Evolving Treatment of Non-Small Cell Lung Cancer

Sally Barbour, PharmD, BCOP, CPP, FHOPA
Clinical Pharmacist Practitioner
Duke University Medical Center

Learning Objectives

• Objective 1. Identify clinical evidence for new and emerging treatment options in advanced non-small cell lung cancer.
• Objective 2. Describe key patient counseling and monitoring considerations for immunotherapy and targeted therapies in non-small cell lung cancer.
• Objective 3. Apply best practices to manage the adverse events associated with the new therapies available for advanced non-small cell lung cancer.

Question 1

• 72yo female with stage IV, metastatic NSCLC. Recent cranial imaging confirmed multiple brain metastases, and biomarker testing reveals an EGFR exon19 deletion (+), T790M mutation (-). The patient is otherwise healthy with no significant comorbidities. What is the most appropriate therapy choice?
  A. Start with erlotinib first line until disease progression and/or acquired resistance
  B. Start with afatinib first line until disease progression and/or acquired resistance
  C. Start with gefitinib first line until disease progression and/or acquired resistance
  D. Start with osimertinib first line until disease progression and/or acquired resistance

Question 2

• Which of the following is true based on the results of the ALEX trial (alectinib vs crizotinib) in ALK(+) NSCLC?
  A. CNS progression was significantly lower in the alectinib trial arm
  B. The primary endpoint investigated was overall survival
  C. Crizotinib showed a lower adverse event rate
  D. Progression free survival was not significantly different between the two treatment arms

Question 3

• 63yo male with newly diagnosed, unresectable, stage IIIa, NSCLC. Driver mutation tests returned negative, and the patient was deemed a candidate for radiation therapy. The patient has controlled T2DM with stage II CKD as the only complication. What would be the most appropriate therapy to be given with radiation?
  A. Paclitaxel 200mg/m2 + Carboplatin AUC=6 IV q21days x 4 cycles
  B. Paclitaxel 50mg/m2 + Carboplatin AUC=2 weekly x 6 cycles, followed by Durvalumab 10mg/kg IV q2wks x 12 months
  C. Cisplatin 75mg/m2 + Docetaxel 75mg/m2 q21days x 4 cycles
  D. Cisplatin 75mg/m2 + Pemetrexed 500mg/m2 IV q21 days x 4 cycles

Incidence

• 2nd most common malignancy
• Most common cause of cancer related death
• Estimated incidence 2019:
  • 228,150 new cases
  • 142,670 deaths
• Approximately 84% NSCLC

NSCLC = non-small cell lung cancer
Where have we been?

NSCLC Treatment in 2019

DRIVER MUTATION POSITIVE

EGFR Landscape

1st/2nd generation EGFR-TKIs have been 1st line standard
- Erlotinib, gefitinib, and afatinib
- PFS 2-13 months
- Primary Resistance
  - E694Q, L858R, or G724C
- Acquired Resistance
  - T790M mutation detected in >50% EGFR(+)-NSCLC progression cases

Osimertinib
- Approved in 2015 for T790M(+) NSCLC
- Demonstrated 20–25x greater affinity for exon-19 del & T790M mutations
- Decreased affinity for wild type EGFR
- Dacomitinib approved Sept 2018 for 1st line treatment
- Compared to gefitinib

FLAURA: First Line Osimertinib

- FLAURA trial: double blind, phase 3 study, interim analysis
- Patients: untreated, EGFR-mutant (+), advanced, NSCLC
- WHO performance status 0 / 1
- Stable CNS metastases allowed
- Dual arm study: 1:1 randomization
- Osimertinib 80mg PO daily
- Standard EGFR-TKI (Erlotinib 150mg PO daily or Gefitinib 250mg PO daily)
- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: OS, ORR, DOR, disease control rate, depth of response, and safety

Studies

- NSCLC with driver mutations
  - FLAURA (EGFR): osimertinib
  - ALEX (ALK): alectinib

- NSCLC with no-driver mutations
  - PACIFIC Trial: durvalumab
  - Keynote-042: pembrolizumab vs chemotherapy
  - Keynote-189: carboplatin/pemetrexed/pembrolizumab (non-squamous)
  - CheckMate 227: PD-L1 nivolumab/ipilimumab, chemotherapy + nivolumab, or chemotherapy alone
  - Keynote-407: carboplatin/taxane +/- pembrolizumab (squamous)
  - IMpower131: carboplatin/nab-paclitaxel +/- atezolizumab (squamous)

EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; PD-L1 = programmed death ligand 1

EGFR Landscape

- EGFR in detectable in majority of NSCLC
  - ~80-85%
- Mutations that activate EGFR confer drug sensitivity
  - Frequency in NSCLC ~10%
  - Exon 19 deletion (45%)
  - Exon 21 L858R mutations (40%)
- More likely to be found in:
  - Adenocarcinoma
  - East Asians
  - Females
  - Never/light smokers

EGFR and ALK in NSCLC

- EGFR: exon 19 deletions (45%)
- ALK: ALK rearrangements (5%)

OS = overall survival; ORR = overall response rate; DOR = duration of response

https://openi.nlm.nih.gov/detailedresult.php?img=PMC4242069_clep‐6‐423Fig1&req=4
FLAURA Trial cont.

- PFS and OS was significantly better with osimertinib in all subgroups
- AEs grade 3 or higher: 34% (osimertinib, Osi) vs 45% (standard TKI, SoC)
- Standard EGFR-TKI adverse events occurred less w/ Osi (i.e. rash, diarrhea, dry skin, stomatitis)
- QT changes higher (10% vs 5%)
- No significant difference in rate of discontinuation, dose interruption, and/or dose reduction


Pharmacy Considerations

- EGFR Toxicity
  - Acneiform rash
  - Associated with efficacy
  - Preventative treatment
    - Sunscreen SPF 30 daily
    - Oral antibiotics (doxycycline/minocycline)
    - Hydrocortisone 1% cream at bedtime
  - Diarrhea
    - Loperamide (Imodium)

Anaplastic Lymphoma Kinase (ALK) in NSCLC

- ALK activation first described in 2007; found as primary oncogenic driver in many cancers
- 3 – 5% patients with NSCLC
- In NSCLC, rearrangements more common in:
  - Adenocarcinoma
  - Tumors without other known oncogenic drivers, such as EGFR and KRAS wild type
  - Never or light smokers
- Crizotinib was standard 1st line agent
- Ceritinib and alectinib after progression
- Brigatinib approved April 2017
  - 2nd line after crizotinib
- Lorlatinib approved December 2018
  - 3rd line after progression on crizotinib and one other ALK inhibitor
  - 2nd line after progression on alectinib or ceritinib


First Line Alectinib: ALEX

- ALEX trial: randomized, open label, phase 3 study
- Patients: untreated, ALK-positive, advanced, NSCLC
- Randomized 1:1
  - Alectinib 600mg PO BID (A)
  - Crizotinib 250mg PO BID (C)
- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: independent-review PFS, time to CNS progression, ORR, and OS

ALEX Trial cont.

- Primary: PFS significantly improved
  - Median: 17.7 vs 11.1 months (C)
  - Updated 2018
    - Median PFS 13.4 months in 174 patients treated with Alectinib
  - OS trended in favor of alectinib
    - OS 0.76, p=0.24
    - Benefit consistent across all subgroups
    - No significant difference in dose intensity
    - Grade 3 or higher adverse events: 41% (A) vs 56% (C)
      - No significant difference in overall and specific adverse events across both groups
      - Alectinib: anemia, myalgia, elev t-bili, photosensitivity
      - Crizotinib: nausea, diarrhea, vomiting

ALEX Trial cont.

- Time to CNS progression longer with alectinib (HR=0.16)
- CNS progression events: 18 pts (A) vs 68 pts (C)
- ALK(+)-NSCLC increased rate of CNS mets at diagnosis and/or lifetime risk of CNS disease
- Alectinib high CNS penetration – not PGP substrate

Implications:

- Alectinib – 1st line
- Improved outcomes regardless of CNS involvement
- Crizotinib still niche in ROS-1

Pharmacy Considerations:

- Education:
  - Bradycardia, myalgias, pulmonary toxicity, hepatotoxicity
  - Take with food
- Monitoring:
  - CK, LFTs


Other Driver Mutations in NSCLC

- ROS1 (1-2%)
  - Crizotinib-preferred in NCCN guidelines
  - Entrectinib approved August 2019 for ROS1 positive metastatic NSCLC
  - Among the 45 responding patients, 55% had response persist for 12 months or longer
  - Common side effects fatigue, appetite loss, nausea, vomiting, diarrhea, dysgeusia, arthralgia, myalgia, cognitive impairment, weight gain, cough, somnolence, rash, arthralgia, and vision disorders
  - Dose: 600mg PO daily

- BRAF V600E (1-2%)
  - Phase 2 trial of 36 patients received dabrafenib 150mg BID and trametinib 2mg PO daily
  - Median follow-up was 15.9 months
  - The proportion of patients with investigator-assessed confirmed ORR was 23 (64%, 95% CI 46-79)
  - Two (6%) patients achieving a complete response and 21 (58%) a partial response

BRAF/MEK inhibitors:

- Dabrafenib 150mg BID
- Trametinib 2mg PO daily
-可耐康


Other Driver Mutations in NSCLC

- NTRK (0.2%)
  - Larotrectinib approved November 2018
  - Based on Phase 1 (adults), Phase 1-2 (peds) and Phase 2 (adolescents and adults) studies combined
  - 22 patients, 17 unique TRK fusion-positive tumor types
  - Primary endpoint ORR
  - ORR was 79% (95% CI 67 to 90) according to investigator assessment
  - At 1 year, 71% of the patients remained progression-free
  - Median DOR and PFS had not been reached
  - At a median follow-up of 14 months, 86% of the patients with a response (38 of 44 patients) were continuing treatment or had undergone surgery that was intended to be curative

- Adult Dose: 100mg BID

- High level MET amplification or MET 14 skipping mutation- crizotinib
- RET rearrangements- cabozantinib, vandetinib
- RBB2 (HER2) mutations- ado-trastuzumab emtansine

NCCN Guidelines, version 6.2018

NSCLC Treatment in 2019

NO DRIVER MUTATIONS

- PACIFIC Trial: durvalumab
- Keynote-189: carbo-taxane/pembrolizumab (non-squamous)
- CheckMate 227: PD-L1 nivolumab/ipilimumab, chemotherapy + nivolumab, or chemotherapy alone
- Keynote-042: PD-L1 ≥1%: pembrolizumab vs chemotherapy
- Impower150: carboplatin, paclitaxel, bevacizumab +/- atezolizumab (non-squamous)
- Keynote-407: carboplatin/taxane +/- pembrolizumab (squamous)
- Impower131: carboplatin/nab-paclitaxel +/- atezolozumab (squamous)

Studies

- NSCLC with driver mutations
  - FLAURA (EGFR): osimertinib
  - ALEX (ALK): alectinib

- NSCLC with no-driver mutations
  - PACIFIC Trial: durvalumab

Mechanism of Checkpoint Inhibitors

http://www.nature.com/nrclinonc/journal/v11/n1/fig_tab/nrclinonc.2013.208_F2.html

Ipilimumab
Nivolumab
Pembrolizumab
Atezolizumab
Durvalumab
**Pacific Trial**

- Phase 3 study comparing durvalumab as consolidation therapy with placebo in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy.
- **Treatment:**
  - Durvalumab (D, 10mg/kg IV) or placebo (P) every 2 weeks for up to 12 months
  - Study drug was administered 1 to 42 days after the patients had received chemoradiotherapy
  - 713 patients randomized, 709 received consolidation therapy
  - 473 received durvalumab and 236 received placebo
- **Co-primary end points:**
  - PFS and OS
- **Secondary end points:**
  - 12-month and 18-month PFS, ORR, DOR, time to death or distant metastasis and safety

**PACIFIC Trial: Results**

- **Results:**
  - PFS: 16.8 (D) vs 5.6 months (P)
  - 12-month PFS rate: 55.9% (D) vs 33.8% (P)
  - 18-month PFS rate: 44.2% (D) vs 27% (P)

**PACIFIC Trial: Secondary Endpoints**

- ORR: 28.4% (D) vs 16% (P)
- DOR (@18 months): 72.8% (D) vs 46.8% (P)
- Time to death or distant metastases:
  - 23.2 (D) vs 14.6 months (P)
- Safety: grade 3/4 AE rate: 29.9% (D) vs 26.1% (P)
  - Discontinuation rate: 15.4% (D) vs 9.8% (P)
- Brain metastases development: 5% (D) vs 11% (P)
- Pneumonitis: 6.3% (D) vs 4.3% (P)
- Benefit observed regardless of PD-L1 status, stage IIIa or IIIb, and histologic type

**PACIFIC Trial: 2019 Update**

- As of January 31, 2019, 48.2% of patients had died (44.1% and 56.5% in the durvalumab and placebo groups, respectively).
- The median duration of follow-up was 33.3 months (range, 0.2–51.3).
- Updated OS remained consistent with that previously reported (stratified HR 0.69, 95% CI, 0.55–0.86)
- Median OS not reached (95% CI, 38.4 months–NR) with durvalumab vs 29.1 months (95% CI, 22.1–35.1) with placebo.
- The 12-, 24- and 36-month OS rates with durvalumab and placebo were 83.1% vs 74.6%, 66.3% vs 55.3%, and 57.0% vs 43.5%, respectively.
- After discontinuation, 43.3% and 57.8% in the durvalumab and placebo groups, respectively, received subsequent anticancer therapy (9.7% and 26.6% subsequently received immunotherapy).

**Keynote-189: Pembrolizumab plus chemotherapy**

- **Keynote-189: double blind, placebo-controlled, phase 3 study**
- **Inclusion criteria:** treatment naive, metastatic, non-squamous, without sensitizing mutations
- **Arms:**
  - Pembrolizumab 200mg + Pemetrexed 500mg/m2 + Cisplatin 75mg/m2 or Carboplatin AUC 5 (chemo) Q3wks x 4 cycles
  - Placebo + chemo Q3wks x 4 cycles
  - Followed by Pembrolizumab or Placebo + Pemetrexed 500mg/m2 Q3wks up to 35 cycles
- **Primary Endpoints:** OS and PFS
- **Secondary Endpoints:** ORR, DOR, and Safety

**Pacific Trial: Practice Implications**

- New standard of care
- Will likely shape design of future trials
- Does it affect use of immunotherapy for metastatic disease?
- Pharmacy considerations:
  - Financial review
  - Timing of start of therapy
  - Education of potential side effects
  - Increase in pneumonitis??
  - Radiation or immunotherapy??

**Keynote-189: Pembrolizumab plus chemotherapy**

- Shows 189: double blind, placebo-controlled, phase 3 study
- Inclusion criteria: treatment naive, metastatic, non-squamous, without sensitizing mutations
- Arms:
  - Pembrolizumab 200mg + Pemetrexed 500mg/m2 + Cisplatin 75mg/m2 or Carboplatin AUC 5 (chemo) Q3wks x 4 cycles
  - Placebo + chemo Q3wks x 4 cycles
  - Followed by Pembrolizumab or Placebo + Pemetrexed 500mg/m2 Q3wks up to 35 cycles
- Primary Endpoints: OS and PFS
- Secondary Endpoints: ORR, DOR, and Safety
Keynote-189: Primary Endpoint - OS

- OS (12-month): 69.2% (pembro) vs 49.4% (HR = 0.49)
- 51% reduction in death
- Improved OS seen across all PD-L1% groups
- OS benefit positive correlation with PD-L1%
- 2019 Update:
  - 18.7-month median follow-up: pembro continued to provide longer OS (HR 0.56; 95% CI, 0.45-0.70, P < .00001; median 22.0 vs 10.7 months)


Keynote-189: Primary Endpoint - PFS

- Median PFS (12 month): 34.1% (pembro) vs 17.3% (8.8 vs 4.9 month)
- Median PFS benefit correlated with PD-L1%
- TPS>50% = 9.4 months
- TPS<1% = 6.1 months
- 2019 Update:
  - 18.7-month median follow-up: PFS (HR 0.48; 95% CI, 0.40-0.58, P < .00001)


Keynote-189: Secondary Endpoints

- ORR: 47.6% (pembro) vs 18.9%
  - ORR correlated with PD-L1%
  - TPS>50% ORR = 61.4% vs TPS<1% ORR = 32.3%
- Median DOR: 11.2 months (pembro) vs 7.8 months
- Safety: grade 3/4 AE rate: 67.2% (pembro) vs 65.8%
  - Acute kidney injury: 5.2% (pembro) vs 0.5%
  - Nephritis: 1.7% (pembro) vs 0%

Keynote-189: Practice Implications

- New standard of care
- Superior OS, irrespective of PD-L %
- Addition of immune-related AEs
- Treatment upon progression??
- Pharmacy considerations:
  - Financial review
  - Education
  - Steroid alternatives?

CheckMate 227 Part 1 Study Design

- Co-primary endpoints: OS in PD-L1–selected populations and PFS in TMB–selected populations treated with nivolumab + ipilimumab vs chemotherapy
- N = 1189 pts, 1004 pts assessed for TMB, 444 pts with TMB
  - No correlation seen between TMB level and PD-L1 status
  - PFS in pts w/ high TMB: (sig. difference)
    - Ipi/nivo: 7.2 months
    - Chemo: 5.5 months
  - PFS in pts w/ low TMB: (not sig. hr=1.07)
    - Ipi/Nivo: 3.2 months
    - Chemo: 5.5 months
  - Safety was not significantly different across groups
  - Greater immune related AEs w/ ip/nivo
  - Greater grade 3/4 events w/ chemo

CheckMate 227 cont.
CheckMate 227: Practice Implications

- Benefit seen in high TMB patients regardless of PD-L1 status and histological type
- Establishes TMB as possible response and outcome biomarker
- 2019 Update
  - BMS press release July 2019:
    - Part 1a: Ipi/nivo met co-primary endpoint of OS, demonstrating a superior benefit vs chemotherapy in first-line NSCLC patients whose tumors express PD-L1 ≥1%
    - Part 2: nivo plus chemotherapy, did not meet the pre-specified primary endpoint of OS in patients with non-squamous histology, regardless of PD-L1 status
  - ps/ratio is now recommended in NCCN guidelines for high TMB
- Clinical considerations:
  - Challenges with testing: no consensus on how to measure TMB
  - Role in setting of frontline chemo/immune
- Pharmacy considerations:
  - Dosing!!
  - Financial review

KEYNOTE-042

**Key Eligibility Criteria**
- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥1%
- No sensitizing EGFR or ALK alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

**Pembrolizumab**
200 mg Q3W for up to 35 cycles

**Carboplatin**
AUC 5 or 6 Q3W + Paclitaxel 200 mg/m² Q3W

**OR**
Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m² Q3W for up to 6 cycles

**N = 637**

**Key Findings**
- **Primary**: OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- **Secondary**: PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%

**End points**
- **Primary**: OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- **Secondary**: PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%

**Survival follow-up**
Stage IV or recurrent/metastatic nonsquamous NSCLC
Chemotherapy-naive
Tumor tissue available for biomarker testing
Any PD-L1 IHC status

**Stratification factors**
- Sex
- PD-L1 IHC expression
- Liver metastases

**Co-primary endpoints**: OS and PFS

**Maintenance Therapy**
Treated with pembrolizumab until PD per RECIST v1.1 or loss of clinical benefit
Treated with bevacizumab until PD per RECIST v1.1 or loss of clinical benefit

**IMpower150**

**Stage IV or recurrent/metastatic nonsquamous NSCLC**
Tumor tissue available for biomarker testing
Any PD-L1 IHC status
- **Stratification factors**
  - Sex
  - PD-L1 IHC expression
  - Liver metastases
- **N = 1310**

**Co-primary endpoints**: OS and PFS

**N = 1202**

**R1:1:1**

**Arm A (ACP)**
Atezolizumab + Carboplatin + Paclitaxel
4 or 6 cycles

**Arm B (ABCP)**
Atezolizumab + Carboplatin + Paclitaxel + Bevacizumab
4 or 6 cycles

**Maintenance Therapy**
Treated with bevacizumab until PD per RECIST v1.1 or loss of clinical benefit
Treated with erlotinib until PD per RECIST v1.1 or loss of clinical benefit

**Adverse Events**
Grade 3–4 treatment-related adverse events possibly attributable to study therapy
- **CNS**
  - Transient increases in intracranial pressure in 1% of patients

**Maintenance Therapy**
Treated with pembrolizumab until PD per RECIST v1.1 or loss of clinical benefit
Interim Analysis of OS in the ABCP Group and the BCP Group

Statistically significant and clinically meaningful OS benefit with atezolizumab + bevacizumab + chemotherapy (ABC) vs bevacizumab + chemotherapy (BCP) was observed; Median follow-up: ~20 mo

Investigator-Assessed PFS in the ABCP Group and the BCP Group

A trend toward OS benefit was observed with atezolizumab + chemotherapy (ACP) vs bevacizumab + chemotherapy (BCP), but the efficacy boundary has not yet been crossed and will be tested again at the time of the final analysis

Median, 19.4 mo (95% CI: 15.7, 21.3)

Overall Survival (%)

Time (months)

OS in the ITT-WT (Arm ACP vs Arm BCP)

IMpower150: Summary

• In patients with untreated advanced non-squamous NSCLC, addition of atezolizumab to carboplatin/paclitaxel + bevacizumab significantly prolonged survival vs carboplatin/paclitaxel + bevacizumab alone
  • Median PFS: 8.3 vs 6.8 months (HR: 0.59; 95% CI, 0.50-0.70; P < .0001)
  • Median OS: 19.2 vs 14.7 months (HR: 0.78; 95% CI, 0.64-0.96; P = .0164)
  • OS data for comparison of atezolizumab + chemo vs bevacizumab + chemo not yet mature

• Combination of an anti–PD-L1 and anti-VEGF therapy does not appear to increase the risk of sAEs

• New SOC option for first-line management of patients with advanced non-squamous NSCLC??

IMpower150: Summary

• Benefit associated with atezolizumab observed in patients with liver metastases or EGFR/ALK genomic aberrations, across PD-L1 subgroups, and regardless of Teff gene signature expression
  • Overall survival HR for ABCP vs BCP in all EGFR-positive patients was 0.61 (95% CI, 0.29–1.28)
  • ABCP regimen showed an improvement in OS compared with the BCP regimen; median OS with ABCP was NE (95% CI NE–NE; 26 of 400 patients) and 17.5 months (95% CI, 11.7–NE; 32 of 400 patients) with BCP (HR 0.31; 95% CI, 0.11–0.83)
  • Median OS was 21.4 months (95% CI, 13.8–NE) with ACP versus 18.7 months (95% CI, 13.4–NE) with BCP in EGFR-positive patients (HR 0.93; 95% CI, 0.51–1.68)

• Other factors
  • BICR, blinded independent central radiologic review. aPercentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.b Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

KEYNOTE-407

Key Eligibility Criteria

- Untreated stage IV NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Key Assessment

- PD-L1 expression (TPS <1% vs ≥1%)
- Choice of taxane (paclitaxel vs nab-paclitaxel)
- Geographic region (east Asia vs rest of world)

Optional Crossover

Pembrolizumab 200 mg Q3W for up to 35 cycles

End points

- Primary: PFS (RECIST v1.1, BICR) and OS
- Secondary: ORR and DOR (RECIST v1.1, BICR), safety

Optional Crossover Pembrolizumab 200 mg Q3W for up to 35 cycles
**Keynote-407: Practice Implications**

- In patients with untreated metastatic squamous NSCLC, addition of pembrolizumab to carboplatin + paclitaxel or nab-paclitaxel significantly improved survival regardless of PD-L1 expression level
  - Median OS: 15.9 (pembro) vs 11.3 months (P = .0008)
  - Median PFS: 6.4 (pembro) vs 4.8 months (P < .0001)
- Pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel should be a standard frontline treatment for metastatic squamous NSCLC with any PD-L1 TPS
- Pharmacy considerations:
  - Financial review
  - Education

**IMpower131: Study Design**

- **Arm A:** Atezolizumab + Carboplatin + Paclitaxel
  - 4 or 6 cycles
- **Arm B:** Atezolizumab + Carboplatin + Nab-Paclitaxel
  - 4 or 6 cycles
- **Arm C:** Carboplatin + Nab-Paclitaxel
  - 4 or 6 cycles
- **Co-Primary endpoints:***
  - Investigator-assessed PFS per RECIST v1.1
  - OS
- **Secondary endpoints:***
  - PFS and OS in PD-L1 subgroups
  - ORR, DOR; Safety

**First Interim OS in the ITT Population (Arm B vs Arm C)**

- **Arm B:**
  - Median OS: 15.9 months
  - HR (95% CI): 0.55 (0.47-0.65)
  - P-value: < .0001
- **Arm C:**
  - Median OS: 14.3 months
  - HR (95% CI): 0.92 (0.76, 1.12)
  - P-value: 0.41

**Co-primary endpoints:**

- Disease progression:
  - OS
- Investigator-assessed PFS per RECIST v1.1
- ORR, DOR; Safety

**Secondary endpoints:**

- PFS and OS in PD-L1 subgroups
- OS
- Investigator-assessed PFS per RECIST v1.1

---

**Overall Survival ITT**

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>0.61</td>
<td>0.0001</td>
</tr>
<tr>
<td>Placebo + Chemo</td>
<td>0.56</td>
<td>0.0056</td>
</tr>
</tbody>
</table>

**Overall Survival by PD-L1 TPS**

<table>
<thead>
<tr>
<th>TPS</th>
<th>Event</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>Pembro + Chemo</td>
<td>0.64</td>
<td>0.0001</td>
</tr>
<tr>
<td>≥50%</td>
<td>Placebo + Chemo</td>
<td>0.64</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Progression-Free Survival (ITT)**

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>0.56</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Placebo + Chemo</td>
<td>0.64</td>
<td>0.0056</td>
</tr>
</tbody>
</table>

**Imaging**

- Stage IV squamous NSCLC:
  - CDDP/PLT or CDDP/TTx
  - EGFR mutation or ALK translocation
- Any PS 0-2, WHO, status
- PD-L1 IHC expression
- Local variations

**Stratification factors:**

- Sex
- PD-L1 expression
- Liver metastases

**N = 1021**

---

**Data cutoff date:** Apr 3, 2018

---

**First Interim OS in the ITT Population (Arm B vs Arm C)**

- Arm B:
  - 12-month OS: 55.6%
  - 24-month OS: 31.9%
- Arm C:
  - 12-month OS: 44.4%
  - 24-month OS: 24.1%
INV-Assessed PFS in the ITT Population (Arm B vs Arm C)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Arm B: atezo + CnP</th>
<th>Arm C: CnP</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.8 mo</td>
<td>14.7%</td>
<td>12.6%</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>12.8 mo</td>
<td>17.1 mo</td>
</tr>
</tbody>
</table>

Minimum follow-up: 12.8 mo
Median follow-up: 17.1 mo

Immune-mediated Toxicities Associated with Checkpoint Inhibitors

- The “revved up” immune system can attack any organ system
- Similar to graft-versus-host disease (GVHD) seen in allogeneic stem cell transplant recipients
- Most common include:
  - GI (colon, liver, pancreas)
  - Endocrine system
  - Skin
  - Lungs/respiratory
  - Renal
  - Neurologic system
- Differs between agents
- More frequent and severe when checkpoint inhibitors are used in combination with each other

Summary

- NSCLC with driver mutations
  - FLAURA (EGFR): osimertinib-SOC (all 1st line in NCCN, osimertinib preferred)
  - ALEX (ALK): alectinib-SOC (preferred in NCCN)
- NSCLC with no-driver mutations
- PACIFIC: durvalumab-SOC
  - Keynote-180: carbo/pem/tax scared pembrolizumab (non-squamous)-SOC
  - Checkmate 227: nivolumab/pembrolizumab +/− chemotherapy, or chemotherapy alone
  - Keynote-042: pembrolizumab vs chemotherapy: SOC in ≥50%, ≥7% for ≥1%
  - Keynote-407: carbo/tax +/- pembrolizumab (squamous)-SOC
  - Mpower131: carbo/pem/tax (pad) +/- atezolizumab (squamous)-≥7%
- Pharmacist important part of team: education, financial burden, management of toxicity

Question 1

- 72yo female with stage IV, metastatic NSCLC. Recent cranial imaging confirmed multiple brain metastases, and biomarker testing reveals an EGFR exon19 deletion (+), T790M mutation (-). The patient is otherwise healthy with no significant comorbidities. What is the most appropriate therapy choice?
  A. Start with erlotinib first line until disease progression and/or acquired resistance
  B. Start with afatinib first line until disease progression and/or acquired resistance
  C. Start with gefitinib first line until disease progression and/or acquired resistance
  D. Start with osimertinib first line until disease progression and/or acquired resistance

Question 2

- 63yo male with newly diagnosed, unresectable, stage IIIa, NSCLC. Driver mutation tests returned negative, and the patient was deemed a candidate for radiation therapy. The patient has controlled T2DM with stage II CKD as the only complication. What would be the most appropriate therapy to be given with radiation?
  A. Paclitaxel 200mg/m2 + Carboplatin AUC=6 IV q21days x 4 cycles
  B. Paclitaxel 50mg/m2 + Carboplatin AUC=2 weekly x 6 cycles, followed by Durvalumab 10mg/kg IV q4weeks x 12 months
  C. Cisplatin 75mg/m2 + Docetaxel 75mg/m2 q21days x 4 cycles
  D. Cisplatin 75mg/m2 + Pemetrexed 500mg/m2 IV q21 days x 4 cycles

Question 3

- Which of the following is true based on the results of the ALEX trial (alectinib vs crizotinib) in ALK(+) NSCLC?
  A. The CNS progression was significantly lower in the alectinib trial arm
  B. The primary endpoint investigated was overall survival
  C. Crizotinib showed a lower adverse event rate
  D. Progression free survival was not significantly different between the two treatment arms