BRIGHAM AND WOMEN'S HOSPITAL

The Lung Center

HARVARD MEDICAL SCHOOL

TEACHING AFFILIATE

Lung Cancer: Current Treatment and Pulmonary Complications

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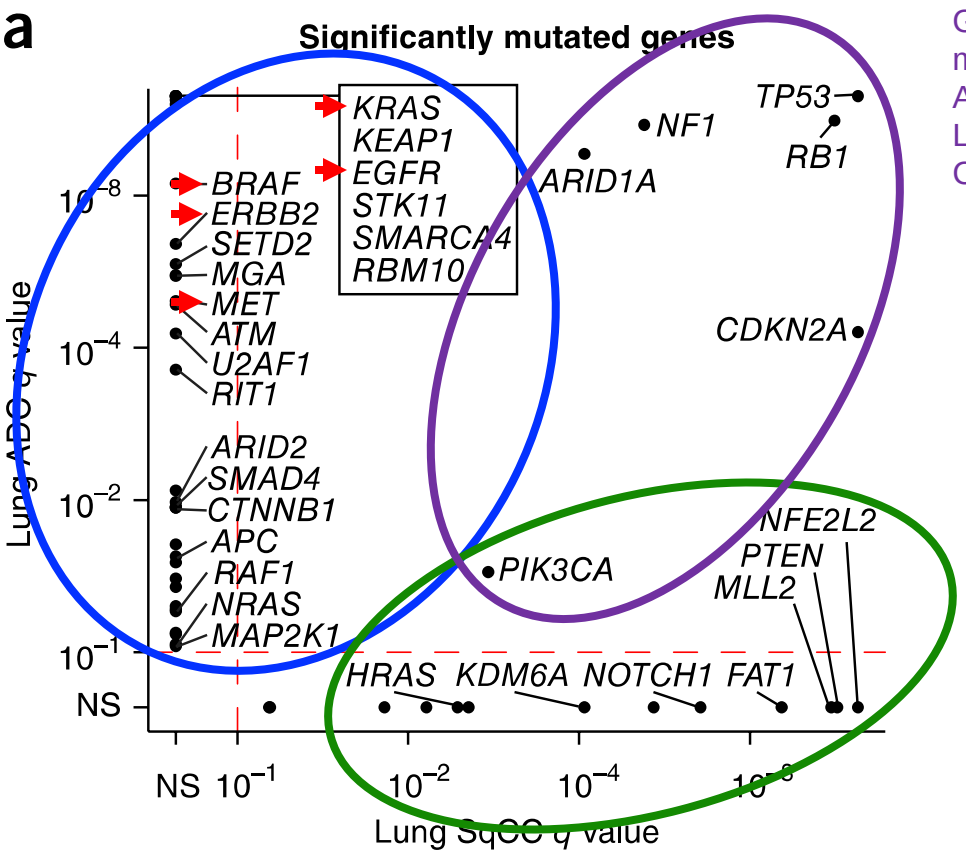
Consultant to AADI, Genentech, Guidepoint, Bridgebio

Research contract from Genentech, AADI

None of these has any impact on my presentation

Squamous cell lung cancer is a distinct entity from adenocarcinoma of the lung, so that the term non-small cell lung cancer should not be used whenever histologic subtype information is available.

TCGA data illustrate this point quite nicely.



Genes commonly mutated in Lung Adenocarcinoma only

Genes commonly mutated in both Lung Adenocarcinoma and Lung Squamous Cell Carcinoma

Genes commonly mutated in Lung Squamous Cell Carcinoma only

→ indicates a gene with a targeted therapy Only in lung adenocarcinoma

Campbell et al., Nature Genetics 2016

Treatment for non-small cell lung cancer (both adeno, squamous)

Early stage disease – Stages I – IIIC (no distant metastases)

Pre-treatment evaluation:

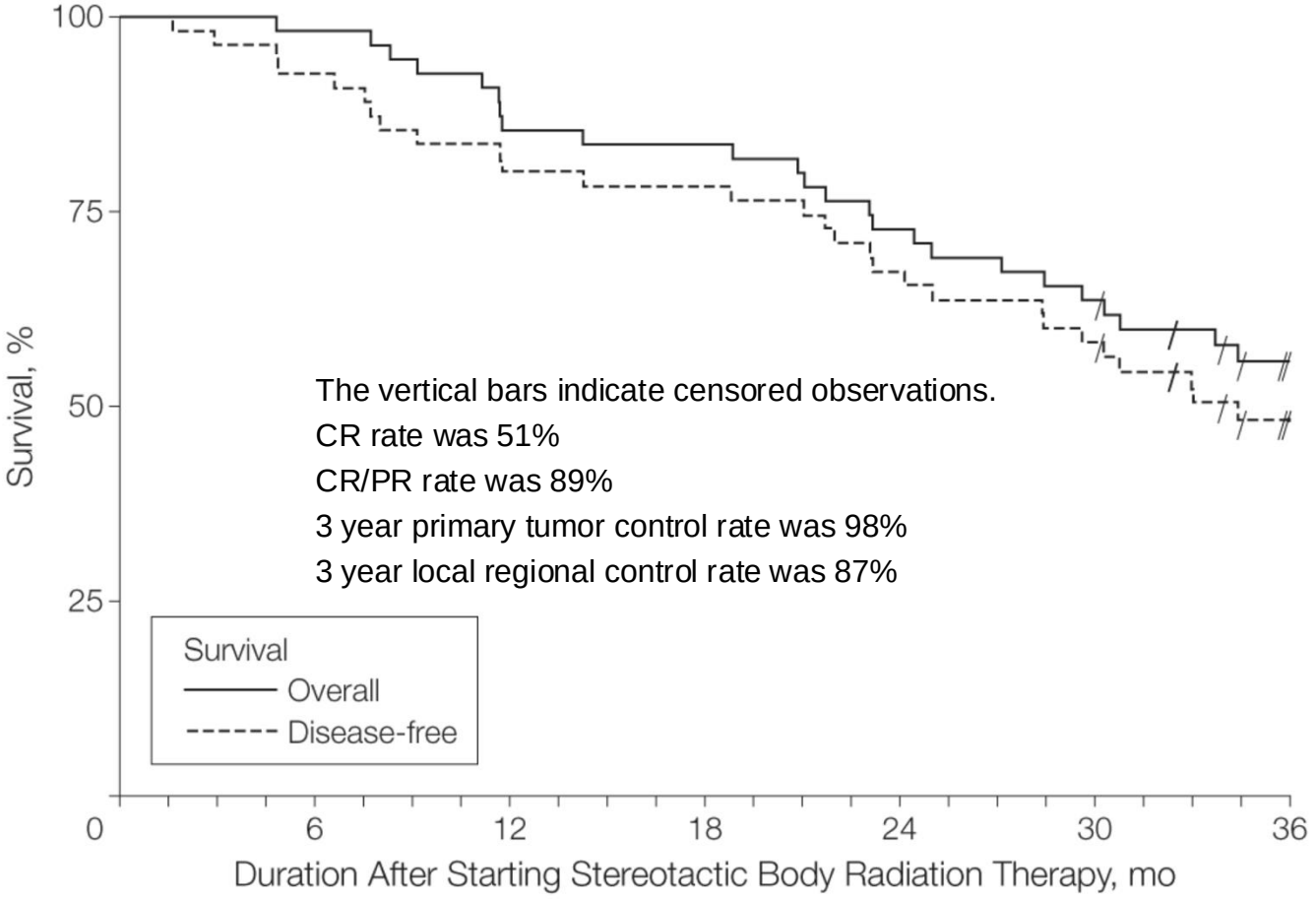
- PFTs
- bronchoscopy
- pathologic mediastinal LN evaluation- EBUS or mediastinoscopy
- FDG PET/CT scan
- Brain MRI

Stage I (T1a – T2b)
(T<4cm, no LNs+)
Surgery alone
Pathology review

Stage IIA –IIIA
(T≥4cm or LN+)
Initial chemo-IO
Surgery
Pathology review

Stage IIIA-IIIC
(T>5cm or invasive,
or LN+ in med/SC)
Initial chemo-IO or chemo-RT ->
surgery; OR Chemo-RT->IO

Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer



No. at risk

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.

JAMA. 2010;303(11):1070-1076

Stage I (T1a – T2b)
(T<4cm, no LNs+)
Surgery alone
Pathology review

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 +- atezolizumab

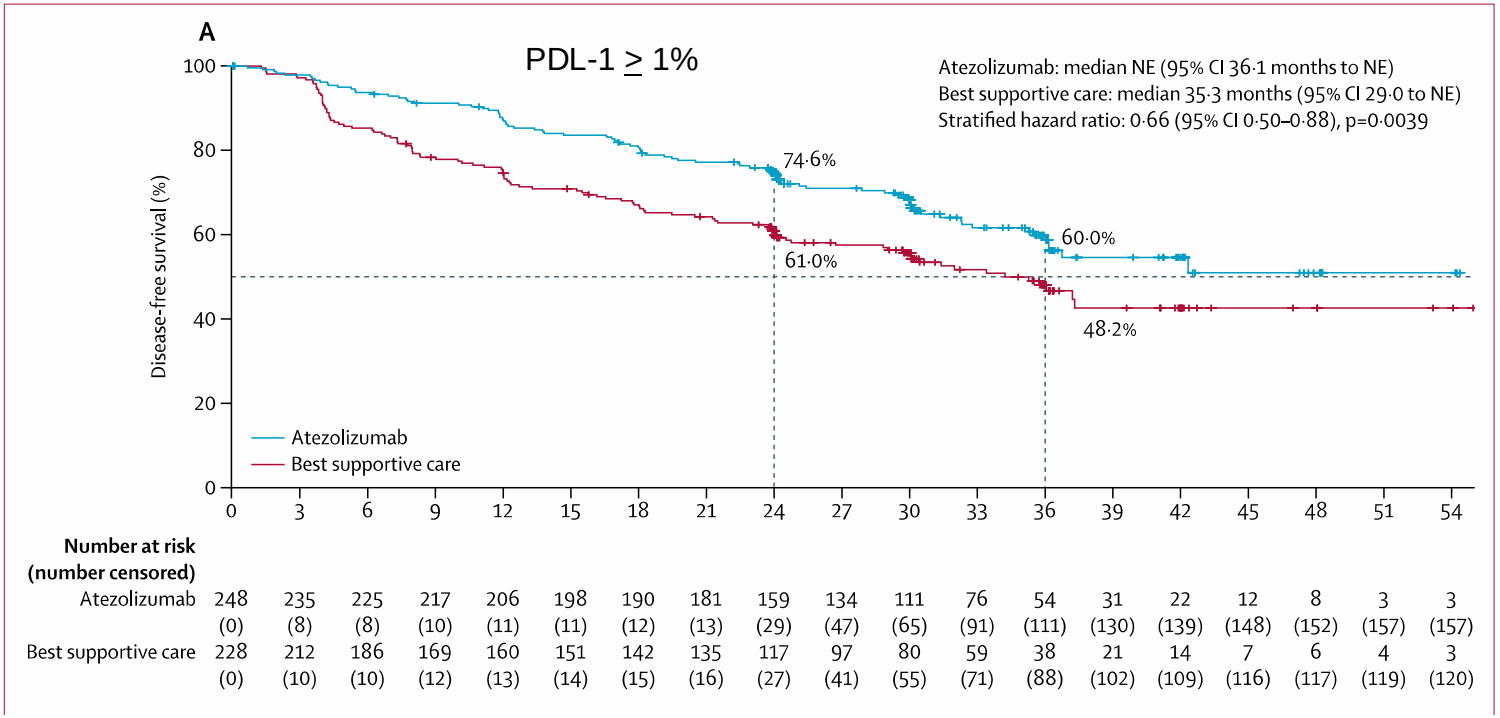
Stage IIIA, IIIB - post-op adjuvant chemotherapy +- atezolizumab
If not a complete resection, then chemoradiotherapy f/by durvalumab

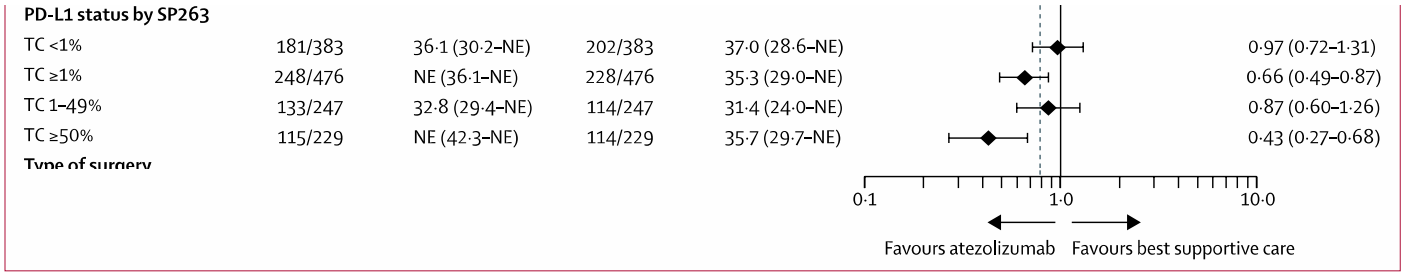
Post-operative adjuvant chemotherapy – benefit is modest – 5-8% improvement in 5 year survival, so always a discussion with the patient.

Adjuvant atezolizumab following adjuvant chemotherapy –

Stage II-IIIA: improvement of ~13% in DFS and ~6% in OS at 3-4 yr FU for those with PD-L1 > 1%

Post-op atezolizumab as adjuvant therapy





IMpower010 – Felip et al. Lancet 2021

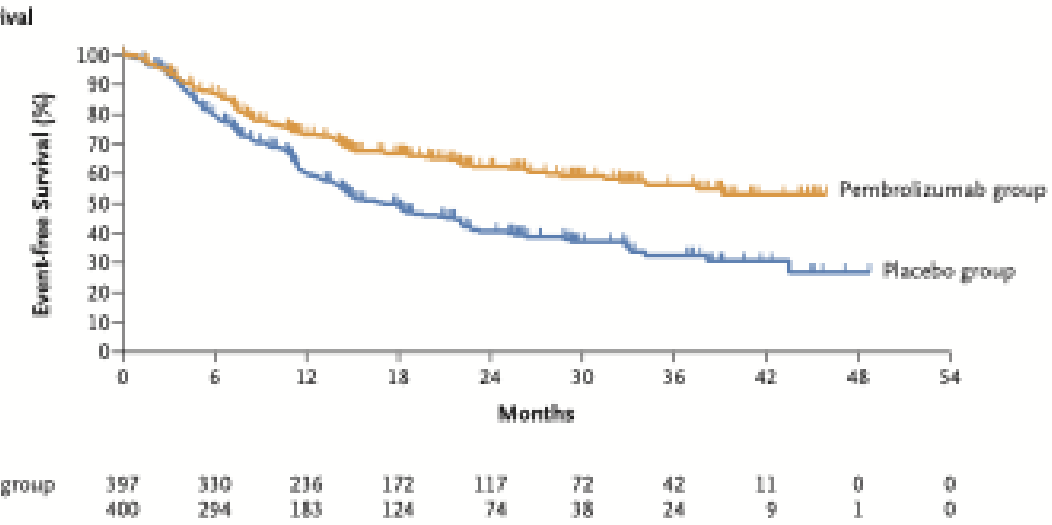
Randomized trial of atezolizumab for 1 year vs. nothing in patients with Stage IB – IIIA NSCLC after surgical resection and adjuvant chemo (1-4 cycles)

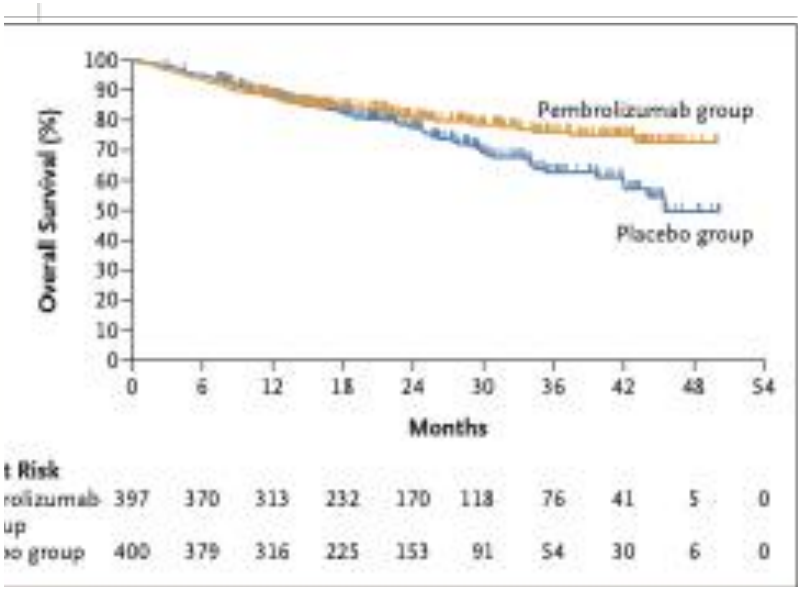
Stage IIA –IIIA
(T≥4cm or LN+)
Initial chemo-IO Surgery
Pathology review

ESTABLISHED IN 1812 AUGUST 10, 2023 VOL. 389 NO. 6

Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer

H. Wakelee, M. Liberman, T. Kato, M. Tsuboi, S.-H. Lee, S. Gao, K.-N. Chen, C. Dooms, M. Majem, E. Eigendorff, G.L. Martinengo, O. Bylicki, D. Rodríguez-Abreu, J.E. Chaft, S. Novello, J. Yang, S.M. Keller, A. Samkari, and J.D. Spicer, for the KEYNOTE-671 Investigators*





RCT
797 Stage II, IIA, IIIB NSCLC patients enrolled
Perioperative therapy
Cisplatin-based chemotherapy +- pembrolizumab x 4 cycles pre-op
Post-op 1 year of +- pembrolizumab
Major pathologic response 30% v 11% in pembro v control
Pathologic complete response 18% v 4% in pembro v control
Treatment related adverse events 45% v 37% in pembro v control
Treatment related deaths 1.0% v 0.8% in pembro v control

Similar results in other trials with nivolumab and durvalumab

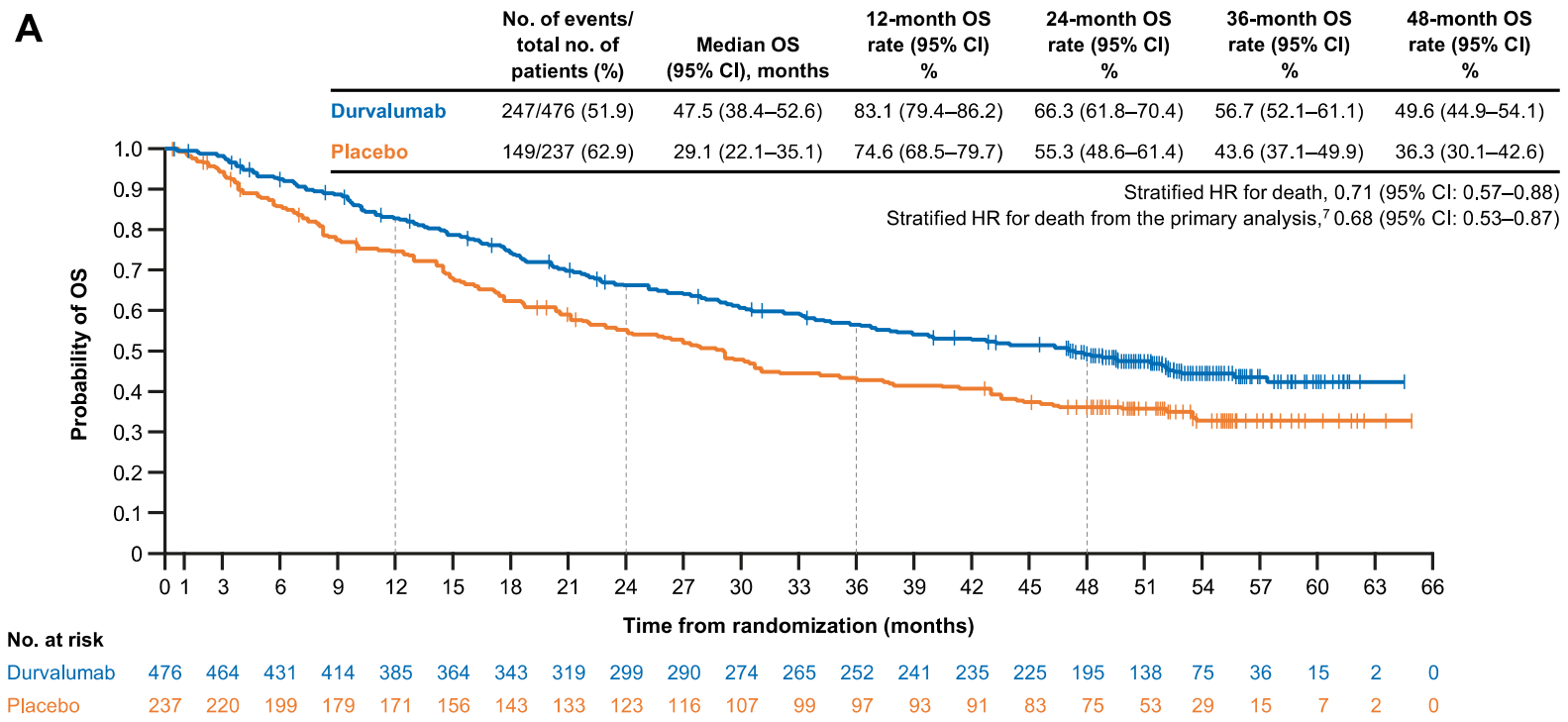
Stage IIIA-IIIC
(T>5cm or invasive,
or LN+ in med/SC
Initial chemo-IO or chemo-RT ->
surgery, OR Chemo-RT->IO

If possibly resectable – preoperative chemo-immunotherapy or chemotherapy-concurrent radiation therapy

-> surgical re-evaluation and resection if possible

If not resectable (or patient preference), chemotherapy-RT f/by 1 year durvalumab (if PD-L1 > 0)

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.

Antonia SJ et al. N Engl J Med 2018
Faivre-Finn et al. JTO 2021

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:

1st 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**:

1st line:

Paclitaxel(taxol)/carboplatin + pembrolizumab

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

many other regimens are used – agents include:

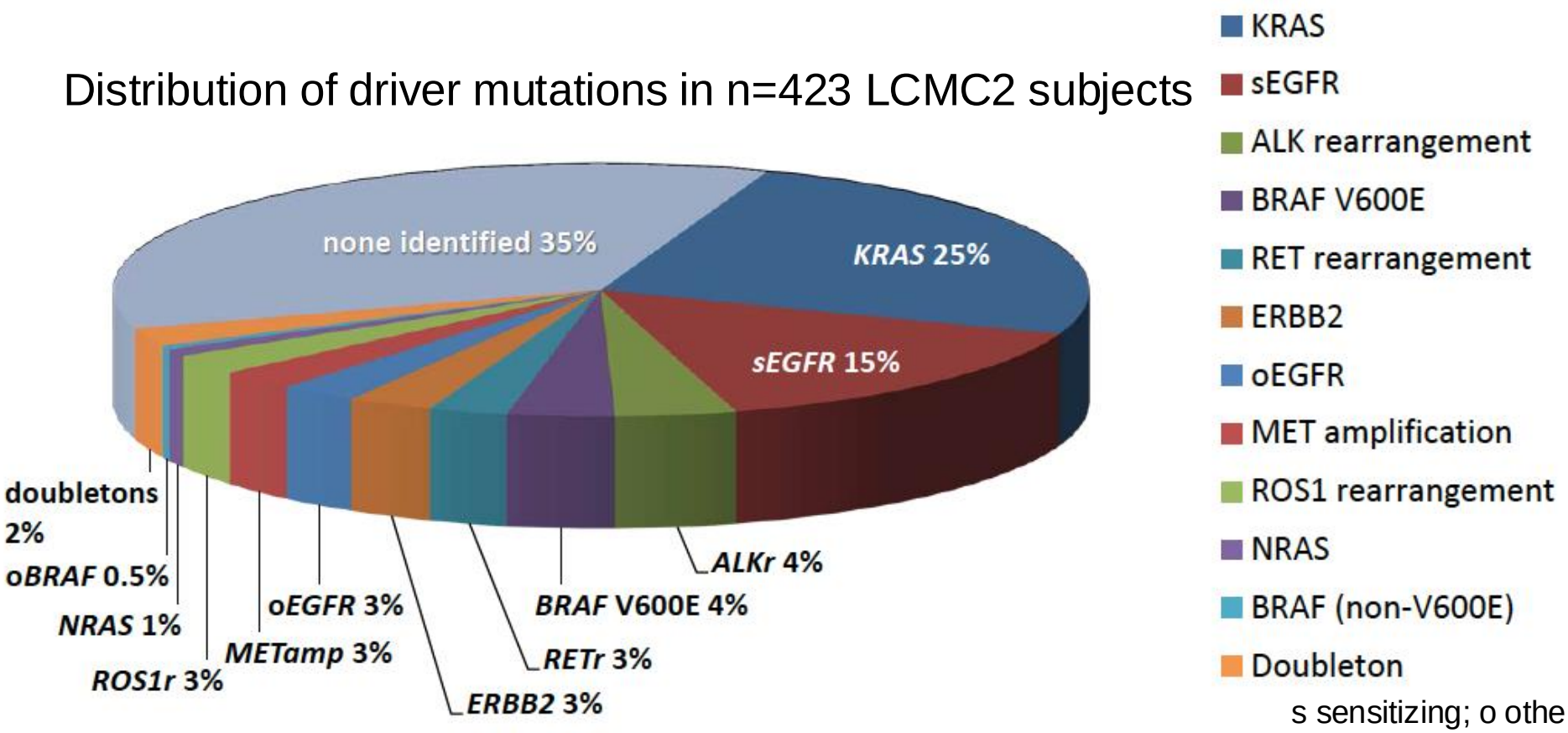
cisplatin, etoposide, gemcitabine, vinorelbine, albumin-bound paclitaxel

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 20 years, and for several mutations are well-established.

Distribution of driver mutations in n=423 LCMC2 subjects



s sensitizing; o other

Aisner, …, Kwiatkowski. Clin Cancer Res 2018

Mutation frequency as a function of smoking exposure

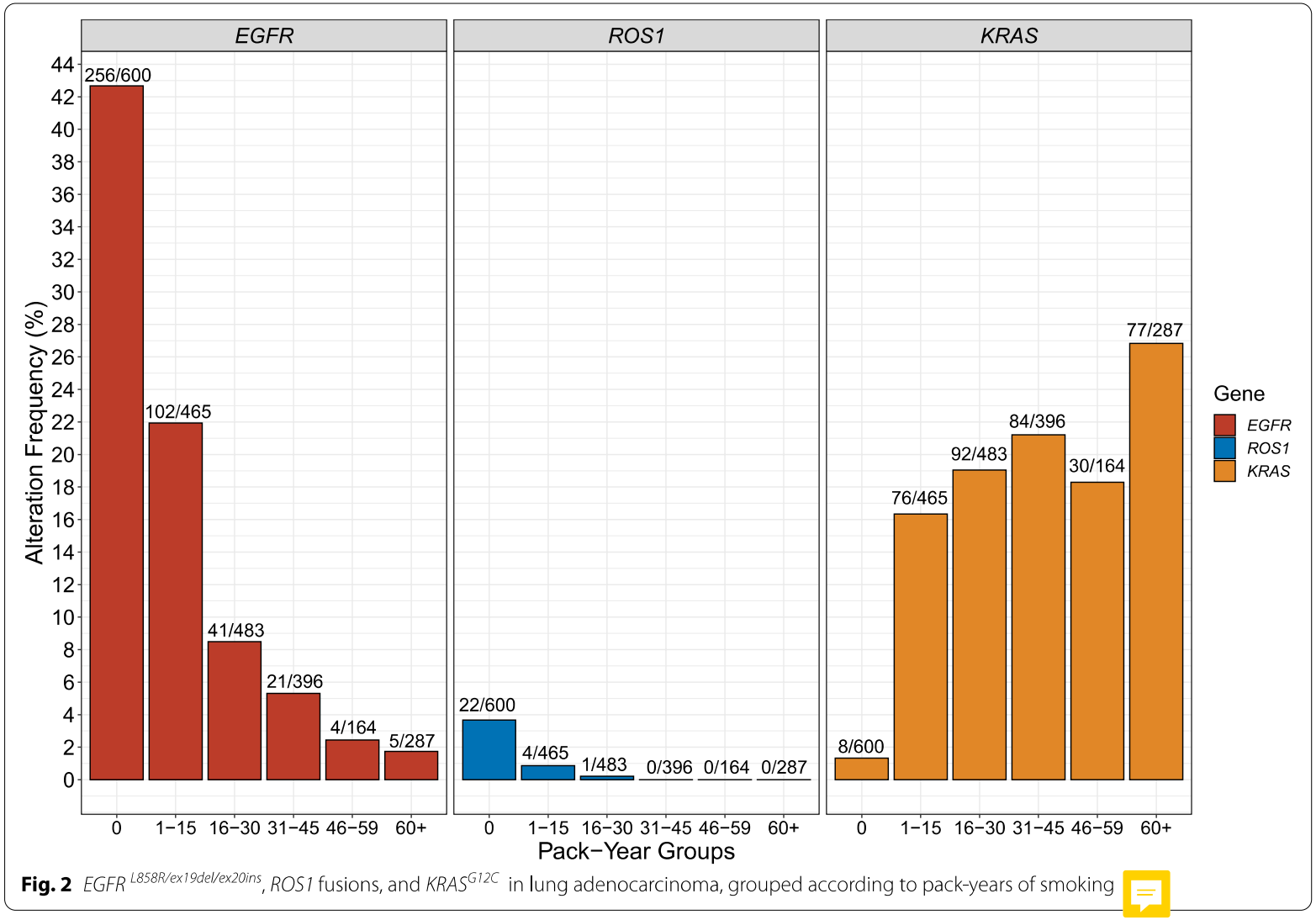


Fig. 2 *EGFR* $^{L858R/ex19del/ex20ins}$, *ROS1* fusions, and *KRAS* ^{G12C} in lung adenocarcinoma, grouped according to pack-years of smoking

Adib, …, Kwiatkowski. Genome Medicine 2022

Mutation frequency as a function of ancestry at DFCI

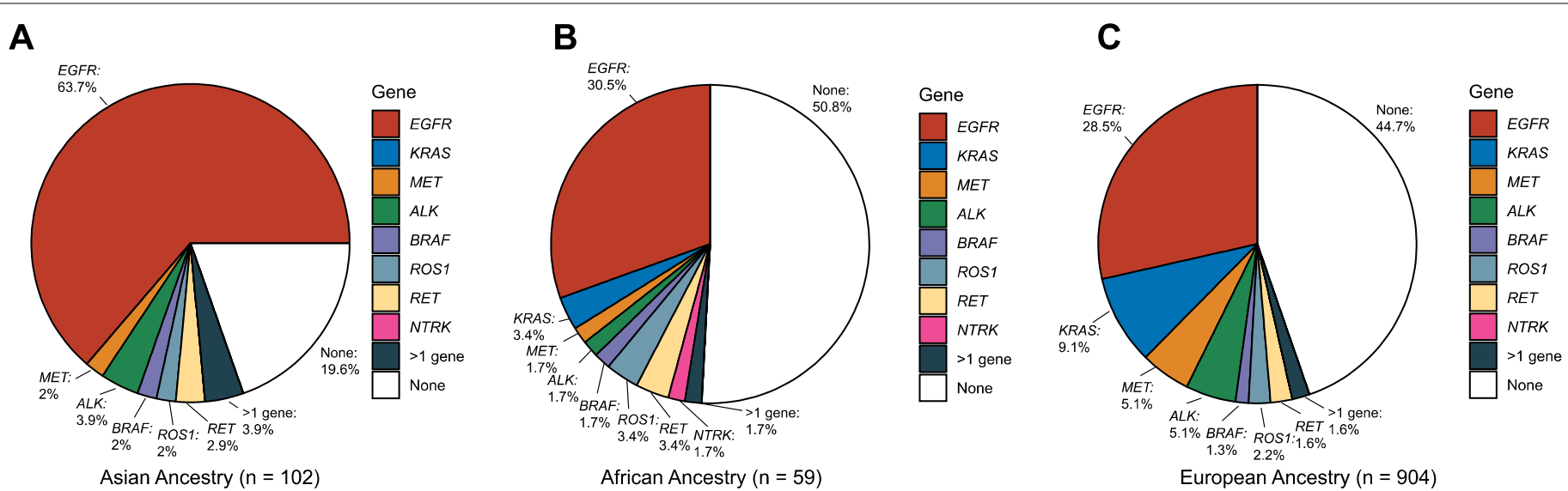


Fig. 4 Distribution of targetable alterations by inferred ancestral groups among light smokers (≤15 pack-year smoking history) with LUAD

Adib, …, Kwiatkowski. Genome Medicine 2022

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 had been osimertinib - 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:

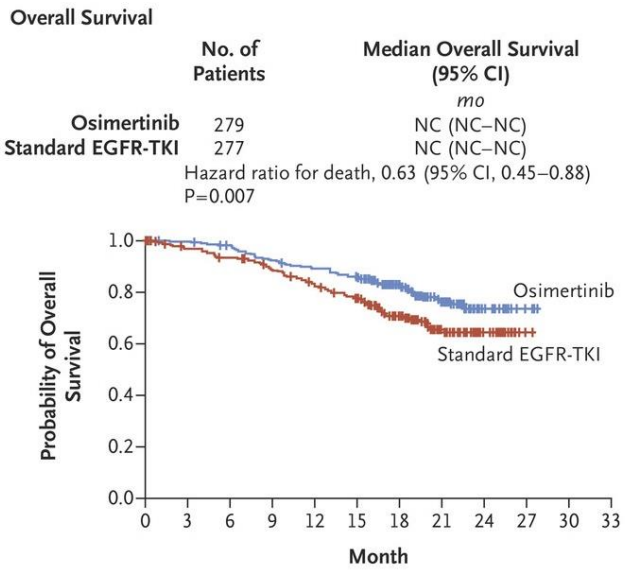
Repeat biopsy or plasma genotyping to ascertain cause of resistance, and guide therapy

Local therapy to sites of disease progression (surgery, radiation)

Clinical trials, based on genetic/tissue findings

Switch to or add chemotherapy

Soria et a. 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

Piper-Vallillo et al., JCO 2020

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)
EGFR T790M	3.5%	✓ Osimertinib ✗ Afatinib, Dacomitinib, Erlotinib, Gefitinib, Neratinib	Yes
EGFR L858R	8.5%	✓ Osimertinib	Yes
EGFR L792P	1.1%	~ Osimertinib	Yes
BRAF V600E	1.4%	✓ Dabrafenib, Trametinib ~ Binimetinib, Cobimetinib, Encorafenib, Vemurafenib	Yes
CTNNB1 S37C	0.4%	~ Celecoxib	Yes

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

Genetic mutations in lung cancer that are targetable:

Gene	Mutation	Therapy
EGFR	E19del, L858R	*Osimertinib, + chemo; amivantamab -lazertinib
EGFR	S768I, L861Q, G719X	*afatinib, osimertinib
EGFR	E20ins	*amivantamab + chemo
KRAS	G12C	sotorasib, adagrasib
	others	investigational
ALK	rearrangement	*alectinib, brigatinib, lorlatinib
ROS1	rearrangement	*entrectinib, crizotinib, repotrectinib
BRAF	V600E	*dabrafenib + trametinib
NTRK1/2/3	rearrangement	*larotrectinib, entrectinib, repotrectinib
MET	exon 14 splice	*capmatinib, tepotinib
MET	amplification (>10x)	capmatinib, tepotinib, crizotinib
RET	rearrangement	*selpercatinib, pralsetinib
ERBB2(HER2)	multiple point mutations	fam-trastuzumab deruxtecan-nxki, ado-trastuzumab emtansine

*drugs shown are indicated as first-line treatment

To achieve full molecular testing for all of these requires substantial tissue – a larger biopsy is better whenever possible to enable comprehensive testing

The NEW ENGLAND JOURNAL of MEDICINE

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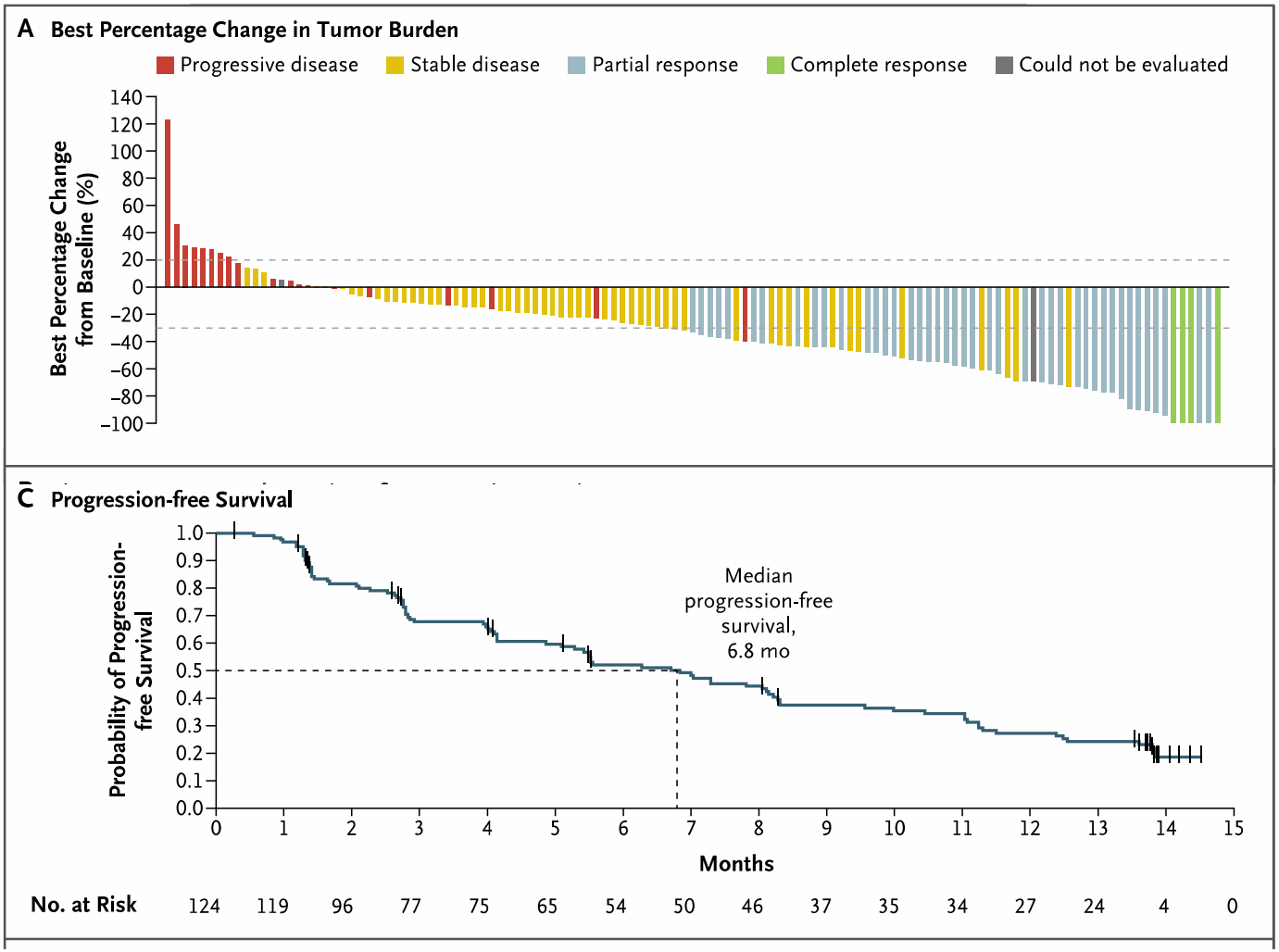
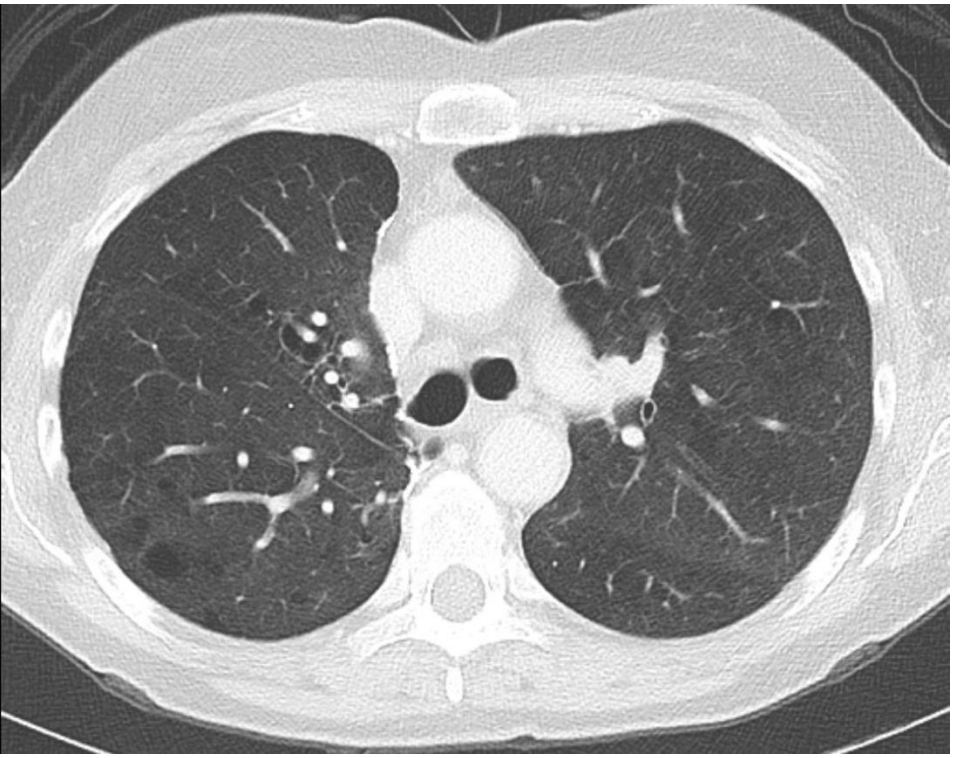
Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan

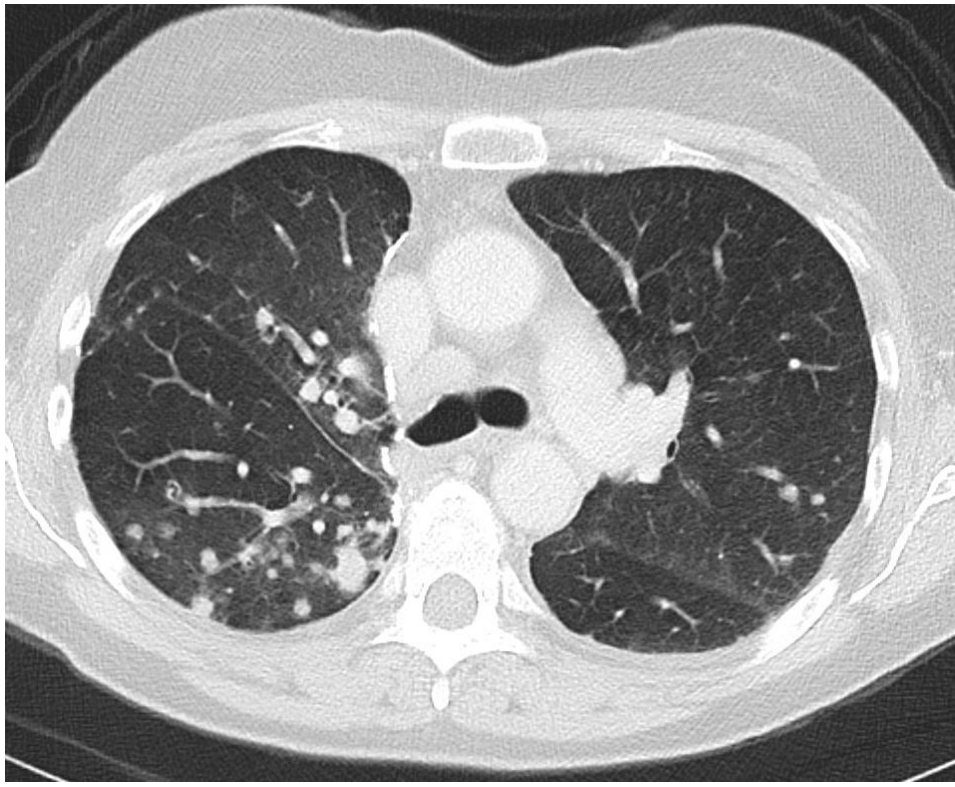


New agents for KRAS G12C mutant Non–Small-Cell Lung Cancer

KRAS G12C accounts for ~45% of the KRAS mutations seen in ~30% of lung adenocarcinoma



9/2022



8/2019

63 yo woman with KRAS G12C mutant lung adenocarcinoma
Treated with Adagrasib 9/4/19 onward, stopped for a week due to intolerable fatigue, then restarted and well-tolerated, worked full time then retired
Now 5 years on drug. One nodule grew, was resected. Doing well.
Sotorasib has similar efficacy in ongoing clinical trials, both FDA-approved.

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 push the immune system to attack a cancer.

Immune checkpoint inhibitors for lung cancer

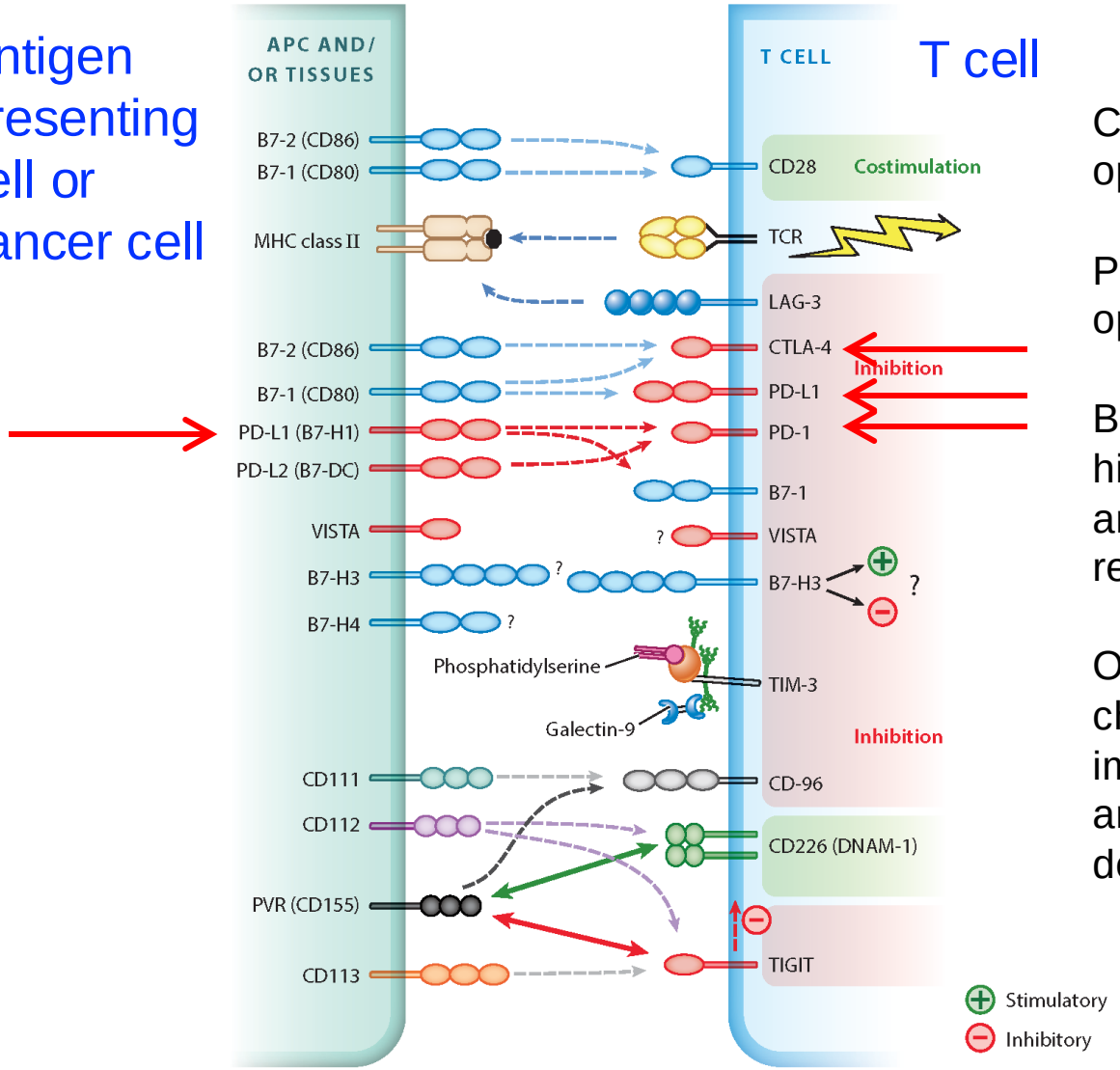
CTLA-4 inhibitors
- ipilimumab (+ nivolumab for NSCLC)
- tremelimumab

PD-1 inhibitors
- nivolumab (FDA-approved)
- pembrolizumab (FDA-approved)
- cemiplimab-rwlc (FDA-approved)

PD-L1 inhibitors
- atezolizumab (FDA-approved)
- durvalumab (FDA-approved)

Multiple coinhibitory pathways regulate T cells

Antigen presenting cell or cancer cell



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

Baumeister et al. Annu. Rev. Immunol. 2016

Response and toxicity to immunotherapy

1/16 – 70yo man (VB) presented with cough; L perihilar mass; 4L LN bx: squamous CC

Rx: concurrent chemo-radiation

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

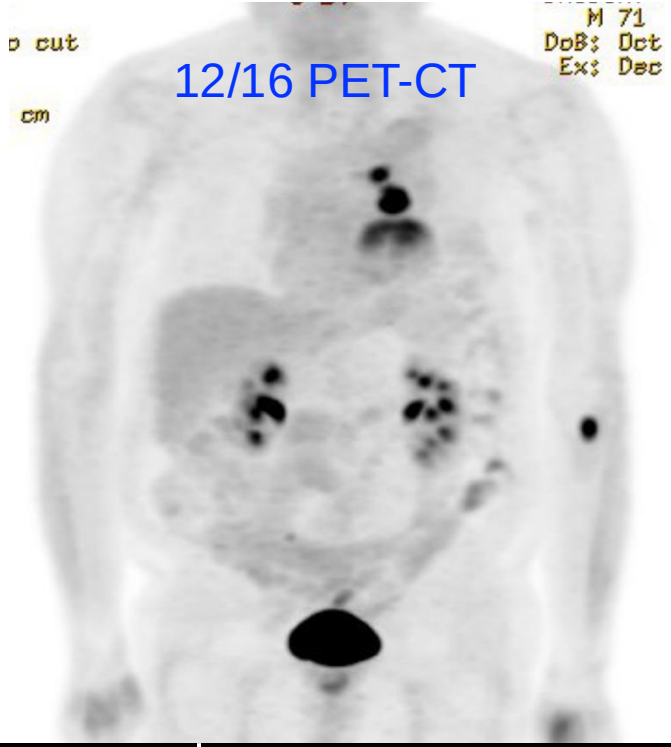
2/17 – 1/18: pembrolizumab w response

12/17: developed Sweet's syndrome - neutrophilic dermatosis; stopped therapy

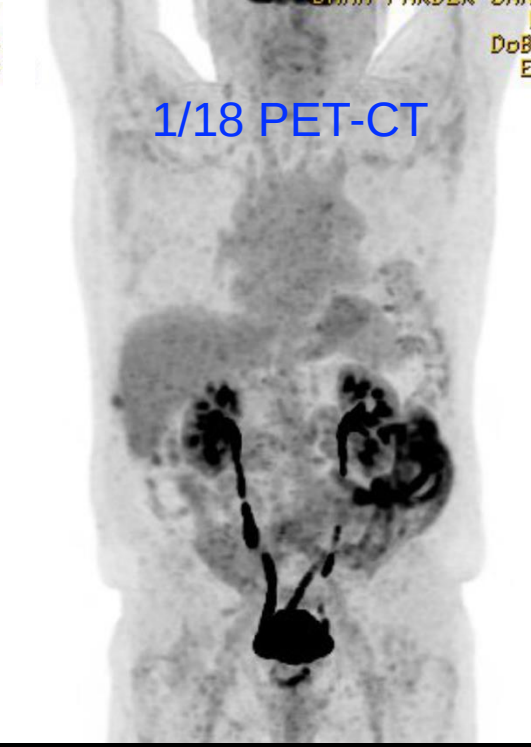
1/18 – 4/21: off treatment

4/21: recurrent disease in same site

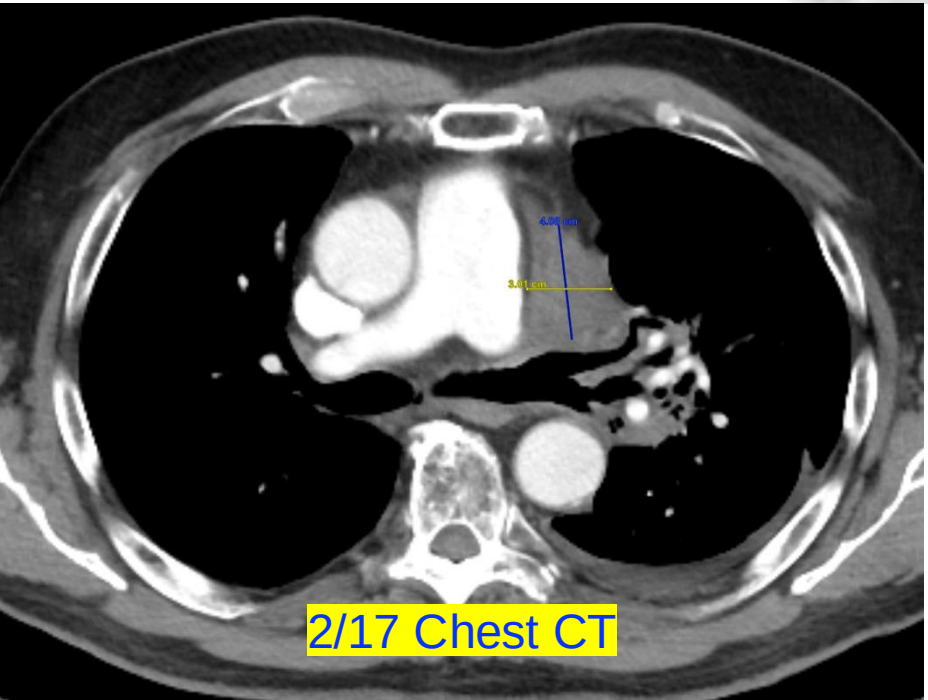
5/21 – 6/22: pembrolizumab



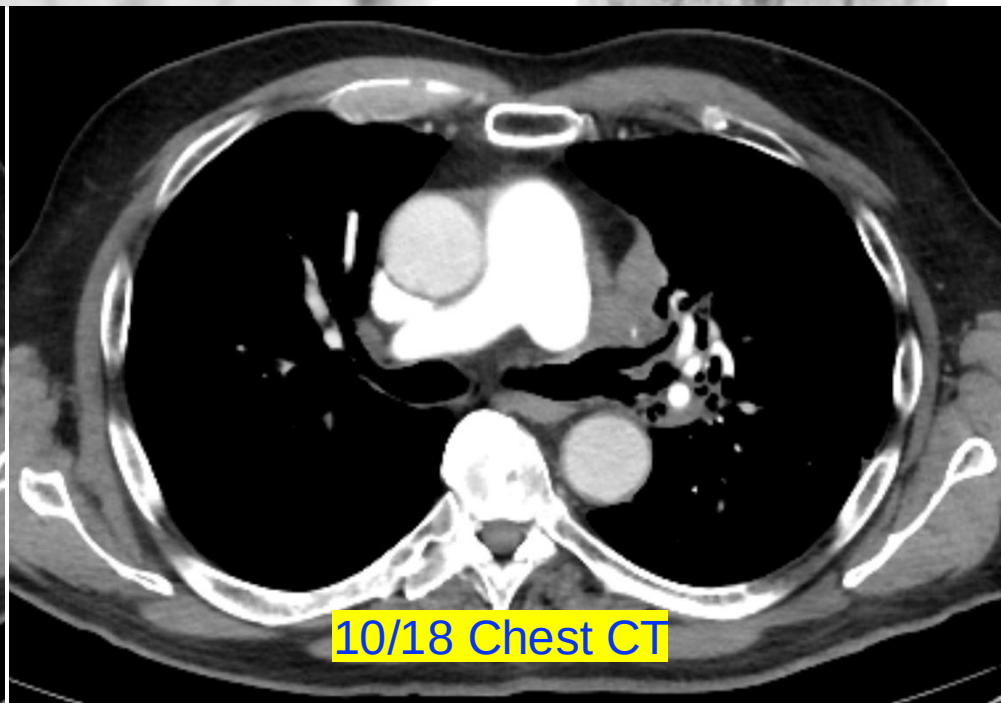
12/16 PET-CT



1/18 PET-CT



2/17 Chest CT



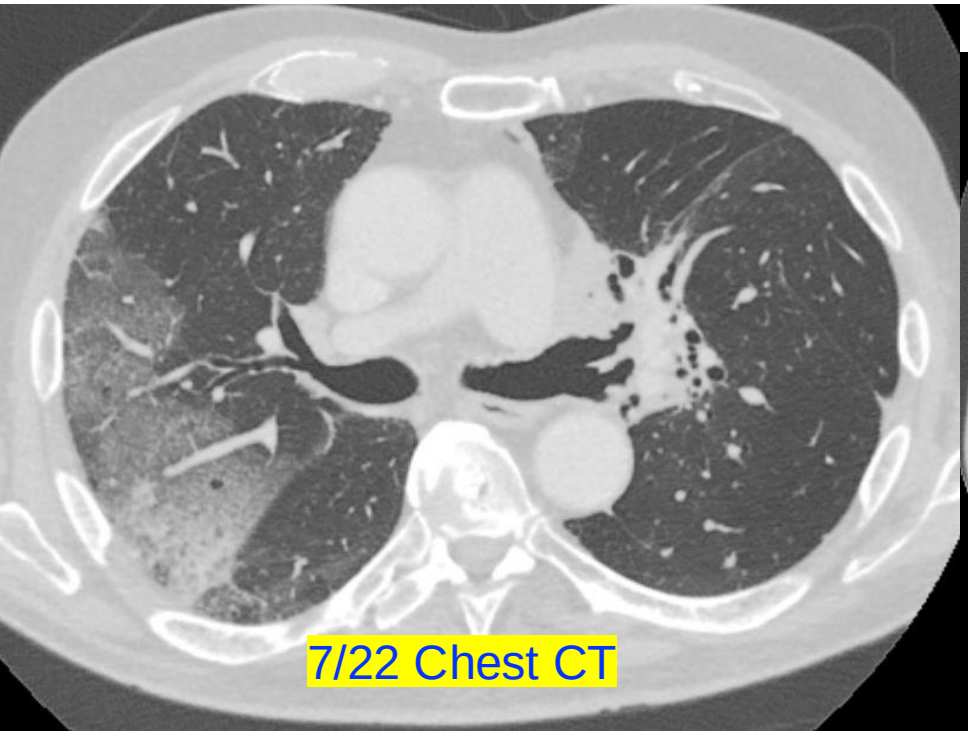
10/18 Chest CT

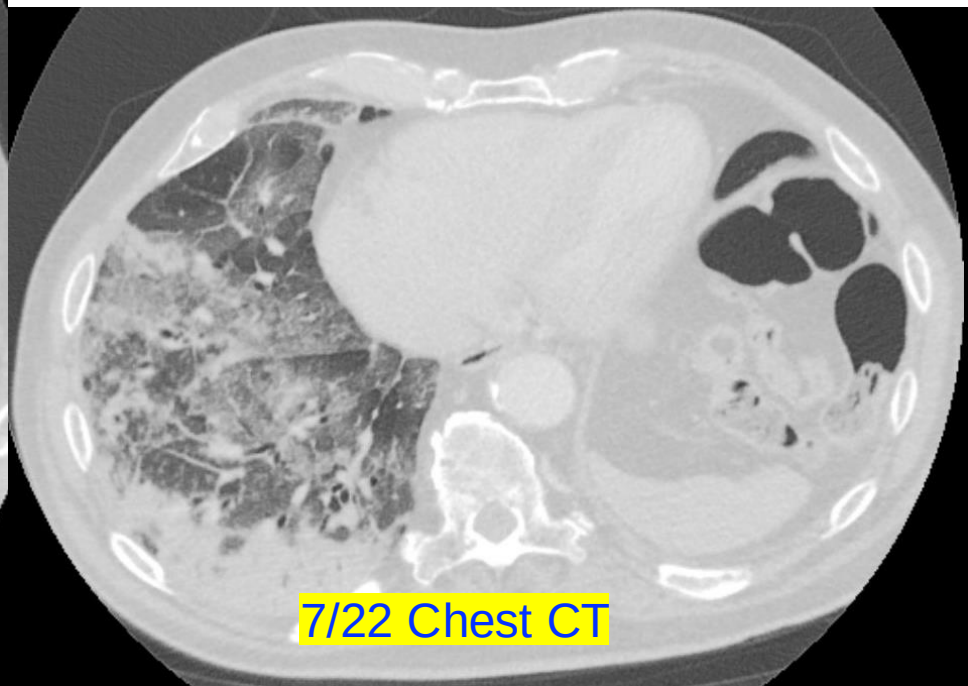
Response to immune therapy (continued)

4/21: now 75yo - recurrent disease in same site; biopsy squamous cell CA
5/21->: on pembrolizumab with response (again)
7/22: developed marked dyspnea, hypoxemia, could not walk
Chest CT: pneumonitis

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

A. Admit, start supplemental oxygen, monitor
B. Hold pembrolizumab for a cycle
C. Stop pembrolizumab and start prednisone
D. Stop pembrolizumab and start prednisone and infliximab
E. Perform bronchoscopy with biopsy
F. Perform nasal swab for COVID-19, other pathogens





Response to immune therapy (continued)

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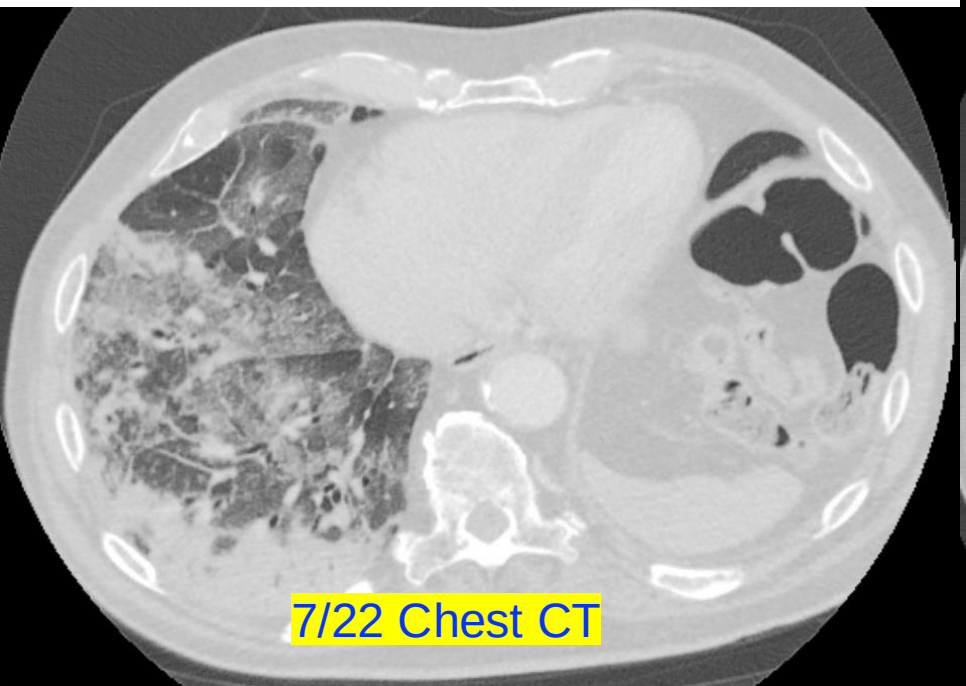
Your treatment approach (**more than 1 answer may be correct**):

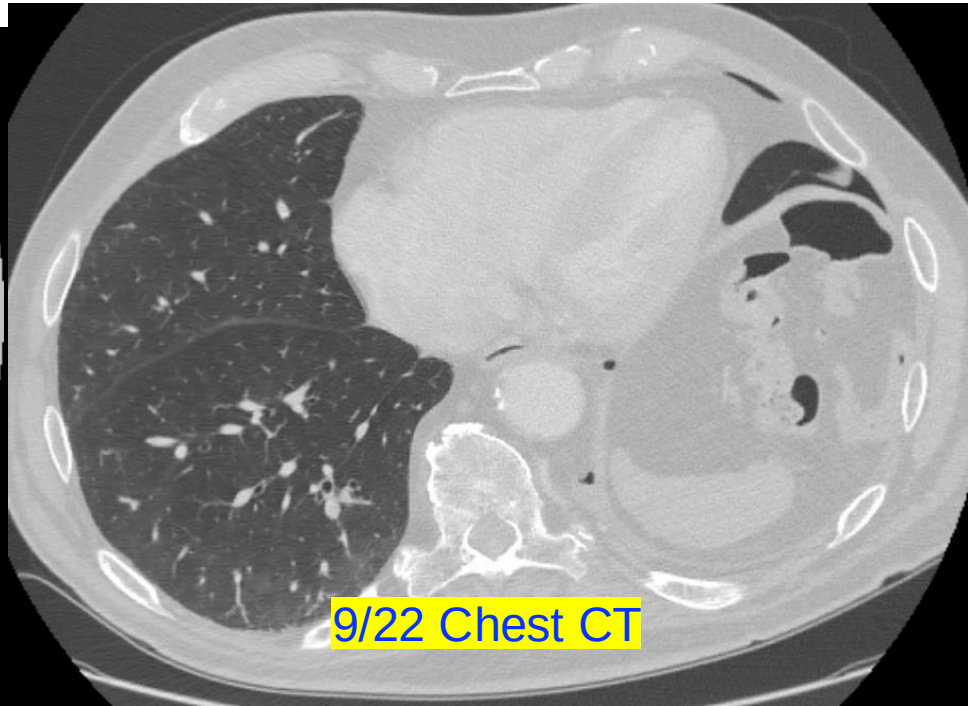
A. Admit, start supplemental oxygen, monitor

C. Stop pembrolizumab and start prednisone

F. Perform nasal swab for COVID-19, other pathogens

FU
Stopped pembro; started prednisone
9/22: steroid taper near complete, breathing near normal, off suppl O2; SpO2 98%; scan improved.
10/22: recurrence of pneumonitis, restart steroids
3/23: saw pulmonary med MD: start mycophenolate
8/23: off steroid, no recurrence of cancer or pneumonitis
8/24: no recurrence of cancer or pneumonitis





Platinum/Pemetrexed +/- Pembrolizumab

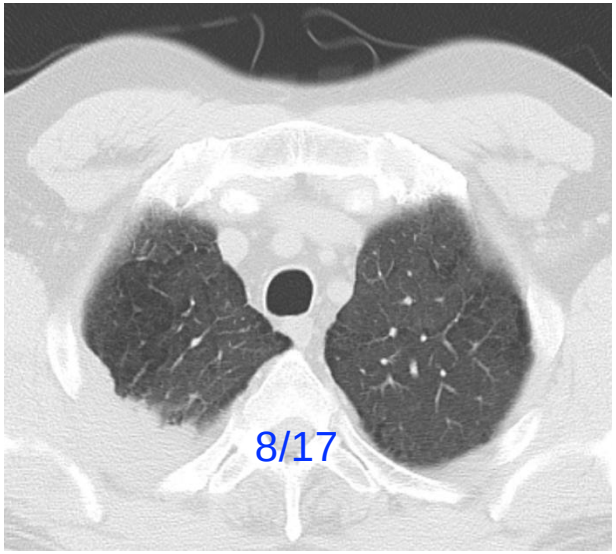
Table 3. Adverse Events of Interest in the As-Treated Population.*

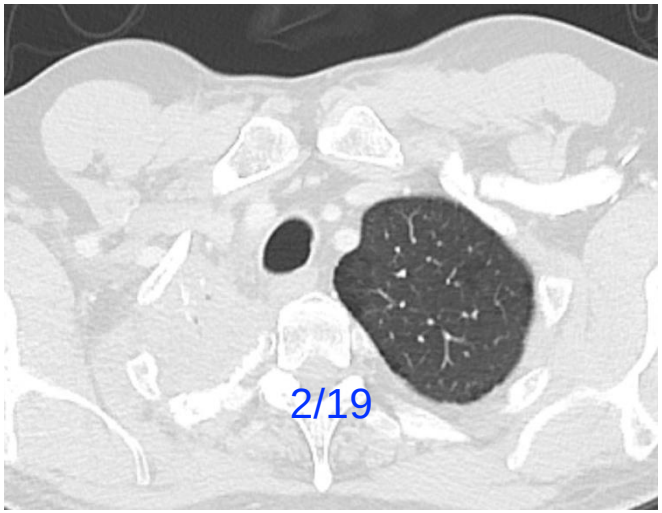
Event	Pembrolizumab Combination (N = 405)		Placebo Combination (N = 202)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any	92 (22.7)	36 (8.9)	24 (11.9)	9 (4.5)
Hypothyroidism	27 (6.7)	2 (0.5)	5 (2.5)	0
Pneumonitis	18 (4.4)	11 (2.7)	5 (2.5)	4 (2.0)
Hyperthyroidism	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

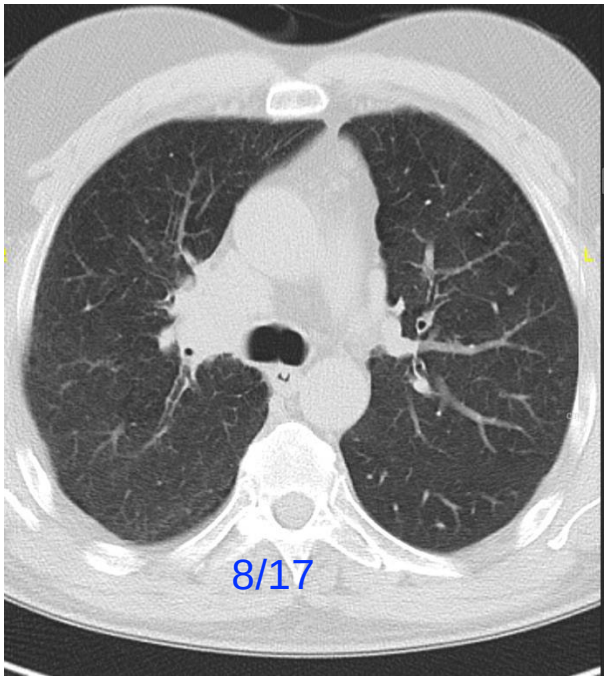
* The events of interest are those with an immune-related cause and are considered regardless of attribution to a trial drug by the investigator. The events are listed in descending order of frequency in the pembrolizumab-combination group. In addition to the specific preferred terms that are listed, 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.

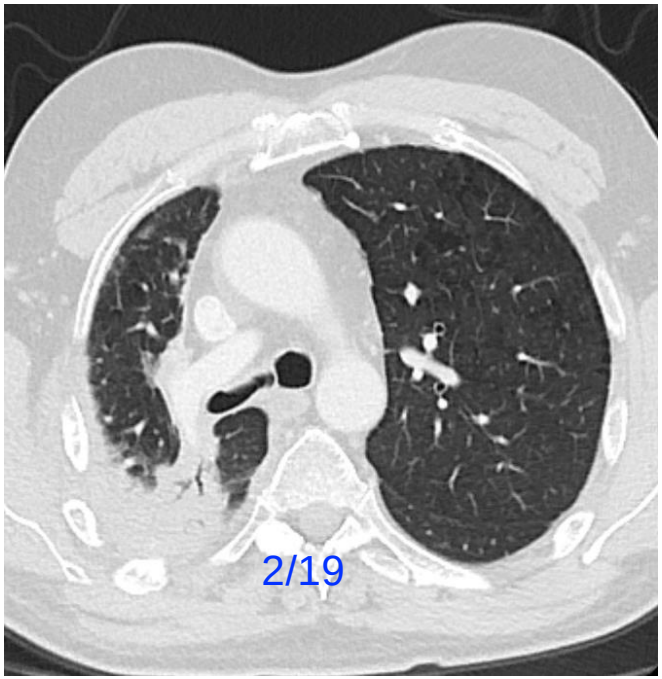
L Gandhi et al. *N Engl J Med* 2018. DOI: 10.1056/NEJMoa1801005

Combination chemo-checkpoint therapy for stage IV





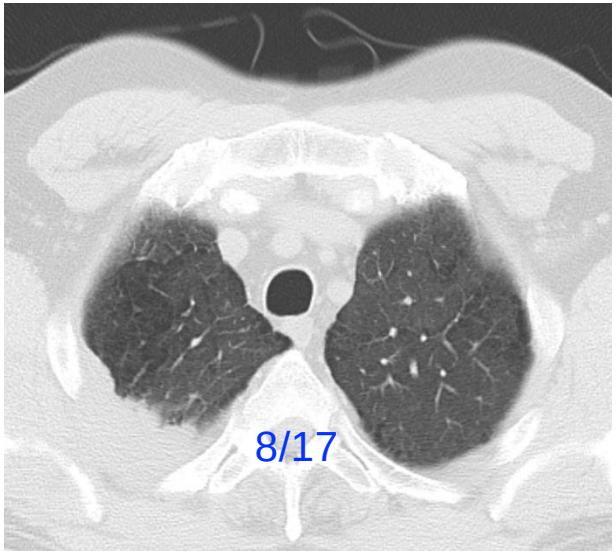


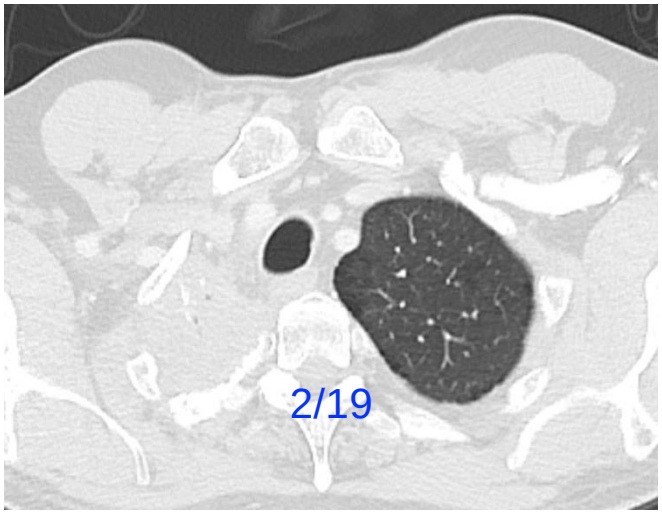


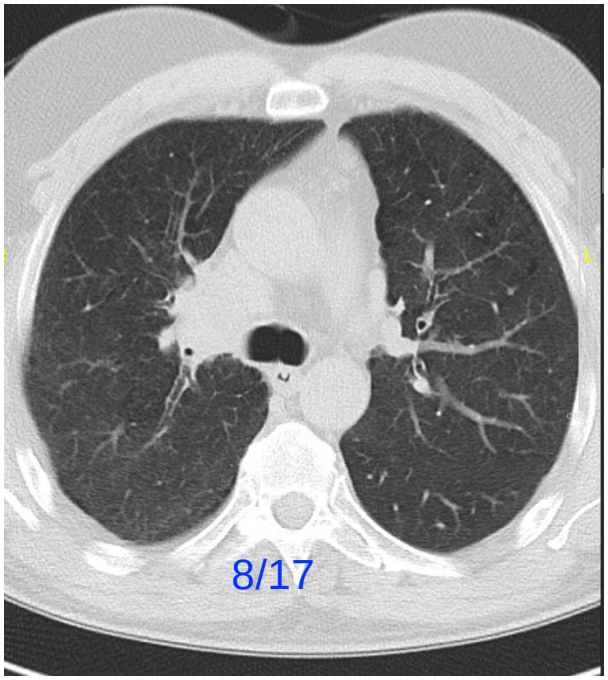
8/16: 43yo man (EB) developed R neck/shoulder pain
8/17: mass seen on CT/MRI involving R lung, CW, T3, R 3rd rib; bx adenocarcinoma; PD-L1 60%; PET-CT: R hilar mass; multiple bone, adrenal mets.
9/17: completed palliative RT to RUL/spine mass
9/17: started pemetrexed-carboplatin-pembrolizumab
F/U: CR by PET-CT, plain CT
9/19: therapy completed; off treatment, 'cured'
Working full time in construction
11/21: routine FU CT suggested recurrence in RUL, R hilar LN, and L adrenal.

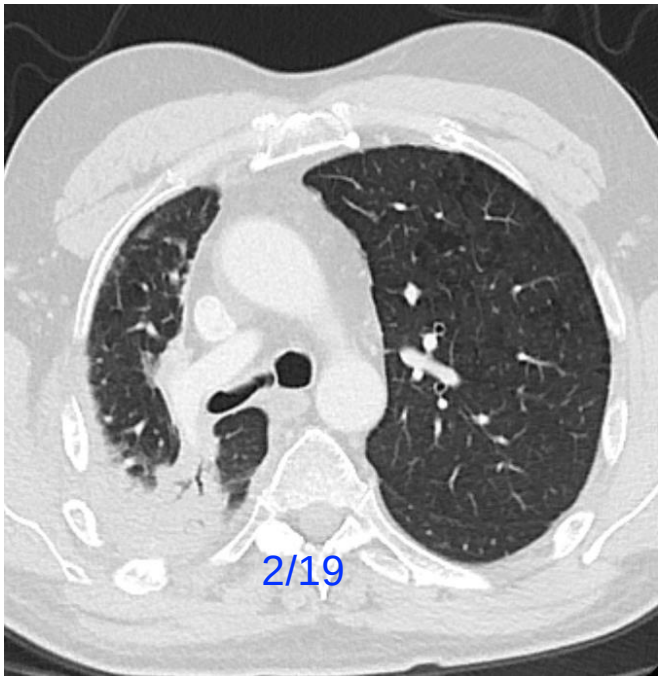
Your treatment approach (**more than 1 answer may be correct**):

A. Perform PET-CT
B. Biopsy some site of disease
C. Treat with pembrolizumab
D. Treat with pemetrexed-carboplatin-pembrolizumab
E. Treat with a standard second line chemotherapy, docetaxel









Combination chemo-checkpoint therapy for stage IV

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Working full time in construction
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Your treatment approach:

A. Perform PET-CT
B. Biopsy some site of disease

D. Treat with pemetrexed-carboplatin-pembrolizumab

FU scans showed a good response; he continues on pemetrexed-pembrolizumab, now age 49, working full time

Who responds to immune checkpoint therapy in lung cancer?

Response correlates with:

tumor expression of PD-L1 (measured by IHC as % tumor cells +)

tumor infiltration by lymphocytes

tumor mutation burden (TMB) = number of new antigens that T cells might respond against; $\geq$ 20 mutations/Mb is a cutpoint.

Multiple mutations associated with lack of response: STK11, KEAP1, SMARCA4, EGFR, ALK

Why don't all patients respond:

'Cold' tumors without immune cells.

TGFβ, IFNγ signaling.

MHC downregulation, B2M mutations.

Tumor associated macrophages that prevent T cell activation

Immune checkpoint therapy in lung cancer

Toxicities:

None in 80-90%.

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

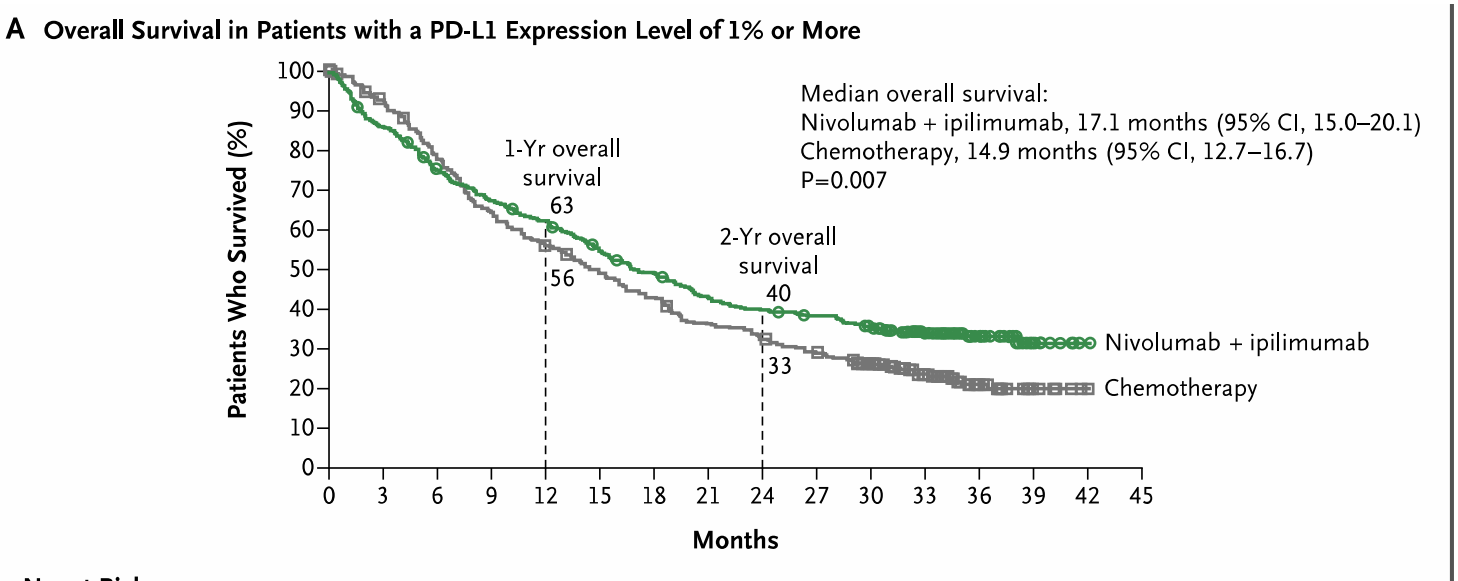
Ipilimumab-nivolumab is the standard combo, anti-CTLA4 + anti-PD1

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, pneumonitis.

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

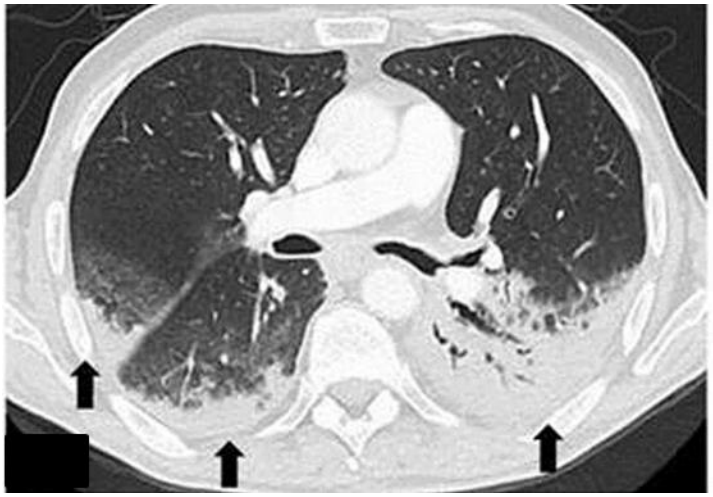
Treatment-related serious adverse events led to discontinuation in 20%

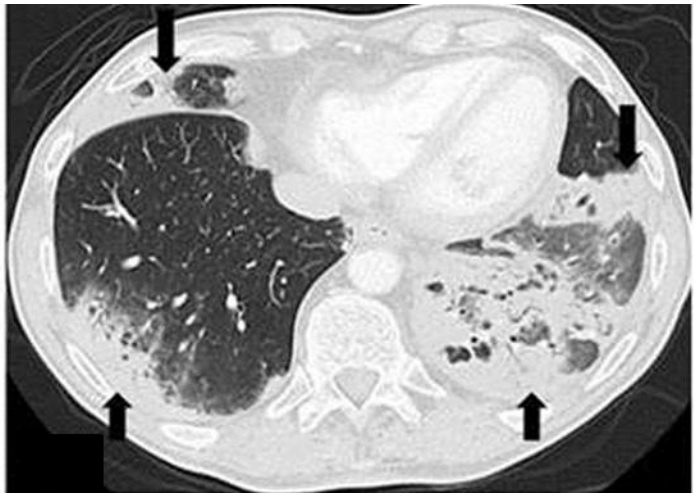


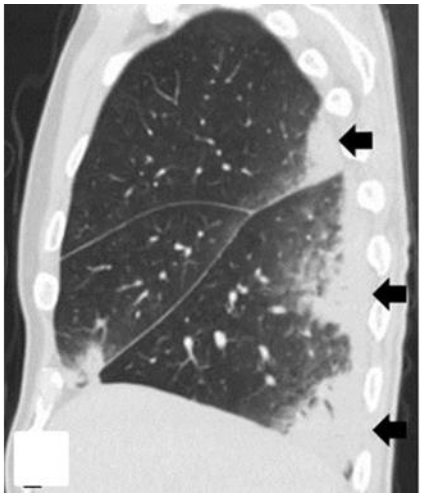
Hellman et al.
N Engl J Med 2019

PD-1 inhibitor-related pneumonitis: COP pattern

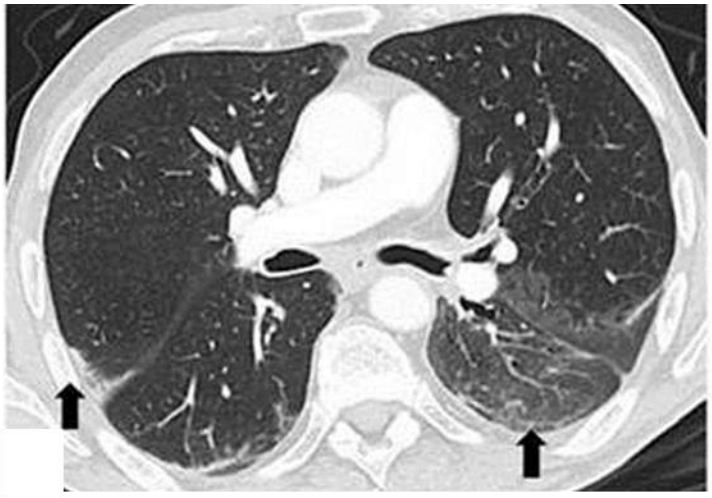
At 15 weeks of nivolumab monotherapy

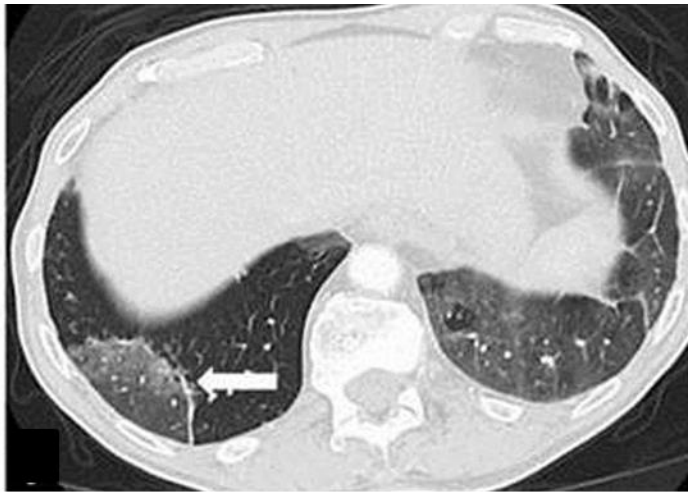






4 weeks after starting prednisone





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

Management of Immune Checkpoint Inhibitor pulmonary toxicity

Grade 1 – asymptomatic, confined to one lobe or <25% lung parenchyma, SpO2 at or close to baseline
- consider holding immunotherapy
- follow carefully for dyspnea, decline in SpO2, chest CT progression

Grade 2 – presence of dyspnea and/or cough; decline in SpO2
- hold immunotherapy
- pulmonary consultation
- infectious workup for other causes, e.g. COVID-19, etc.
- consider bronchoscopy and BAL
- consider empiric antibiotics
- high dose prednisone or equivalent
- monitor closely as outpatient

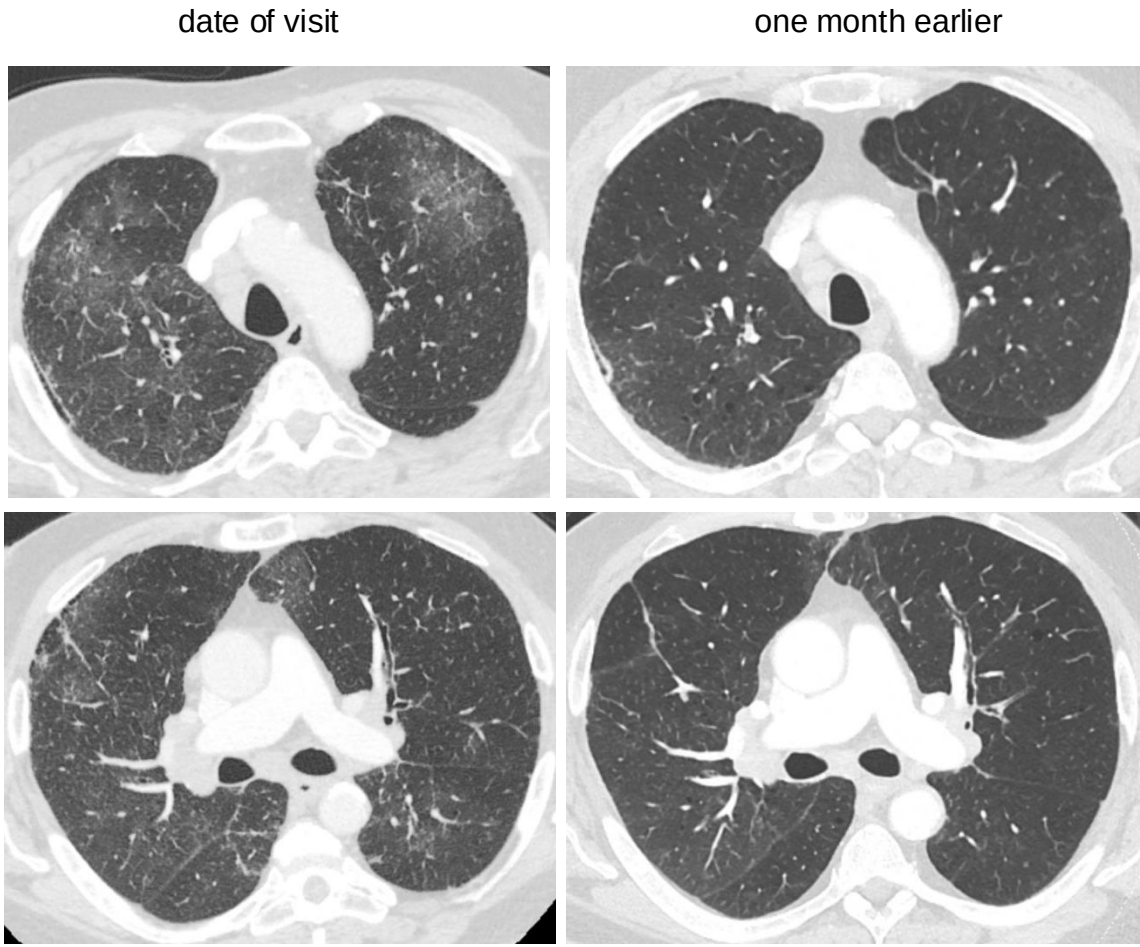
Grade 3/4 – respiratory failure
- stop immunotherapy
- hospitalize
- same as for grade 2
- high dose prednisone or equivalent
- consider infliximab, IVIG, mycophenolate

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-atezolizumab, and then 3 cycles of atezolizumab 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, SpO2 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. Hold atezolizumab for a cycle
C. Stop atezolizumab and start prednisone
D. Perform bronchoscopy with biopsy
E. Perform nasal swab for COVID-19, test for other viral pathogens



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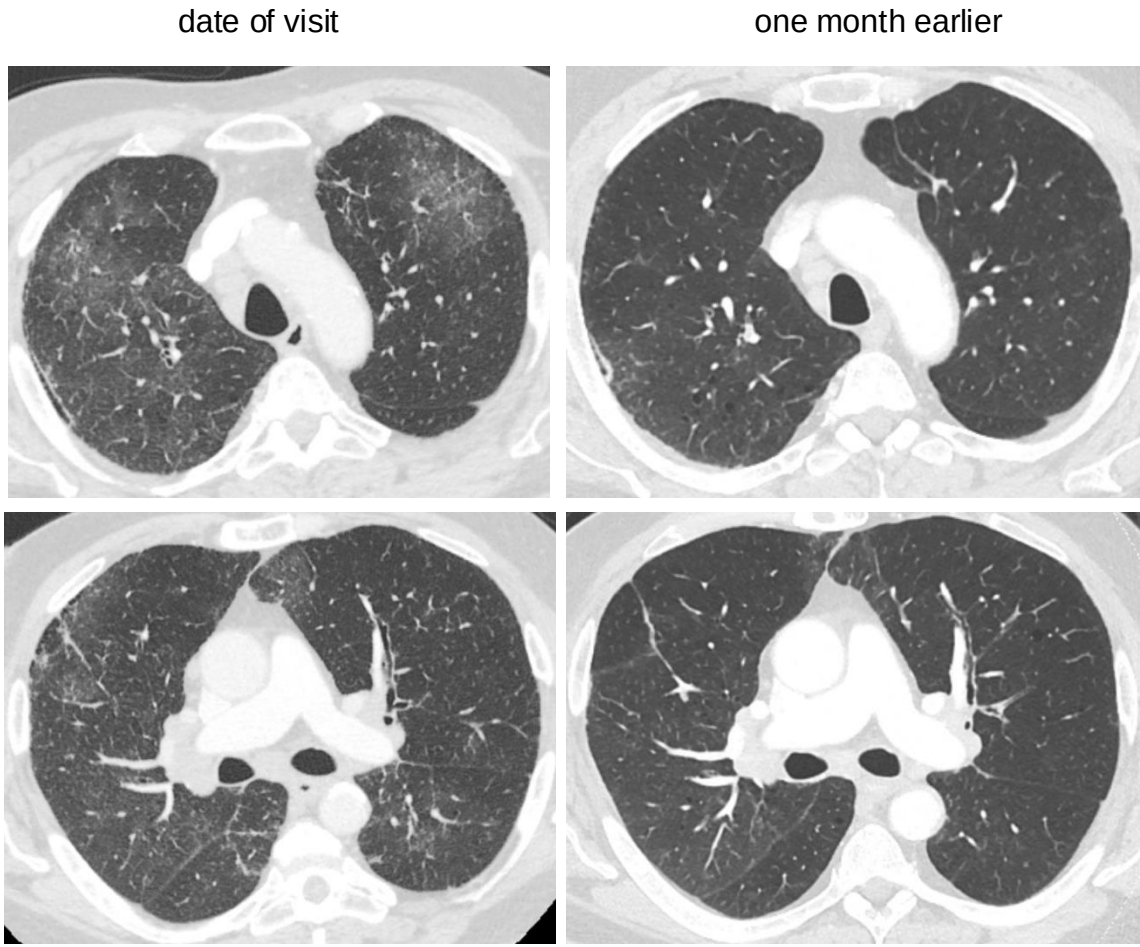


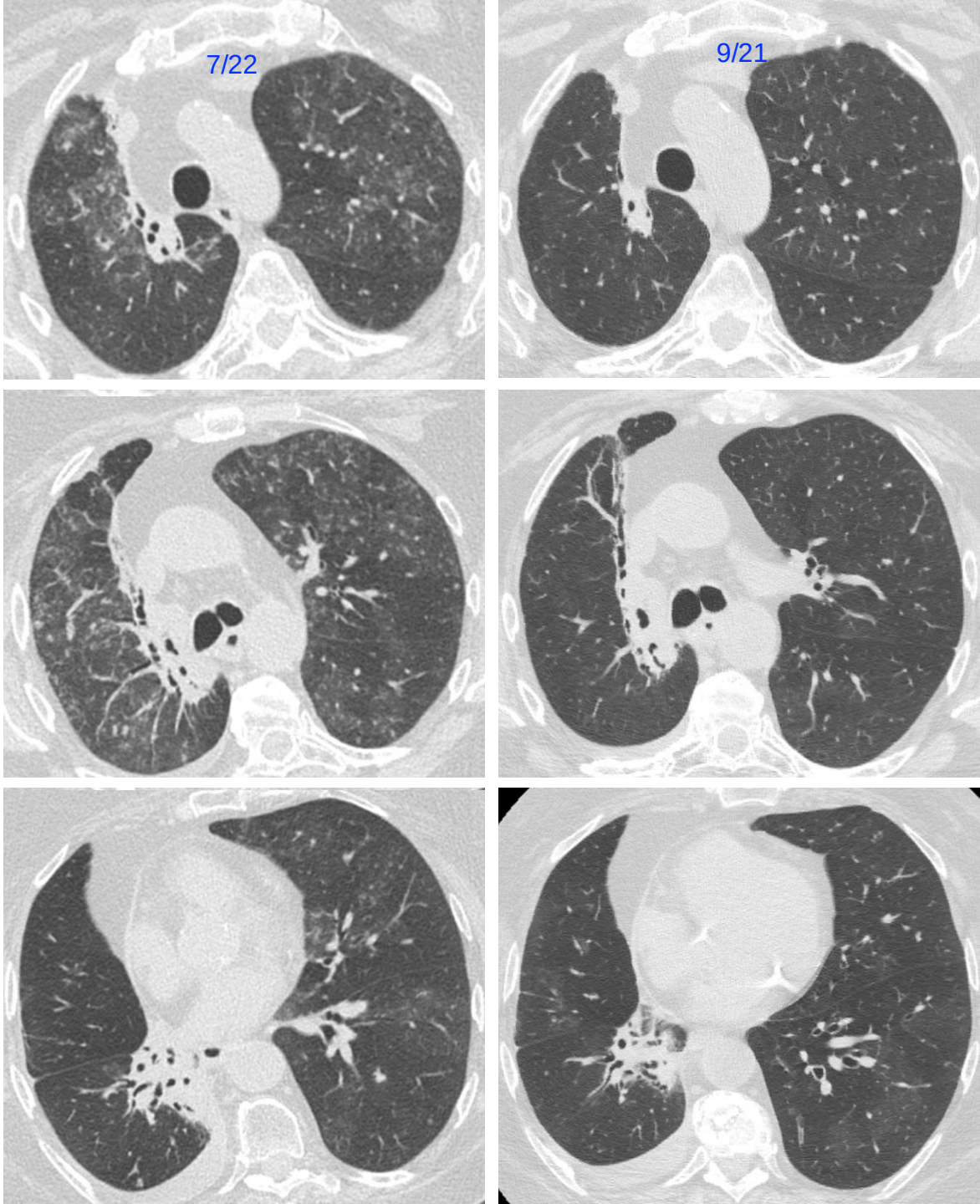
Board question:

In 7/16 at age 69 she had abd hernia surgery, and scans identified a RLL mass.
9/16 biopsy showed small cell carcinoma.
Limited extent disease by scans.
9/16-12/16: four cycles of chemotherapy with concurrent radiation therapy.
2017-2020: CHF/COPD exacerbations, hospitalized, resolved.
9/21: last seen, stable, with recurrent COPD flares, on 2L NP O2
7/22: presented with worsening cough, dyspnea, on usual Lasix, leukopenia with 1.6wbc, H/H 10/30, nl plts

Your treatment approach:

A. Start Prednisone for pneumonitis
B. Refer to Hematology
C. Perform nasal swab for COVID-19, test for other viral pathogens
D. Perform bronchoscopy with biopsy, BAL
E. Plan chemotherapy for recurrent SCLC

Your diagnosis:



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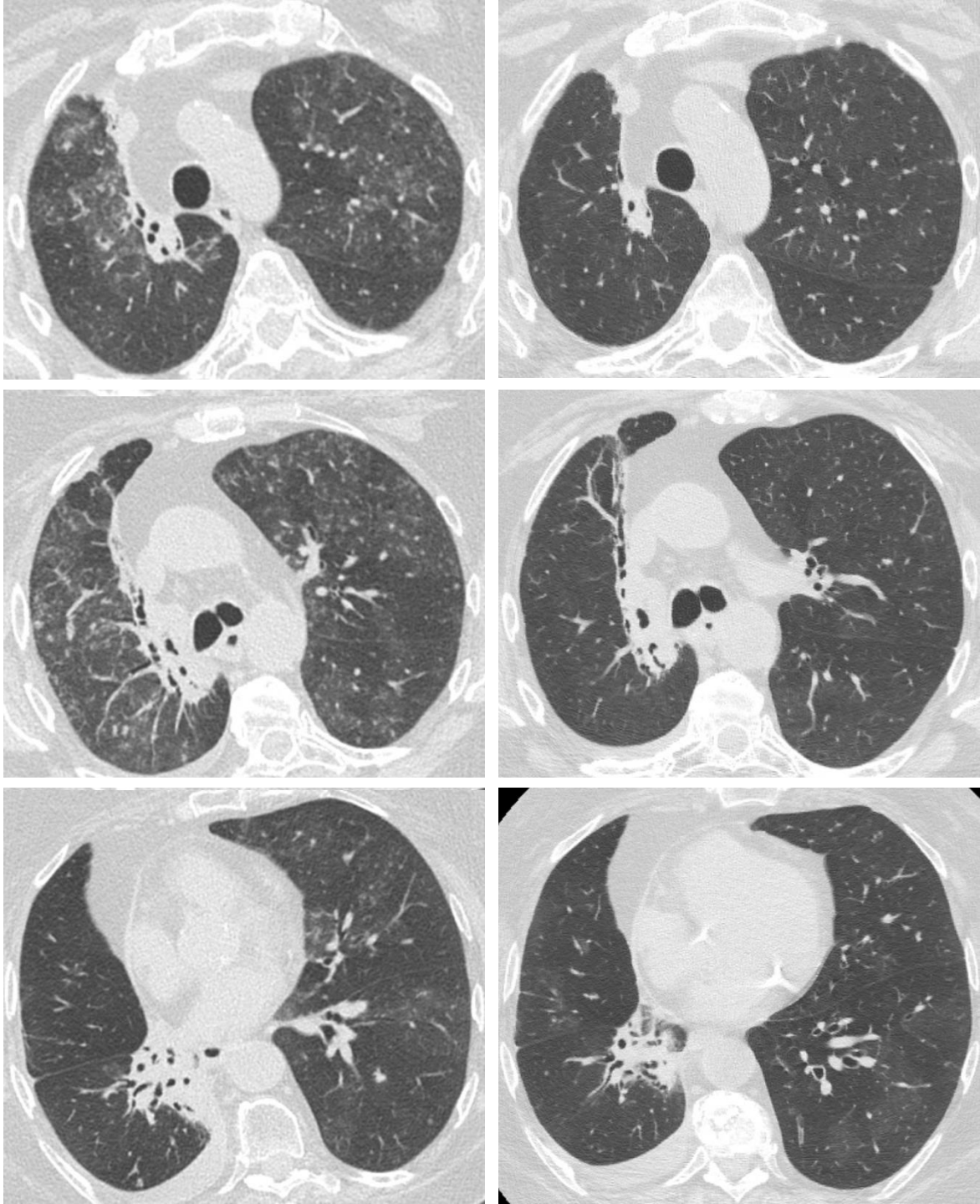
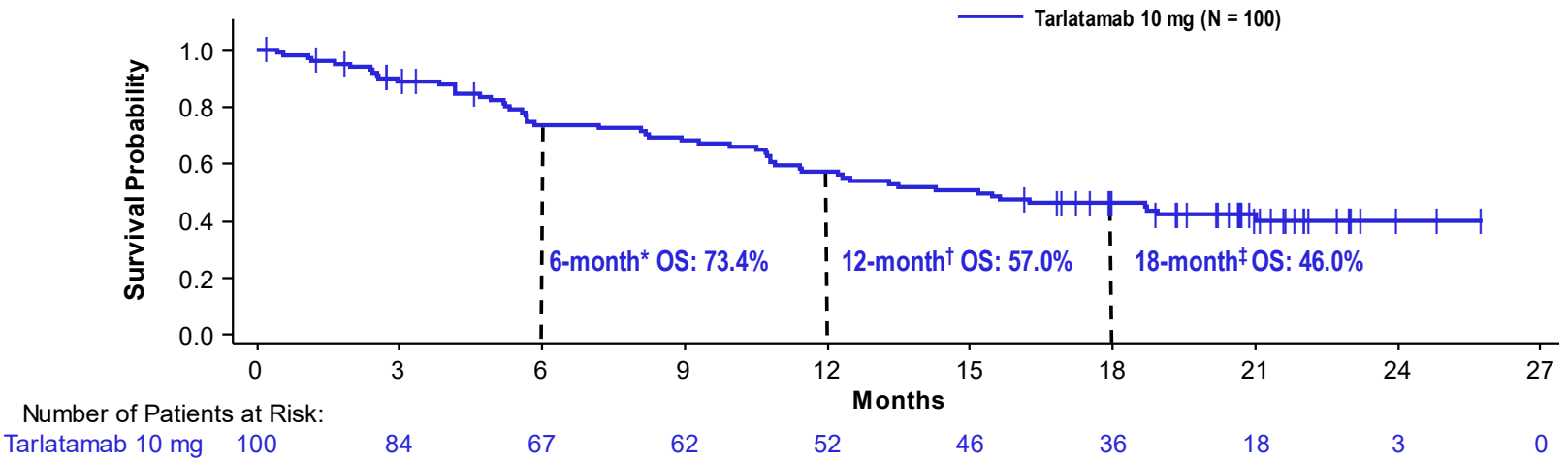
Your treatment approach:

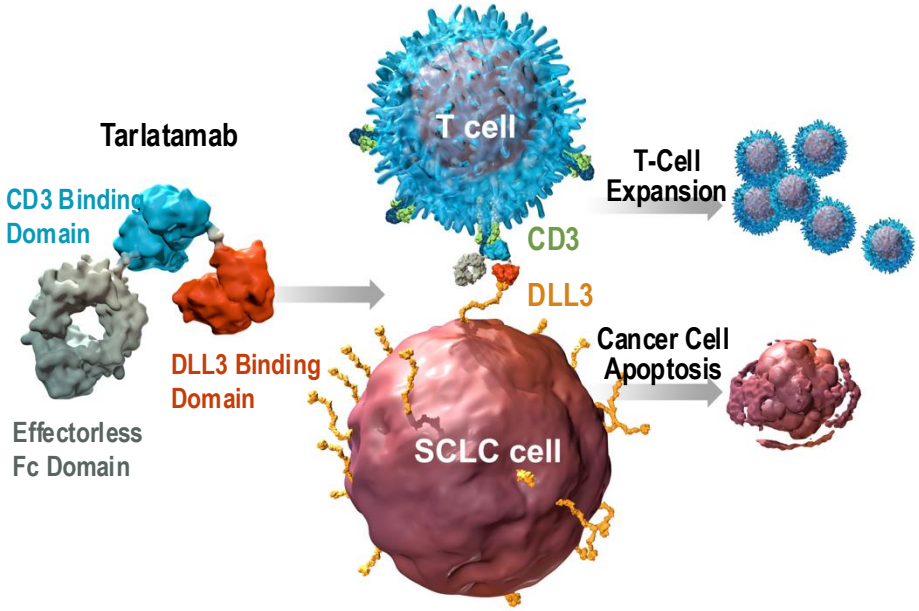
B. Refer to Hematology
C. Perform nasal swab for COVID-19, test for other viral pathogens
D. Perform bronchoscopy with biopsy, BAL, full viral, bacterial, etc. screens

Diagnosis:
Pneumocystis jirovecii pneumonia by PCR
Responded to Bactrim-steroids



Tarlatamab, BITE therapy for small cell lung cancer
BITE = bi-specific T cell engager





Very promising long-term survival for recurrent small cell lung cancer

<u>Multiple serious side-effects:</u>

Cytokine release syndrome (CRS) in 50%:
fever, nausea, headache, rash, rapid heartbeat, low blood pressure, and trouble breathing

Pyrexia

Decreased appetite

Dysgeusia

Fatigue

Immune effector cell-associated neurotoxicity syndrome (ICANS) in 15%:
word finding difficulties, confusion, impaired fine motor skills

Severe ICANS consists of seizures, coma, and cerebral oedema

Acknowledgements

Thanks to all my colleagues at BWH/DFCI:
Mike Rabin
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Jacob Sands