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

sitc Society for Immunotherapy of Cancer

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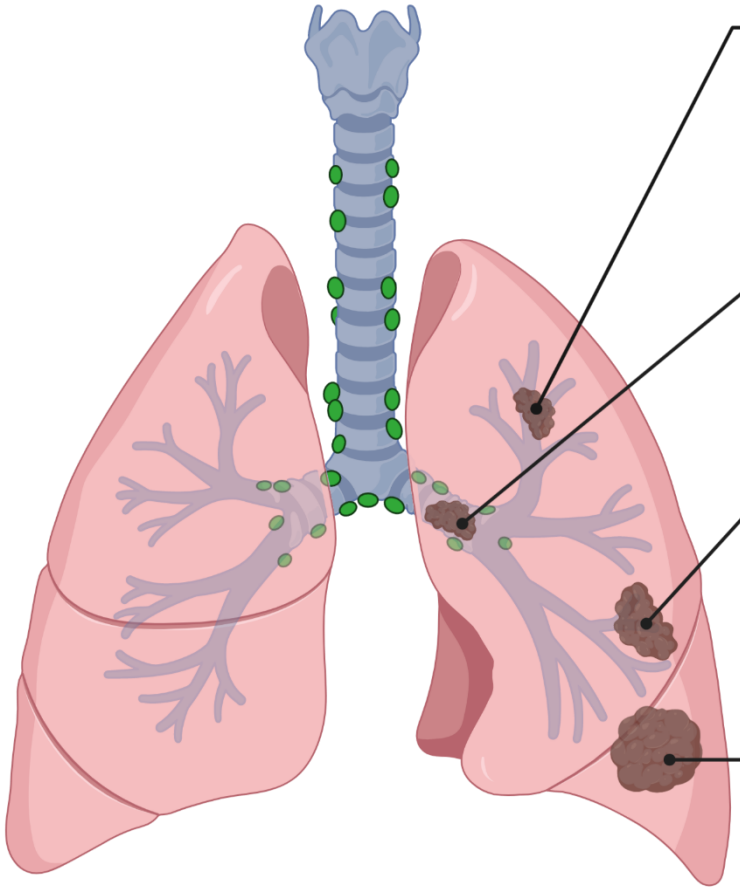
Disclosures

- Consulting Fees: Astra Zeneca, Bristol Myer Squibb, Novartis, Jazz Pharmaceuticals, Genentech;
- Fees for Non-CE Services Received Directly from an Ineligible Entity *or their Agents* (e.g., speakers' bureaus): Bristol Myer Squibb
- 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

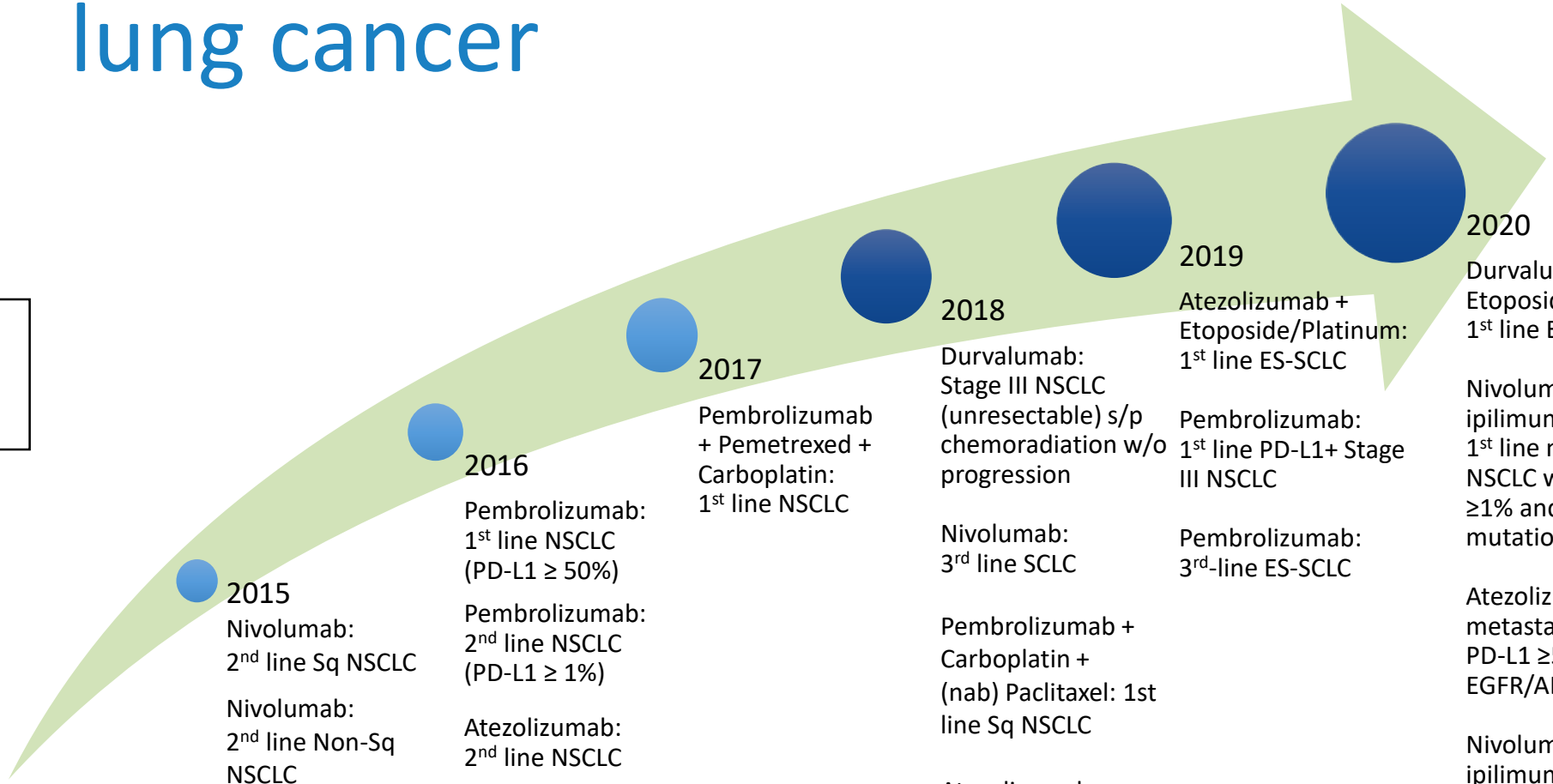
Nivolumab
PD-1

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

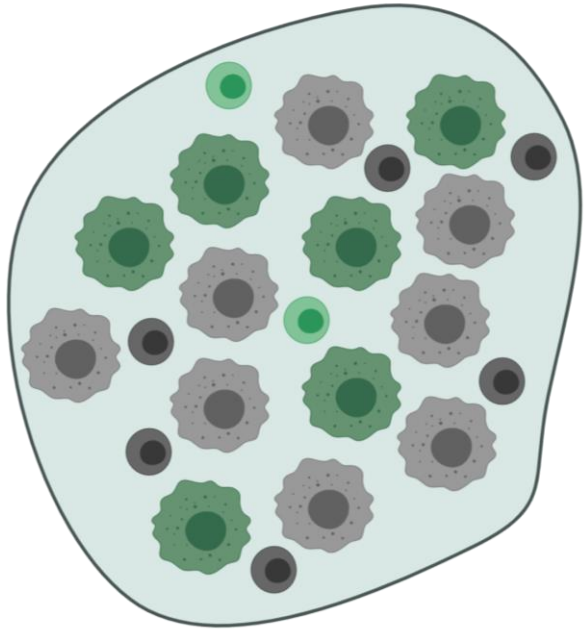
Immunotherapy for first-line treatment of metastatic NSCLC

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

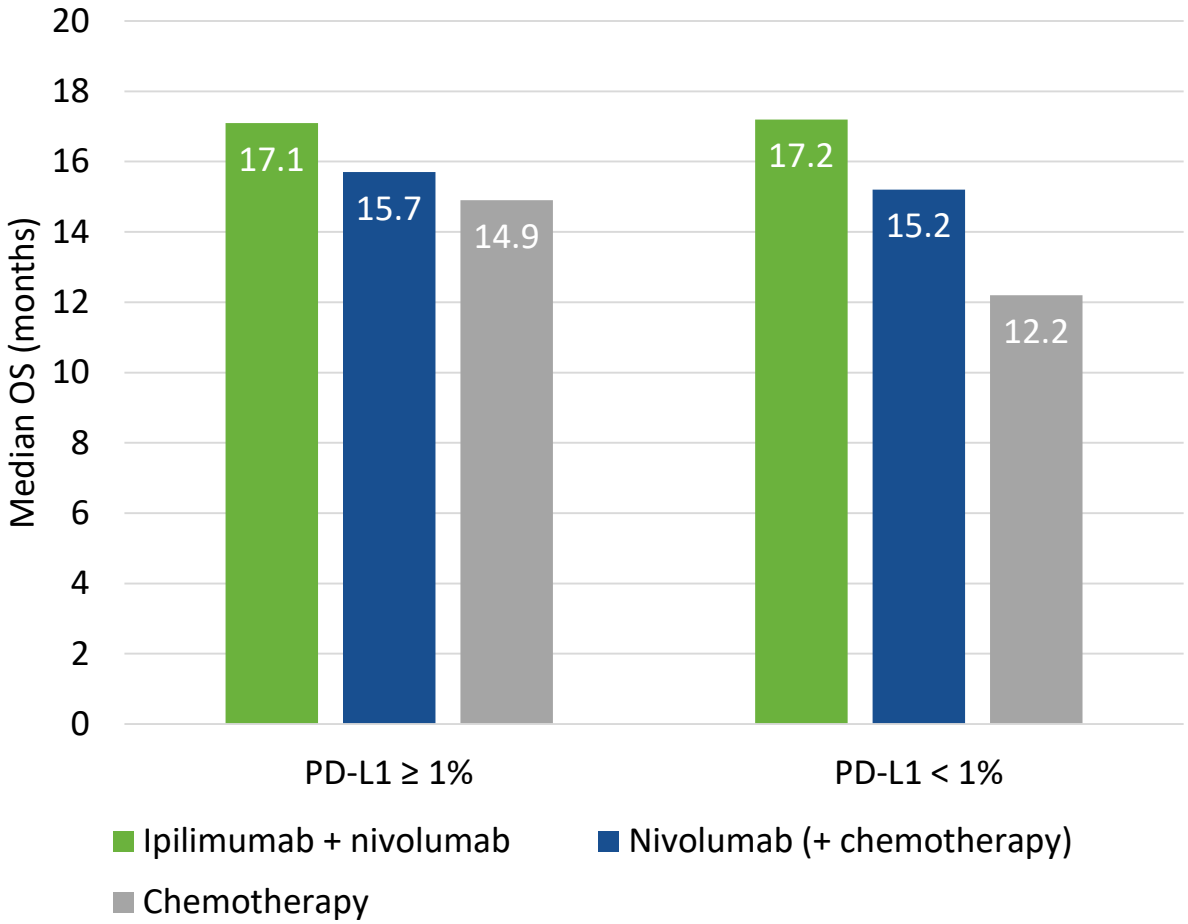
$$TPS = \frac{6\ positive\ tumor\ cells}{14\ total\ tumor\ cells} \times 100 = 43$$

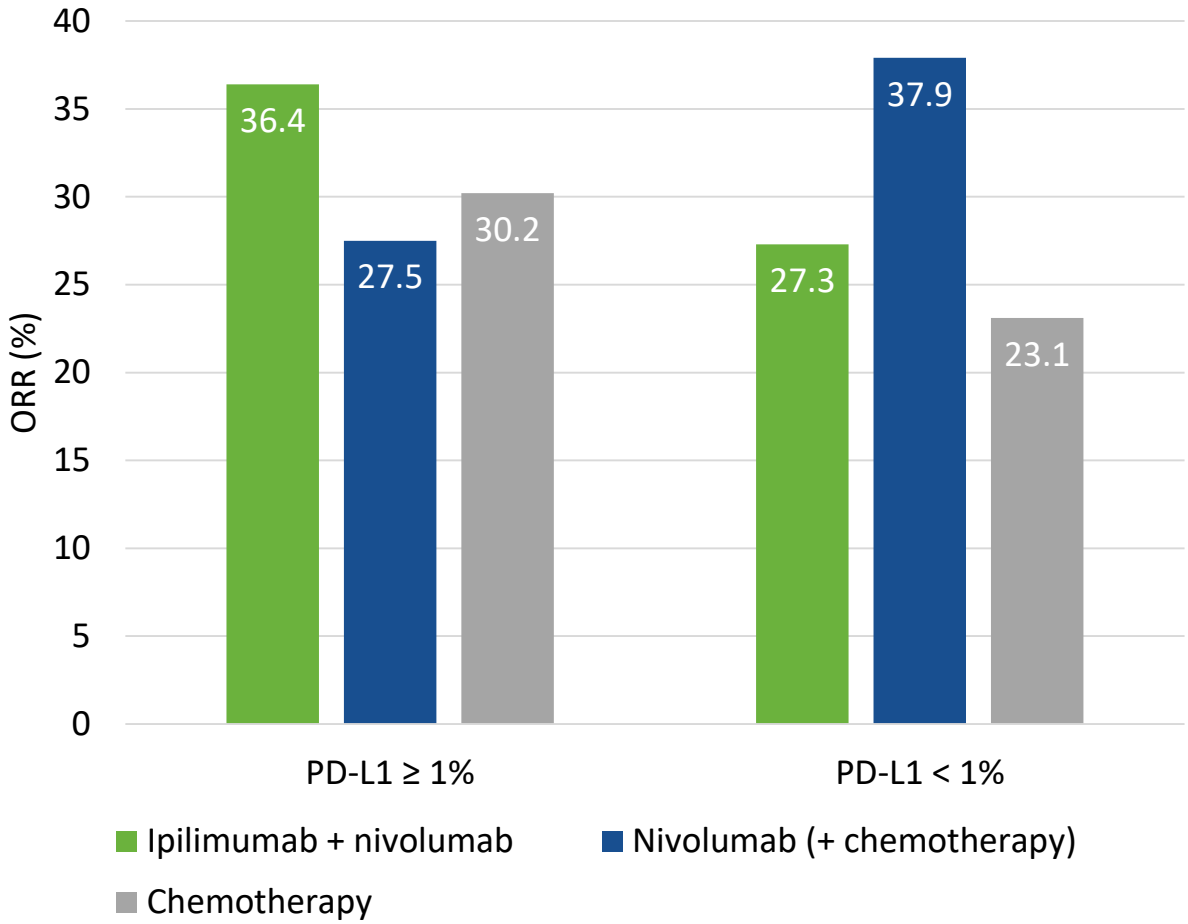
$$CPS = \frac{6\ positive\ tumor\ cells + 2\ positive\ immune\ cells}{22\ total\ cells} \times 100 = 36$$

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*

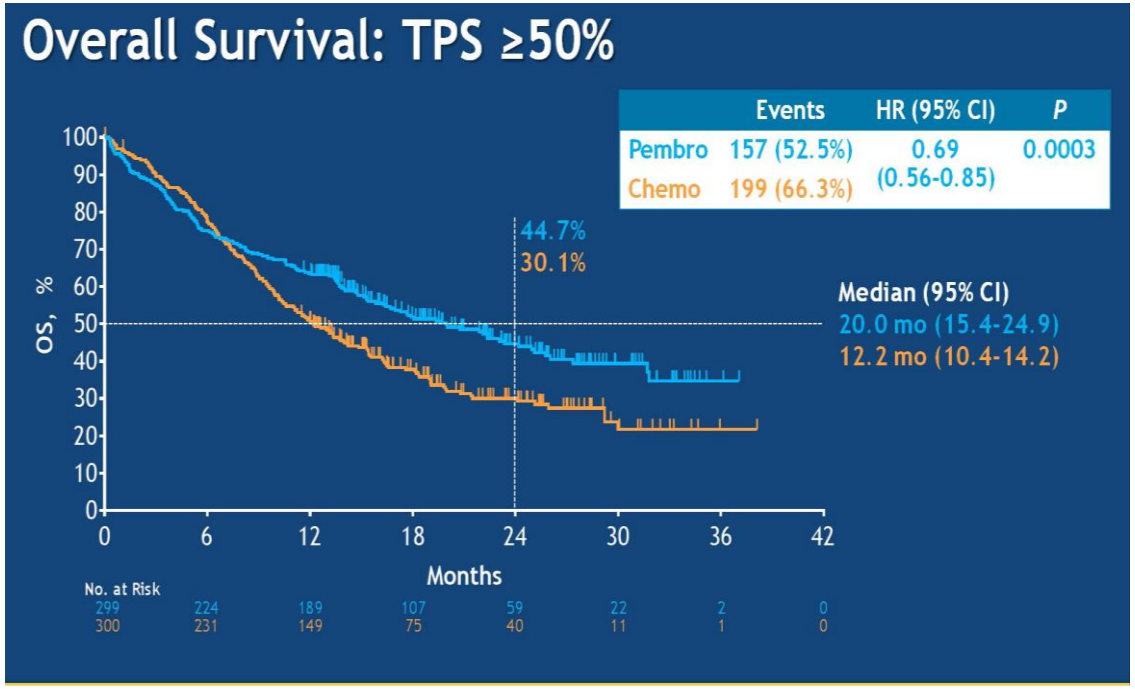
CheckMate 227: Ipilimumab + nivolumab vs chemotherapy for 1L NSCLC

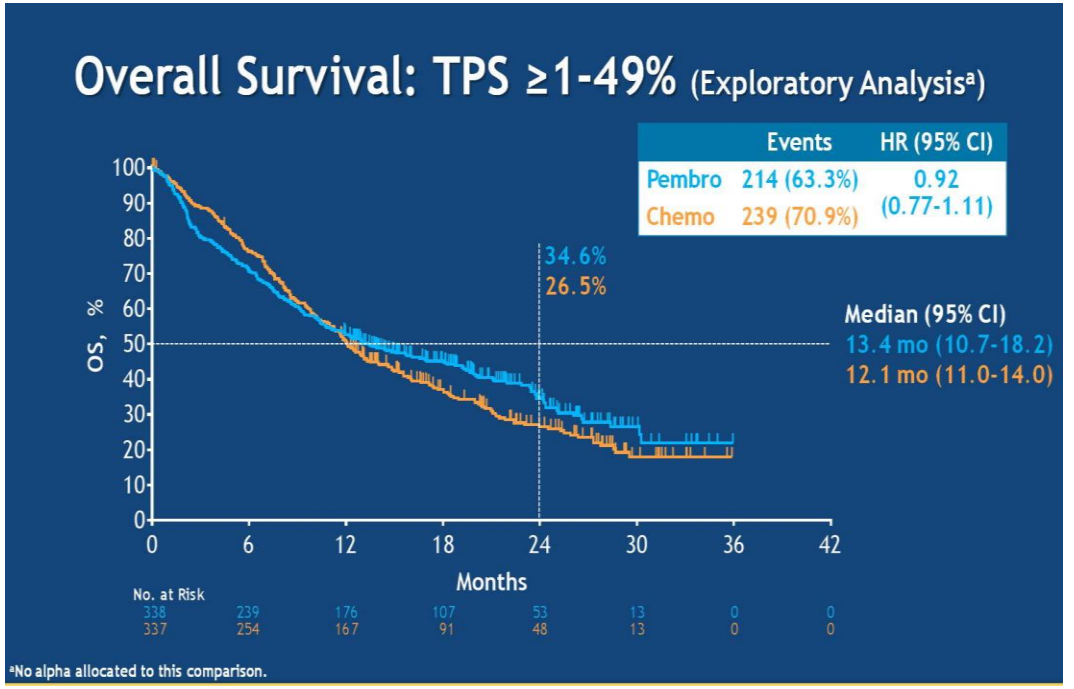




Ramalingam, ASCO 2020.

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



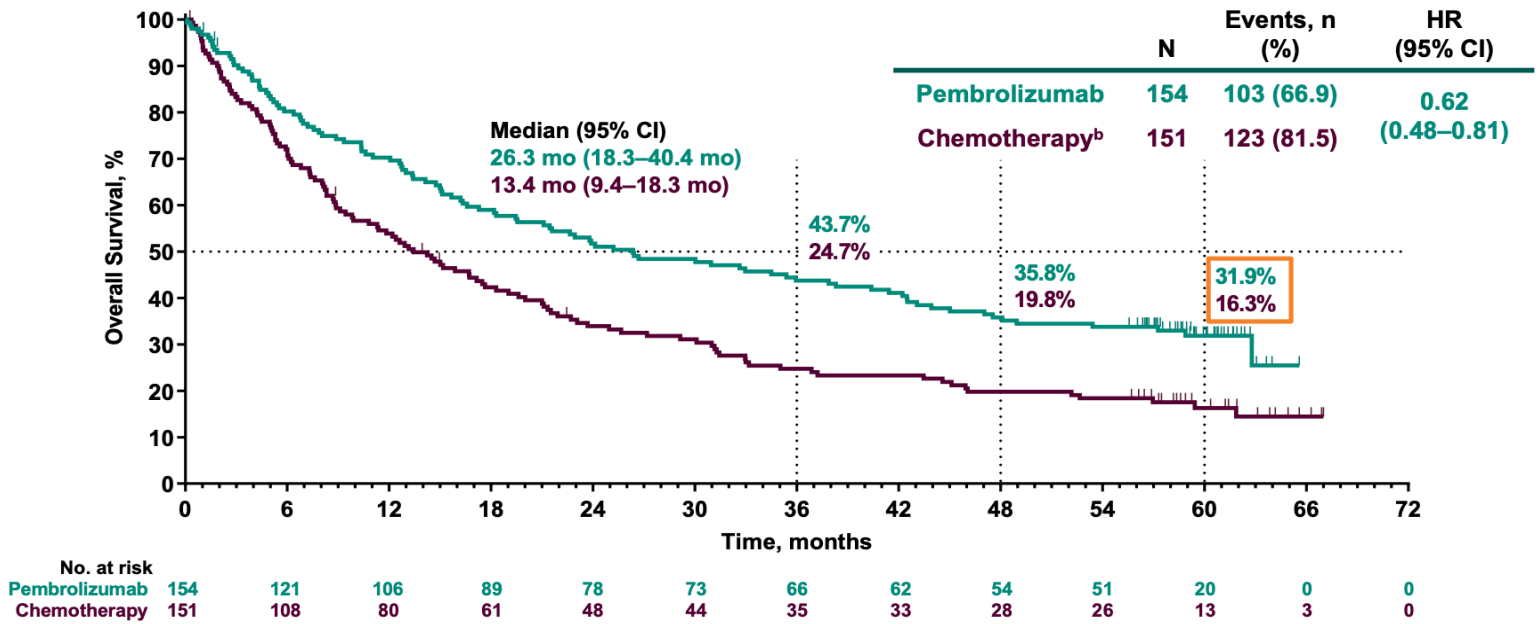


Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%

Lopes et al, ASCO 2018

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

Overall Survival[a]

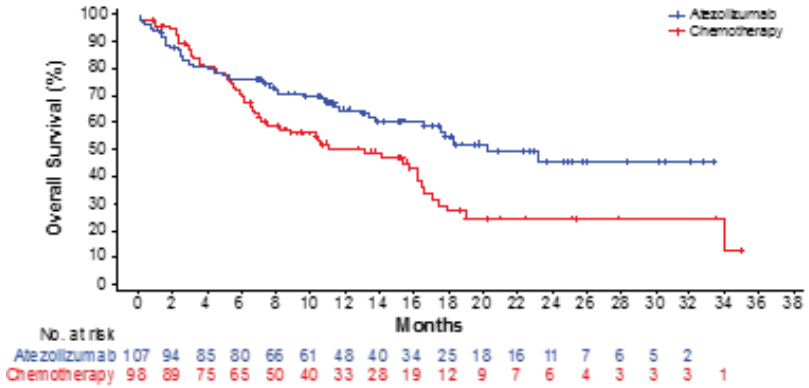


Ongoing benefit demonstrated at 5-year analysis

J. R. Brahmer Annals of Oncology Sept 2020

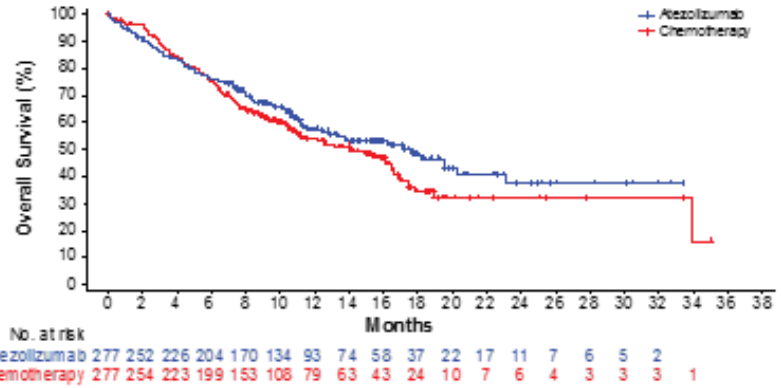
IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

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]



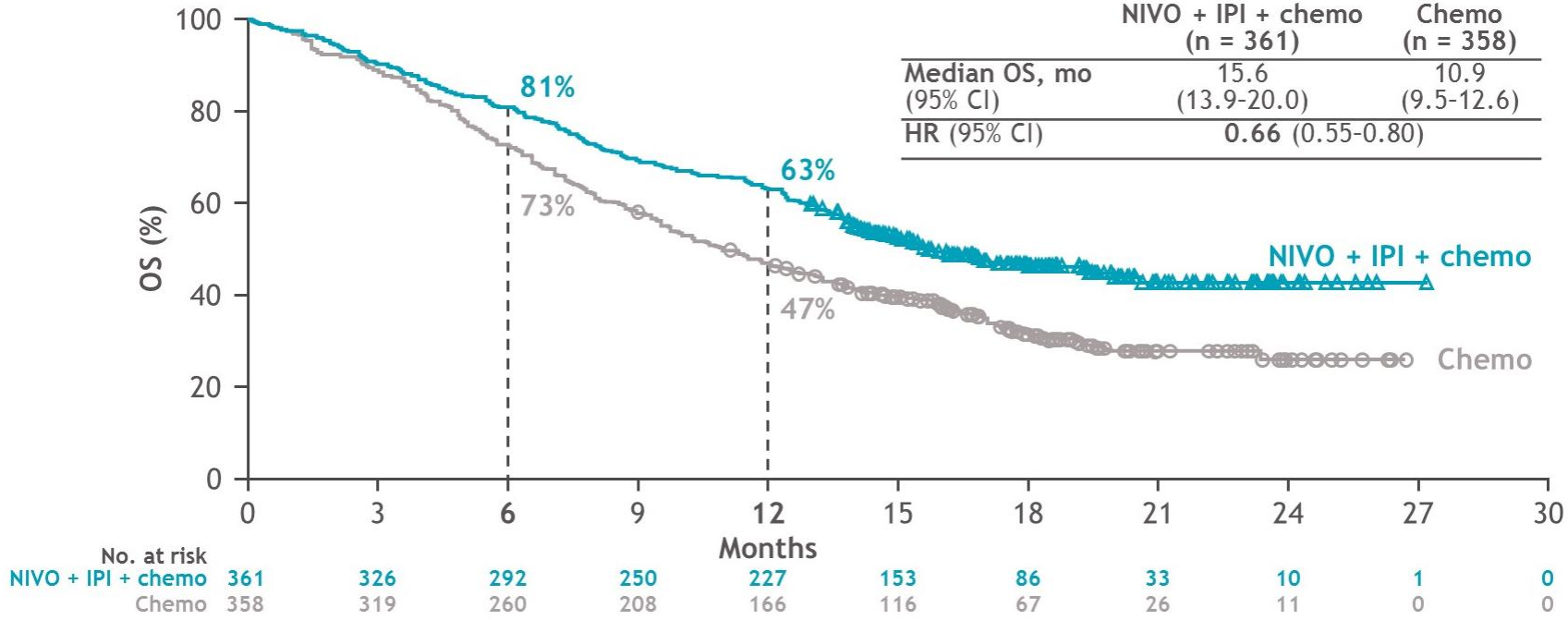
	Atezo (n = 277)	Chemo (n = 277)
mOS, mo	17.5	14.1
HR[b] (95% CI)	0.83 (0.65, 1.07)	

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



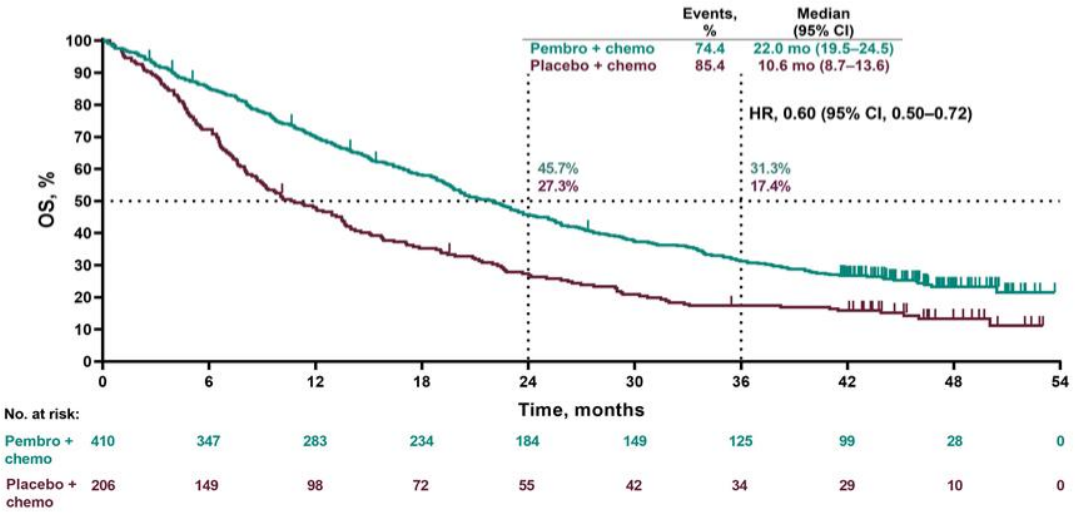
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	0.66 (0.55-0.80)	

	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.

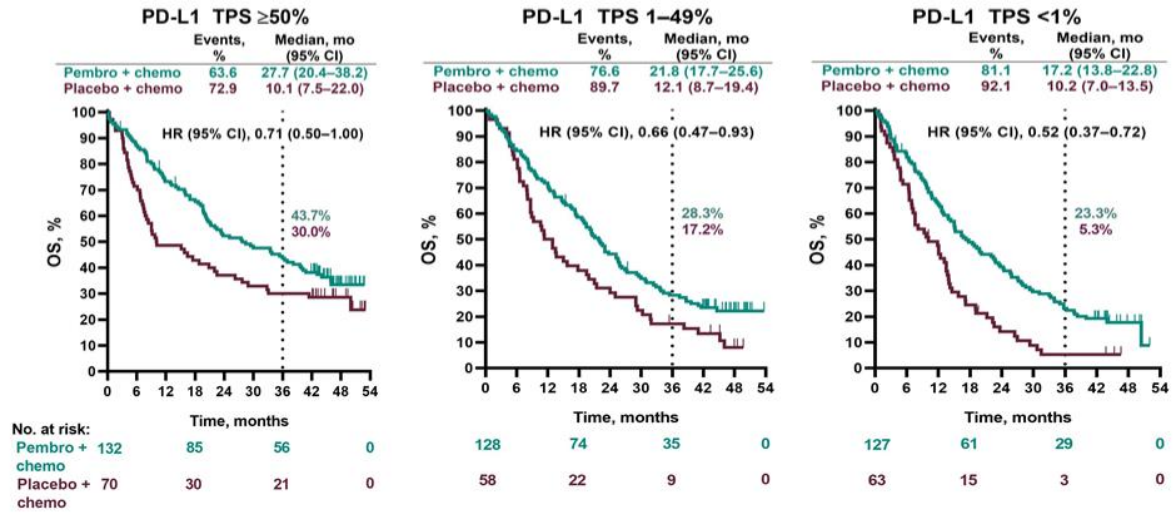
KEYNOTE-189: Pembrolizumab/chemotherapy vs Chemotherapy Alone for Advanced Non-Squamous NSCLC

OS, ITT Population



Data cutoff: August 28, 2020.

OS by PD-L1 TPS



Data cutoff: August 28, 2020.

Gray MK-3475 KN189 WCLC 2020

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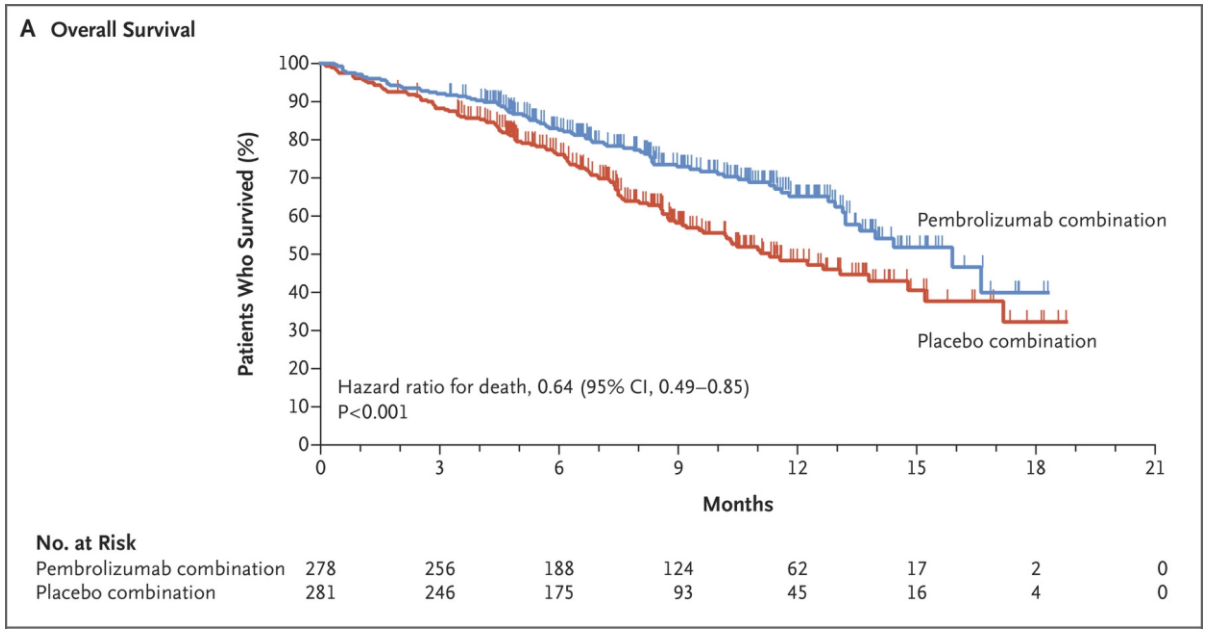
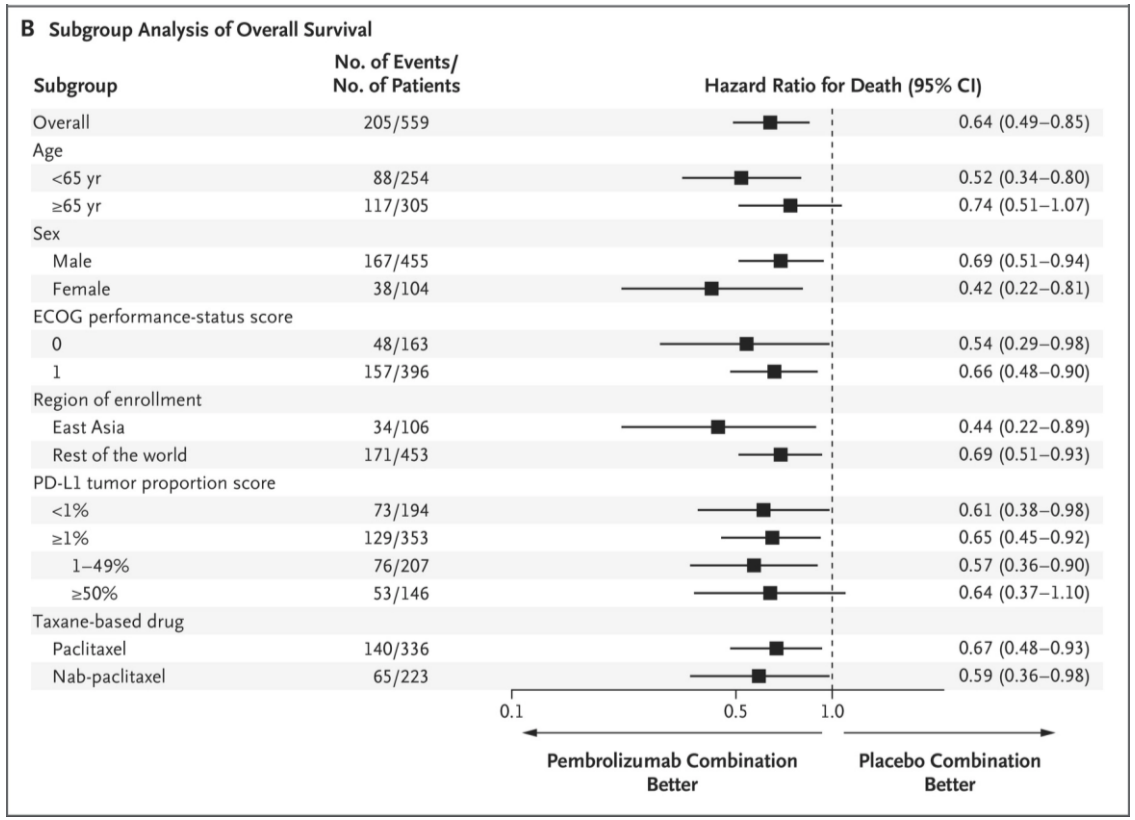
KEYNOTE-407: Pembrolizumab/Chemotherapy vs Chemotherapy Alone for Advanced Squamous-Cell NSCLC





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

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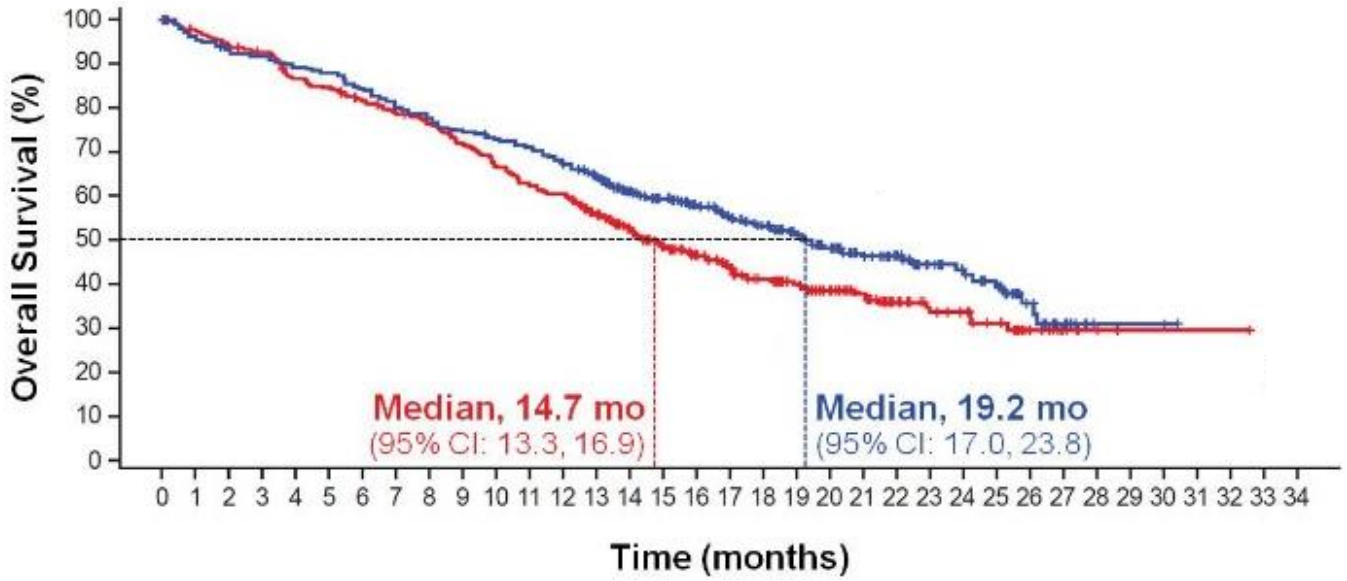
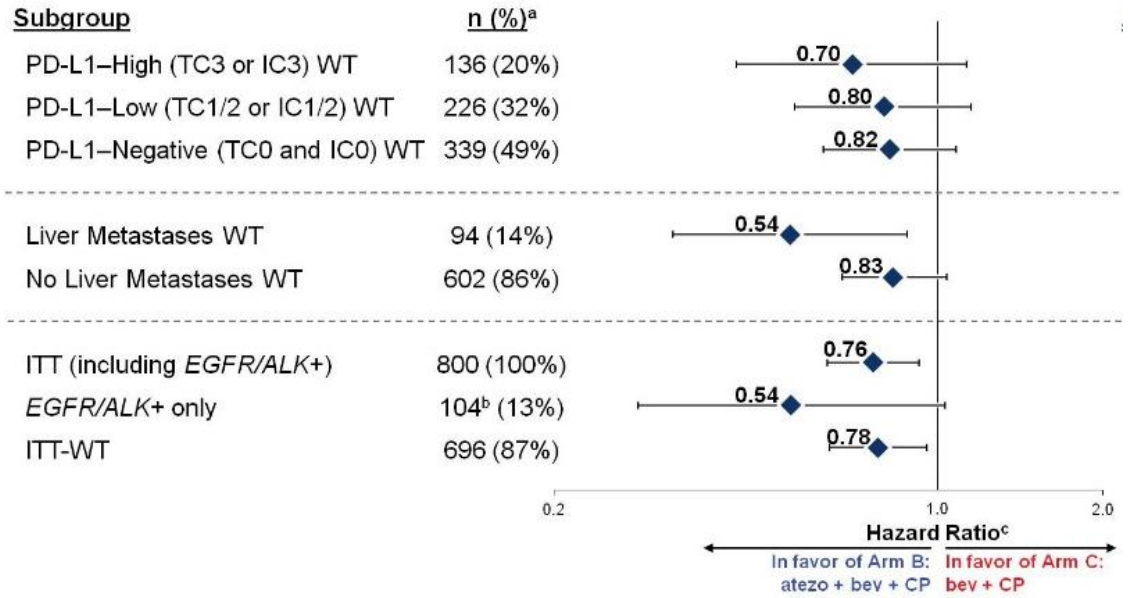
IMpower150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/ Bevacizumab in Advanced Non-Squamous NSCLC

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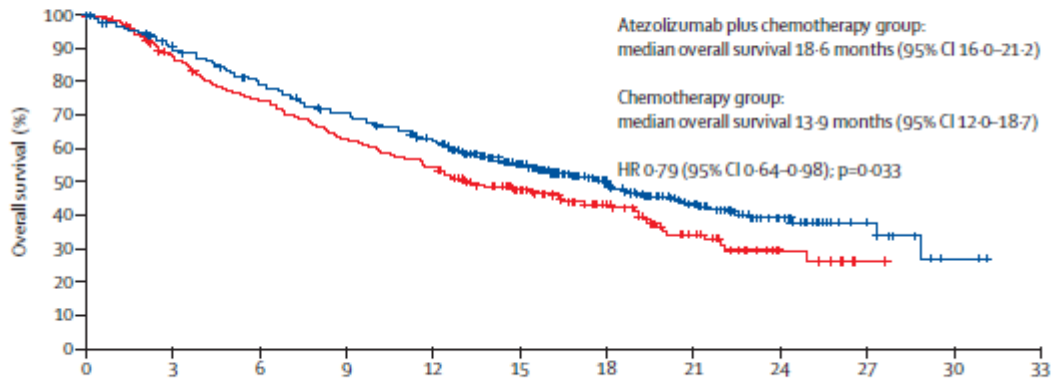
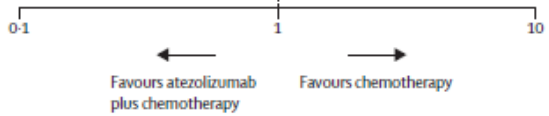
IMpower130: Atezolizumab + chemo vs chemo alone for non-squamous NSCLC

	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

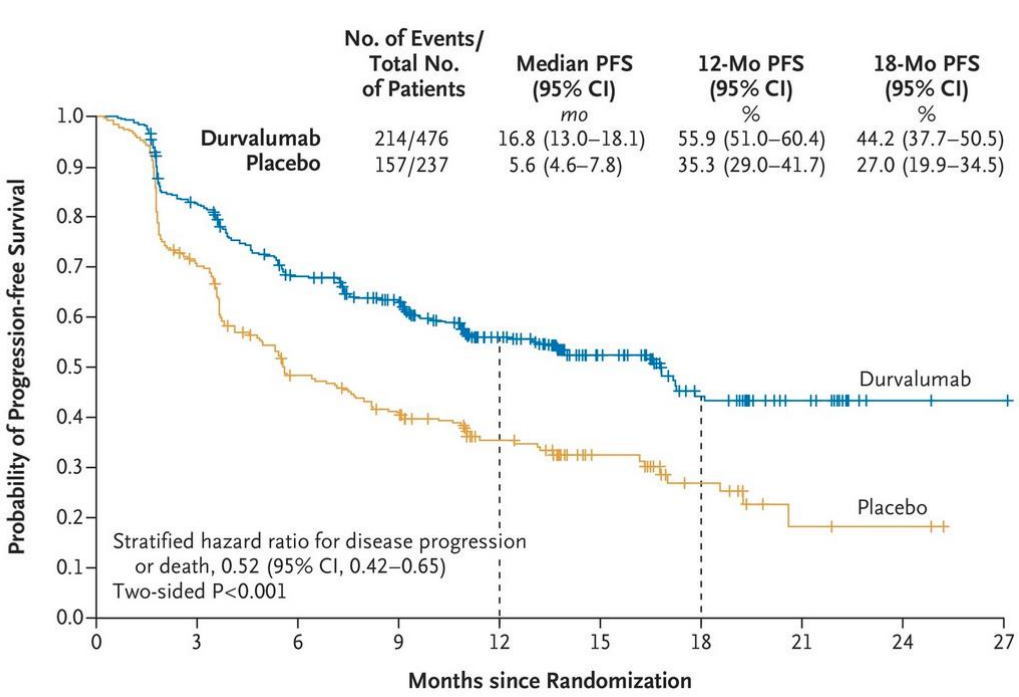
Study	Treatment arms	ORR	Median PFS (months)	Median OS (months)
CheckMate 017 and CheckMate 057	Nivolumab	19%	2.56	11.1
	Docetaxel	11%	3.52	8.1
KEYNOTE-010 (PD-L1 TPS ≥ 1%)	Pembrolizumab	18%	4.0	12.7
	Docetaxel	9%	4.0	8.5
OAK	Atezolizumab	14%	2.8	13.8
	Docetaxel	13%	4.0	9.6

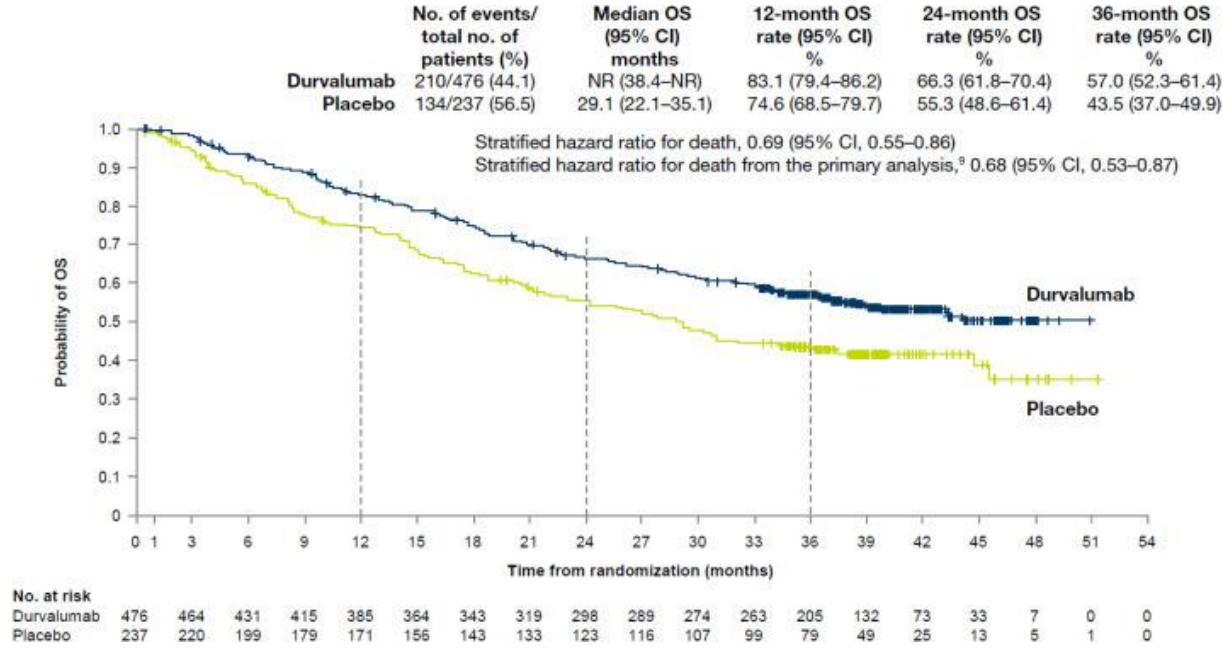
Vokes, Ann Oncol 2018.
Herbst, Lancet 2016.
Fehrenbacker, J Thorac Oncol 2018.

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
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  - Later lines of treatment
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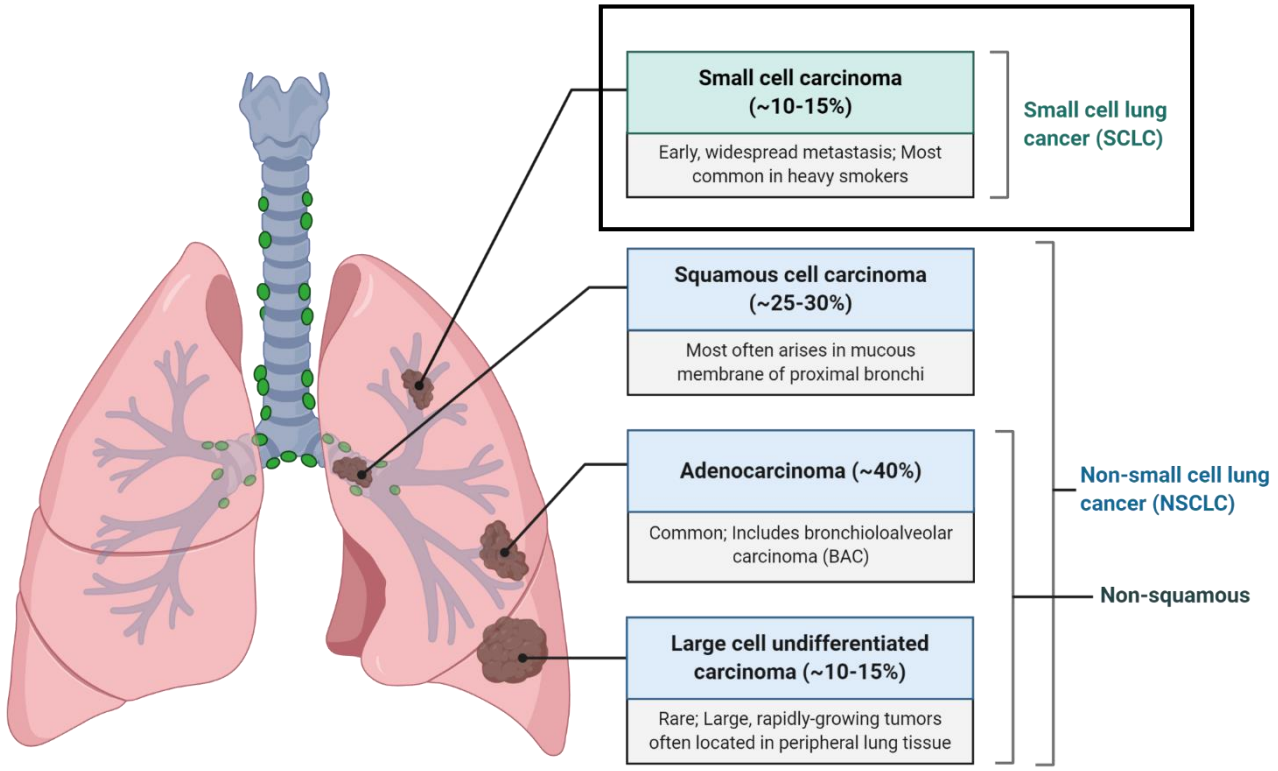
- Small cell lung cancer
- Future directions for lung cancer immunotherapy

Small cell lung cancer

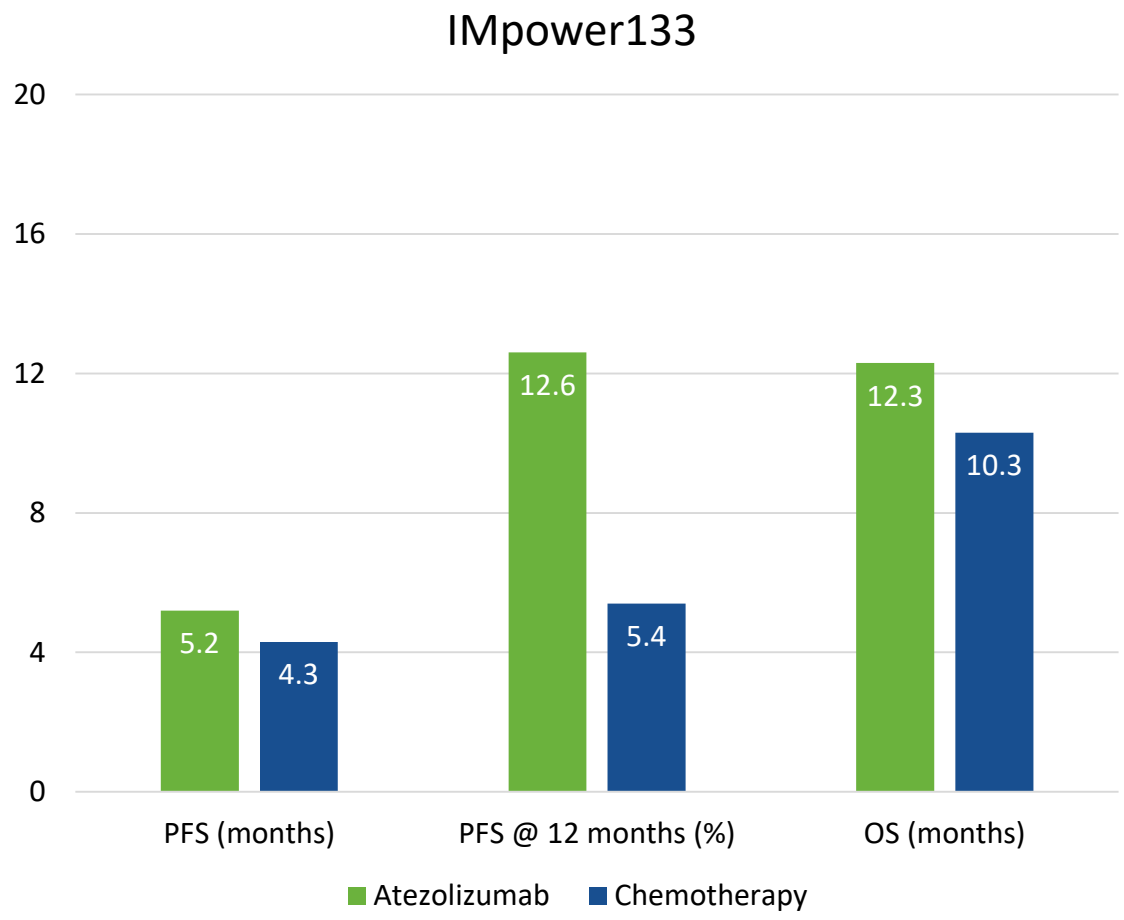
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

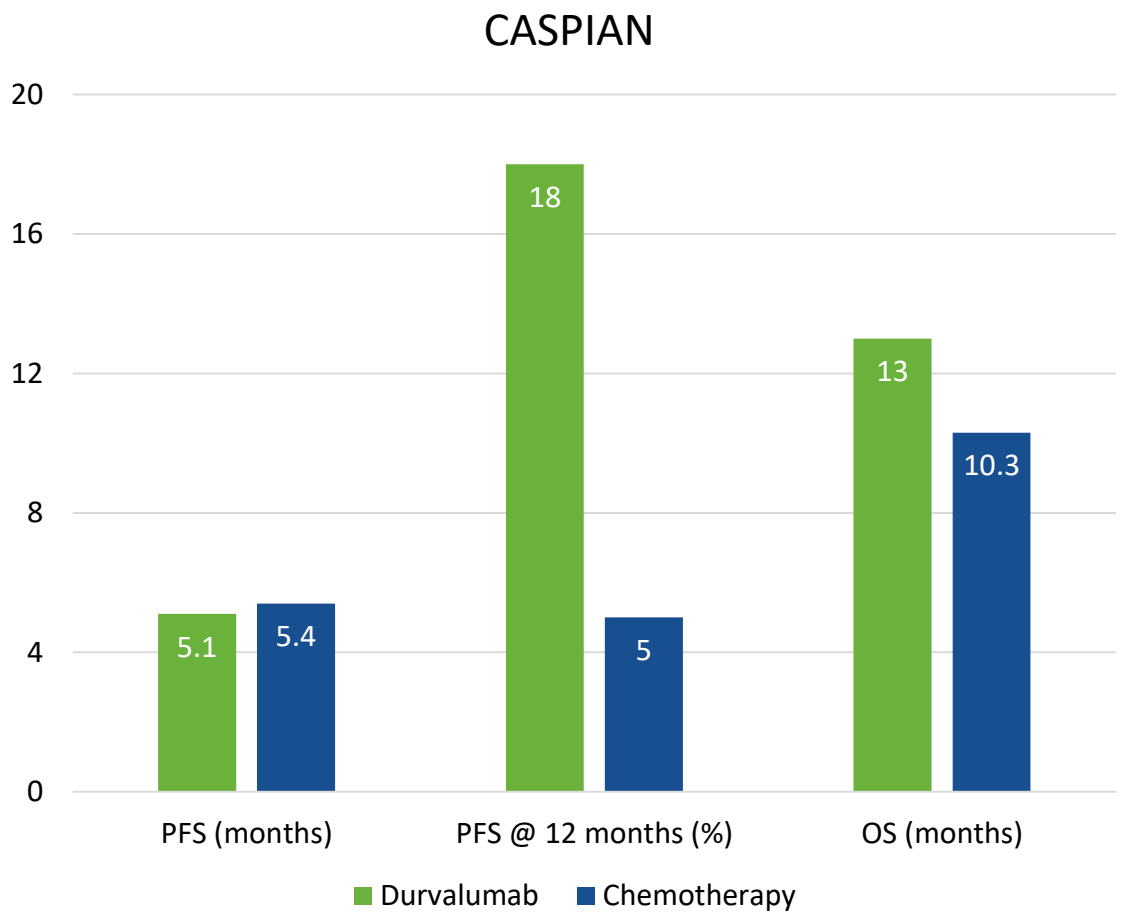


Approved checkpoint inhibitors in SCLC

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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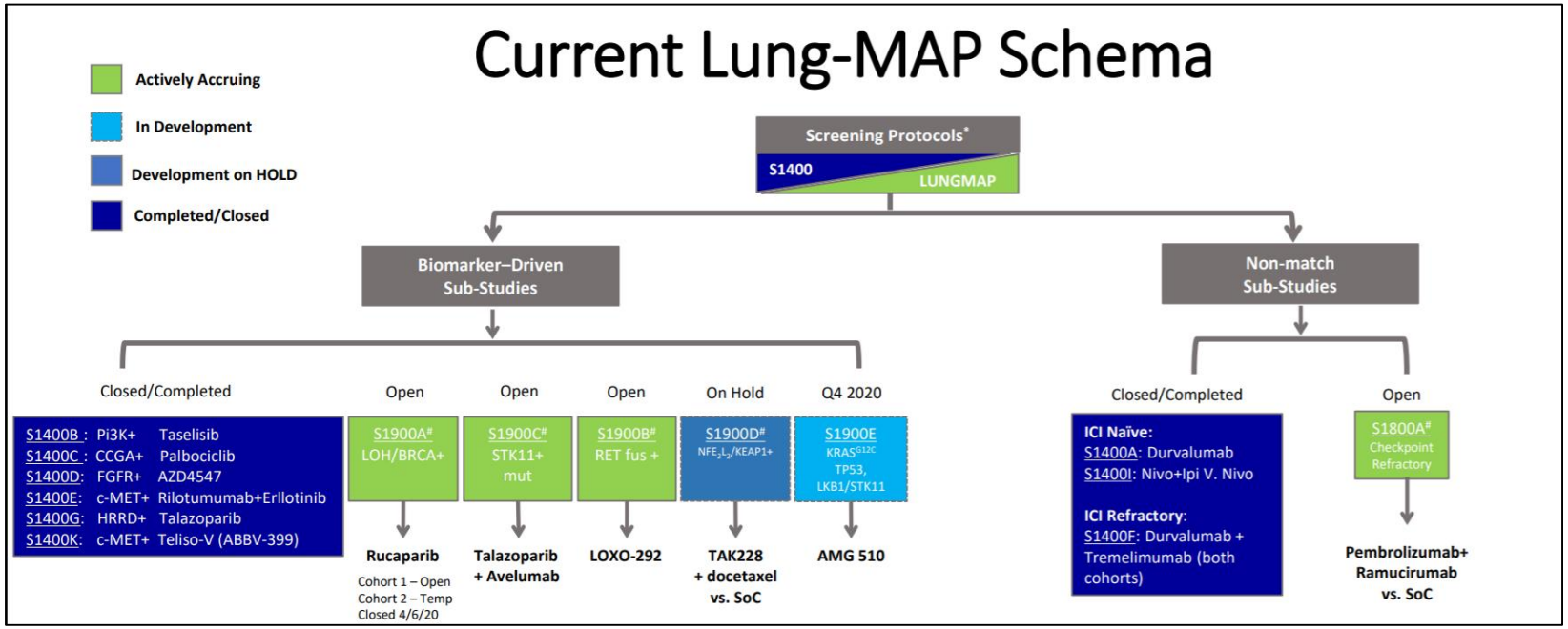
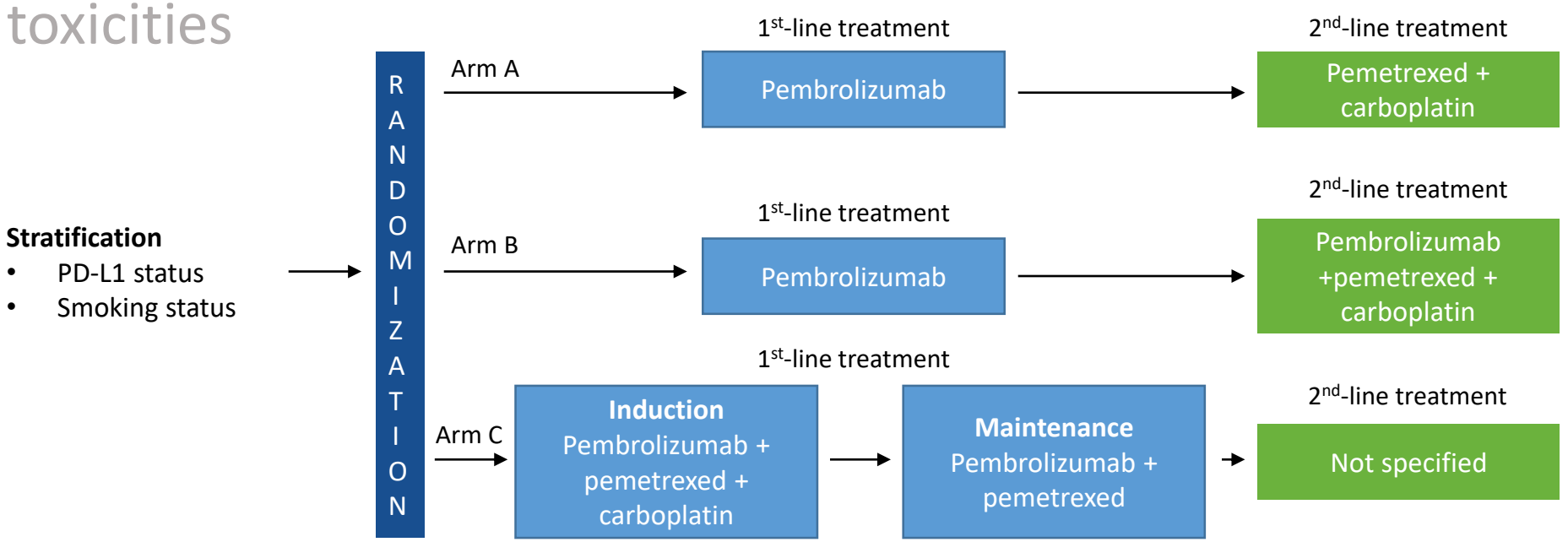


Lung-map.org

In development: answering outstanding questions

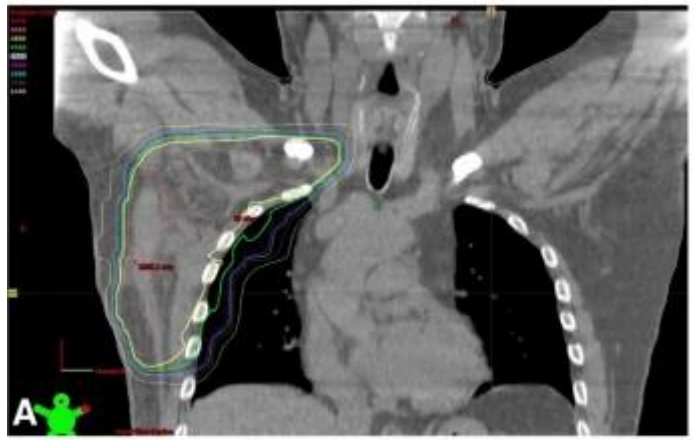
- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities



INSIGNIA trial

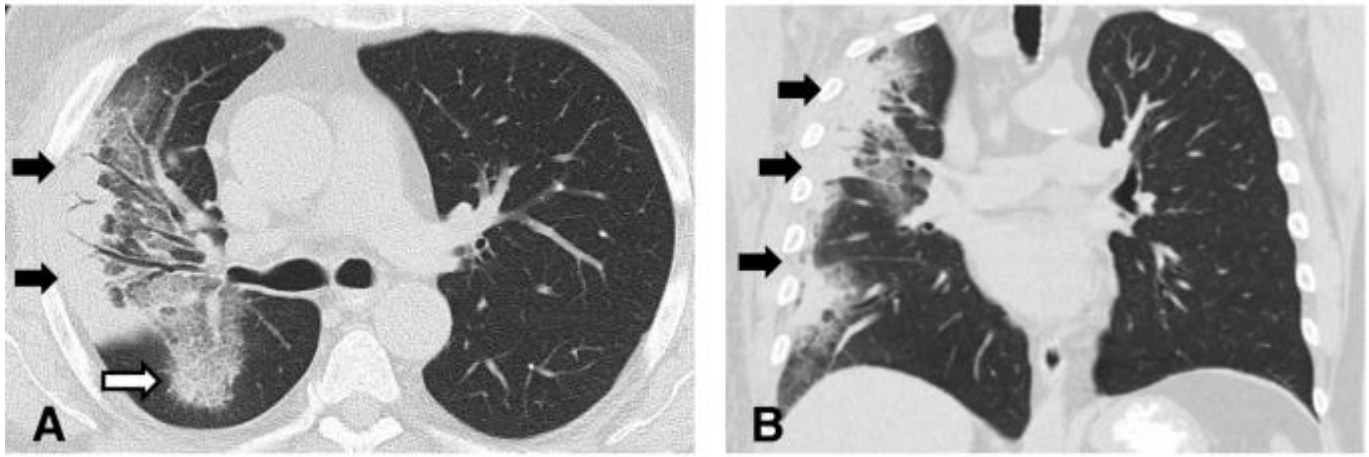
In development: answering outstanding questions

- 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

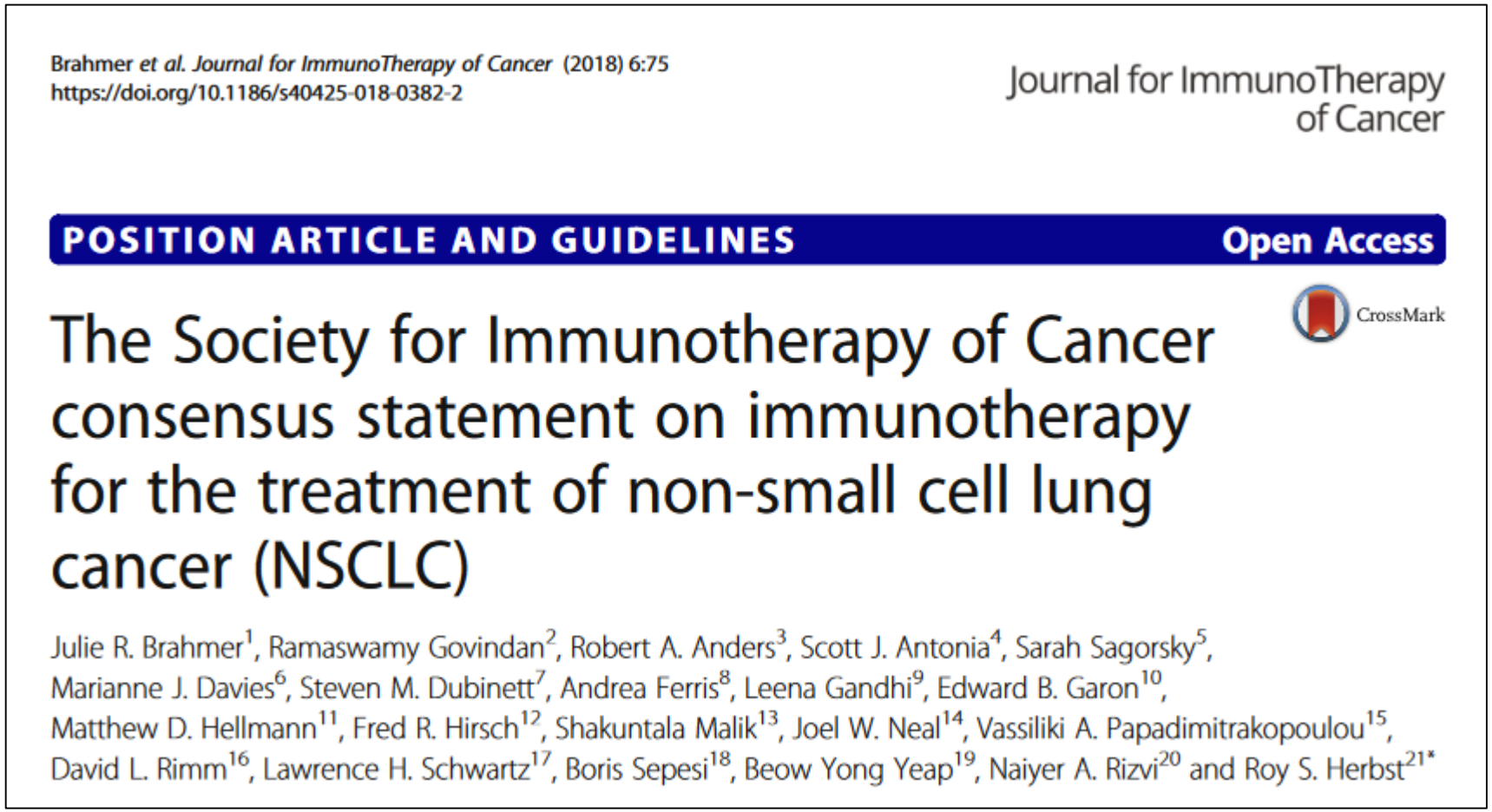
Drug	Indication	Dose
Nivolumab + ipilimumab	Frontline unresectable malignant pleural mesothelioma	Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W

- 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 Studies

Case 1

- 63 y/o male presented to PCP with persistent cough for months
- x-ray showed left upper lobe pneumonia, and close follow up imaging was recommended or a CT to rule out central obstructing lesion
- CT was performed and it revealed a 7.3 cm x 4.6 cm x 4.6 cm left suprahilar mass, reticular nodular changes suggesting lymphangitic spread
- Biopsy was performed: Positive immunohistochemical stains include cytokeratin 5/6 and 40. Negative immunohistochemical stains include cytokeratin 7, TTF-1, and Napsin A.
- PET/CT confirmed malignant effusion: Clinical stage IVA (T4 N3 M1a)

Case 1

BIOMARKER	METHOD	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
PD-L1 (22c3)	**IHC**	**Positive, Low Expression, TPS: 40%**	**BENEFIT**	**pembrolizumab**	**Level 1**
			BENEFIT	atezolizumab	Level 2
			BENEFIT	durvalumab, nivolumab	Level 3A
ALK	IHC	Negative | 0	LACK OF BENEFIT	alectinib, brigatinib	Level 1
			LACK OF BENEFIT	ceritinib	Level 1
			LACK OF BENEFIT	crizotinib	Level 1
BRAF	NGS	Mutation Not Detected	LACK OF BENEFIT	dabrafenib and trametinib combination therapy	Level 1
			LACK OF BENEFIT	vemurafenib	Level 2
EGFR	NGS	Mutation Not Detected	LACK OF BENEFIT	erlotinib, gefitinib	Level 1
ROS1	FISH	Negative	LACK OF BENEFIT	crizotinib	Level 1
			LACK OF BENEFIT	ceritinib	Level 2
MET	CNA-NGS	Amplification Not Detected	LACK OF BENEFIT	crizotinib	Level 3A

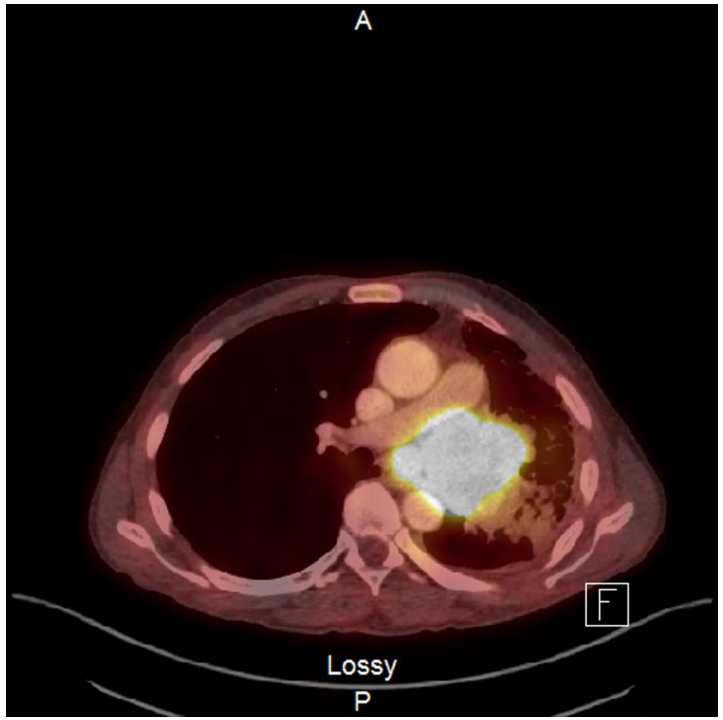
Case Study 1

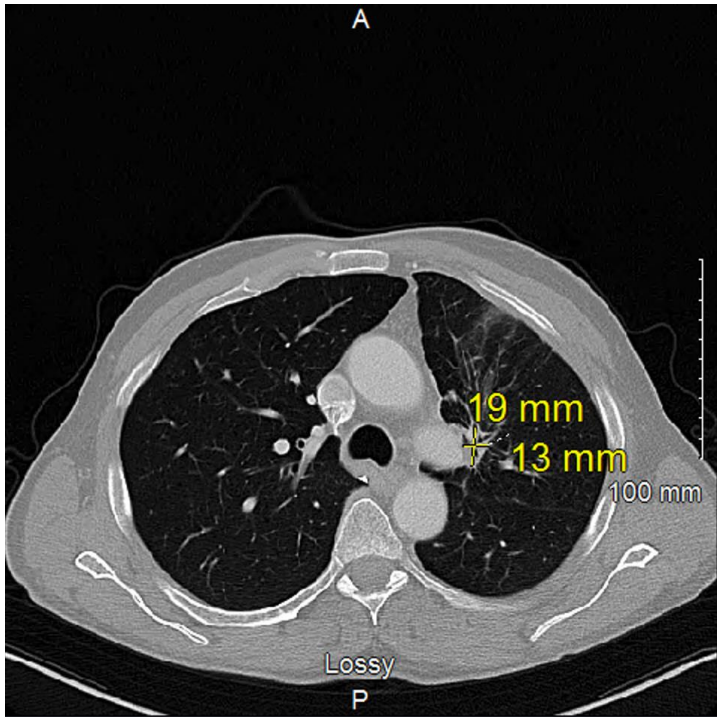
- What initial therapy would you recommend for this patient?

1. Carboplatin/Paclitaxel/Bevacizumab
2. Carboplatin/Paclitaxel/Pembrolizumab
3. Nivolumab/Ipilimumab
4. Pembrolizumab/Carboplatin/Pemetrexed
5. Pembrolizumab

Case 1

- Started on treatment with Carboplatin/Paclitaxel/Pembrolizumab
- Treated through 4 cycles followed by maintenance Pembrolizumab





Case 1

- JL completed 2 years of the maintenance pembrolizumab. He tolerated the therapy with no adverse effects. How would you proceed?

1. Annual CT CAP for surveillance
2. Continue pembrolizumab until intolerable side effects or progressive disease
3. Q 3-month CT CAP with physical exams
4. Maintenance Erlotinib

Case 1

- Patient continues to do well
- On observation with routine CT scans
- Most recent imaging 03/08/2021 with no active disease