Oncology Clinical Pathways
Lung Cancer

May 2025 – V3.2025

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Lung Cancer – Presumptive Conditions

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Vietnam Veterans – Agent Orange Exposure or Specified Locations

- Respiratory cancers

Atomic Veterans Exposed to Ionizing Radiation

- Lung cancer
- Bronchioloalveolar carcinoma

Gulf War and Post 9/11 Veterans

If the patient served any amount of time in Afghanistan, Djibouti, Syria, or Uzbekistan during the Persian Gulf War, from Sept. 19, 2001, to the present or the Southwest Asia theater of operations from Aug. 2, 1990, to the present, specific conditions include:

- Adenosquamous carcinoma of the lung
- Large cell carcinoma of the lung
- Salivary gland-type tumors of the lung
- Sarcomatoid carcinoma of the lung
- Typical and atypical carcinoid of the lung

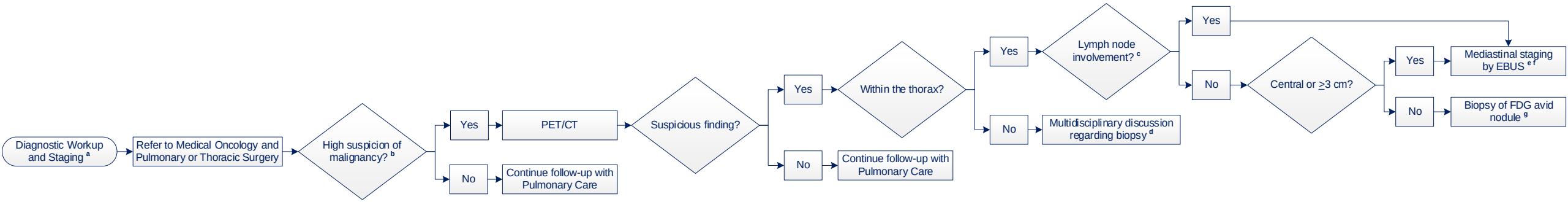
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if the patient served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Respiratory cancer of any type

* The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov)

Lung Cancer – Diagnostic Workup and Staging



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Diagnostic Workup and Staging** for pulmonary nodule evaluation, nodule with a high probability of cancer, nodule already diagnosed with lung cancer, or abnormal thoracic findings with concerns of cancer

[b] **High Suspicion of Malignancy** includes but is not limited to growth, radiographic properties, or large size

[c] **Lymph Node Involvement** includes any thoracic lymph node pathologic enlargement or FDG avidity

[d] **Molecular Testing** adequacy of tumor tissue should be considered in selection of the biopsy site and the amount of tissue; pursue the least invasive/risk biopsy when appropriate

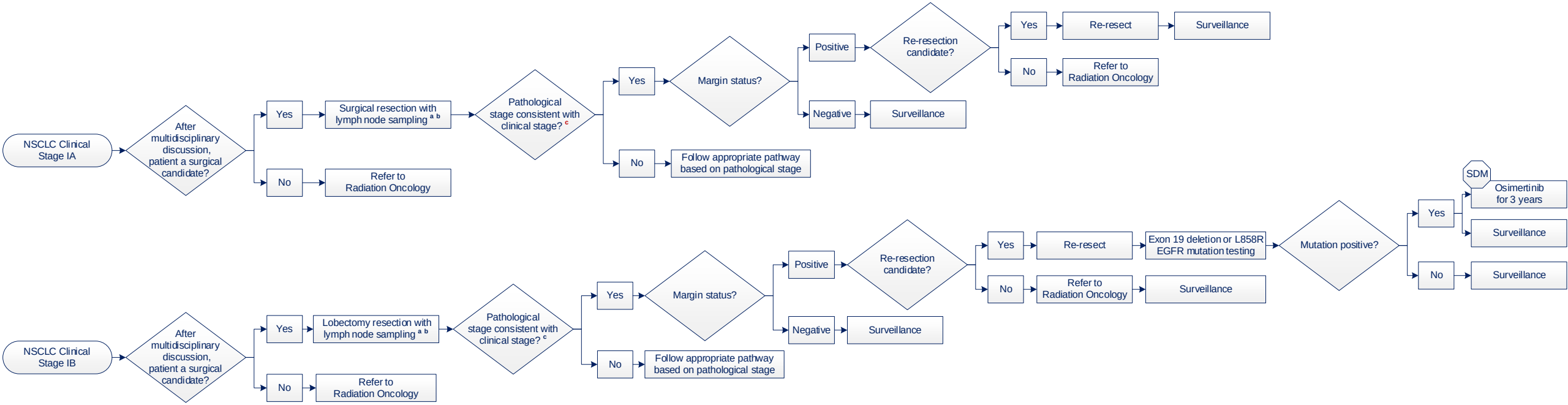
[e] **Mediastinal Staging** includes EBUS examination of all paratracheal and hilar stations with sampling of any nodes > 0.5 cm; EUS or mediastinoscopy may be an alternative staging modality based upon the location of the concerning lymph node(s)

[f] **Imaging** brain MRIs are indicated for Stage II and above

[g] **FDG Avid Nodules** can be evaluated by percutaneous biopsy, surgical biopsy, or navigational bronchoscopy; multidisciplinary discussion can assist in the care plan

EBUS Endobronchial Ultrasound
EUS Endoscopic Ultrasound
FDG Fluorodeoxyglucose

Lung Cancer – NSCLC Clinical Stage IA and IB



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[a] **Surgical Resection** includes lobectomy as preferred resection but sublobar can be considered as clinically indicated; consider sublobar resection for <2cm, peripheral, confirmed negative 10, 4, 7 nodes

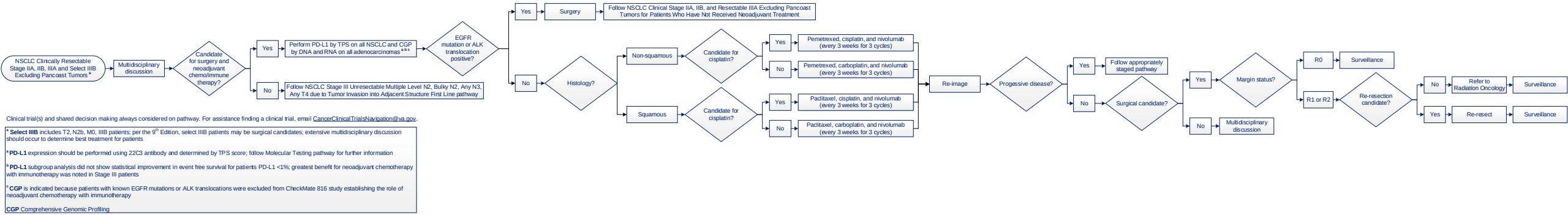
[b] **Lymph node sampling** is strongly encouraged as part of standard of care during surgical resection; minimum recommendation should include examination and/or sampling of ≥3 mediastinal and ≥1 hilar station

[c] **Pathology Review** includes a comprehensive pathology review for high risk features such as poorly differentiated tumors, vascular invasion, wedge resection, visceral pleural involvement, or lymph known status unknown; if ≥1 of these features are present, consider assessment by Medical Oncology post-operatively

SDM Osimertinib shared decision making is critical at the time of consideration of adjuvant Osimertinib for 3 years; adjuvant Osimertinib was shown to improve DFS and OS in EGFR exon 19 or exon 21 mutant NSCLC patients with stage II-III; the study had limitations including the majority of patients not receiving Osimertinib at the time of disease recurrence and inadequate staging; adjuvant Osimertinib is FDA approved in Stage IB but OS benefit is smaller in this subset and HR crosses 1 stressing the importance of discussing both adjuvant Osimertinib and surveillance with the patient

SDM Shared Decision Making

Lung Cancer – NSCLC Clinically Resectable Stage IIA, IIB, IIIA, and Select IIIB Excluding Pancoast Tumors



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[a] **Select IIIB** includes T2, N2b, M0, IIIB patients; per the 9th Edition, select IIIB patients may be surgical candidates; extensive multidisciplinary discussion should occur to determine best treatment for patients

[a] **PD-L1** expression should be performed using 22C3 antibody and determined by TPS score; follow Molecular Testing pathway for further information

[b] **PD-L1** subgroup analysis did not show statistical improvement in event free survival for patients PD-L1 <1%; greatest benefit for neoadjuvant chemotherapy with immunotherapy was noted in Stage III patients

[c] **CGP** is indicated because patients with known EGFR mutations or ALK translocations were excluded from CheckMate 816 study establishing the role of neoadjuvant chemotherapy with immunotherapy

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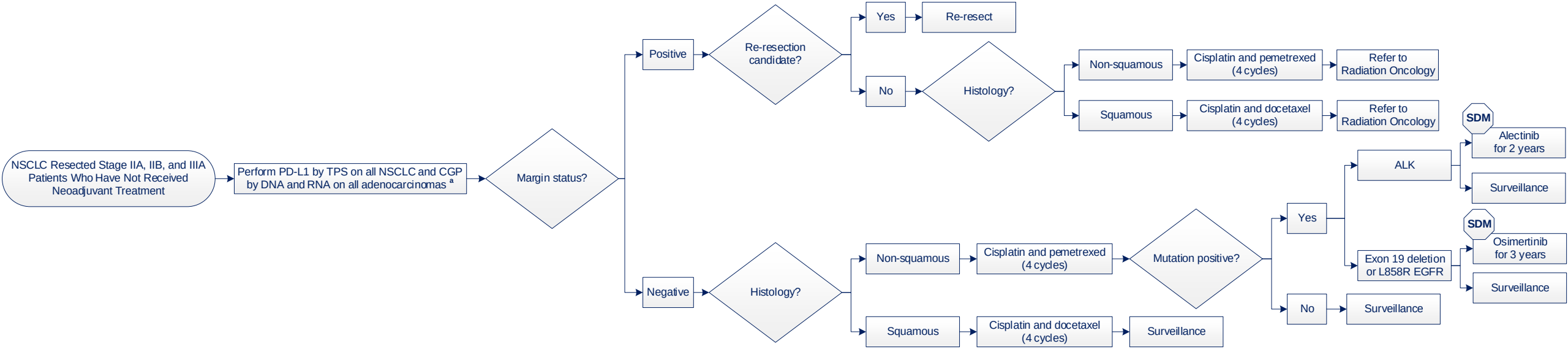
Lung Cancer – NSCLC Resected Stage IIA, IIB, and IIIA Patients Who Have Not Received Neoadjuvant Treatment



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

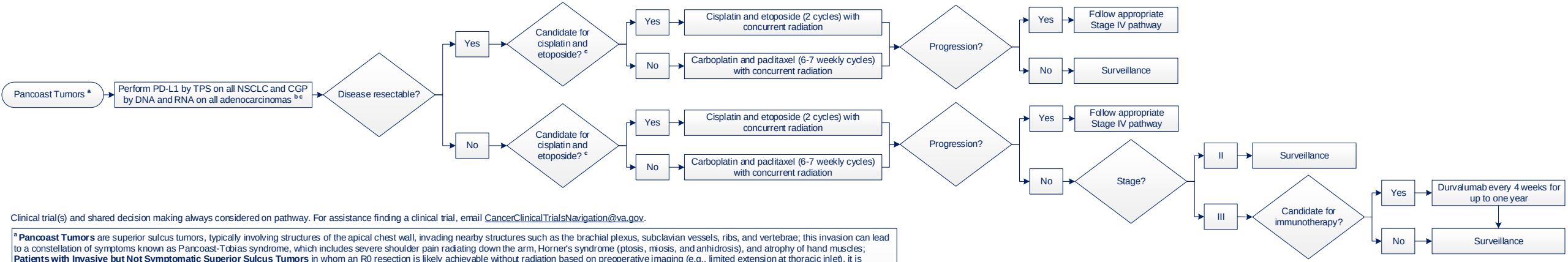
[a] **PD-L1** expression should be performed using 22C3 antibody and determined by TPS score; follow Molecular Testing pathway for further information

SDM Alectinib shared decision making is critical at the time of consideration of adjuvant alectinib for 2 years; adjuvant alectinib was shown to improve DFS in ALK rearranged NSCLC patients with Stage II-III; the study had limitations including inadequate staging and randomization of patients to either adjuvant chemotherapy or alectinib; OS are not available yet and will likely not be available for years

SDM Osimertinib shared decision making is critical at the time of consideration of adjuvant Osimertinib for 3 years; adjuvant Osimertinib was shown to improve DFS and OS in EGFR exon 19 or exon 21 mutant NSCLC patients with Stage II-III; the study had limitations including the majority of patients not receiving Osimertinib at the time of disease recurrence and inadequate staging

CGP Comprehensive Genomic Profiling
SDM Shared Decision Making

Lung Cancer – Pancoast Tumors



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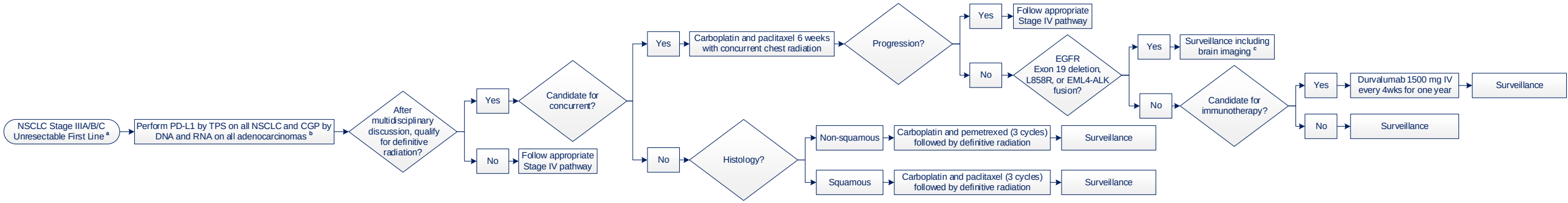
[a] **Pancoast Tumors** are superior sulcus tumors, typically involving structures of the apical chest wall, invading nearby structures such as the brachial plexus, subclavian vessels, ribs, and vertebrae; this invasion can lead to a constellation of symptoms known as Pancoast-Tobias syndrome, which includes severe shoulder pain radiating down the arm, Horner's syndrome (ptosis, miosis, and anhidrosis), and atrophy of hand muscles; **Patients with Invasive but Not Symptomatic Superior Sulcus Tumors** in whom an R0 resection is likely achievable without radiation based on preoperative imaging (e.g., limited extension at thoracic inlet), it is appropriate to proceed with neoadjuvant chemoimmunotherapy; clinical diagnosis that includes any of these stages: T3N0, T4N0, and T4N1 are generally considered resectable and T4N2 is considered unresectable

[b] **PD-L1** expression should be performed using 22C3 antibody and determined by TPS score; follow Molecular Testing pathway for further information

[c] **Candidate for Cisplatin and Etoposide** contraindications include abnormal renal function, ECOG 2, or abnormal heart function

Lung Cancer – NSCLC Stage IIIA/B/C Unresectable First Line



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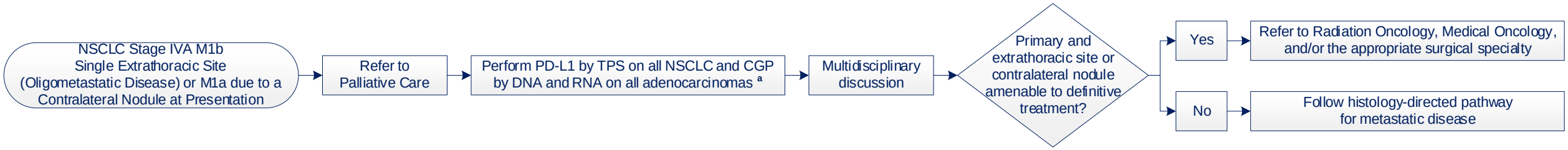
[a] **NSCLC Stage IIIA/B/C Unresectable** includes multiple level N2, bulky N2, any N3, any T4 due to tumor invasion into adjacent structure or poor surgical candidates due to prohibitive risk

[b] **PD-L1** expression should be performed using 22C3 antibody and determined by TPS score; follow Molecular Testing pathway for further information; CGP is indicated because the role of consolidation durvalumab is unclear in EGFR mutant or ALK translocation positive patients

[c] **Surveillance Including Brain Imaging** includes brain MRI and CT scan of the chest to the adrenals every 3-4 months for 2 years with reduced frequency of imaging as clinically appropriate after 2 years

CGP Comprehensive Genomic Profiling

Lung Cancer – NSCLC Stage IVA M1b Single Extrathoracic Site or M1a Due To A Contralateral Nodule at Presentation

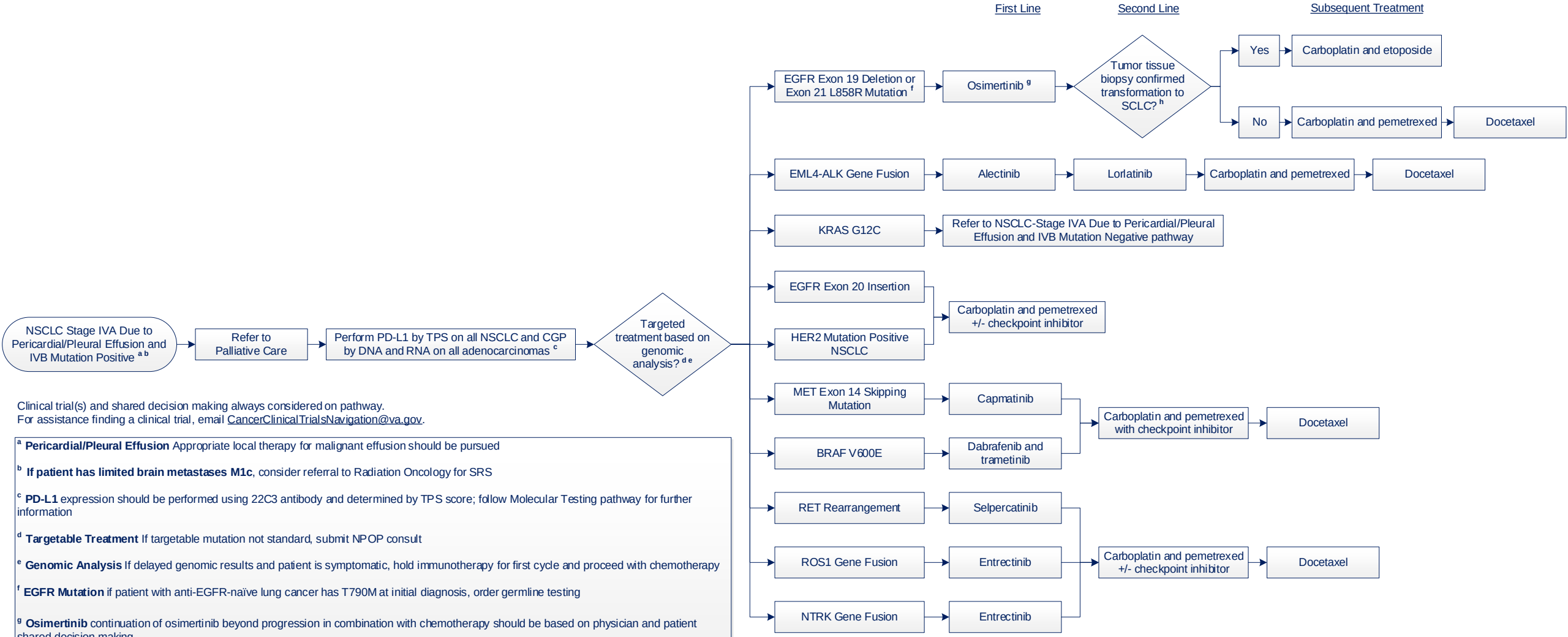


Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **PD-L1** expression should be performed using 22C3 antibody and determined by TPS score; follow Molecular Testing pathway for further information

CGP Comprehensive Genomic Profiling

Lung Cancer – NSCLC Stage IVA Due to Pericardial/Pleural Effusion and IVB Mutation Positive



Clinical trial(s) and shared decision making always considered on pathway.
For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Pericardial/Pleural Effusion** Appropriate local therapy for malignant effusion should be pursued

[b] **If patient has limited brain metastases M1c**, consider referral to Radiation Oncology for SRS

[c] **PD-L1** expression should be performed using 22C3 antibody and determined by TPS score; follow Molecular Testing pathway for further information

[d] **Targetable Treatment** If targetable mutation not standard, submit NPOP consult

[e] **Genomic Analysis** If delayed genomic results and patient is symptomatic, hold immunotherapy for first cycle and proceed with chemotherapy

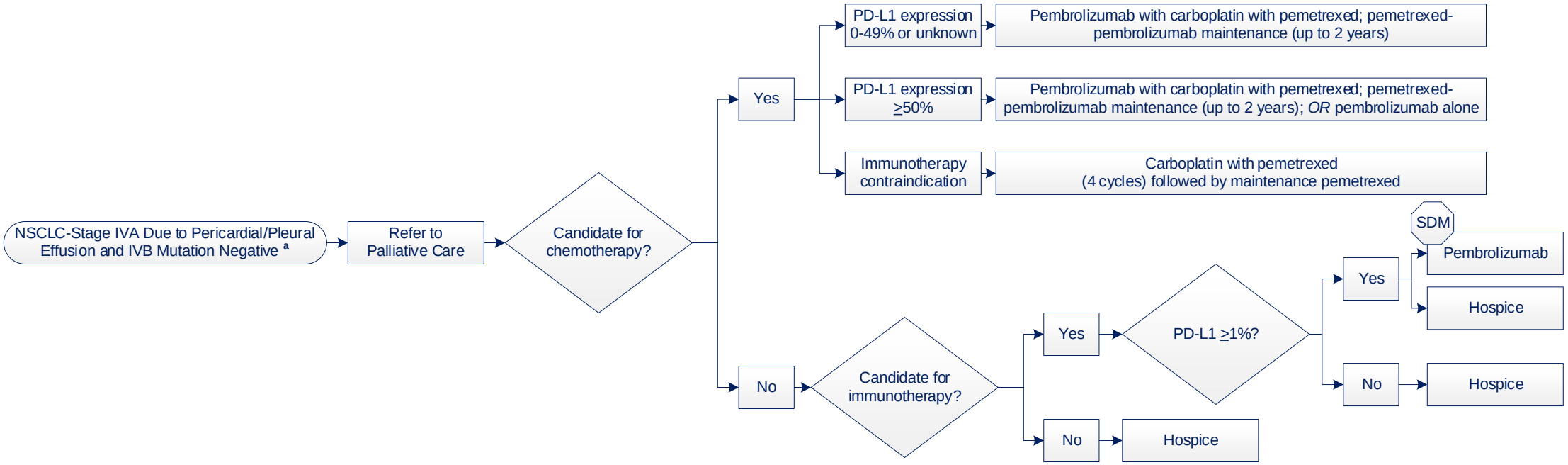
[f] **EGFR Mutation** if patient with anti-EGFR-naïve lung cancer has T790M at initial diagnosis, order germline testing

[g] **Osimertinib** continuation of osimertinib beyond progression in combination with chemotherapy should be based on physician and patient shared decision making

[h] **Driver Mutation Repeat Testing** recommendations on NGS testing for patients with driver mutations can be found on the NPOP SharePoint

CGP Comprehensive Genomic Profiling

Lung Cancer – NSCLC Stage IVA Due to Pericardial/Pleural Effusion and IVB Mutation Negative



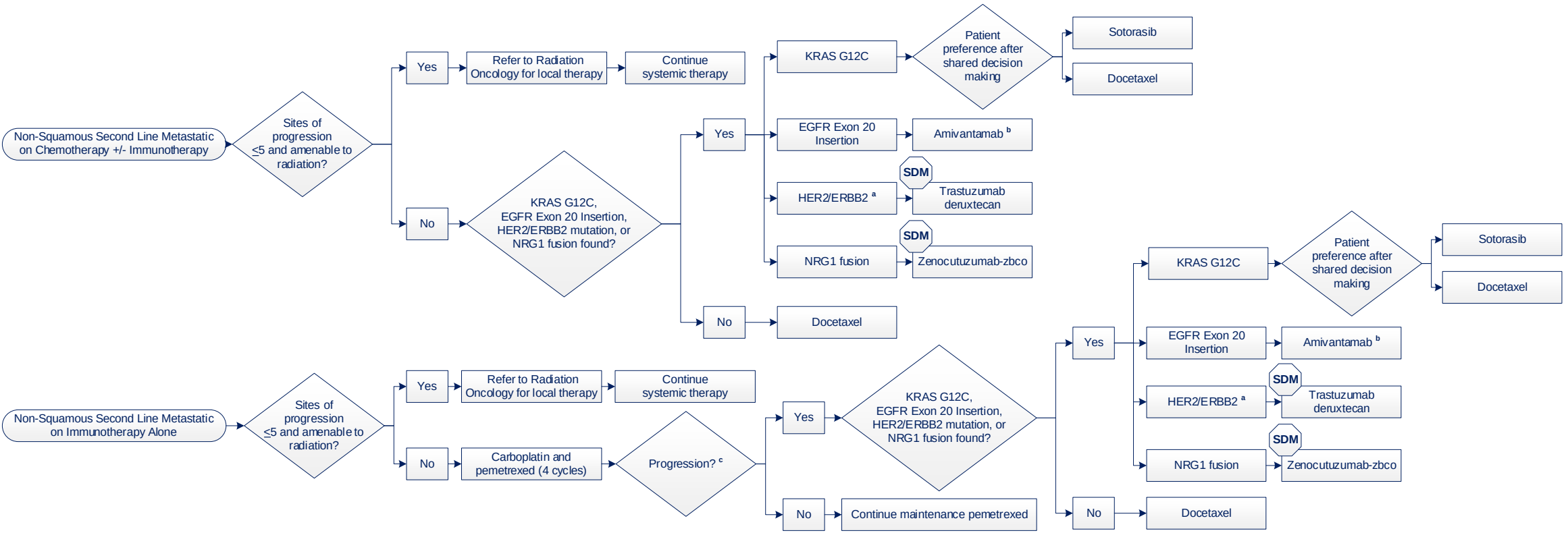
Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Pericardial/Pleural Effusion** appropriate local therapy for malignant effusion should be pursued; pathway also applicable for first line treatment of KRAS G12C, EGFR Exon 20 insertion, and HER2 mutation positive NSCLC

SDM Pembrolizumab shared decision making is critical at the time of consideration of pembrolizumab if PD-L1 >1%; pembrolizumab was approved as single agent in PD-L1 ≥1% based on KEYNOTE-042; the inclusion of PD-L1 >50% patients in the study limits the interpretation of the benefit of single agent pembrolizumab in the 1-50% group; therefore while this is an FDA approved indication, shared decision making in patients that do not qualify for chemotherapy and that have a PD-L11-50% should include a thorough discussion of the limited activity of single agent immunotherapy noted in this subset in other trials

SDM Shared Decision Making

Lung Cancer – Non-Squamous Relapse



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **HER2/ERBB2 positive mutation** the majority of HER2 mutations allowed on trial were exon 20 insertions; other mutations included single-nucleotide variants in exon 19 or 20 of the kinase domain or in exon 8 of the extracellular domain; for other less common mutations consult NPOP

[b] **Amivantamab** initial frequency of administration might make this drug challenging for patients with transportation issues; do not use if patient cannot take pre-medications

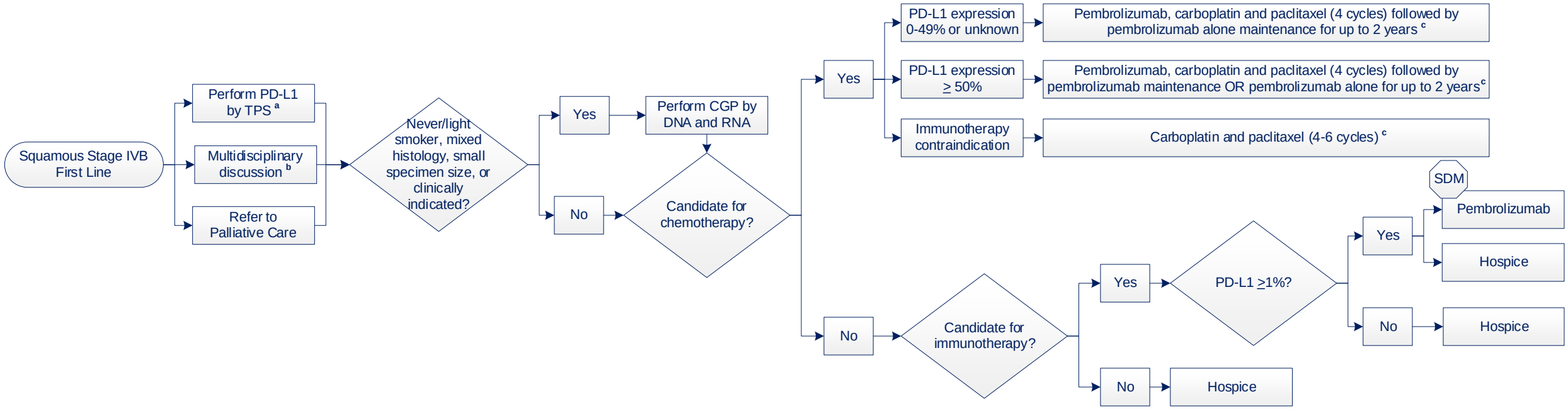
[c] **Progression** if limited progression, consider referral to Radiation Oncology

SDM Trastuzumab Deruxtecan shared decision making is critical at the time of consideration of trastuzumab deruxtecan; trastuzumab deruxtecan was approved based on initial activity showing a response rate in patients with HER2 mutations; confirmatory studies are pending; it is unclear if preliminary activity will be associated with improvements in survival; trastuzumab deruxtecan has unique toxicities and patients should be educated on these side effects and monitored closely

SDM Zenocutuzumab-zbco accelerated FDA approval based on response rate in single-arm trial; do not use if patient cannot take pre-medications

SDM Shared Decision Making

Lung Cancer – Squamous Stage IVB First Line



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **PD-L1** expression should be performed using 22C3 antibody and determined by TPS score; follow Molecular Testing pathway for further information

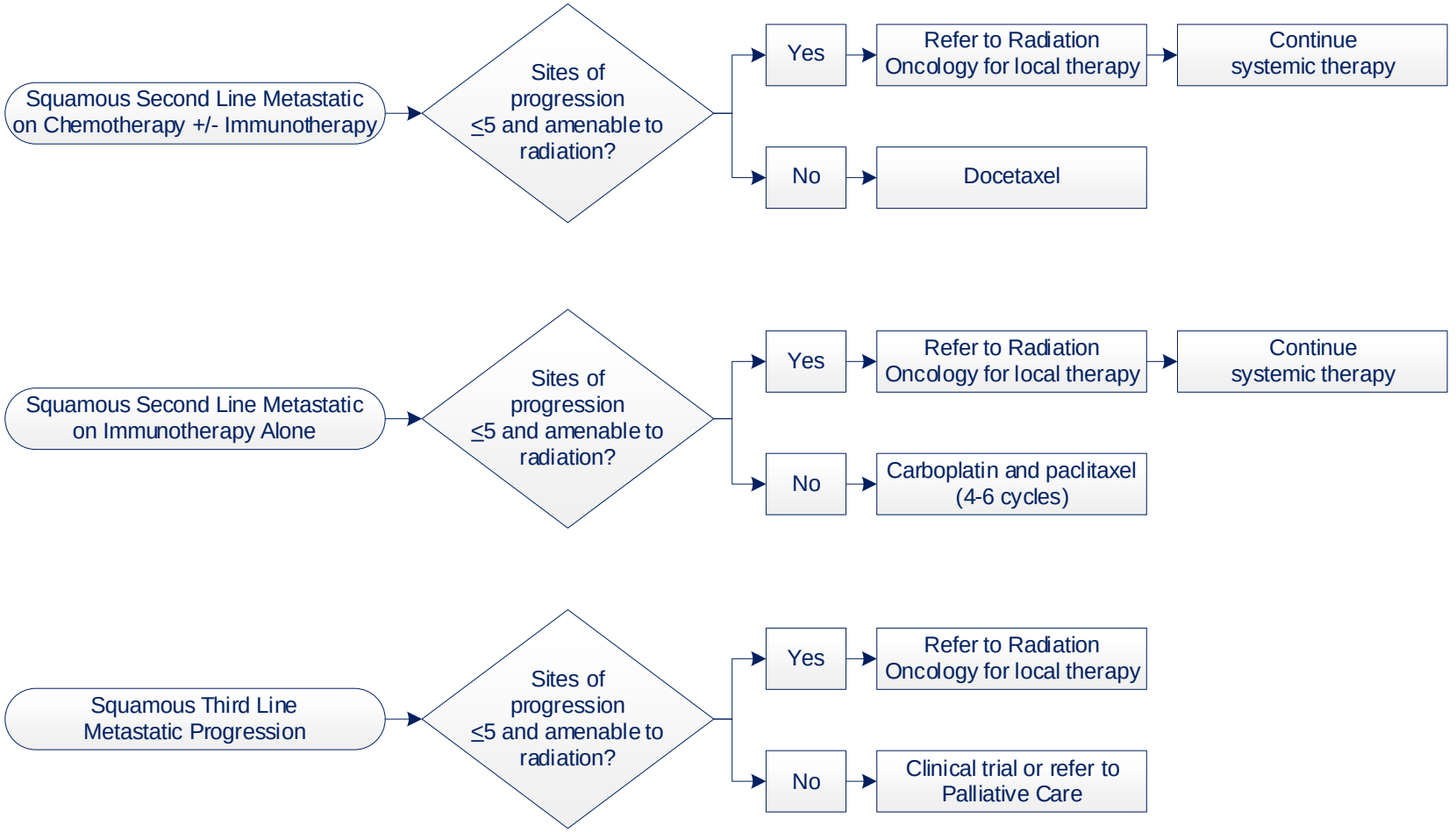
[b] **If patient is symptomatic** refer to Radiation Oncology

[c] **If limited progression**, consider referral to Radiation Oncology and continuation of first-line systemic therapy

SDM Pembrolizumab shared decision making is critical at the time of consideration of pembrolizumab if PD-L1 >1%; pembrolizumab was approved as single agent in PD-L1 ≥1% based on KEYNOTE-042; the inclusion of PD-L1 >50% patients in the study limits the interpretation of the benefit of single agent pembrolizumab in the 1-50% group; therefore while this is an FDA approved indication, shared decision making in patients that do not qualify for chemotherapy and that have a PD-L11-50% should include a thorough discussion of the limited activity of single agent immunotherapy noted in this subset in othertrials

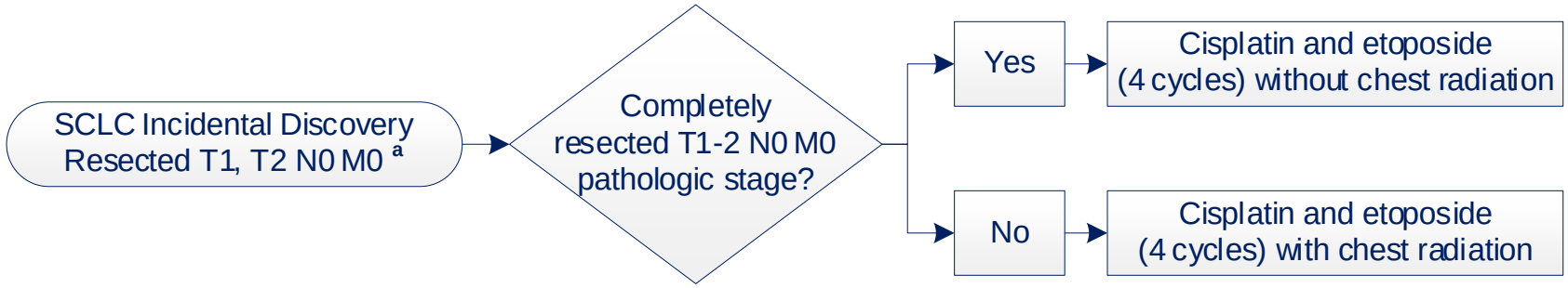
SDM Shared Decision Making

Lung Cancer – Squamous Second and Third Lines Metastatic



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

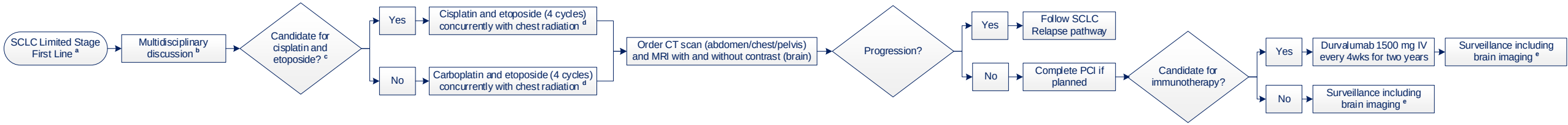
Lung Cancer – SCLC Incidental Discovery Resected T1, T2 N0 M0



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Large Cell Neuroendocrine Tumors** can be treated like SCLCs

Lung Cancer – SCLC Limited Stage First Line



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Large Cell Neuroendocrine Tumors** can be treated like SCLCs

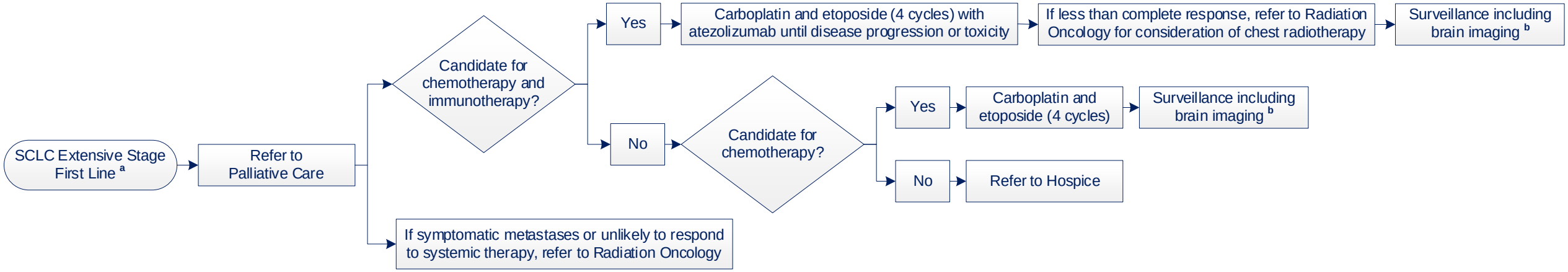
[b] **In the rare case of T1-2 N0 M0**, surgery can be considered followed by adjuvant chemotherapy

[c] **Candidate for cisplatin and etoposide** contraindications include abnormal renal function, ECOG 2, or abnormal heart function

[d] **Initiate radiation** as early as possible, within the first or second cycle of chemotherapy

[e] **Surveillance Including Brain Imaging** includes brain MRI and CT scan of the chest to the adrenals every 3-4 months for 2 years with reduced frequency of imaging as clinically appropriate after 2 years

Lung Cancer – SCLC Extensive Stage First Line

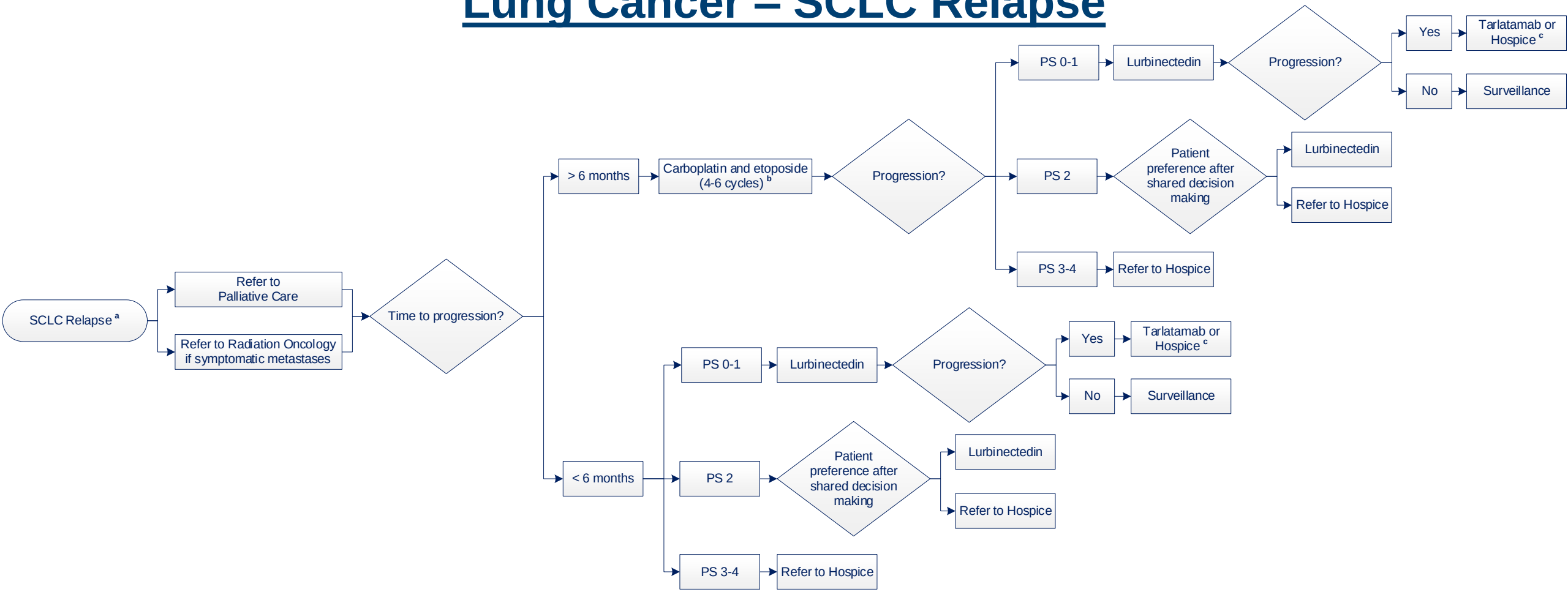


Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Large Cell Neuroendocrine Tumors** can be treated like SCLCs

[b] **Surveillance Including Brain Imaging** includes brain MRI and CT scan of the chest to the adrenals every 3-4 months for 2 years with reduced frequency of imaging as clinically appropriate after 2 years

Lung Cancer – SCLC Relapse



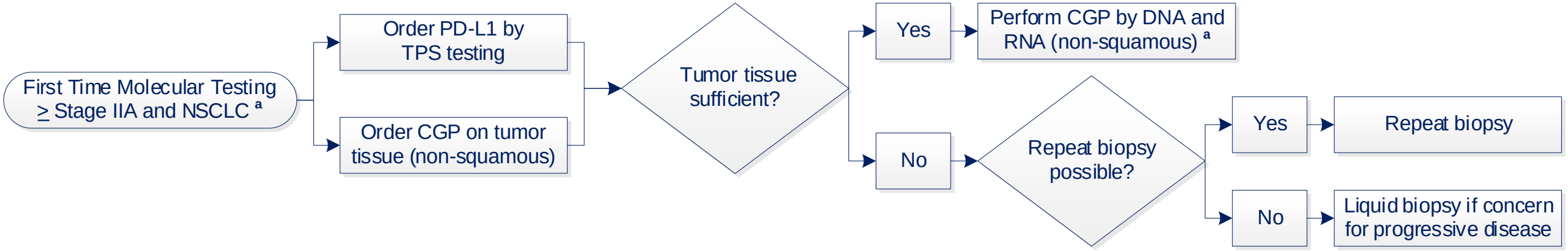
Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Large Cell Neuroendocrine Tumors** can be treated like SCLCs

[b] **If patient is progressing** and did not receive immunotherapy upfront, patient can receive carboplatin, etoposide, and atezolizumab

[c] **Tarlatamab** this therapy is highly toxic and administration requires significant facility support and comprehensive protocols with experienced personnel capable of identifying, monitoring and managing CRS and Neurotoxicity (ICANS); in addition, patient requirements: PS 0-1, cardiac ejection fraction ≥50%, no evidence or ILD, estimated GFR ≥30 mL/min/1.73m2, adequate blood counts and liver function, and the absence of known or suspected infectious diseases

Lung Cancer – Molecular Testing



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Molecular Testing** is not routinely recommended for SCLC or large cell neuroendocrine tumors; molecular testing may be ordered for mixed histology or squamous cell carcinoma as clinically appropriate

CGP Comprehensive Genomic Profiling

Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Stage IIA and Higher NSCLC	IHC	PD-L1 expression by IHC using 22C3 antibody	Tempus Foundation Medicine Local Vendor	Yes (when ordered with CGP) Yes (when ordered with CGP) No	Tumor Tissue
Stage IIA and Higher NSCLC Non-Squamous	Somatic NGS*	DNA and RNA-based comprehensive genomic profiling (CGP)	Tempus Foundation Medicine	Yes Yes	Tumor Tissue, Blood
Stage IV Squamous Never/Light Smoker, Mixed Histology, or Small Specimen Size	Somatic NGS*	DNA and RNA-based comprehensive genomic profiling (CGP)	Tempus Foundation Medicine	Yes Yes	Tumor Tissue, Blood
* Somatic NGS testing should adequately cover point mutations, small insertion/deletion mutations, amplifications, and fusion oncogenes; at minimum testing should include coverage of EGFR, ALK, ROS1, RET, MET, BRAF, KRAS, NTRK1, NTRK2, NTRK3, and HER2					
** Tissue testing strongly preferred because it is the only method for RNA based testing. Liquid testing is suboptimal but acceptable only if adequate tissue cannot be obtained.					

Lung Cancer – Surveillance for Surgically Treated NSCLC Stage IA/IB, IIA/IIB, or IIIA

Surveillance for Surgically Treated NSCLC Stage IA/IB, IIA/IIB, or IIIA [a]

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 5+
H&P [b]	Every 6 months			Annually		
CT Chest [c]	Every 6 months			Annually		Annual low dose CT [d]

Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Surveillance** once treatment is completed; routine brain imaging is not recommended unless otherwise specified on pathway

[b] **H&P** to include smoking cessation

[c] **CT of Chest** initial baseline scan within 3 months of definitive treatment; more frequent scanning may be required

[d] **Annual Low Dose CT** more frequent scanning intervals may be appropriate in some patients, to include SBRT patients; for years 3-5+, low-dose CT scans may be used to screen for a second primary malignancy

Lung Cancer – Surveillance for NSCLC Stage III Curative Intent with Definitive Chemoradiation

Surveillance for NSCLC Stage III Curative Intent with Definitive Chemoradiation [a]

	Year 1 [d]	Year 2	Year 3	Year 4	Year 5	Year 5+
H&P [b]	Every 3 months	Every 4 months	Every 6 months			
CT Chest [c]	Every 3 months	Every 4 months	Every 6 months			Annual low dose CT [e]

Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Surveillance** once treatment is completed; routine brain imaging is not recommended unless otherwise specified on pathway

[b] **H&P** to include smoking cessation

[c] **CT of Chest** initial baseline scan within 3 months of definitive treatment; more frequent scanning may be required

[d] **Year 1** not intended to provide guidance for imaging consolidation immunotherapy

[e] **Annual Low Dose CT** more frequent scanning intervals may be appropriate in some patients, to include SBRT patients; for years 3-5+, low-dose CT scans may be used to screen for a second primary malignancy

Lung Cancer – References

Stage IA and 1B

Surveillance in Stage IB as Compared to Adjuvant Chemotherapy

1. Strauss GM, Herndon JE, Maddaus MA, et al. Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): update of Cancer and Leukemia Group B (CALGB) protocol 9633. *J Clin Oncol. 2006 Jun 20;*24(18): suppl, abstr 7007.

XRT in Patients That Do Not Qualify for Surgery

1. Woody NM, Stephans KL, Marwaha G, et al. Stereotactic body radiation therapy for non-small cell lung cancer tumors greater than 5 cm: safety and efficacy. *Int J Radiat Oncol Biol Phys.* 2015 Jun 1;92(2):325-31.
2. Hobbs CJ, Ko SJ, Paryani NN, et al. Stereotactic body radiotherapy for medically inoperable stage I-II non-small cell lung cancer: The Mayo Clinic experience. *Mayo Clin Proc Innov Qual Outcomes*. 2017 Dec 26;2(1)40-48.

Surgery in Stage IA/IB Disease

1. Mentzer SJ, DeCamp MM, Harpole Jr DH, et al. Thoracoscopy and video-assisted thoracic surgery in the treatment of lung cancer. *Chest*. 1995 Jun;107 (6 Suppl):298S-301S.

Lymph Node Dissection

1. Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0300 trial. *Chest*. 2011 May;139(5):1124-1129.
2. Manser R, Wright G, Hart D, et al. Surgery for early-stage non-small cell lung cancer. *Cochrane Database Syst Rev*. 2005 Jan 25;2005(1):CD004699.
3. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2006 Nov;30(5):787-92.
4. Lim E, Baldwin D, Beckles M, et al. Guidelines on the radical management of patients with lung cancer. *Thorax*. 2010 Oct:65 Suppl 3:iii1-27.

Stage II-III

Adjuvant Chemotherapy

1. Pignon J, Tribodet H, Scagliotti G, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol.* 2008 Jul 20;26(21)3552-9.
2. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-cased adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. *N Engl J Med* 2004;350:351-360.
3. Douillard JY, Rosell R, De Lena M, et al: Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol.* 2006 Sep;7(9):719-27.
4. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin-versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst.* 2007 Jun 6;99(11):847-57.

Lung Cancer – References

Stage II-III Continued

Adjuvant Osimertinib

1. Wu Y, Tsuboi M, He J, et al. Osimertinib in resected EGFR mutated non-small cell lung cancer. *N Engl J Med*. 2020 Oct 29;383(18):1711-1723.
2. Tsuboi M, Herbst R, John T, et al. Overall survival with osimertinib in resected EGFR mutated NSCLC. *N Engl J Med*. 2023 Jun 4;389(2):137-147.

Adjuvant Alectinib

1. Wu Y, Dziadziuszko R, Ahn JS, et al. Alectinib in resected ALK-positive non–small-cell lung cancer. *N Engl J Med.* 2024 Apr 11;390(14):1265-1276.

Choice of Chemotherapy Based on Histology

1. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non–small-cell lung cancer. *J Clin Oncol.* 2008 Jul 20;26(21):3543-3551.

Concurrent or Sequential Chemotherapy and Radiation

1. Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 Trial. *J Natl Cancer Inst.* 1996 Sep 4;88(17):1210-5.
2. Sause W, Kolesar P, Taylor S, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest.* 2000 Feb;117(2):358-64.
3. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non–small-cell lung cancer. *J Clin Oncol.* 1999 Sep;17(9):2692-9.
4. Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer.* 2004 Oct;46(1):87-98.
5. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non–small-cell lung cancer: a Randomized phase II locally advanced multi-modality protocol. *J Clin Oncol.* 2005 Sep 1;23(25):5883-91.

Pancoast Tumors

1. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Thorac Cardiovasc Surg*. 2001 Mar;121(3):472-83.

Durvalumab Consolidation in Stage III Unresectable

1. Antonia SJ, Villega A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *N Engl J Med*. 2017 Nov 16;377(20):1919-1929.
2. Antonia SJ, Villega A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018 Dec 13;379(24):2342-2350.

Neoadjuvant Chemotherapy and Immunotherapy in Resectable NSCLC

1. Forde P, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med.* 2022 May 26’386(21):1973-1985.

Lung Cancer – References

Stage IV Mutation Positive

Palliative Care
1. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010 Aug 19;363(8):733-742.

Osimertinib
1. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018 Jan 11;378(2):113-125.
2. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med.* 2020 Jan 2;382(1):41-50.

ALK Positive Alectinib
1. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib patients with ALK-positive non-small-cell lung cancer (J-Alex): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2017 Jul 1;390(10089):29-39.
2. Hotta K, Hida T, Nokihara H, et al. Final overall survival analysis from the phase III J-ALEX study of alectinib versus crizotinib in ALK inhibitor-naïve Japanese patients with ALK-positive non-small-cell lung cancer. *ESMO Open.* 2022 Aug;7(4):100527.
3. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med.* 2017 Aug 31;377(9):829-838.

KRAS G12C
1. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med.* 2021 Jun 24;384(25):2371-2381.

MET Skipping Mutation
1. Wolf J, Takashi S, Han J, et al. Capmatinib in *MET Exon 14*-mutated or *MET*-amplified non-small-cell lung cancer. *N Engl J Med.* 2020 Sep 3;383(1):944-957.

RET
1. Drilon A, Oxnard G, Tan DSW, et al. Efficacy of selperacatinib in *RET*Fusion-positive non-small-cell lung cancer. N Engl J Med. 2020 Aug 27;383(9):813-824.

ROS1
1. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol.* 2020 Feb;21(2):261-270.

BRAF
1. Planchard D, Smit E, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017 Oct;18(10):1307-1316.

NTRK1
1. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumors: integrated analysis of three phase 1-2 trials. *Lancet Oncol.* 2020;21(2):271-282.

Lung Cancer – References

Stage IV Mutation Negative and Second Line

Palliative Care
1. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010 Aug 19;363(8):733-742.

Carboplatin Pemetrexed Pembrolizumab
1. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med.* 2018 May 31; 378(22):2078-2092.
2. Garassino M, Gadgeel S, Speranza G, et al. Pembrolizumab plus pemetrexed and platinum in nonsqamous non-small cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. *J Clin Oncol.* 2023 Apr 10;41(11):1192-1998.

Pembrolizumab for PDL1 ≥ 50% and ≥1%
1. Garon E, Rizvi NA, Leighl N, et al. Pembrolizumab for the treatment of non-small cell lung cancer. *N Engl J Med.* 2015 May 21;372(21):2018-28.
2. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1 positive non-small cell lung cancer. *N Engl J Med.* 2016 Nov 10;375(19):1823-1833.

Carboplatin Pemetrexed Followed by Maintenance Pemetrexed
1. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final Overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol.* 2013 Aug 10;31(23):2895-902.

Docetaxel Second Line
1. Herbst RS, Garon EG, Kim D, et al. Five year survival update from KEYNOTE-010: pembrolizumab versus docetaxel for previously treated, programmed death-ligand 1–positive advanced NSCLC. *J Thorac Oncol*. 2021 Oct;16(10):1718-1732.

KRAS G12C
1. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with *KRAS* p.G12C mutation. *N Engl J Med.* 2021 Jun 24;384(25):2371-2381.
2. De Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small cell lung cancer with KRAS G12C mutation: a randomized, open label, phase 3 trial. *Lancet.* 2023 Mar 4;401(10378):733-746.

Squamous Cell Lung Cancer First Line
1. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small cell lung cancer. *J Engl J Med.* 2018 Nov 22;379(21):2040-2051.
2. Novello S, Kowalski DM, Luft A, et al. Pembrolizumab plus chemotherapy in squamous non–small-cell lung cancer: 5-year update of the phase III KEYNOTE-407 study. *J Clin Oncol.* 2023 Apr 10;41(11):1999-2006.

Lung Cancer – References

Stage IV Mutation Negative and Second Line Continued

Exon 20 Insertion Mutation

1. Park K, Haura EB, Leighl NB, et al. Amivantamab in EGFR exon 20 insertion-mutated non-small cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS phase 1 study. J. Clin Oncol. 2021 Oct 20;39(30):3391-3402.

HER2

1. Li BT, Smit EF, Goto Y, et al. Trastuzumab deruxtecan in HER2-mutant non-small cell lung cancer. *N Engl J Med.* 2022 Jan 20;386(3):241-251.

SCLC Incidental Discovery

Surgery for Incidental SCLC Discovery

1. Wakeam E, Acuna SA, Leighl NB, et al. Surgery versus chemotherapy and radiotherapy for early and locally advanced small cell lung cancer: a propensity-matched analysis of survival. *Lung Cancer*. 2017 Jul;109:78-88.

Adjuvant Chemotherapy for Patients with Incidentally Resected SCLC

1. Yang CJ, Chan DY, Speicher PJ, et al. Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. *J Clin Oncol*. 2016 Apr 1;34(10):1057-64.

SCLC Limited Stage

Chemotherapy with Radiation in SCLC Limited Stage

1. Sundstrom S, Bremnes R, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years; follow-up. *J Clin Oncol*. 2002 Dec 15;20(24):4655-72.
2. Skarlos DV, Samantas E, Kosmidis P, et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. *Ann Oncol*. 1994 Sep;5(7):601-7.
3. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol*. 1992 Jun;10(6):890-5.
4. Pignon J, Arriagada R, Ihde DC, et al. A met-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med.* 1992;327(23):1618-1624.
5. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. *J Clin Oncol.* 2006 Mar 1;24(7):1057-63.
6. Fried DB, Morris DE, Poole C, et al. Systemic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol*. 2004 Dec 1;22(23):4837-45.

Lung Cancer – References

SCLC Limited Stage Continued

Prophylactic Cranial Irradiation in Limited Stage SCLC

1. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999 Aug 12;341(7):476-84.
2. Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systemic review of the literature with meta-analysis. *BMC Cancer*. 2001:1:5.

Consolidation Durvalumab

1. Spigel DR, Cheng Y, Cho BC, et al. ADRIATIC: Durvalumab (D) as consolidation treatment (tx) for patients (pts) with limited-stage small-cell lung cancer (LS-SCLC). *J Clin Oncol*. 2024 Jun 5:42(17).

SCLC Extensive Stage

Carboplatin with Etoposide and Atezolizumab

1. Horn L, Mansfield A, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018 Dec 6;379(23):2220-2229.

SCLC Relapse

Lurbinectedin Second Line

1. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label phase 2 basket trial. *Lancet Oncol*. 2020 May;21(5):645-654.

Tarlatamab in SCLC

2. Ahn M, Cho BC, Felip Em et al. Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med*. 2023 Nov 30;389(22):2063-2075.