Case 1

- 69 yo male never-smoker presents with scant hemoptysis and progressive shortness of breath. PS=1
- Imaging: PET/CT: RUL mass 3.8x3.9cm, right hilar LN, right para-tracheal LN. No distant metastases.
- Bronchoscopy with EBUS: adenocarcinoma, TTF1+
  - Positive: 4R
  - Negative: station 7, 4L, 11L
- MRI brain without evidence of disease.
- Clinical Stage: T2aN2M0, or stage IIIA

Question 1.1

Would you send for molecular testing & immunophenotyping in this patient with Stage IIIA NSCLC?

A. Yes
B. No
Case 1

Results of Molecular studies & PD-L1 testing:
- EGFR exon 21 L858R mutation
- PD-L1 IHC: 0% staining

Case 1

• Patient is presented at thoracic tumor board and plan is made to proceed with neoadjuvant chemotherapy
• PET scan following completion of 3 cycles of neoadjuvant cisplatin/pemetrexed reveals decrease in size of lung and nodal masses, and patient proceeded to lobectomy.
• R0 resection was achieved. Nodal sampling during surgery was negative
  • ypT1cN2M0

Question 1.2
What therapeutic regimen would you recommend for this patient with Stage IIIA (T2aN2M0) NSCLC?
A. Proceed directly to surgical resection
B. Neoadjuvant EGFR TKI (erlotinib or osimertinib)
C. Neoadjuvant cisplatin+pemetrexed
D. Neoadjuvant chemoradiation with cisplatin+etoposide
E. Definitive chemoradiation with cisplatin+etoposide

Case 1

Question 1.3
What would you recommend for this patient following surgical resection?
A. Observation alone
B. Adjuvant EGFR TKI (erlotinib or osimertinib)
C. Consolidation checkpoint immunotherapy (durvalumab)
D. Two additional cycles of adjuvant chemotherapy
E. Post-operative radiotherapy (PORT)
Case 1

- The patient declines post-operative therapy.
- At 6 months, restaging PET/CT scan reveals only post-surgical changes.

Case 1 takeaway points

- Patients with stage IIIA NSCLC are candidates for combined modality therapy
  - Either neoadjuvant chemoradiation or chemoradiation dependent on clinical-pathologic characteristics
- Patients with stage IIIA NSCLC treated with chemoradiotherapy are candidates for consolidation immunotherapy (durvalumab), but not yet after surgical resection
- In patients with stage III NSCLC and an underlying oncogene driver (e.g. EGFR mutation), concomitant or adjuvant EGFR TKI is not yet standard of care in the USA (no OS benefit reported to date)
- Patients with stage III NSCLC and residual N2 disease after surgical resection may be candidates for PORT

Case 2

A 68 yo Japanese woman with distant 15 pack year history of smoking presents after a fall in which she hit her head.

On further questioning she endorsed persistent dizziness, a 30lb weight loss in the past two months as well as progressive shortness of breath. PS=2.
Case 2

- CT chest: multiple pulmonary emboli, a 4 cm mass in LLL, multiple enlarged mediastinal LNs, bony and liver lesions.
- Liver biopsy: TTF1+ adenocarcinoma

MRI brain: numerous subcentimeter enhancing masses with mild surrounding vasogenic edema, some of which are hemorrhagic.
No midline shift or hydrocephalus

She is treated emergently with anti-coagulation and dexamethasone to reduce brain edema, after which she is completely asymptomatic.

Question 2.1
Would you send for molecular testing & immunophenotyping in this patient?

A. Yes
B. No

Results of molecular testing and immunophenotyping:
EML4-ALK fusion by plasma ctDNA (confirmed by subsequent tissue NGS).
PD-L1 was <1%.
TMB=4mt/mb (low)
**Case 2**

**Question 2.2**
How would you manage this patient’s metastatic ALK+ lung adenocarcinoma with multiple CNS metastases, now asymptomatic?

A. Crizotinib + WBRT  
B. Alectinib alone  
C. Alectinib + WBRT  
D. Ceritinib + WBRT  
E. Carboplatin/Pemetrexed + WBRT

**ALEX (Alectinib vs Crizotinib in ALK+ NSCLC): Primary end points (PFS) & Activity in CNS Metastases**

- **Progression-free survival (PFS)**
  - Crizotinib: 57%  
  - Alectinib: 24%

**Results**

- **Patients with metastases (n=324)**
  - **Crizotinib**: 156  
  - **Alectinib**: 168

- **Median PFS**: 11.2 vs 26.1 months
- **HR (95% CI)**: 0.47 (0.30-0.71)

**Patients without CNS metastases at baseline**

- **Crizotinib**: 168  
- **Alectinib**: 156

- **HR (95% CI)**: 0.54 (0.33-0.83)

**The patient received emergency WBRT due to degree of initial symptoms and shortly thereafter also was started on alectinib.**

- **Repeat MRI at 2 months and 6 months showed significant improvement in intracranial disease burden**
- **Restaging CT scan also showed good extra-cranial partial response**
Case 2

Approximately 16 months after presentation, restaging CT scan shows progressive disease in multiple sites, except brain.

The patient is asymptomatic and maintains a PS=0.

Question 2.3

What would be your approach at this time?

A. Switch to Loratinib (if available)
B. Switch to Brigatinib
C. Switch to Carboplatin/Pemetrexed
D. Tumor re-biopsy to assess mechanism of acquired resistance
E. “Liquid biopsy” for ctDNA to assess mechanism of acquired resistance

Case 2 takeaway points

- ALK+ NSCLC has a high incidence of brain metastases at the time of presentation
- Alectinib, among others, has excellent CNS activity in ALK+ NSCLC, and can also delay onset of brain metastases
- In ALK+ NSCLC with small asymptomatic brain metastases at presentation, WBRT or SBRT can be deferred when alectinib or other ALK TKIs with high CNS penetrance are employed
- At the time of acquired resistance to ALK TKI, re-biopsy or liquid biopsy may identify a secondary resistance mutation with selective sensitivity to 1 ALK inhibitor or another
Case 3

- CT guided biopsy of mass consistent with squamous cell carcinoma
- Brain MRI is negative for metastatic disease
- Staged as IIIB (T4N2M0)

Question 3.1
Is this particular patient with stage IIIB (T4N2M0) NSCLC a candidate for a surgical combined modality approach?
A. Yes. Upfront surgical resection is feasible.
B. No.
C. Yes, after neoadjuvant chemotherapy +/- thoracic radiation

Question 3.2
In this patient with planned chemo-radiation for a new diagnosis of stage IIIB NSCLC, would you check PDL1 status?
A. Yes
B. No

Question 3.3
What systemic treatment would you offer this patient with stage IIIB squamous lung cancer?
A. Chemoradiation with weekly low dose carboplatin+paclitaxel
B. Chemoradiation with cisplatin+etoposide
C. Chemoradiation with weekly low dose carboplatin+paclitaxel followed by consolidation with durvalumab
D. Chemoradiation with cisplatin+etoposide followed by consolidation with durvalumab
Case 3

A decision is made to treat the patient with definitive Chemo-radiation.

**Question 3.4** What radiation dose schedule would you recommend

A. 45 Gy in 1.5 Gy fractions BID
B. 54 Gy in 1.8 Gy fractions QD
C. 60 Gy in 30 fractions QD
D. 66 Gy in 33 fractions QD
E. 74 Gy in 37 fractions QD

Case 3

The patient completes chemoradiation with cisplatin-etoposide and is started on consolidation durvalumab. After 6 months of durvalumab, he is hospitalized with persistent severe diarrhea, incontinence, and volume depletion.

**Question 3.5**: In addition to stool cultures and GI consult, you:

A. Start Imodium. Continue durvalumab.
B. Start Imodium and empiric steroids. Continue durvalumab.
C. Start Imodium. Hold durvalumab.
D. Start imodium and empiric steroids. Hold duvalumab.
Case 3
The patient is started on steroids with resolution of diarrhea over 10 days. He is now at home and being tapered off steroid.

Question 3.6 In this patient now after 7 months of durvalumab consolidation, you next decide to:
A. Rechallenge with durvalumab to complete 1 year of therapy
B. Switch to nivolumab (PD-1 inhibitor instead of PD-L1)
C. Permanently discontinue durvalumab and observe only
D. Rechallenge with durvalumab and keep on prednisone 15 mg/day

Case 4
60 yo male, previous heavy smoker, presented with cough, shortness of breath, and hemoptysis. PS=1

CT chest: large R hilar mass with invasion into the mediastinum, occlusion of the RUL bronchus, and encasement of the R upper lobe vessels.

PET/CT: R hilar mass, hypermetabolic LNs above and below the diaphragm as well as diffuse bony metastatic disease.

MRI brain without evidence of disease

Case 4 Takeaway Points
- Management of stage III NSCLC requires a multidisciplinary evaluation and individualized care planning.
- Chemo-radiation followed by consolidation durvalumab in stage III NSCLC leads to significant improvement in both PFS and OS, and represents a new standard of care. Whether patients with PD-L1<1% should get this approach is debatable (EMA approval only in +PD-L1)
- Immune-related side effects of checkpoint immunotherapy (CPI) can be severe and/or life-threatening. For grade III or higher toxicity, permanent discontinuation of CPI should be considered.
Case 4

**Question 4.1**
What regimen would you select for this patient with extensive SCLC?

A. Cisplatin+etoposide  
B. Carboplatin+etoposide  
C. Nivolumab + Ipilimumab  
D. Cisplatin+etoposide+atezolizumab  
E. Carboplatin+etoposide+atezolizumab

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Case 4

- Patient was started on cisplatin-etoposide + atezolizumab for extensive stage small cell lung cancer.
- CT following 3 cycles revealed significant decrease in size of mass

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**IMpower133**: Global Phase 1/3, double blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1st Line Ext-SCLC

Patient is scheduled to receive 3 more cycles of cisplatin and etoposide plus maintenance atezolizumab.

**Question 4.2**
If patient has a good partial response following 6 cycles of therapy, with persistent thoracic disease and extra-thoracic sites, would you recommend consolidative thoracic radiotherapy?

A. Yes  
B. No
Case 4

Question 4.3
If the patient has a good partial response after 6 cycles of therapy, would you recommend PCI?

A. Yes
B. No