

Immunotherapy for the Treatment of Lung Cancer

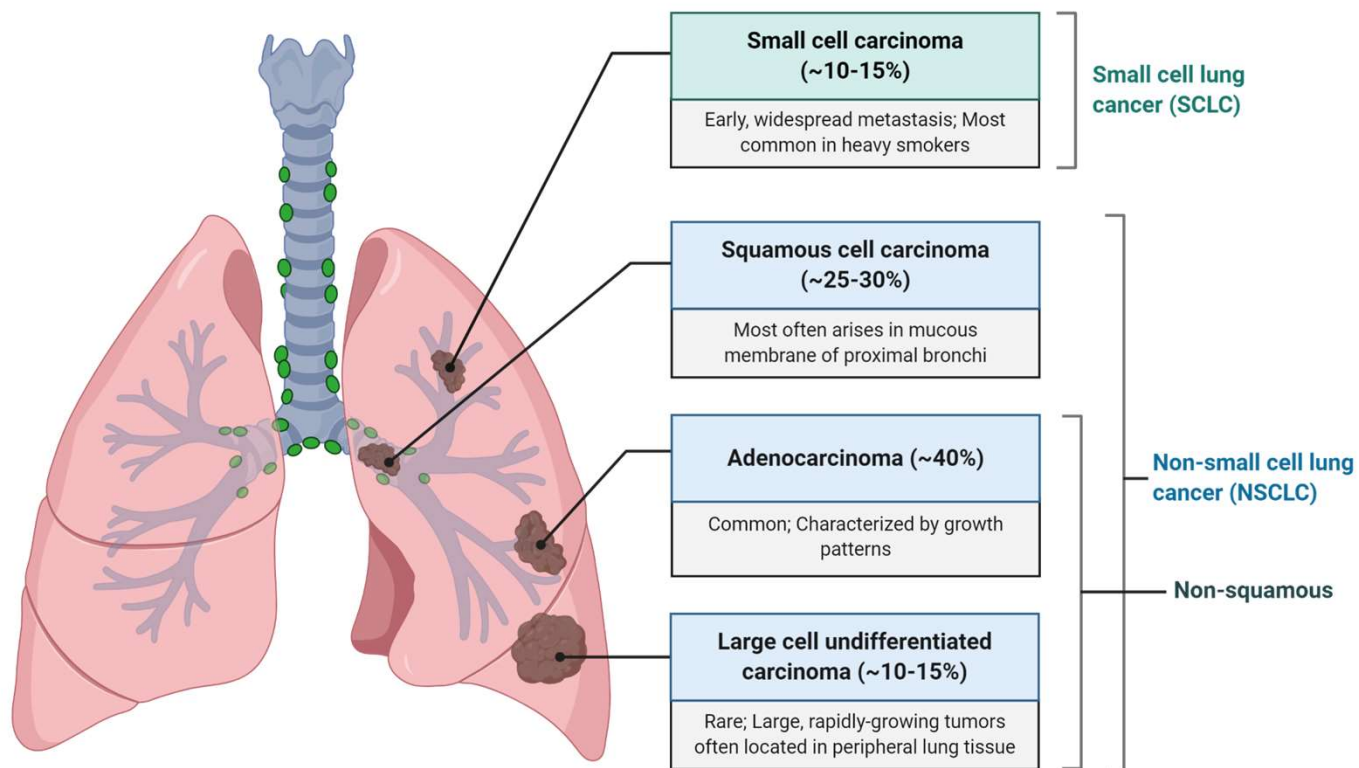
Adam Lye, MD

Medical Oncology Norton Cancer Institute

Disclosures

- Merck – Speakers Bureau
- Bristol Myers Squibb – Speakers Bureau
- I will be discussing non-FDA approved indications during my presentation.

Lung cancer



#LearnACI

Treatment options for NSCLC

Local disease

- Surgery
- Stereotactic body radiation therapy
- Chemotherapy

Stage III unresectable disease

- Concurrent chemo-radiation
- Immunotherapy

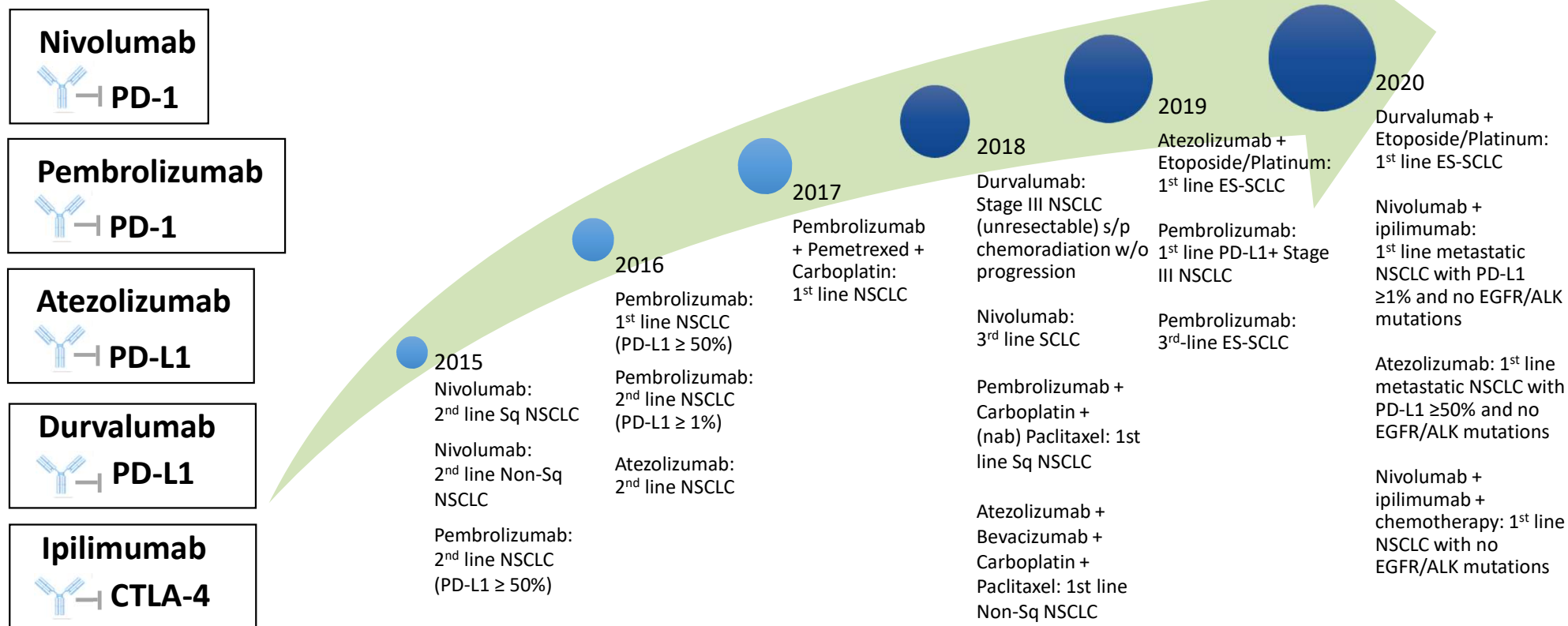
Metastatic disease

- Chemotherapy
- Targeted therapies
- Immunotherapy
- Radiation therapy

Metastatic NSCLC treatment options overview

Drug type	Molecular format	Administration route	Example for NSCLC	Typical dosing regimen
Chemotherapy	Small molecule	Intravenous, occasionally oral	Nab-paclitaxel	100 mg/m ² on days 1, 8, 15 of 21-day cycle
Targeted therapy	Small molecule	Oral	Osimertinib (kinase inhibitor)	80 mg tablet once a day
Targeted antibody therapy	Antibody	Intravenous	Bevacizumab (VEGF-A inhibitor)	15 mg/kg Q3W
Immune checkpoint inhibitor	Antibody	Intravenous	Pembrolizumab (PD-1 inhibitor)	200 mg Q3W or 400 mg Q6W

Immune checkpoint inhibitors in lung cancer



Outline

- Non-small cell lung cancer
 - Front-line – PD-L1-selected and unselected
 - Later lines of treatment
 - Stage III
- Small cell lung cancer
- Future directions for lung cancer immunotherapy

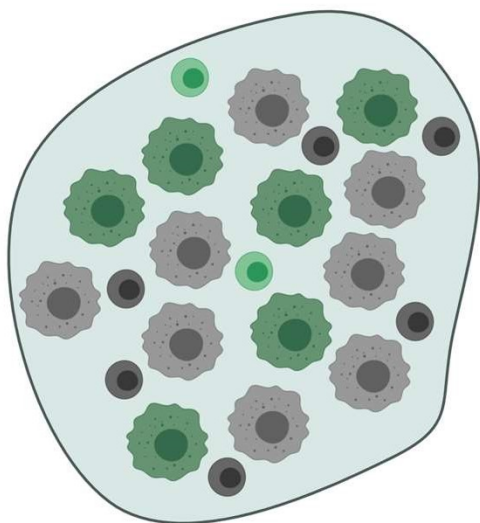
Immunotherapy for first-line treatment of metastatic NSCLC

Drug	Indication	Dose
Pembrolizumab	1 st line metastatic NSCLC with PD-L1 TPS ≥ 1% and no EGFR/ALK mutations	200 mg Q3W or 400 mg Q6W
Atezolizumab	1 st line metastatic NSCLC with PD-L1 ≥ 50% of tumor cells or ≥ 10% of immune cells with no EGFR/ALK mutations	840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W
Nivolumab + ipilimumab	1 st line metastatic NSCLC with PD-L1 ≥ 1% and no EGFR/ALK mutations	Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
Nivolumab + ipilimumab + platinum-doublet chemotherapy	1 st line metastatic NSCLC with no EGFR/ALK mutations	Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of chemotherapy
Pembrolizumab + pemetrexed + platinum	1 st line metastatic non-squamous NSCLC with no EGFR/ALK mutations	200 mg Q3W or 400 mg Q6W
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel	1 st line metastatic squamous NSCLC	200 mg Q3W or 400 mg Q6W
Atezolizumab + bevacizumab + paclitaxel + carboplatin	1 st line metastatic non-squamous NSCLC with no EGFR/ALK mutations	For 4-6 cycles: atezolizumab 1200 mg Q3W + chemotherapy + bevacizumab; Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W
Atezolizumab + nab-paclitaxel + carboplatin	1 st line metastatic non-squamous NSCLC with no EGFR/ALK mutations	For 4-6 cycles: atezolizumab 1200 mg Q3W + chemotherapy Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W

Brief aside: PD-L1 TPS vs CPS

$$TPS = \frac{\# \text{ of PD-L1 positive tumor cells}}{\text{number of viable tumor cells}} \times 100$$

$$CPS = \frac{\# \text{ of PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\text{total number of tumor and immune cells}} \times 100$$



-  PD-L1-positive immune cell
-  PD-L1-negative immune cell
-  PD-L1-positive tumor cell
-  PD-L1-negative tumor cell

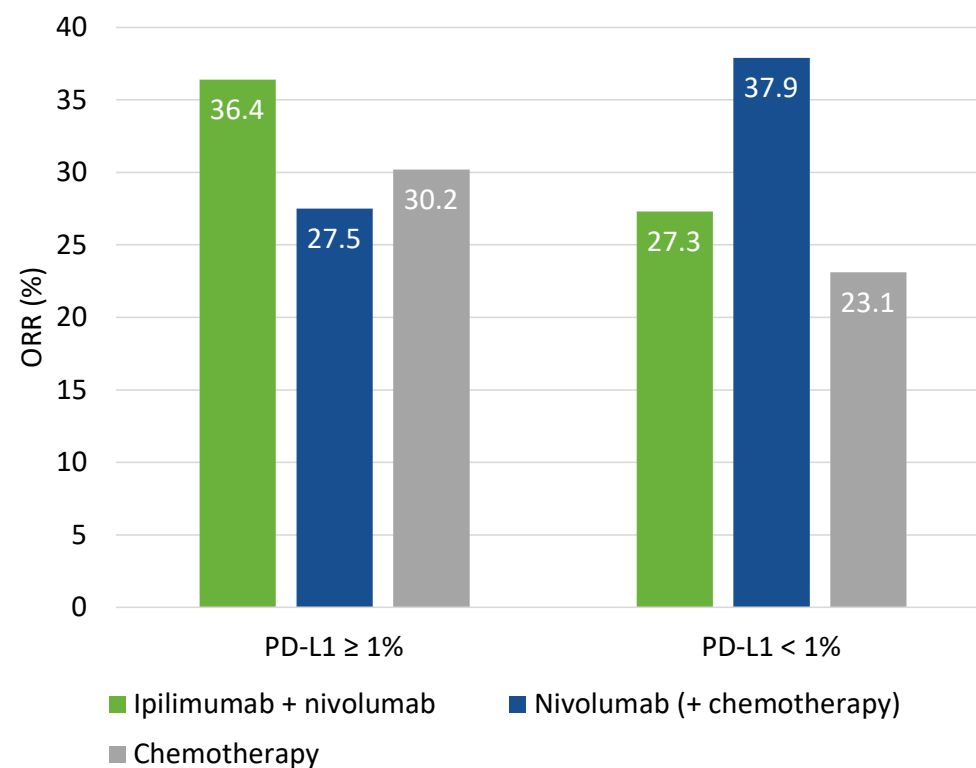
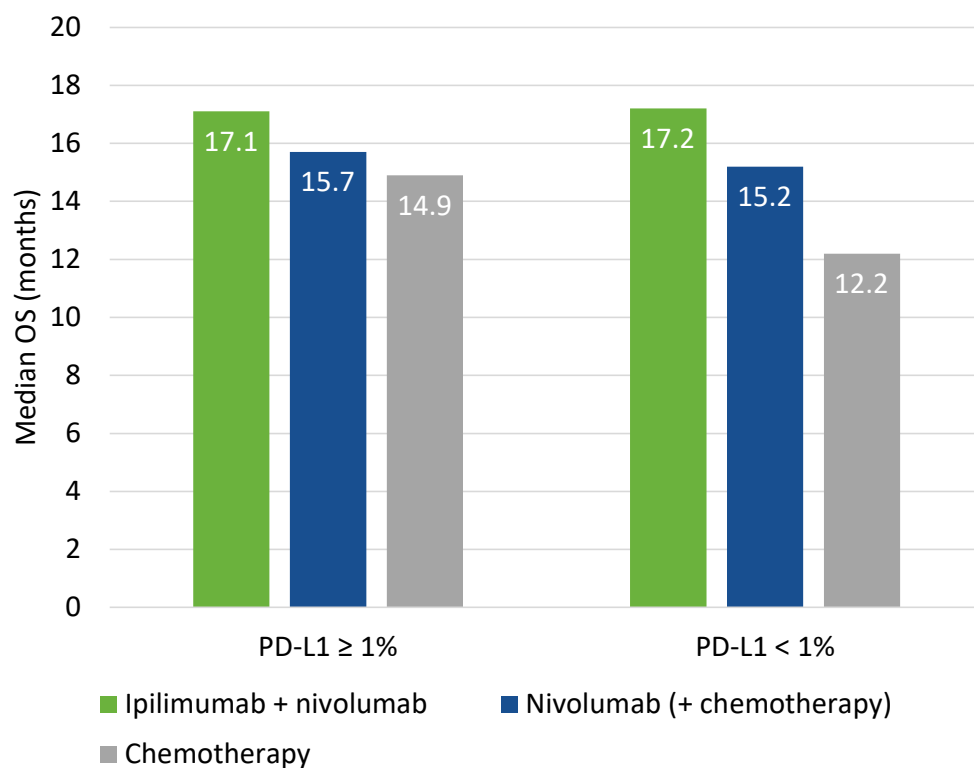
$$TPS = \frac{6 \text{ positive tumor cells}}{14 \text{ total tumor cells}} \times 100 = 43$$

$$CPS = \frac{6 \text{ positive tumor cells} + 2 \text{ positive immune cells}}{22 \text{ total cells}} \times 100 = 36$$

Treatment Naïve Regimens: Competing Strategies in NSCLC by biomarker status

PD-L1-selected	PD-L1-unselected
Nivolumab + ipilimumab <i>CheckMate 227</i>	Nivolumab + ipilimumab + platinum-doublet <i>CheckMate 9LA</i>
Pembrolizumab <i>KEYNOTE-024, -042</i>	Pembrolizumab + chemotherapy <i>KEYNOTE-189, -407</i>
Atezolizumab <i>IMpower110</i>	Atezolizumab + bevacizumab + chemotherapy <i>IMpower150</i>
	Atezolizumab + chemotherapy <i>IMpower130</i>

CheckMate 227: Ipilimumab + nivolumab vs chemotherapy for 1L NSCLC

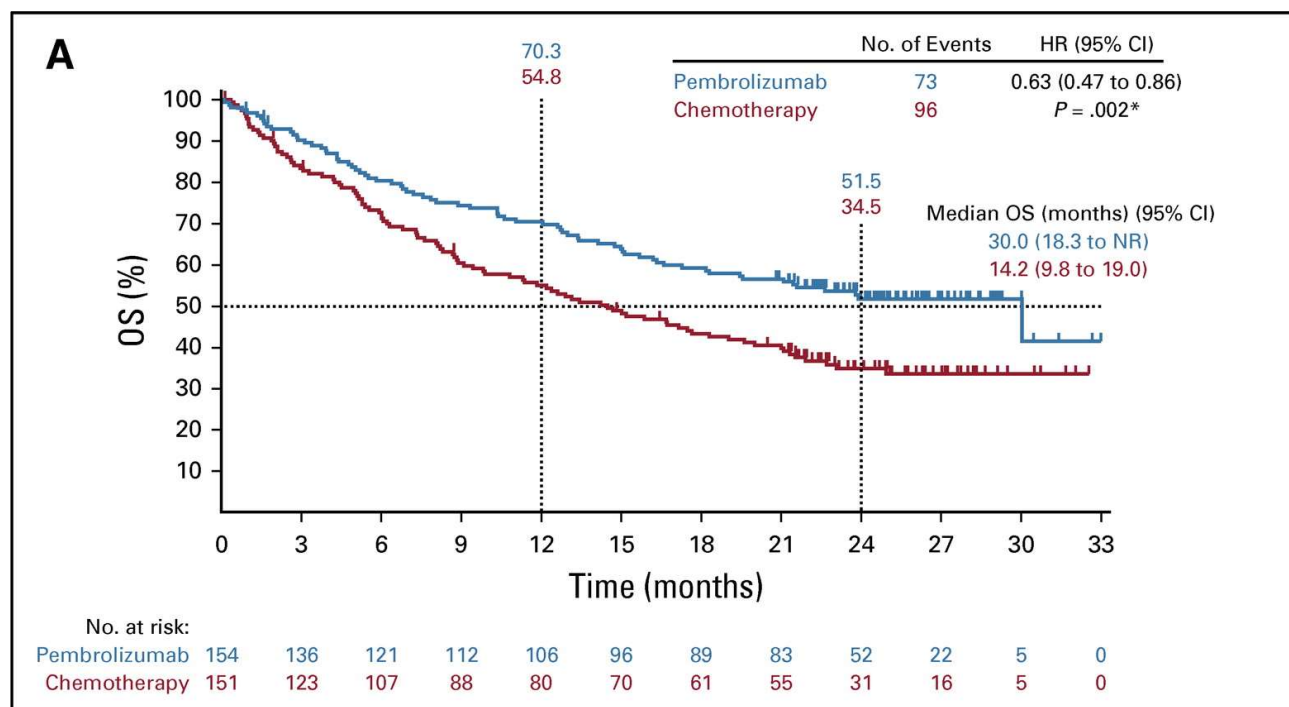


Ramalingam, ASCO 2020.

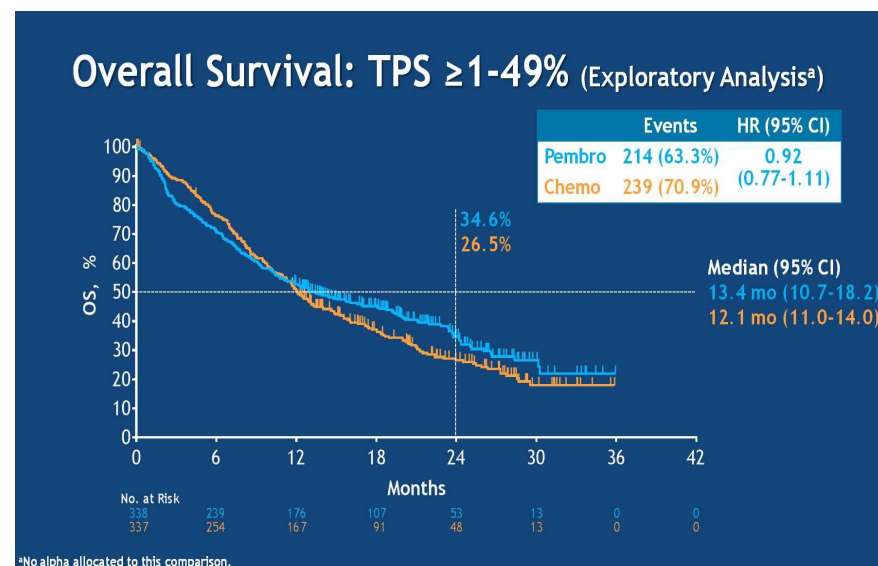
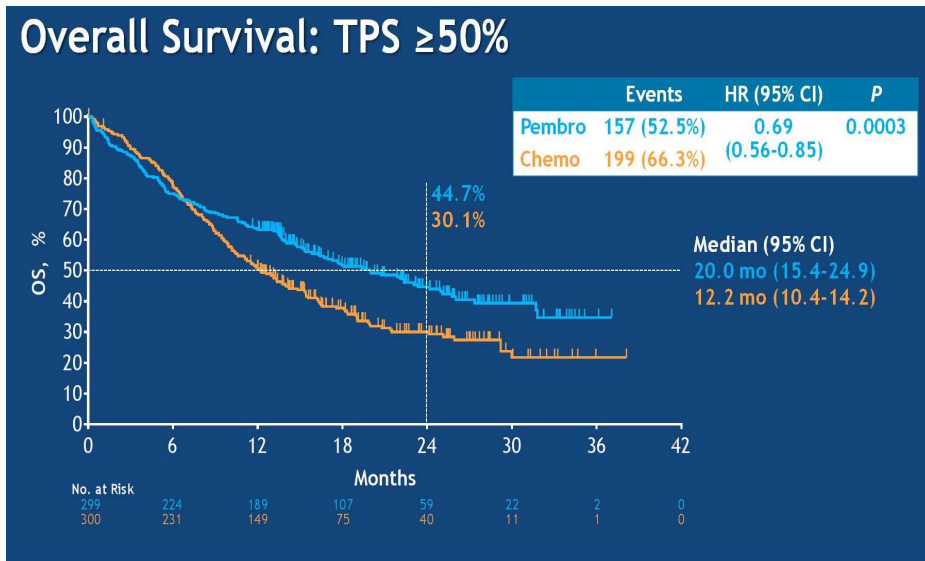
© 2020–2021 Society for Immunotherapy of Cancer

#LearnACI

KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 50% NSCLC



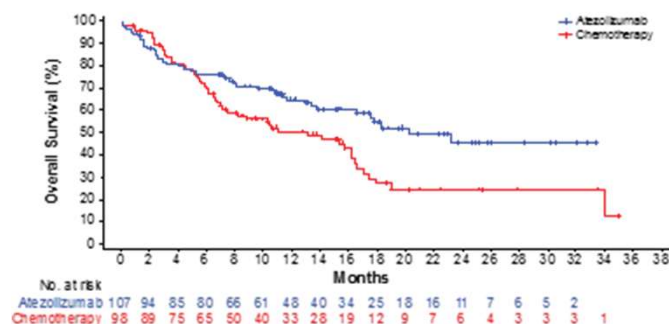
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 $\geq 1\%$ NSCLC



Survival benefit seemed to be driven by the TPS $\geq 50\%$ subset with little benefit witnessed in the subset TPS = 1 - 49%

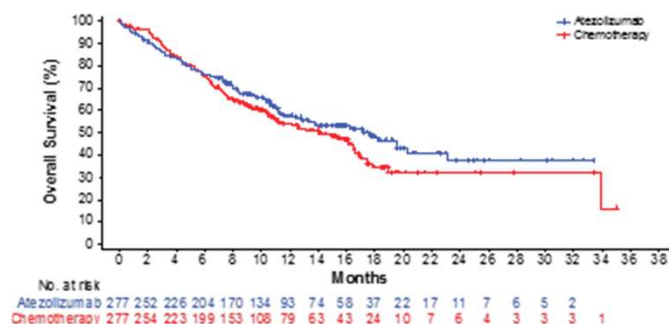
IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

SP142 (TC3 or IC3-WT)^a



	Atezo (n = 107)	Chemo (n = 98)
mOS, mo	20.2	13.1
HR ^b	0.59	
(95% CI)	(0.40, 0.89)	

SP142 (TC1/2/3 or IC1/2/3-WT)^a

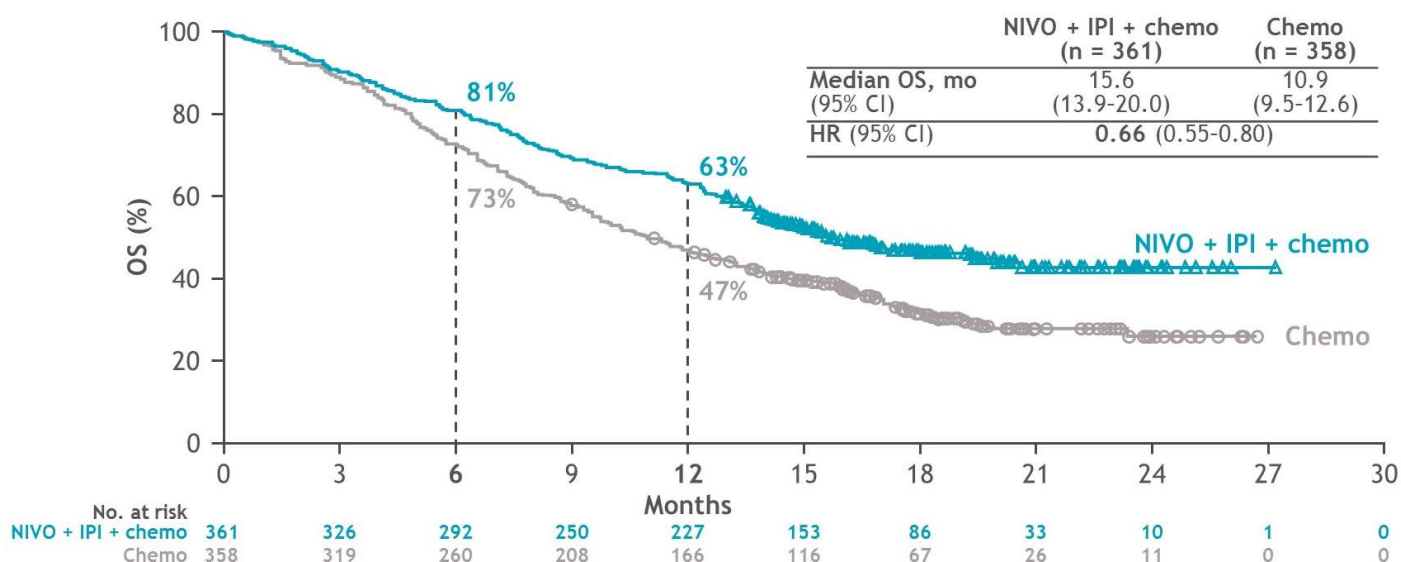


	Atezo (n = 277)	Chemo (n = 277)
mOS, mo	17.5	14.1
HR ^b	0.83	
(95% CI)	(0.65, 1.07)	

TC3 IC3	TC ≥ 50% IC ≥ 10%
TC2/3 IC2/3	TC ≥ 5% IC ≥ 5%
TC1/2/3 IC1/2/3	TC ≥ 1% IC ≥ 1%

Treatments not reliant on PD-L1 expression

CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo



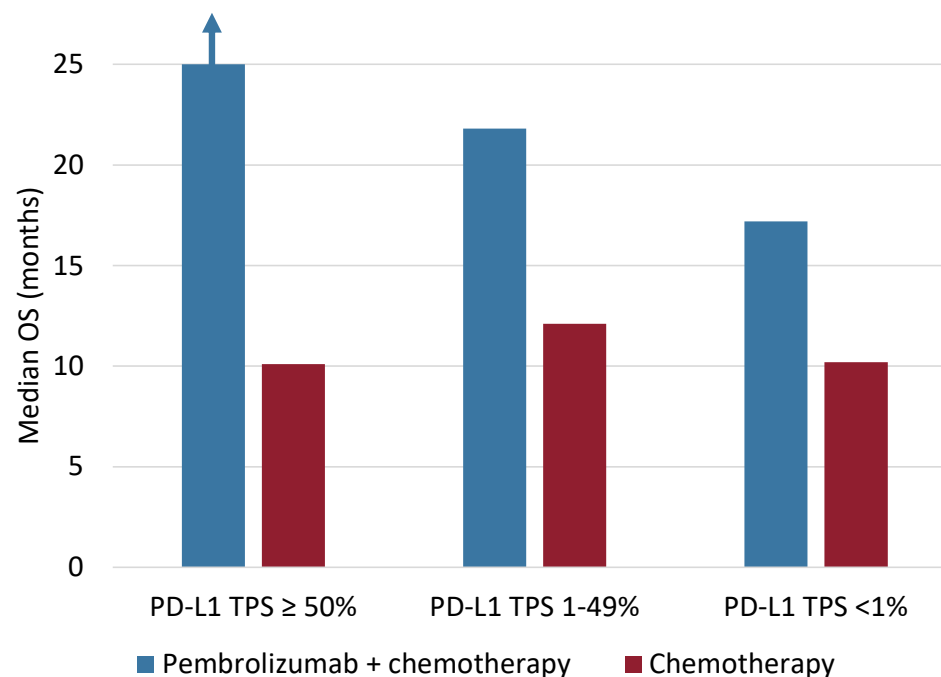
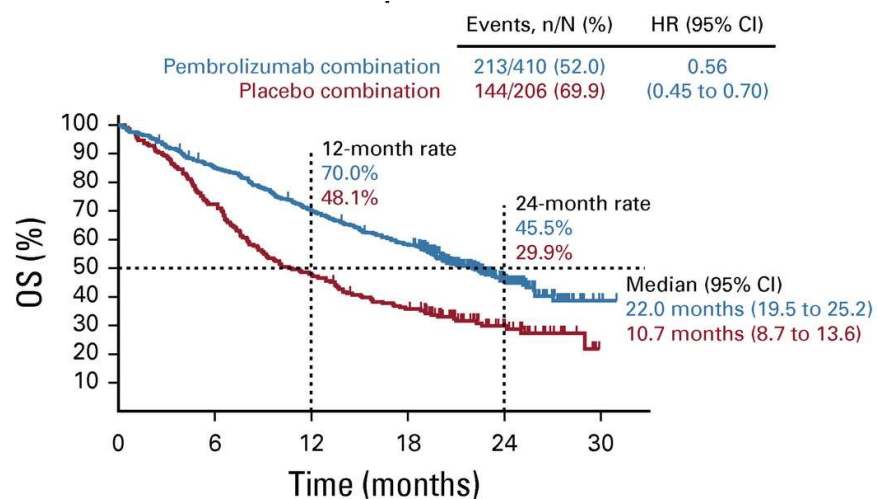
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	138 (38)	89 (25)
Odds ratio (95% CI)	1.9 (1.4-2.6)	
BOR, n (%)		
CR	8 (2)	4 (1)
PR	130 (36)	85 (24)
SD	164 (45)	185 (52)
PD	32 (9)	45 (13)
DCR, n (%)	302 (84)	274 (76)

Reck M et al, ASCO 2020.

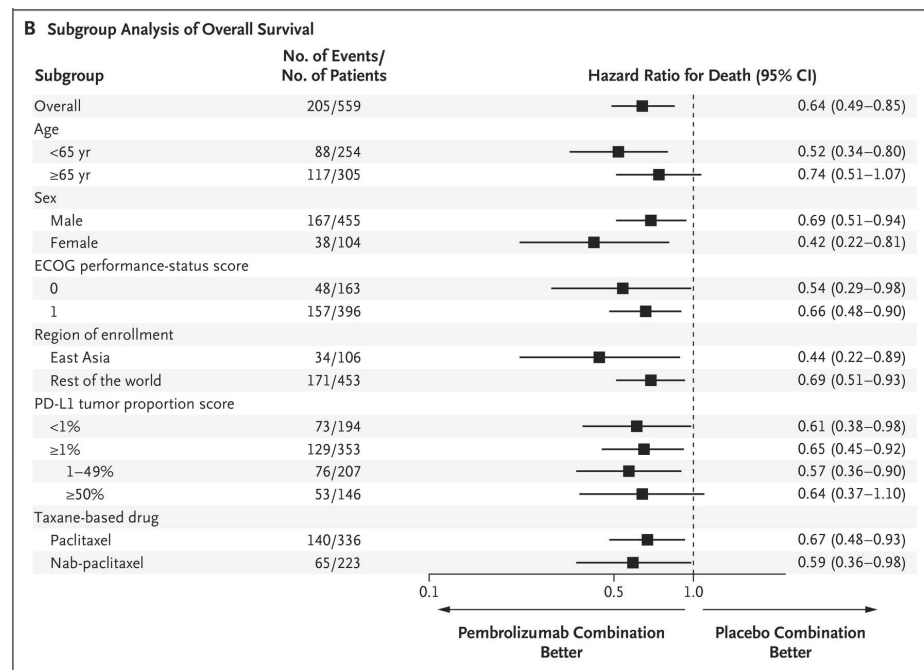
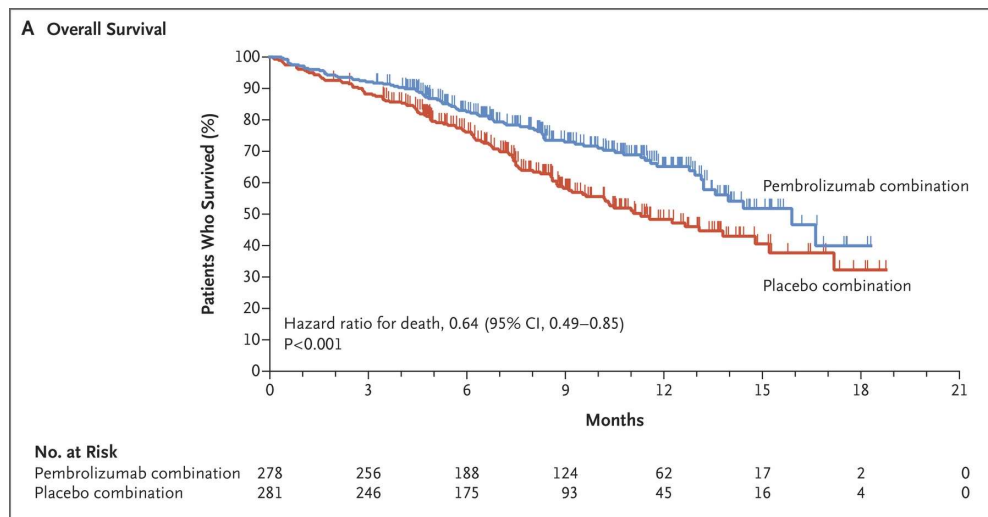
© 2020–2021 Society for Immunotherapy of Cancer

#LearnACI

KEYNOTE-189: Pembrolizumab/chemotherapy vs Chemotherapy Alone for Advanced Non-Squamous NSCLC



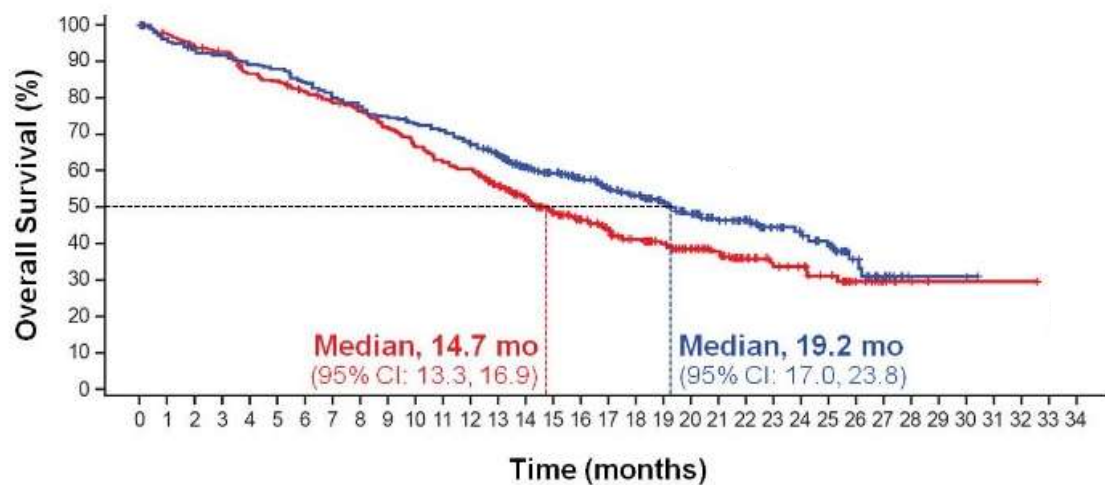
KEYNOTE-407: Pembrolizumab/Chemotherapy vs Chemotherapy Alone for Advanced Squamous-Cell NSCLC



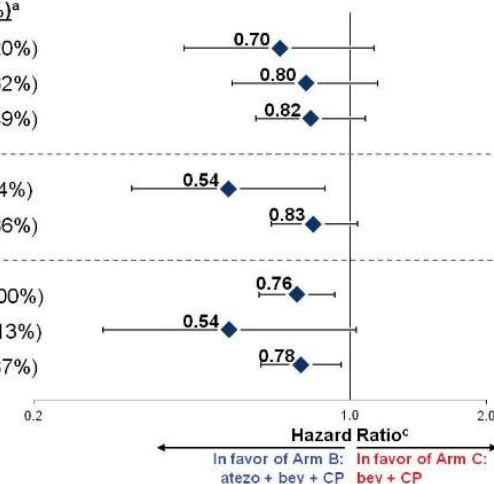
IMpower150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/ Paclitaxel/ Bevacizumab in Advanced Non-Squamous NSCLC

Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

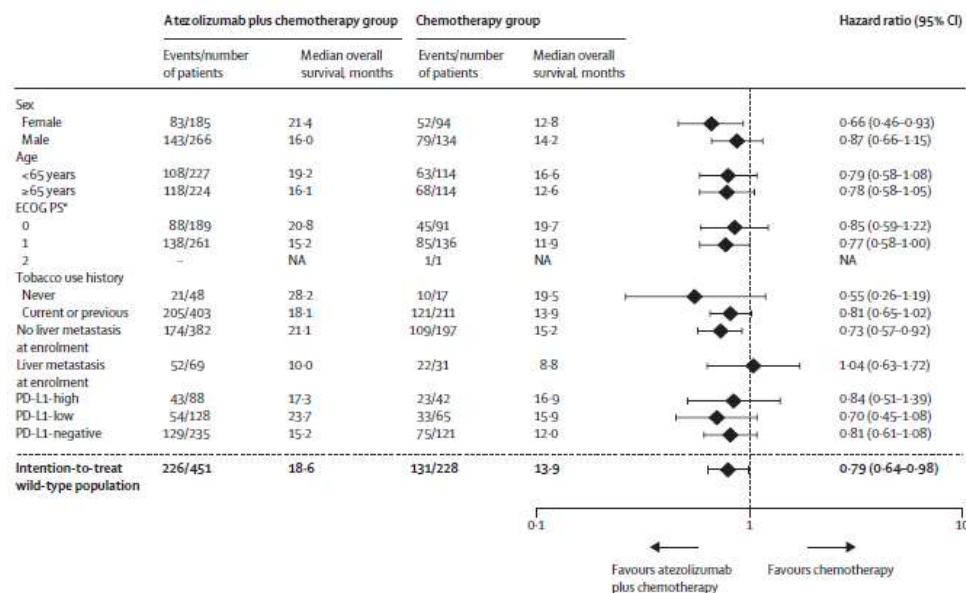
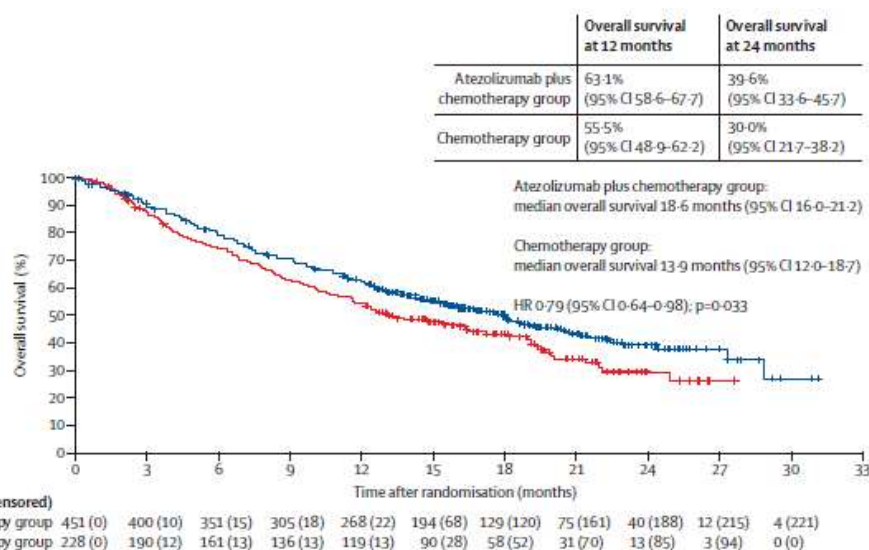
HR^a, 0.78
 (95% CI: 0.64, 0.96)
P = 0.0164
 Median follow-up: ~20 mo



Subgroup	n (%) ^a
PD-L1–High (TC3 or IC3) WT	136 (20%)
PD-L1–Low (TC1/2 or IC1/2) WT	226 (32%)
PD-L1–Negative (TC0 and IC0) WT	339 (49%)
Liver Metastases WT	94 (14%)
No Liver Metastases WT	602 (86%)
ITT (including EGFR/ALK+)	800 (100%)
EGFR/ALK+ only	104 ^b (13%)
ITT-WT	696 (87%)



IMpower130: Atezolizumab + chemo vs chemo alone for non-squamous NSCLC



Immunotherapy for relapsed/refractory NSCLC

Drug	Indication	Dose
Nivolumab	Metastatic squamous or non-squamous NSCLC with progression after chemotherapy (2 nd line)	240 mg Q2W or 480 mg Q4W
Pembrolizumab	Metastatic NSCLC with progression after chemotherapy and PD-L1 ≥ 1%	200 mg Q3W or 400 mg Q6W
Atezolizumab	Metastatic NSCLC with progression after Pt-chemotherapy and targeted therapy if EGFR/ALK mutation-positive	840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W

Second-line use of ICI in NSCLC

Study	Treatment arms	ORR	Median PFS (months)	Median OS (months)
CheckMate 017 and CheckMate 057	Nivolumab	19%	2.56	11.1
	Docetaxel	11%	3.52	8.1
KEYNOTE-010 (PD-L1 TPS ≥ 1%)	Pembrolizumab	18%	4.0	12.7
	Docetaxel	9%	4.0	8.5
OAK	Atezolizumab	14%	2.8	13.8
	Docetaxel	13%	4.0	9.6

Vokes, Ann Oncol 2018.
 Herbst, Lancet 2016.
 Fehrenbacher, J Thorac Oncol 2018.

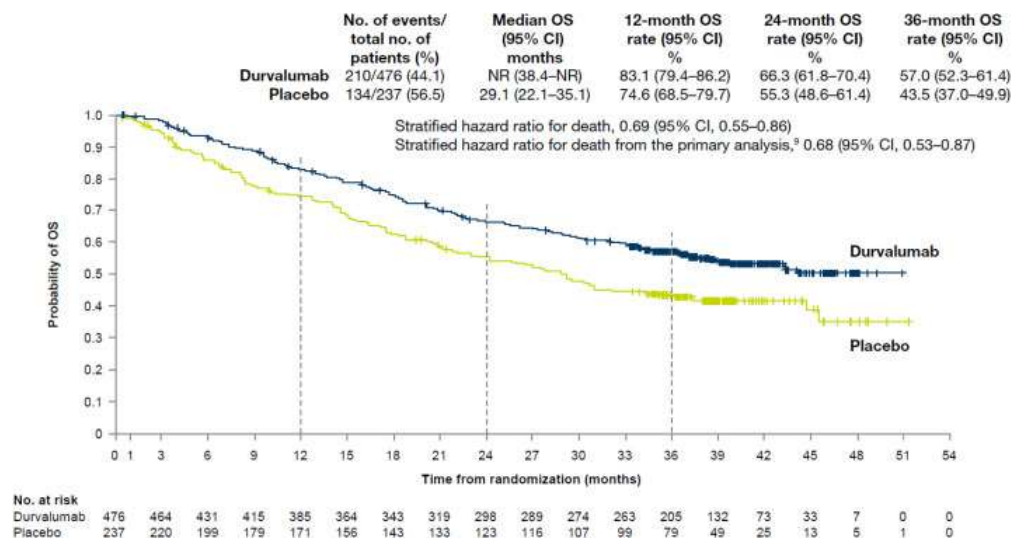
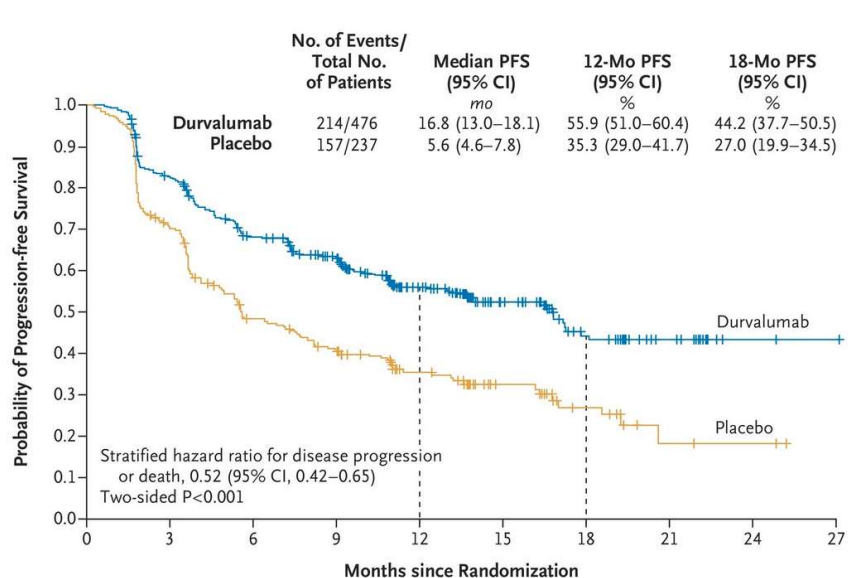
© 2020–2021 Society for Immunotherapy of Cancer

#LearnACI

Immunotherapy for stage III NSCLC

Drug	Indication	Dose
Durvalumab	Stage III NSCLC, ineligible for surgery and without progression after chemoradiation	10 mg/kg Q2W
Pembrolizumab	1 st line stage III NSCLC (not candidate for resection or definitive chemoradiation) with PD-L1 TPS ≥ 1%	200 mg Q3W or 400 mg Q6W

PACIFIC: durvalumab consolidation therapy for stage III NSCLC



Antonia, N Engl J Med 2017.
Gray, J Thorac Oncol 2020.

© 2020–2021 Society for Immunotherapy of Cancer

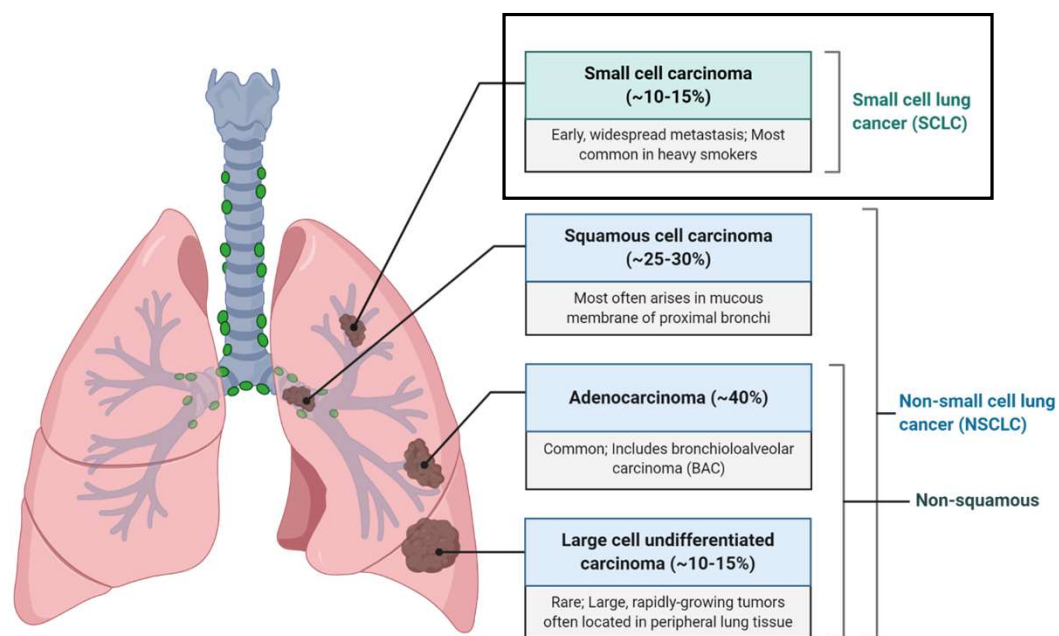
#LearnACI

Outline

- Non-small cell lung cancer
 - Front-line – PD-L1-selected and unselected
 - Later lines of treatment
 - Stage III
- Small cell lung cancer
- Future directions for lung cancer immunotherapy

Small cell lung cancer

- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

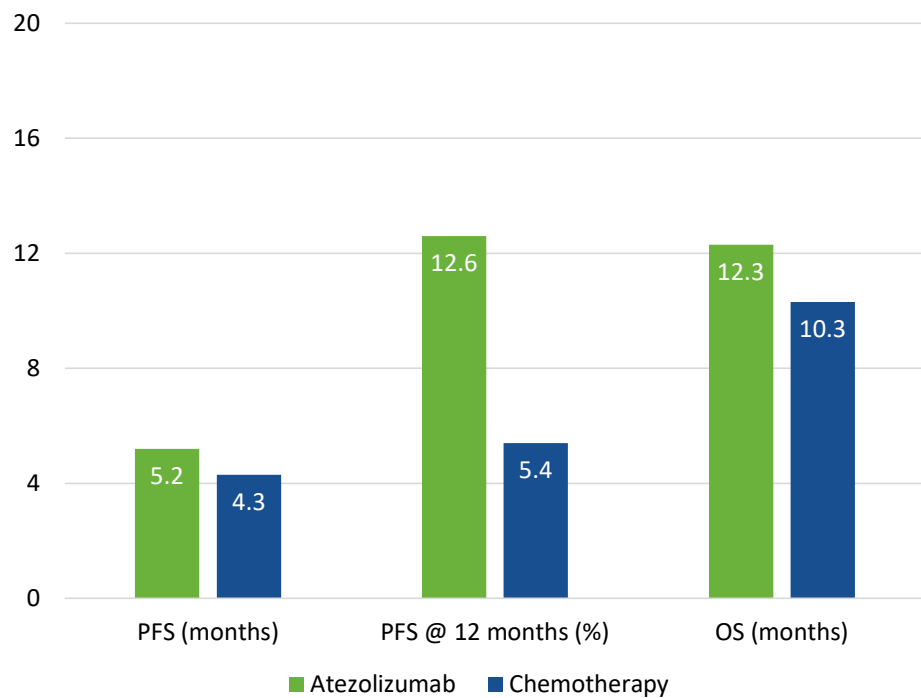


Approved checkpoint inhibitors in SCLC

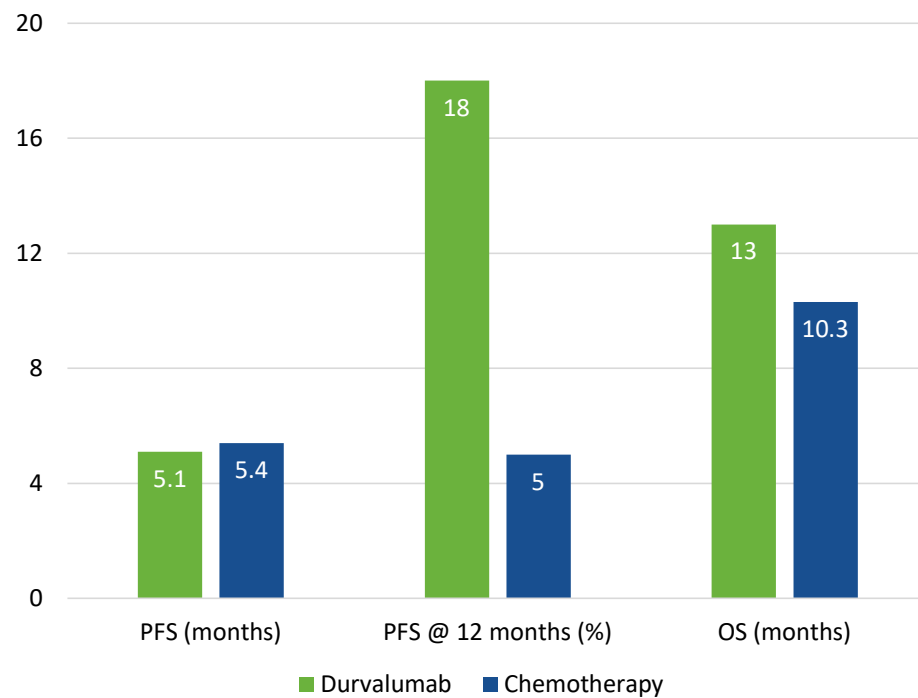
Drug	Indication	Dose
Nivolumab	Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy (3rd line)	240 mg Q2W
Pembrolizumab	Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy (3rd line)	200 mg Q3W or 400 mg Q6W
Atezolizumab + carboplatin + etoposide	1st line extensive stage SCLC	For 4 cycles: atezolizumab 1200 mg + carboplatin + etoposide Q3W Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W
Durvalumab + etoposide + carboplatin/cisplatin	1st line extensive stage SCLC	For 4 cycles: 1500 mg durvalumab Q3W + chemotherapy; Maintenance: 1500 mg durvalumab Q4W

Front-line ICI in SCLC

IMpower133



CASPIAN

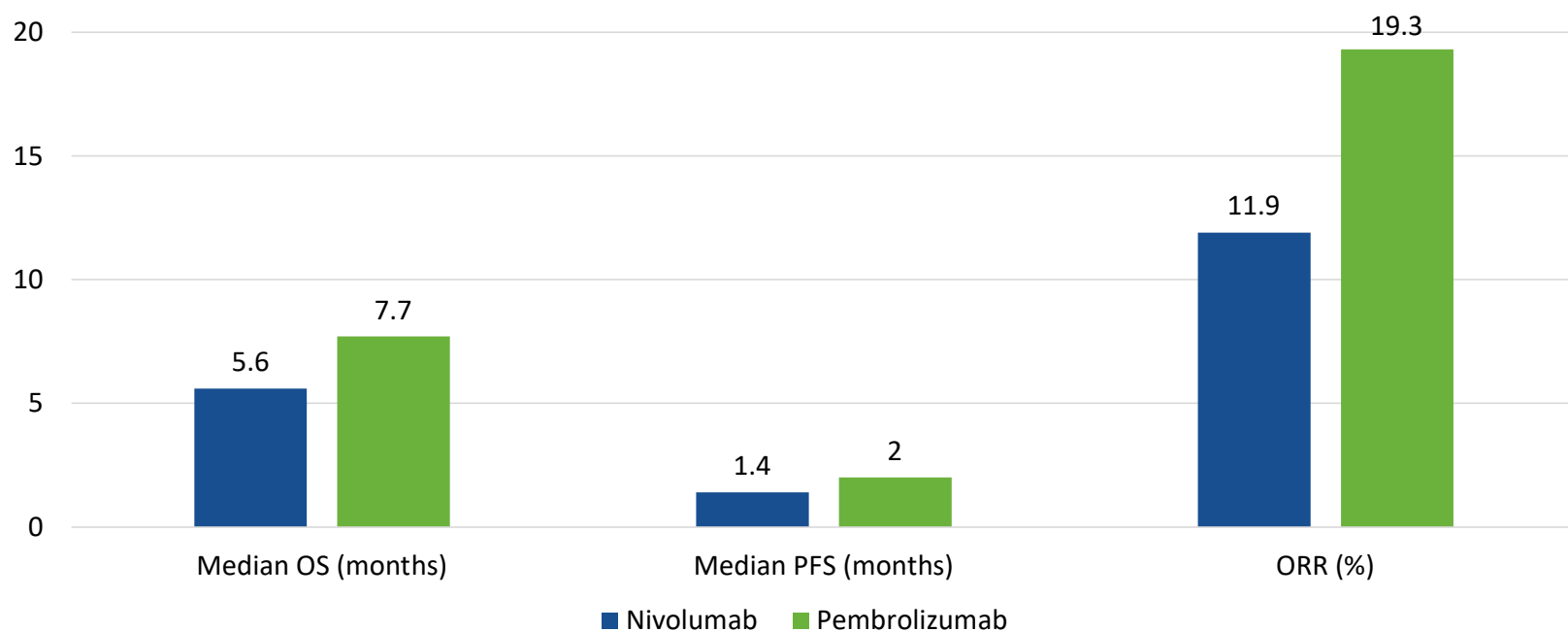


Huang, J Hematol Oncol 2020.

© 2020–2021 Society for Immunotherapy of Cancer

#LearnACI

Later-line ICI in SCLC



Ready, J Thorac Oncol 2019.
 Chung, J Thorac Oncol 2020.
 Ott, J Clin Oncol 2017.

© 2020–2021 Society for Immunotherapy of Cancer

#LearnACI

Outline

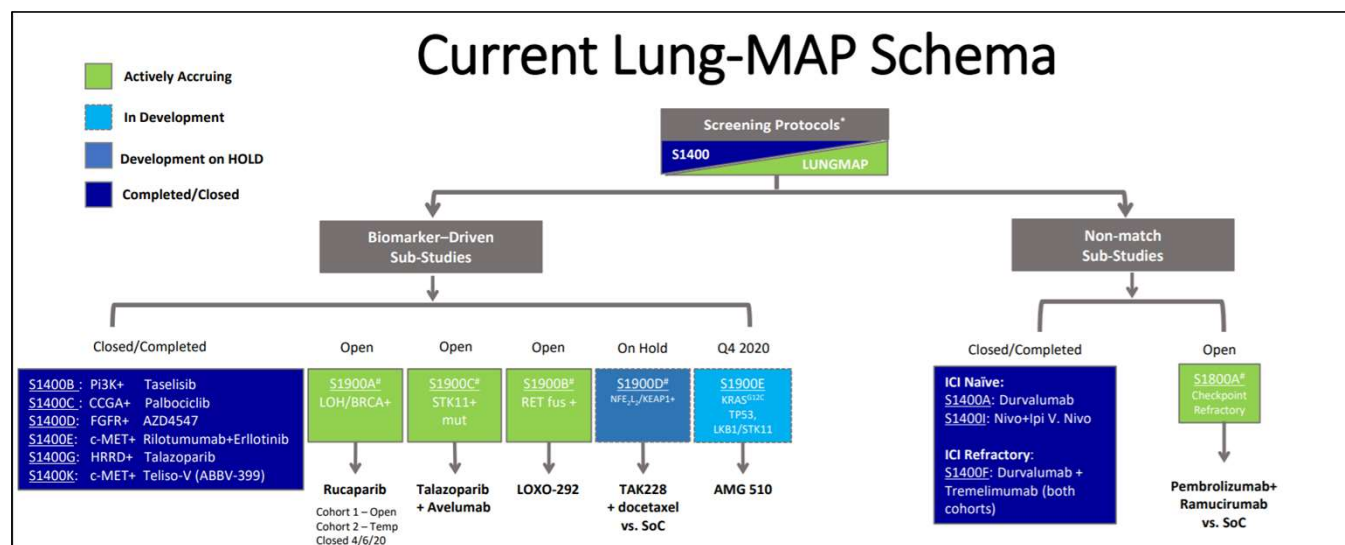
- Non-small cell lung cancer
 - Front-line – PD-L1-selected and unselected
 - Later lines of treatment
 - Stage III
- Small cell lung cancer
- Future directions for lung cancer immunotherapy

In development: answering outstanding questions

- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities

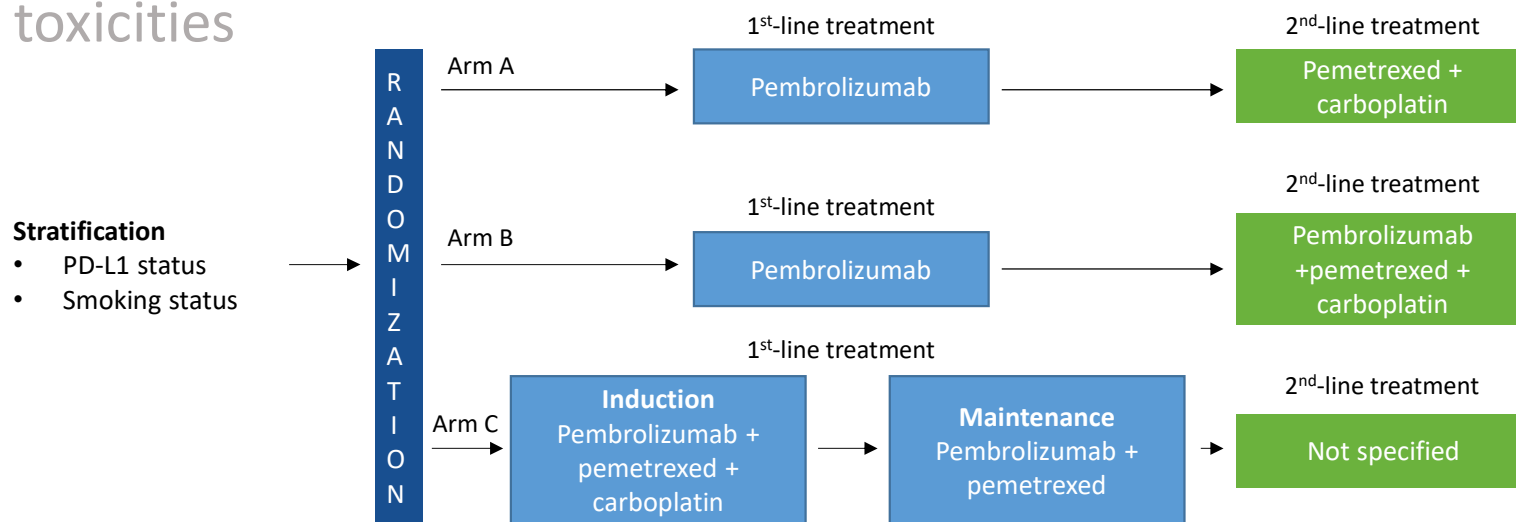
In development: answering outstanding questions

- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities



In development: answering outstanding questions

- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities



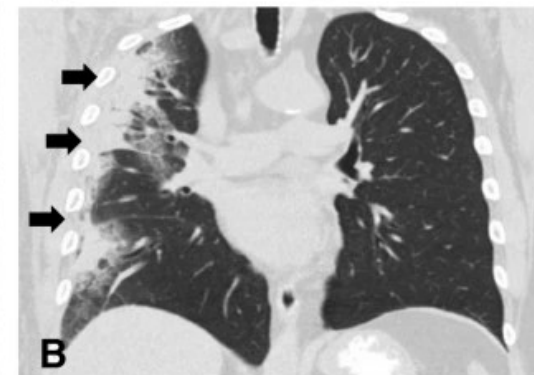
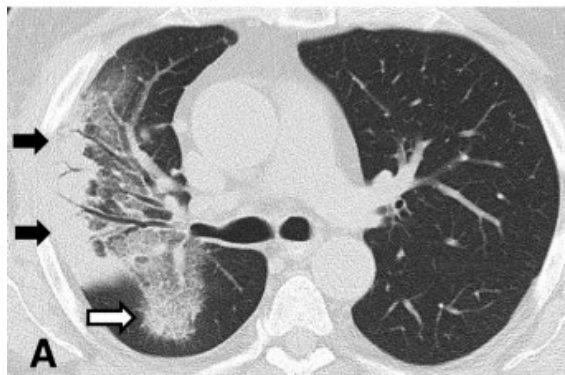
In development: answering outstanding questions

- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities – radiation and ICIs



Axillary radiation treatment field from September-October 2017 demonstrating overlap with peripheral lung.

Chest CT performed 5 months after completing right axillary radiotherapy (March 2018) and 1.5 months after initiating nivolumab therapy



Schoenfeld, J Immunother Cancer 2019.

© 2020–2021 Society for Immunotherapy of Cancer

#LearnACI

Immunotherapy for mesothelioma

Drug	Indication	Dose
Nivolumab + ipilimumab	Frontline unresectable malignant pleural mesothelioma	Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W

- Approval based on CheckMate 743
 - Nivolumab + ipilimumab vs platinum-based chemotherapy
 - Median OS: 18.1 months vs 14.1 months
 - 2-year OS: 41% vs 27%
 - Median PFS: 6.8 months vs 7.2 months
- First FDA approval for mesothelioma since 2004

Conclusions

- NSCLC has been a proving ground for checkpoint inhibitors
- Many front-line options available for NSCLC
- Clear-cut biomarkers still lacking
- SCLC is beginning to benefit from immune checkpoint inhibitor treatments

Brahmer et al. *Journal for Immunotherapy of Cancer* (2018) 6:75
<https://doi.org/10.1186/s40425-018-0382-2>

Journal for Immunotherapy
of Cancer

POSITION ARTICLE AND GUIDELINES

Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC)



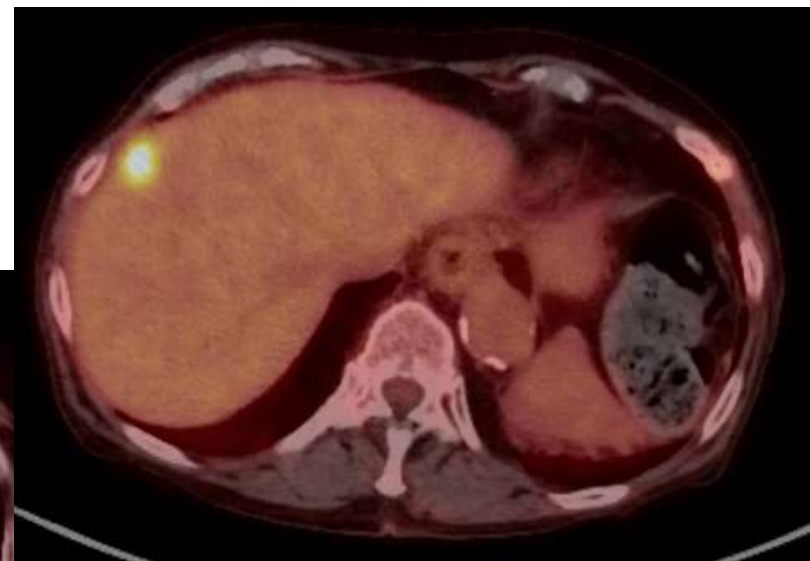
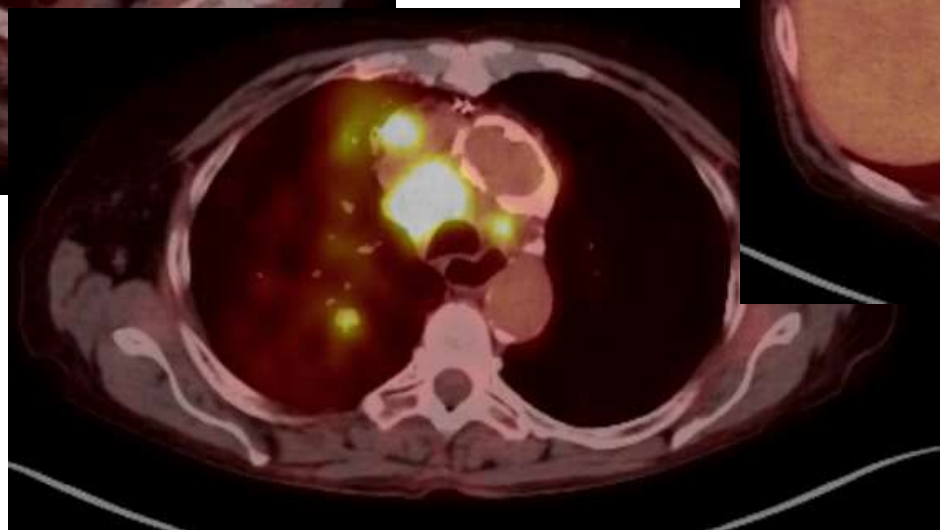
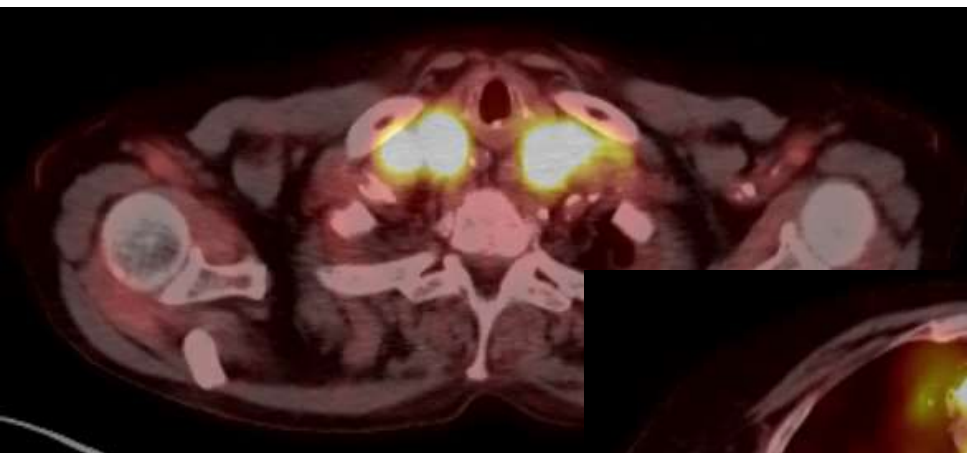
Julie R. Brahmer¹, Ramaswamy Govindan², Robert A. Anders³, Scott J. Antonia⁴, Sarah Sagorsky⁵,
Marianne J. Davies⁶, Steven M. Dubinett⁷, Andrea Ferris⁸, Leena Gandhi⁹, Edward B. Garon¹⁰,
Matthew D. Hellmann¹¹, Fred R. Hirsch¹², Shakuntala Malik¹³, Joel W. Neal¹⁴, Vassiliki A. Papadimitrakopoulou¹⁵,
David L. Rimm¹⁶, Lawrence H. Schwartz¹⁷, Boris Sepesi¹⁸, Beow Yong Yeap¹⁹, Naiyer A. Rizvi²⁰ and Roy S. Herbst^{21*}

Case Studies

79 year old female

- 60 pack year smoking history
- Extensive adenopathy, liver involvement, neck involvement at presentation
- EBUS showed poorly differentiated adenocarcinoma
- MOLECULAR LUNG PANEL RESULTS
KRAS, EGFR, BRAF, ALK, ROS1 MUTATION NOT DETECTED
- PD-L1 IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS (22C3 CLONE)
TUMOR RESULT: **Tumor Proportion Score (TPS) (%) – 1%**

79 year old female – PD-L1 1%

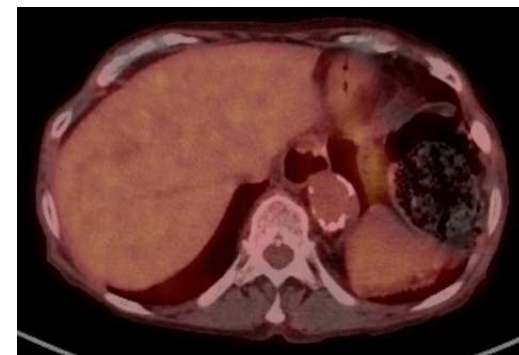
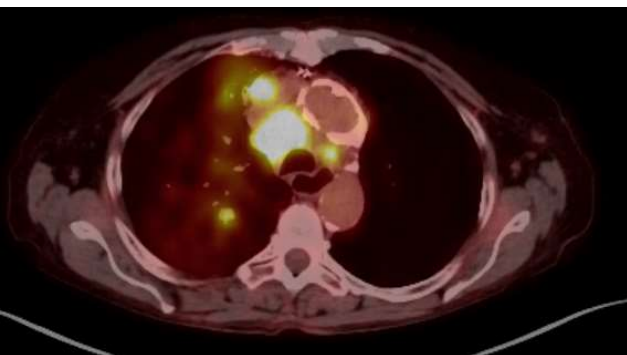
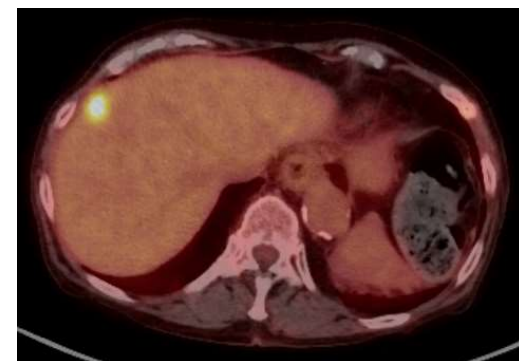
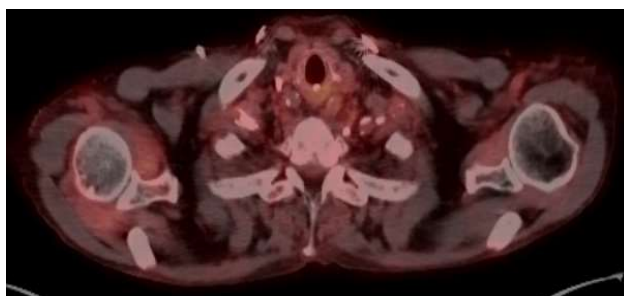
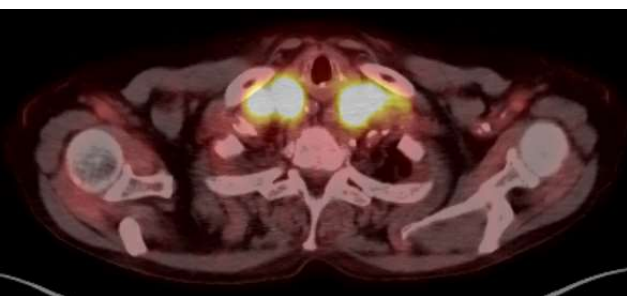


79 year old female – PD-L1 1%

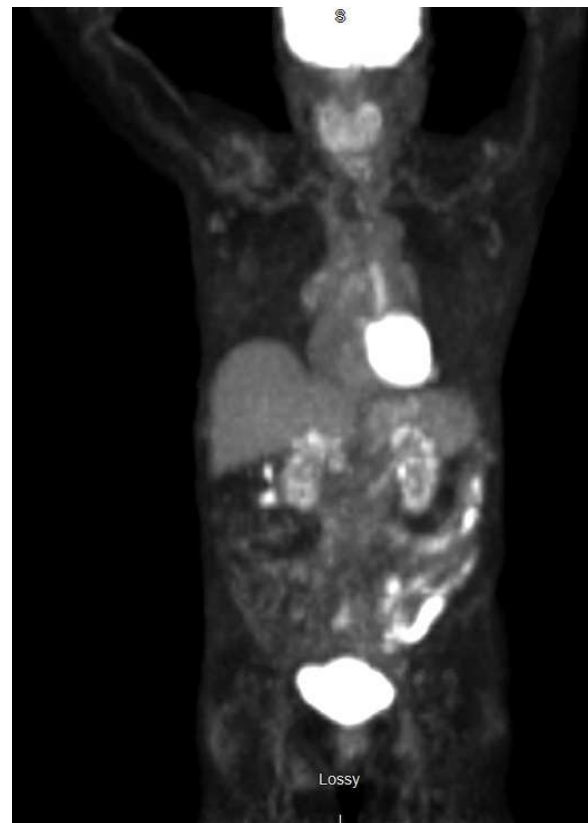
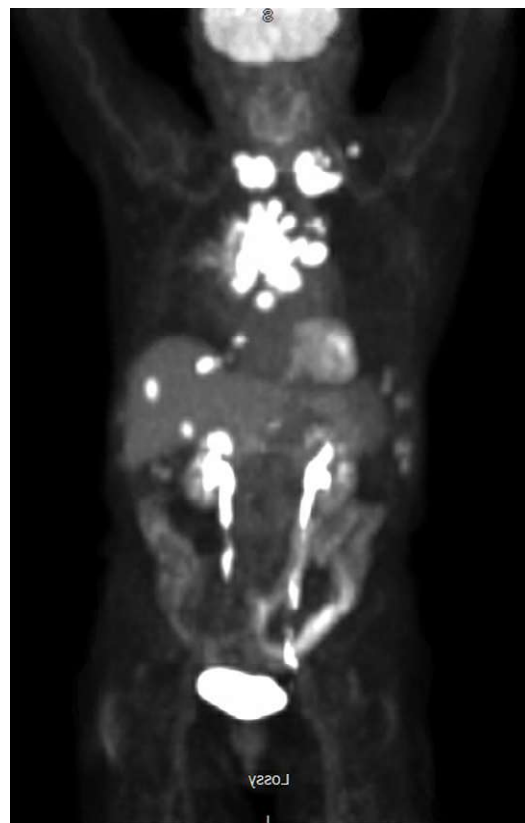
- What would you do now?
 1. Hospice
 2. Doublet chemotherapy
 3. Chemotherapy Immunotherapy
 4. Immunotherapy alone
- How would this change if the patient refused any chemotherapy?
 - Immunotherapy
- Started on ipilimumab + nivolumab doublet immunotherapy

79 year old female – PD-L1 1%

- Subsequent imaging after doublet immunotherapy



79 year old female – PD-L1 1%



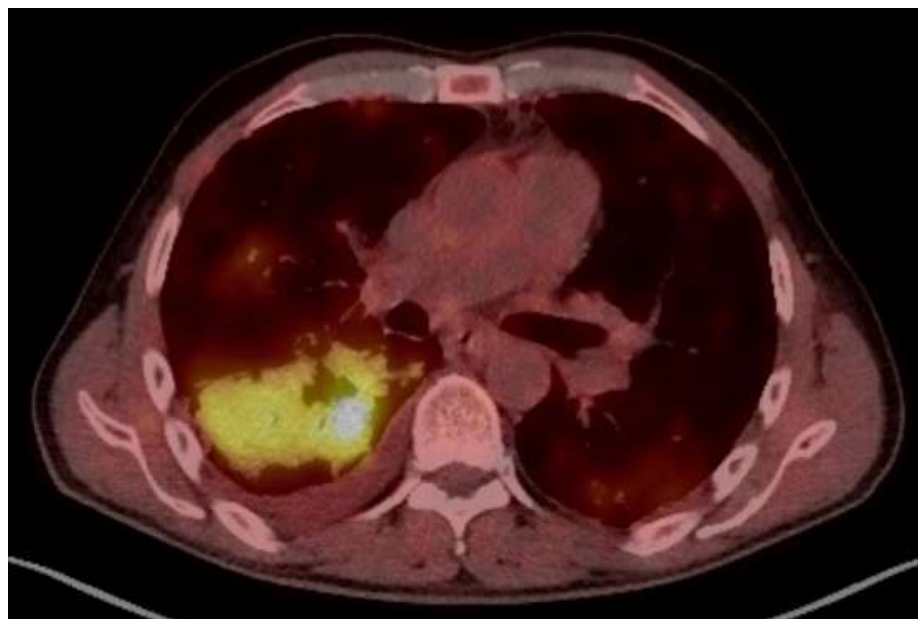
79 year old female – PD-L1 1%

- Update: Late November 2020 was admitted with hyperglycemia
- Treatment on hold
- Now receiving treatment as well for DMT1

52 year old male

- Heavy smoking history
- Presented with pericardial tamponade requiring pericardial window surgery
- TNTC pulmonary metastases, pleural effusion, osseous metastatic disease
- Developed extensive clot of pulmonary arteries requiring anticoagulation
- Pericardial tissue surgical biopsy revealed pulmonary poorly differentiated adenocarcinoma
- Molecular testing negative
- PD-L1 95%

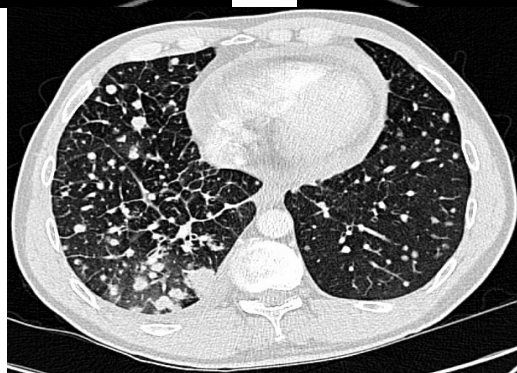
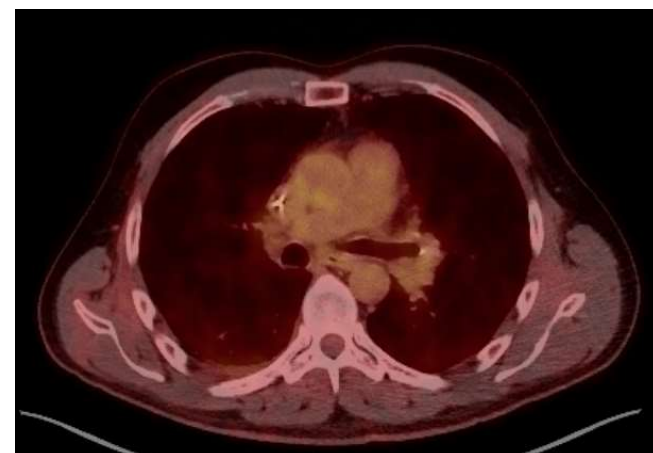
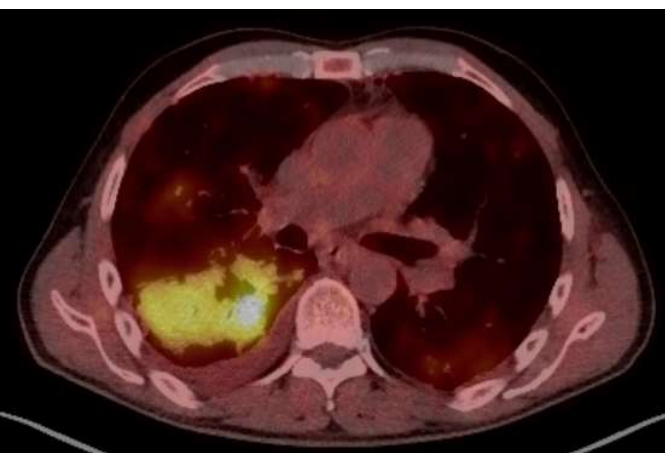
52 year old male – PD-L1 95%



52 year old male – PD-L1 95%

- What would you do now?
 1. Hospice
 2. Chemotherapy doublet
 3. Immunotherapy alone
 4. Chemotherapy + Immunotherapy
- Would this patient benefit from the addition of chemotherapy?
In my opinion YES!
- Patient was started on treatment with carboplatin + pemetrexed + pembrolizumab

52 year old male – PD-L1 95%



Thank You!

