Oncology Clinical Pathways
Lung Cancer

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Lung Cancer – NSCLC Clinical Stage IA and IB

1. **NSCLC Clinical Stage IA and IB**
   - After multidisciplinary discussion, patient a surgical candidate?
     - Yes → **Lobectomy resection** with lymph node sampling
     - No → Refer to Radiation Oncology

2. **Lobectomy resection** with lymph node sampling
   - Pathological stage consistent with clinical stage?
     - Yes → Margin status?
       - No → Follow appropriate pathway based on pathological stage
       - Yes → Re-resection candidate?
         - Yes → Re-resect
         - No → Refer to Radiation Oncology
     - No → Surveillance

3. **Clinical trial(s) always considered on pathway.**

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*If contraindications to lobectomy, sublobar resection may be considered; segmentectomy is preferred

*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*
Lung Cancer – NSCLC Clinical Stage IIA, IIB, and Resectable IIIA Excluding Pancoast Tumors for Patients Who Have Not Received Neoadjuvant Treatment

NSCLC Clinical Stage IIA, IIB, and Resectable IIIA Excluding Pancoast Tumors for Patients Who Have Not Received Neoadjuvant Treatment

After multidisciplinary discussion, patient a surgical candidate?

- Yes
  - Lobectomy or anatomic resection * with lymph node sampling *
  - Refer to Medical Oncology and Radiation Oncology for definitive therapy
  - Perform PD-L1 by TPS and CGP *

- No
  - Re-section candidate?
    - Yes
      - Re-sect
      - Non-squamous: cisplatin and pemetrexed (4 cycles)
      - Squamous: cisplatin and docetaxel (4 cycles)
    - No
      - Non-squamous: cisplatin and pemetrexed (4 cycles)
      - Squamous: cisplatin and docetaxel (4 cycles)
  - Margin status?
    - R0
      - Non-squamous: cisplatin and pemetrexed (4 cycles)
    - R1 or R2
      - Re-section candidate?
        - Yes
          - Re-sect
          - Non-squamous: cisplatin and pemetrexed (4 cycles)
          - Squamous: cisplatin and docetaxel (4 cycles)
        - No
          - Squamous: cisplatin and docetaxel (4 cycles)

Clinical trial(s) always considered on pathway.

* Lung-sparing anatomic resection (sleeve lobectomy) preferred over pneumonectomy if anatomically appropriate and margin-negative resection can be achieved
* 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
* 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

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Shoulder to Shoulder
Every Step of the Way

VA
U.S. Department of Veterans Affairs
Lung Cancer – NSCLC Clinically Resectable Stage IIA, IIB, and IIIA Excluding Pancoast Tumors

Clinical trial(s) always considered on pathway.

NSCLC Clinically Resectable Stage IIA, IIB, and IIIA Excluding Pancoast Tumors

Multidisciplinary discussion

Candidate for surgery and neoadjuvant chemotherapeutic or immune therapy?

Yes

Perform PD-L1 by TPS and CGP a b

No

Follow NSCLC Stage III Unresectable Multiple Level N2, Bulky N2, Any N3, Any T4 Line pathway

EGFR mutation or ALK translocation positive?

Yes

Surgery

Follow NSCLC Clinical Stage IIA, IIB, and Resectable IIIA Excluding Pancoast Tumors for Patients Who Have Not Received Neoadjuvant Treatment

No

Non-squamous: pemteatrexed or paclitaxel, cisplatin a d and nivolumab (every 3 weeks for 3 cycles)

Squamous: gemcitabine or paclitaxel, cisplatin a d and nivolumab (every 3 weeks for 3 cycles)

Surgery

Margin status?

R0

Surveillance

R1 or R2

Re-resection candidate?

Yes

No

Refer to Radiation Oncology

*PD-L1 expression should be performed using 22C3 antibody and determined by TPS score; follow Molecular Pathway for further information

**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

a 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

b If contraindication to cisplatin, prescribe carboplatin

c Comprehensive Genomic Profiling
Lung Cancer – Pancoast Tumors T4N1 or T4N0

Pancoast Tumors T4N1 or T4N0

After multidisciplinary discussion, patient a surgical candidate?

Yes

Contraindication to cisplatin and etoposide? *

No

Contraindication to cisplatin and etoposide? *

Yes

Cisplatin and etoposide (2-3 cycles) with concurrent radiation

Yes

Carboplatin and paclitaxel (2-3 cycles) with concurrent radiation

No

Cisplatin and etoposide (2-3 cycles) with concurrent radiation

Yes

Carboplatin and paclitaxel (6 weekly cycles or 2-3 cycles) with concurrent radiation

No

Durvalumab 1500 mg IV every 4 weeks for one year

Surgery

Clinical trial(s) always considered on pathway.

* Contraindications include abnormal renal function, ECOG 2, or abnormal heart function
Lung Cancer – NSCLC Clinical Stage III Unresectable Multiple Level N2, Bulky N2, Any N3, Any T4 Due To Tumor Invasion Into Adjacent Structure First Line

- NSCLC Stage III Unresectable Multiple Level N2, Bulky N2, Any N3, Any T4 due to Tumor Invasion into Adjacent Structure First Line
  - Perform PD-L1 by TPS and CGP.
  - After multidisciplinary discussion, qualify for definitive radiation?
    - Yes
      - Candidate for concurrent?
        - Yes
          - Carboplatin and paclitaxel 6 weeks with concurrent chest radiation
          - Progression?
            - Yes
              - Follow Stage IV Pathway
            - No
              - Non-squamous: carboplatin and pemetrexed (3 cycles) followed by definitive radiation
              - Progression?
                - Yes
                  - Follow Stage IV Pathway
                - No
                  - Squamous: carboplatin and paclitaxel (3 cycles) followed by definitive radiation
    - No
      - Follow appropriate Stage IV pathway

- Clinical trial(s) always considered on pathway.

**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.

CGP: Comprehensive Genomic Profiling
Lung Cancer – Molecular Testing

Molecular Testing

- Order CGP on tumor tissue (non-squamous)
- Order PD-L1 by TPS testing

Is tissue biopsy sufficient?

- Yes
- No

Repeat biopsy possible?

- Yes
- No

- Repeat biopsy
- Perform liquid biopsy if concern for progressive disease
Lung Cancer – NSCLC Stage IVA M1b Single Extrathoracic Site or M1a Due To A Contralateral Nodule at Presentation

NSCLC Stage IVA M1b Single Extrathoracic Site (Oligometastatic Disease) or M1a due to a Contralateral Nodule at Presentation

Perform PD-L1 by TPS and CGP

Multidisciplinary discussion

Primary and extrathoracic site or contralateral nodule amenable to definitive treatment?

Yes

Refer to Radiation Oncology, Medical Oncology, and/or the appropriate surgical specialty

No

Follow histology-directed pathway for metastatic disease

Clinical trial(s) always considered on pathway.

*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

NSCLC-Stage IVA Due to Pericardial/Pleural Effusion and IVB Mutation Positive

**Refer to Palliative Care**

**Perform PD-L1 by TPS and CGP**

**Targeted treatment based on genomic analysis**

- **EGFR Exon 19 Deletion or Exon 21 L858R Mutation**
  - First Line: Osimertinib
  - Biopsy confirmed transformation to SCLC?
    - Yes: Follow SCLC pathway
    - No: Carboplatin and pemetrexed +/- checkpoint inhibitor
  - Second Line: Alectinib
  - Subsequent Treatment: Lorlatinib

- **ALK Gene Fusion**
  - ALK Gene Fusion
  - Refer to NSCLC-Stage IVA Due to Pericardial/Pleural Effusion and IVB Mutation Negative pathway

- **KRAS G12C**
  - KRAS G12C
  - Refer to NSCLC-Stage IVA Due to Pericardial/Pleural Effusion and IVB Mutation Negative pathway

- **EGFR Exon 20 Insertion**
  - EGFR Exon 20 Insertion
  - Refer to NSCLC-Stage IVA Due to Pericardial/Pleural Effusion and IVB Mutation Negative pathway

- **HER2 Mutation Positive NSCLC**
  - HER2 Mutation Positive NSCLC
  - Refer to NSCLC-Stage IVA Due to Pericardial/Pleural Effusion and IVB Mutation Negative pathway

- **MET Exon 14 Skipping Mutation**
  - MET Exon 14 Skipping Mutation
  - Capmatinib

- **RET Rearrangement**
  - RET Rearrangement
  - Selpercatinib

- **ROS1 Gene Fusion**
  - ROS1 Gene Fusion
  - Entrectinib

- **BRAF V600E**
  - BRAF V600E
  - Dabrafenib and trametinib

- **NTRK Gene Fusion**
  - NTRK Gene Fusion
  - Entrectinib

Clinical trial(s) always considered on pathway.

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

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

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

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

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

* **CGP** Comprehensive Genomic Profiling

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

NSCLC-Stage IVA Due to Pericardial/Pleural Effusion and IVB Mutation Negative → Refer to Palliative Care

Candidate for chemotherapy?

- No → PD-L1 ≥1%?
  - No → Pembrolizumab with carboplatin with pemetrexed; pemetrexed-pembrolizumab maintenance (up to 2 years)
  - Yes → Pembrolizumab

- Yes → PD-L1 expression 0-49% or unknown
  - PD-L1 expression >50% → Pembrolizumab with carboplatin with pemetrexed; pemetrexed-pembrolizumab maintenance (up to 2 years); OR pembrolizumab alone
  - Immunotherapy contraindication → Carboplatin with pemetrexed (4 cycles) followed by maintenance pemetrexed

Clinical trial(s) always considered on pathway.

a Pericardial/Pleural Effusion appropriate local therapy for malignant effusion should be pursued
Lung Cancer – Non-Squamous Relapse

Non-Squamous 2nd Line Progression Chemotherapy with or without Immunotherapy

- KRAS G12C, EGFR Exon 20 Insertion, or HER2 mutation found?
  - Yes
    - Sotorasib (KRAS G12C)
    - EGFR Exon 20 Insertion
    - Trastuzumab deruxtecan (HER2/ERBB2 mutation and/or amplification)
  - No
    - Docetaxel

Non-Squamous 2nd Line Progression Immunotherapy Alone

- Carboplatin and pemetrexed (4 cycles) Progression?
  - Yes
    - Continue maintenance pemetrexed
  - No
    - Docetaxel

Non-Squamous 3rd Line Progression

- Patient received docetaxel?
  - No
    - Docetaxel
  - Yes
    - Clinical trial or refer to Hospice

Patient preference after shared decision making

Mobocertinib

Amivantamab

Patient preference after shared decision making

Mobocertinib

Amivantamab

Clinical trial(s) always considered on pathway.

HER2/ERBB2 positive mutation and/or amplification consider consult to the National Precision Oncology Program (NPOP) regarding treatment

Mobocertinib do not use if you can’t avoid use of other drugs that prolong the QTc interval, or with moderate or strong CYP3A4 inhibitors (Boxed Warning)

Amivantamab do not use if patient has transportation issues, cannot take pre-medications, or prefers to avoid prolonged exposure in facility

Progression if limited progression, consider referral to Radiation Oncology
Lung Cancer – Squamous Stage IVB First Line

Squamous Stage IVB
First Line

- Refer to Palliative Care
- Multidisciplinary discussion *

Never/light smoker, mixed histology, small specimen size, or clinically indicated?

- No
  - Qualify for chemotherapy?
    - No
      - Perform PD-L1 by TPS and CGP b
    - Yes
      - PD-L1 expression 0-49% or unknown
        - Yes
          - Pembrolizumab, carboplatin and paclitaxel (4 cycles) followed by pembrolizumab alone maintenance for up to 2 years *
        - No
          - PD-L1 expression > 50%
            - Yes
              - Pembrolizumab, carboplatin and paclitaxel (4 cycles) followed by pembrolizumab maintenance OR pembrolizumab alone for up to 2 years *
            - Immunotherapy contraindication
              - Carboplatin and paclitaxel (4-6 cycles) *
      - PD-L1 expression > 1%?
        - Yes
          - Pembrolizumab
        - No
          - Hospice

- Yes
  - Qualify for immunotherapy?
    - Yes
      - PD-L1 ≥1%
        - Yes
          - Pembrolizumab
        - No
          - Hospice
    - No
      - Yes
        - Never/light smoker, mixed histology, small specimen size, or clinically indicated?
          - No
            - Qualify for chemotherapy?
              - No
                - Perform PD-L1 by TPS and CGP b
              - Yes
                - PD-L1 expression 0-49% or unknown
                  - Yes
                    - Pembrolizumab, carboplatin and paclitaxel (4 cycles) followed by pembrolizumab alone maintenance for up to 2 years *
                  - No
                    - PD-L1 expression > 50%
                      - Yes
                        - Pembrolizumab, carboplatin and paclitaxel (4 cycles) followed by pembrolizumab maintenance OR pembrolizumab alone for up to 2 years *
                      - Immunotherapy contraindication
                        - Carboplatin and paclitaxel (4-6 cycles) *
          - Yes
            - Refer to Palliative Care

Clinical trial(s) always considered on pathway.

* If patient is symptomatic refer to Radiation Oncology
b PD-L1 expression should be performed using 22C3 antibody and determined by TPS score; follow Molecular Testing pathway for further information
* If limited progression, consider referral to Radiation Oncology and continuation of first-line systemic therapy

CGP: Comprehensive Genomic Profiling
Lung Cancer – Squamous Relapse

1. **Squamous 2nd Line Progression on Chemotherapy +/- Immunotherapy**
   - Progression in ≤4 sites that are amenable to radiation?
     - Yes → Refer to Radiation Oncology for local therapy → Continue systemic therapy
     - No → Docetaxel

2. **Squamous 2nd Line Progression on Immunotherapy Alone**
   - Progression in ≤4 sites that are amenable to radiation?
     - Yes → Refer to Radiation Oncology for local therapy → Continue systemic therapy
     - No → Carboplatin and paclitaxel (4-6 cycles)

3. **Squamous 3rd Line Progression**
   - Progression in ≤4 sites that are amenable to radiation?
     - Yes → Refer to Radiation Oncology for local therapy
     - No → Clinical trial or refer to Palliative Care

Clinical trial(s) always considered on pathway.
Lung Cancer – SCLC Incidental Discovery Resected T1, T2 N0 M0

SCLC Incidental Discovery Resected T1, T2 N0 M0

Completely resected T1-2 N0 M0 pathologic stage?

Yes  Cisplatin and etoposide (4 cycles) without chest radiation

No  Cisplatin and etoposide (4 cycles) with chest radiation

Clinical trial(s) always considered on pathway.
Lung Cancer – SCLC Limited Stage First Line

- Cisplatin and etoposide (4 cycles) concurrently with chest radiation
- Order CT scan (abdomen/chest/pelvis) and MRI with and without contrast (brain)
- Multidisciplinary discussion

Progression?

- Yes
  - PS 3-4 or impaired neurocognition?
    - Yes
      - Brain MRI and systemic surveillance as clinically indicated
    - No
      - Refer to Radiation Oncology for consideration of PCI
  - No
    - Follow SCLC Relapse pathway

- No
  - Initiating radiation as early as possible, within the first or second cycle of chemotherapy

Clinical trial(s) always considered on pathway.

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a In the rare case of T1-2 N0 M0, surgery can be considered followed by adjuvant chemotherapy
b Initiate radiation as early as possible, within the first or second cycle of chemotherapy
Lung Cancer – SCLC Extensive Stage First Line

SCLC Extensive Stage First Line

- Contraindication to chemo/immuno therapy?
  - Yes → Refer to Palliative Care
  - No → Symptomatic metastases or unlikely to respond to systemic therapy?
    - Yes → Refer to Radiation Oncology
    - No → Progression?
      - Yes → Follow SCLC Relapse pathway
      - No → Carboplatin with etoposide (4-6 cycles) with atezolizumab

Maintenance atezolizumab until progression or toxicity

If less than complete response, refer to Radiation Oncology for chest radiotherapy

Chemotherapy contraindication

Immunotherapy contraindication

Refer to Hospice

Clinical trial(s) always considered on pathway.
**Lung Cancer – SCLC Relapse**

SCLC Relapse → Refer to Palliative Care

Refer to Radiation Oncology if symptomatic metastases → Time to progression?

- **< 6 months**
  - PS 0-1-2 → Lurbinectedin → Progression? → Restart pathway
  - PS 3-4 → Refer to Hospice

- **> 6 months**
  - Carboplatin and etoposide (4-6 cycles) → Progression? → Restart pathway

Clinical trial(s) always considered on pathway.

*a If patient is progressing and did not receive immunotherapy upfront, patient can receive carboplatin, etoposide, and atezolizumab*
Questions?

Contact VHAOncologyPathways@va.gov