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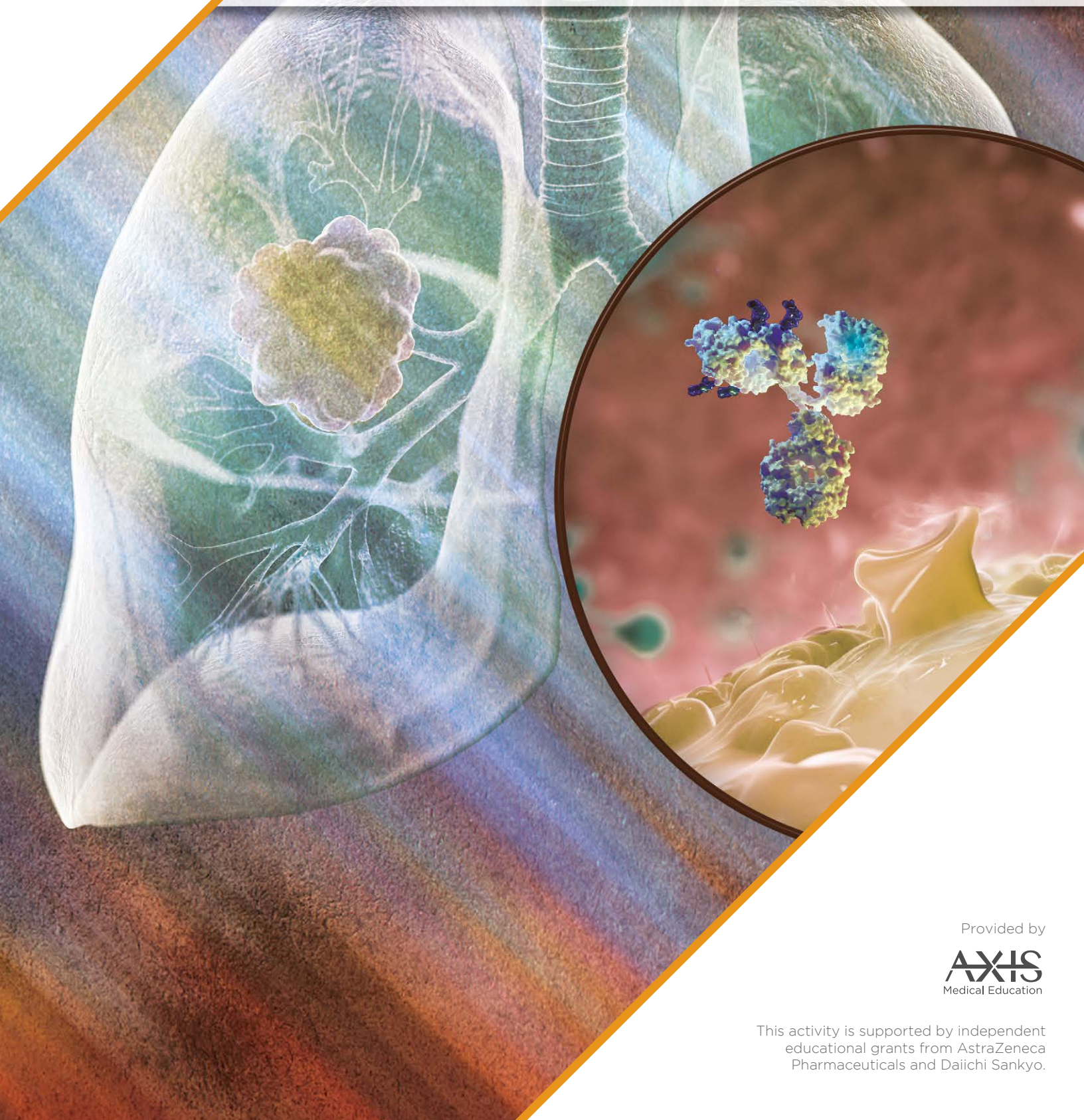
Advancing Shared Decision-Making in NSCLC with HER2-Mutant/ Overexpressing Tumors:

A Shared Decision-Making Guide



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Shared Decision-Making

WHAT IS SHARED DECISION-MAKING?

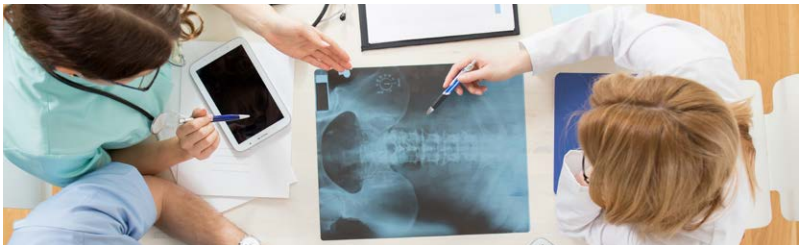
Shared decision-making (SDM) occurs when a healthcare provider and a patient work together to make a healthcare decision that is best for the patient. Optimal decision-making takes into account evidence-based information about available options, the provider's knowledge and experience, and the patient's values, goals and preferences. Patients and their families/caregivers who are engaged in an SDM process are more likely to arrive at a treatment decision that works best for all those involved.

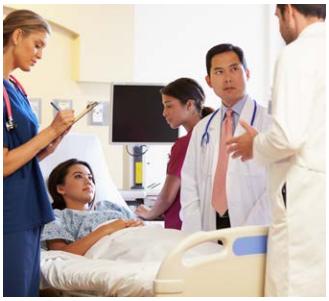
WHY IS SDM IMPORTANT IN CANCER?

Making informed decisions about cancer treatment is challenging and can be daunting to the patient, who may be overwhelmed by therapeutic options and how they differ based on benefits, risks, and potential complications. Quite often, the choice of treatment may hinge on patient preferences. Patients and caregivers can play a collaborative and integral role with their healthcare team in determining a course of therapy that is in line with their lifestyles, goals, and desires for disease control.

Two-way communication between patients/caregivers and providers can facilitate shared decision-making, helping to improve patient adherence to therapy, enhance satisfaction with care delivery, and elevate quality of life. By successfully engaging with the healthcare team through shared decision-making, patients may experience better therapeutic outcomes and higher quality care.

Optimal care of cancer involves the use of effective therapies that are supported by the latest evidence and guidelines, selected through a shared decision-making process, and individualized to each patient's needs.





National Quality Partners Playbook™ on Shared Decision-Making in Healthcare

- The National Quality Forum issued a call to action to make SDM a standard of care for all patients, across all settings and conditions
- Offers vital guidance for this process of communication in which clinicians and patients work together to make healthcare decisions that align with what matters most to patients

SDM REQUIRES 3 COMPONENTS

1. Delivering clear, accurate, and unbiased medical evidence about reasonable alternatives/treatment options – including no medical intervention – and the risks and benefits of each.
2. Clinician expertise in communicating and tailoring evidence for individual patients.
3. Eliciting and integrating patient values, goals, informed preferences, and concerns, which may include treatment burdens, into treatment planning.

6 FUNDAMENTALS TO GUIDE SDM IN HEALTHCARE ORGANIZATIONS

1. **Promote Leadership and Culture**
2. **Enhance Patient Education and Engagement**
3. **Provide Healthcare Team Knowledge and Training**
4. **Take Concrete Actions for Implementation**
5. **Track, Monitor, and Report**
6. **Establish Accountability for Organizations, Clinicians, and Patients**

National Quality Forum. *National Quality Partners Playbook™: Shared Decision-Making in Healthcare*. Washington DC: National Quality Forum; 2018.

The AXIS 6 Ease ("E's") to SDM

ENSURE
Ensure you see and treat the patient as an individual not a disease.

ELEVATE
Elevate the patient-centric experience and improve satisfaction with care.

ENABLE
Enable a long-term personal connection with your patients.

ESTABLISH
Establish co-created treatment plans that align medical evidence with patient preferences to foster adherence and optimize outcomes.

ELICIT
Elicit patient/caregiver preferences, values, and goals for therapy.

EVALUATE
Evaluate the risk/benefits and costs of treatment so they are aligned with patient expectations.

AXIS Oncology Shared Decision-Making Resource Center. https://axismeded.com/slides-and-resources/?order_by=2&page=1&specialty=857

The SHARE Decision-Making Approach

STEP 1 **SEEK** your patient's participation.

STEP 2 **HELP** your patient explore & compare treatment options.

STEP 3 **ASSESS** your patient's values and preferences.

STEP 4 **REACH** a decision with your patient.

STEP 5 **EVALUATE** your patient's decision.

AHRQ. The SHARE Approach. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html

Molecular Testing Based on Guideline Recommendations

- Biomarker testing for *ERBB2 (HER2)* is recommended for patients with advanced or metastatic NSCLC
  - Testing of lung cancer specimens for gene alterations is important for identification of potentially efficacious targeted therapies
  - Broad molecular profiling is a key component of the improvement of care of patients with NSCLC
- Comprehensive broad next-generation sequencing (NGS) is the gold standard, utilizing both tissue and blood-based testing platforms
  - Comprehensive NGS is preferred
  - Can also be assessed via Sanger sequencing and targeted PCR techniques
  - Data support complementary ctDNA and tissue testing to reduce turnaround time and increase yield of targetable alteration detection

Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer (Version 3.2024). © 2024 National Comprehensive Cancer Network. To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org.

Weighing Risks/Benefits of Therapy Selection

- First-line therapy for HER2-mutated NSCLC typically consists of platinum-doublet chemotherapy +/- anti-PD1 immunotherapy (patient- and provider-specific decision on adding anti-PD-(L)1 to frontline chemotherapy)
- HER2 ADC trastuzumab deruxtecan (T-DXd) is now FDA-approved (accelerated approval) for activating **HER2-mutant** metastatic NSCLC in the second-line
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) include fam-trastuzumab deruxtecan-nxki as the only preferred second-line treatment option (Category 2A) for **HER2-mutant** mNSCLC
- T-DXd was granted accelerated FDA approval for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

FDA.gov. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for HER2-mutant non-small cell lung cancer. Press release. August 16, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-her2-mutant-non-small-cell-lung

FDA.gov. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors. April 5, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2

Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer (Version 3.2024). © 2024 National Comprehensive Cancer Network. To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org.

HER2-mutated NSCLC

	Indication	Guideline Recommendation	Trial Results	Common/Important Adverse Events
HER2 Tyrosine Kinase Inhibitors (TKIs)				
Neratinib	–	–	Limited; ORR 3.8%	Skin reactions, rash, diarrhea, ocular toxicity, ILD
Poziotinib	–	–	ORR 35%; limited by toxicity	
Afatinib	–	–	Limited; ORR ~10-19%	
HER2 Monocolonal Antibodies				
Trastuzumab	–	–	Limited retrospective data; ORR ~50%	Cardiomyopathy, infusion reactions, pulmonary toxicity, fever, chills, headache
Pertuzumab	–	–	Limited data from phase II basket study; ORR 11%	Infusion reactions, hypersensitivity reactions, LVEF, CHF, nausea, alopecia, fatigue
HER2 Antibody-Drug Conjugates (ADCs)				
T-DXd	Accelerated approval for adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2/ERBB2 mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy	**Preferred** subsequent line therapy in advanced/metastatic HER2-mutated NSCLC	5.4 mg/kg Q3W: - ORR: 49% - mPFS: 9.9 months - mOS: 19.5 months *recommended dosage 6.4 mg/kg Q3W: - ORR: 56% - mPFS: 15.4 months - mOS: NE	Nausea, neutropenia, fatigue, anemia, thrombocytopenia, GI upset, ILD
T-DM1	–	Subsequent line therapy in advanced/metastatic HER2-mutated NSCLC	Phase II basket study ORR 50% mPFS 5 months	Transaminitis, thrombocytopenia, nausea, fatigue

CHF, congestive heart failure; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; mPFS, median progression-free survival; mOS, median overall survival; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; Q3W, every 3 weeks.

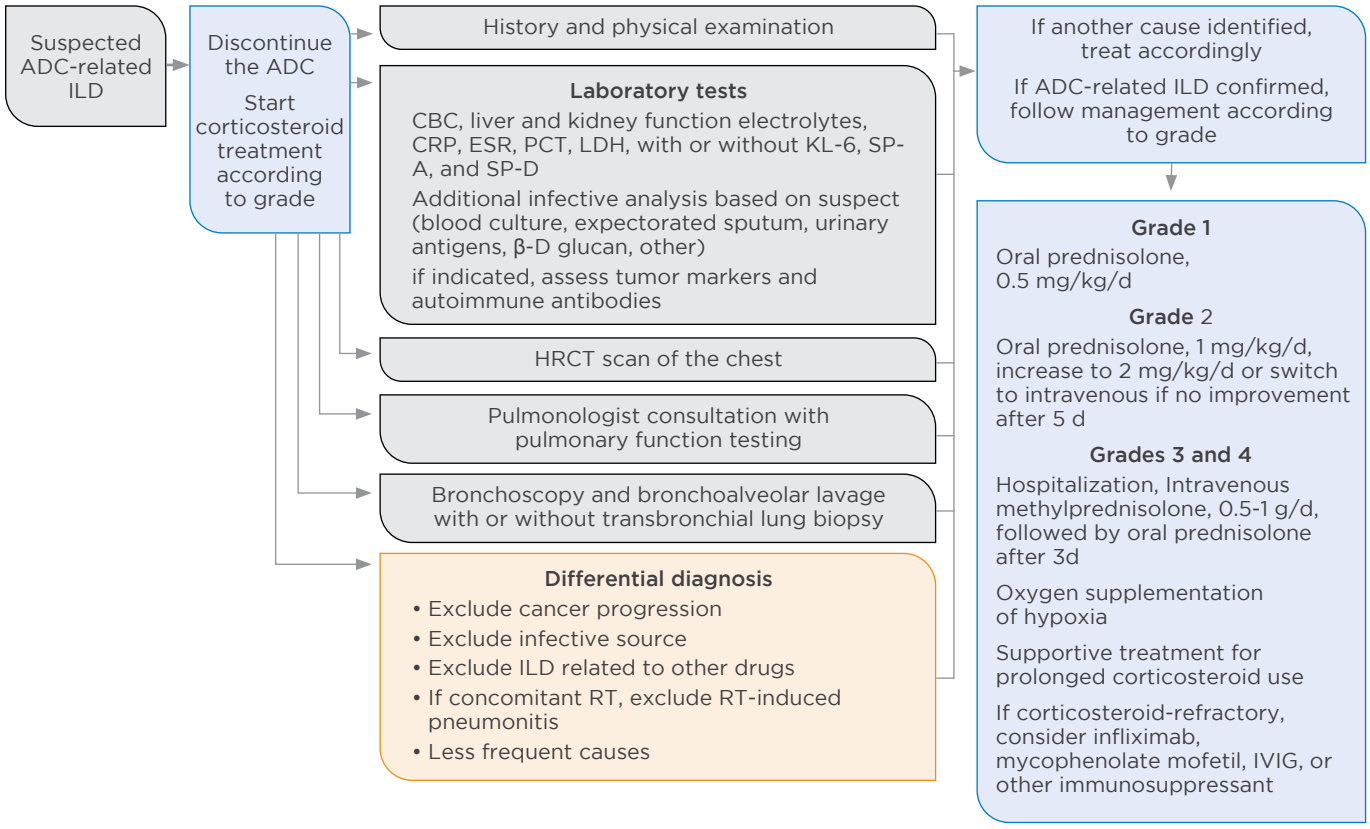
Clinical Management of ILD

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with T-DXd
  - Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms
  - Permanently discontinue in all patients with Grade 2 or higher ILD/pneumonitis
  - Advise patients of the risk and to immediately report symptoms
- Maintain high index of suspicion, especially in face of new cough, shortness of breath, dyspnea on exertion, fever, etc
- If suspected, **STOP** T-DXd and initiate steroids unless clear alternative cause identified
- Work-up should include:
  - High resolution chest CT, CBC, blood culture, PFTs, pulse oximetry
  - Consult pulmonology to assist with management
  - Consider bronchoscopy to r/o infection, disease progression, etc
  - Consider ID input if infection suspected
- Differential Diagnosis: Infection, cancer progression, RT pneumonitis, ILD – other cause
- Management: Prednisone (typically 1 mg/kg/d)
- Observed less frequently with T-DXd at lower dose of 5.4 mg/kg (FDA approval)
  - 12.9% any grade; 1% grade 3+
  - Median time to onset of 88 days

Goto K, Goto Y, Kubo T, et al. Trastuzumab deruxtecan in patients with HER2-mutant metastatic non-small-cell lung cancer: primary results from the randomized, phase II DESTINY-Lung02 trial. *J Clin Oncol.* 2023;41(31):4852-4863.

Jänne P, Goto Y, Kubo T, et al. Trastuzumab deruxtecan in patients with HER2-mutant metastatic non-small cell lung cancer: primary results of DESTINY-Lung02. Abstract presented at: World Conference on Lung Cancer; Singapore, September 9-12, 2023. Abstract MA13.10.

Tarantino P, Modi S, Tolaney SM, et al. Interstitial lung disease induced by anti-ERBB2 antibody-drug conjugates: a review. *JAMA Oncol.* 2021;7(12):1873-1881.



Tarantino P, Modi S, Tolaney SM, et al. Interstitial lung disease induced by anti-ERBB2 antibody-drug conjugates: a review. *JAMA Oncol.* 2021;7(12):1873-1881.

ADC, antibody-drug conjugate; CBC , complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; PCT, procalcitonin; RT, radiation therapy; SP-A, surfactant protein A; SP-D, surfactant protein D.

Glossary of Terms

Non-small cell lung cancer (NSCLC)	A group of lung cancers named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of NSCLC are adenocarcinoma (most common), squamous cell carcinoma, and large cell carcinoma. NSCLC is the most common of the two main types of lung cancer (non-small cell lung cancer and small cell lung cancer).
Antibody-drug conjugate (ADC)	A substance made up of a monoclonal antibody chemically linked to a drug. The monoclonal antibody binds to specific proteins or receptors found on certain types of cells, including cancer cells. The linked drug enters these cells and kills them without harming other cells. Some antibody-drug conjugates are used to treat cancer.
Human epidermal growth factor receptor 2 (HER2)	A protein involved in normal cell growth. HER2 may be made in larger than normal amounts by some types of cancer cells. This may cause cancer cells to grow more quickly and spread to other parts of the body. Checking the amount of HER2 on some types of cancer cells may help plan treatment. Also called HER2/neu proteins.
HER2/ERBB2 alterations	HER2 alterations consist of three distinct forms in NSCLC: gene mutations, gene amplification, and protein overexpression. They are considered distinct tumor subtypes with different biological behaviors and infrequent overlap. ERBB2 encodes for HER2, a receptor tyrosine kinase found on the surface of normal epithelial cells that is often overexpressed or mutated in a variety of human malignancies.
HER2 gene mutation	Mutations in the *HER2 (ERBB2)* gene. Most commonly insertion/duplication events in exon 20. Assessed by NGS, Sanger sequencing, and targeted PCR techniques.
HER2 gene amplification	The HER2 gene makes too many copies of itself resulting in abnormally high *HER2 (ERBB2)* gene copies. Assessed by fluorescence in-situ hybridization (FISH), defined as HER2/CEP17 ratio ≥2.0.
HER2 protein overexpression	Extra HER2 genes make too many HER2 receptors leading to an overabundance of HER2 receptors on the surface of cancer cells. Assessed by immunohistochemistry (IHC), defined as 2+ or 3+.
HER2-positive	Describes cells that have a protein called HER2 on their surface. In normal cells, HER2 helps control cell growth. Cancer cells that make too much HER2 may grow more quickly and are more likely to spread to other parts of the body. Checking to see if a cancer is HER2 positive may help plan treatment, which may include drugs that kill HER2-positive cancer cells.
HER2 test	A laboratory test that measures the amount of HER2 protein on cancer cells or how many copies of the HER2 gene are in the DNA of cancer cells. The HER2 protein helps control normal cell growth. Larger than normal amounts of the HER2 protein or too many copies of the HER2 gene may be made by some types of cancer. This may cause cancer cells to grow more quickly and spread to other parts of the body. A HER2 test may be done to help plan treatment, which may include drugs that target the HER2 protein. It is a type of tumor marker test. Also called HER2/neu test.
Fluorescence in situ hybridization (FISH)	A laboratory method used to look at genes or chromosomes in cells and tissues. Pieces of DNA that contain a fluorescent dye are made in the laboratory and added to a cell or tissue sample. When these pieces of DNA bind to certain genes or areas on chromosomes in the sample, they light up when viewed under a microscope with a special light. FISH can be used to identify where a specific gene is located on a chromosome, how many copies of a gene are present, and any chromosomal abnormalities. It is used to help diagnose diseases, such as cancer, and help plan treatment.
Immunohisto-chemistry (IHC)	A laboratory method that uses antibodies to check for certain antigens (markers) in a sample of tissue. The antibodies are usually linked to an enzyme or a fluorescent dye. After the antibodies bind to the antigen in the tissue sample, the enzyme or dye is activated, and the antigen can then be seen under a microscope. Immunohistochemistry is used to help diagnose diseases, such as cancer. It may also be used to help tell the difference between different types of cancer.
Next-generation sequencing (NGS)	A term that describes methods used in the lab to learn the order of building blocks (called nucleotides) for millions of DNA or RNA fragments at the same time. Computers are used to piece together the fragments in order to sequence a person or other organism's entire DNA, large segments of DNA or RNA, or the DNA in specific types of cells from a sample of tissue. Next-generation sequencing can also identify changes in certain areas of the genome or in specific genes. There are many different types of next-generation sequencing methods, including whole-genome sequencing, whole-exome sequencing, multigene panel testing, and transcriptome sequencing. Next-generation sequencing may help researchers understand the cause of certain diseases, such as cancer.

Glossary of Terms (continued)

Circulating tumor DNA (ctDNA)	Small pieces of DNA that are released into a person's blood by tumor cells as they die. A sample of blood can be used to look for and measure the amount of circulating tumor DNA and identify specific mutations (changes) in the DNA. Circulating tumor DNA is being used as a biomarker to help diagnose some types of cancer, to help plan treatment, or to find out how well treatment is working or if cancer has come back.
Polymerase chain reaction (PCR)	A laboratory method used to make many copies of a specific piece of DNA from a sample that contains very tiny amounts of that DNA. Polymerase chain reaction allows these pieces of DNA to be amplified so they can be detected. Polymerase chain reaction may be used to look for certain changes in a gene or chromosome, which may help find and diagnose a genetic condition or a disease, such as cancer. It may also be used to look at pieces of the DNA of certain bacteria, viruses, or other microorganisms to help diagnose an infection.
Disease progression	In medicine, the course of a disease, such as cancer, as it becomes worse or spreads in the body.
Adverse event	An undesired effect of a drug or other type of treatment, such as surgery. Adverse events can range from mild to severe and can be life-threatening. Also called adverse effect or adverse reaction.
Side effect	An effect of a drug or other type of treatment that is in addition to or beyond its desired effect. Side effects can be harmful or beneficial, and most go away on their own over time. Others may last past treatment or appear long after treatment has ended. Some common side effects of cancer treatment are nausea, vomiting, fatigue, pain, decreased blood cell counts, hair loss, and mouth sores.
Anemia	A condition in which the number of red blood cells is below normal.
Leukopenia	A condition in which there is a lower-than-normal number of leukocytes (white blood cells) in the blood.
Neutropenia	A condition in which there is a lower-than-normal number of neutrophils (a type of white blood cell) in the blood.
Thrombocyotpe-nia	A condition in which there is a lower-than-normal number of platelets in the blood. It may result in easy bruising and excessive bleeding from wounds or bleeding in mucous membranes and other tissues.
Nausea	A feeling of sickness or discomfort in the stomach that may come with an urge to vomit. Nausea is a side effect of some types of cancer therapy.
Fatigue	An extreme sense of tiredness and lack of energy that can interfere with a person's usual daily activities. A person with fatigue may feel weak, worn out, heavy, slow, or run down. They may also have trouble speaking or concentrating, short-term memory loss, and mood or emotional changes. There are many causes of fatigue. Fatigue may also be caused by cancer or cancer treatment. Certain types of fatigue, including cancer-related fatigue, may not be completely relieved by sleep and may last for a long time after treatment ends.
Constipation	A condition in which stool becomes hard, dry, and difficult to pass, and bowel movements don't happen very often. Other symptoms may include painful bowel movements, and feeling bloated, uncomfortable, and sluggish.
Interstitial lung disease (ILD)	A group of several disorders that can cause scarring in your lungs. The scar tissue in your lungs affects your lungs' ability to carry oxygen and can make it harder for you to breathe normally. ILDs can be mild, serious, or even life-threatening. Symptoms of ILDs may include shortness of breath, dry cough, chest discomfort, and extreme tiredness.
Pneumonitis	Inflammation of the lungs. This may be caused by disease, infection, radiation therapy, allergy, or irritation of lung tissue by inhaled substances.

NCI. NCI Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/.

NHLBI. What Are Interstitial Lung Diseases? https://www.nhlbi.nih.gov/health/interstitial-lung-diseases.

Yu Y, Yang Y, Li H, et al. Targeting HER2 alterations in non-small cell lung cancer: Therapeutic breakthrough and challenges. *Cancer Treatment Reviews*. 2023;114:102520.

Tips for Eliciting Patient Participation in Treatment Planning

TIPS FOR ENGAGING YOUR PATIENT

- Summarize for your patient the current status of their disease.
- Ask your patient and their caregivers to participate with the healthcare team in making treatment and disease management decisions. Explain that this open dialogue will assist the patient in selecting an option that will align with their preferences and goals of therapy.
- Ask your patient to share their feelings, challenges, and triumphs with regards to living with lung cancer. This can help uncover what is most important to them or barriers that may inform the selection of one treatment approach over another.
- Help your patient feel empowered to share their opinion by explaining to them that they are an important contributor to the successful management and control of their lung cancer.

TIPS FOR EXPLORING TREATMENT OPTIONS WITH YOUR PATIENT

- Determine the patient's preferred role in the decision-making process.
- Assess what your patient already knows about his or her current treatment options.
- Provide your patient and/or caregivers with a printed list of the currently available treatment options with a brief description of each in plain language; review and describe the options for their type of cancer.
- Clearly communicate the risks and benefits of each option. Explain the limitations of what is known and unknown about the treatment options and what would happen with no treatment.
- Communicate numbers in a way that your patient can understand. Use simple visual aids (graphs, charts, pictographs) to help your patient understand your explanations.
- Offer evidence-based decision aid tools whenever possible and explain how to use them to arrive at a decision that reflects their preferences, goals, and values.
- Encourage patients to play an active role in treatment selection.
- Use the teach-back technique to check for understanding: ask your patients to explain the options in his or her own words.

TIPS FOR ASSESSING VALUES AND PREFERENCES

- Encourage your patient to talk about what matters most to him or her.
- Ask open-ended questions (See sample questions below).
- Listen actively to your patient. Show empathy and interest in what is currently impacting your patient's everyday life.
- Acknowledge the values and preferences that matter to your patient.
- Agree on what is important to your patient.
- Recap with your patient your interpretation of what is most important to them as a priority for consideration when mutually selecting the best treatment option.

Tips for Eliciting Patient Participation in Treatment Planning (continued)

TIPS FOR ASSESSING VALUES AND PREFERENCES (CONTINUED)

Sample Questions

- What is your #1 priority that we accomplish during our visit today?
- How do feel? Are you experiencing any symptoms?
- Are you experiencing any side effects related to your treatment? How has this impacted your lifestyle and quality of life?
- Is your condition interfering with your work, social events, or everyday activities at home?
- Do you have any questions about the benefits or risks of the different treatments we are considering for your disease?
- What goals do you have regarding your treatment? Have these goals changed since our last visit?

Sample goals

- Keeping the symptoms of disease under control
- Minimizing risks and side effects from treatment
- Finding a treatment with a dosing option that's easy and convenient
- Selecting a treatment that is cost effective

- What is most important to you/your family as we discuss current or new treatment options?
  - What is most important to your patient? It might be:
    - Keeping out-of-pocket costs low
    - Resolving disease symptoms
    - Avoiding treatment-related adverse events
    - Maintaining a specific level of functionality
    - Improving quality of life

TIPS FOR DECISION-MAKING

- Help your patient move to a decision by asking if he or she is ready to make a decision.
- Ask if your patient would like additional information or tools such as educational materials or decision aids to help make a decision. Review the treatment's Patient Information.
- Check to see if your patient needs more time to consider the options or discuss the options with others.
- Confirm the decision with your patient, if he or she is ready.
- Schedule follow-up appointments as needed.

TIPS FOR EVALUATION OF THE DECISION

- Monitor the response to the treatment that is implemented.
- Reflect with your patient on whether the decision was consistent with the patient's goals.
- Revisit the decision with your patient and determine if other decisions need to be made.

Applying SDM Tactics in Clinical Practice

CONSIDER THESE QUESTIONS TO ELICIT PATIENTS' PERSPECTIVES AND CONCERNS ABOUT THEIR DISEASE AND TREATMENT

- Would you like to discuss your medical care plan and treatment goals?
- Of the goals, which are the most important to you?
- What bothers you most about having lung cancer?
- What would you like most from your treatment?
- Are you able to tolerate the treatment we've chosen? If not, why not? How can we provide improved support to enhance your treatment?
- Do you understand the different treatment choices? What else would you like to know about them?
- Do you understand why we've chosen this treatment? What else would you like to know about it?
- Are you able to make a decision now, or do you need more time to think about it?
- What are the biggest challenges you face as a result of your condition?
- How can we better support you to cope with these challenges?
- Would you like to be involved with a patient/caregiver support group?

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