**Questions and Responses**

Expert consensuses, modified questions, and ChatGPT responses are numerically ordered by NCCN guideline to allow for cross referencing across tables. Relevant preferred or category 1 therapies used for grading are bolded.

Expert Consensus

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| Q# | NCCN Reccomendation |
| NSCL-21 | For EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS discovered prior to first-line systemic therapy:  **Preferred Osimertinib (category 1**) Other Recommended Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous) (category 1) or Erlotinib (category 1) or Afatinib (category 1) or Gefitinib (category 1) or Dacomitinib (category 1) or Erlotinib + ramucirumab or Erlotinib + bevacizumab |
| NCSL-22 | For EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS with progression on osimertinib which is symptomatic, systemic, and contains multiple lesions:  **Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous) (category 1) (Preferred)** or Systemic therapy,  Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5) |
| NCSL-23 | For EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS with progression on erlotinib (± ramucirumab or bevacizumab), afatinib, gefitinib, or dacomitinib:  • Consider definitive local therapy (eg, SABR or surgery) for limited lesions • Osimertinib (if T790M+) (category 1) or Continue erlotinib (± ramucirumab or bevacizumabss) or afatinib or gefitinib or dacomitinib (if T790M-) |
| NSCL-24 | For EGFR S768I, L861Q, and/ or G719X mutations discovered prior to first-line systemic therapy:  **Preferred Afatinib  or Osimertinib**  Other Recommended Erlotinib  or Gefitinib  or Dacomitinib |
| NSCL-25 | For EGFR EXON 20 INSERTION MUTATION: **Amivantamab-vmjw + carboplatin/ pemetrexed (nonsquamous) (category 1) (Preferred)** or Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5) |
| NSCL-27 | For ALK rerrangment discovered prior to first-line systemic therapy: **Preferred** **Alectinib (category 1) or Brigatinib (category 1**) or **Lorlatinib (category 1**) Other Recommended Ceritinib (category 1) Useful in Certain Circumstances Crizotinib (category 1) |
| NSCL-30 | For ROS1 rearrangment discovered prior to first-line systemic therapy:  **Preferred Entrectinib or Crizotinib  or Repotrectinib** or Other Recommended Ceritinib |
| NSCL-32 | For BRAF V600E mutation discovered prior to first-line systemic therapy:  **Preferred Dabrafenib + trametinib  or Encorafenib + binimetinib**  Useful in Certain Circumstances Vemurafenib or dabrafenib  Other Recommended Systemic Therapy for Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell C |
| NSCL-33 | For NTRK1/2/3 gene fusion discovered prior to first line systemic therapy:  **Preferred Larotrectinib or Entrectinib or Repotrectinib** Useful in Certain Circumstances Systemic Therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5) |
| NSCL-34 | For METex14 skipping mutation discovered prior to first-line systemic therapy:  **Preferred Capmatinib  or Tepotinib**  Useful in Certain Circumstances Crizotinib  or Systemic Therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5) |
| NSCL-35 | For RET rearrangement discovered prior to first-line systemic therapy:  **Preferred** **Selpercatinib  or Pralsetinib**  Useful in Certain Circumstances Cabozantinib  Other Recommended Systemic Therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5) |
| NSCL-36 | For patients with ERBB2 (HER2) MUTATION who demonstrate progression following systemic therapy with carboplatin: **Preferred Fam-trastuzumab deruxtecan-nxki** or Other Recommended Ado-trastuzumab emtansine |

Modified Question

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| Q# | Modified Question |
| NSCL-21 | Given an advanced lung adenocarcinoma patient with EGFR p. L858R mutations. What therapy or therapies would be preferred? |
| NCSL-22 | Given an advanced lung adenocarcinoma patient with EGFR p. L858R mutations, demonstrating progression on osimertinib and multiple metastases. What therapy or therapies would be preferred? |
| NCSL-23 | Given an advanced lung adenocarcinoma patient with progression on aftatinib and EGFR p. L858R, T790M mutations. What therapy or therapies would be preferred? |
| NSCL-24 | Given an advanced lung adenocarcinoma patient with G719X mutations. What therapy or therapies would be preferred? |
| NSCL-25 | Given an advanced lung adenocarcinoma patient with EGFR Exon 20 Asp770\_Asn771ins mutations. What therapy or therapies would be preferred? |
| NSCL-27 | Given an advanced lung adenocarcinoma patient with EML4-ALK fusion mutations. What therapy or therapies would be preferred? |
| NSCL-30 | Given an advanced lung adenocarcinoma patient with no prior treatment and CD74-ROS1 fusion mutations. What therapy or therapies would be preferred? |
| NSCL-32 | Given an advanced lung adenocarcinoma patient with no prior treatment and BRAF V600E fusion mutations. What therapy or therapies would be preferred? |
| NSCL-33 | Given an advanced lung adenocarcinoma patient with ETV6-NTRK3 mutations. What therapy or therapies would be preferred? |
| NSCL-34 | Given an advanced lung adenocarcinoma patient with MET c.3028 + 2T>C mutations. What therapy or therapies would be preferred? |
| NSCL-35 | Given an advanced lung adenocarcinoma patient with CCDC6::RET gene fusion mutations. What therapy or therapies would be preferred? |
| NSCL-36 | Given an advanced lung adenocarcinoma patient with ERBB2 A775\_G776insYVMA mutations, demonstrating recurrence after treatment with cisplatin and pemetrexed. What therapy or therapies would be preferred? |

ChatGPT4

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| Q# | ChatGPT4 Response |
| NSCL-21 | For patients with advanced lung adenocarcinoma who have an EGFR exon 21 L858R mutation, targeted therapy with tyrosine kinase inhibitors (TKIs) is typically recommended. Here are some of the specific treatment options often considered:  First-Generation EGFR TKIs: These include drugs like erlotinib and gefitinib. These have been widely used as first-line treatments in patients with EGFR mutations, including the L858R mutation. They target the ATP binding site of the EGFR tyrosine kinase, which is critical for the cancer cell's growth and survival.  Second-Generation EGFR TKIs: Afatinib and dacomitinib fall into this category. They offer a broader inhibition of the ErbB family of receptors and may be used as initial treatment in some settings. These drugs tend to have a slightly different side effect profile and may be more potent but can also have increased toxicity.  Third-Generation EGFR TKIs: Osimertinib is a more recent addition, highly effective for patients with EGFR T790M mutations, which often develop as resistance mechanisms to first- and second-generation TKIs. However, it's also increasingly used as a first-line treatment due to its effectiveness and better penetration of the blood-brain barrier, which is beneficial for patients with or at risk of brain metastases.  Combination Therapies: Research is ongoing into the benefits of combining EGFR TKIs with other therapies, including chemotherapy, angiogenesis inhibitors (like bevacizumab), and potentially immunotherapy, though the latter may be less effective in EGFR-mutant lung cancer compared to other types of non-small cell lung cancer.  The choice of specific therapy often depends on several factors including the patient's overall health, presence of other mutations or health conditions, potential side effects, and prior treatments. Decisions are typically made by an oncologist specializing in lung cancer, often in consultation with a multidisciplinary team. Furthermore, clinical trials might offer access to newer therapies and combinations that are not yet widely available but could be beneficial depending on the individual patient’s condition. |
| NCSL-22 | For a patient with advanced lung adenocarcinoma harboring EGFR p.L858R mutations, showing progression on osimertinib with multiple metastases, the treatment approach needs to consider several factors including the specific mechanisms of resistance to osimertinib, the patient’s performance status, previous treatments, and the presence of specific genomic alterations. Here are some potential strategies:  Biopsy and Molecular Testing: It's crucial to identify the mechanism of resistance to osimertinib. A repeat biopsy and comprehensive genomic profiling can reveal mutations or alterations such as C797S mutation, MET amplification, or other bypass track activations, which can guide further treatment. Liquid biopsy might also be considered if a tissue biopsy is not feasible.  Combination Therapies: Based on the results of the resistance mechanisms, combination therapies can be considered. For example:  If MET amplification is detected, combining a MET inhibitor (like capmatinib or crizotinib) with osimertinib might be effective. For patients with a C797S mutation, a combination of a first or second-generation EGFR TKI (like erlotinib or afatinib) with osimertinib could be considered. Chemotherapy: If targeted therapy options are not viable or if the cancer has a broad resistance profile, systemic chemotherapy could be the next step. Options typically include pemetrexed-based regimens, possibly combined with platinum agents, depending on what the patient has previously received.  Clinical Trials: Enrolling in a clinical trial could provide access to novel therapies or combinations that are not available otherwise. Trials may focus on new EGFR inhibitors, combination therapies targeting resistance mechanisms, or emerging treatments like antibody-drug conjugates or immune therapies tailored to specific genetic alterations.  Supportive Care and Local Treatments: In addition to systemic therapy, supportive care to manage symptoms and improve quality of life is essential. Palliative radiotherapy might be considered for symptom control or to manage specific sites of painful or life-threatening metastases.  Each of these options should be discussed with a multidisciplinary team to tailor the approach based on the specific clinical situation of the patient. The choice of therapy often involves balancing the potential benefits with the side effects and the patient’s preferences and overall health status. |
| NCSL-23 | For a patient with advanced lung adenocarcinoma who has shown progression on afatinib and has EGFR mutations p.L858R and T790M, the preferred treatment option is typically a third-generation EGFR tyrosine kinase inhibitor (TKI). Osimertinib is specifically designed to target both the initial activating EGFR mutations (like L858R) and the resistant T790M mutation. It has shown significant efficacy in this patient population.  Osimertinib is approved for the treatment of patients with metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR TKI therapy. This recommendation is based on clinical trials that have demonstrated osimertinib’s ability to improve progression-free survival and overall survival in this specific group of patients.  Additionally, it would be prudent to conduct comprehensive genomic profiling at the time of progression to identify any other potential actionable mutations or alterations that could influence therapy choices. This can include testing for other resistance mechanisms or mutations in genes such as MET, HER2, or BRAF, which might open up additional targeted therapy options or eligibility for clinical trials.  Furthermore, discussing the case in a multidisciplinary team setting and considering the patient’s overall health status, previous treatments, and potential side effects is crucial in making an individualized treatment plan. If osimertinib is not suitable, or if further progression occurs, options may include chemotherapy, immunotherapy, or participation in clinical trials exploring novel agents or combinations.  It’s also recommended to closely monitor the patient for side effects and to manage these proactively to improve the quality of life and treatment adherence. |
| NSCL-24 | In the case of a lung adenocarcinoma patient with G719X mutations, targeted therapy options are particularly important to consider. The G719X mutation is a specific type of mutation in the epidermal growth factor receptor (EGFR) gene, which can be effectively targeted with certain tyrosine kinase inhibitors (TKIs). Here are the preferred therapies based on current guidelines and clinical evidence:  Osimertinib: This is a third-generation EGFR tyrosine kinase inhibitor that is highly effective against tumors with EGFR mutations, including G719X. Osimertinib is generally well-tolerated and has shown high efficacy in various clinical trials. It is often used as a first-line treatment for EGFR-mutant non-small cell lung cancer (NSCLC).  Other EGFR TKIs: First- and second-generation EGFR TKIs like erlotinib, gefitinib, and afatinib may also be considered. These agents have been used effectively in treating NSCLC with EGFR mutations. Among these, afatinib has been specifically studied and shown efficacy in treating patients with uncommon EGFR mutations including G719X.  Combination Therapies and Clinical Trials: For some patients, especially those who progress on initial therapy or have additional complicating factors, participation in clinical trials may be advisable. Trials might offer access to newer therapies or combinations of therapies that could be more effective based on the tumor’s genetic profile and previous treatment responses.  The choice of therapy should be guided by a thorough evaluation of the patient’s overall health, specific characteristics of the cancer, potential side effects, and the presence of any other mutations that might affect treatment efficacy. Regular monitoring and follow-up are essential to adjust the treatment plan as needed based on the patient’s response and any side effects experienced. |
| NSCL-25 | The treatment of advanced lung adenocarcinoma with EGFR Exon 20 insertion mutations involves specific targeted therapies. These mutations are somewhat less common and can be more challenging to treat than the more typical EGFR mutations like Exon 19 deletions or the L858R mutation. However, recent developments have led to new options specifically targeting Exon 20 insertions.  For patients with EGFR Exon 20 insertion mutations in non-small cell lung cancer (NSCLC), the following therapies are commonly considered:  Amivantamab (Rybrevant): This is a bispecific antibody targeting EGFR and MET receptors, approved by the FDA specifically for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutations. Amivantamab has shown effectiveness in shrinking tumors and managing disease progression in this particular subgroup of patients.  Mobocertinib (Exkivity): Mobocertinib is an oral tyrosine kinase inhibitor (TKI) that specifically targets EGFR Exon 20 insertion mutations. It has been approved by the FDA for patients with metastatic NSCLC harboring these mutations who have received prior platinum-based chemotherapy.  These therapies represent the most targeted and recent advancements for treating this specific mutation in lung adenocarcinoma. In practice, the choice between these options might depend on the patient's overall health, prior treatments, potential side effects, and specific characteristics of the mutation.  It is also important to discuss the case in a multidisciplinary team and consider clinical trials, as ongoing research may provide access to emerging therapies or novel combinations that could be beneficial.  In addition to targeted therapy, the management plan may include other supportive care measures and treatments depending on the patient's general condition and the presence of symptoms or complications from the disease. |
| NSCL-27 | For patients with advanced lung adenocarcinoma who have an EML4-ALK fusion mutation, targeted therapy using ALK inhibitors is typically the preferred treatment approach. This mutation leads to the expression of an abnormal ALK protein that drives cancer cell growth, and ALK inhibitors can specifically target and block the activity of this protein. Here are some of the common ALK inhibitors used:  Crizotinib: This was the first ALK inhibitor approved by the FDA and is often used as a first-line treatment for ALK-positive non-small cell lung cancer (NSCLC).  Ceritinib: Approved for use in patients who have become resistant to crizotinib or as a first-line treatment.  Alectinib: It has shown high efficacy and is often used as a first-line therapy due to its ability to also effectively treat or prevent brain metastases, which are common in ALK-positive NSCLC.  Brigatinib: Also used after crizotinib resistance, or as a first-line treatment. It has shown potent activity against ALK mutations and good control of brain metastases.  Lorlatinib: A newer ALK inhibitor that is effective against several known ALK mutations that confer resistance to earlier-generation ALK inhibitors. It is typically used after other ALK inhibitors have failed.  The choice of specific ALK inhibitor can depend on several factors, including:  The patient's overall health and presence of other medical conditions. Potential side effects of the drug. Previous treatments the patient has undergone. The presence of brain metastases. Resistance mutations in the ALK gene. Ongoing clinical trials continue to evaluate the efficacy of existing ALK inhibitors and explore new therapeutic options, which could potentially offer better outcomes and manage resistance mechanisms. Regular testing and monitoring for resistance mutations can guide adjustments in therapy to maintain control of the disease.  It is important for treatment to be guided by a medical oncologist who specializes in lung cancer, and who can provide personalized treatment plans based on the most up-to-date research and clinical guidelines. |
| NSCL-30 | For an advanced lung adenocarcinoma patient with the CD74-ROS1 fusion mutation who has not previously been treated, the preferred therapeutic approach typically centers on targeted therapy using ROS1 inhibitors. ROS1 is a receptor tyrosine kinase, and mutations involving ROS1 fusions can drive cancer development by activating signaling pathways that promote cell growth and survival. Here are some key points and treatment options:  Crizotinib: This is an oral small-molecule inhibitor that targets ROS1 and has been shown to be effective in treating ROS1-positive non-small cell lung cancer (NSCLC). It was the first ROS1 inhibitor approved by the FDA for this purpose based on the results of clinical trials demonstrating significant tumor response rates and progression-free survival benefits.  Other ROS1 Inhibitors: Additional targeted therapies for ROS1-positive NSCLC include:  Entrectinib: This drug is a newer generation inhibitor that also targets NTRK and ALK in addition to ROS1. It is particularly noted for its ability to penetrate the central nervous system, making it useful in cases where there is brain involvement. Lorlatinib: Another option for patients, particularly those who may have developed resistance to earlier treatments like crizotinib. Lorlatinib is a third-generation inhibitor that targets ALK and ROS1 and has shown activity against brain metastases. Monitoring and Management of Resistance: While ROS1 inhibitors can be highly effective, resistance to therapy often develops. It is important to monitor the patient’s response and consider biopsies or liquid biopsies to detect resistance mutations. This can guide the choice of subsequent lines of therapy, including switching to different ROS1 inhibitors or combining with other treatments.  Clinical Trials: Given the rapidly evolving landscape of targeted therapies, participation in clinical trials can be considered to access novel therapeutic options that might be beneficial.  Comprehensive Care: Beyond targeted therapies, the management of an advanced lung cancer patient should include supportive care to manage symptoms, improve quality of life, and address any complications of the disease or its treatment.  It is crucial for treatment to be guided by an oncologist specialized in lung cancer, who can tailor therapy choices to the specific genetic profile and overall health status of the patient. Regular follow-ups and adjustments in the treatment plan based on the response to therapy and evolving clinical evidence are key components of effective management. |
| NSCL-32 | For a patient with advanced lung adenocarcinoma harboring a BRAF V600E mutation, specific targeted therapies are recommended based on current clinical guidelines and research findings. The BRAF V600E mutation is a specific genetic alteration that can be effectively targeted by BRAF inhibitors, which are drugs designed to directly inhibit the activity of the mutated BRAF protein.  The standard therapy for lung adenocarcinoma patients with this mutation typically involves:  BRAF Inhibitors: These drugs specifically target the BRAF V600E mutation. Vemurafenib and dabrafenib are examples of BRAF inhibitors that have shown efficacy in treating various cancers with BRAF mutations, including melanoma and lung cancer.  Combination Therapy with MEK Inhibitors: Combining BRAF inhibitors with MEK inhibitors (another type of targeted therapy) has been found to enhance treatment efficacy and overcome resistance that might develop with BRAF inhibitor monotherapy. For instance, the combination of dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) has been approved for use in non-small cell lung cancer (NSCLC) with BRAF V600E mutations. This combination has been shown to improve survival rates and reduce the risk of disease progression compared to treatment with BRAF inhibitors alone.  Clinical trials have supported the use of these combinations, demonstrating significant benefits in terms of response rate and progression-free survival. It's crucial for treatment decisions to be based on a comprehensive evaluation by an oncologist, who can consider the patient’s overall health, the extent of the disease, potential side effects, and the latest clinical guidelines and research data.  Additionally, supportive care to manage symptoms and improve quality of life is vital in the treatment plan for advanced lung adenocarcinoma patients. |
| NSCL-33 | The presence of the ETV6-NTRK3 fusion gene in a patient with advanced lung adenocarcinoma suggests that targeted therapy using TRK inhibitors could be particularly effective. The ETV6-NTRK3 gene fusion results in the expression of a chimeric tropomyosin receptor kinase (TRK) protein, which can be specifically targeted by TRK inhibitors. Here’s a breakdown of the relevant therapies:  TRK Inhibitors: Drugs like larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) are FDA-approved TRK inhibitors that have shown high efficacy in treating tumors harboring NTRK gene fusions, including those in lung cancer. These drugs work by specifically targeting and inhibiting the activity of TRK fusion proteins, which drive the growth and survival of cancer cells.  Clinical Trials: For patients with this specific mutation, participation in clinical trials can be considered if standard therapies do not yield satisfactory results or if the patient is eligible for trials exploring new therapies or combinations of existing therapies.  Comprehensive Genomic Profiling: It's also important to perform comprehensive genomic profiling of the tumor to identify any other potential actionable mutations that might inform additional targeted therapy options or combinations.  Other Therapies: Depending on the patient's overall health, extent of disease, and previous treatments, other standard treatments for advanced lung adenocarcinoma—such as chemotherapy, immunotherapy, or a combination thereof—might also be considered, often in conjunction with targeted therapies.  Deciding on the best course of action should involve a detailed discussion with a multidisciplinary oncology team, taking into account the patient's overall condition, prior treatment history, and specific genetic findings. Always, the patient's preferences and quality of life considerations should play a central role in choosing the therapy. |
| NSCL-34 | For patients with advanced lung adenocarcinoma harboring specific MET mutations, treatment approaches can vary based on the type of mutation and the evidence supporting the efficacy of certain therapies. The MET c.3028+2T>C mutation is a splice-site mutation, which could potentially affect the normal splicing of the MET gene transcript, thereby altering the function of the MET protein. Such mutations can lead to aberrant activation of the MET signaling pathway, which is implicated in tumor growth and survival.  The treatment options might include the following:  MET Inhibitors: Targeted therapies with MET inhibitors could be beneficial. Currently, there are several MET inhibitors that have shown promise in clinical trials for treating MET-altered lung cancers, including:  Capmatinib (Tabrecta): Approved by the FDA for metastatic non-small cell lung cancer (NSCLC) with MET exon 14 skipping mutations. Although primarily indicated for exon 14 skipping mutations, it might also show activity in other MET dysregulations. Tepotinib: Another MET inhibitor approved for MET exon 14 skipping mutations in NSCLC. Similar to capmatinib, its efficacy could potentially extend to other MET-related alterations depending on the specific mutation characteristics and clinical evidence. Clinical Trials: Given the specific and less common nature of the MET c.3028+2T>C mutation, participation in clinical trials could be a valuable option to access novel therapies or new uses of existing drugs that are not yet approved for this specific mutation.  Comprehensive Genomic Profiling: It's crucial to perform comprehensive genomic profiling of the tumor to identify any other actionable mutations or alterations that could influence treatment decisions. This may open up additional targeted therapy options or combination therapies based on the tumor’s genomic landscape.  Chemotherapy and Immunotherapy: If targeted therapy is not suitable or if the disease progresses on targeted treatments, standard treatment options such as chemotherapy and immunotherapy may be considered, depending on the patient’s overall health, prior treatments, and specific clinical factors.  It is essential for treatment decisions to be made in a multidisciplinary setting, incorporating the insights from oncologists, pathologists, and possibly genetic counselors. This ensures that all aspects of the patient's disease and personal health are considered to optimize treatment outcomes. Furthermore, ongoing monitoring and re-evaluation of the disease response to treatment are important to adjust the therapy plan as needed. |
| NSCL-35 | For a patient with advanced lung adenocarcinoma featuring a CCDC6-RET gene fusion, targeted therapy specifically designed to inhibit the RET protein would be the preferred treatment option. RET gene fusions are a known driver mutation in non-small cell lung cancer (NSCLC), including adenocarcinomas, and can be effectively targeted by certain drugs.  As of my last update, several RET-specific inhibitors have shown promise and have been approved by regulatory agencies like the FDA:  Selpercatinib (Retevmo): This drug is a selective RET kinase inhibitor that has been approved for the treatment of adult patients with metastatic RET fusion-positive NSCLC. Clinical trials have demonstrated significant efficacy in shrinking tumors and in some cases, prolonged disease control.  Pralsetinib (Gavreto): Similar to selpercatinib, pralsetinib is another RET inhibitor that has been approved for use in patients with RET fusion-positive NSCLC. It offers another effective option for targeting tumors driven by RET alterations.  Both of these drugs are typically considered when a RET fusion is identified, given their targeted mechanism of action which can lead to better outcomes and potentially fewer side effects compared to conventional chemotherapy.  The choice between these therapies may depend on specific patient factors including the overall health of the patient, presence of any other mutations or health conditions, prior treatments, and potentially the specific characteristics of the RET fusion. Moreover, the choice might be influenced by the availability of the drug, insurance coverage, and patient or physician preference.  Continual monitoring and testing are crucial as resistance to these therapies can develop, and adjustments to the treatment regimen may be necessary over time. Also, it’s important for the medical team to manage any side effects associated with these therapies to ensure the best possible quality of life for the patient. |
| NSCL-36 | The treatment for a lung adenocarcinoma patient with an ERBB2 (also known as HER2) A775\_G776insYVMA mutation who has shown recurrence after initial treatment with cisplatin and pemetrexed can be complex and should be guided by updated clinical data and trials, along with the advice of a multidisciplinary oncology team. The A775\_G776insYVMA is a specific insertion mutation in the HER2 gene that can affect treatment response and options. Here are some considerations and potential therapies:  1. HER2-Targeted Therapy: Patients with HER2 mutations may benefit from HER2-targeted therapies. Drugs such as trastuzumab (an anti-HER2 monoclonal antibody), often used in breast cancer, have been studied in lung cancers with HER2 mutations. However, the efficacy in lung cancer, especially with specific mutations like A775\_G776insYVMA, may vary and is still under investigation. 2. Tyrosine Kinase Inhibitors (TKIs): Small molecule TKIs that target HER2, such as afatinib, have shown some promise in non-small cell lung cancer (NSCLC) with HER2 mutations. These drugs inhibit the kinase activity of the HER2 protein, which can help control tumor growth. 3. Clinical Trials: Given the recurrent nature of the disease and the specific mutation, participation in clinical trials may be an optimal approach to access novel therapies and regimens that are not yet widely available. These might include newer HER2 inhibitors or combination therapies targeting multiple pathways. 4. Chemotherapy and Immunotherapy: Depending on the patient’s overall health, performance status, and previous treatment history, further chemotherapy or immunotherapy might be options. Drugs such as docetaxel (a chemotherapy agent) or pembrolizumab (a PD-1 inhibitor immunotherapy) could be considered, particularly if there is no specific targeted therapy available. 5. Comprehensive Genomic Profiling: It’s also advisable to perform comprehensive genomic profiling of the tumor if not already done. This can help identify additional actionable mutations or fusions that may be targeted with specific therapies. 6. Palliative Care: For managing symptoms and maintaining quality of life, palliative care should be integrated into the treatment plan, especially in cases of advanced disease.  The choice of therapy should be personalized based on the detailed genetic makeup of the tumor, the patient’s prior treatment history, and overall health. Consultation with a specialist in thoracic oncology who is knowledgeable about the latest treatments and research is crucial. |

ChatGPT4o

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| Q# | ChatGPT4o Response |
| NSCL-21 | For an advanced lung adenocarcinoma patient with EGFR p. L858R mutations, the preferred therapy is typically a targeted therapy using an EGFR tyrosine kinase inhibitor (TKI). The choice of EGFR TKIs includes:  First-line therapy options:  Osimertinib (Tagrisso): This is often the preferred first-line treatment due to its efficacy and favorable side effect profile. Osimertinib has shown superior overall survival and progression-free survival compared to first- and second-generation TKIs in patients with EGFR mutations. Erlotinib (Tarceva), Gefitinib (Iressa), and Afatinib (Gilotrif): These are first- and second-generation TKIs that were previously standard first-line treatments. While still effective, they are generally considered less favorable compared to osimertinib due to a higher risk of certain side effects and lower overall efficacy. Subsequent therapy options if resistance develops or if there is disease progression:  If the patient initially receives a first- or second-generation TKI and develops resistance due to a secondary EGFR T790M mutation, Osimertinib can be used as a second-line therapy. In the absence of T790M mutation, or after progression on osimertinib, subsequent treatment options may include chemotherapy, other targeted therapies based on additional molecular profiling, or inclusion in clinical trials. Combination therapies:  Recent studies and ongoing clinical trials are exploring the combination of EGFR TKIs with other agents like anti-angiogenic drugs (e.g., bevacizumab) or immune checkpoint inhibitors. However, these combinations are not yet standard and should be considered based on individual patient factors and availability of clinical trials. Summary For an advanced lung adenocarcinoma patient with EGFR p. L858R mutations, Osimertinib is currently the preferred first-line therapy due to its efficacy and safety profile. If resistance develops, especially due to T790M mutation, osimertinib remains a viable second-line option. Otherwise, further treatment decisions should be guided by additional molecular testing and patient-specific factors. |
| NCSL-22 | For a patient with advanced lung adenocarcinoma with EGFR p. L858R mutation who has progressed on osimertinib and has multiple metastases, the following therapeutic options can be considered:  Combination Chemotherapy: Platinum-based doublet chemotherapy (e.g., carboplatin or cisplatin combined with pemetrexed) is often considered standard treatment after progression on EGFR TKIs like osimertinib.  Immunotherapy: Immune checkpoint inhibitors such as pembrolizumab, nivolumab, or atezolizumab can be considered, especially if the tumor expresses PD-L1. However, the efficacy of immunotherapy in EGFR-mutant lung cancers has been generally lower compared to EGFR wild-type cancers.  Combination of Chemotherapy and Immunotherapy: Combining chemotherapy with immunotherapy, such as pembrolizumab plus pemetrexed and platinum-based chemotherapy, may be considered based on the patient's overall health and PD-L1 status.  Clinical Trials: Enrolling in clinical trials can provide access to novel therapies, including new targeted therapies, combination regimens, or next-generation EGFR TKIs. For instance, trials involving drugs targeting MET amplification or other resistance mechanisms might be relevant.  Targeted Therapies for Resistance Mechanisms: If specific resistance mechanisms are identified (e.g., MET amplification, HER2 mutations, or BRAF mutations), targeted therapies against those alterations might be beneficial. This requires molecular testing to identify these mechanisms.  Local Therapy: For patients with oligometastatic disease (limited number of metastases), local treatments such as stereotactic body radiation therapy (SBRT) or surgery might be considered for disease control.  Supportive Care and Symptom Management: In cases where further aggressive therapy is not suitable, focusing on symptom management and improving quality of life through palliative care is important.  It is crucial to personalize the treatment plan based on the patient's overall health, performance status, specific resistance mechanisms, and preferences. Multidisciplinary discussions involving oncologists, radiologists, and other healthcare professionals are often necessary to determine the best approach. |
| NCSL-23 | For a patient with advanced lung adenocarcinoma who has the EGFR p.L858R and T790M mutations and has progressed on afatinib, the next line of therapy typically involves a third-generation EGFR tyrosine kinase inhibitor (TKI). The preferred therapy in this case is:  Osimertinib (Tagrisso): This third-generation EGFR TKI is specifically designed to target both the EGFR T790M resistance mutation and the common activating mutations such as p.L858R. Osimertinib has shown significant efficacy in patients with the T790M mutation and is often the treatment of choice in this scenario. Additional Considerations:  Clinical Trials: Participation in clinical trials can provide access to new therapies and combinations that might be beneficial, especially if standard options are exhausted.  Combination Therapies: Emerging evidence suggests potential benefits from combining EGFR TKIs with other treatments such as immune checkpoint inhibitors, anti-angiogenic agents, or other targeted therapies. However, these approaches are generally considered within clinical trials or specific clinical contexts.  Systemic Chemotherapy: If the patient progresses on osimertinib or if osimertinib is not suitable, standard chemotherapy regimens such as pemetrexed and platinum-based doublet chemotherapy might be considered.  Local Therapies: For oligoprogression (progression limited to a few sites), local treatments such as radiotherapy or surgery combined with continuation of osimertinib may be considered.  The choice of therapy should be personalized based on the patient's overall health, prior treatments, specific genetic mutations, and other factors. Regular monitoring and assessment by an oncologist specializing in lung cancer are essential to optimize treatment outcomes. |
| NSCL-24 | For a patient with advanced lung adenocarcinoma harboring G719X mutations, the preferred therapies typically involve targeted treatments, specifically those that target EGFR (epidermal growth factor receptor) mutations. G719X mutations are less common but still significant EGFR mutations that can respond to EGFR tyrosine kinase inhibitors (TKIs). The preferred therapies include:  First-Generation EGFR TKIs:  Gefitinib Erlotinib These drugs have shown efficacy in patients with uncommon EGFR mutations, including G719X, though they might have varying degrees of effectiveness compared to more common mutations. Second-Generation EGFR TKI:  Afatinib: Clinical data suggest that afatinib can be effective in patients with G719X mutations. It has been shown to provide a more comprehensive inhibition of the EGFR family and can be effective against a broader spectrum of EGFR mutations. Third-Generation EGFR TKI:  Osimertinib: While primarily used for T790M-positive EGFR mutations, osimertinib has shown some activity against a variety of uncommon EGFR mutations, though specific data for G719X mutations might be limited. In some cases, combination therapies or clinical trials involving novel agents may be considered, especially if the patient has progressed on standard EGFR TKIs.  It is also essential for the treating oncologist to consider the overall clinical condition of the patient, potential side effects, and other comorbidities when choosing the appropriate therapy. Molecular testing and a multidisciplinary approach can further help in tailoring the best treatment strategy for the patient. |
| NSCL-25 | For a patient with advanced lung adenocarcinoma harboring EGFR exon 20 insertions, including the specific Asp770\_Asn771ins mutation, the treatment landscape is evolving, but there are several preferred therapies based on the latest clinical guidelines and research.  Mobocertinib (Exkivity): This is an oral tyrosine kinase inhibitor specifically approved by the FDA for patients with EGFR exon 20 insertion mutations in advanced non-small cell lung cancer (NSCLC) who have progressed on or after platinum-based chemotherapy. Mobocertinib targets these specific mutations and has shown efficacy in clinical trials.  Amivantamab-vmjw (Rybrevant): This is an intravenous bispecific antibody that targets EGFR and MET. It is also approved by the FDA for the treatment of patients with NSCLC with EGFR exon 20 insertion mutations who have disease progression on or after platinum-based chemotherapy.  Platinum-Based Chemotherapy: Traditionally, patients with advanced lung adenocarcinoma, including those with EGFR exon 20 insertions, might be treated initially with platinum-based chemotherapy regimens (such as cisplatin or carboplatin combined with pemetrexed). This approach can still be used, especially in patients who have not received prior chemotherapy.  Clinical Trials: Participation in clinical trials can provide access to emerging therapies and novel targeted treatments that may be effective against EGFR exon 20 insertion mutations. Ongoing research and clinical trials are essential for discovering new treatments and combinations.  Immune Checkpoint Inhibitors: While generally less effective as monotherapy in patients with EGFR mutations, immune checkpoint inhibitors like pembrolizumab (Keytruda) or nivolumab (Opdivo) may be considered in combination with chemotherapy or in patients with high PD-L1 expression after other options have been exhausted.  It is important for the treating oncologist to consider the patient's overall health, prior treatments, and specific mutation characteristics when selecting the most appropriate therapy. Consulting with a specialized cancer center or a molecular tumor board can also help in tailoring the best treatment approach for the individual patient. |
| NSCL-27 | For a patient with advanced lung adenocarcinoma harboring an EML4-ALK fusion mutation, the preferred therapies would typically be ALK inhibitors. These targeted therapies are designed to specifically inhibit the activity of the ALK fusion protein, which drives cancer cell growth. The following ALK inhibitors are commonly used:  Alectinib (Alecensa): Often preferred as the first-line treatment due to its efficacy and favorable side effect profile. Brigatinib (Alunbrig): Another effective first-line treatment option. Ceritinib (Zykadia): Can be used as a first-line treatment or for patients who have progressed on crizotinib. Crizotinib (Xalkori): The first ALK inhibitor approved, but now often used when other therapies are not available or suitable. Lorlatinib (Lorbrena): Typically used for patients who have progressed on other ALK inhibitors. The choice among these therapies can depend on various factors, including the patient's overall health, presence of brain metastases, and prior treatments. Alectinib and brigatinib are frequently preferred due to their higher efficacy and better central nervous system penetration compared to crizotinib.  It's essential for treatment to be personalized, considering potential side effects and the patient's overall condition. Consultation with a medical oncologist specializing in lung cancer is crucial to determine the most appropriate therapy. |
| NSCL-30 | For a patient with advanced lung adenocarcinoma harboring a CD74-ROS1 fusion mutation and no prior treatment, the preferred therapies are typically targeted therapies that specifically inhibit ROS1. The following therapies are recommended based on current clinical guidelines and evidence:  Crizotinib: This is often the first-line treatment for patients with ROS1-positive lung adenocarcinoma. Crizotinib is a tyrosine kinase inhibitor (TKI) that targets ALK, ROS1, and MET. It has shown significant efficacy in patients with ROS1 rearrangements.  Entrectinib: Another targeted therapy option, entrectinib is also a TKI that inhibits ROS1, TRK, and ALK. It is approved for the treatment of ROS1-positive non-small cell lung cancer (NSCLC) and has shown efficacy in both systemic disease and brain metastases.  Lorlatinib: This TKI is primarily known for its use in ALK-positive NSCLC, but it is also effective against ROS1-positive lung cancer. Lorlatinib can be considered especially in cases where the cancer has progressed on crizotinib, due to its ability to penetrate the blood-brain barrier and its activity against certain ROS1 resistance mutations.  In addition to these targeted therapies, comprehensive genomic profiling should be considered to identify any other potential mutations or alterations that could influence treatment decisions. Close monitoring for response to therapy and any emerging resistance mutations is also crucial, as it may necessitate a change in therapeutic strategy.  These therapies are preferred due to their targeted mechanism of action, which tends to result in higher response rates and more favorable side effect profiles compared to traditional chemotherapy. |
| NSCL-32 | For an advanced lung adenocarcinoma patient with no prior treatment and BRAF V600E fusion mutations, targeted therapy is the preferred treatment option. The recommended therapies are as follows:  Dabrafenib (Tafinlar) plus Trametinib (Mekinist): This combination targets the BRAF V600E mutation and has shown significant efficacy in treating lung adenocarcinoma patients with this specific mutation. Dabrafenib is a BRAF inhibitor, and Trametinib is a MEK inhibitor. Together, they block the signaling pathways that contribute to cancer cell growth and survival.  Monotherapy with Dabrafenib: In some cases, especially if the combination therapy is not tolerated, monotherapy with Dabrafenib can be considered.  These targeted therapies are preferred because they specifically inhibit the aberrant signaling caused by the BRAF V600E mutation, leading to more effective and tailored treatment outcomes for patients with this genetic alteration. |
| NSCL-33 | For a patient with advanced lung adenocarcinoma and an ETV6-NTRK3 gene fusion, the preferred therapy would involve targeting the NTRK (neurotrophic tyrosine receptor kinase) fusion. The main options for this specific genetic alteration are:  Larotrectinib (Vitrakvi): This is a highly selective TRK inhibitor designed to treat solid tumors with NTRK gene fusions. It is often the first choice due to its specificity and efficacy in targeting NTRK fusions.  Entrectinib (Rozlytrek): Another TRK inhibitor that targets NTRK gene fusions as well as ROS1 and ALK gene fusions. Entrectinib is effective in treating tumors with these genetic alterations, including those in the central nervous system.  Both of these therapies have shown substantial efficacy in patients with NTRK fusion-positive cancers, including lung adenocarcinoma. The choice between the two may depend on specific patient factors, such as the presence of brain metastases (where entrectinib might be preferred due to its better CNS penetration) and the side effect profile.  It's essential to have a multidisciplinary team approach, involving oncologists, genetic counselors, and other specialists, to tailor the treatment plan to the patient's specific clinical scenario. Regular monitoring and adjustments based on response and tolerance to the therapy are also crucial. |
| NSCL-34 | For a patient with advanced lung adenocarcinoma harboring a MET c.3028 + 2T>C mutation, targeted therapy options are particularly relevant. The MET exon 14 skipping mutations are known to be sensitive to MET inhibitors. Here are the preferred therapies:  Capmatinib (Tabrecta): Capmatinib is a MET inhibitor specifically approved for the treatment of metastatic non-small cell lung cancer (NSCLC) with MET exon 14 skipping mutations. Clinical trials have shown significant efficacy in patients with this mutation.  Tepotinib (Tepmetko): Tepotinib is another MET inhibitor approved for the treatment of adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations. It has demonstrated efficacy in clinical studies.  Crizotinib (Xalkori): Crizotinib, initially approved for ALK-positive NSCLC, has also shown activity against MET exon 14 skipping mutations. It can be considered when other MET inhibitors are not available or suitable.  These therapies specifically target the aberrant MET signaling pathway caused by the exon 14 skipping mutation, which is believed to drive cancer growth and progression in this subset of lung adenocarcinoma patients.  Additional Considerations: Biopsy and Molecular Testing: It is crucial to confirm the presence of the MET exon 14 skipping mutation through comprehensive genomic profiling. This ensures the mutation is accurately identified and targeted therapy is appropriate. Combination Therapy: In certain cases, combining MET inhibitors with other treatments such as immune checkpoint inhibitors or chemotherapy may be considered, depending on the patient’s overall condition and response to initial treatments. Monitoring and Management of Side Effects: MET inhibitors can have side effects, including gastrointestinal issues, edema, and liver function abnormalities. Regular monitoring and supportive care are essential to manage these effects. Emerging Therapies and Clinical Trials: Patients may also consider enrolling in clinical trials investigating new MET inhibitors or combination therapies that might provide additional benefit. Consulting with a medical oncologist who specializes in lung cancer and is aware of the latest research and clinical trials is crucial for optimal treatment planning. |
| NSCL-35 | For a patient with advanced lung adenocarcinoma harboring a CCDC6::RET gene fusion mutation, the preferred therapies would typically include targeted therapies specifically designed to inhibit RET (rearranged during transfection) kinase activity. The main options include:  Selpercatinib (Retevmo): This is a highly selective RET inhibitor that has shown efficacy in patients with RET fusion-positive non-small cell lung cancer (NSCLC). It has been approved by the FDA for this indication.  Pralsetinib (Gavreto): Another selective RET inhibitor, also approved by the FDA for the treatment of RET fusion-positive NSCLC.  These therapies are preferred due to their targeted action against RET gene fusions, leading to more effective management of the cancer with potentially fewer side effects compared to traditional chemotherapy.  In addition to targeted therapies, treatment plans might also consider:  Clinical trials: Participation in clinical trials exploring new RET inhibitors or combination therapies might be an option, depending on the patient's eligibility and availability of trials. It is important for the treating oncologist to evaluate the patient’s overall health, prior treatment history, and specific characteristics of the tumor before deciding on the best course of therapy. Regular monitoring and adjustments may also be necessary based on the patient's response and any side effects experienced. |
| NSCL-36 | For a patient with advanced lung adenocarcinoma harboring ERBB2 (HER2) A775\_G776insYVMA mutations who has shown recurrence after treatment with cisplatin and pemetrexed, the following targeted therapies are preferred:  1. Trastuzumab Deruxtecan (T-DXd): This is an antibody-drug conjugate specifically targeting HER2. It has shown significant efficacy in patients with HER2-mutant non-small cell lung cancer (NSCLC). 2. Afatinib: This is a pan-HER tyrosine kinase inhibitor (TKI) that has shown activity against HER2 mutations. While it is not as specific as trastuzumab deruxtecan, it can still be effective in this setting. 3. Poziotinib: Another TKI that has shown promising results in clinical trials for HER2-mutant NSCLC, particularly for those with exon 20 insertion mutations. 4. Mobocertinib (TAK-788): This is another TKI that has been shown to be effective against HER2 exon 20 insertion mutations. 5. Neratinib: A pan-HER inhibitor that has shown activity in HER2-mutant lung cancer in clinical trials. 6. Clinical Trials: Consideration should also be given to enrolling the patient in clinical trials investigating novel agents targeting HER2 or other pathways relevant to their specific mutation profile.  It is essential to have a multidisciplinary team involved in the decision-making process, including oncologists with expertise in targeted therapies and genetic counselors, to determine the most appropriate treatment plan based on the patient’s overall health, previous treatments, and specific mutation profile. |

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| NSCL-21 | For an advanced lung adenocarcinoma patient with EGFR p. L858R mutations, the preferred therapy is:  Osimertinib Evidence Supporting the Recommendation: Osimertinib is recommended as the preferred first-line therapy for patients with EGFR mutations, including p. L858R, due to its efficacy in improving progression-free survival and overall survival compared to earlier-generation EGFR inhibitors. Citation: ASCO Guidelines: "Osimertinib is the preferred first-line therapy for patients with EGFR p. L858R mutations"​​. NCCN Guidelines: "Osimertinib is recommended as the preferred treatment for EGFR mutation-positive NSCLC patients"​​. |
| NCSL-22 | For an advanced lung adenocarcinoma patient with EGFR p.L858R mutations who has demonstrated progression on osimertinib and has multiple metastases, the preferred therapies according to the latest guidelines are:  Amivantamab-vmjw + Carboplatin + Pemetrexed  Evidence Supporting the Recommendation: The combination of amivantamab-vmjw, a bispecific antibody targeting EGFR and MET, with carboplatin and pemetrexed has shown to improve progression-free survival (PFS) compared to chemotherapy alone. This is based on the MARIPOSA-2 phase 3 randomized trial, which demonstrated a longer median PFS for the combination therapy group compared to the chemotherapy group. Citation: NCCN NCSL 2024 Guidelines​​. Local Therapy (if limited progression)  Evidence Supporting the Recommendation: For patients with asymptomatic progression or symptomatic systemic progression limited in nature (oligoprogression), definitive local therapy such as stereotactic ablative radiotherapy (SABR) or surgery is recommended. This approach is also supported by the NCCN guidelines for specific scenarios including CNS progression. Citation: NCCN NCSL 2024 Guidelines​​. Re-biopsy and Testing for Resistance Mechanisms  Evidence Supporting the Recommendation: If systemic progression occurs, a biopsy is recommended to rule out transformation to small cell lung cancer (SCLC) and to evaluate mechanisms of resistance, which may guide subsequent therapy choices. Citation: NCCN NCSL 2024 Guidelines​​. These options align with the latest NCCN and ASCO guidelines for managing advanced NSCLC with EGFR mutations post-osimertinib progression​​​​. |
| NCSL-23 | For an advanced lung adenocarcinoma patient with progression on afatinib and the presence of EGFR p.L858R and T790M mutations, the preferred therapy according to the latest guidelines is:  Osimertinib Evidence Supporting the Recommendation: Osimertinib is specifically recommended for patients with EGFR T790M mutations who have progressed on first- or second-generation EGFR inhibitors such as afatinib. It has shown efficacy in targeting both the L858R and T790M mutations, providing a significant clinical benefit. Citation: NCCN Guidelines: "For patients with EGFR T790M mutation-positive NSCLC who have progressed on prior EGFR TKI therapy, osimertinib is the preferred treatment option." ​​ ASCO Guidelines: "Osimertinib is the preferred therapy for patients with EGFR T790M mutations after progression on previous EGFR inhibitors." ​​ |
| NSCL-24 | For an advanced lung adenocarcinoma patient with G719X mutations, the preferred therapies based on the latest guidelines are as follows:  Preferred First-Line Therapies Afatinib  Evidence Supporting the Recommendation: Afatinib has shown a response rate of 77.8% in patients with G719X mutations . Citation: NCCN NCSL 2024 Guidelines, Page NSCL-24; ASCO With Driver 2024 Guidelines, Page 42. Osimertinib  Evidence Supporting the Recommendation: Osimertinib demonstrated a median progression-free survival (PFS) of 8.2 months with an objective response rate of 53% in patients with G719X mutations . Citation: NCCN NCSL 2024 Guidelines, Page NSCL-24; ASCO With Driver 2024 Guidelines, Page 42. Other Recommended Therapies Erlotinib  Evidence Supporting the Recommendation: Erlotinib is listed as a recommended option, though it is not the preferred choice . Citation: NCCN NCSL 2024 Guidelines, Page NSCL-24. Gefitinib  Evidence Supporting the Recommendation: Gefitinib is included as an alternative therapy . Citation: NCCN NCSL 2024 Guidelines, Page NSCL-24. Dacomitinib  Evidence Supporting the Recommendation: Dacomitinib is mentioned as an alternative option . Citation: NCCN NCSL 2024 Guidelines, Page NSCL-24. The preference for afatinib and osimertinib is due to their higher efficacy in patients with uncommon EGFR mutations, including G719X, based on clinical trial data and guideline recommendations . |
| NSCL-25 | For a patient with advanced lung adenocarcinoma harboring EGFR Exon 20 Asp770\_Asn771ins mutations, the preferred therapy is:  Amivantamab Evidence Supporting the Recommendation: Amivantamab has shown efficacy in patients with EGFR Exon 20 insertions, including Asp770\_Asn771ins mutations. Clinical trials have demonstrated significant antitumor activity in this subgroup of patients, providing a viable treatment option. Citation: NCCN Guidelines, page 130​​. ASCO Guidelines, page 36​​. |
| NSCL-27 | For a patient with advanced lung adenocarcinoma with EML4-ALK fusion mutations, the preferred therapies based on the latest NCCN and ASCO guidelines are:  Alectinib  Evidence Supporting the Recommendation: Alectinib has demonstrated superior efficacy compared to crizotinib in the first-line setting for ALK-positive NSCLC, with improved progression-free survival (PFS) and a better safety profile. It is recommended as a preferred first-line therapy for ALK rearrangement-positive metastatic NSCLC. Citation: NCCN NCSL 2024 Guidelines , ASCO With Driver 2024 Guidelines . Brigatinib  Evidence Supporting the Recommendation: Brigatinib has shown superior PFS compared to crizotinib in clinical trials for ALK-positive NSCLC. It is also recommended as a preferred first-line therapy. Citation: NCCN NCSL 2024 Guidelines , ASCO With Driver 2024 Guidelines . Lorlatinib  Evidence Supporting the Recommendation: Lorlatinib has demonstrated significant intracranial efficacy and systemic responses in patients with advanced ALK-positive NSCLC, including those who have progressed on first- and second-generation ALK inhibitors. It is recommended as a preferred first-line therapy. Citation: NCCN NCSL 2024 Guidelines , ASCO With Driver 2024 Guidelines . These therapies are categorized as first-line treatments for patients with ALK rearrangements, with alectinib, brigatinib, and lorlatinib being the preferred options due to their efficacy and safety profiles. |
| NSCL-30 | For a patient with advanced lung adenocarcinoma with a CD74-ROS1 fusion mutation and no prior treatment, the preferred therapies according to the latest guidelines are:  Crizotinib  Evidence Supporting the Recommendation: Crizotinib has demonstrated significant efficacy in ROS1-positive NSCLC patients. In multiple studies, it has shown an objective response rate (ORR) of approximately 70-80%, with median progression-free survival (PFS) ranging from 15.9 to 20 months and median overall survival (OS) of 51.4 months. Citation: NCCN NCSL 2024 Guidelines​​ . Entrectinib  Evidence Supporting the Recommendation: Entrectinib has shown a high ORR of 77% in ROS1-positive NSCLC patients, with a median PFS of 15.7 months. It is particularly noted for its effectiveness in patients with CNS metastases. Citation: NCCN NCSL 2024 Guidelines​​ . Repotrectinib  Evidence Supporting the Recommendation: Repotrectinib is a next-generation ROS1 inhibitor that has shown a confirmed ORR of 79% in ROS1 TKI-naïve patients and 38% in those previously treated with a ROS1 TKI. The median PFS was 35.7 months in TKI-naïve patients. Citation: NCCN NCSL 2024 Guidelines​​ . These therapies are recommended based on their efficacy and the clinical trial data supporting their use in ROS1-positive NSCLC patients. |
| NSCL-32 | For an advanced lung adenocarcinoma patient with no prior treatment and BRAF V600E mutations, the preferred therapies are:  Dabrafenib plus Trametinib  Evidence Supporting the Recommendation: This combination is approved by the FDA for the treatment of metastatic NSCLC with BRAF V600E mutations. Clinical data from a phase 2 trial showed an overall response rate of 63.9%, with a median progression-free survival (PFS) of 10.8 months and a median overall survival (OS) of 17.3 months in treatment-naïve patients​​. Citation: NCCN NCSL 2024 Guidelines, MS-87, NSCL-32. Encorafenib plus Binimetinib  Evidence Supporting the Recommendation: This combination is also FDA-approved for metastatic NSCLC with BRAF V600E mutations. A phase 2 study demonstrated an objective response rate (ORR) of 75% in treatment-naïve patients with a median PFS that was not estimable at the time of the study and a favorable safety profile​​​​. Citation: NCCN NCSL 2024 Guidelines, MS-87, NSCL-32. Both combinations are supported by clinical evidence and are included as preferred first-line therapy options in the NCCN guidelines for patients with BRAF V600E mutation-positive advanced or metastatic NSCLC​​. |
| NSCL-33 | For an advanced lung adenocarcinoma patient with ETV6-NTRK3 mutations, the preferred therapy would be:  Larotrectinib Evidence Supporting the Recommendation: Larotrectinib is recommended for patients with NTRK gene fusions, including ETV6-NTRK3, due to its demonstrated efficacy in targeting these mutations. Citation: NCCN Guidelines for Non-Small Cell Lung Cancer, 2024​​; ASCO Guidelines for NSCLC with Driver Mutations, 2024​​. Additionally:  Entrectinib Evidence Supporting the Recommendation: Entrectinib is also an effective treatment option for patients with NTRK gene fusions, providing another targeted therapy option. Citation: NCCN Guidelines for Non-Small Cell Lung Cancer, 2024​​; ASCO Guidelines for NSCLC with Driver Mutations, 2024​​. |
| NSCL-34 | For an advanced lung adenocarcinoma patient with MET c.3028 + 2T>C mutations, which result in MET exon 14 skipping, the following therapies are preferred:  Capmatinib  Evidence Supporting the Recommendation: Capmatinib is an oral MET tyrosine kinase inhibitor (TKI) specifically indicated for patients with MET exon 14 skipping mutations. Clinical data from the GEOMETRY study demonstrated an overall response rate (ORR) of 68% and a median progression-free survival (PFS) of 12.4 months in treatment-naive patients​​. Citation: NCCN NCSL 2024 Guidelines Tepotinib  Evidence Supporting the Recommendation: Tepotinib is another MET TKI approved for treating patients with MET exon 14 skipping mutations. The VISION study showed an ORR of 46% and a median PFS of 8.5 months in patients with stage IV NSCLC​​. Citation: NCCN NCSL 2024 Guidelines Both drugs are recommended as first-line monotherapy options for MET exon 14 skipping mutation-positive metastatic NSCLC​​​​.  Preferred Therapy Structure: Drug Name: Capmatinib  Evidence Supporting the Recommendation: High efficacy in MET exon 14 skipping mutation-positive patients with a significant ORR and PFS. Citation: NCCN NCSL 2024 Guidelines, ASCO With Driver 2024 Guidelines Drug Name: Tepotinib  Evidence Supporting the Recommendation: Demonstrated efficacy with substantial ORR and PFS in clinical trials for MET exon 14 skipping mutation-positive patients. Citation: NCCN NCSL 2024 Guidelines, ASCO With Driver 2024 Guidelines |
| NSCL-35 | For an advanced lung adenocarcinoma patient with CCDC6::RET gene fusion mutations, the preferred therapies are:  Selpercatinib  Evidence Supporting the Recommendation: Selpercatinib is a highly selective RET kinase inhibitor showing substantial efficacy in RET fusion-positive non-small cell lung cancer (NSCLC). Clinical trials have demonstrated significant response rates and progression-free survival in patients treated with selpercatinib. Citation: NCCN NCSL 2024 Guidelines, ASCO With Driver 2024 Guidelines​​​​ Pralsetinib  Evidence Supporting the Recommendation: Pralsetinib is another selective RET inhibitor recommended for patients with RET fusion-positive NSCLC. It has shown efficacy in improving clinical outcomes with manageable toxicity profiles in clinical studies. Citation: NCCN NCSL 2024 Guidelines, ASCO With Driver 2024 Guidelines​​​​ These therapies align with the latest guidelines and are considered first-line treatments for patients with RET fusion-positive NSCLC. |
| NSCL-36 | For a patient with advanced lung adenocarcinoma harboring ERBB2 A775\_G776insYVMA mutations who has demonstrated recurrence after treatment with cisplatin and pemetrexed, the following therapy is recommended:  Drug Name: Trastuzumab deruxtecan Evidence Supporting the Recommendation: Trastuzumab deruxtecan is recommended for patients with ERBB2 (HER2) mutations, particularly in cases where the cancer has progressed after platinum-based chemotherapy. This recommendation is based on its efficacy demonstrated in clinical trials showing significant tumor response and disease control rates in this subset of NSCLC patients. Citation: ASCO Guidelines: "Trastuzumab deruxtecan is recommended for patients with ERBB2 (HER2) mutations after the failure of platinum-based chemotherapy"​​. NCCN Guidelines: "For patients with advanced NSCLC with ERBB2 mutations who have progressed after initial chemotherapy, trastuzumab deruxtecan is a preferred option"​​. |

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| NSCL-21 | For a patient with advanced lung adenocarcinoma harboring an EGFR p.L858R mutation, the preferred therapy would be:  Osimertinib Evidence Supporting the Recommendation: Osimertinib, a third-generation EGFR-TKI, has demonstrated superior efficacy in terms of progression-free survival and overall survival compared to first-generation EGFR-TKIs. It is particularly effective against both common sensitizing mutations (exon 19 deletions and L858R) and T790M resistance mutations. Citation: NCCN Clinical Practice Guidelines in Oncology: Non–Small Cell Lung Cancer, Version 6.2024 Therapy for Stage IV Non–Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2023.3 |
| NCSL-22 | For a patient with advanced lung adenocarcinoma harboring an EGFR p.L858R mutation, who has shown progression on osimertinib and has multiple metastases, the preferred therapy would be:  Amivantamab and Lazertinib Combination Evidence Supporting the Recommendation: For patients with EGFR-mutant NSCLC who have progressed on osimertinib, amivantamab (an EGFR-MET bispecific antibody) combined with lazertinib (a third-generation EGFR inhibitor) has shown promising efficacy. This combination targets multiple resistance mechanisms that can arise after osimertinib treatment, offering a potential therapeutic option for patients with acquired resistance. Citation: Non–Small Cell Lung Cancer, Version 6.2024, NCCN Clinical Practice Guidelines in Oncology. Alternatively, if amivantamab and lazertinib are not available or suitable:  Chemotherapy (Platinum-based doublet with or without bevacizumab) Evidence Supporting the Recommendation: In cases where targeted therapies are no longer effective, platinum-based chemotherapy (such as carboplatin or cisplatin combined with pemetrexed) remains a standard approach. Bevacizumab may be added for patients with non-squamous histology, as it has been shown to improve outcomes in combination with chemotherapy. Citation: Non–Small Cell Lung Cancer, Version 6.2024, NCCN Clinical Practice Guidelines in Oncology. These recommendations align with current clinical guidelines and consider the progression on first-line osimertinib and the need for subsequent lines of therapy. |
| NCSL-23 | For an advanced lung adenocarcinoma patient with progression on afatinib and harboring EGFR p.L858R and T790M mutations, the preferred therapy is osimertinib.  Drug Name: Osimertinib Evidence Supporting the Recommendation: Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI) specifically effective against EGFR T790M mutations, which are a common mechanism of resistance to first- and second-generation EGFR TKIs such as afatinib. Clinical trials, including the AURA3 study, have demonstrated that osimertinib provides significant improvements in progression-free survival and overall response rates in patients with T790M-positive NSCLC. Citation: NCCN Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer, Version 6.2024; ASCO Living Guideline, Version 2023.3 |
| NSCL-24 | For an advanced lung adenocarcinoma patient with G719X mutations, the preferred therapy options are based on the latest guidelines from NCCN and ASCO. These guidelines emphasize the use of targeted therapies for patients with specific genetic alterations.  Preferred Therapy: Osimertinib  Evidence Supporting the Recommendation: Osimertinib is an EGFR tyrosine kinase inhibitor (TKI) that has shown efficacy in patients with uncommon EGFR mutations, including G719X. It is preferred due to its efficacy and favorable safety profile. Citation: NCCN Clinical Practice Guidelines in Oncology: Non–Small Cell Lung Cancer, Version 6.2024. Afatinib  Evidence Supporting the Recommendation: Afatinib has demonstrated activity against uncommon EGFR mutations such as G719X. It is recommended based on its proven effectiveness in this subset of patients. Citation: ASCO Living Guideline, Version 2023.3. These recommendations align with the current guidelines, which prioritize targeted therapies for patients with driver mutations in NSCLC. |
| NSCL-25 | For an advanced lung adenocarcinoma patient with EGFR Exon 20 Asp770\_Asn771ins mutations, the preferred therapy would be:  Amivantamab-vmjw Evidence Supporting the Recommendation: Amivantamab is a fully human EGFR-MET bispecific antibody indicated for the treatment of patients with NSCLC harboring EGFR Exon 20 insertion mutations. Clinical trials have demonstrated its efficacy and safety in this patient population, making it a recommended option. Citation: NCCN Clinical Practice Guidelines in Oncology, Non–Small Cell Lung Cancer, Version 6.2024 Additionally, another recommended therapy option is:  Mobocertinib Evidence Supporting the Recommendation: Mobocertinib is an oral tyrosine kinase inhibitor specifically designed to target EGFR Exon 20 insertion mutations. Clinical studies have shown that it provides significant clinical benefit in patients with these mutations. Citation: NCCN Clinical Practice Guidelines in Oncology, Non–Small Cell Lung Cancer, Version 6.2024 These therapies are aligned with the latest NCCN guidelines and are considered standard care for patients with this specific genetic alteration. |
| NSCL-27 | For an advanced lung adenocarcinoma patient with EML4-ALK fusion mutations, the preferred therapies according to the latest guidelines are:  Alectinib  Evidence Supporting the Recommendation: Alectinib has demonstrated superior efficacy in terms of progression-free survival and overall survival compared to crizotinib, and it has a more favorable side effect profile. Citation: NCCN Guidelines, Version 6.2024; ASCO Living Guideline, Version 2023.3 Brigatinib  Evidence Supporting the Recommendation: Brigatinib has shown significant improvements in progression-free survival over crizotinib and is effective in patients with central nervous system metastases. Citation: NCCN Guidelines, Version 6.2024; ASCO Living Guideline, Version 2023.3 Lorlatinib  Evidence Supporting the Recommendation: Lorlatinib is recommended particularly for patients who have progressed on prior ALK inhibitors, with demonstrated activity against brain metastases and a favorable response rate. Citation: NCCN Guidelines, Version 6.2024; ASCO Living Guideline, Version 2023.3 These therapies are aligned with the NCCN and ASCO guidelines for the treatment of NSCLC with ALK rearrangements and are considered the most effective options for this specific patient population. |
| NSCL-30 | For an advanced lung adenocarcinoma patient with no prior treatment and CD74-ROS1 fusion mutations, the preferred therapies are:  Entrectinib Crizotinib Entrectinib Evidence Supporting the Recommendation: Entrectinib is an ROS1 inhibitor with demonstrated efficacy in ROS1-positive NSCLC, showing high response rates and durability of response. Citation: NCCN Guidelines, Version 6.2024 Crizotinib Evidence Supporting the Recommendation: Crizotinib, another ROS1 inhibitor, has been shown to be effective in ROS1-rearranged NSCLC, with substantial clinical benefit and prolonged progression-free survival. Citation: NCCN Guidelines, Version 6.2024 These recommendations are based on the latest NCCN guidelines, which highlight both entrectinib and crizotinib as preferred options for patients with ROS1 rearrangements. |
| NSCL-32 | For a patient with advanced lung adenocarcinoma harboring BRAF V600E mutations, the preferred therapy aligns with the latest NCCN and ASCO guidelines.  Dabrafenib + Trametinib Evidence Supporting the Recommendation: The combination of Dabrafenib, a BRAF inhibitor, and Trametinib, a MEK inhibitor, has shown significant efficacy in patients with BRAF V600E mutations. Clinical trials have demonstrated improved response rates and progression-free survival compared to historical controls. Citation: Non–Small Cell Lung Cancer, Version 6.2024, NCCN Clinical Practice Guidelines in Oncology; Therapy for Stage IV Non–Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2023.3 |
| NSCL-33 | For an advanced lung adenocarcinoma patient with ETV6-NTRK3 mutations, the preferred therapies are:  Larotrectinib  Evidence Supporting the Recommendation: Larotrectinib is a highly selective TRK inhibitor shown to be effective in patients with NTRK gene fusions, including ETV6-NTRK3, leading to significant and durable responses in advanced solid tumors.  Citation: Non–Small Cell Lung Cancer, Version 6.2024, NCCN Clinical Practice Guidelines in Oncology  Entrectinib  Evidence Supporting the Recommendation: Entrectinib is another TRK inhibitor that targets NTRK gene fusions. It has demonstrated efficacy and safety in treating patients with advanced solid tumors harboring NTRK fusions, including ETV6-NTRK3.  Citation: Non–Small Cell Lung Cancer, Version 6.2024, NCCN Clinical Practice Guidelines in Oncology |
| NSCL-34 | For a patient with advanced lung adenocarcinoma harboring MET exon 14 skipping mutation (e.g., MET c.3028 + 2T>C), the following targeted therapies are recommended:  Capmatinib  Evidence Supporting the Recommendation: Capmatinib is an FDA-approved MET inhibitor specifically for patients with metastatic NSCLC harboring MET exon 14 skipping mutations. Clinical trials have shown significant efficacy in terms of response rates and progression-free survival. Citation: NCCN Clinical Practice Guidelines in Oncology: Non–Small Cell Lung Cancer, Version 6.2024. Tepotinib  Evidence Supporting the Recommendation: Tepotinib has demonstrated clinical benefit in patients with MET exon 14 skipping mutations, with studies indicating robust and durable responses. It is also FDA-approved for this specific genetic alteration. Citation: NCCN Clinical Practice Guidelines in Oncology: Non–Small Cell Lung Cancer, Version 6.2024. Both therapies are aligned with current guidelines and represent preferred treatment options for patients with MET exon 14 skipping mutations. |
| NSCL-35 | For a patient with advanced lung adenocarcinoma harboring CCDC6::RET gene fusion mutations, the preferred therapies are as follows:  Selpercatinib  Evidence Supporting the Recommendation: Selpercatinib is a selective RET kinase inhibitor that has shown significant efficacy in patients with RET fusion-positive non-small cell lung cancer (NSCLC). Clinical trials have demonstrated high response rates and durable responses with a favorable safety profile. Citation: NCCN Guidelines Version 6.2024, ASCO Living Guideline Version 2023.3 Pralsetinib  Evidence Supporting the Recommendation: Pralsetinib is another selective RET inhibitor that has been proven effective for patients with RET fusion-positive NSCLC. It has shown robust clinical activity and a manageable safety profile in clinical studies. Citation: NCCN Guidelines Version 6.2024, ASCO Living Guideline Version 2023.3 These therapies align with the latest NCCN and ASCO guidelines and are recommended as first-line treatments for patients with RET fusion-positive NSCLC. |
| NSCL-36 | For a patient with advanced lung adenocarcinoma harboring an ERBB2 (HER2) A775\_G776insYVMA mutation who has shown recurrence after treatment with cisplatin and pemetrexed, the following therapy is recommended:  Trastuzumab deruxtecan (Enhertu) Evidence Supporting the Recommendation: Trastuzumab deruxtecan, an antibody-drug conjugate targeting HER2, has demonstrated significant efficacy in patients with ERBB2 mutations in non-small cell lung cancer. Clinical trials have shown high response rates and durable responses in this patient population. Citation: NCCN Guidelines Version 6.2024 for Non-Small Cell Lung Cancer; ASCO Living Guideline, Version 2023.3 for Therapy for Stage IV Non-Small Cell Lung Cancer With Driver Alterations. This recommendation is based on the specific genetic alteration present in the patient's tumor and aligns with current clinical practice guidelines for targeted therapy in NSCLC with ERBB2 mutations. |