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# Lung Cancer: Current Treatment and Pulmonary Complications

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BROAD  
INSTITUTE

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Consultant to Novartis, AADi, Genentech  
Research contract from Genetech, Revolution  
Medicines

None of these has any impact on my  
presentation

Topics to be covered:

Staging

Histology

Lung cancer genetics

Chemotherapy

Personalized medicine, mutation-targeted therapy

Immune checkpoint therapy

Pulmonary complications



Overview of treatment approaches to non-small cell lung cancer  
NCCN guidelines (<https://www.nccn.org>)

Early stage disease – Stages I – IIIA (Tumor not invading major structures; metastasis to ipsilateral mediastinal and/or subcarinal LNs only; no distant metastases)

Pre-treatment evaluation:

PFTs

bronchoscopy

pathologic mediastinal LN evaluation

FDG PET/CT scan

Brain MRI

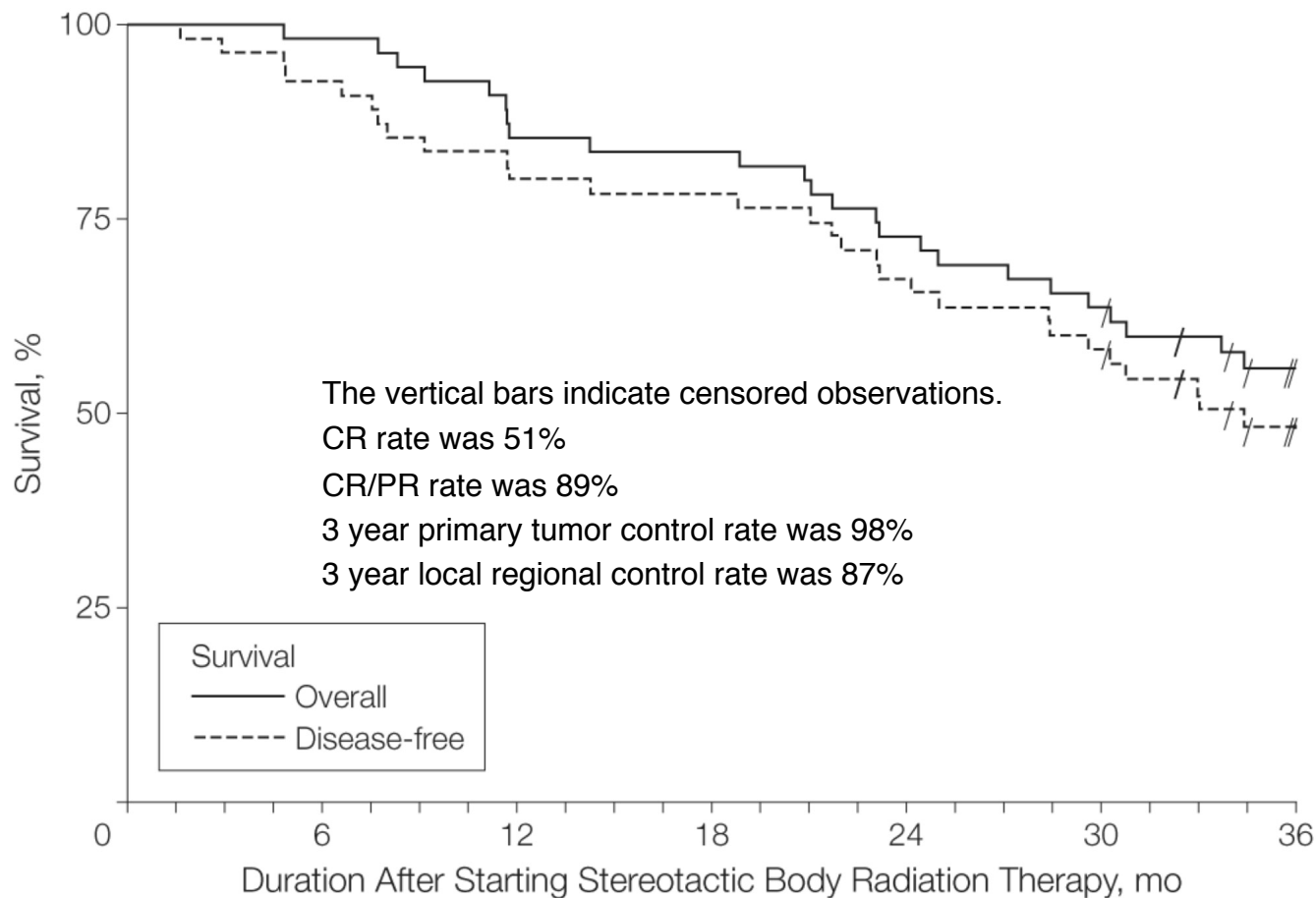
Post-evaluation:

If N0 or N1 (no mediastinal LN involvement)

Surgical resection if medically possible

If medically inoperable, then stereotactic ablative radiotherapy (SABR) if possible or definitive chest radiotherapy

# Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer



No. at risk	0	6	12	18	24	30	36
Overall survival	55	54	47	46	40	35	24
Disease-free survival	55	51	44	43	37	32	20

Phase 2 North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small cell tumors (measuring <5 cm in diameter) and medical conditions precluding surgical treatment. The radiation dose was 18 Gy per fraction × 3 fractions (54 Gy total) during an interval of 1 - 2 weeks.

Early stage disease – Stages I – IIIA

Post-surgical resection:

Stage IA – no treatment

Stage IB – no treatment in general, but consider for high-risk

Stage IIA, IIB – post-op adjuvant chemotherapy

Stage IIIA - post-op adjuvant chemotherapy unless N2 disease, for which sequential chemotherapy – radiotherapy is preferred

Post-operative adjuvant chemotherapy – benefit is modest – 5-8% improvement in 5 year survival, so always a discussion with the patient.

Locally invasive disease – Stages IIB – IIIA (T3 or T4 with invasion, N0-1) - superior sulcus tumors, chest wall invasion, invasion of proximal airway or mediastinum

If possibly resectable – preoperative concurrent chemoradiation therapy -> surgical re-evaluation and resection if possible

In some cases (chest wall invasion), initial surgery is appropriate, followed by chemotherapy +/- radiation

Stage IIIA without local invasion

Definitive concurrent chemoradiation or

Induction concurrent chemoradiation followed by surgical resection +/- additional chemotherapy +/- additional radiotherapy

Stage IIIA with local invasion

Definitive concurrent chemoradiation

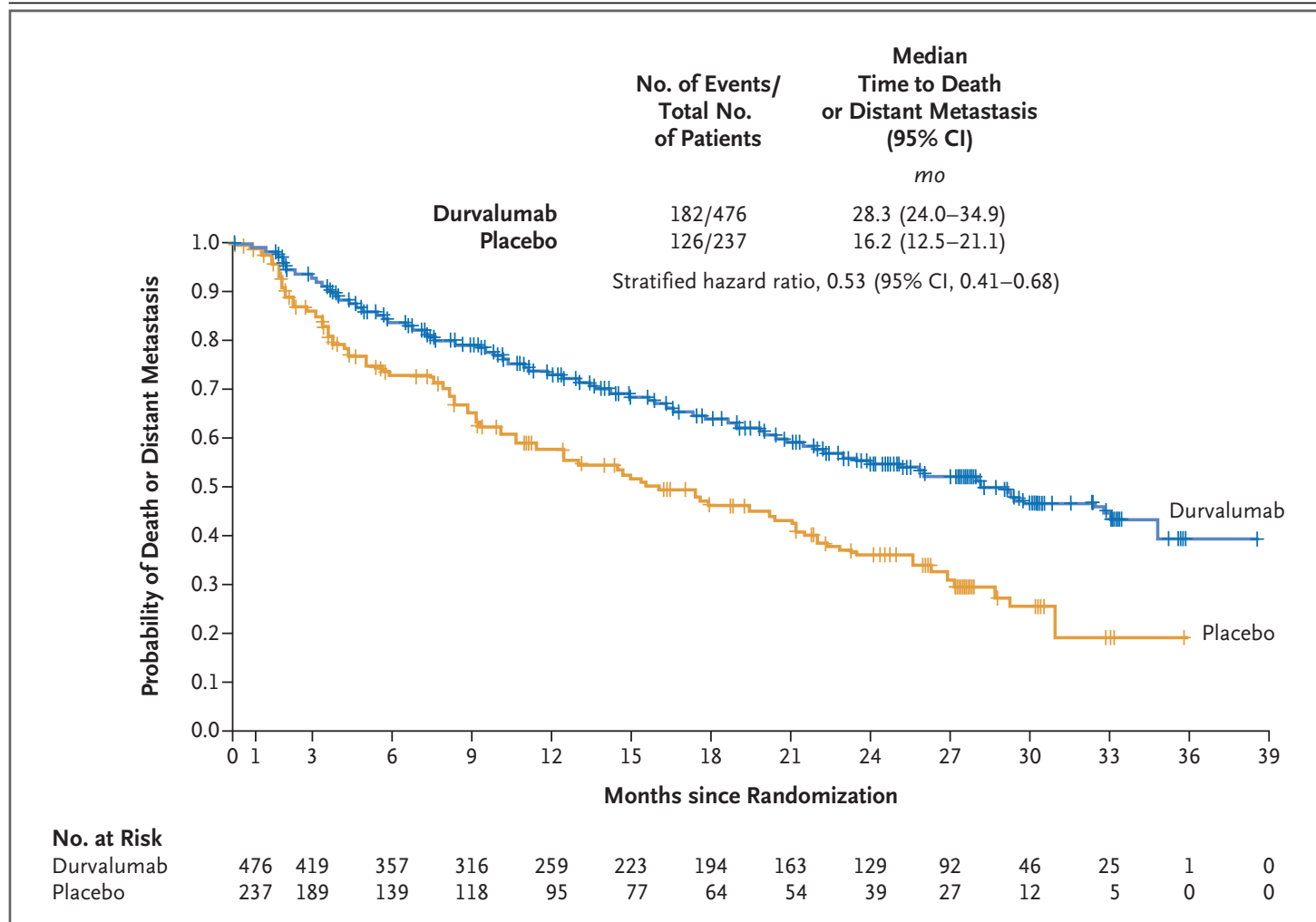
Stage IIIB

Definitive concurrent chemoradiation

Stage III(A or B) after completion of chemoradiation therapy:

Durvalumab (anti-PD-L1) 10mg/kg IV q2weeks for up to 12 months

# Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer



Phase 3 RCT compared the anti-PDL-1 antibody durvalumab as consolidation therapy with placebo in patients with stage III NSCLC (both adeno- and squamous) who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy. Durvalumab was given every 2 weeks for up to 12 months, starting 1 to 42 days after end of chemoradiotherapy.

Stage IV, limited sites of metastasis 'oligometastatic disease' –  
e.g. brain or adrenal metastases only:

Treat lung disease as you would for no metastatic disease—  
surgery followed by adjuvant type chemotherapy  
definitive chemoradiation therapy

For brain metastases:

surgical resection f/b whole brain radiotherapy (WBRT) or  
stereotactic radiosurgery (SRS)

SRS alone

For adrenal metastasis:

adrenalectomy

radiotherapy, including stereotactic ablative radiotherapy

Stage IV disease

adenocarcinoma/NOS

There are always at least 3 options for the treatment of metastatic lung adenocarcinoma, which should be considered in every patient:

Chemotherapy

Immune checkpoint therapy

Mutation-directed therapy (personalized or targeted)

Combinations

## Stage IV disease

Conventional chemotherapy options for **adenocarcinoma/NOS**:

1<sup>st</sup> line:

Pemetrexed-carboplatin-pembrolizumab

Pemetrexed-carboplatin-ipilimumab-nivolumab

many other regimens are used – agents include: carboplatin, albumin-bound paclitaxel, docetaxel, etoposide, gemcitabine, vinorelbine

If PD-L1 IHC > 50% tumor cells, pembrolizumab alone, or first regimen

Maintenance regimens:

Pemetrexed-pembrolizumab

Pembrolizumab

For poor overall health (PS 2 or higher) or advanced age, consider single agent regimens, though pemetrexed-carboplatin-pembrolizumab usually tolerated well

PS 2 = ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours

## Stage IV disease

Conventional chemotherapy options for **squamous cell carcinoma**:

1<sup>st</sup> line:

Paclitaxel(taxol)/carboplatin + pembrolizumab

If PD-L1 IHC > 50% tumor cells, pembrolizumab alone, or the above

many other regimens are used – agents include:

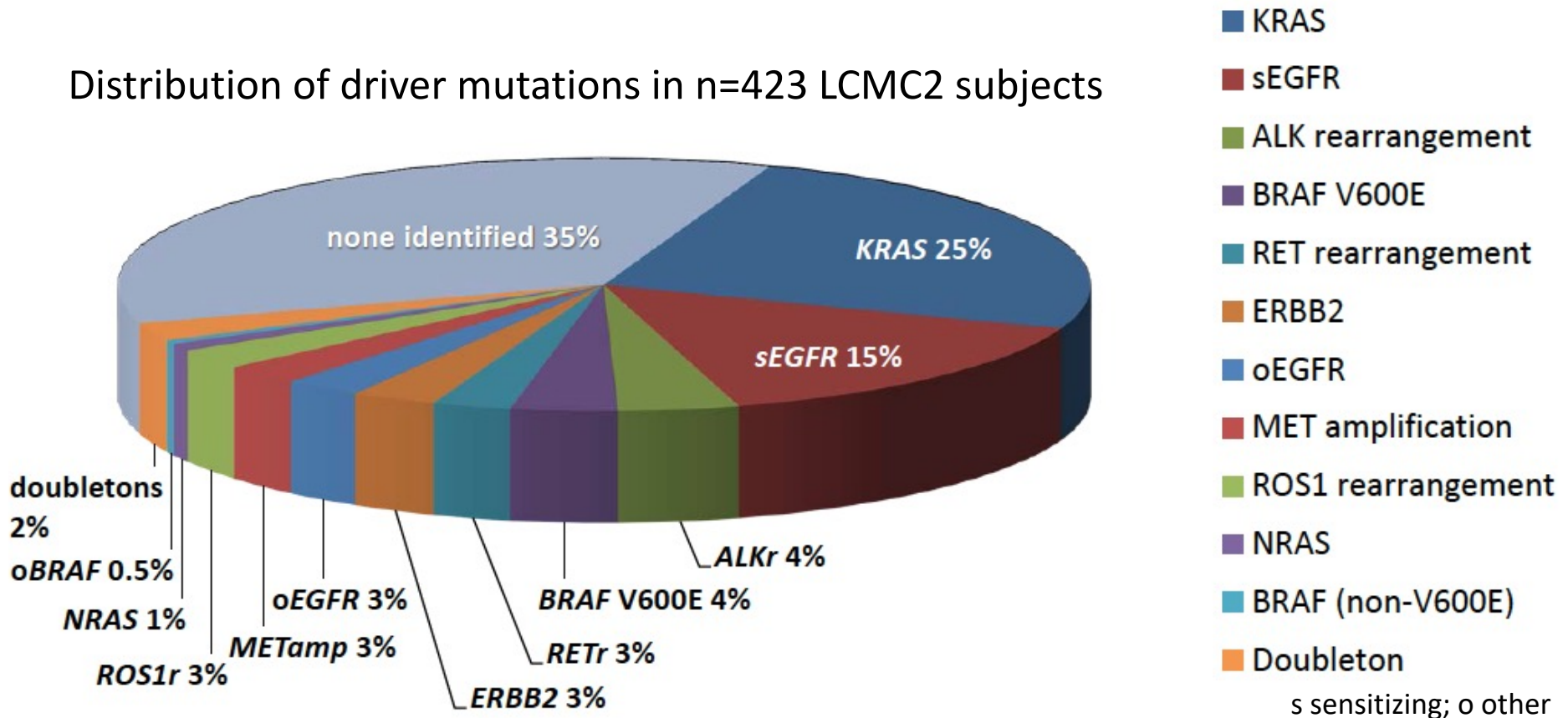
cisplatin, etoposide, gemcitabine, vinorelbine, albumin-bound paclitaxel

For poor overall health (PS 2 or higher) or advanced age, consider single agent regimens, though albumin-bound paclitaxel/carboplatin can be tolerated well, and can dose reduce

## Targeted or personalized therapy for lung cancer

Mutation-directed therapies have been used for many years, and for several mutations (EGFR, ALK, ROS1, BRAF, RET, MET) are well-established. Others are investigational.

Distribution of driver mutations in n=423 LCMC2 subjects



# EGFR mutant lung cancer

Known since 2004

Two mutations account for 85% of EGFR mutations – L858R and exon 19 in-frame deletions of various sizes

More common in never-smokers where incidence is about 50%.

Also more common in women and those of Asian origin

First line therapy is osimertinib (others also) see curve

Response rate 80%; median progression-free survival 1.5 years

Progression often develops slowly, leading to continued

treatment if asymptomatic. ‘Treatment beyond progression’

Multiple options at time of progression:

Repeat biopsy or plasma genotyping to ascertain

cause of resistance, and guide therapy

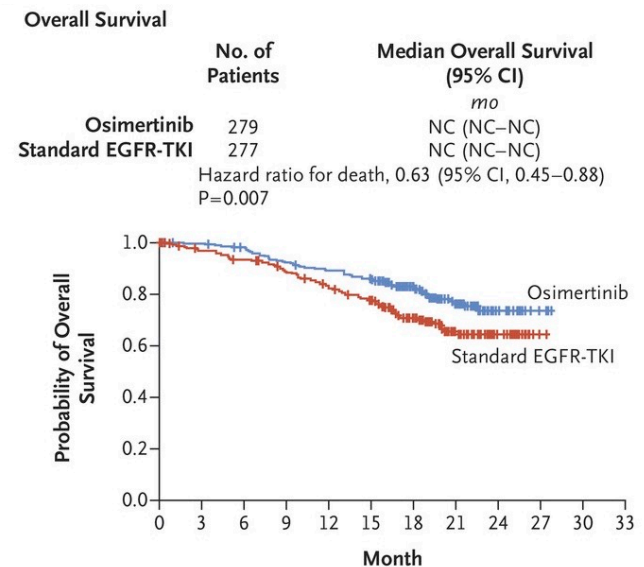
Local therapy to sites of disease progression

(surgery, radiation)

Clinical trials, based on genetic/tissue findings

Switch to chemotherapy

Soria et al. NEJM 2018  
Osimertinib in Untreated  
EGFR-Mutant  
adenocarcinoma



## EGFR mutant lung cancer and resistance to osimertinib

Multiple mechanisms of resistance develop in patients with EGFR mutant lung adenocarcinoma who are treated with Osimertinib:

- 10-25% secondary mutation in EGFR, C797X, which disrupts the covalent binding site on EGFR for osimertinib; others as well
- 10-25% MET amplification
- 5-10% Oncogene fusions: RET, ALK, BRAF, FGFR3
- 5-10% Histologic transformation to small cell
- 30-80% unknown

Biopsy and/or cfDNA analysis are recommended in this circumstance








Polyclonal resistance in an individual patient is common

Chemotherapy treatment is always an option for these patients, and is as effective as chemotherapy for lung adenocarcinoma without EGFR mutation

## Plasma cell-free genotyping in lung cancer

Circulating cell-free DNA can be isolated from the plasma from all humans, and is thought mainly to be derived from normal physiologic cell death with release of nucleosome size DNA fragments, ~160nt

Cancer cells are prone to cell death, and can contribute significantly to the fraction of DNA present in plasma. Next generation sequencing of plasma cell free DNA can be used to identify mutations that can guide cancer therapy in multiple settings.

Alteration	% cfDNA or Amplification	Associated FDA-approved therapies	Clinical trial availability (see page 3)
<i>EGFR</i> T790M	3.5%	 Osimertinib  Afatinib, Dacomitinib, Erlotinib, Gefitinib, Neratinib	Yes
<i>EGFR</i> L858R	8.5%	 Osimertinib	Yes
<i>EGFR</i> L792P	1.1%	 Osimertinib	Yes
<i>BRAF</i> V600E	1.4%	 Dabrafenib, Trametinib  Binimetinib, Cobimetinib, Encorafenib, Vemurafenib	Yes
<i>CTNNB1</i> S37C	0.4%	 Celecoxib	Yes

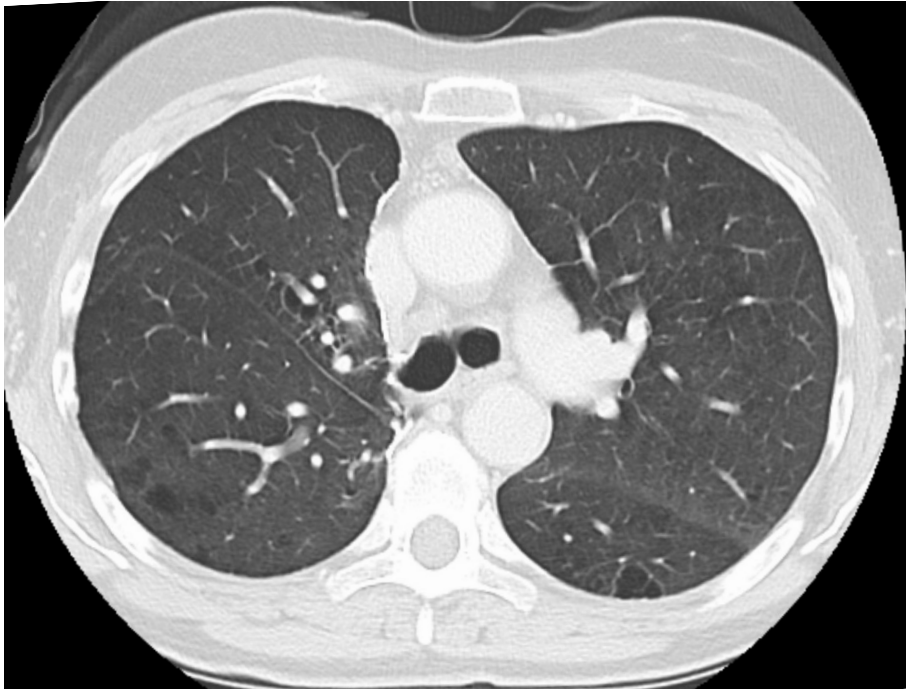
Guardant 360  
Report of a patient with EGFR-mutant lung cancer progressing on osimertinib

## Other genetic mutations in lung cancer that are targetable:

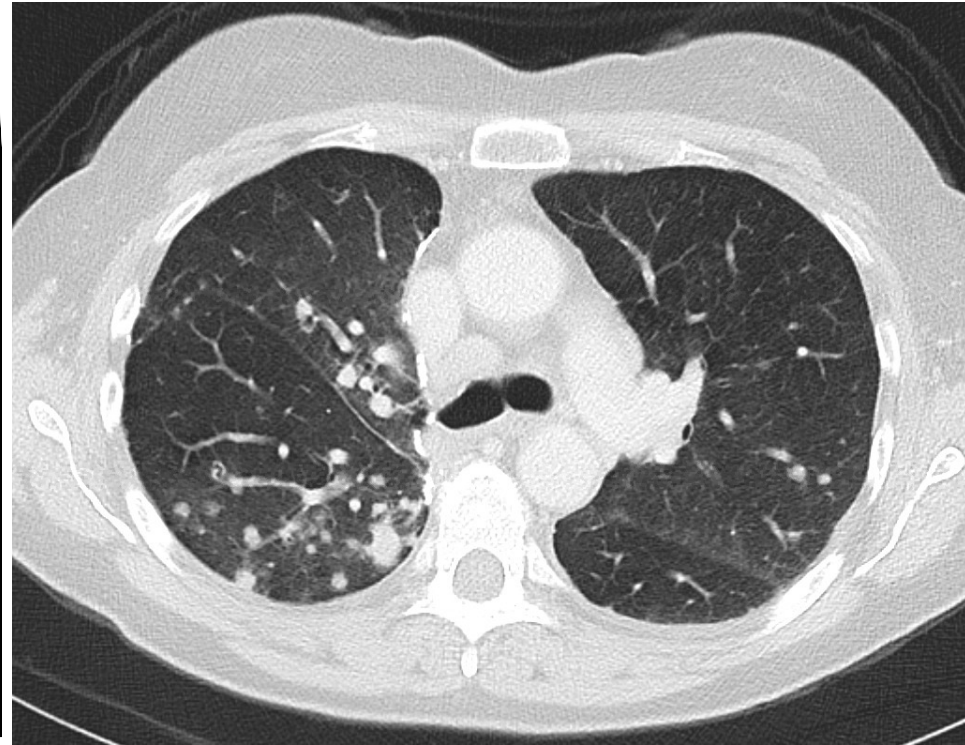
Gene	Mutation	Therapy
KRAS	**G12C codons 12,13	sotorasib <sup>FDA</sup> , Adagrasib/MRTX849 investigational
ALK	rearrangement	alectinib, brigatinib, lorlatinib, others
BRAF	V600E	dabrafenib + trametinib
MET	amplifications, exon 14 splice	capmatinib, crizotinib
ERBB2(HER2)	multiple point mutations	ado-trastuzumab emtansine, investigational
RET	rearrangement	selpercatinib, pralsetinib
ROS1	rearrangement	crizotinib, entrectinib, ceritinib
NTRK1/2/3	rearrangement	larotrectinib, entrectinib
EGFR	E20ins	amivantamab, mobocertinib

To achieve full molecular testing for all of these requires substantial tissue – take more whenever possible when performing a biopsy to enable comprehensive testing

New agents for KRAS G12C mutant Non–Small-Cell Lung Cancer  
KRAS G12C accounts for ~45% of the KRAS mutations seen in ~30% of lung adenocarcinoma

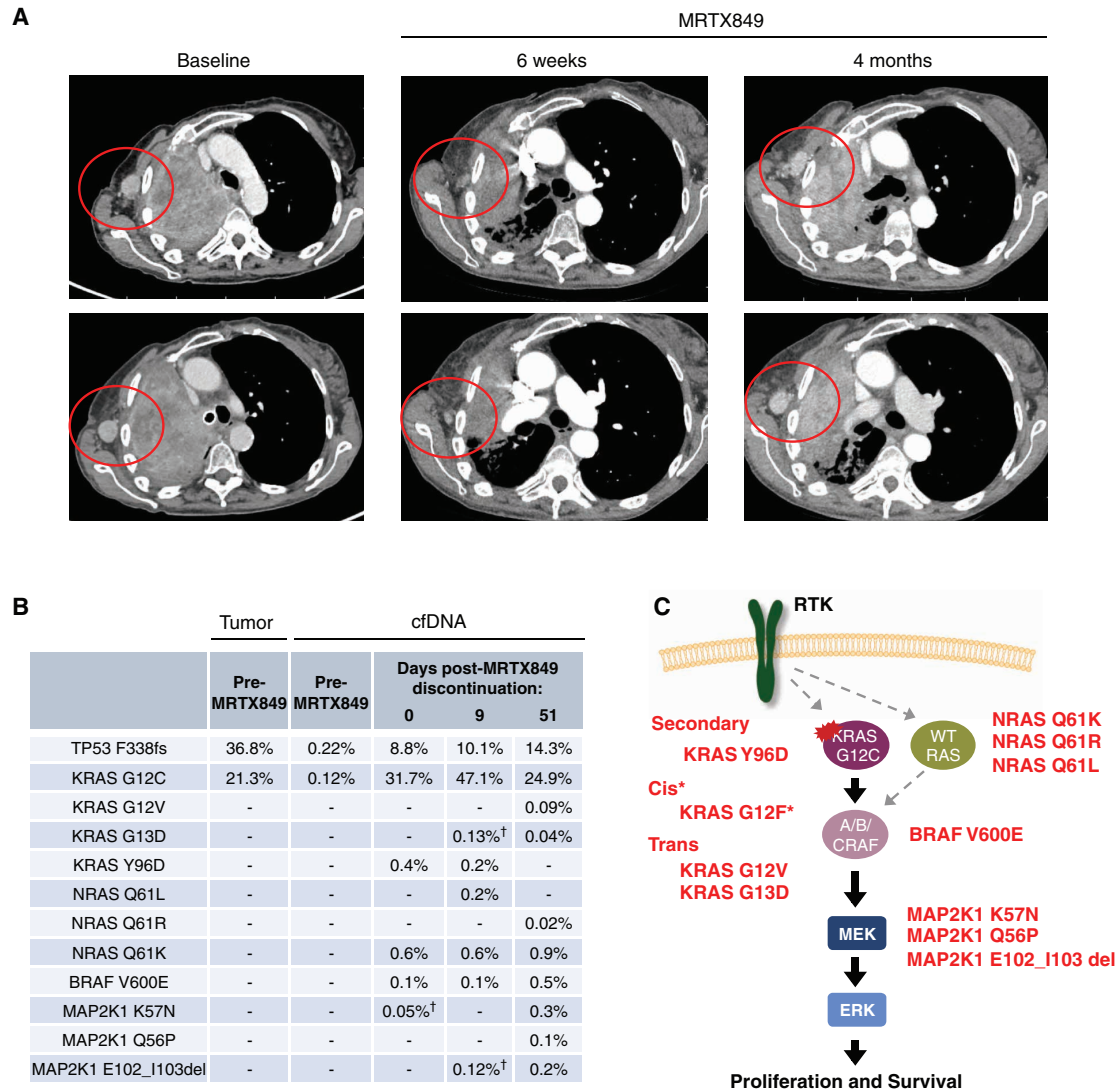


7/2021



8/2019

62 yo woman with KRAS G12C mutant lung adenocarcinoma  
Treated with Adagrasib/MRTX849 9/4/19 onward, stopped for a week due to intolerable fatigue, then restarted and well-tolerated, working full time  
Sotorasib (Amgen) has similar efficacy in ongoing clinical trials, now FDA-approved



**Figure 1.** Acquired resistance to KRAS<sup>G12C</sup> inhibitor MRTX849 (adagrasib). **A**, Computed tomography images of the patient's axillary lymph node metastasis at baseline, during response to MRTX849, and at progression on MRTX849. **B**, Variant allele fractions of mutations detected in the patient's serial plasma samples. <sup>†</sup>, indicates the mutations were detected by ddPCR but not by plasma next-generation sequencing. **C**, Alterations detected in post-MRTX849 cfDNA include acquired mutations in KRAS as well as multiple components of the MAPK signaling cascade. <sup>\*</sup>, KRAS<sup>G12F</sup> represents a potential resistance mechanism supported by limited sequencing reads, as shown in Supplementary Fig. S2.

## Immune checkpoint therapy in lung cancer

The native immune system has multiple molecular mechanisms for regulation of immune activation in host defense against infectious and other agents.

Unregulated immune activity contributes to many immune disorders including inflammatory bowel disease (colitis), systemic lupus erythematosus, and rheumatoid arthritis

Since many cancers express proteins that are either unusual or mutated and therefore not 'normal', the immune system can react against a cancer and lead to disease control or even elimination

This is thought to occur commonly in early stages of cancer, and can occur spontaneously in metastatic disease in rare instances. Historically perhaps this was the basis for Coley's toxin, a concoction of bacterial species that was thought to foster the immune system attack on cancer

# Immune checkpoint inhibitors for lung cancer

## CTLA-4 inhibitors

ipilimumab (+ nivolumab for NSCLC)

tremelimumab

## PD-1 inhibitors

nivolumab (FDA-approved)

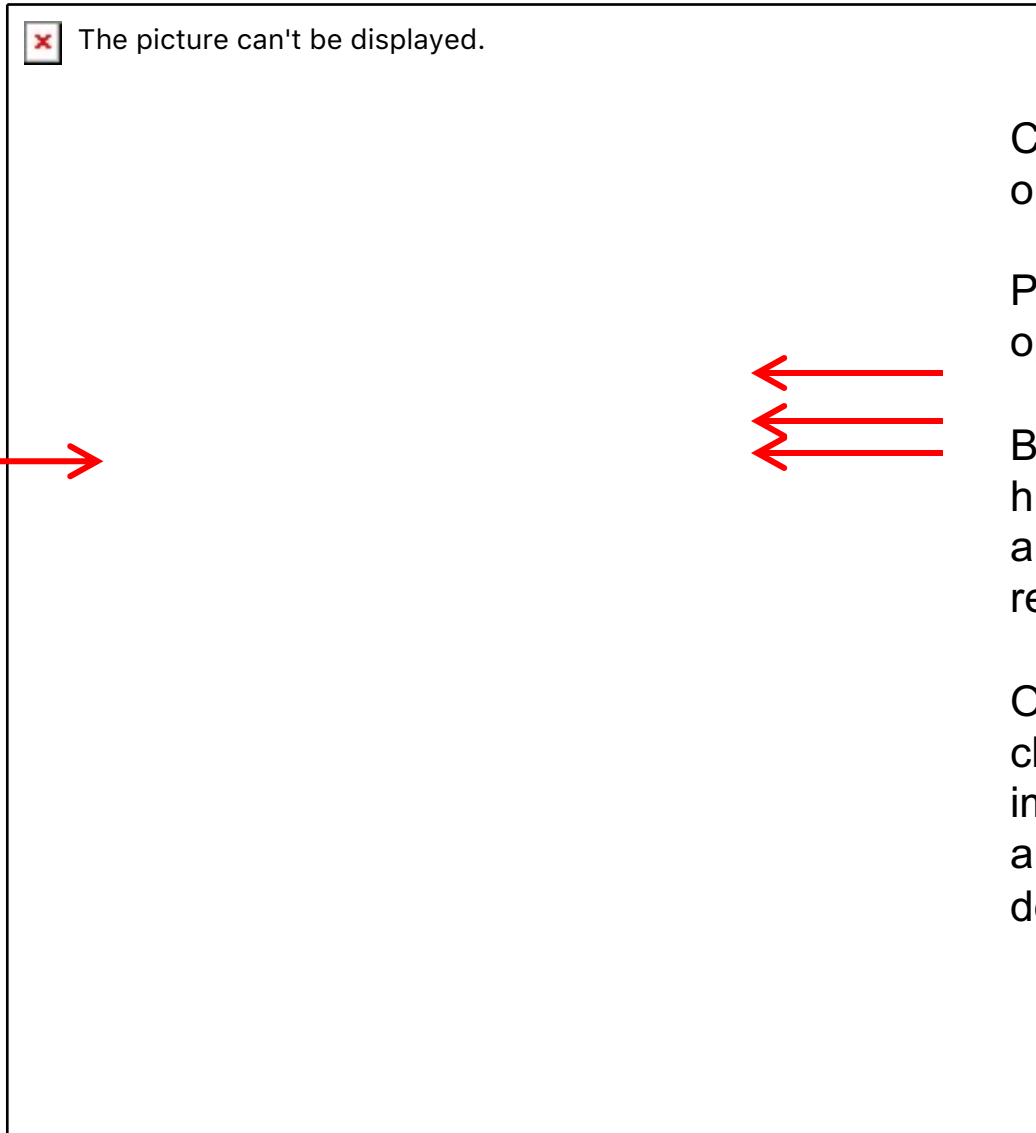
pembrolizumab (FDA-approved)

## PD-L1 inhibitors

atezolizumab (FDA-approved)

durvalumab (FDA-approved)

# Multiple coinhibitory pathways regulate T cells




CTLA-4 checkpoint mainly operative in lymph nodes

PD1 checkpoint mainly operative in the periphery

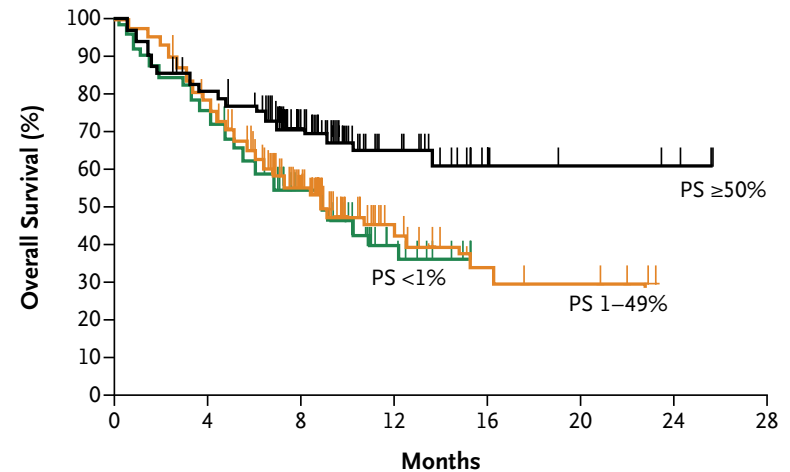
Both checkpoints can be hijacked by tumors to avoid anti-tumor immune responses.

Other coinhibitory checkpoints are also important in tumor evasion, and inhibitors are in clinical development

# Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer

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**A All Patients**



**No. at Risk**

PS $\geq$ 50%	119	92	56	22	5	4	3	0
PS 1-49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

Stage III or IV NSCLC; not randomized

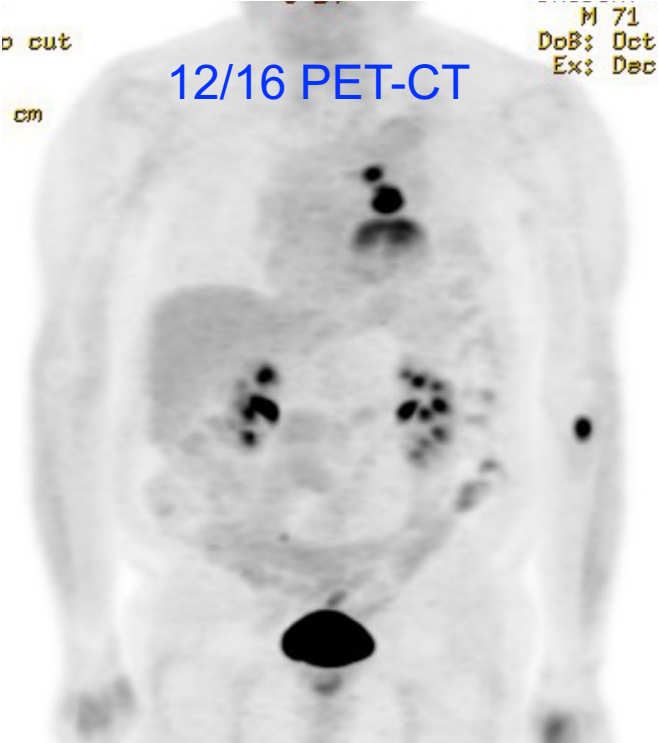
PS 0 or 1; 80% had prior treatment; 20% previously untreated


Exclusion criteria: history of pneumonitis, systemic immunosuppressive therapy, or active autoimmune disease.

SEs: fatigue, pruritus, decreased appetite

Objective response rate 19%

Used proportion score (PS) meaning % of tumor cells expressing PD-L1 as a biomarker of response



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1/18 PET-CT

## Response to immune therapy

1/16 – 70yo man with onset cough; L perihilar mass; 4L LN bx: NSCLC  
Rx: concurrent chemo-radiation, with response

12/16 PET CT: recurrence in L perihilar region, biopsy confirmed


2/17 – 1/18 pembrolizumab q3wks

no SEs, response seen on scan


1/18 – 4/21: no evidence of disease (off treatment)

4/21: recurrent disease in same site

5/21->: on pembrolizumab with response

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2/17 Chest CT

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10/18 Chest CT

Double-blind, randomized phase 3 trial  
 Metastatic nonsquamous NSCLC without sensitizing EGFR or  
 ALK mutations

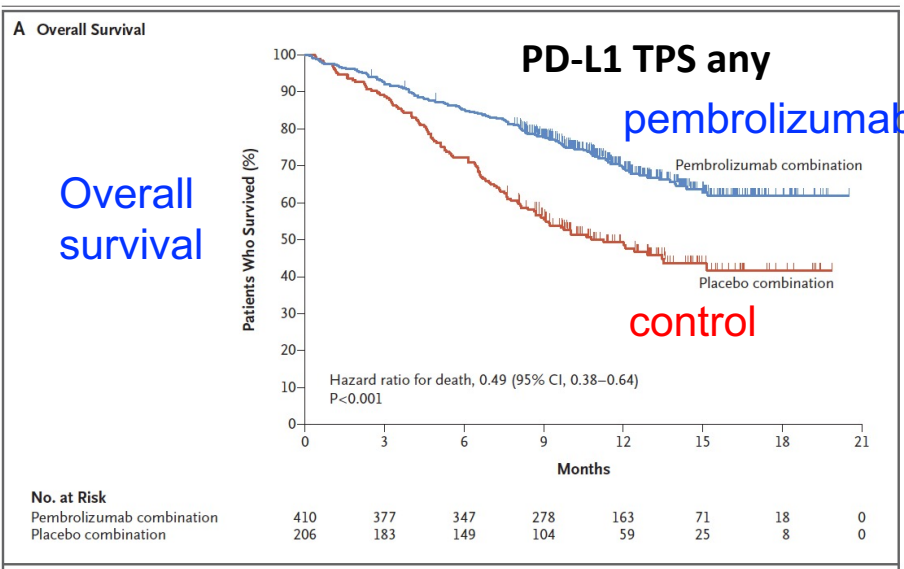
Pemetrexed and a platinum drug plus either 200 mg of  
 pembrolizumab or placebo every 3 weeks for 4 cycles,  
 followed by pembrolizumab or placebo for up to a total of  
 35 cycles plus pemetrexed maintenance therapy.

Crossover to pembrolizumab permitted

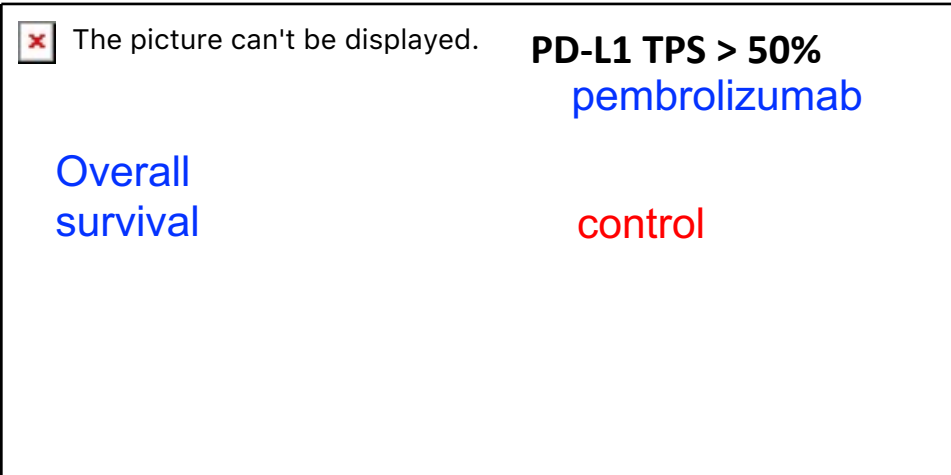


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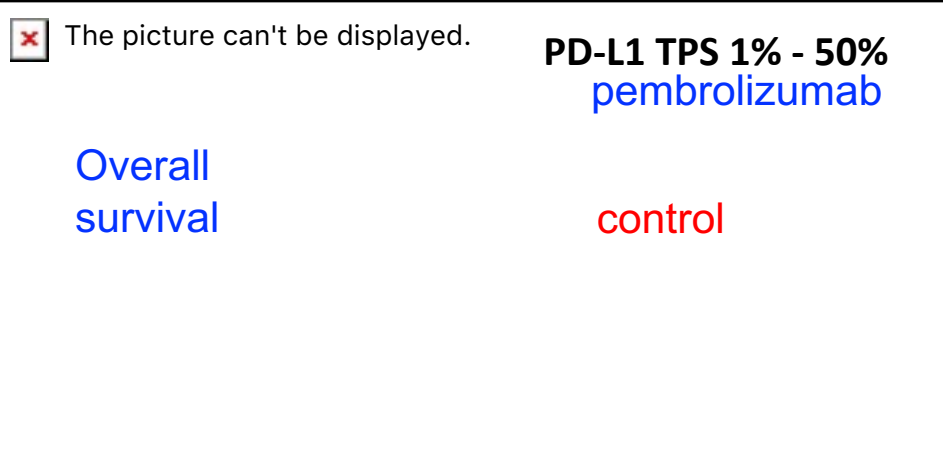
2018



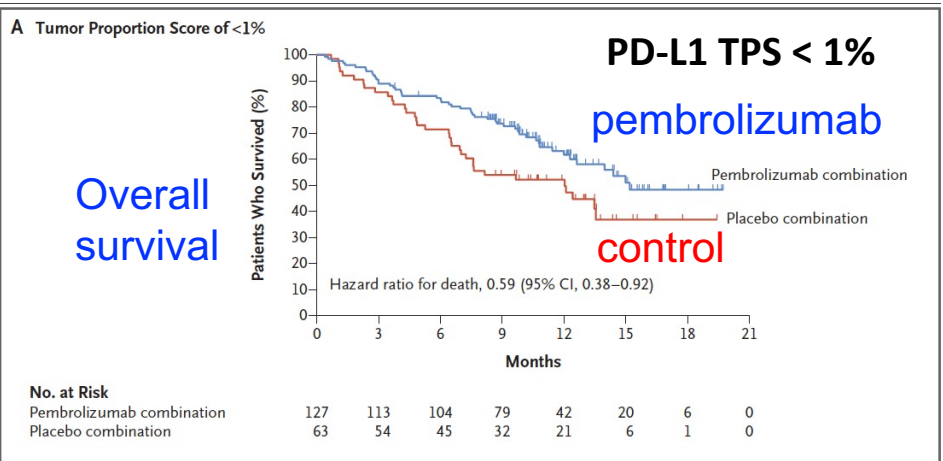
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**A Tumor Proportion Score of <1%**



# Platinum/Pemetrexed +/- Pembrolizumab

**Table 3.** Adverse Events of Interest in the As-Treated Population.\*

Event	Pembrolizumab Combination (N = 405)		Placebo Combination (N = 202)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
<i>number of patients (percent)</i>				
Any	92 (22.7)	36 (8.9)	24 (11.9)	9 (4.5)
Hypothyroidism	27 (6.7)	2 (0.5)	5 (2.5)	0
Pneumonitis ★	18 (4.4)	11 (2.7)	5 (2.5)	4 (2.0)
Hyperthyroidism	16 (4.0)	0	6 (3.0)	0
Infusion reaction	10 (2.5)	1 (0.2)	2 (1.0)	0
Colitis ★	9 (2.2)	3 (0.7)	0	0
Severe skin reaction	8 (2.0)	8 (2.0)	5 (2.5)	4 (2.0)
Nephritis ★	7 (1.7)	6 (1.5)	0	0
Hepatitis ★	5 (1.2)	4 (1.0)	0	0
Hypophysitis	3 (0.7)	0	0	0
Pancreatitis ★	3 (0.7)	2 (0.5)	0	0
Adrenal insufficiency	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)
Myositis	1 (0.2)	0	0	0
Thyroiditis	1 (0.2)	0	0	0
Type 1 diabetes mellitus	1 (0.2)	1 (0.2)	0	0

\* The events of interest are those with an immune-related cause and are considered regardless of attribution to a trial drug by the investigator. The events are listed in descending order of frequency in the pembrolizumab-combination group. In addition to the specific preferred terms that are listed, related terms were also included. The as-treated population included all the patients who had undergone randomization and received at least one dose of the assigned combination therapy.

## Combination chemo-checkpoint therapy for stage IV

8/16- 43yo man (EB) developed R  
neck/shoulder pain

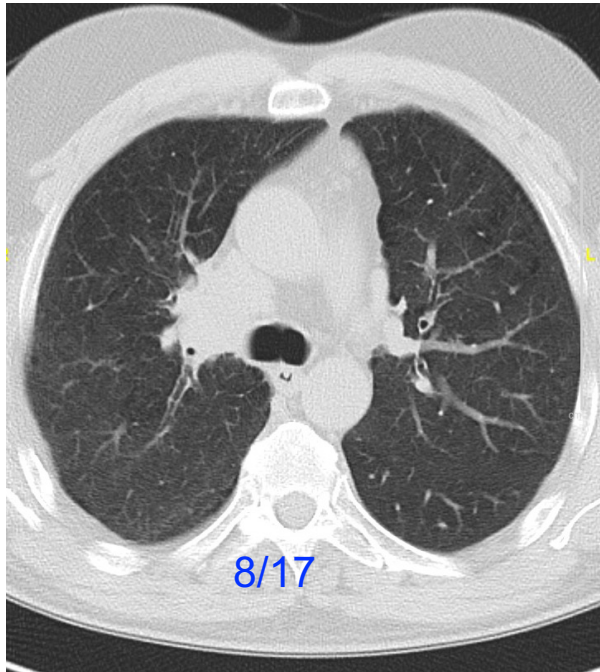
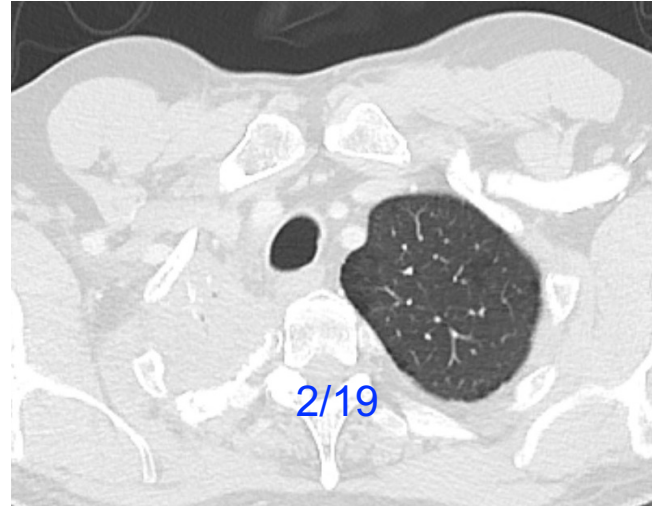
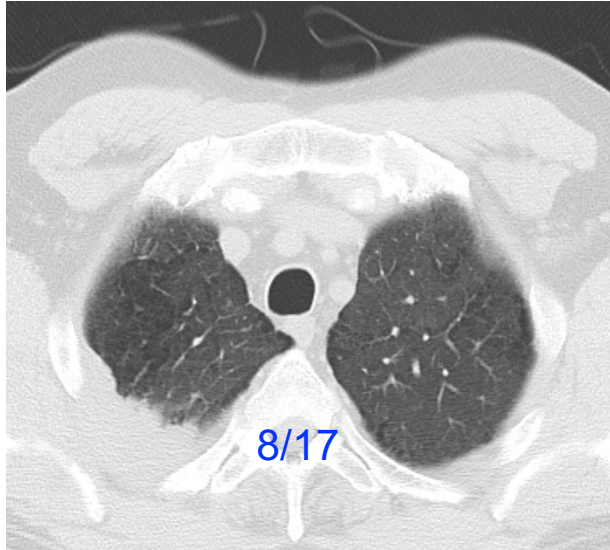
8/17- mass seen on CT/MRI  
involving R lung, CW, T3, R 3<sup>rd</sup> rib;  
bx adenocarcinoma; PD-L1 60%;  
PET-CT: R hilar mass; multiple  
bone, adrenal mets.

9/17 completed palliative RT to  
RUL/spine mass

9/17 started pemetrexed-  
carboplatin-pembrolizumab

F/U: CR by PET-CT, plain CT

9/19-present therapy completed,  
works full time, NED



## Immune checkpoint therapy in lung cancer

Who responds:

Uncertain.

Response correlates with:

tumor and immune cell infiltrate PD-L1 expression

tumor mutation burden (TMB) = number of new antigens that T cells might respond against

Why don't all patients respond:

'Cold' tumors without immune infiltrates.

TGF $\beta$ , IFN $\gamma$  signaling.

MHC downregulation, B2M mutations.

Tumor associated macrophages that prevent T cell activation

Some specific mutations seem to engender resistance, e.g. LKB1/STK11 mutations.

Low TMB

## Immune checkpoint therapy in lung cancer

### Toxicities:

None in 80%.

Rash, colitis, pneumonitis, thyroiditis (high or low TFTs).

Many others, can be life-threatening, but in aggregate rare.

## Combination immune checkpoint therapy in lung cancer

Ipilimumab-nivolumab is the standard combo, many others in development

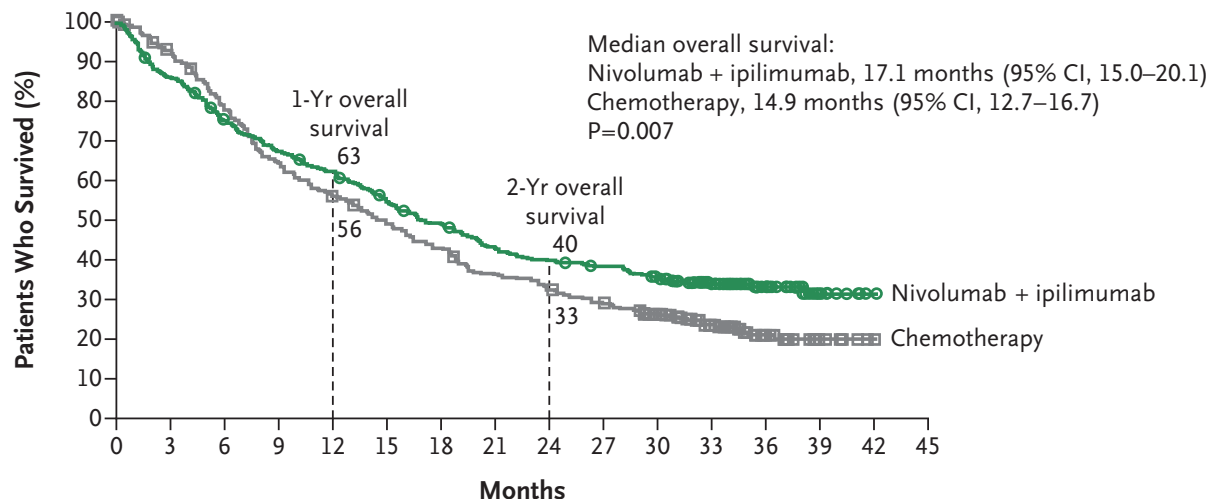
In general has a higher response rate than single agent (e.g. pembrolizumab or nivolumab)

Toxicity is increased in many ways, including: diarrhea/colitis, rash, pruritus, fatigue, N/V/anorexia.

Treatment-related serious (gr 3-4) adverse events seen in 33%

Treatment-related serious adverse events led to discontinuation in 20%

A Overall Survival in Patients with a PD-L1 Expression Level of 1% or More



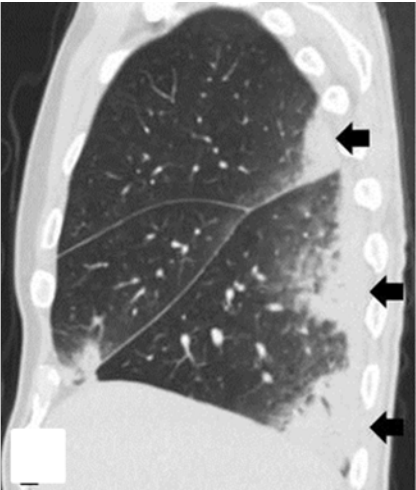
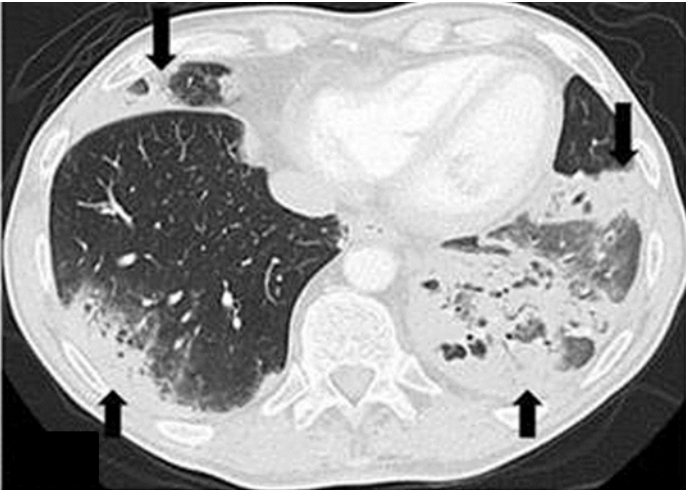
Hellman et al.  
*N Engl J Med* 2019

# PD-1 pneumonitis in advanced cancer patients

- Among 170 patients treated in 10 trials of nivolumab, 20 patients (10 melanoma, 6 lymphoma, 4 lung cancer) developed pneumonitis (Grade 1, n=5; 2, n=10; 3, n=5)
- Radiographic pattern was COP in 13, NSIP in 3, HP in 2, and AIP/ARDS in 2 patients
- COP pattern was most common in all tumors and treatment regimens
- AIP/ARDS pattern had the highest grade, followed by COP pattern, while NSIP pattern and HP pattern had lower grade (median Grade: 3, 2, 1, 1, respectively; p=0.006)
- Most patients (17/20; 85%) received corticosteroids, and 3 (15%) also required infliximab
- 7 patients restarted nivolumab therapy, and two of them developed recurrent pneumonitis and were successfully retreated with corticosteroids
- One of the patients experienced a pneumonitis flare after completion of corticosteroid taper without nivolumab retreatment

# PD-1 inhibitor-related pneumonitis: COP pattern

At 15 weeks of nivolumab monotherapy



4 weeks after starting prednisone



Mizuki Nishino  
Nishino M, et al. Cancer  
Immunol Res.  
2016;4:289-93.

PULMONARY ADVERSE EVENT(S)	GRADING	MANAGEMENT <sup>e</sup>
Pneumonitis <sup>a</sup> Asymptomatic Confined to one lobe, or < 25% lung parenchyma	Mild (G1) <sup>b</sup>	<ul style="list-style-type: none"> <li>• Consider holding immunotherapy<sup>f</sup></li> <li>• Reassess in 1–2 weeks                             <ul style="list-style-type: none"> <li>▶ H&amp;P</li> <li>▶ Pulse oximetry (resting and with ambulation)</li> </ul> </li> <li>• Consider chest CT with contrast<sup>g</sup> <ul style="list-style-type: none"> <li>▶ Consider repeat chest CT in 4–6 weeks or as clinically indicated if patient develops symptoms</li> </ul> </li> </ul>
	Moderate (G2) <sup>c</sup>	<ul style="list-style-type: none"> <li>• Hold immunotherapy<sup>f</sup></li> <li>• Consider pulmonary consultation</li> <li>• Minimally invasive evaluation                             <ul style="list-style-type: none"> <li>▶ Consider infectious workup:                                     <ul style="list-style-type: none"> <li>◊ Nasal swab for potential viral pathogens<sup>h</sup></li> <li>◊ Sputum culture (including bacterial, fungal, and acid-fast bacilli [AFB]), blood culture, and urine antigen test (pneumococcus, legionella)</li> </ul> </li> <li>▶ Consider chest CT with contrast<sup>g</sup> and repeat chest CT in 3–4 weeks</li> </ul> </li> <li>• Invasive evaluation                             <ul style="list-style-type: none"> <li>▶ Consider bronchoscopy with bronchoalveolar lavage (BAL) (send for institutional immunocompromised panel<sup>i</sup>) and consider transbronchial lung biopsy if clinically feasible</li> </ul> </li> <li>• Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded</li> <li>• Prednisone/methylprednisolone 1–2 mg/kg/day<sup>j</sup></li> <li>• Monitor every 3–7 days with:<sup>k</sup> <ul style="list-style-type: none"> <li>▶ H&amp;P</li> <li>▶ Pulse oximetry (resting and with ambulation)</li> </ul> </li> <li>• If no improvement after 48–72 hours of corticosteroids, treat as grade 3</li> </ul>
	Severe (G3–4) <sup>d</sup>	<a href="#">See ICI_PULM-2</a>

Presence of new/  
worsening symptoms

**ASSESSMENT/  
GRADING**

**MANAGEMENT<sup>e</sup>**

Severe (G3–4)<sup>d</sup>  
pneumonitis<sup>a</sup> →

- Permanently discontinue immunotherapy<sup>f</sup>
- Inpatient care
- Pulmonary and infectious disease consultation
- Minimally invasive evaluation
  - ▶ Infectious workup:
    - ◇ Consider that patient may be immunocompromised
      - ◇ Nasal swab for potential viral pathogens<sup>h</sup>
      - ◇ Sputum culture (including bacterial, fungal, and AFB), blood culture, and urine antigen test (pneumococcus, legionella)
      - ◇ Consider cardiac evaluation to exclude cardiac causes for clinical presentation
- Invasive evaluation
  - ▶ Bronchoscopy with BAL (send for institutional immunocompromised panel<sup>i</sup>) if feasible to rule out infection and malignant lung infiltration and consider transbronchial lung biopsy if feasible and clinically indicated
- Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded
- Methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks<sup>e</sup>
- Consider adding any of the following if no improvement after 48 hours:<sup>l</sup>
  - ▶ Infliximab<sup>m</sup> 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider
  - ▶ IVIG<sup>n</sup>
  - ▶ Mycophenolate mofetil 1–1.5g BID then taper in consultation with pulmonary service

<sup>a</sup> Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging). Symptoms may include dry cough, shortness of breath, fever, chest pain, and increased oxygen requirement. The imaging features of pneumonitis are known to be variable and may include ground-glass opacities, organizing pneumonia, hypersensitivity, reticulonodular changes, or a mixture of all these appearances.

<sup>d</sup> G3-severe symptoms involve all lung lobes or >50% of lung parenchyma; limiting self-care ADLs, oxygen indicated; G4-life-threatening respiratory compromise.

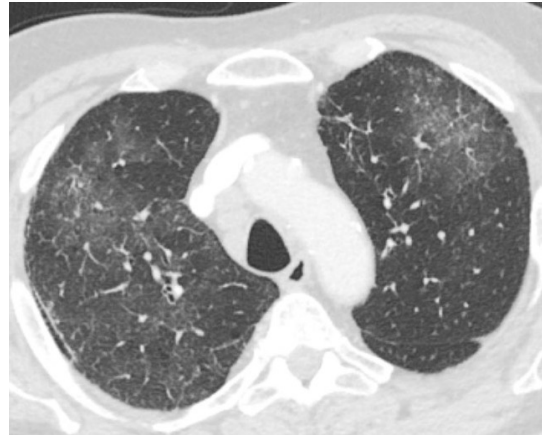
Board question:

A 66yo man had presented with chest pain 8 months ago, and was found to have a 2 cm left upper lobe nodule, mediastinal adenopathy, and 2 probable brain metastases. A retroperitoneal LN biopsy showed small cell lung carcinoma. He was treated with initial brain radiation therapy, followed by 4 cycles of etoposide-carboplatin-atézolizumab, and then 3 cycles of atézolizumab maintenance therapy. He returns in routine FU, and reports increased cough with some reddish phlegm, and mild variable increased dyspnea on exertion. He shows no obvious dyspnea or cough on exam, no rales, SpO<sub>2</sub> is stable at 97%, afebrile with no history of fever/chills. Chest CT scan at right:

Your treatment approach (**more than 1 answer may be correct**):

- A. Start Prednisone with planned taper
- B. Stop atézolizumab
- C. Stop atézolizumab and start prednisone
- D. Perform bronchoscopy with biopsy
- E. Perform nasal swab for COVID-19, test for other viral pathogens

date of visit



one month earlier



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