Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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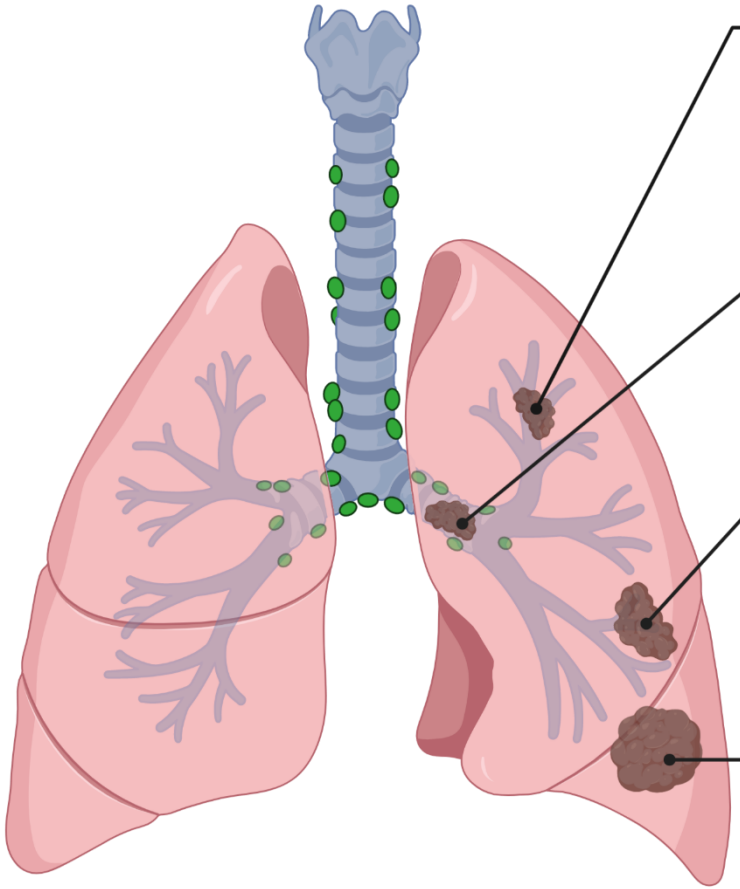
Disclosures

- Consulting Fees: Astra Zeneca, Blueprint Medicine
- I will be discussing non-FDA approved indications during my presentation.

Lung cancer



Small cell carcinoma (~10-15%)

Early, widespread metastasis; Most common in heavy smokers

Small cell lung cancer (SCLC)

Squamous cell carcinoma (~25-30%)

Most often arises in mucous membrane of proximal bronchi

Adenocarcinoma (~40%)

Common; Characterized by growth patterns

Large cell undifferentiated carcinoma (~10-15%)

Rare; Large, rapidly-growing tumors often located in peripheral lung tissue

Non-small cell lung cancer (NSCLC)

Non-squamous

Treatment options for NSCLC

Local disease

- Surgery
- Stereotactic body radiation therapy
- Chemotherapy

Metastatic disease

- Chemotherapy
- Targeted therapies
- Immunotherapy
- Radiation therapy

Stage III unresectable disease

- Concurrent chemo-radiation
- Immunotherapy

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

Mancheril, Hosp Pharm 2014.

Immune checkpoint inhibitors in lung cancer

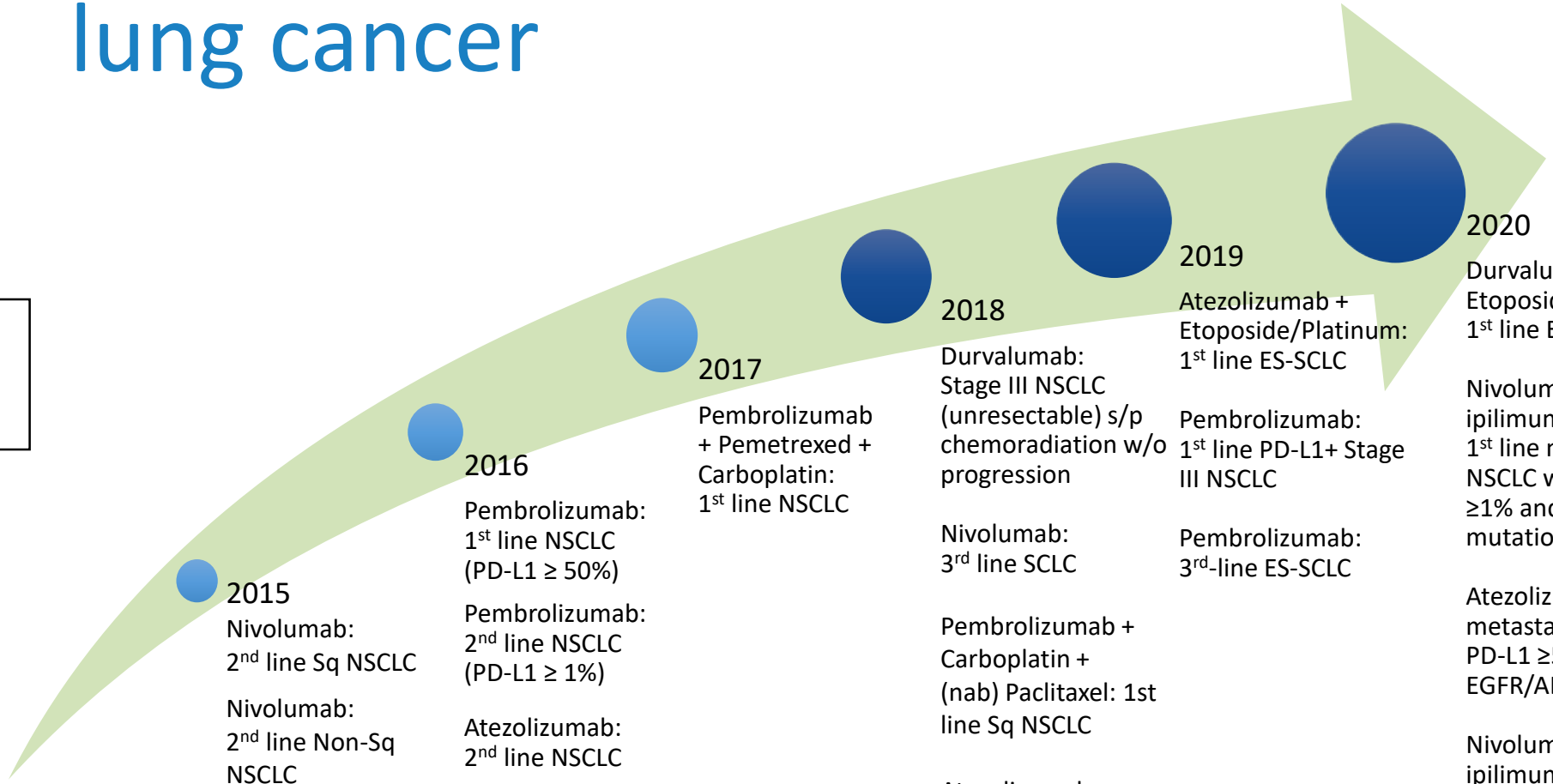
Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1

Durvalumab
PD-L1

Ipilimumab
CTLA-4



2015
Nivolumab:
2nd line Sq NSCLC

Nivolumab:
2nd line Non-Sq NSCLC

Pembrolizumab:
2nd line NSCLC
(PD-L1 ≥ 50%)

2016
Pembrolizumab:
1st line NSCLC
(PD-L1 ≥ 50%)

Pembrolizumab:
2nd line NSCLC
(PD-L1 ≥ 1%)

Atezolizumab:
2nd line NSCLC

2017
Pembrolizumab + Pemetrexed + Carboplatin:
1st line NSCLC

2018
Durvalumab:
Stage III NSCLC (unresectable) s/p chemoradiation w/o progression

Nivolumab:
3rd line SCLC

Pembrolizumab + Carboplatin + (nab) Paclitaxel: 1st line Sq NSCLC

Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel: 1st line Non-Sq NSCLC

2019
Atezolizumab + Etoposide/Platinum:
1st line ES-SCLC

Pembrolizumab:
1st line PD-L1+ Stage III NSCLC

Pembrolizumab:
3rd-line ES-SCLC

2020
Durvalumab + Etoposide/Platinum:
1st line ES-SCLC

Nivolumab + ipilimumab:
1st line metastatic NSCLC with PD-L1 ≥1% and no EGFR/ALK mutations

Atezolizumab: 1st line metastatic NSCLC with PD-L1 ≥50% and no EGFR/ALK mutations

Nivolumab + ipilimumab + chemotherapy: 1st line NSCLC with no EGFR/ALK mutations

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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

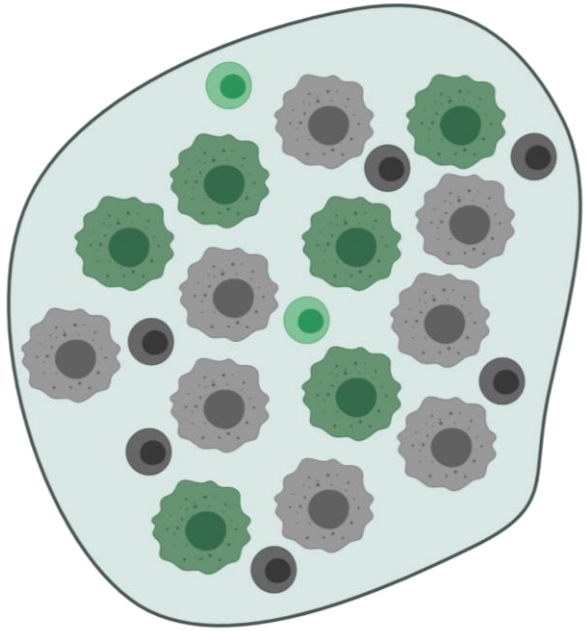
Immunotherapy for first-line treatment of metastatic NSCLC

Drug	Indication	Dose
Pembrolizumab	1st line metastatic NSCLC with **PD-L1 TPS ≥ 1%** and no EGFR/ALK mutations	200 mg Q3W or 400 mg Q6W
Atezolizumab	1st 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	1st line metastatic NSCLC with **PD-L1 ≥1%** and no EGFR/ALK mutations	Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
Cemiplimab	1st line advanced/metastatic NSCLC with **PD-L1 TPS ≥50%** and no EGFR/ALK/ROS1 mutations	350 mg Q3W
Nivolumab + ipilimumab + platinum-doublet chemotherapy	1st line metastatic NSCLC with no EGFR/ALK mutations	Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of chemotherapy
Pembrolizumab + pemetrexed + platinum	1st line metastatic non-squamous NSCLC with no EGFR/ALK mutations	200 mg Q3W or 400 mg Q6W
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel	1st line metastatic squamous NSCLC	200 mg Q3W or 400 mg Q6W
Atezolizumab + bevacizumab + paclitaxel + carboplatin	1st 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	1st 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

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

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



PD-L1-positive immune cell

PD-L1-negative immune cell

PD-L1-positive tumor cell

PD-L1-negative tumor cell

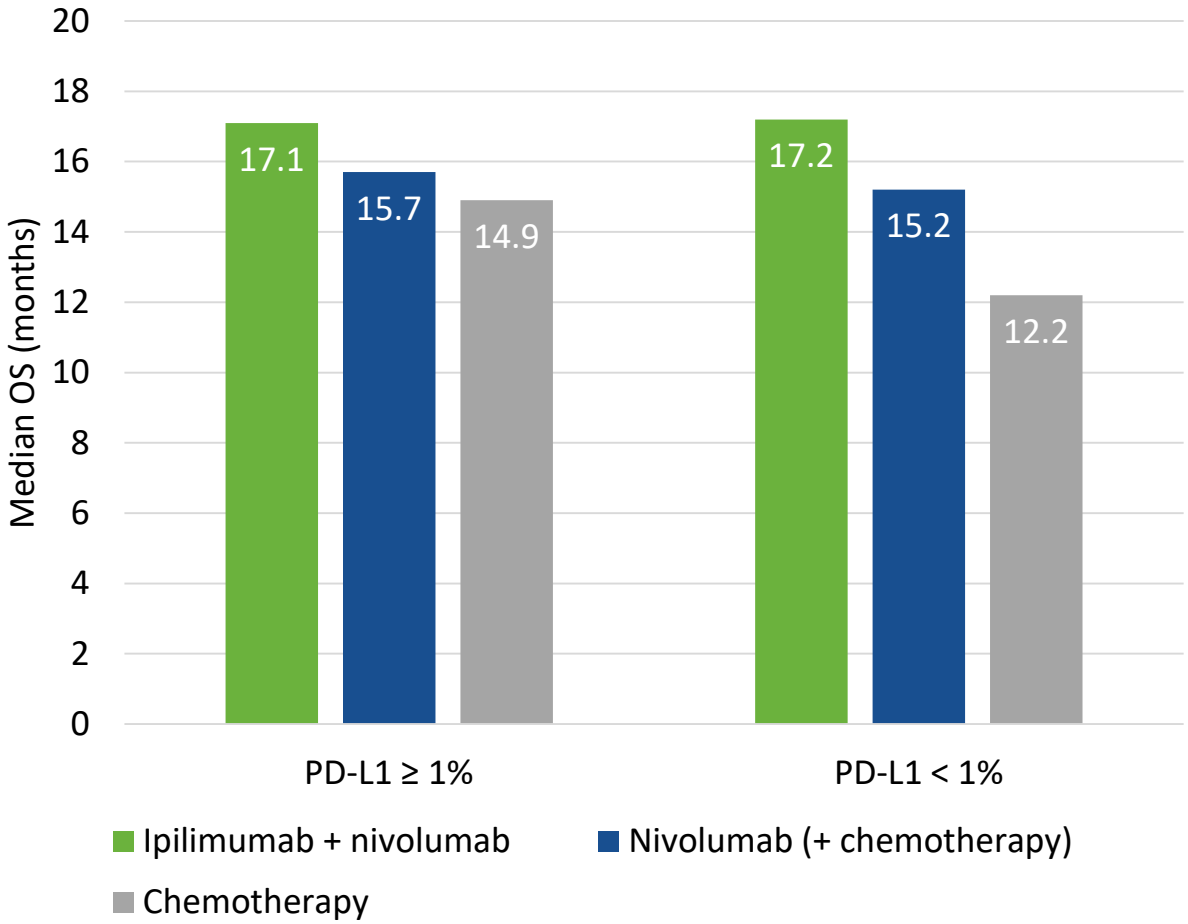
$$TPS = \frac{6\ positive\ tumor\ cells}{14\ total\ tumor\ cells} \times 100 = 43$$

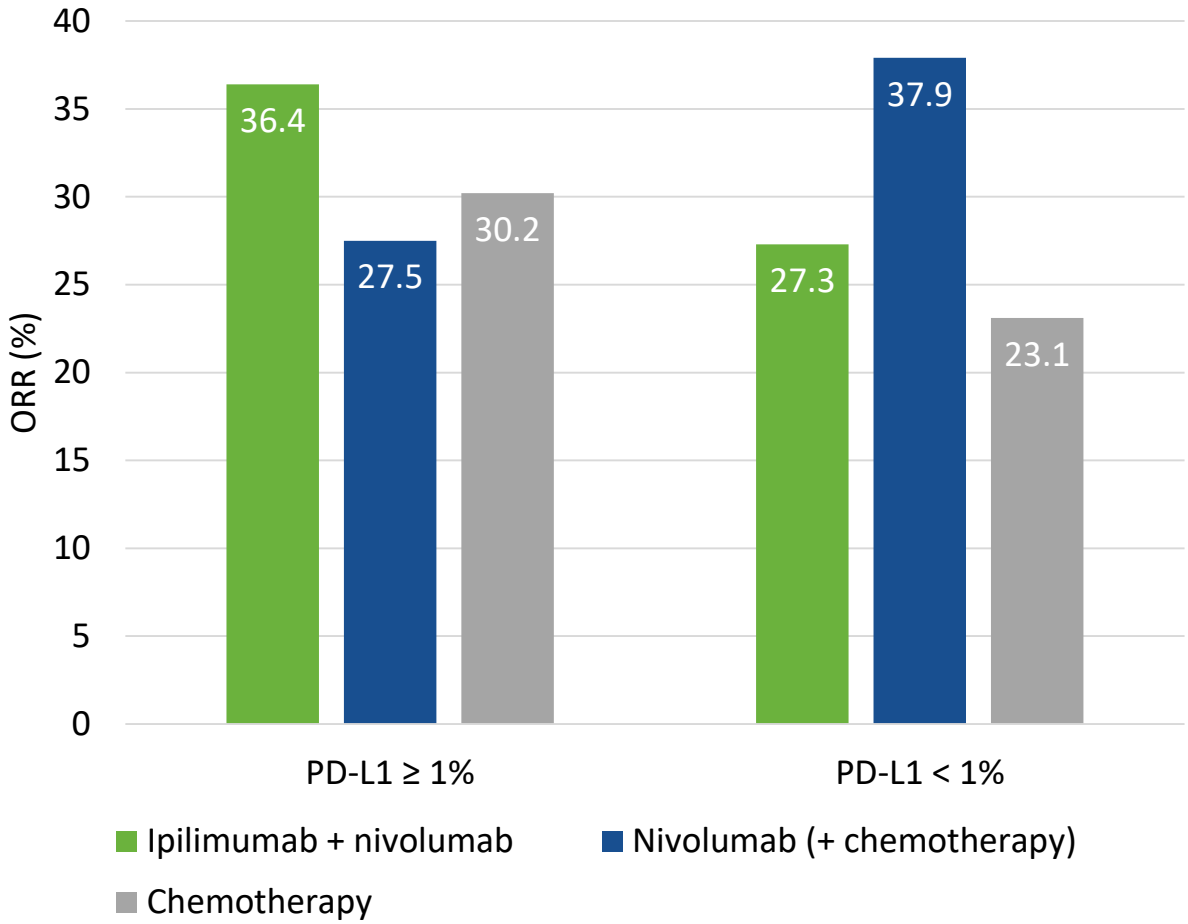
$$CPS = \frac{6\ positive\ tumor\ cells + 2\ positive\ immune\ cells}{22\ total\ cells} \times 100 = 36$$

Treatment Naïve Regimens: Competing Strategies in NSCLC by biomarker status

PD-L1-selected	PD-L1-unselected
Nivolumab + ipilimumab *CheckMate 227*	Nivolumab + ipilimumab + platinum-doublet *CheckMate 9LA*
Pembrolizumab *KEYNOTE-024, -042*	Pembrolizumab + chemotherapy *KEYNOTE-189, -407*
Atezolizumab *IMpower110*	Atezolizumab + bevacizumab + chemotherapy *IMpower150*
	Atezolizumab + chemotherapy *Impower130*

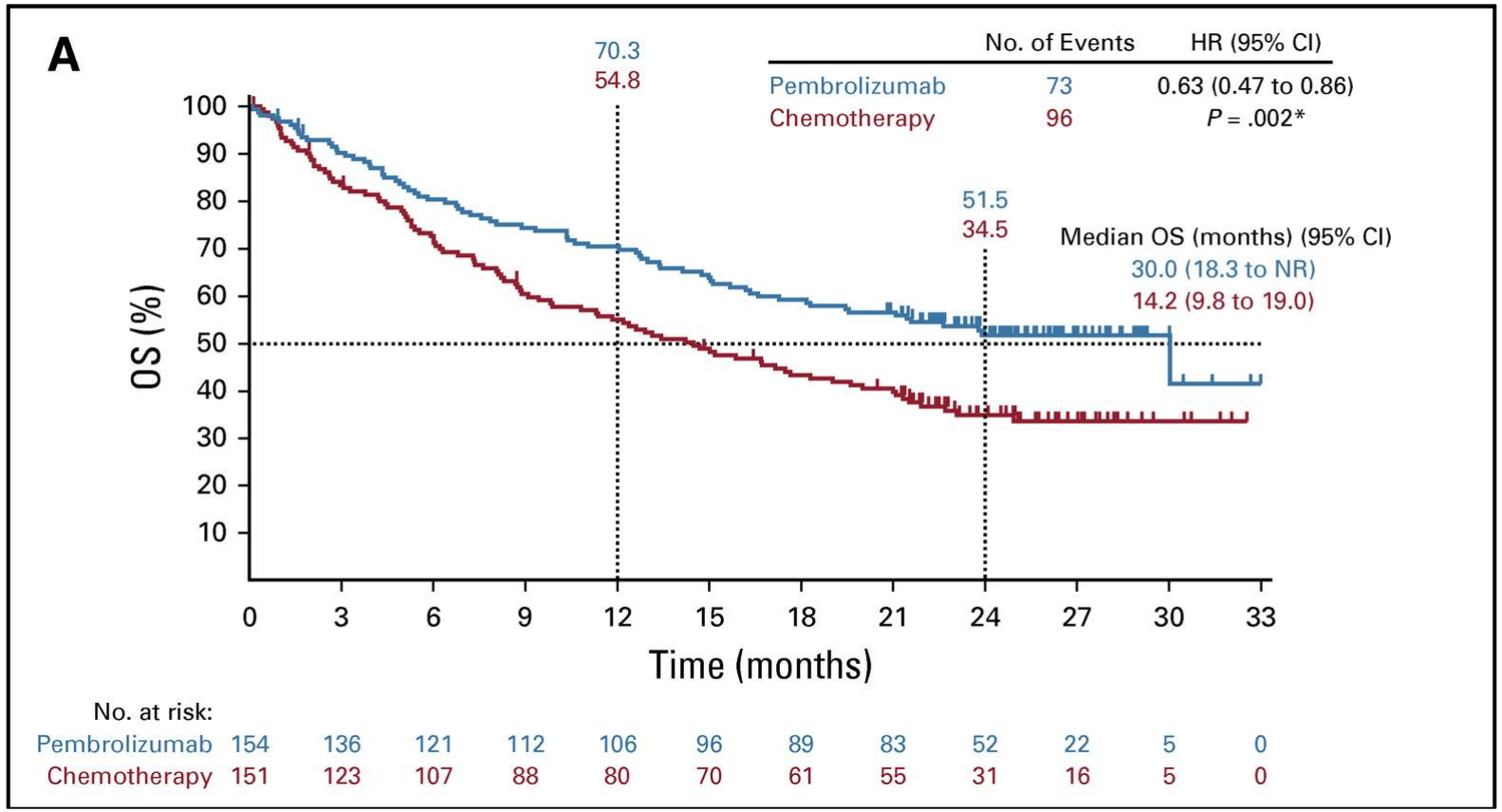
CheckMate 227: Ipilimumab + nivolumab vs chemotherapy for 1L NSCLC





Ramalingam, ASCO 2020.

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



Reck, J Clin Oncol 2019.

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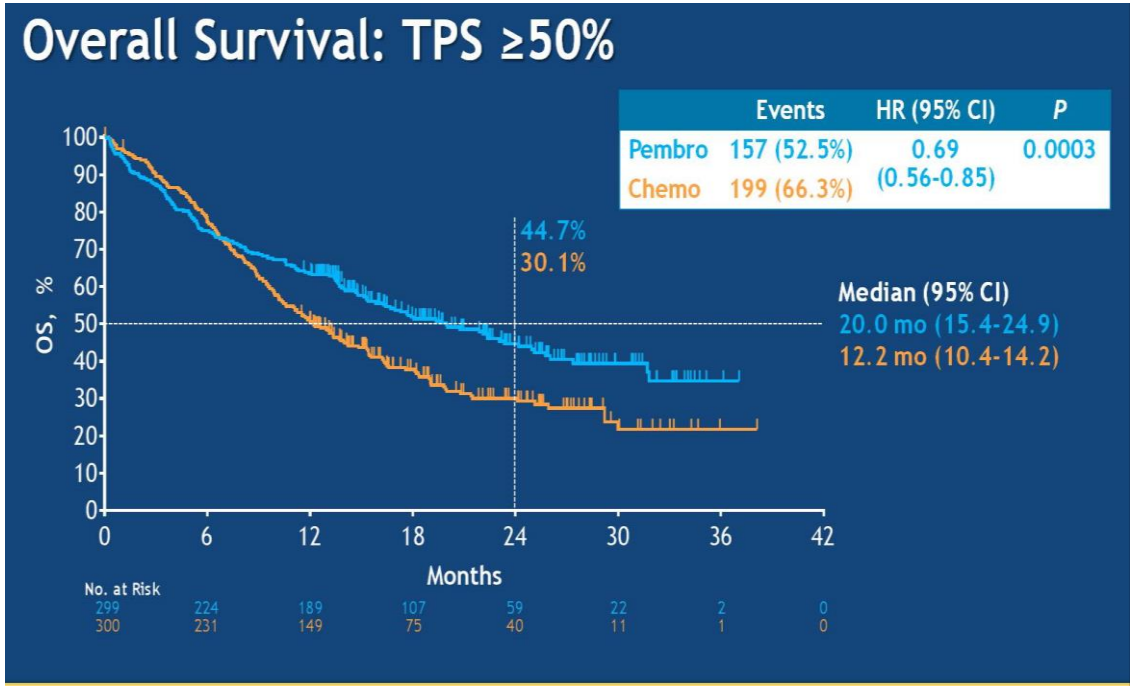
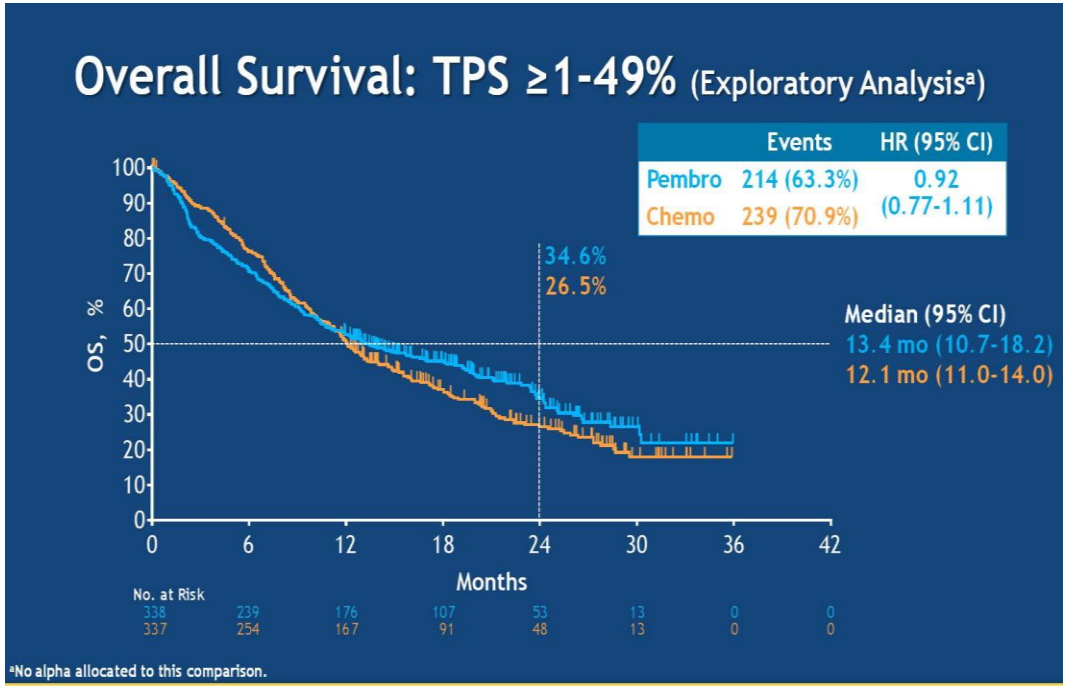
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC



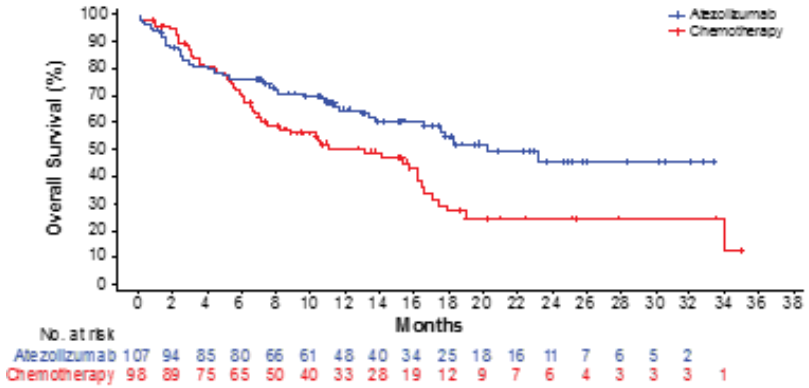


Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%

Lopes et al, ASCO 2018

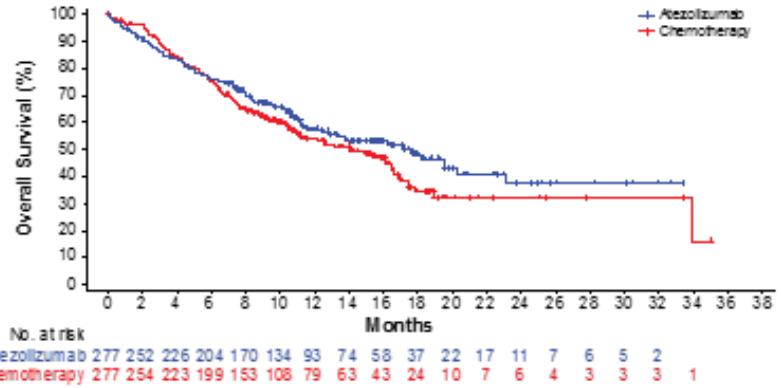
IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

SP142 (TC3 or IC3-WT)[a]



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

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



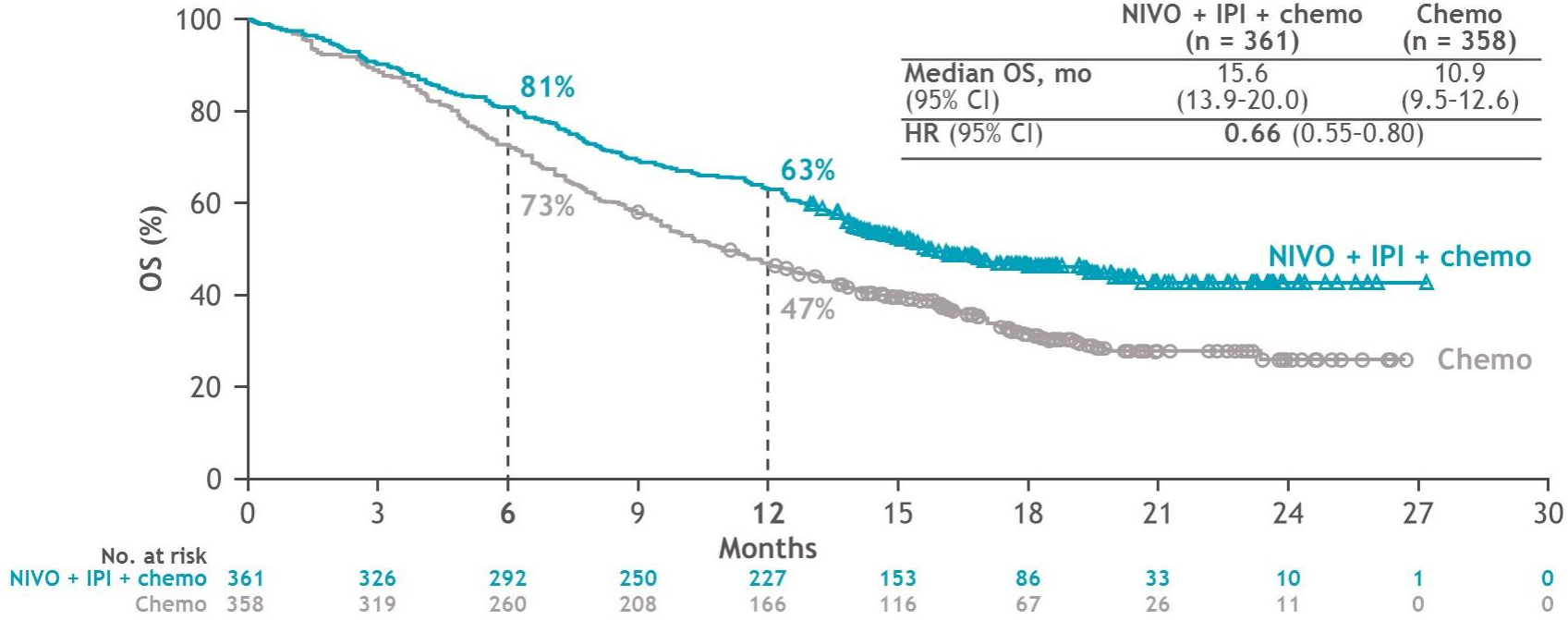
	Atezo (n = 277)	Chemo (n = 277)
mOS, mo	17.5	14.1
HR[b] (95% CI)	0.83 (0.65, 1.07)	

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

Herbst, ESMO-IO 2019.

Treatments not reliant on PD-L1 expression

CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo

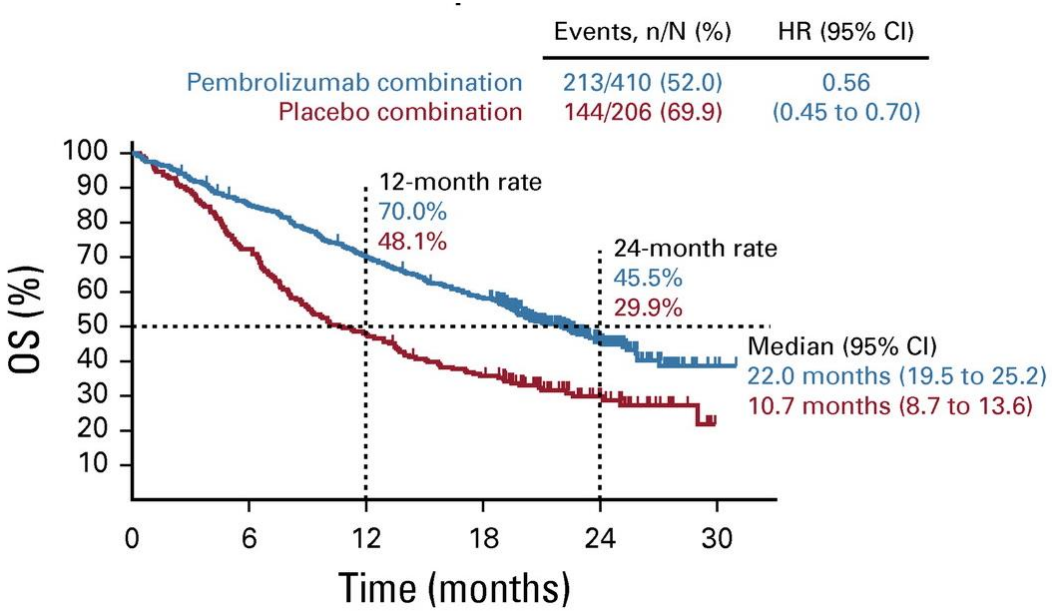


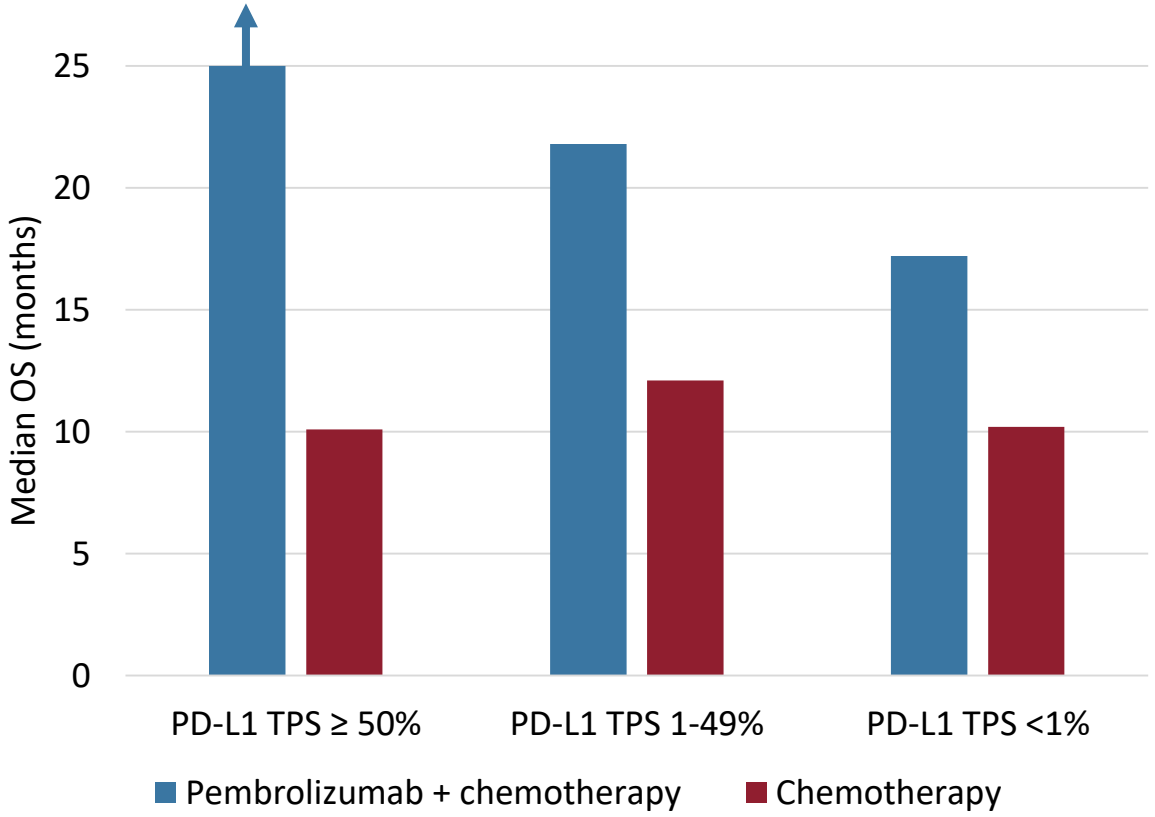
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	0.66 (0.55-0.80)	

	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.

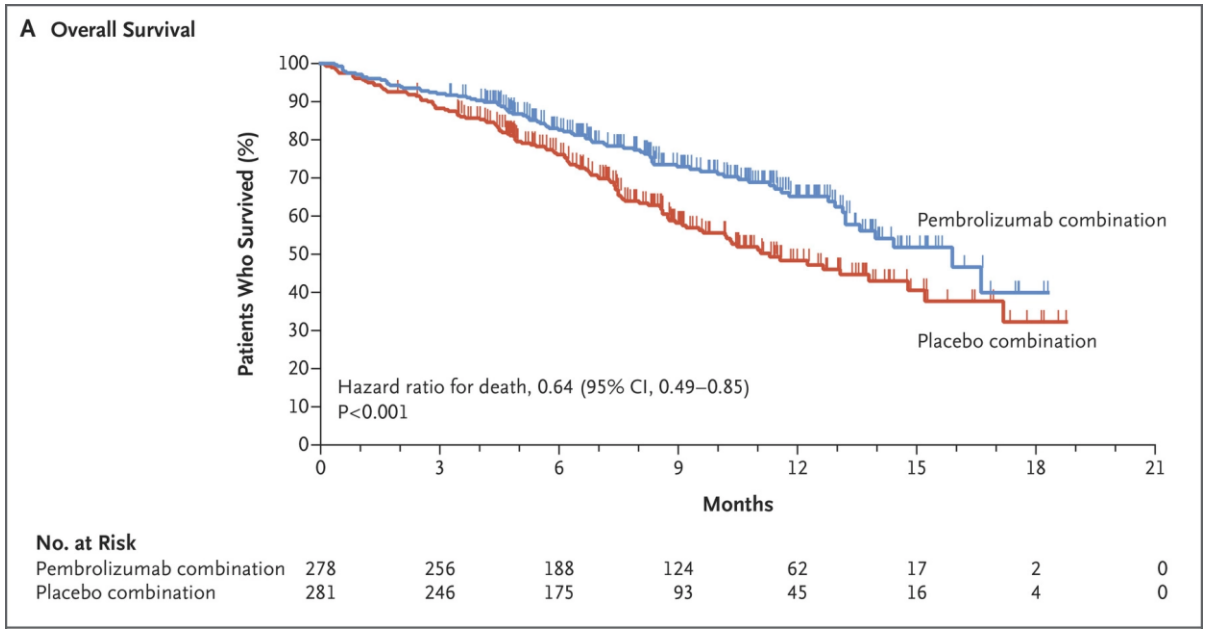
KEYNOTE-189: Pembrolizumab/chemotherapy vs Chemotherapy Alone for Advanced Non-Squamous NSCLC

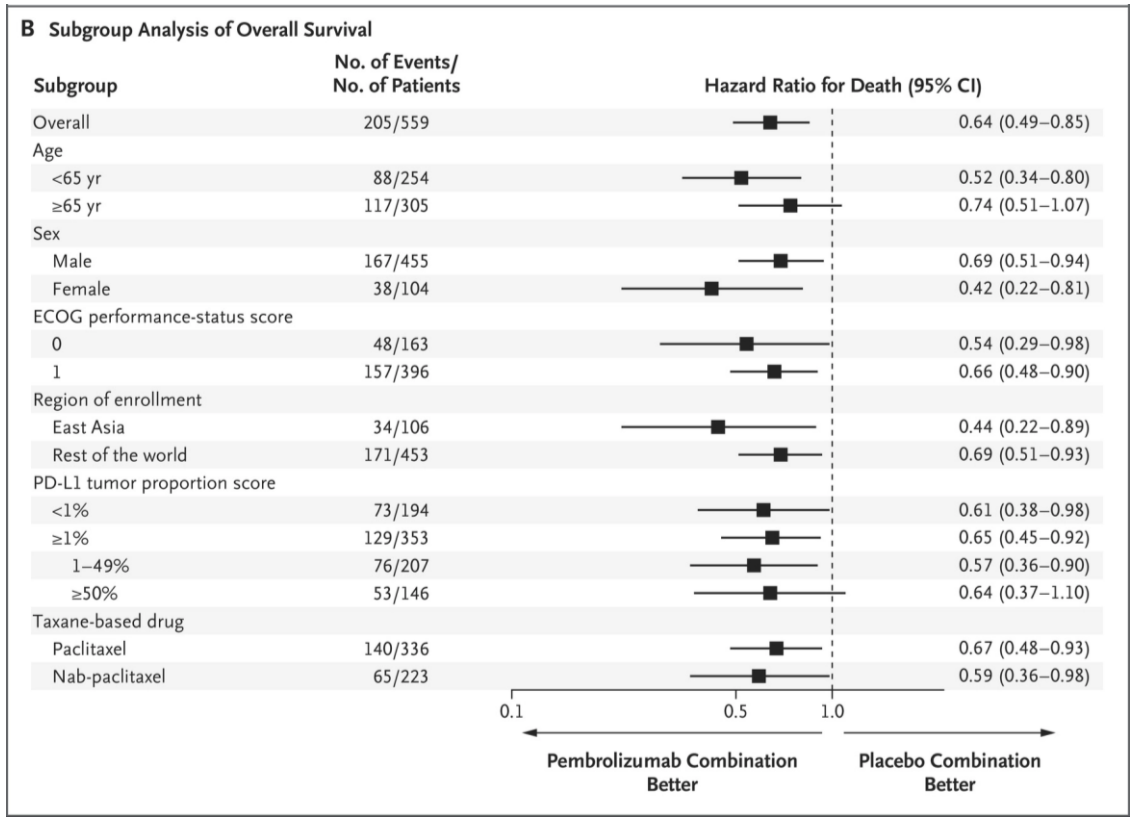




Gadgeel, J Clin Oncol 2020.

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





Paz-Ares et al, N Engl J Med 2018.

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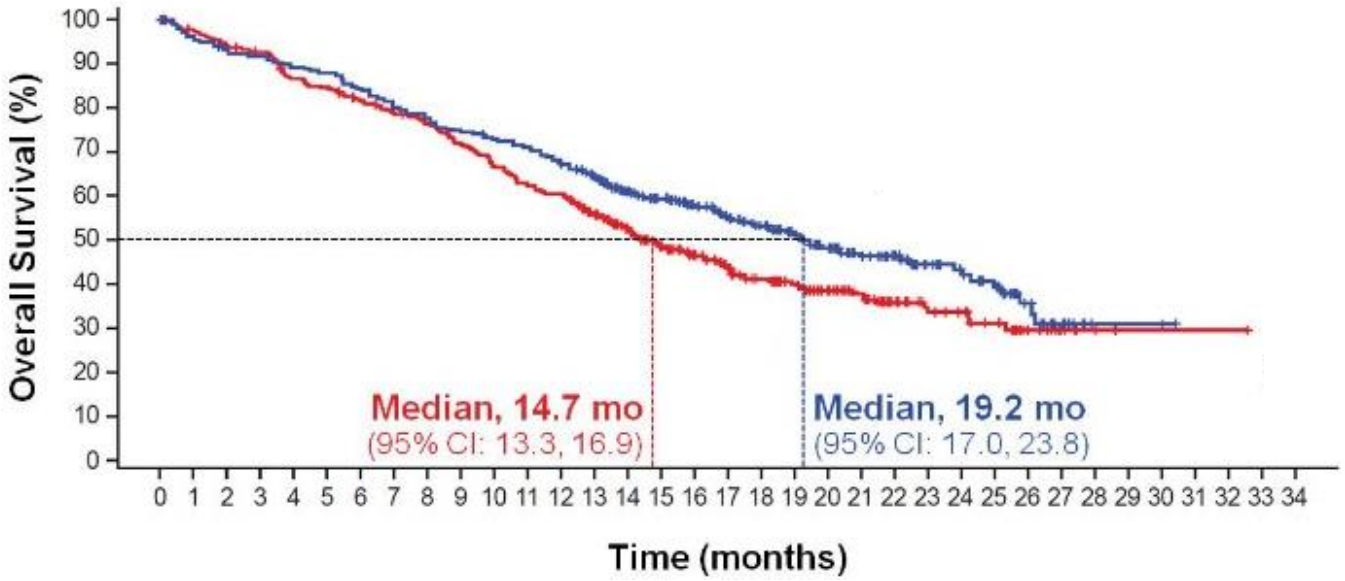
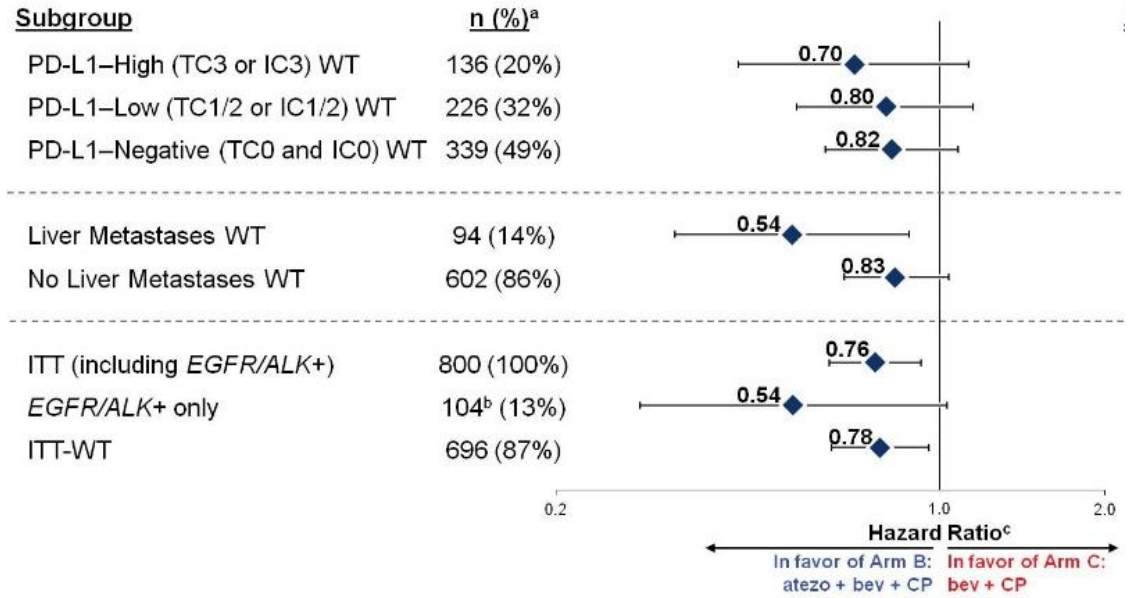
IMpower150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/ Bevacizumab in Advanced Non-Squamous NSCLC

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





Socinski et al, NEJM 2018

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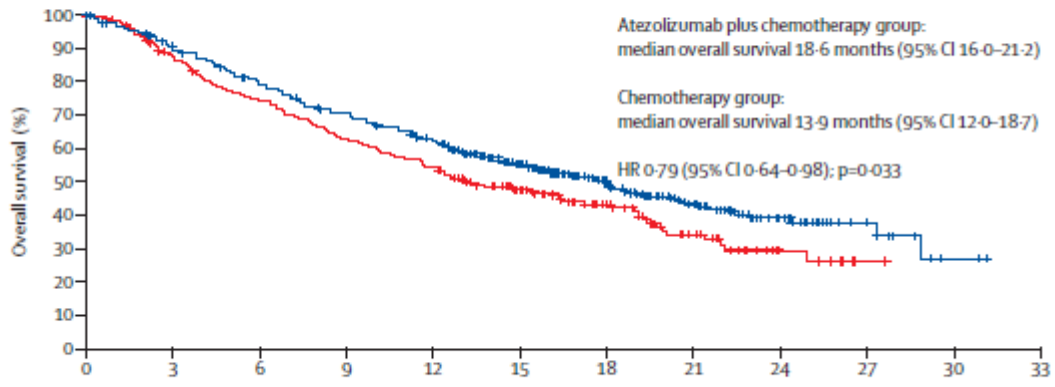
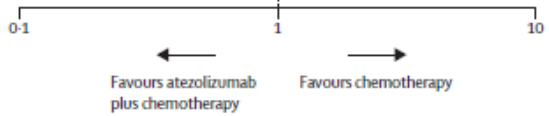
IMpower130: Atezolizumab + chemo vs chemo alone for non-squamous NSCLC

	Overall survival at 12 months	Overall survival at 24 months
Atezolizumab plus chemotherapy group	63·1% (95% CI 58·6–67·7)	39·6% (95% CI 33·6–45·7)
Chemotherapy group	55·5% (95% CI 48·9–62·2)	30·0% (95% CI 21·7–38·2)



Number at risk (number censored)											
Atezolizumab plus chemotherapy group	451 (0)	400 (10)	351 (15)	305 (18)	268 (22)	194 (68)	129 (120)	75 (161)	40 (188)	12 (215)	4 (221)
Chemotherapy group	228 (0)	190 (12)	161 (13)	136 (13)	119 (13)	90 (28)	58 (52)	31 (70)	13 (85)	3 (94)	0 (0)

	Atezolizumab plus chemotherapy group		Chemotherapy group		Hazard ratio (95% CI)
	Events/number of patients	Median overall survival, months	Events/number of patients	Median overall survival, months	
Sex					
Female	83/185	21·4	52/94	12·8	0·66 (0·46–0·93)
Male	143/266	16·0	79/134	14·2	0·87 (0·66–1·15)
Age					
<65 years	108/227	19·2	63/114	16·6	0·79 (0·58–1·08)
≥65 years	118/224	16·1	68/114	12·6	0·78 (0·58–1·05)
ECOG PS*					
0	88/189	20·8	45/91	19·7	0·85 (0·59–1·22)
1	138/261	15·2	85/136	11·9	0·77 (0·58–1·00)
2	..	NA	1/1	NA	NA
Tobacco use history					
Never	21/48	28·2	10/17	19·5	0·55 (0·26–1·19)
Current or previous	205/403	18·1	121/211	13·9	0·81 (0·65–1·02)
No liver metastasis at enrolment	174/382	21·1	109/197	15·2	0·73 (0·57–0·92)
Liver metastasis at enrolment	52/69	10·0	22/31	8·8	1·04 (0·63–1·72)
PD-L1-high	43/88	17·3	23/42	16·9	0·84 (0·51–1·39)
PD-L1-low	54/128	23·7	33/65	15·9	0·70 (0·45–1·08)
PD-L1-negative	129/235	15·2	75/121	12·0	0·81 (0·61–1·08)
Intention-to-treat wild-type population	**226/451**	**18·6**	**131/228**	**13·9**	**0·79 (0·64–0·98)**



West, Lancet 2019

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Immunotherapy for relapsed/refractory NSCLC

Drug	Indication	Dose
Nivolumab	Metastatic squamous or non-squamous NSCLC with progression after chemotherapy (2nd 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 ICIs in NSCLC

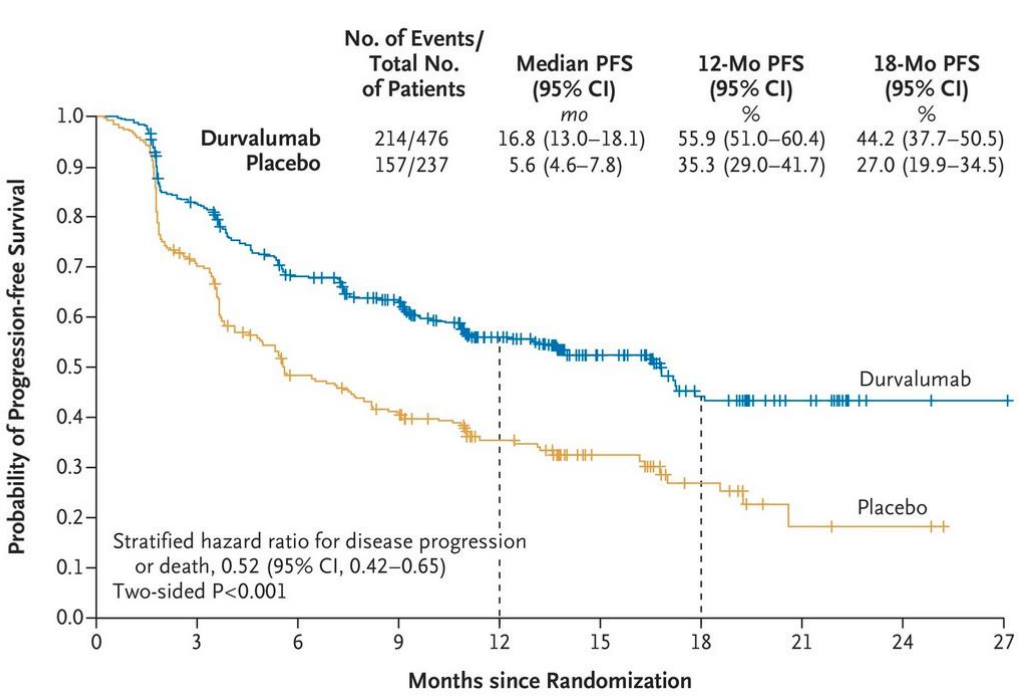
Study	Treatment arms	ORR	Median PFS (months)	Median OS (months)
CheckMate 017 and CheckMate 057	Nivolumab	19%	2.56	11.1
	Docetaxel	11%	3.52	8.1
KEYNOTE-010 (PD-L1 TPS ≥ 1%)	Pembrolizumab	18%	4.0	12.7
	Docetaxel	9%	4.0	8.5
OAK	Atezolizumab	14%	2.8	13.8
	Docetaxel	13%	4.0	9.6

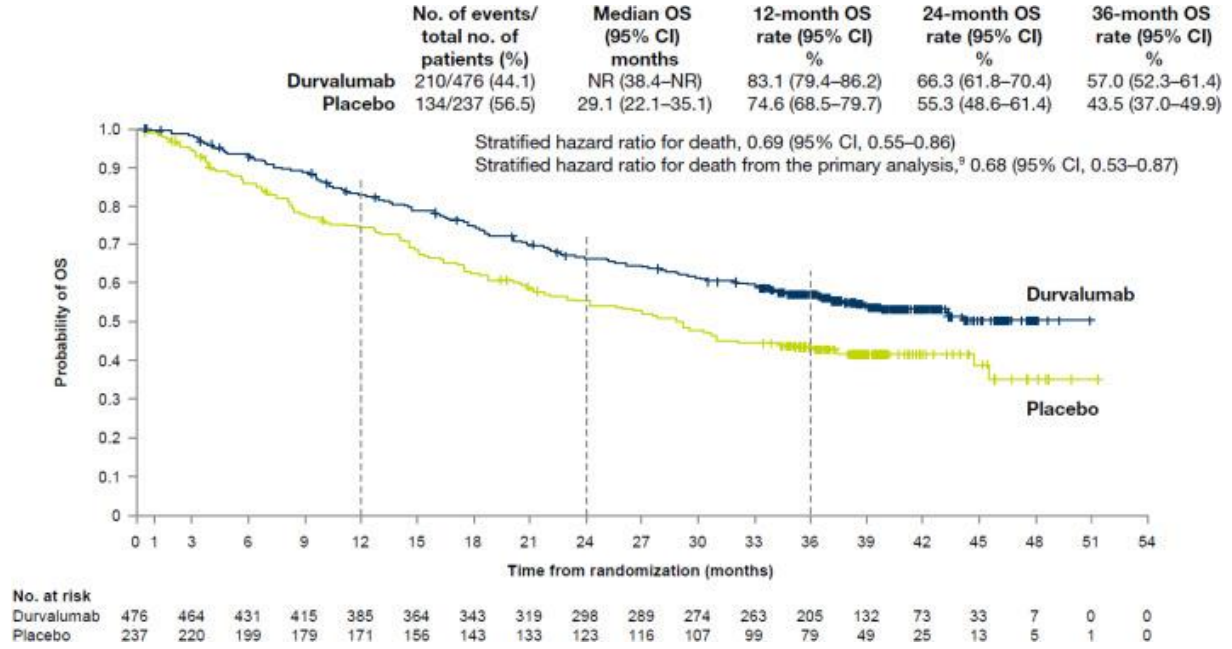
Vokes, Ann Oncol 2018.
Herbst, Lancet 2016.
Fehrenbacker, J Thorac Oncol 2018.

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	1st 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





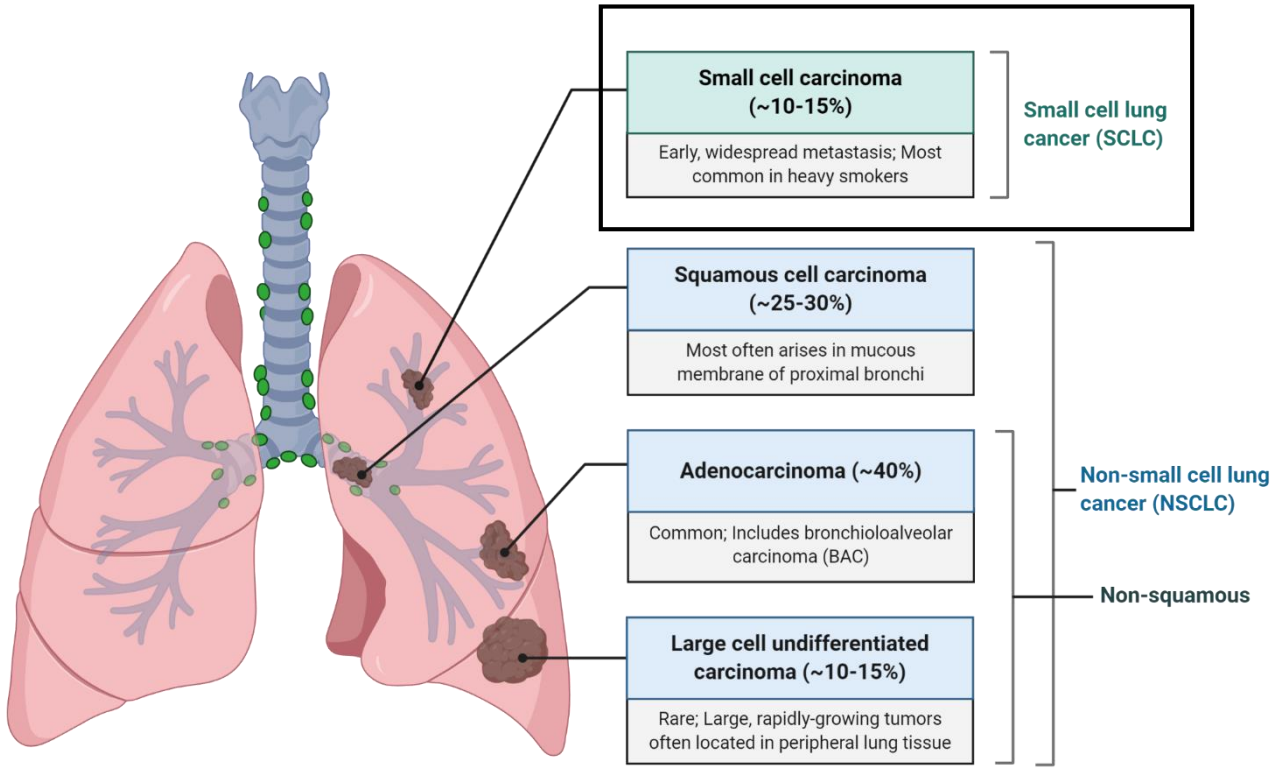
Antonia, N Engl J Med 2017.
Gray, J Thorac Oncol 2020.

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

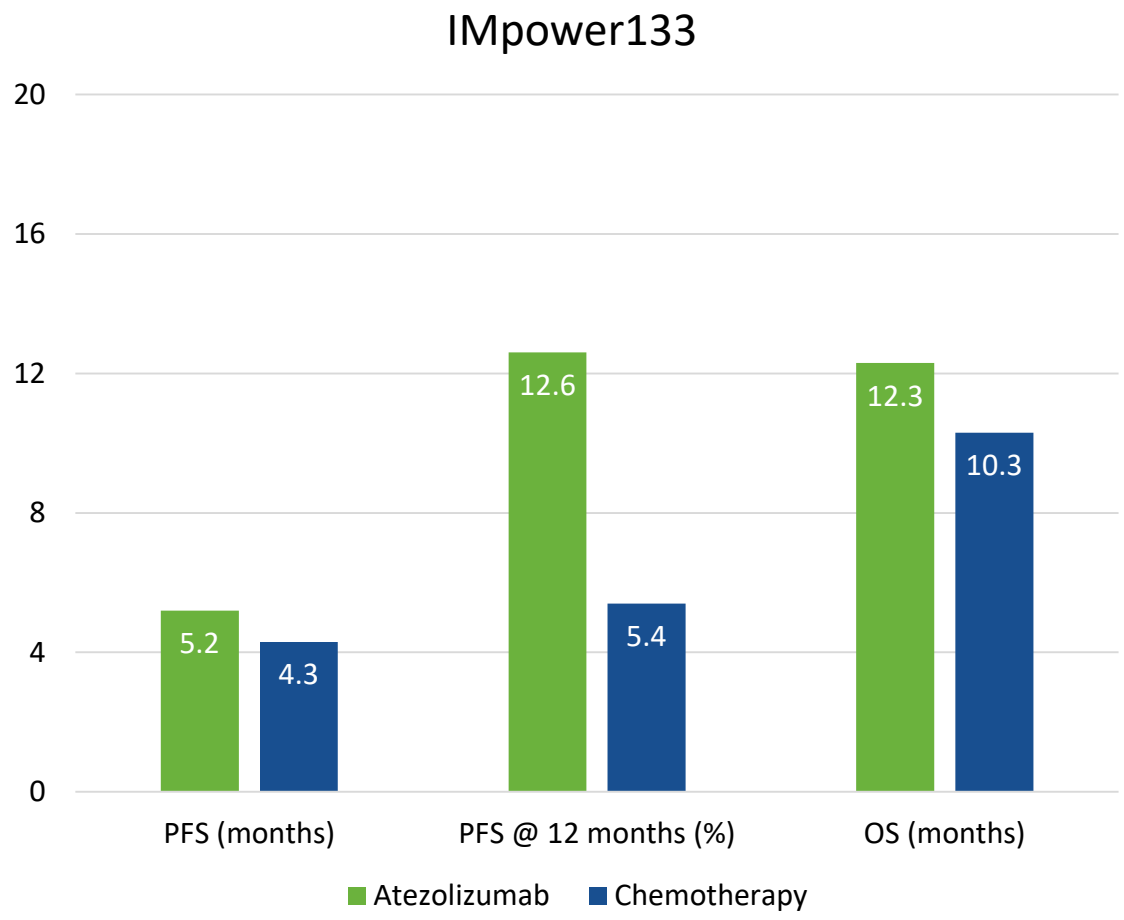
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

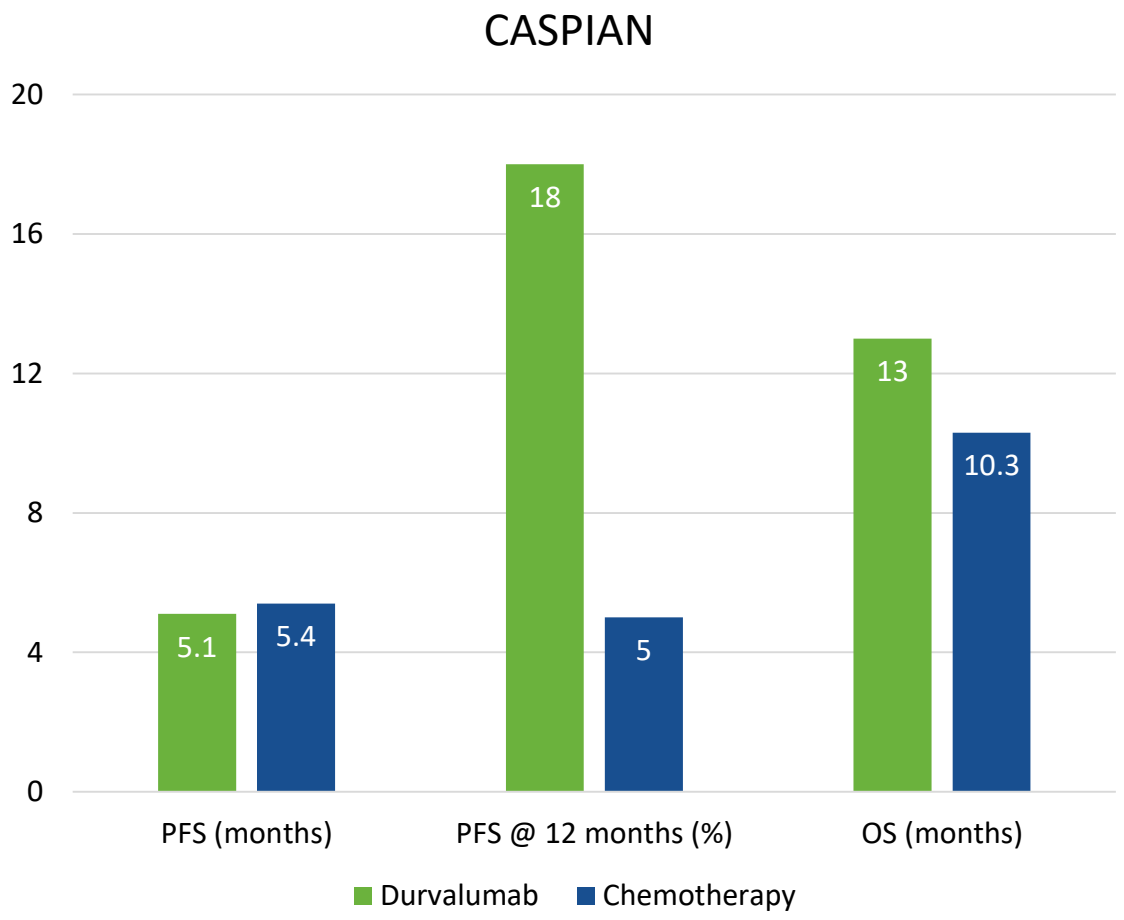


Approved checkpoint inhibitors in SCLC

Drug	Indication	Dose
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 ICIs in SCLC





Huang, J Hematol Oncol 2020.

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In development: answering outstanding questions

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

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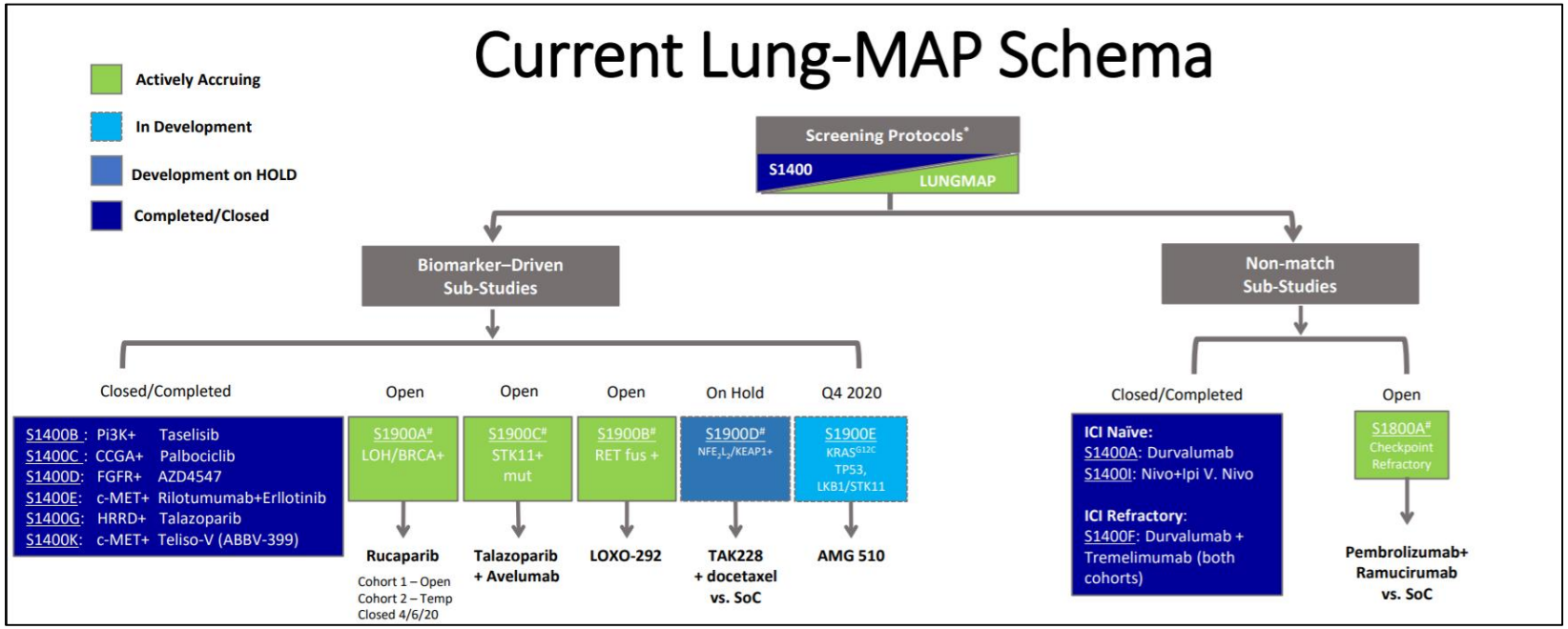
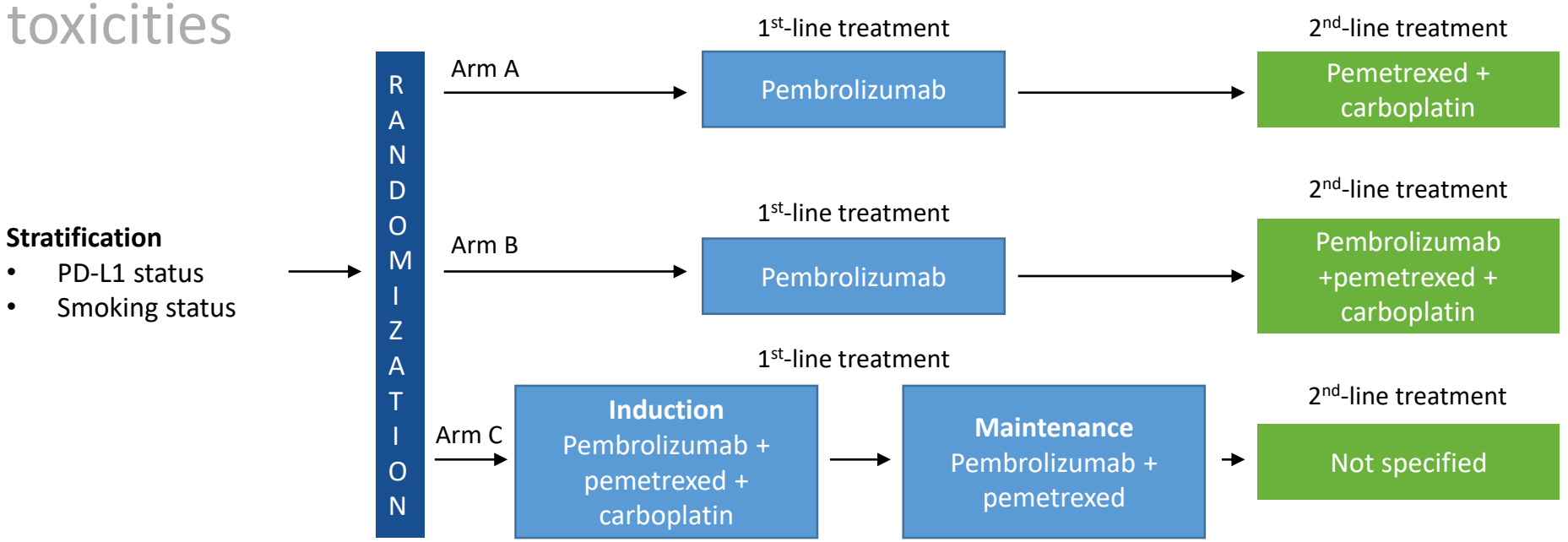


Lung-map.org

In development: answering outstanding questions

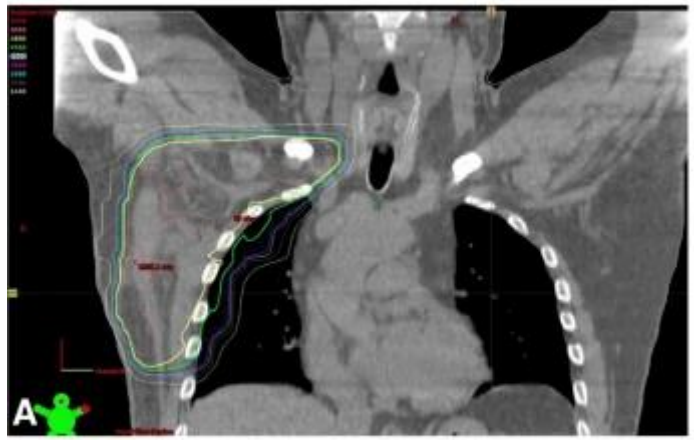
- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities



INSIGNIA trial

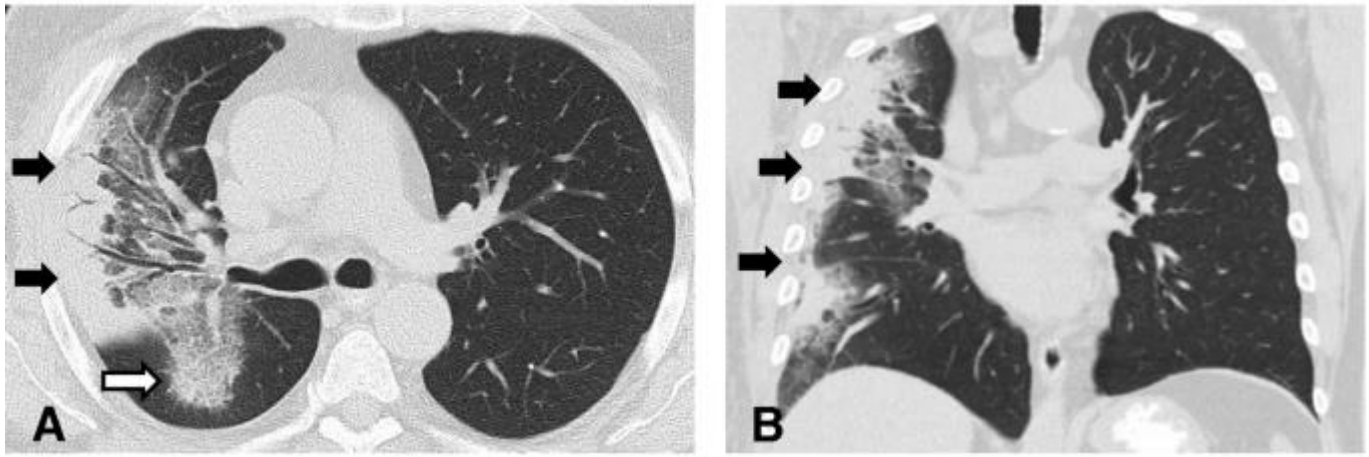
In development: answering outstanding questions

- 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.

Immunotherapy for mesothelioma

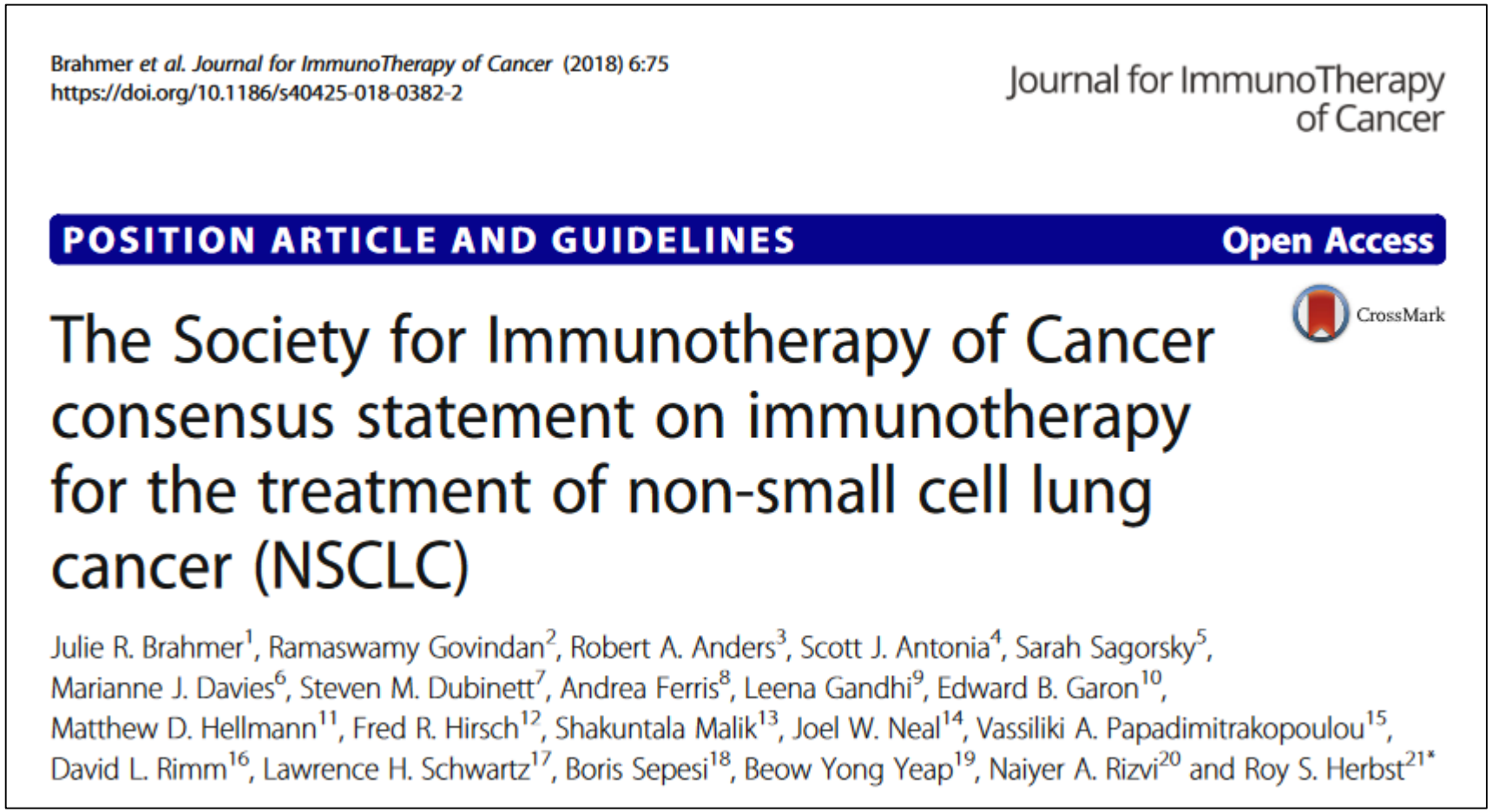
Drug	Indication	Dose
Nivolumab + ipilimumab	Frontline unresectable malignant pleural mesothelioma	Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W

- 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 and mesothelioma are beginning to benefit from immune checkpoint inhibitor treatments

Resources



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. Brahmer[1], Ramaswamy Govindan[2], Robert A. Anders[3], Scott J. Antonia[4], Sarah Sagorsky[5], Marianne J. Davies[6], Steven M. Dubinett[7], Andrea Ferris[8], Leena Gandhi[9], Edward B. Garon[10], Matthew D. Hellmann[11], Fred R. Hirsch[12], Shakuntala Malik[13], Joel W. Neal[14], Vassiliki A. Papadimitrakopoulou[15], David L. Rimm[16], Lawrence H. Schwartz[17], Boris Sepesi[18], Beow Yong Yeap[19], Naiyer A. Rizvi[20] and Roy S. Herbst[21*]

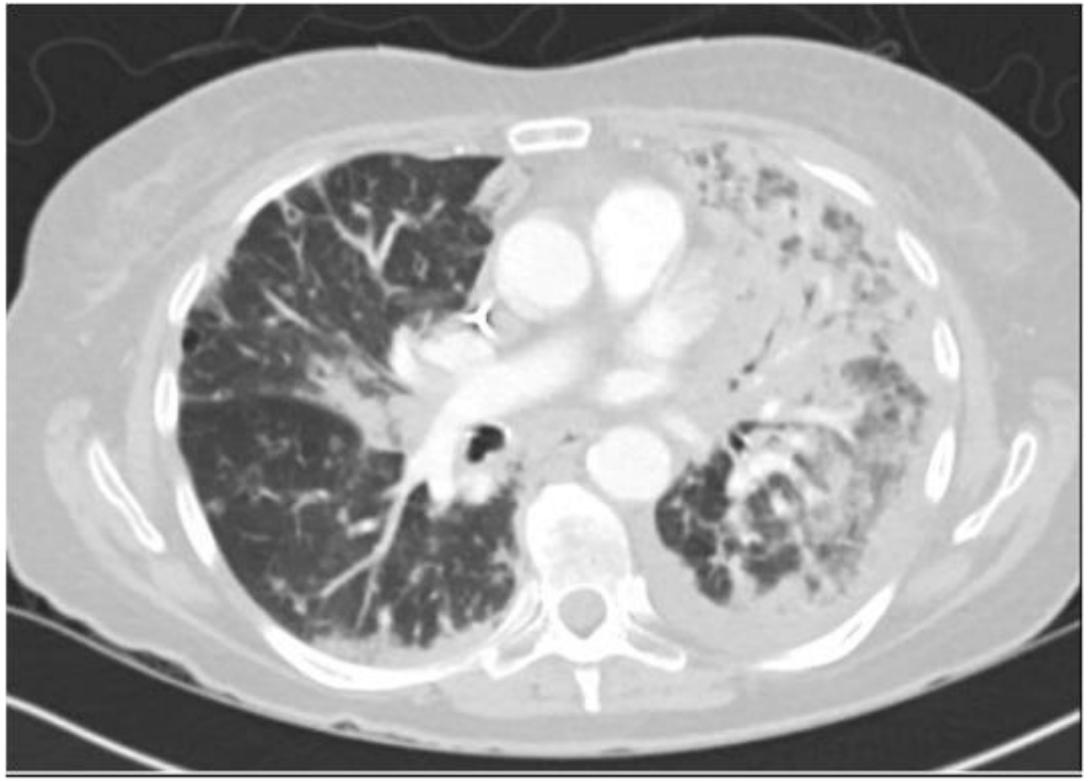
Case Study

- 75 year old Caucasian male, former smokers (35 pack-years), PMH of hypertension
- Diagnosed in Aug 2020 with unresectable stage III NSCLC
- Treated with definitive chemoradiation for 6 weeks, completed Oct 2020 (weekly carboplatin & paclitaxel; radiation 55 Gy)
- Started consolidation durvalumab (anti-PDL1) in Dec 2020

Presented in Mar 2021 for 4th dose of durvalumab with worsening cough and SOB

Case Study

- Oxygen saturation 89%, drops to 83% with exertion
- Heart rate 110
- Reduced b/l breath sounds
- Rest of the exam WNL



What will you do next?

Case Study

- Grade 3 pneumonitis
- Admitted and started on solumedrol 1 mg/kg
- Also antibiotics till infection ruled out (bronchoscopy and viral swab)
- Day 3: solumedrol increased to 2 mg/kg
- Day 5: oxygen levels still at <90%, patient reports SOB unchanged

What will you do next?

Case Study

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Treated with infliximab.

Questions?