JADPRO CE
Regional Education

From Inquiry to Investigation to Insight: Clinical Clarity in Non–Small Cell Lung Cancer

Managing Patients With Other Mutations in Metastatic NSCLC

The Horizon: Upcoming Trials

Program Chair

Beth Eaby-Sandy
MSN, CRNP
Abramson Cancer Center

Faculty

Tyler Beardslee, PharmD
Winship Cancer Institute at Emory University

Marianne Davies
DNP, ACNP, AOCNP®
Yale School of Nursing

Elizabeth Gilbert
MS, PA-C
Abramson Cancer Center

Rasheda Persinger, NP-C
Johns Hopkins Sidney Kimmel Cancer Center

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For further information concerning Lilly grant funding, visit www.lillygrantoffice.com.

Learning Objective

- Evaluate efficacy and safety data supporting the use of targeted and immune checkpoint inhibitor therapy used to treat NSCLC

Audience Response Question

A 65-year-old male is currently taking dabrafenib/trametinib for his metastatic *BRAF*+ NSCLC. After 3 weeks on the drugs, he develops a fever ranging from 100.2°F to 101.2°F for 2 days that resolves with 650 mg of acetaminophen. He feels a little fatigued and achy, but is generally able to perform ADLs. Given this scenario, you should:

A. Hold both trametinib and dabrafenib and perform an infectious workup.

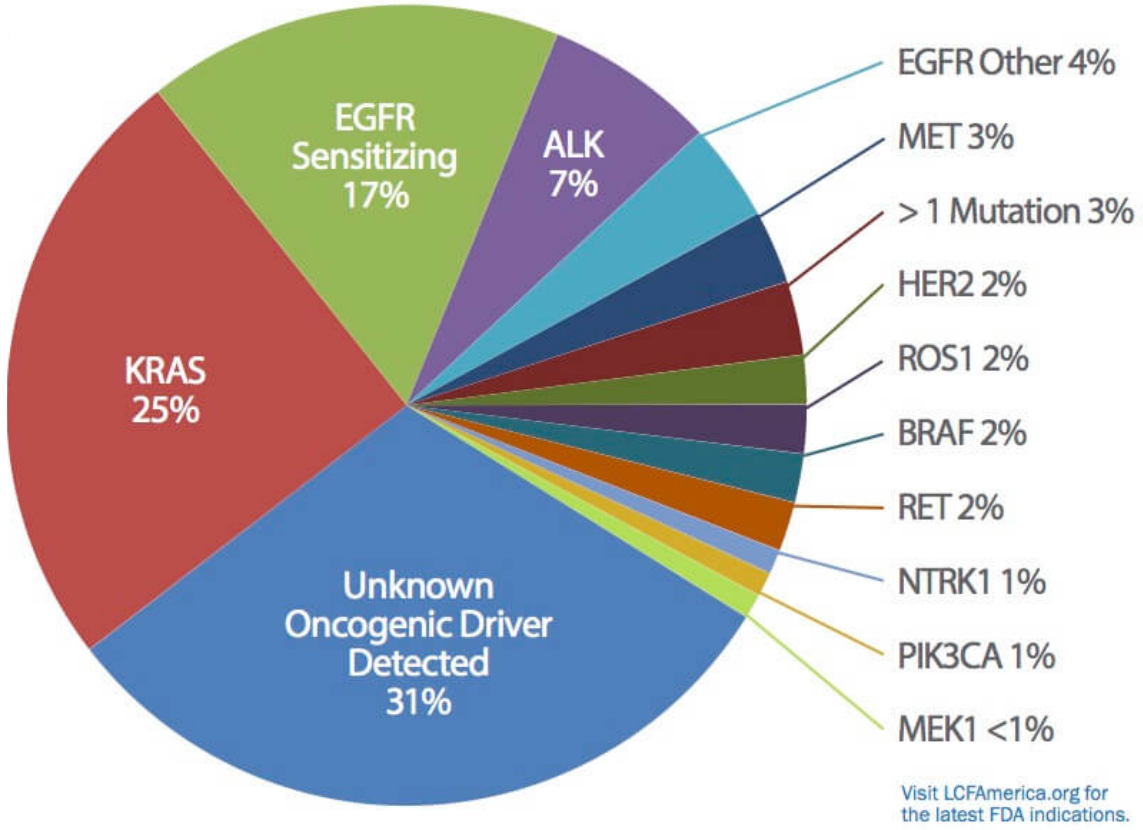
B. Hold trametinib but continue dabrafenib for a week, then resume both at the same dose

C. Continue with both drugs and monitor temps. If acetaminophen stops working or he begins to have significant symptoms, hold treatment.

D. Hold both drugs for a week and then resume with a dose reduction of the dabrafenib.

E. Unsure

What Other Mutations?



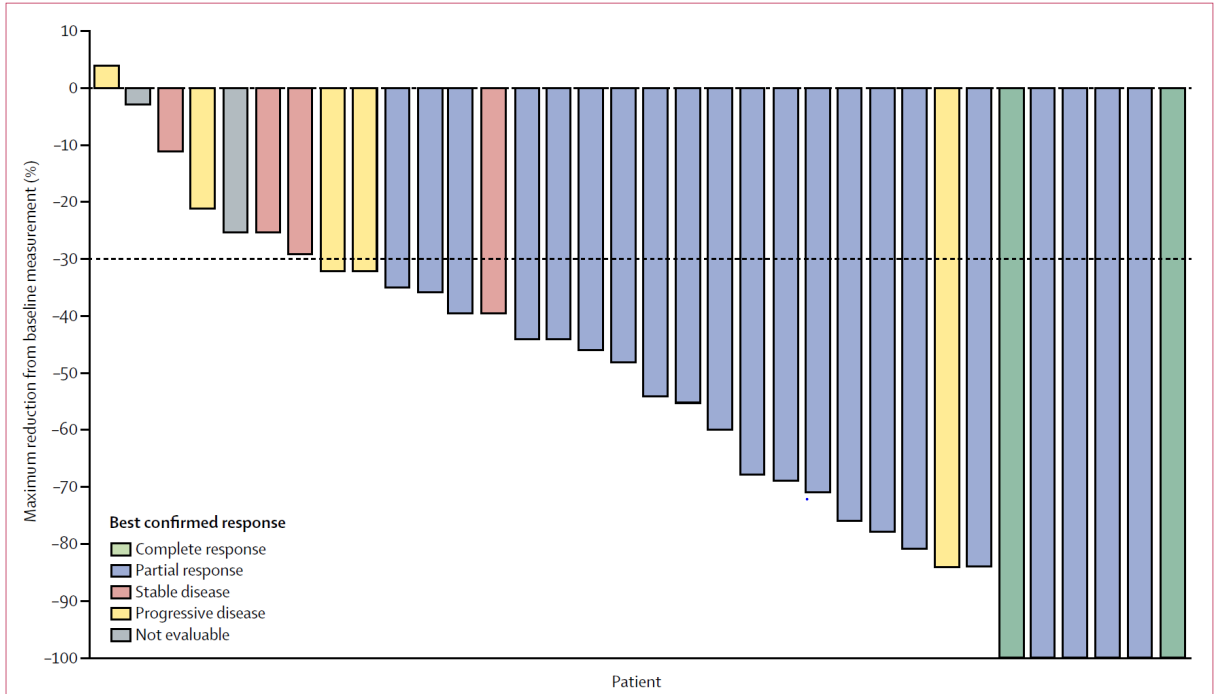
Retrieved from https://lcfamerica.org/research-grants/therapies/available-targeted-therapies

BRAF

- About 2% of nonsquamous NSCLC
- Must be done on a DNA sequencing platform
- Most common, and only targetable mutation is the *BRAF* V600E
- Interestingly is more common in smokers! TESTING IMPORTANT.
- Most commonly known in melanoma as a biomarker for treatment
- There is one drug combination FDA approved for treatment for NSCLC, based solely on response rates: dabrafenib/trametinib

Dabrafenib Plus Trametinib in *BRAF*+ NSCLC

- First-line treatment, 64% response rate
- Only 5%–7% disease progression rate



Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non–small cell lung cancer: an open-label multicenter phase 2 trial. *Lancet Oncol.* 2017;18:1307-1316.

Toxicities of Dabrafenib/Trametinib

- Fever most common side effect
- Some GI: nausea and diarrhea
- Hypertension 11%
- Rash 22%
- Oral and dosing is complicated
  - Dabrafenib 150 mg twice a day
  - Trametinib 2 mg once a day

Toxicities From Planchard Study in NSCLC

	Grade 1–2	Grade 3	Grade 4	Grade 5
Total	10 (28%)	23 (64%)	2 (6%)	1 (3%)
Pyrexia	19 (53%)	4 (11%)	0	0
Nausea	20 (56%)	0	0	0
Diarrhoea	12 (33%)	1 (3%)	0	0
Fatigue	13 (36%)	0	0	0
Peripheral oedema	13 (36%)	0	0	0
Vomiting	9 (25%)	3 (8%)	0	0
Dry skin	12 (33%)	0	0	0
Decreased appetite	12 (33%)	0	0	0
Chills	9 (25%)	0	0	0
Headache	9 (25%)	0	0	0
Rash	7 (19%)	1 (3%)	0	0

Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non–small cell lung cancer: an open-label multicenter phase 2 trial. *Lancet Oncol.* 2017;18:1307-1316.

Pyrexia (Fever) From BRAF Inhibitor Tx

- Usual onset in first 4 weeks: median time 9 days
- Leads to dose interruption 32% and dose reduction 14%, rare 3% to discontinue drug.
- First episode usually 9 days, followed by subsequent episodes 4–5 days
- Do not need routine infectious workup unless obvious symptoms of infection
- Usually associated with chills, headache, night sweats, rash, dehydration, hypotension

Daud A, Tsai K. *Oncologist.* 2017;22:832-833
Welsh SJ, Corrie PG. *Ther Adv Med Oncol.* 2015;7:122-136.

Treatment: Pyrexia From BRAF Inhibitor Tx

- Hold drug: Dabrafenib is the one to hold
- Add acetaminophen or NSAIDs, and corticosteroids
- Almost always can restart dabrafenib at same dose
- Likely to experience again; however, same regimen as above
- Past experience shows that dose reduction vs. interruption results in same amount of recurrences of fever
- Some cases may require dose reduction

Daud A, Tsai K. *Oncologist.* 2017;22:832-833
Welsh SJ, Corrie PG. *Ther Adv Med Oncol.* 2015;7:122-136.

Skin Rash or Secondary Malignancies

- Skin rash usually minimal
- Red, itchy, bumpy
- Recommend antihistamines and emollient creams
- Often just dry skin
- Both drugs responsible

- Oddly, combining dabrafenib/trametinib there are less secondary malignancies (2%) vs. with dabrafenib alone (9%).
- Per package insert, recommend dermatology follow; however, can just do skin exam
- Usually occur in areas that are previously sun-exposed and are eruptive

NTRK: Larotrectinib and Entrectinib

- *NTRK* is less than 1% of NSCLC (0.23% in this database search)
- 11 patients found on a database search, median age 47
- All with adenocarcinoma, all never smokers
- It is a gene fusion, found on a gene fusion panel
- It is more common in other cancers, thyroid and sarcomas and some pediatric cancers, GBMs.
- Both drugs have the odd neurotoxicity/cognitive side effects.

Farago AF, Taylor MS, Doebele RC et al. JCO Precis Oncol. 2018 ;

KRAS

- The most common mutation found in NSCLC, about 25% of adenocarcinoma patients
- The most common is KRAS G12C
- Found on a DNA sequencing panel and usually mutually exclusive to other mutations
- More in smokers, but sometimes in non-smokers
- Various drugs to target *KRAS* have not worked in past
- Conveys resistance to other targeted therapies; chemotherapy and/or immunotherapy is the treatment of choice

New KRAS G12C Update From WCLC 9/2019

- AMG 510 is a novel oral targeted therapy that targets KRAS G12C
- Early phase I trial of 34 patients, 23 evaluable at data cutoff
- There were some responses and the drug was found to be very safe with no adverse events that led to discontinuation.

Govindan R. Data presented at WCLC, Barcelona 2019.

RET Rearrangements in NSCLC

- Most commonly in thyroid cancers, rare: less than 1% in NSCLC
- Median age 61, gender balanced, 63% never smokers
- Found by FISH testing, 98% were adenocarcinomas
- Phase II data on cabozantinib and vandetinib show some clinical activity
- Other drugs that have been looked at are lenvatinib, alectinib, sorafenib, sunitinib, ponatinib

Gautschi O, et al. 2017; *J Clin Oncol.* 35(13): 1403-1410.

RET Rearrangements in NSCLC: Efficacy in One Database Review

Note: Chemotherapy Has About a 50% Response Rate

Table 2. Best Response to RET Inhibitor Therapy

RET Inhibitor	Complete Response	Partial Response	Stable Disease	Disease Progression	Not Evaluable	Missing Data
All agents (n = 53)	2 (4%)	11 (22%)	16 (32%)	20 (40%)	1 (2%)	3
Cabozantinib (n = 21)	1 (5%)	6 (32%)	5 (26%)	7 (37%)	0	2
Vandetanib (n = 11)	0	2 (18%)	3 (27%)	6 (55%)	0	0
Sunitinib (n = 10)	0	2 (22%)	3 (33%)	3 (33%)	1 (11%)	1
Sorafenib (n = 2)	0	0	2	0	0	0
Alectinib (n = 2)	0	0	0	2	0	0
Lenvatinib (n = 2)	0	1	0	1	0	0
Nintedanib (n = 2)	1	0	1	0	0	0
Ponatinib (n = 2)	0	0	2	0	0	0
Regorafenib (n = 1)	0	0	0	1	0	0

NOTE. The best response to a multikinase inhibitor with activity against RET is summarized for 53 patients with advanced *RET*-rearranged lung cancers.

Gautschi O, et al. 2017; *J Clin Oncol.* 35(13): 1403-1410.

MET Exon Skipping Mutation

- Not run-of-the-mill *MET*. Looking for a *MET exon* 14 skipping mutation: about 4%–5% of NSCLC.
- Can be in squamous or adenocarcinoma, common in sarcomatoid carcinomas
- In both smokers and non-smokers
- Crizotinib has good clinical activity. No FDA indication, but generally covered and considered first-line treatment

Drillon AE, et al. *J Clin Oncol.* 2016 34:15_suppl, 108-108

HER2 Mutations in NSCLC

- Not the breast cancer HER overexpression, not amplification
- This is an ERBB2 or HER2 mutation (EGFR is HER1) found on DNA sequencing panel
- 1.7% of patients, a little more women than men, 35% never smokers
- 65 patient database case series of patients treated
- Trastuzumab added to chemotherapy did not add a benefit, although a few case studies had some benefit
- Case studies of lapatinib, afatinib with some clinical activity

Mazie`res J et al. *J Clin Oncol.* 2013;31.1-8.

Others

- PI3K is a pathway without targeted drugs approved for but there are drugs in clinical trials
- MEK is a MAPKinase pathway, drugs like trametinib for BRAF, which is in similar pathway are MEK inhibitors, but data sparse
- NRAS, HRAS each about 1% but unknown how to target

Where Are We Going in Lung Cancer Clinical Trials?

- At last assessment (5/2019) of University of Penn clinical trials open/about to open in medical oncology in Lung/Head and Neck, we are currently studying these **NOVEL** drugs:
  - 9 targeted therapy drugs
  - 14 immunotherapy (including vaccines) drugs
  - **0 novel** chemotherapy drugs

Clinical Trials for EGFR Inhibitors

- Poziotinib: EGFR TKI that has strong inhibition for not only EGFR but also HER2 and exon 20 mutations that have been traditionally hard to treat.
  - At WCLC, data presented on poziotinib showed promising results on a waterfall plot, that most patients with typical *EGFR* resistance mutations benefited with some sort of response. However, there is toxicity, namely skin rash.
- JNJ-372: an EGFR and cMET antibody
  - Starting phase II, selective for EGFR resistance, looking at different resistance mechanisms. Has had responses. Although again, skin rash an issue, and some infusion reactions also an issue.

Clinical Trials for EGFR Inhibitors (cont.)

- TAK-788: another EGFR TKI that is focused on HER2 as well as exon 20 insertions
- Seen here is the phase 1/2 data for 26 patients
- Promising results, only 1 progressed and 50% partial response rate
- AEs are consistent with other EGFR TKIs

	Expanded Cohort 160 mg qd n = 26[a]
Best response (unconfirmed), n (%)[b]	
CR	0
PR	14 (54)
SD[c]	9 (35)
PD	1 (4)
NE	2 (8)
Objective response, n (%)	14 (54)
95% CI	33·37–73·41
Disease control, n (%)	23 (89)
95% CI	69·85–97·55

Janne P. et al. DOI: 10.1200/JCO.2019.37.15_suppl.9007 *Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) 9007-9007.

Immunotherapy and Radiation

- Abscopal effect: Where untreated tumors can experience shrinkage when other tumors are treated with ionizing radiation
  - Idea is that radiation will activate tumor cell antigens which can be recognized by dendritic cells. These dendritic cells will in turn prime cytotoxic T cells which then can circulate in the body.
  - By adding a PD-1/L1 checkpoint inhibitor, that could make the tumor even more vulnerable to these now circulating cytotoxic T cells resulting in this abscopal effect.

Immunotherapy and Radiation (cont.)

- Several ongoing trials looking at rather than sequencing radiation and immunotherapy, overlapping
- In both locally advanced setting as well as metastatic setting

Clinical Trials

- Immunotherapy of all types of pathways, too many to name, this is the future
- Immunotherapy with radiation: Is there a synergy?
- PARP inhibitors: Trialed in past, some activity, looking for right population
- mTOR inhibitors: Again, trialed in past, but still looking for select populations
- CAR T-cell therapy in NSCLC? Need the vector…
- Vaccines: Have been trialed for many years in lung cancer
  - But now adding to immune checkpoint inhibitors seems to show promise, finally!

Clinical Pearls

- Test for all of these mutations, even where there aren’t approvals, since if there is clinical activity, that may be worth a shot
- The future lies with immunotherapy, not just checkpoint inhibitors, but all sorts of immune systems pathways, stimulatory, suppressive.

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Questions?

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Small Cell Lung Cancer

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Learning Objective

- Select therapy in accordance with evidence-based best practices

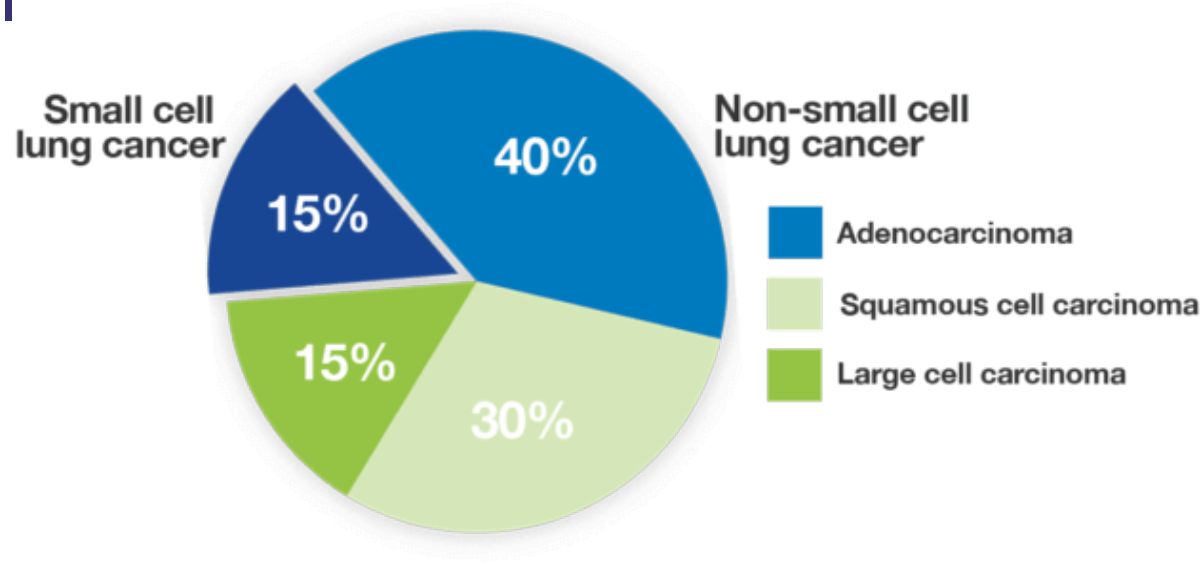
Audience Response Question

A patient with extensive stage SCLC received etoposide/carboplatin/atezolizumab front line. After 4 cycles of this regimen, the patient should then receive:

A. Maintenance atezolizumab
B. Maintenance atezolizumab and etoposide
C. 2 additional cycles and then start maintenance atezolizumab
D. Take a treatment break and conduct surveillance CT scans
E. Unsure

Small Cell Lung Cancer

- Strongly associated with heavy smoking
- Very aggressive; median survival within weeks of diagnosis if left untreated
- 13% of all lung cancers according to 2019 American Cancer Society Facts & Figures, but dropping



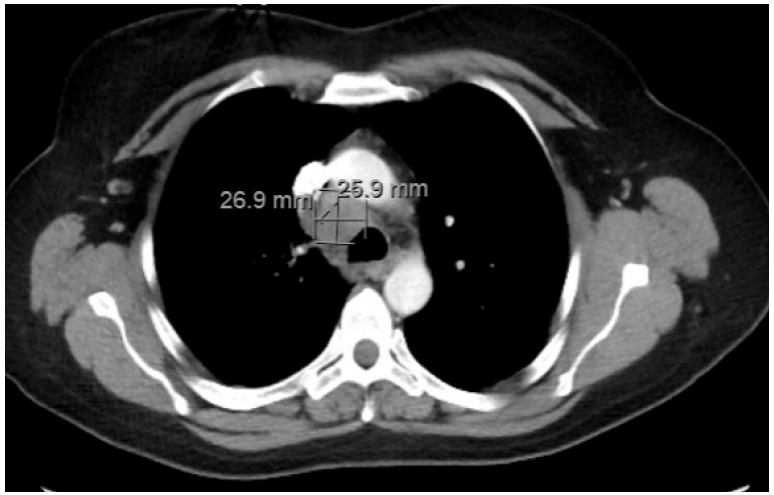
Lung Cancer Foundation of America
American Cancer Society Facts & Figures 2019.

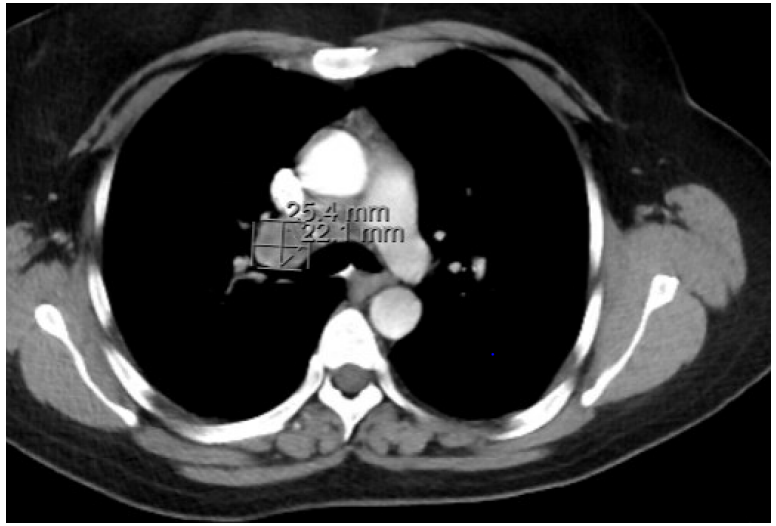
Staging and Pathology of SCLC

- No molecular testing, pathology often consistent with neuroendocrine features
- Two stages
  - Limited stage: Disease is confined to chest and can fit into a safe radiation portal to be managed with both chemotherapy and radiation therapy for definitive management
  - Extensive stage: Disease has spread outside the chest or within the chest, but too extensive to be managed in a radiation field

Clinical Presentation

- Symptoms are generally revealing: bulky nodal disease
  - Cough, dyspnea, chest pain
  - Superior vena cava syndrome
- Symptoms related to metastases common
  - Bone pain, neurological symptoms
- Constitutional symptoms
- Fatigue, weight loss
- Paraneoplasia
  - Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) manifests as hyponatremia
  - Neurologic symptoms

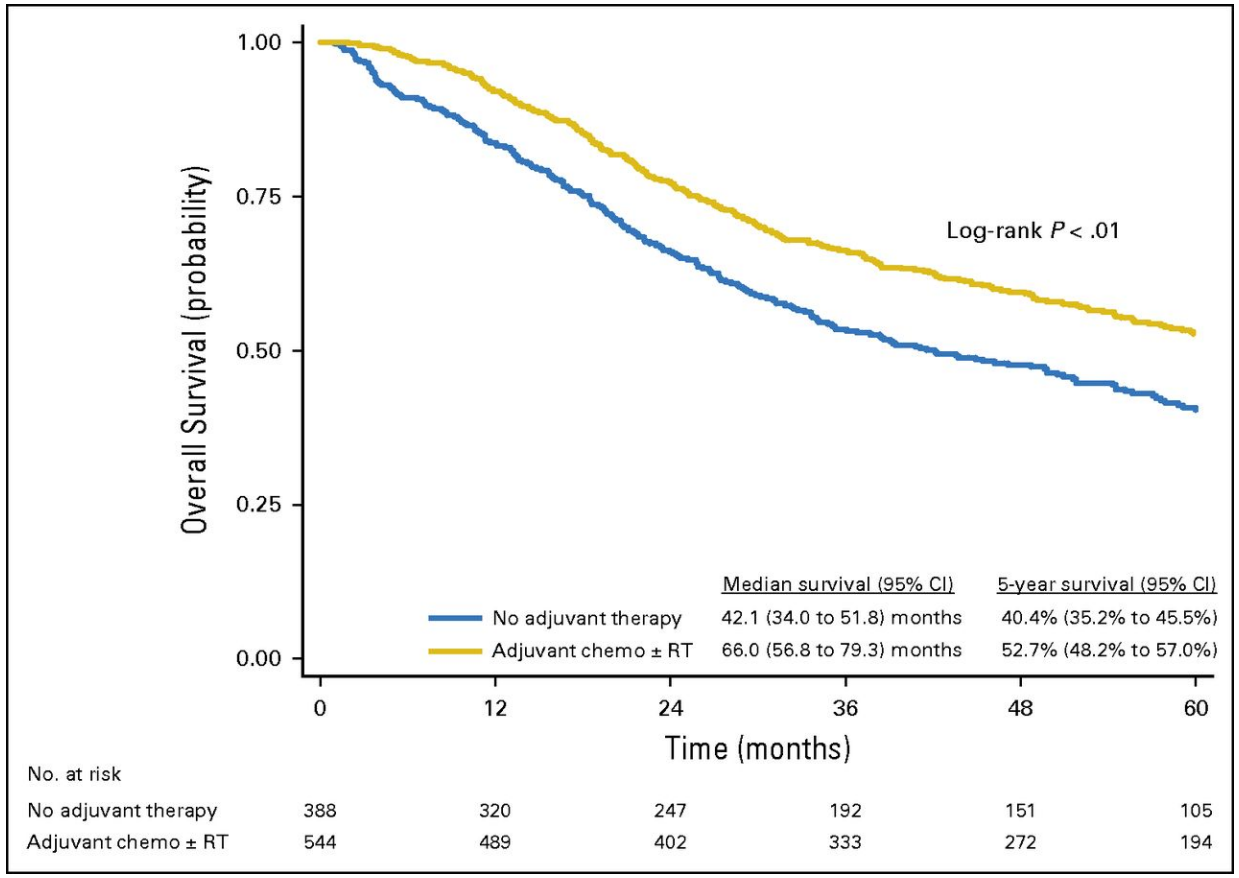




Limited stage SCLC

- If found early stage, as in there are no lymph nodes positive on bronchoscopy, should be resected; however, finding SCLC this early is very rare.
- Best management is concurrent chemotherapy and radiation
- Sequential chemotherapy then radiation only in patients with poor performance score, but this is far inferior to concurrent

Survival of pT1–2N0M0 SCLC, Stratified by No Adjuvant Therapy vs. Adjuvant Chemotherapy With Or Without Radiation Therapy



Chi-Fu Jeffrey Yang et al. *JCO* 2016;34:1057-1064

Radiation in Limited Stage SCLC: Bid or Daily?

Daily XRT

- 6 weeks daily
- Easier tolerated than bid
- Logistics
- Inferior in OS: not overwhelmingly in more recent studies

Bid XRT

- 3 weeks bid
- More toxicity generally (esophagitis)
- Logistically difficult for some, usually 6–8 hours apart
- Superior OS to daily XRT
  - 19 months vs. 23 months overall survival in favor of bid XRT

Turrisi AT et al. *N Engl J Med.* 1999 Jan 28;340(4):265-71

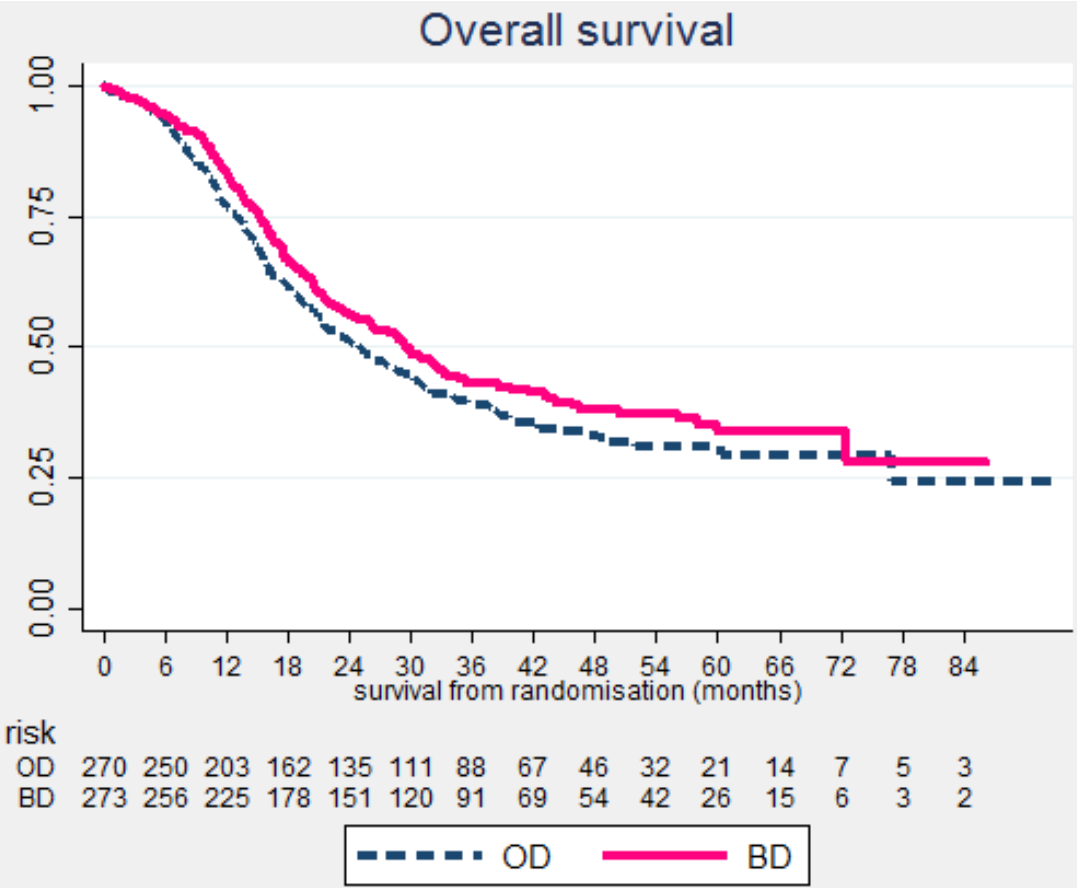
To Do Radiation Qd or Bid?

CONVERT trial:

45 Gy bid vs. 60 Gy qd

- Over 500 patients
- Randomized to chemotherapy plus either daily or bid XRT
- Powered for daily to be superior, which was not.

OS (n = 543)	BD	OD	Log-rank
Median mo.	30 (24-34)	25 (21-31)	*p* = .15
1-year	83% (78-87)	76% (71-81)	
2-year	56% (50-61)	51% (45-57)	
3-year	43% (37-49)	39% (33-45)	



Faivre-Finn C, et al. *Lancet Oncol* 2017; 18: 1116–25

Prophylactic Cranial Irradiation (PCI) in Limited Stage SCLC

- A definite survival advantage: strong data
- Should be recommended
- Downsides
  - Potential for cognitive decline down the road
  - Logistics and alopecia (were already an issue with the chemo/XRT)

Extensive Stage SCLC

- Disease cannot be safely fit into radiation portal or metastasized outside of the chest

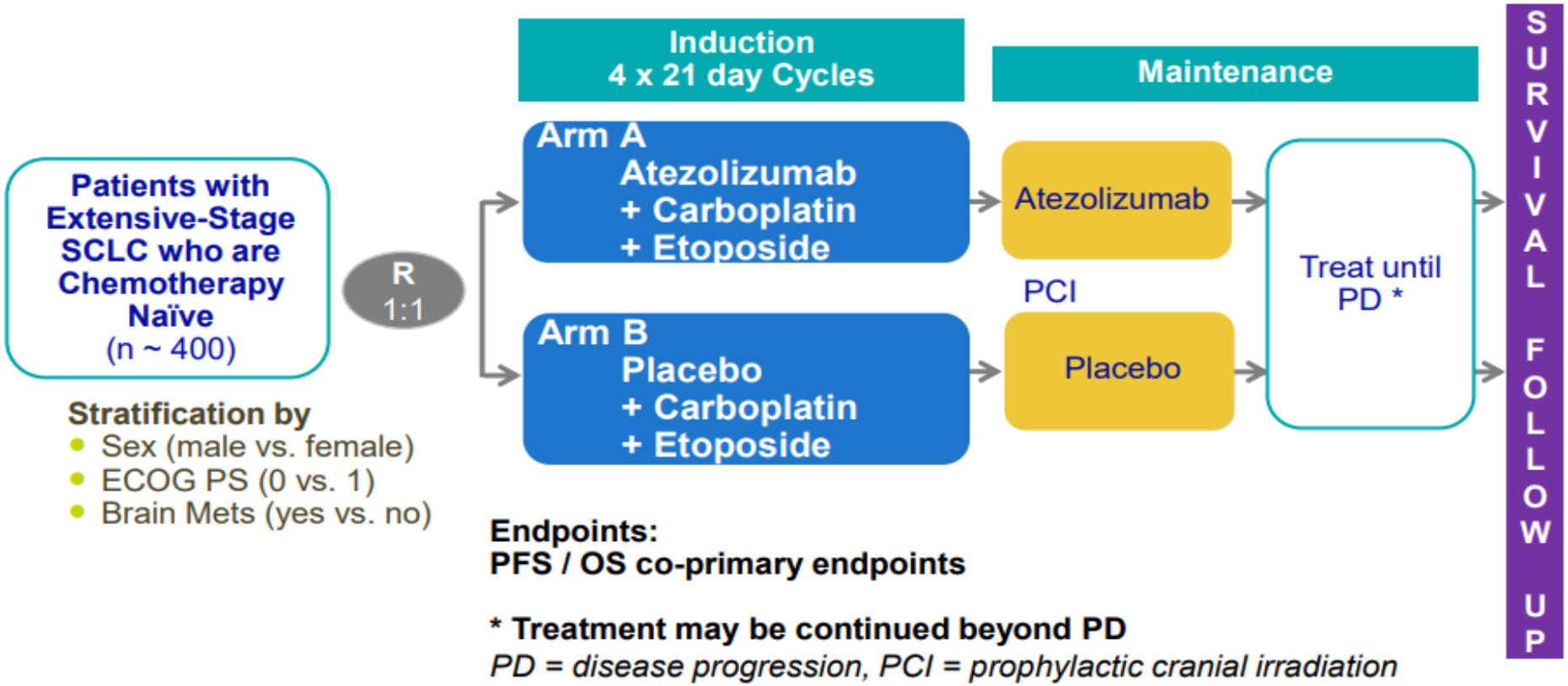
SCLC Chemotherapy

- 1st line
  - Etoposide + carboplatin or cisplatin
  - Irinotecan + carboplatin or cisplatin
- 2nd line
  - Topotecan is the only CHEMO drug that is FDA approved
  - Irinotecan
  - Paclitaxel
  - Gemcitabine
  - CAV (cyclophosphamide, doxorubicin, vincristine)

Immunotherapy in Small Cell Lung Cancer: First Line

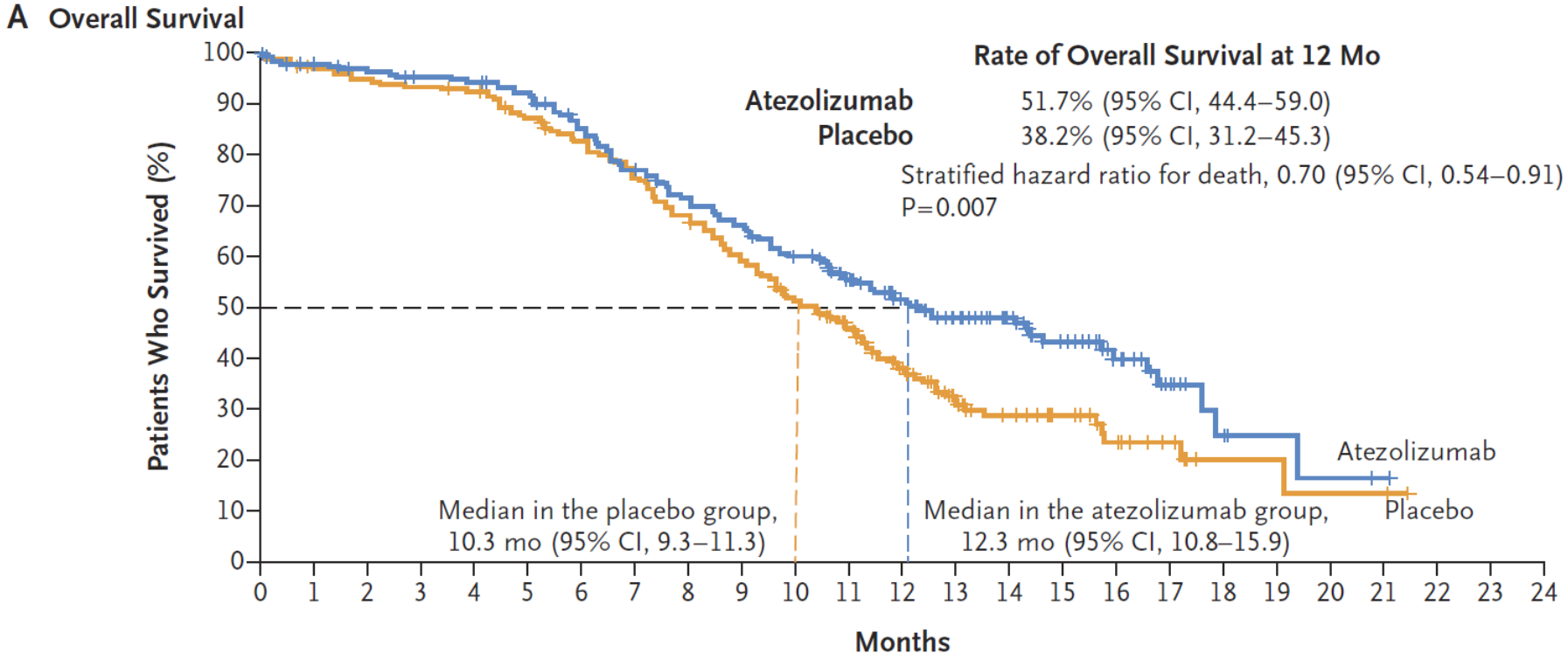
- Etoposide/platinum (carboplatin or cisplatin) standard of care for 20 years
- First time that addition of any drug has shown benefit
- Addition of atezolizumab once every 3 weeks on day 1 to etoposide/platinum showed improved OS and PFS vs. the chemotherapy alone arm.

Study Schema for IMpower133 (GO30081): Phase I/III – 1L ES-SCLC



Data presented at WCLC Sept 2018

Immunotherapy in Small Cell Lung Cancer: First-Line Atezolizumab Plus Chemotherapy vs. Chemotherapy Alone Overall Survival (IMpower133)



Horn L, et al. *N Engl J Med* 2018;379:2220-9.

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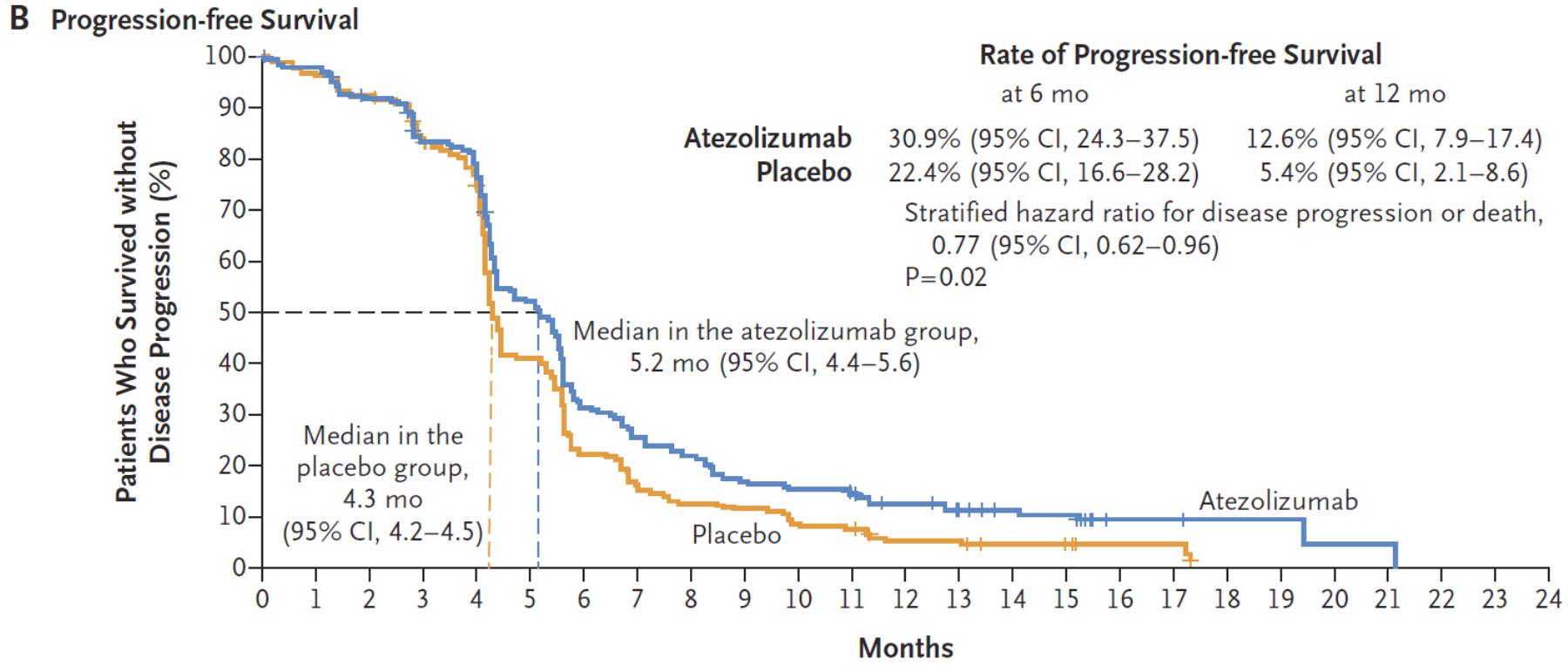


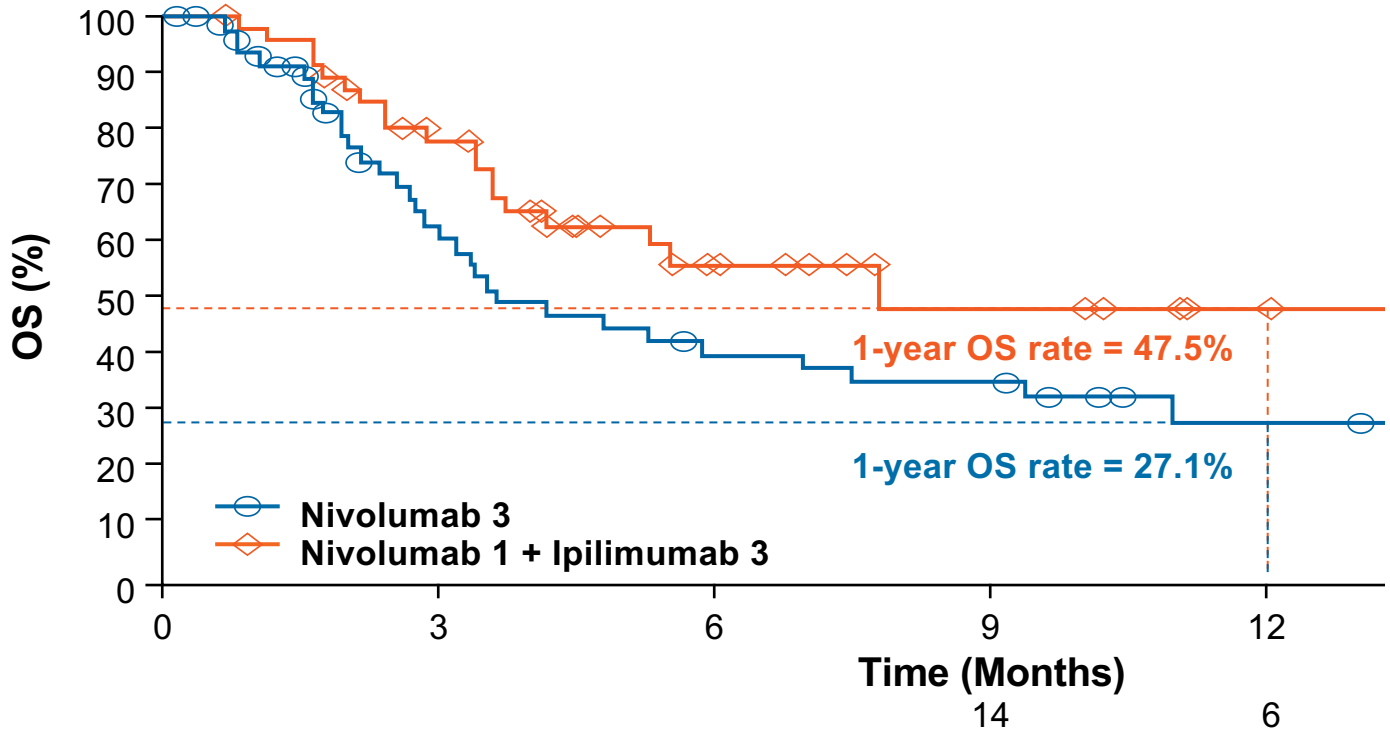
Horn L, et al. *N Engl J Med* 2018;379:2220-9.

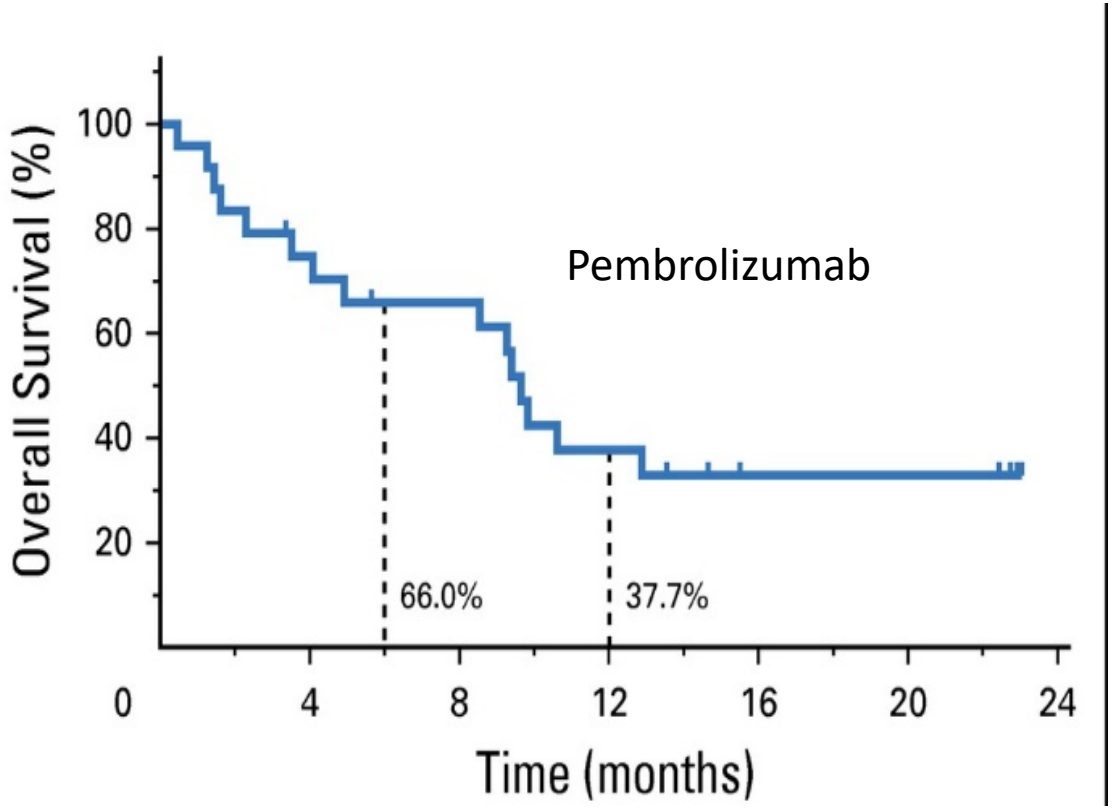
Immunotherapy in SCLC Second Line: Nivolumab or Ipilimumab/Nivolumab

- 3 arms
  - Nivolumab vs. ipilimumab 1 mg/kg + nivolumab 3 mg/kg vs. ipilimumab at 3 mg/kg + nivolumab 1 mg/kg
  - Dosing is complex, arms were similar though slight advantage to ipilimumab arms, but high toxicity in 3 mg/kg arm of ipilimumab
  - Nivolumab only drug FDA approved in this setting, although many clinicians using ipilimumab as well, which is in the NCCN Guideline recommendations
  - However, survival advantage over chemotherapy is yet to be proven
  - With IO in first line, this is not much an issue, wouldn't use it second line

Antonia SJ, et al. *Lancet Oncol*. 2016;17(7):P883-895

CheckMate 032 and KEYNOTE-028 Overall Survival: SCLC





- NCCN Guidelines and FDA have all 3 options: Nivo, nivo + ipi, and pembrolizumab
- FDA approved nivolumab for third-line therapy

S. Antonia et al: ASCO 2015 & E. Calvo; ESMO, 2015

PCI in Extensive Stage SCLC

- Recommended in NCCN Guidelines
- However, the data is not as strong, less of survival advantage than limited stage disease
- Risk vs. benefit of cognitive decline in poor prognosis disease. Flip side: likely won't live long enough to experience it…

Limited Stage SCLC Immunotherapy Trials

- AZ phase III: CT/RT followed by durvalumab, durvalumab/tremilimumab or placebo
- MD Anderson phase I: CT/RT plus pembrolizumab

New Agents for SCLC
(all second or third line)

- Stem cell inhibitors
  - Hedgehog/Wnt
  - Notch (DLL3)
- Aurora kinase inhibitors
- Lurbinectedin
- DNA Repair PARP, ATR, ATM
- FGFR inhibitors
- RRx1000
- Bromodomain Inhibitors
- JAK inhibitors
- EZH2 inhibitors
- LSD1 inhibitors
- PIK3/mTOR
- CDK4/6 inhibitors to protect BM

Rova-T seems to have failed after much speculation that it may be approved.

Clinical Pearls

- Atezolizumab + EP doublet therapy is a standard first-line therapy for extensive stage SCLC. Randomized trials of other checkpoint inhibitors (I/Os) are ongoing
- Durvalumab + EP doublet has been reported to improve survival compared to EP but results not yet presented or published.
- NCCN Guidelines approve pembro and nivo + ipi after chemo.
- Randomized trials of I/Os with CT/RT in limited stage are ongoing.
- Rova-T has failed in several trials, lurbinectedin is in phase III trial, PARP inhibitors in phase II.

Audience Response Question

A patient with extensive stage SCLC received etoposide/carboplatin/atezolizumab front line. After 4 cycles of this regimen, the patient should then receive:

A. Maintenance atezolizumab
B. Maintenance atezolizumab and etoposide
C. 2 additional cycles and then start maintenance atezolizumab
D. Take a treatment break and conduct surveillance CT scans
E. Unsure

Questions?