Multidisciplinary Management of Cancers
Thoracic Oncology Tumor Board

Case 1

74 year old male with 20 pack-year smoking history recently developed hypertension to 200/100 and Cushing syndrome, with markedly elevated ACTH.

Workup includes a CT chest that shows 4.6 cm left perihilar soft tissue mass encasing the left upper lobe bronchus and pulmonary artery, and associated ipsilateral and contralateral mediastinal and ipsilateral supravacular necrotic lymph nodes. CT abdomen/pelvis shows bilateral adrenal hyperplasia without focal nodules.

Patient undergoes bronchoscopy with FNA of LUL mass and mediastinal nodes; pathology shows small cell lung cancer, with bilateral mediastinal LN involvement.

PET/CT shows widespread metastatic disease, including abdominal nodes, peritoneal masses, hepatic lesions, small bowel lesion, and skeletal metastases.

Brain MRI is negative.
When the patient is seen in clinic, he is relatively asymptomatic, and BP is 142/78, on anti-hypertensives started by endocrinology. His ECOG PS is 1.

**Question 1.1**
What systemic therapy would you give this patient with newly diagnosed extensive-stage small cell lung cancer with Cushing syndrome?
1. Cisplatin/etoposide
2. Carboplatin/etoposide
3. Carboplatin/etoposide/atezolizumab
4. Cisplatin/etoposide/durvalumab
5. Carboplatin/etoposide/durvalumab

The patient is started on carboplatin/etoposide. He is also referred to urology for bilateral adrenalectomy.

CT chest/abdomen/pelvis after 2 cycles shows significant decrease in tumor burden. The patient undergoes bilateral adrenalectomy after the 2nd cycle of chemotherapy and is started on hydrocortisone + fludrocortisone.

**Question 1.2**
Once hydrocortisone is tapered down to maintenance dosing, would you add immunotherapy to remaining cycles of chemotherapy and for maintenance?
1. Yes, atezolizumab
2. Yes, durvalumab
3. No

**Question 1.3**
If the patient has a good partial response after 4 cycles of chemotherapy, with persistent thoracic disease and low-volume extrathoracic disease, would you recommend consolidative thoracic radiation therapy?
1. Yes
2. No
Question 1.4
If the patient has a good partial response after 4 cycles of therapy, would you recommend prophylactic cranial irradiation?
1. Yes
2. No

The patient develops progressive disease after 7 months on maintenance atezolizumab.

Question 1.5
What treatment would you offer now for this patient who had initial good response to carboplatin/etoposide/atezolizumab, followed by disease progression 7 months later?
1. Topotecan or irinotecan
2. Carboplatin/etoposide
3. Pembrolizumab
4. Nivolumab/Ipilimumab

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**20th Multidisciplinary Management of Cancers: A Case-based Approach**

### Extensive-Stage Small Cell Lung Cancer: Phase III Trials of Frontline Chemo-Immunotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Primary endpoint(s)</th>
<th>Findings (immunotherapy combination arm versus control arm)</th>
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<tr>
<td>IMpower133</td>
<td>Carboplatin/etoposide +/- atezolizumab</td>
<td>PFS, OS</td>
<td>OS: 12.3 months vs 10.3 months (HR 0.70; p=0.007)</td>
<td>FDA approved (March 2019)</td>
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<tr>
<td>CASPIAN</td>
<td>Platinum/etoposide +/- durvalumab (or durval/tremelimumab)</td>
<td>OS</td>
<td>OS: 12.9 months durva + chemo vs 10.5 months chemo alone (HR 0.75; p=0.0032)</td>
<td>FDA approved (March 2020)</td>
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<td>KEYNOTE-604</td>
<td>Platinum/etoposide +/- pembrolizumab</td>
<td>PFS, OS</td>
<td>OS: 10.8 months vs 9.7 months (HR 0.80, p=0.0164, not statistically significant) PFS: HR 0.75, p=0.0003</td>
<td>Presented at ASCO 2020</td>
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**Case 1 – Key Take-Away Points**

Platinum/etoposide + checkpoint inhibitor is the new standard of care first-line treatment for extensive-stage small cell lung cancer as of 2019, with modest overall survival benefit.

Weigh risks/benefits of immunotherapy in patients with paraneoplastic syndromes.

Consider consolidative thoracic radiation therapy in patients with good response to systemic therapy, with residual thoracic disease.
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**Case 2**

48 year old woman, never smoker, presents with persistent cough to urgent care. Chest X-ray shows an irregular 3 cm left lung mass. ECOG PS is 0.

PET/CT shows FDG avid 4 cm lingula mass, left supraclavicular, right thoracic inlet, right paratracheal, left hilar and subcarinal adenopathy, scattered bone metastases.

EBUS biopsy of stations 4R, 4L, and 7 lymph nodes reveal lung adenocarcinoma, with 60% PD-L1 expression.

MRI brain is negative for intracranial metastases.

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The patient has stage IV lung adenocarcinoma.

**Question 2.1**

What is your next step?
1. Send rapid limited molecular testing (EGFR PCR, ALK FISH, ROS1 FISH – turnaround time <1 week)
2. Send molecular panel (NGS panel for >200 genes – turnaround time 2 weeks)
3. Start single agent pembrolizumab
4. Start carboplatin/pemetrexed/pembrolizumab
5. Start carboplatin/pemetrexed

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Targeted molecular testing results, and reveals an ALK gene rearrangement.

**Question 2.2**

What treatment do you prescribe?
1. Crizotinib
2. Brigatinib
3. Alectinib
4. Ceritinib
5. Lorlatinib

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The patient is started on first line alectinib for her Stage IV ALK+ lung adenocarcinoma.

She has an overall favorable treatment response, with PET scan 3 months after starting therapy showing near-complete metabolic resolution of lingular mass and lymphadenopathy in the chest. Bone metastases appear more sclerotic, favored to represent reparative response to treatment.
Six months after starting alectinib, a PET scan shows an increase in size and activity of a clival lesion, now 1.6 cm x 0.8 cm, previously 0.4 cm. A few other bone lesions are minimally increased (for example, humeral head lesion 0.9 cm, previously 0.7 cm). She continues to have no FDG-avid pulmonary lesions or adenopathy. Brain MRI shows clival lesion as above; it is negative for intracranial metastases.

Given asymptomatic oligoprogression, the patient undergoes stereotactic radiosurgery to the clival metastasis, and is continued alectinib. 2 months later, a PET scan shows increased size and FDG-avidity of numerous (>10) scattered osseous metastases.

Question 2.3
What is your next step for this patient with Stage IV ALK+ lung adenocarcinoma who has now had systemic progression on first-line alectinib?
1. Obtain tissue biopsy
2. Send circulating tumor DNA
3. Switch empirically to second-line lorlatinib

Alectinib is stopped and the patient is started on lorlatinib. 3 months later a PET scan again shows progression of disease, with increased size and activity of numerous osseous metastases.
The patient has now progressed through two ALK TKIs (1st line alectinib, 2nd line lorlatinib). Her ECOG PS is 1.

**Question 2.4**

What third-line therapy do you offer this patient, assuming no new targetable mutations are found on a repeat biopsy?

1. Brigatinib
2. Carboplatin/pemetrexed
3. Carboplatin/pemetrexed/pembrolizumab
4. Carboplatin/pemetrexed/bevacizumab
5. Carboplatin/paclitaxel/atezolizumab/bevacizumab

The patient was started on carboplatin/pemetrexed. Bevacizumab had been planned in combination with chemotherapy, but patient had elevated blood pressure (140s/90s), in the setting of inconsistent use of her blood pressure medication, thus this was held.

She is also receiving denosumab for her bone metastases.

Scans after 2 cycles of chemotherapy show stable disease.

Among the first 13 patients treated with nivolumab + crizotinib, 38% (5 of 13) developed severe hepatic toxicity
- Two of these five patients died
- Enrollment was closed as a result of observed toxicity rates

**EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer: A Retrospective Analysis**

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- Of 58 patients treated with PD-1/PD-L1 inhibitors at MGH from 2011-2016, 28 patients were EGFR+ or ALK+
- ORR was 3.6% (1 of 28) in EGFR+ or ALK+ patients, compared with 23% (7 of 30) in EGFR wild-type and ALK-negative patients
Case 2 – Key Take-Away Points

Especially in a patient with high likelihood of driver mutation, it is vitally important to await molecular testing prior to starting immunotherapy, even in PD-L1 high patients.

For oligo-progression in a patient on targeted therapy, one option is to do focused radiation or surgery and continue targeted systemic therapy.

Case 3

76 year old gentleman, former smoker (10 pack-years, quit 25 years ago), presents to the emergency room with fevers, cough, and chills, and is found to have E coli bacteremia, with unclear source.

As part of his initial workup, he has a CT chest that shows a 1.5 cm spiculated apical lesion and a 1.9 cm left upper lobe posterior nodule near the fissure.

CT-guided needle biopsy is unsuccessful for the apical LUL nodule, and shows necrotizing granulomatous inflammation for the posterior LUL nodule.

Repeat CT scan 6 months later shows increasing irregular masses near the left apex – an apical ovoid mass 2.1 cm, and a posterior multi-lobulated elongated structure 3.6 x 2.1 cm.
PET/CT shows 2.2 x 1.6 cm left apical nodule, SUV 12.4, and elongated 2.9 x 1.3 cm anterior left upper lobe nodule, SUV max 4.7. No FDG-avid lesions are seen in the abdomen or pelvis.

The patient undergoes CT-guided biopsy of the LUL apical nodule; this reveals poorly differentiated lung adenocarcinoma.

The LUL nodule near the fissure is felt unlikely to be malignant given that the biopsy showed necrotizing granuloma and the FDG avidity is much lower than the biopsy-proven LUL apical nodule.

The patient has Stage 1A3 (cT1cN0M0) lung adenocarcinoma.

This 76 year old patient also has a past medical history notable for coronary artery disease, STEMI with drug eluting stent placed in the RCA (1.5 years ago), a thoracic aortic aneurysm, and hyperlipidemia. His ECOG PS is 1.

Pulmonary function tests show an FEV1 2.5L/82% and DLCO 106%.

**Question 3.1**
What do you recommend next for this patient?
1. Referral for surgery
2. Referral for definitive radiation (SABR)
3. Referral for bronchoscopy with mediastinal lymph node sampling (EBUS-TBNA)
The patient is referred to thoracic surgery, and surgical clearance is obtained from the patient’s cardiologist.

He undergoes flexible bronchoscopy, robotic left upper lobectomy, and mediastinal lymph node dissection.

Surgical pathology shows moderately differentiated adenocarcinoma, 2.3 cm, with extensive vascular invasion and visceral pleural invasion. PD-L1 expression is 0%. Multiple lymph nodes from levels 5, 7, 9, 10, 11 are all negative.

The patient’s pathologic stage is thus Stage IB (pT2aN0M0).

**Question 3.2**

Our 76 year old patient with Stage IB adenocarcinoma is now status post lobectomy, with surgical pathology showing extensive vascular invasion. Brain MRI is negative for metastases. Would you recommend adjuvant chemotherapy?
1. Yes – cisplatin doublet
2. Yes – carboplatin doublet
3. No

The patient was not given adjuvant chemotherapy, and will be monitored with CT chest every 6 months for 2-3 years followed by low-dose annual CTs thereafter.

**Case 3 – Key Take-Away Points**

Staging in lung cancer continues to evolve; keep this in mind when making decisions about adjuvant therapy based on data from older adjuvant chemotherapy trials.
Case 4

39 year old Chinese American woman presents with nonproductive cough, fatigue, anorexia.

Chest X-ray shows 4.7 x 3.7 x 3.0 cm right middle lobe mass, concerning for malignancy versus infection.

After a course of antibiotics, chest X-ray shows persistent mass.

PET/CT shows hypermetabolic mass in RML, satellite nodules, hypermetabolic bilateral mediastinal lymph nodes, involving ipsilateral and contralateral lymph nodes, and right supraclavicular stations.

MRI brain is negative.

Flexible bronchoscopy and mediastinoscopy are performed. Pathology reveals poorly differentiated adenocarcinoma of the right supraclavicular and paratracheal lymph nodes.

The patient has T2b N3 M0 (Stage IIIB) disease.

Question 4.1
Do you send for EGFR and PD-L1?
1. Yes
2. No
The case was reviewed at thoracic tumor board. Due to N3 node (right supraclavicular node), patient is deemed to not be a surgical candidate.

Molecular testing shows an EGFR exon 19 deletion. PD-L1 expression is 5%.

You decide to proceed with definitive concurrent chemo-radiation. The patient's radiation oncologist plans for 60-66 Gy in 30-33 fractions over the course of 6 weeks using volume-modulated arc therapy (a form of IMRT).

**Question 4.2**
Which chemotherapy regimen would you give, with concurrent radiation therapy, to this 39 year old patient with stage IIIB lung adenocarcinoma?
1. Cisplatin/etoposide
2. Carboplatin/paclitaxel
3. Cisplatin/pemetrexed
4. Carboplatin/pemetrexed

**Question 4.3**
After definitive chemoradiation for EGFR+ Stage IIIB lung cancer, would you give consolidation durvalumab?
1. Yes
2. No

After completing cisplatin/pemetrexed with concurrent radiation, she was started on consolidation durvalumab. After 7 months of durvalumab, a PET/CT showed scattered hypermetabolic changes in the liver, abdominal lymph nodes, and left adrenal gland.

The patient was seen in the ED for abdominal pain. CT abdomen/pelvis showed branching hypodensities in left liver lobe, concerning for infectious or inflammatory etiology; also showed diffuse "near fluid" attenuation infiltration of retroperitoneum.

MRI abdomen showed chronic inflammation of liver and retroperitoneal edema. She was noted to be in DIC and to have elevated liver enzymes (AST and ALT ~2x ULN; tbili and alk phos normal).
Durvalumab was held, and she was started on prednisone 60mg daily due to concern for autoimmune hepatitis.

However, she had no significant improvement in her liver enzymes with steroids.

She then underwent a liver biopsy, which showed metastatic carcinoma, lung primary.

Question 4.4
What therapy would you start now for this patient with stage IIIB lung adenocarcinoma who has been on consolidation durvalumab, but now has developed liver metastases, and currently has elevated LFTs and is in DIC?
1. Osimertinib
2. Erlotinib
3. Afatinib
4. Docetaxel

The patient was started on erlotinib.

A PET/CT obtained 2 months later showed evolving postradiation opacities in the RML and anterior RUL; previous moderate diffuse uptake in the left lateral liver was no longer appreciated.

Symptomatically the patient is doing well: DIC resolved, LFTs normalized.
Severe immune-related adverse events are common with sequential PD- (L)1 blockade and osimertinib
A J Schoenfeld, K C Arbour, H Ricci, A N Iqbal, S M Gadgeel, J Glishman, M G Kris, G J Riely, H A Yu, M D Hellmann
Published: 07 March 2019
- Among patients with EGFR-mutant lung cancer treated with osimertinib after PD-1/PD-L1 inhibitor at MSKCC from 2011-2018, 15% (6 of 41 patients) developed severe irAEs (grade 3 or 4).
- Severe irAEs were pneumonitis (4), hepatitis (1), colitis (1); 5 of the 6 patients required hospitalization.
- Risk of developing a severe irAE appeared highest in those who started osimertinib within 3 months of receiving immunotherapy.

Case 4 – Key Take-Away Points

In unresectable stage III NSCLC, durvalumab after concurrent chemoradiation improves overall survival; however, patients with no PD-L1 expression, as well as patients with driver mutations, may not derive the same benefit.

Using osimertinib after immunotherapy carries a risk of serious immune-related adverse events; this risk is perhaps higher with osimertinib than other EGFR-targeted therapies.
Thoracentesis is performed and yields 1200 mL of bloody fluid. Pleural fluid cytology preliminarily shows malignant cells.

PET/CT shows an FDG-avid soft tissue mass surrounding the right mainstem bronchus, metastatic pleural nodules, left cervical lymph nodes, and a 5 cm splenic lesion.

Brain MRI shows two indeterminate punctate foci in the supratentorial parenchyma, felt unlikely to represent metastases.

She is discharged with follow-up in your clinic two days later.

On the day of her clinic visit, her cytology results reveals lung adenocarcinoma (CK7+, TTF-1+, napsin-A+). PD-L1 TPS shows 95% positivity.

Her oxygen saturation is 97% on room air, but she reports that her breathing is worsening again since the thoracentesis, particularly when she lies down at night. On exam, she has diminished breath sounds and dullness to percussion over lower 2/3 of her R posterior lung fields. Her ECOG PS is 2.

Question 5.1
For this patient, a former heavy smoker, with newly diagnosed Stage IV lung adenocarcinoma, with PD-L1 95%, what further testing, if any, would you await prior to starting treatment?
1. None – start systemic therapy now
2. Await rapid molecular panel (EGFR, ALK, ROS1) from pleural fluid - turnaround time 3 days
3. Send blood test for circulating tumor DNA today and await these results (EGFR, ALK, ROS1, RET, BRAF, KRAS) – turnaround time 1 week
4. Send full molecular panel today and await these results (NGS panel for >200 genes) – turnaround time 2-3 weeks
The patient is referred to interventional pulmonology and has another thoracentesis. She again has rapid re-accumulation of pleural fluid, and is admitted with worsening shortness of breath and hypoxia. An indwelling pleural catheter is placed.

Her rapid molecular profile results and is negative for EGFR mutation; ALK and ROS1 by FISH are negative.

You decide to start therapy.

**Question 5.2**

For this 84 year old patient with newly diagnosed Stage IV lung adenocarcinoma, with PD-L1 95%, what systemic treatment would you start?

1. Carboplatin/pemetrexed/pembrolizumab
2. Carboplatin/pemetrexed
3. Pembrolizumab monotherapy
4. Nivolumab/ipilimumab

Our 84 year old patient is started on carboplatin (AUC 4)/pemetrexed (75% dose)/pembrolizumab.

Her NGS panel results 2 weeks later and shows a KRAS G13D mutation. She is continued on the regimen as above.

After 3 cycles of chemo-immunotherapy, a CT scan shows dramatic improvement in disease.

Brain MRI shows stable punctate foci, now felt to represent vessels.

After 4 cycles of carboplatin/pemetrexed/pembrolizumab, the patient is switched maintenance pemetrexed/pembrolizumab, and 3 cycles later, to maintenance pembrolizumab.

Scans 12 months after initiation of therapy continue to show stable disease – this includes stable spiculated nodules in the bilateral lungs, calcified right hilar lymph node, and splenic lesions.
Question 5.3
For this patient who had a rapid excellent partial response to chemo-immunotherapy and now has been on maintenance pembrolizumab for 1 year with stable scans, how long would you continue maintenance pembrolizumab?
1. Stop now (at 1 year)
2. Stop after 2 years
3. Continue indefinitely

Case 5 – Key Take-Away Points
For patients with stage IV NSCLC, with no targetable driver mutation and high PD-L1 expression (>50%), consider symptoms and disease burden when deciding between single-agent pembrolizumab versus chemo-immunotherapy combination.

Patients who receive immunotherapy in the first-line setting could continue maintenance immunotherapy for 2 years, then can consider stopping if sustained CR or PR.

Thank you!