cells, the small molecule drugs kill the cancer cells and slow or stop tumor growth. In normal cells, tyrosine kinase enzymes activate a phosphorylation cascade that regulates signals sent to the cell nucleus and governs the timing of cellular proliferation, differentiation, and programmed cell death (apoptosis). In malignant cells, this communication cascade may be switched on permanently, resulting in unregulated cellular proliferation and tumor growth. Tyrosine kinase inhibitors are small molecule drugs that interfere with this sequence of reactions, stopping cell proliferation and causing cell death. New tyrosine kinase inhibitors continue to be studied for use in lung cancer, and several are now commercially available for patients with specific, targetable mutations in tumor DNA. During treatment with small molecules the cancer cells may develop additional mutations that confer resistance to first-line therapy. Identification of second and third-line therapies that continue to exploit the underlying driver mutation but also block resistance mutations has become increasingly important. EGFR and ALK are two well established therapeutic targets for small molecule inhibitors. However, multiple newer targets continue to be identified, offering patients a chance at treating their disease while maintaining better quality of life with fewer side effects than they might have with chemotherapy.

EGFR inhibitors

Nazartinib (EGF816) is a third generation EGFR inhibitor with activity against exon 19 deletion, L858R and T790m mutations. It is currently being evaluated in Phase III trials in the first-line setting. Common side effects included rash, diarrhea, itching, mouth sores, and fatigue. Response rate in the Phase 2 trial was 64%, The 6-month duration of response rate was 91%, and the median duration of response was not estimable. Nazartinib also demonstrated good intracranial efficacy, with 53% of patients with baseline brain metastasis experiencing resolution of their intracranial disease. Currently this drug is available only through clinical trials.[5]

"We may encounter many defeats, but we must not be defeated."
- Maya Angelou

Because of the higher prevalence of EGFR mutations in Asian patients, there are several trials being conducted exclusively in Asia to evaluate the safety and tolerability of novel EGFR directed compounds. Two examples of these medications are DO316 and YH25448.[6-7]

ALK inhibitors

Brigatinib (AP-26113) is an ALK inhibitor that is being evaluated for use in the first-line after recently receiving approval in the second-line setting for patients whose tumors harbor an EML4-ALK rearrangement. Phase 3 trial results are promising, with a greater than 70% response rate.[8] Like several other second and third generation ALK inhibitors it also showed anti-cancer activity in the brain, which was exciting as ALK+ NSCLC tends to spread to the brain. Respiratory changes were seen in a small percentage of patients within the first 7 days of dosing, additional research is being done to further evaluate this phenomenon. This compound is tolerated quite well, with mild side effects including diarrhea, nausea, vomiting, and fatigue.

Ensartinib (X-396) is a potent ALK inhibitor with anti-cancer activity against both treatment naïve tumors and those that developed resistance to first-line therapy with Crizotinib. In the Phase 1 trial over 80% of patients responded to therapy, with observed activity in the brain.[9] Response lasted for a median duration of more than 20 weeks with some responses lasting for over 50 weeks. Common side effects included rash, fatigue, nausea, vomiting and swelling. Responses were also observed in the central nervous system, with an intracranial response rate of 64%. Phase 3 trial data are expected to be published in 2020. However, it is unclear how this agent would fit into the treatment paradigm, as it does not appear to have unique properties when compared to current ALK-inhibitors that are already FDA approved.

ROS-1 Inhibitors

Because the ROS1 signaling receptor target is conformationally quite similar to that of ALK and TRK, Lorlatinib (FDA approved for use with ALK rearrangements) is also being evaluated for efficacy against ROS1 in Phase 2 trials, with promising results.[10] Although not FDA approved, Lorlatinib is recommended by NCCN guidelines for second-line therapy in patients with ROS1 rearrangement after they progress on Crizotinib.

AB-106 (DS-6051b) is a new selective ROS1/NTRK inhibitor that showed promising pre-clinical data and is currently undergoing Phase 1 testing in both the US and Japan.[11] In the initial first in human dose escalation trial there were six NSCLC patients with ROS1 rearrangements who were treated with AB-106. Of these six patients two had partial responses and two had stable disease.[12] The compound is exciting to researchers as it has been shown to have activity against the secondary resistance mutation G2032R, which commonly develops after first-line ROS directed targeted therapies such as crizotinib, and also confers resistance to the next-generation inhibitors Lorlatinib and Entrectinib.

Ceritinib has been shown to have activity in the front-line setting for lung cancer patients whose tumors have a ROS-1 rearrangement. Unlike for those patients with ALK rearrangement, Ceritinib does not seem to have second-line activity after progression on Crizotinib for ROS1-rearranged

tumors. A Phase 2 trial with 32 patients showed a 62% response rate and 81% disease control rate. Activity in the brain was demonstrated, with a 63% disease control rate, although the sample size was small at only 5 patients with brain metastases.[13] Common side effects include diarrhea, nausea, vomiting, loss of appetite, and lab value changes including increased liver function enzymes and low phosphate levels.[14] Currently Ceritinib is recommended in the NCCN guidelines for first-line use in ROS1rearranged NSCLC, but it does not yet have FDA approval in this indication.

Cabozantinib is a multi-kinase inhibitor with activity against several cell signaling targets including ROS-1 rearrangement. It is being evaluated in lung cancer following progression on Crizotinib and Ceritinib. In particular, it has shown efficacy against the G2032R and L2026M resistance mutations found in ROS-1 rearranged tumors.[15-16] Safety and efficacy of Cabozantinib continues to be evaluated in lung cancer, but common side effects when used in other types of cancer included nausea, diarrhea, fatigue, mouth sores, and hand-foot syndrome (redness, pain, tingling and numbness to hands and feet).[17]

Repotrectinib has demonstrated safety and activity in clinical trials (TRIDENT-1) for patients with advanced ROS-1 fusion NSCLC, with response rates of 82% in the TKI-naïve patient population. Repotrectinib also showed a potential to overcome TKI resistance mutations after treatment with Crizotinib. It is generally well tolerated, with mild dizziness, dyspnea and hypoxia in some patients. Given the promising results from the Phase 1 trial, the Phase 2 portion of TRIDENT-1 is set to begin in the fall of 2019.[18-19]

BRAF Inhibitors

Encorafenib (Braftovi) is a BRAF inhibitor currently being studied in clinical trial in combination with Binimetinib in patients with advanced NSCLC whose tumors have a BRAF V600E mutation. Trial enrollment began in June 2019, no results in lung cancer patients have been published to date. The combination was approved for melanoma patients with this mutation in 2018. Side effects have been shown to include fatigue, nausea, diarrhea, vomiting, abdominal pain, and arthralgia. This combination may be less likely to cause fevers than other BRAF targeted therapies .[20]

LGX818 is a new BRAF inhibitor that is being evaluated both as monotherapy in an open-label, and in combination with the MEK inhibitor MEK162. A triplet therapy with MEK162 and LEE011 is also being considered in early phase clinical trials.[21] Because these compounds are in early stages of clinical trial evaluation little safety, efficacy and response data are available. However, pre-clinical data suggests that these agents and combinations show promising activity in the BRAF mutant lung cancer patient population.[22]

MEK inhibitor

Selumetinib is a small molecule drug that has been studied in early phase clinical trials. It inhibits the mitogen-activated protein kinases MEK-1 and MEK-2. It stops cellular proliferation and induces apoptosis in some cell lines.[23] Common side effects include rash, diarrhea, nausea, vomiting, hypertension, visual disturbance, and decreased liver function. It has been evaluated in combination with chemotherapy for KRAS mutant lung cancer, and unfortunately was not found

to improve progression free survival when combined with docetaxel in the second-line setting. The TATTON trial showed that when combined with Tagrisso for EGFR-mutant patients Selumetinib does appear to have benefit, with 34-42% of patients having partial response, and disease control rate up to 81%.[24] Selumetinib continues to be evaluated in combination with immunotherapy in ongoing clinical trials.[25]

Bimetinib (MEK162) is being evaluated in combination with other therapeutic agents for lung cancer, including standard of care chemotherapy agents as well as other targeted therapies. Common side effects include diarrhea, fatigue, elevated lipase levels, and rash.[26] It continues to be evaluated in Phase 2 clinical trial for BRAF mutant NSCLC in combination with Encorafenib. It remains available through clinical trials only.

Additional Small Molecule Inhibitors

Multiple other targets continue to be discovered for NSCLC as science advances and the ability to test patients for multiple gene targets becomes a reality. These additional gene targets include HER2, MET amplification, MET exon 14 mutation, KRAS, RET, NTRK, PIK3CA, and MAP2K1 (also known as MEK1). Numerous drugs are currently being investigated that show activity against one or more of these targets. Interestingly, many of these drugs have more than one intra-cellular target and are being evaluated for application in different types of cancer as well as potentially being useful for multiple different tumor mutations. As the science of tumor genetic sequencing progresses more drug-gene targets will be established in an effort to truly personalize treatment to the genetic fingerprint of an individual patient's cancer, with continued improvement in treatment options and therapeutic outcomes for lung cancer patients.

MET

Capmatanib is a MET inhibitor that has been granted FDA breakthrough designation for first- and second-line treatment of patients with MET Exon 14 deletion mutations. It continues to be evaluated in the GEOMETRY mono-1 Phase 2 multi-cohort trial in the second-line setting. For patients in the first-line setting an initial response rate of 71% was reported, while in the second-line setting response rate was 39%. The drug appears tolerable with mainly mild side effects including nausea, vomiting, and swelling of the extremities. The GEOMETRY mono-1 trial remains ongoing and results will be updated as they become available.[27]

Savolitinib is a MET inhibitor currently being evaluated in combination with Osimertinib for use in patients who progress on first-line EGFR TKI therapy and demonstrate a MET exon 14 deletion as a resistance mechanism. In the TATTON trial the safety and efficacy of the combination of Savolitinib with Osimertinib was established. Results showed a response rate of 28% - 52%, depending on what treatment the patient had received in the front-line setting.[28-29] Side effects were somewhat more severe than observed with single agent dosing, with the most frequent side effects being nausea, diarrhea, fatigue, fevers, decreased appetite. and decreased blood cell counts (white blood cells and platelets). The combination of Savolitinib with Osimertinib continues to be evaluated in the Phase 2 SAVANNAH trial which began enrollment in early January 2019 .[30]

Tepotinib was recently granted breakthrough therapy designation by the FDA as second-line treatment for patients with MET exon 14 mutations based on data from the ongoing VISION study. There are currently no approved therapies that specifically target MET alternations. Overall response rates have been reported at 40-50% with median duration of response at 12.4 months. Most treatment-related adverse events were mild, and primarily included peripheral edema, nausea, diarrhea, and elevated creatinine. Of note, Tepotinib is also currently being evaluated in combination with Osimertinib for patients with EGFR mutated, MET amplified, locally advanced or metastatic NSCLC who acquired resistance prior to EGFR TKI therapy. Trial enrollment is ongoing.[31]

RET

Pralsetinib (BLU-667) is a novel selective RET inhibitor that was granted FDA Breakthrough Therapy Designation for patients with RET fusion-positive NSCLC who had progressed after platinum-based chemotherapy. In the Phase 1 ARROW trial, 58% of patients responded, including noted activity against intracranial metastases. Most common side effects were constipation, anemia, fatigue and hypertension, and were typically mild.[32]

Selpercatinib (LOXO-292) was granted breakthrough therapy designation by the FDA in 2018 after initial data form the Phase I/II LIBRETTO-001 trial showed promising results in patients with RET fusion-positive NSCLC. Response rates were reported at 68% with median duration of response of 20.3 months. Intracranial response rates were even higher, at 91% for patients with target lesions in the brain at baseline. Treatment related adverse events were mild and included diarrhea, hypertension, increased liver enzymes and fatigue.[33]

KRAS

KRAS mutations are among the most commonly found oncogenic drivers of tumorigenesis in lung cancer, however KRAS has historically been considered an "undruggable" mutation due to a lack of a traditional small-molecule binding pocket on the protein. As a result, there are currently no approved KRAS targeted therapies.

AMG-510 is being studied at the Phase 1 level as a novel small molecule inhibitor of KRAS-G12C and has showed encouraging anti-tumor activity. Out of 23 evaluable patients 48% had an objective response and the disease control rate was 96%. AMG-510 was well tolerated, and common side effects included decreased appetite, anemia, diarrhea, fatigue and headache. More severe events of anemia and diarrhea were reported in 9% of patients.[34] The promising nature of these data led the FDA to grant Fast Track status to AMG-510 in September 2019.[35] Additional clinical trial results are expected in 2020.

EGFR / HER2 Exon 20 insertion

Poziotinib is an oral tyrosine kinase inhibitor that is being evaluated in the Phase II ZENITH20 trial for lung cancer patients with EGFR or HER2 Exon 20 insertion mutations. Poziotinib irreversibly blocks signaling through the HER family of receptors, including HER1 (ErbB1/EGFR), HER2 (ErbB2), and HER4 (ErbB4). Response rates were encouraging, with tumor reduction seen in up to 58% of patients treated and at least stable disease seen in up to 90% of patients. Unfortunately, side effects have been problematic, with over 50% of patients experiencing moderate to severe symptoms, including rash, diarrhea, paronychia, mucositis, and fatigue. Enrollment in the ZENITH20 trial is ongoing.[36]

TAK-788 is an oral inhibitor of tumors with EGFR/HER2 exon 20 insertions. Currently in Phase 1/2 trial testing, it has a demonstrated overall response rate of 54%, however the cohort size tested was small, at 26 patients. Side effects included rash, GI symptoms such as diarrhea, nausea, loss of appetite, and mouth sores.[37]

Pyrotinib is another TKI with irreversible binding and pan-HER activity (i.e. it has activity against HER1 (EGFR), HER2 and HER4. It has been evaluated in several Phase 2 trials, in one case after patient had received at least one prior line of chemotherapy, with almost 60% having had at least 2 prior lines of chemotherapy.[38] Overall response rate was 31%. In another trial of 15 patients the response rate was higher, at 53%.[39] Although the data appear promising, the small cohort size warrants broader testing. Side effects were reported to be diarrhea as well as lab abnormalities.

Tarloxotinib and TAS6417 are two additional compounds being evaluated for use in the EGFR Exon 20 insertion mutation patient population, however the bulk of the data remain pre-clinical at this time.

Immunotherapy

Cancers develop and spread in part because they evade detection by the immune system. The goal of immunotherapy is to make cancer cells recognized as abnormal or "non-self" by the immune system, enabling natural immune defense mechanisms to eliminate the cancer. With immunotherapy, side effects are typically mild because the drugs affect only certain types of cells, and they use the body's own defenses (not cytotoxic drugs) to kill cancer cells. However, in some cases the immune system may become over-engaged, creating auto-immune inflammatory side effects. These side effects can be severe and may require treatment with immune suppressant medications.

Several antibodies have been developed that target immune checkpoints, which play a role in cell signaling and driving cancer growth. Some of the most promising developments in treating lung cancer have been seen with drugs that target the Programmed Death 1 (PD-1) receptor pathway, including Opdivo (Nivolumab), Keytruda (Pembrolizumab), Tecentriq (Atezolizumab), and

Imfinzi (Durvalumab). Currently all four of these have been approved by the FDA for at least one indication in lung cancer treatment.

Ipilimumab and Tremelimumab are monoclonal antibodies that inhibit the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immune checkpoint pathway. Although these agents have been used extensively in the treatment of melanoma, they are now being evaluated in NSCLC, typically in combination with the Anti-PD1 class of drugs.[40] They have a similar side effect profile to the Anti-PD1 antibodies, including rash, diarrhea/colitis, hepatitis, iritis/uveitis, hormonal changes and pneumonitis. However, side effects tend to be more common with Anti-CTLA-4 drugs compared to Anti PD-1 and Anti-PD-L1 compounds.[41]

NKTR-214 (Bempegaldesleukin) is a CD122-preferential IL-2 pathway agonist that was designed to enhance the patient's own immune response in order to fight their cancer. It is currently being evaluated in clinical trials in combination with Nivolumab or with Nivolumab and Ipilimumab. Common side effects are fatigue, fevers, chills, and flu-like symptoms. Enhancing the immune response is felt to be particularly important for those patients whose tumors do not express PD-L1.

APX005M is a CD40 Agonistic Antibody being studied in combination With Nivolumab and Cabiralizumab. This drug was designed to stimulate the immune system and enhance the anti-cancer immune response. There is limited data for NSCLC, however a Phase 1 trial reported on four patients of whom one had a partial response, two had stable disease and the fourth progressed.[42] Side effects include fatigue, malaise, nausea, fevers, chills and flu like symptoms. The Phase 2 trial continues to enroll patients, with results forthcoming.

NC318 is a novel monoclonal antibody targeting Siglec-15. It was designed to function in the tumor microenvironment and enhance t-cell function, thereby restoring the ability of the immune system to recognize and fight off cancer cells. Currently only pre-clinical data have been published and suggest a tolerable safety profile with less risk of serious immune-related toxicity than the anti-PD-1 and anti-CTLA4 targeted antibodies have previously demonstrated.[43] The initial Phase1/2 clinical trial is currently enrolling patients and has an expected completion date in May 2021.

While the compounds noted above and the majority of lung cancer clinical trials continue to be designed to help patients diagnosed with stage IV disease, many immunotherapy drugs are also being tested for use in patients diagnosed with earlier stage lung cancer because of their potential for considerable clinical benefit. In stage III unresectable disease Durvalumab was FDA approved for use as maintenance therapy and other immunotherapies are now being used in combination with chemotherapy and radiation. In stage II and resectable stage III patients, the LCMC3 trial is investigating the use of atezolizumab prior to surgery. This approach has demonstrated major pathologic response with less than 10% viable tumor remaining after 2 cycles of atezolizumab in 19% of patients.[44]Another trial evaluating response to combination immunotherapy prior to surgery is the NEOSTAR trial, which is enrolling stage I – IIIA patients and is using a combination of Nivolumab and Ipilimumab. In this trial major pathologic responses were seen in 44% of patients following resection .[45]

Another type of cancer treatment that has received a lot of attention recently is CAR-T therapy. It is currently approved for several types of blood cancers, but its utility in solid tumors, and in lung cancer in particular remains unclear. Part of the challenge in lung cancer is identifying a target unique to the cancer cells that is not present elsewhere in the body. Too much overlap between the presence of the target in the tumor and healthy tissues will result in the patient suffering severe side effects due to off target impacts of the treatment. Rather than CAR-T cells, a perhaps more promising avenue in solid tumor is to develop specific tumor infiltrating lymphocytes (TILs) that are unique to a particular patient and will recognize and eliminate their specific cancer cells. Trials are currently enrolling patients where researchers collect a tumor specimen from a patient and then isolate the active TILs, increase their number exponentially in a lab, and then infuse them back into the patient. The TIL therapy regimen is quite intense, almost like a mini bone marrow transplant. First the patient undergoes a biopsy to collect tumor tissue. If adequate tissue is obtained, then the patient is admitted to the hospital for several weeks of chemotherapy. During this time the TILs are being isolated and grown in the lab. If the patient is clinically stable after the chemotherapy, they will then receive the infusion of TILs along with other immune stimulatory agents, after which they a monitored closely for potentially severe side effects.

Tumor Mutational Burden

Immune Checkpoint Inhibitors are a mainstay of lung cancer treatment and continue to show improved efficacy in comparison with chemotherapy in the first- and second-line setting. Unfortunately, only about 20% of patients demonstrate durable long-term responses to these drugs, while a significant proportion of patients experience disease progression within the first months of treatment. PD-L1 expression level is currently the only biomarker approved by the FDA, yet it is not perfect, and seems to correlate with treatment response in some but not all patients. One cannot ignore the high cost of these immunotherapy medications (as much as $150,000/year), and from a purely economic perspective a better marker to identify response is needed to avoid wasteful spending of healthcare dollars. For these reasons, a new set of biomarkers must be developed that will better guide clinicians and help identify those patients who will benefit from immune checkpoint inhibitors.

Tumor mutational burden (TMB) is one potential marker of response to immunotherapies. TMB is defined as the number of mutations per DNA megabases. It continues to be studied as a potential biomarker to predict response to immune checkpoint inhibitors in NSCLC.[46] To date, responses from clinical trials have been mixed, with some trials showing a predictive association between high TMB and treatment response, while others not finding the same predictive relationship.[47-48]

Because of the potential for long-term durable responses with immunotherapies, any marker selected to guide treatment selection will have to be well validated with extensive clinical support. Limiting treatment options and potentially preventing patients from the benefit of these novel therapies needs to be considered with the utmost caution.

Corticosteroids and ICI

Recent research has brought into question whether or not steroid use affects clinical outcomes during treatment with immunotherapies. Some studies have demonstrated that patients who received corticosteroids prior to starting ICI therapy experienced lower overall response rates, worse progression free survival, and poorer overall survival.[49]

One large retrospective study looked to determine the effect of corticosteroid use specifically in the treatment of immune-related adverse effects and found that there was no significant difference in overall survival (median; 14.5 vs 30.0 months), progression-free survival (median; 7.8 vs 9.6 months), and objective response rate (46% vs 41%) in patients who required steroids (>10mg per day) vs those who did not. They concluded that steroids should not be avoided in patients with moderate to severe immune-related adverse effects due to concerns over reduced efficacy.[50]

Gut Microbiome and Cancer Treatment

Another avenue of research in cancer treatment is the effect of the gut microbiome on overall health, promotion of pathogenic conditions including tumor development and treatment outcomes. A recent report documented stark differences in gut flora of patients following cancer treatments compared to their healthy peers. It has long been understood that antibiotics can change the gut microbiome, and it has become clear that use of antibiotics can impact response to immune checkpoint inhibitor therapy. Several studies have demonstrated significant reduction in progression free and overall survival when antibiotics are administered in the 30 days prior to initiation of immunotherapy treatment.[51-53] Methods for how best to restore gut balance and enhance the positive effects of the microbiome on health are currently under investigation.

Vaccines

Vaccines are also being used to treat lung cancer and as maintenance therapy with the goal of decreasing or preventing the risk of recurrence. Analogous to vaccines that may prevent the spread of communicable diseases, these cancer vaccines stimulate the immune system to identify and attack cancer cells without damaging normal cells.

Vaccines are also being used to treat lung cancer and as maintenance therapy with the goal of decreasing or preventing the risk of recurrence.

CIMAvax-EGF is also known as the "Cuban Vaccine" and is currently available in the US through a Phase 1/2 trial. It is being evaluated in combination with the anti-PD1 checkpoint inhibitor nivolumab (Opdivo®) in patients previously treated for advanced non-small cell lung cancer (NSCLC). Response rate was 51%. Side effects have been reported to include fevers, injection site irritation, diarrhea, nausea, vomiting, rash and muscle aches.[54-55]

TG4010 is targeted immunotherapy based on a pox virus (the Modified Vaccinia Ankara virus) that codes for the MUC1 tumor-associated antigen and

interleukin-2. TG4010 has been assessed in combination with first-line chemotherapy in advanced NSCLC and has shown an improvement in progression-free survival.[56] Common side effects include injection site reaction and flu-like symptoms.[57] TG4010 continues to be evaluated in Phase 2 and 3 clinical trials, and is now being combined with chemotherapy as well as Opdivo (Nivolumab).[58] Additional data on this combination of drugs is expected to be published in late 2019.

BI 1361849 (CV9202) is a vaccine that is made up of six mRNAs that code for six different NSCLC-associated antigens. Phase 1 trials have demonstrated safety and tolerability of the compound, as well as an enhanced anti-tumor effect when combined with radiation.[59] Collection of survival data remains ongoing. The most common side effects were injection site reactions and mild to moderate flu like symptoms. As it is thought that this compound may increase tumor infiltrating lymphocytes, a trial combining it with an immunotherapeutic agent targeting Anti-PD-1 was performed with modest responses seen in the 26 enrolled patients, including one partial response and 46% of patients with stable disease.[60]

Chemotherapy

Although much research is focusing on new approaches to lung cancer treatment, research also is being done to develop new drugs for chemotherapy or improve existing chemotherapy regimens. Combination therapy has long been the hallmark of cancer treatment. As promising new agents are identified, they are evaluated in clinical trials in an effort to identify novel treatment modalities that will improve quality of life and prolong survival. Multiple trials evaluating the addition of small molecules, monoclonal antibodies, as well as immunotherapy are currently underway.

Chemoprevention

Multiple studies have been conducted to identify compounds that might prevent the development of lung cancer. Unfortunately, to date none have been identified that have demonstrated a dramatic decrease in cancer rates.[61] Antioxidants and anti-inflammatory drugs like COX-2 inhibitors did not ultimately show a decreased cancer incidence, but aspirin seemed to slightly decrease risk in several studies, particularly in those at highest risk for developing lung cancer.[62] A better understanding of features of pre-malignant lesions continues to develop, and a personalized "cocktail" may ultimately offer the best protection against developing lung cancer in high risk individuals.[63] Unfortunately no compound has been identified that has protective effects against lung cancer. Smoking cessation remains the best approach available to prevent an individual from developing lung cancer.

Lung Cancer Screening Programs

Because 1 in 9 smokers will go on to develop lung cancer, avoiding exposure to tobacco smoke and smoking cessation remain the best defense against lung cancer.[63] See Chapter 11: *How to Quit Smoking Confidently and Successfully*. However, novel screening algorithms are being developed for use of low-dose screening CT scans in order to identify both those individuals at highest risk for lung cancer, as well as to identify cancers in an early, asymptomatic, surgically resectable and thus more treatable stage. The best lung cancer screening programs are comprehensive, and include the services of pulmonary experts, as well as oncologists and counselors who can educate patients regarding their risk of developing cancer as well as interpret and appropriately act on any screening test results.

Conclusion

Lung cancer is a devastating diagnosis, but research is improving both the options for treatment of this disease as well as patient outcomes. Chemotherapy has been the mainstay of treatment for most advanced lung cancers for many years. However, new targeted therapies and immunotherapies are changing the treatment landscape for lung cancer, with several new drugs demonstrating remarkable improvement in patient outcomes in terms of both progression free and overall survival. Additional novel agents used both alone and in combination with existing agents are being studied in clinical trials, with the goal of further improving patient outcomes and survival. More therapies will become available in the near future. With advances in lung cancer treatment, patients will benefit from treatments that have fewer side effects and provide long term responses to treatment, such that even if lung cancer remains incurable, it may be treated as a chronic disease and managed for many years.

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When you need treatment for lung cancer, you may want to think about joining a clinical trial. Like all treatment options, clinical trials have possible benefits and risks. By looking closely at all options, including clinical trials, you are taking an active role in shared decision making in your treatment plan. See Questions to Ask at the end of the book for a comprehensive list of suggested questions to ask yourself, your doctor, and the clinical trial coordinator.

Notes

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