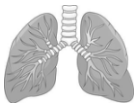
Immunotherapy in Lung Cancer



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Objectives

- Describe the recent advances in immunotherapy for patients with lung cancer
- Outline pertinent side effects, management of side effects, and appropriate patient counseling of immune therapy for lung cancer patients receiving treatment

Lung Cancer Epidemiology

- Lung cancer is the leading cause of cancer-related deaths in men and women in the United States
  - Estimated 224,390 cases in 2016
    - 158,080 deaths
- Smoking leads to almost 80% of all lung cancers
- Lung cancer subtypes
  - Non small cell lung cancer (85%)
    - Adenocarcinoma, squamous, large cell
  - Small cell (25%)

American Cancer Society 2016
NCCN Guidelines 2016

The Path to Immunotherapy

- Immune activity plays a crucial step in the destruction of malignant cells
- Historically, lung cancer has not been identified as cancer that is acknowledged by the immune system
- Immunotherapeutic treatment approaches to lung cancer have been disappointing over the past decade
- Advances in manipulation of the immune system instead of stimulation have proven to be more effective

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Checkpoint Inhibitors: Mechanism of Action

PD-1 Inhibitors

- Programed death 1 (PD-1) receptor is an inhibitory T-cell receptor
  - Reacts with PD-L1 (primary ligand) and PD-L2 (secondary ligand) within the tumor cell
  - Negatively regulates the effector phase of T cell response
- By blocking the interaction between PD-1 and PD-L1, cytotoxic results can be achieved without as many immune based adverse reactions

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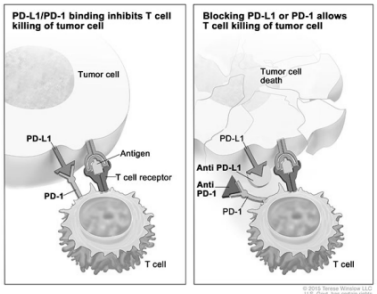
PD-1 Inhibitors Mechanism of Action



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PD-L1 Expression = Biomarker or Not?

- Controversy around PD-L1 expression as a biomarker
  - Many different assays are used
  - Variation in tissue expression
  - What is the best cutoff of expression?
- Tumors with overexpression of PD-LI have improved outcome
- Tumor with low expression of PD-L1 have also demonstrated long term benefits

There is no clear guideline on the use of PD-LI expression as a biomarker of response

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Nivolumab
Advanced Squamous NSCLCA

- Randomized, open-label, international, phase 3 study
  - Second line in advanced SCC
- Primary endpoint
  - Overall survival
- Randomized
  - Nivolumab 3 mg/kg Q2 weeks (n=135)
  - Docetaxel 75 mg/m2 Q3 weeks (n=137)
- More grade 3 and 4 adverse effects with docetaxel (55% vs. 7%)
- PD-L1 status with neither prognostic or predictive

	Overall Survival (Months)	1-year Overall Survival	PFS (Months)	Response rate
Nivolumab	**9.2**	**42%**	**3.5**	**20%**
Docetaxel	**6**	**24%**	**2.8**	**9%**

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Brahmer et al. *NEJM* 2015.373:123-135.

Nivolumab
Advanced Squamous NSCLCA

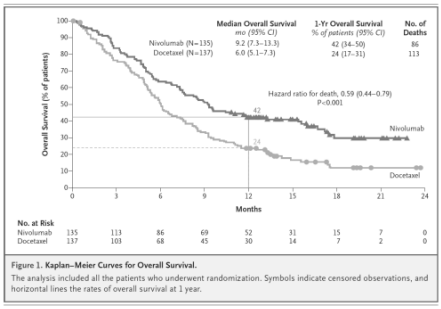

Figure 1. **Kaplan–Meier Curves for Overall Survival.**
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

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Brahmer et al. *NEJM* 2015.373:123-135.

Nivolumab
Advanced Non-Squamous NSCLCA

- Randomized, open-label, international, phase 3 study
  - Second line after a platinum-based doublet
- Primary endpoint
  - Overall survival
- Randomized
  - Nivolumab 3 mg/kg Q2 weeks (n=292)
  - Docetaxel 75 mg/m2 Q3 weeks (n=290)
- More grade 3 and 4 adverse effects with docetaxel (54% vs. 10%)
- Appeared higher levels of PD-L1 correlated with ORR, PFS, and OS

	Overall Survival (Months)	1-year Overall Survival	18-month Overall Survival	Response rate
Nivolumab	**12.2**	**51%**	**39%**	**19%**
Docetaxel	**9.4**	**39%**	**23%**	**8%**

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Borghaei et al. *NEJM* 2015.373:1627-1639.

Pembrolizumab
Advanced Squamous and Non-Squamous NSCLC

- Multi-center, open label multi-cohort (n=280)
  - Second line after progression with a platinum-containing regimen
  - Non-squamous or squamous histology with >50% PD-L1 expression
    - 61 patients
- Primary endpoint
  - Overall response rate
- Randomized
  - Pembrolizumab 2 mg/kg or 10 mg/kg Q2 weeks (n=27) or 3 weeks (n=34)
- Results
  - 41% response rate
  - CR-0%, PR-41%

Garon et al. *NEJM* 2015.372:2018-2028.

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Checkpoint Inhibitors in Advanced NSCLC

Nivolumab

- March 2015 approval was granted for second line treatment of squamous cell
- October 2015 approval was extended to include non-squamous cell
- Both trials looked at PD-L1 expression, but did not require it for use.
  - Approval granted without need for PD-L1 biomarker
- Approved dose 3 mg/kg IV over 1 hr Q2 weeks
  - **A flat 240 mg IV Q2 weeks has been recently been approved**
  - Short stability: 4 hrs
  - Infuse with 0.2 micron filter

Pembrolizumab

- In October 2015, the FDA granted accelerated approval for second line treatment with pembrolizumab in patients with metastatic NSCLC with PD-L1 expression
- Approved dose 2 mg/kg IV over 30 min Q3 weeks
  - Infuse with 0.2 micron filter

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PD-1 Clinical Trial Pearls

- Around 20% of patients respond to anti-PD-1 therapy
  - Biomarkers remain unclear
- Agents are well tolerated
- Tumor flare phenomena
- A link has been observed between response and current/former smokers
- EGFR mutants do not appear to respond to anti PD-1 therapy

Brahmer et al. *NEJM* 2015; 373:123-135.
Borghaei et al. *NEJM* 2015; 373:1627-1639.
Garon et al. *NEJM* 2015; 372:2018-2028.

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Pembrolizumab and Nivolumab: Adverse Effects

- Common
  - Fatigue, rash, pruritis, nausea, diarrhea, decreased appetite, arthralgias
- Immune related adverse effects
  - Pneumonitis (2.9%)
  - Colitis (1%)
  - Hepatitis (0.5%)
  - Hypophysitis (0.5%)
  - Nephritis (0.7%)
  - Hyperthyroidism & hypothyroidism (1.2%)
- Lab Abnormalities
  - Hyperglycemia
  - Hyponatremia
  - Hypoalbumenia
  - Hypertriglyceridemia
  - ↑ AST
  - Hypocalcemia
  - Anemia

Keytruda (pembrolizumab) [Package Insert]. Whitehouse Station, NJ: Merck; Revised September. 2016.
Opdivo (nivolumab) [Package Insert]. Princeton, NJ: BMS. Revised September. 2016.

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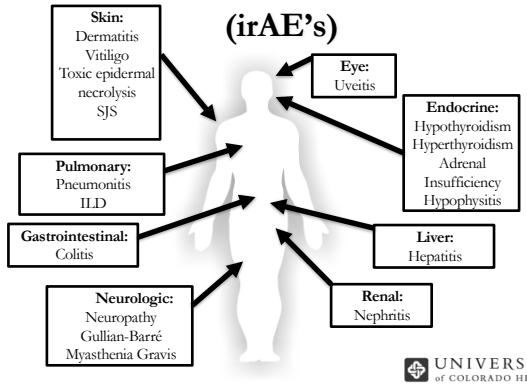
Immune Related Adverse Effects (irAE's)



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Immune-Related Adverse Effects NSCLC

- Clinical trials reported up to 60% incidence in irAE's with ipilimumab in melanoma
- irAE's in PD-1 inhibitors are < 5%
- Pneumonitis of greater concern for NSCLC

Immune-Related Adverse Events from Immune Checkpoint Inhibitors in Patients with NSCLC

Immune checkpoint Inhibitor	N	Incidence of Grade 3/4 irAE's	Most common Grade 3/4 irAE's
Ipilimumab (Lynch 2012)	70	15-20%	Diarrhea (n = 8), rash (n = 4), hypersensitivity reaction (n = 3), pulmonary embolism (n = 2), colitis (n = 2), increased LFTs (n = 2)
Nivolumab (Brahmer 2015)	135	2%	Tubulointerstitial nephritis (n = 1), colitis (n = 1), and pneumonitis (n = 1)
Pembrolizumab (Garon 2015)	495	NR	Pneumonitis (n = 9 [1.8%]), fatigue (0.8%), elevation in AST (0.6%), and diarrhea (0.6%)

Adapted from Socinski MA. *Seminars in Oncology* 2015.42(5):S19-S28.

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irAE Timing
Know when to expect your irAE's

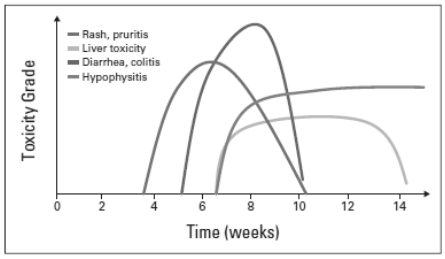

Fig 2. Kinetics of appearance of immune-related adverse event.

Weber et al. Management of Immune-Related Adverse Effects and Kinetics of Response With Ipilimumab. *Journal of Oncology* 2012.30(21):2691-2697.

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Monitoring and Labs

- Drug interactions…none known!
- Labs
  - Baseline and routine: CBC and CMP
  - TFT's-baseline, every 6-12 weeks, and for 6 months after therapy
- Beware of non-specific symptoms and fatigue
  - Obtain ACTH and cortisol with fatigue and non-specific symptoms

Weber JS, et al. *Journal of Clinical Oncology* 2015; 33:2092-2099.

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General Management of Immune-Related Adverse Effects

Grade	
1	Supportive Care (Lomotil, loperamide, topical corticosteroids)
2	Withhold drug, consider re-initiation once symptoms resolved, if symptoms do not resolve consider corticosteroids
3-4	Discontinue drug, High-dose corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Once resolved to grade 1-taper slowly over a month (Inflixamab, mycophenoplate, or cyclosporine)

Endocrinopathies may require lifetime hormonal replacement

Weber JS, et al. *Journal of Clinical Oncology* 2015; 33:2092-2099

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Patient Counseling

- Patient Counseling
  - New or worsening cough, chest pain or shortness of breath
  - Severe diarrhea or abdominal pain
  - Yellowing of skin
  - Muscle pain
  - Decreased appetite
  - Unusual headaches, extreme weakness, dizziness, fainting, or vision changes
  - Routine blood work including thyroid function tests
  - Contraception

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Immunotherapy in Lung Cancer Future Directions

- Biomarkers
  - Continued work in progress
- First line therapy
  - Single agent nivolumab recently failed to meet primary endpoint of PFS for first line therapy
- Adjuvant setting
- Sequencing
- Combination with chemotherapy or other immunotherapy
  - Ipilimumab/carboplatin/paclitaxel untreated squamous NSCLCA underway
  - Ipilimumab/nivolumab combination
  - CTLA-4/PD-L1 inhibitor combination

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Conclusions

- The arrival of immunotherapy into the treatment of lung cancer represents a significant advancement
- A survival advantage has been observed in a subset of NSCLC patients treated with these therapies
- Nivolumab and pembrolizumab are well tolerated with few autoimmune adverse effects which, with appropriate patient education and early treatment, can be effectively managed

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