

Advanced Topics in Immunotherapy

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11/11/22

Objectives

- Review types of immunotherapy
- Review mechanism of action of checkpoint inhibitors
- Review evidence for immunotherapy in managing lung cancer in the curative and metastatic settings
- Review toxicities of immunotherapy and the importance of early diagnosis and treatment

What is immunotherapy?

- Immune checkpoint inhibitors
 - PD-1 and PD-1L inhibitors
 - CTLA4 inhibitors
- Antibody-drug conjugates
- Adoptive cell therapies
 - Chimeric antigen receptor T-cell therapy (CAR-T) – hematologic malignancies so far
 - Tumor-infiltrating lymphocytes (TIL)
 - Engineered T-cell receptors
 - Natural Killer cell therapies
- Monoclonal antibodies
- Bispecific antibodies
- High dose IL-2, interferon
- Tumor vaccines

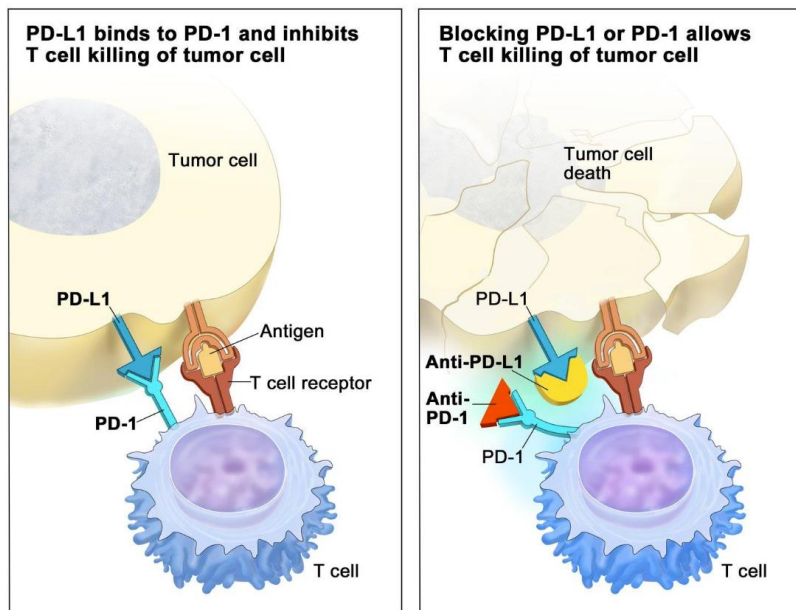
Immunotherapy Use in Lung Cancer

- Immune checkpoint inhibitors
 - PD-1 and PD-L1 inhibitors
 - Widest variety of medications and indications
 - Pembrolizumab, nivolumab, atezolizumab, durvalumab, cemiplimab
 - CTLA-4 inhibitors
 - Occasionally used in combination with PD-1/PD-L1 inhibitor in chemotherapy-sparing metastatic NSCLC regimens
 - Ipilimumab
- Antibody drug conjugates
 - Trastuzumab deruxtecan

What does a checkpoint inhibitor do?

- Cancer surveillance and elimination is an important immune function
- Cancers develop the ability to evade or suppress immune responses
- Immune checkpoints are a tool for the immune system to recognize “self”
 - PD-1 expressed on T cells and PD-L1 expressed on healthy, normal tissues
 - When PD-1 binds PD-L1, cytokine release and T cell proliferation are inhibited
 - If a cancer expresses PD-L1, it can trick the immune system into leaving it alone
- Immune checkpoint inhibitors prevent PD-1 from binding to PD-L1
 - Cancer cells lose ability to hide from immune system
 - Immune system controls cancer
- In a petri dish with just cancer cells, checkpoint inhibitors do...nothing

Onoi, et al. Immune checkpoint inhibitors for lung cancer treatment: a review. *Journal of clinical medicine*. 2020; 9(5): 1362.



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How does an antibody drug conjugate work?

- A cytotoxic drug (chemotherapy) linked to a monoclonal antibody
 - Monoclonal antibody directed at a protein relatively specific to cancer
- Allows for treatment only where

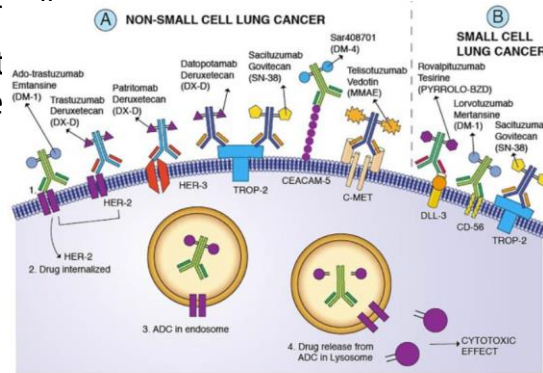


Fig. 1 Mechanisms of various Antibody Drug Conjugates being studied in non-small cell and small cell lung cancer.

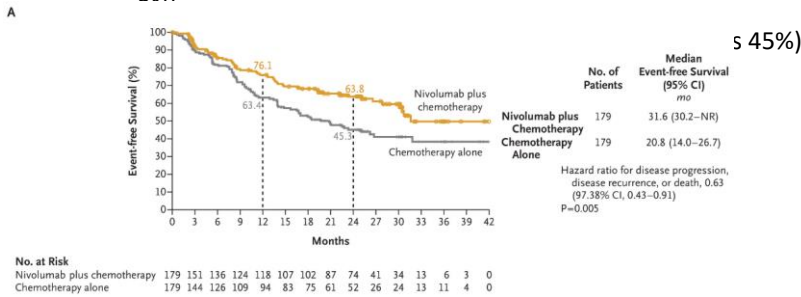
Desai, et al. Antibody-drug conjugates: a promising novel therapeutic approach in lung cancer. Lung Cancer. 2022; 163:96-106.

How is immunotherapy currently used in lung cancer?

- Curative setting – non-small cell lung cancer only
 - Prior to surgery
 - After surgery
 - After curative-intent chemoradiation
- Metastatic setting – small cell and non-small cell lung cancer
 - First line in combination with chemotherapy
 - First line in combination (PD-1 + CTLA4 inhibitors) without or with minimal chemotherapy
 - First line as single agents (PD-1 inhibitor)
 - Second line after targeted agents or chemotherapy

Neoadjuvant

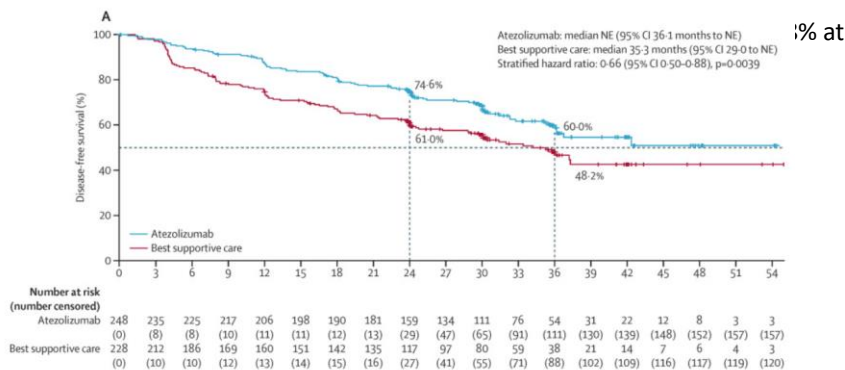
- CHECKMATE 816: Nivolumab (PD-1 inhibitor) or placebo plus chemotherapy given every 3 weeks for 3 cycles prior to surgery
- Patients: Untreated NSCLC stages Ib-IIIa (surgical candidates, tumor >4 cm or node positive)
- Results:
 - More likely to actually be able to have curative surgery (83% vs 75%)
 - More likely to have pathologic complete response - no living cancer cells left under the microscope in the lung that was removed (24% vs 45%)



Forde, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. NEJM. 2022; 386:1973-1985

Adjuvant

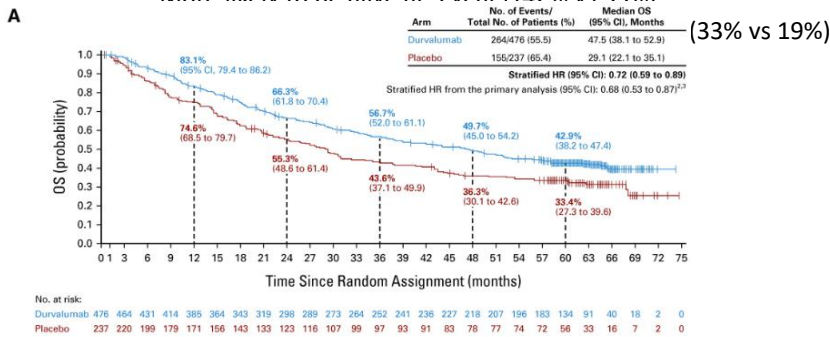
- IMpower010: Atezolizumab (PD-L1 inhibitor) every 3 weeks for 1 year vs no further treatment
- Patients: Already completed surgery and chemotherapy for stage II-IIIa NSCLC
 - PD-L1 expression >1% on the tumor
- Results:



Felip, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage II-IIIa non-small-cell lung cancer (IMpower010): a randomized, multicenter, open-label, phase 3 trial. The Lancet. 2021; 398 (10308):1344-1357.

Maintenance after Curative Chemoradiation

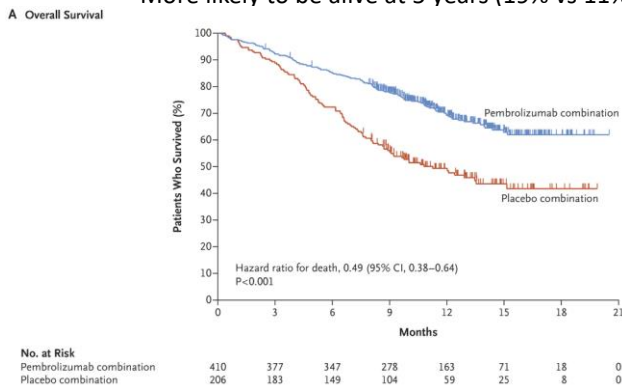
- PACIFIC: Durvalumab (PD-L1 inhibitor) vs placebo every 2 weeks for 1 year
 - Patients: Unresectable stage III NSCLC who had completed chemotherapy concurrent with radiation therapy
 - Results:
 - More likely to be alive at 5 years (47% vs 33%)



Spigel, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. Journal of clinical oncology. 2022; 40(12) 1301-1311.

Metastatic NSCLC – In addition to chemo

- KEYNOTE-189: Pembrolizumab (PD-1 inhibitor) vs placebo plus chemotherapy indefinitely
 - Patients: Untreated metastatic nonsquamous NSCLC
 - Results:
 - More likely to be alive at 1 year (69% vs 49%)
 - More likely to be alive at 5 years (19% vs 11%)

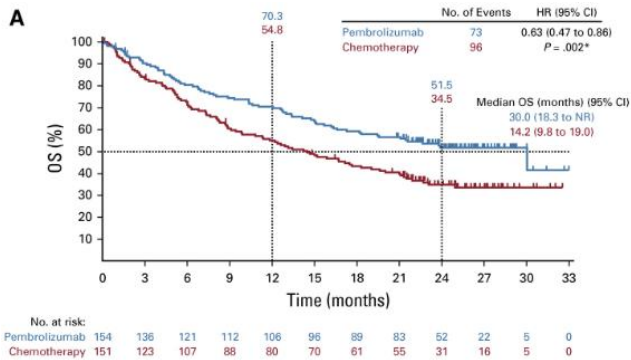


Gandhi, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. NEJM. 2018; 378:2078-2092

Garassino, et al. 973MO – KEYNOTE-189 5 year update: first line pembrolizumab (pembro) + pemetrexed (pem) and platinum vs placebo (pbo) + pem and platinum for metastatic nonsquamous NSCLC. Abstract. Annals of Oncology (2022) 33 (suppl_7):S448-S554. 10.1016/annonc/annonc1064

Metastatic NSCLC – PD-1 Monotherapy

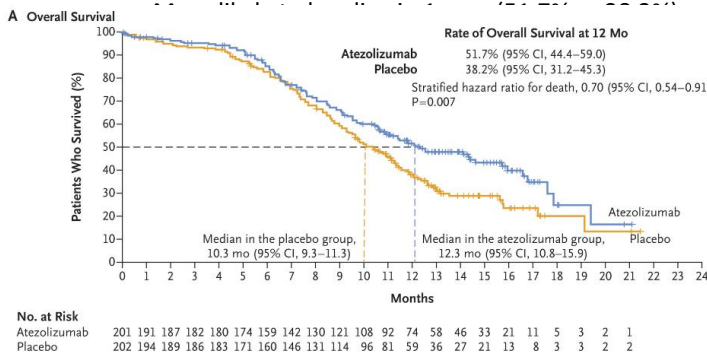
- KEYNOTE-024: Pembrolizumab vs chemotherapy given indefinitely
 - Patients: Untreated metastatic NSCLC
 - PD-L1 expressed on >50% of tumor cells
 - Results:



Reck, et al. Updated analysis of KEYNOTE-024: pembrolizumab vs platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *Journal of clinical oncology*. 2019; 37(7):537-546.

Extensive stage small cell lung cancer

- IMpower133: Atezolizumab (PD-L1 inhibitor) vs placebo in combination with 4 cycles of chemotherapy and then as maintenance indefinitely
 - Patients: Untreated extensive stage small cell lung cancer
 - Results:



is were still alive

Horn, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *NEJM*. 2018; 379:2220-2229.

What are the common and serious side problems immunotherapy can cause?

- Immune system ability to recognize healthy tissues that it should leave alone is impaired
- Side effects are auto-immune
- Common:
 - Itching or rash (~40%)
 - Permanent hypothyroidism (5-10%)
- Serious/Fatal (<1-4%):
 - Pneumonitis
 - Hepatitis
 - Colitis
 - Myocarditis
 - Nephritis
 - Hypophysitis or adrenal insufficiency
 - Neurologic disorders (MG, GBS, Encephalitis)
 - Really any organ...

National Comprehensive Cancer Network. Management of immunotherapy-related toxicities. Version 1.2022. 2/28/22.

Management of immunotherapy related toxicities

- Early recognition is key
- Patient counseling is crucial
- Promptly rule out alternative causes (usually infections)
- Steroids are a mainstay
 - Can require very long tapers
- Low threshold to add more potent immunosuppression for a serious toxicity

National Comprehensive Cancer Network. Management of immunotherapy-related toxicities. Version 1.2022. 2/28/22.

Questions?

