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

- Research Funding: AstraZeneca, Astex, Tesaro
- Consulting Fees: Adaptimmune
- I will be not be discussing non-FDA approved indications during my presentation.

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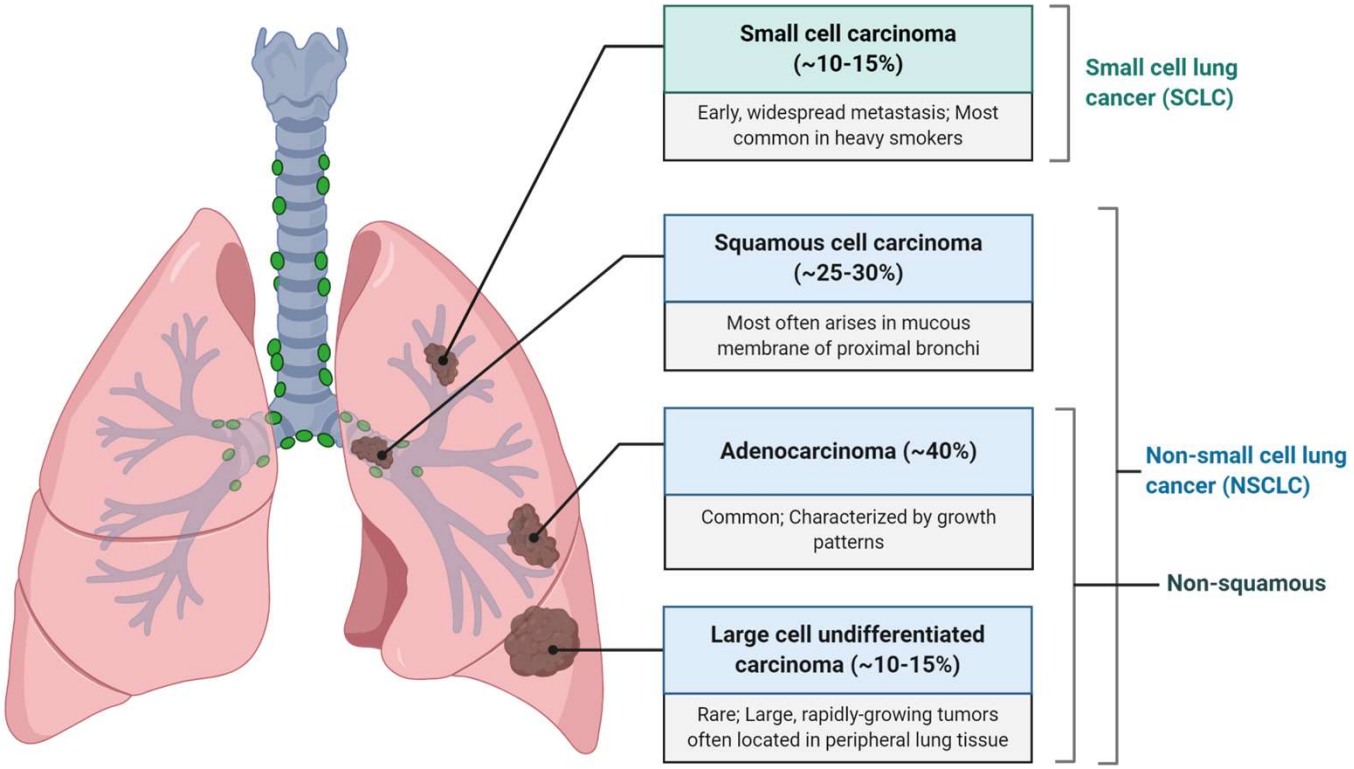
Lung cancer



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

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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.

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Immune checkpoint inhibitors in lung cancer

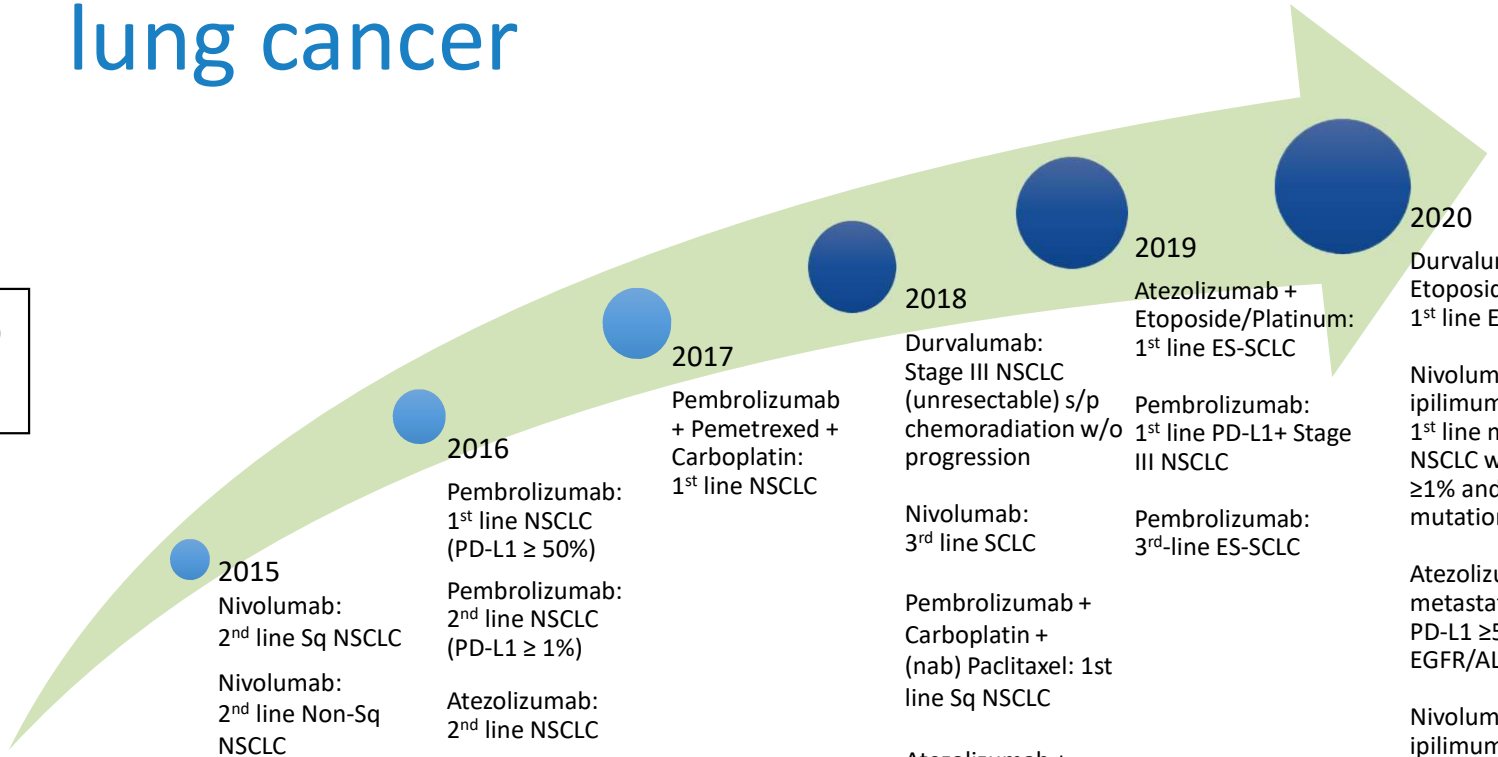
Nivolumab — **PD-1**

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
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

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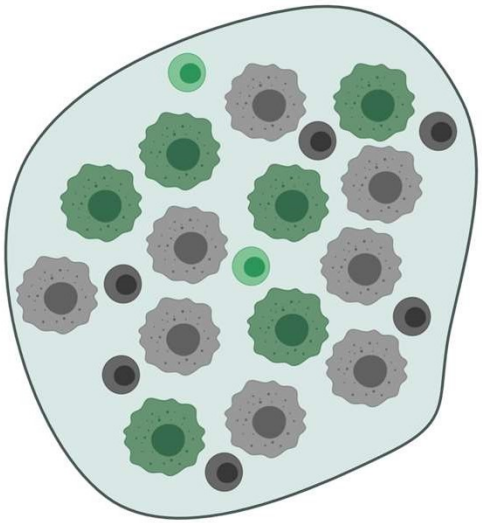
Brief aside: PD-L1 TPS vs CPS

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

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



PD-L1-positive immune cell

PD-L1-negative immune cell

PD-L1-positive tumor cell

PD-L1-negative tumor cell

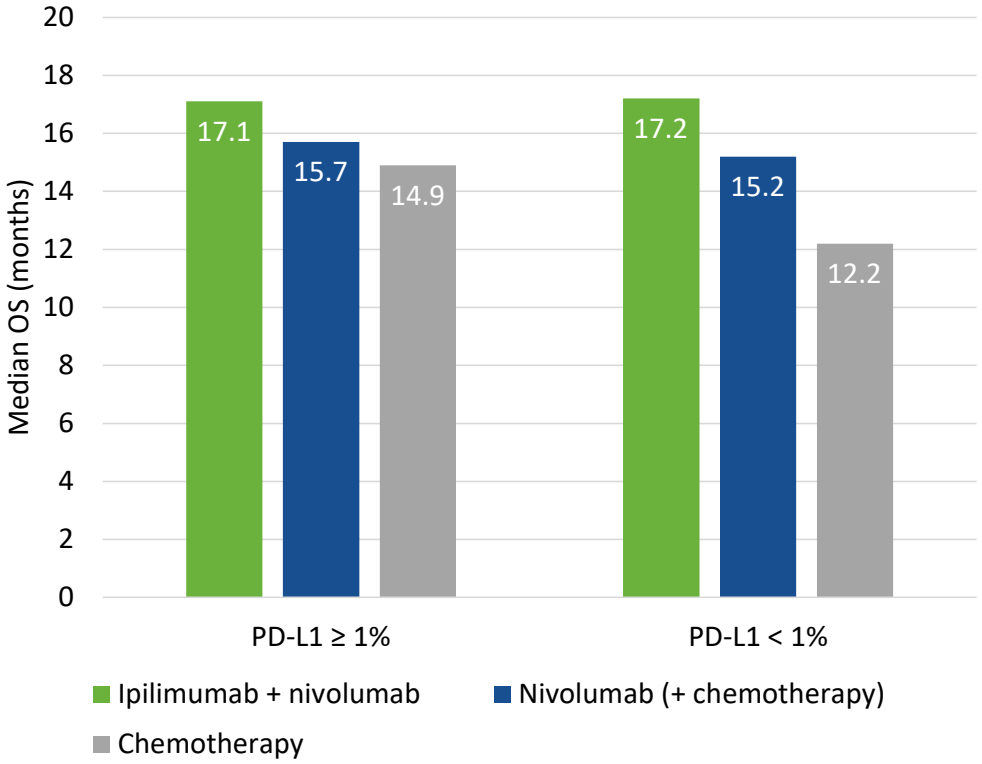
$$TPS = \frac{6\ positive\ tumor\ cells}{14\ total\ tumor\ cells} \times 100 = 43$$

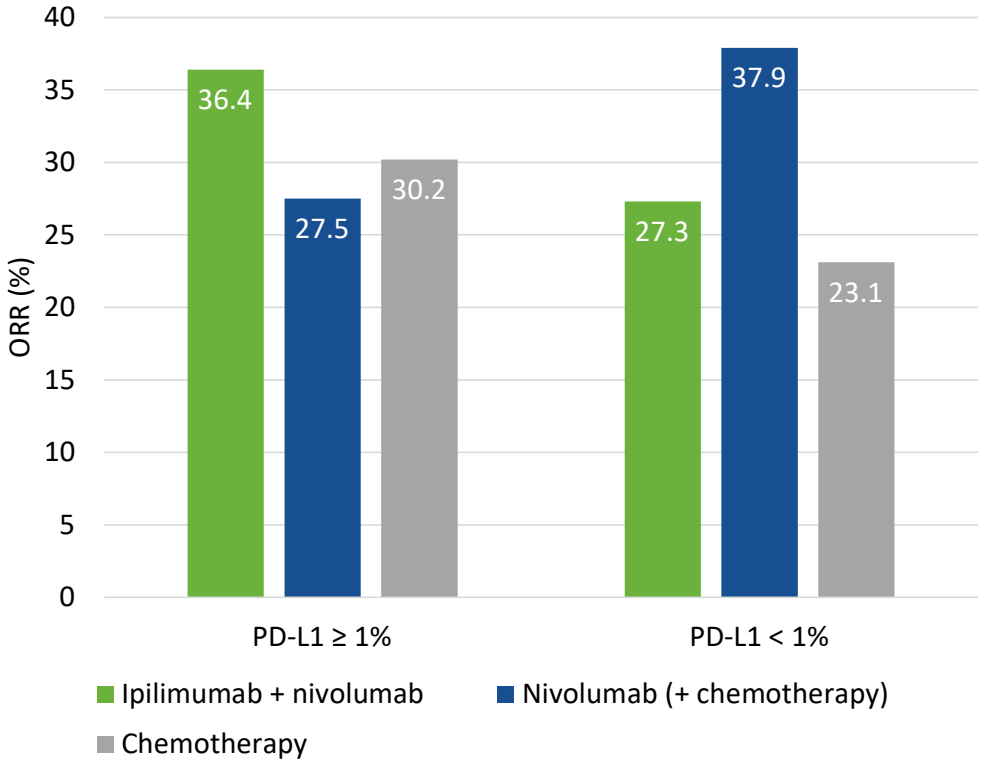
$$CPS = \frac{6\ positive\ tumor\ cells + 2\ positive\ immune\ cells}{22\ total\ cells} \times 100 = 36$$

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*

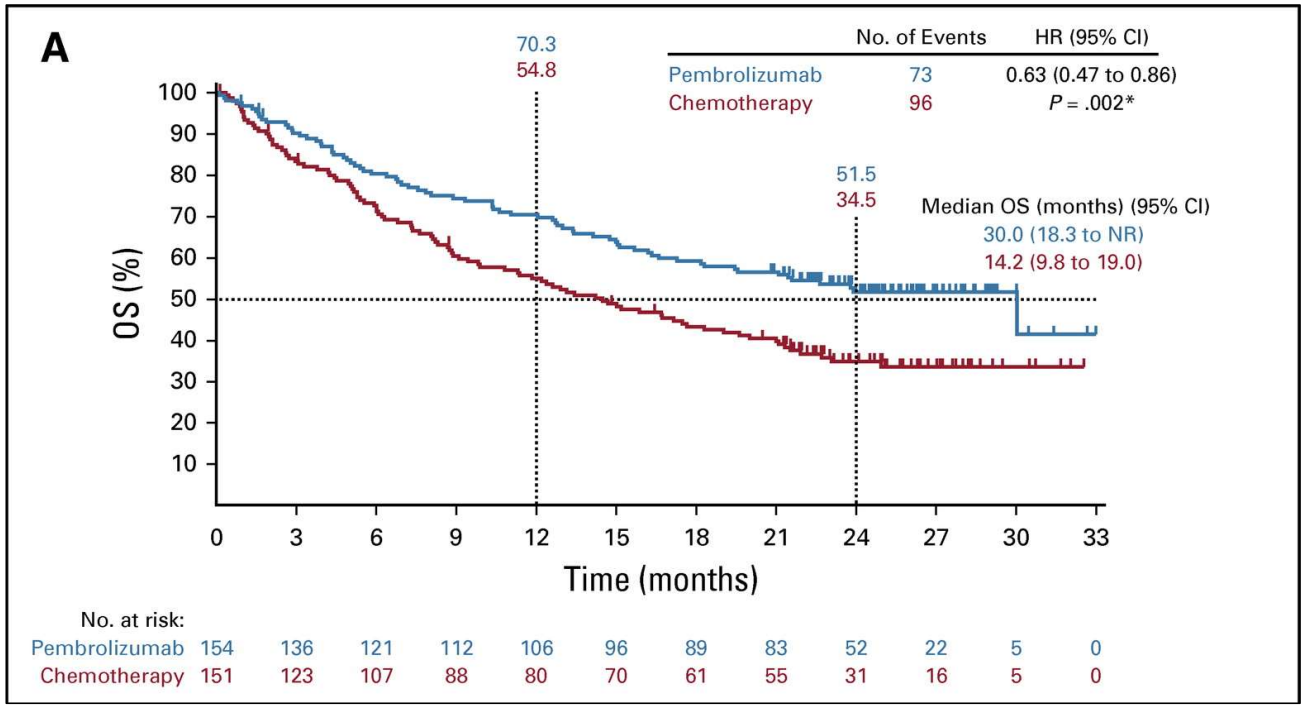
CheckMate 227: Ipilimumab + nivolumab vs chemotherapy for 1L NSCLC





Ramalingam, ASCO 2020.

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



Reck, J Clin Oncol 2019.

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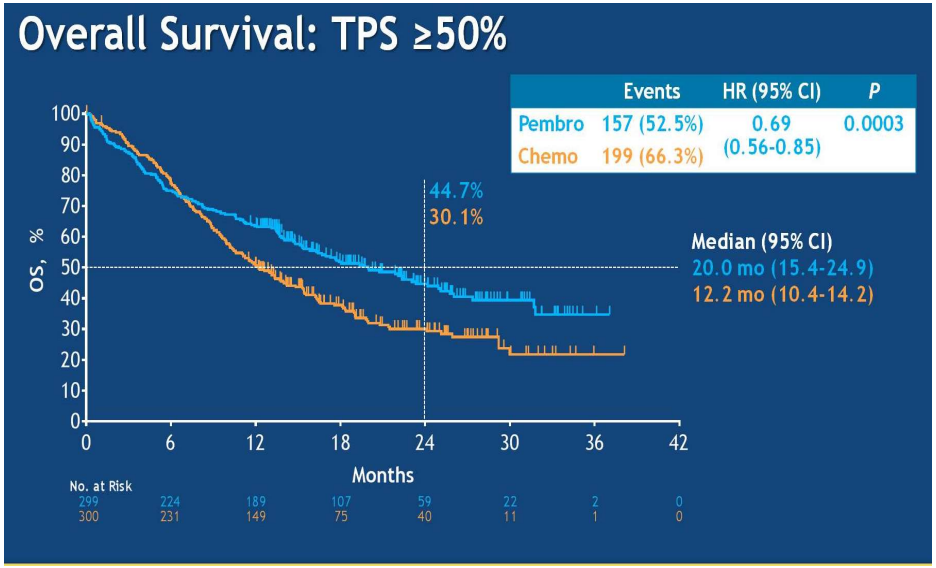
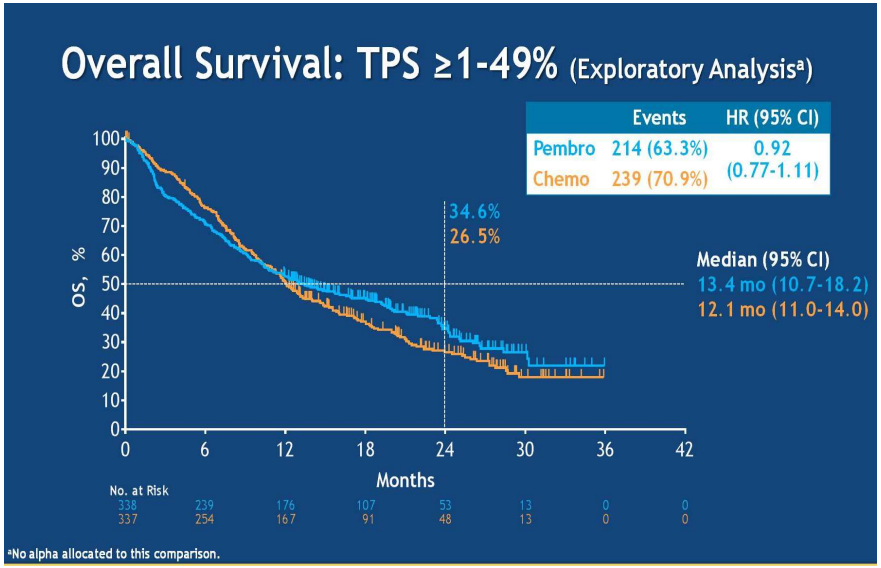
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC





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

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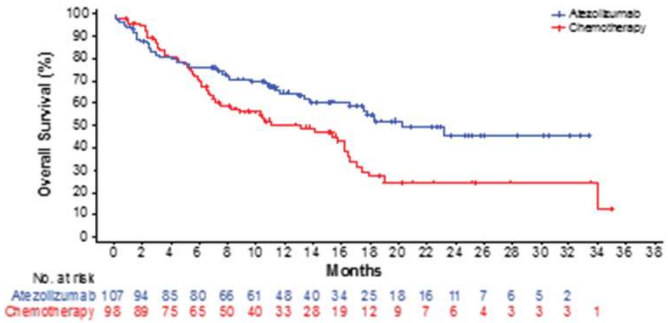
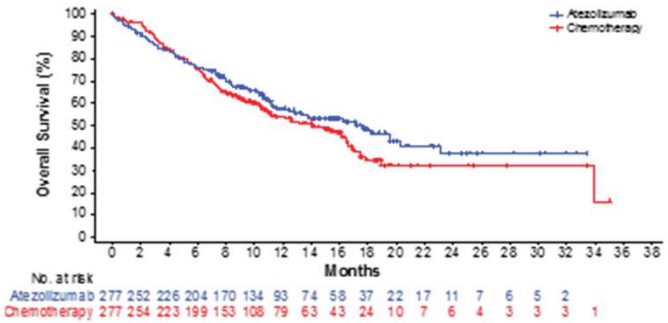
IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

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.

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Treatments not reliant on PD-L1 expression

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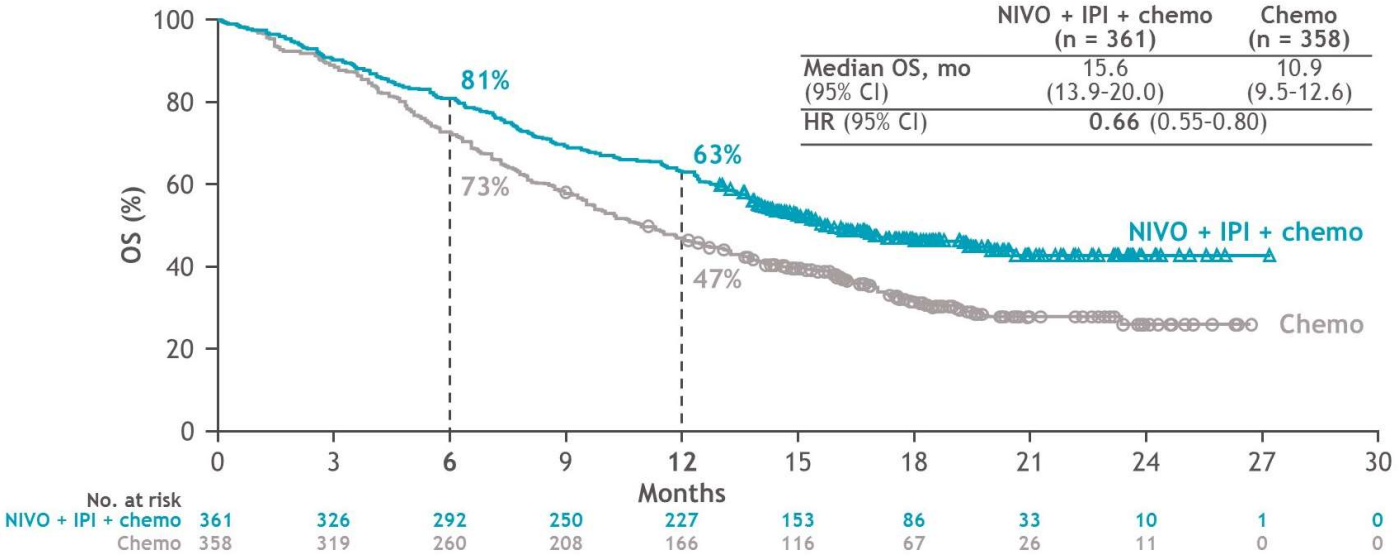
CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo

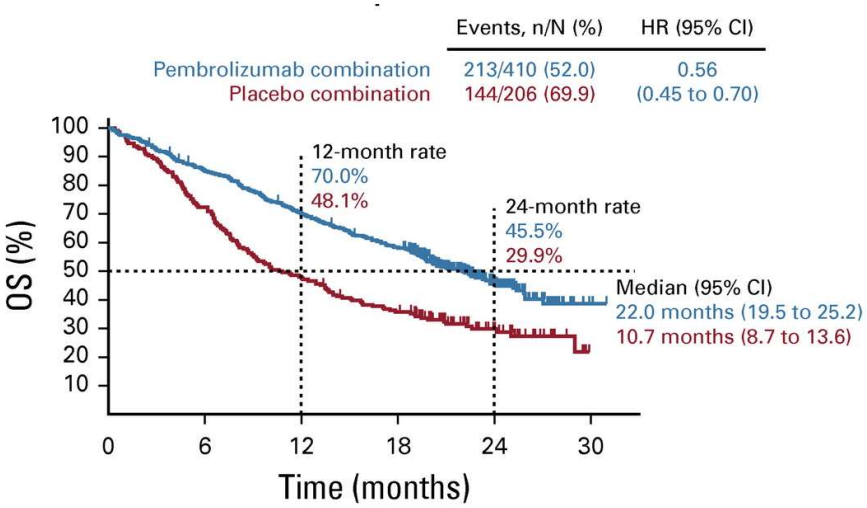


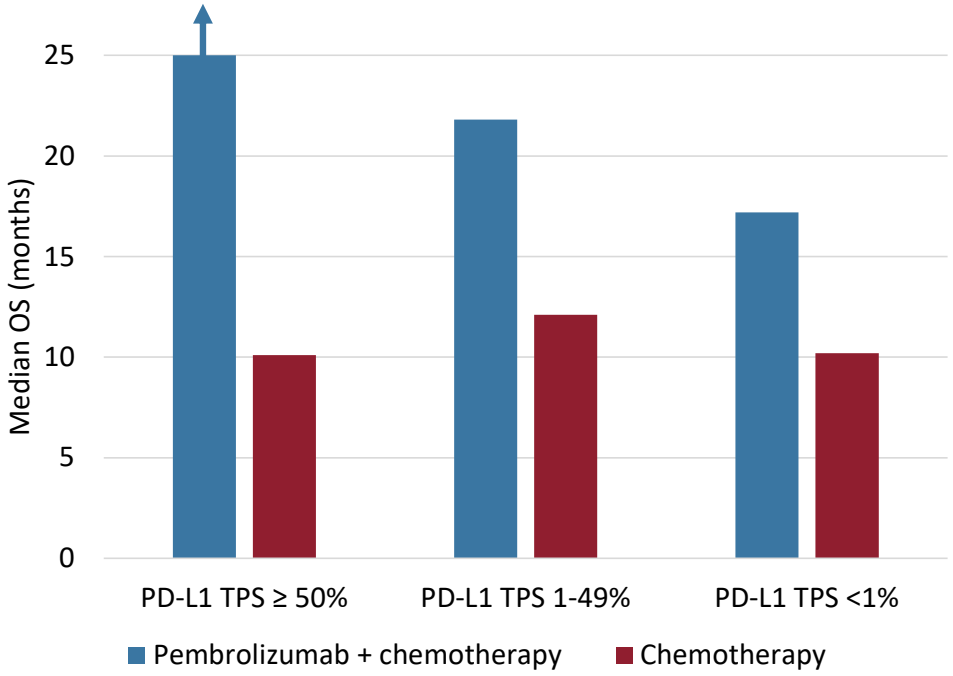
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	**0.66** (0.55-0.80)	

	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.

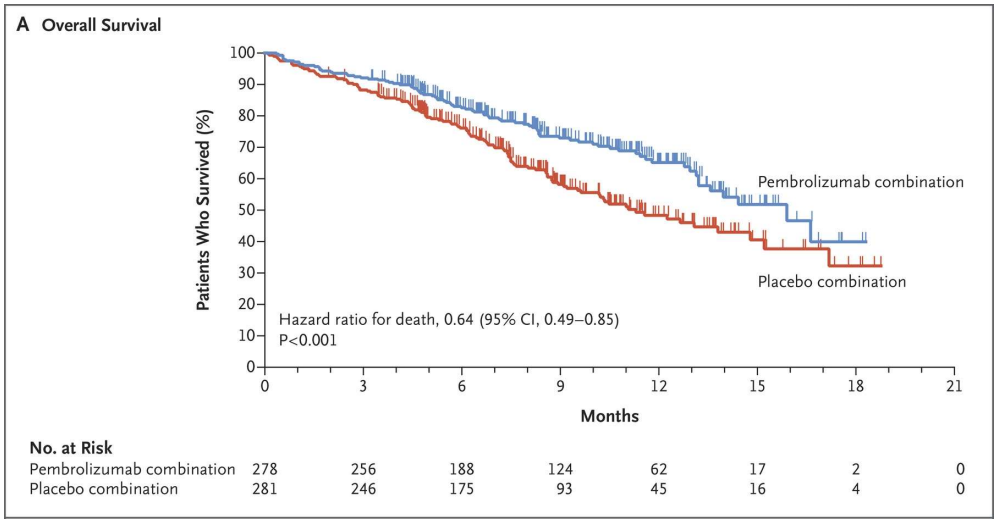
KEYNOTE-189: Pembrolizumab/chemotherapy vs Chemotherapy Alone for Advanced Non-Squamous NSCLC

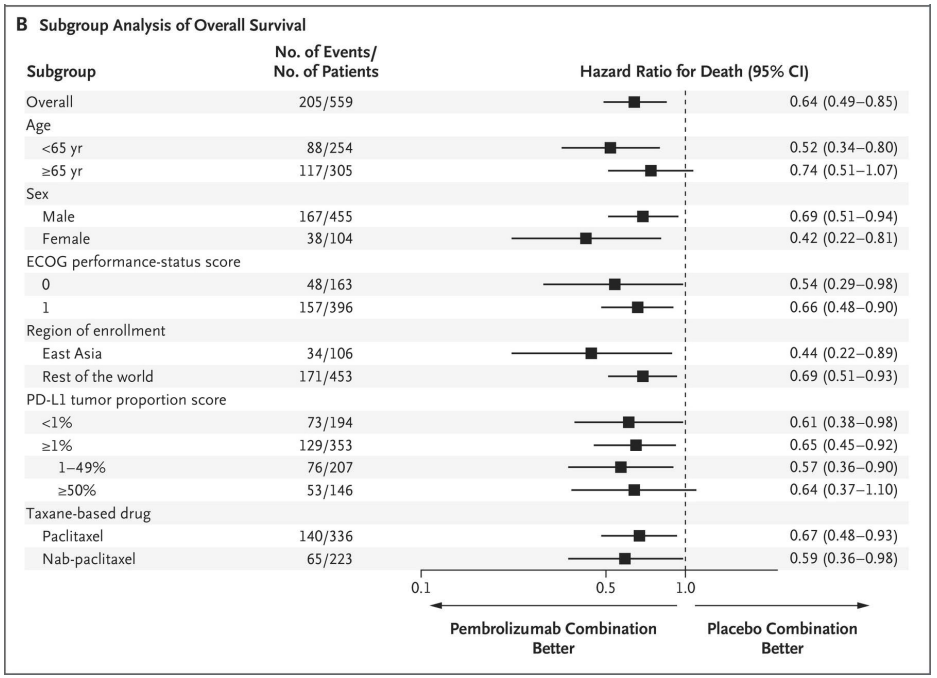




Gadgeel, J Clin Oncol 2020.

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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EE15

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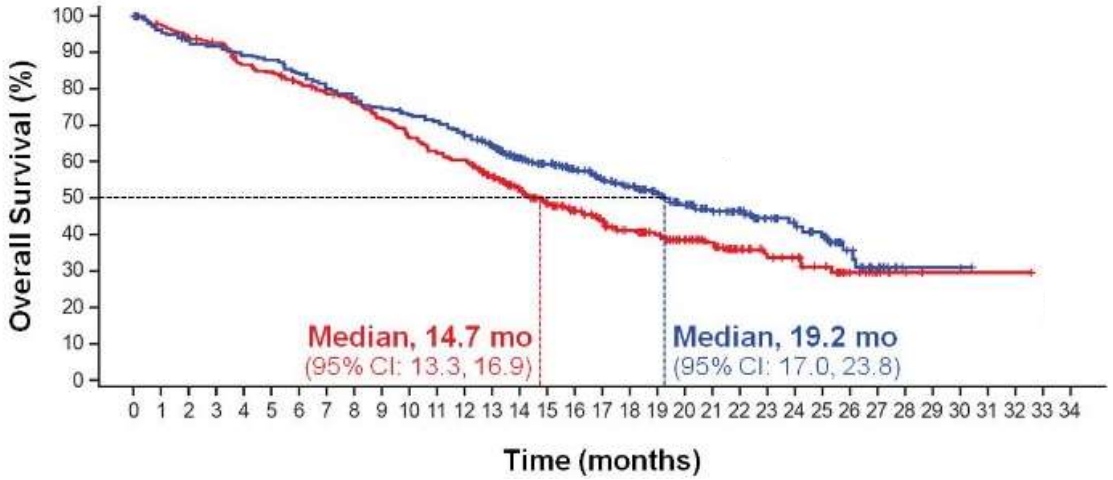
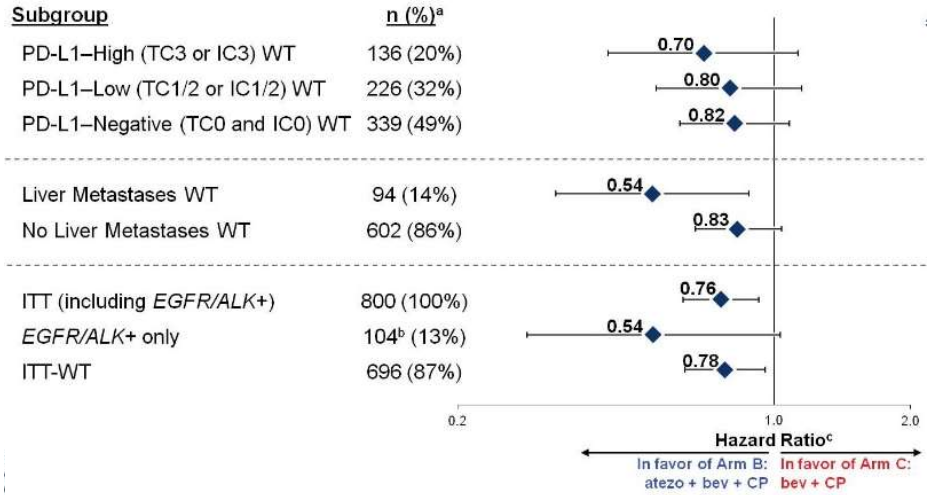
IMpower150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/ Bevacizumab in Advanced Non-Squamous NSCLC

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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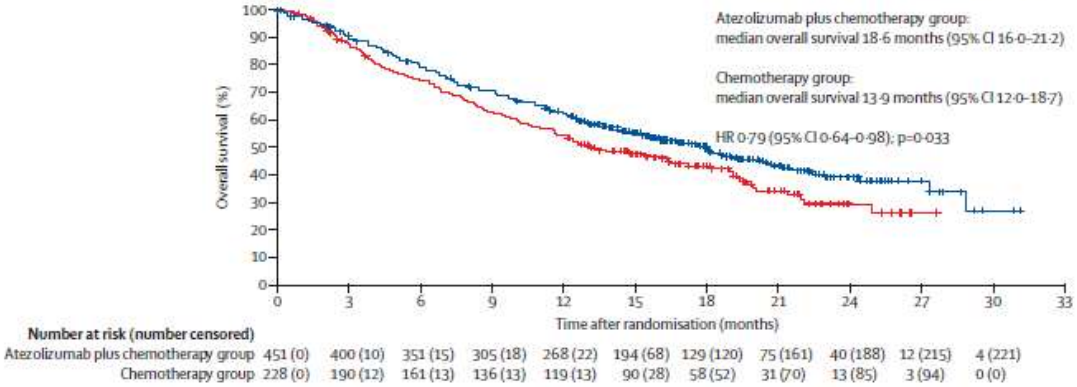
Slide 19

EE15 https://www.abstractsonline.com/pp8/#!/9045/presentation/10719

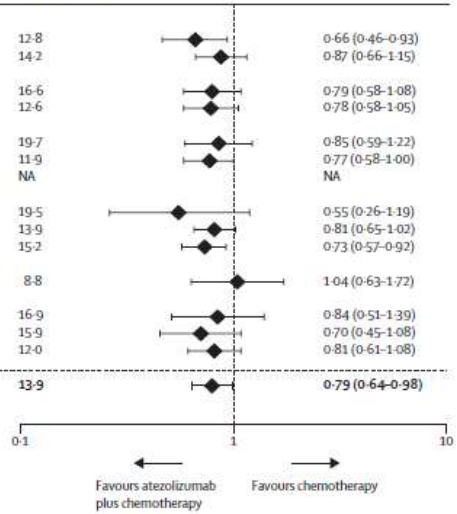
Emily Ehlerding, 7/27/2020

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)



	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

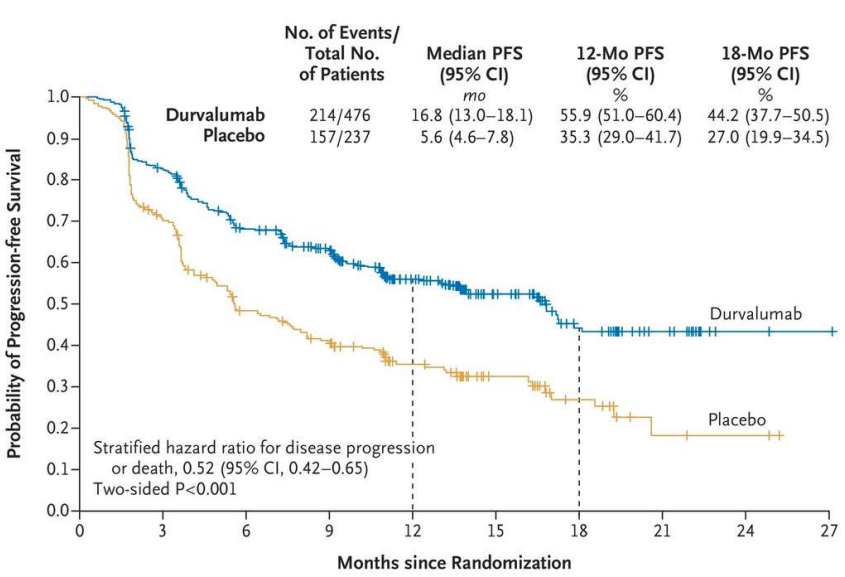
Study	Treatment arms	ORR	Median PFS (months)	Median OS (months)
CheckMate 017 and CheckMate 057	Nivolumab	19%	2.56	11.1
	Docetaxel	11%	3.52	8.1
KEYNOTE-010 (PD-L1 TPS ≥ 1%)	Pembrolizumab	18%	4.0	12.7
	Docetaxel	9%	4.0	8.5
OAK	Atezolizumab	14%	2.8	13.8
	Docetaxel	13%	4.0	9.6

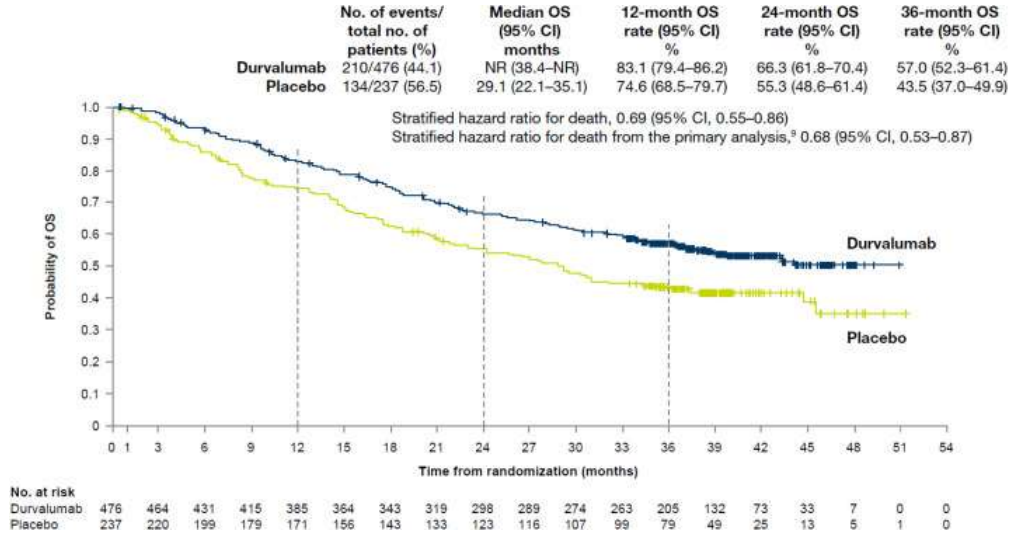
Vokes, Ann Oncol 2018.
Herbst, Lancet 2016.
Fehrenbacker, J Thorac Oncol 2018.

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





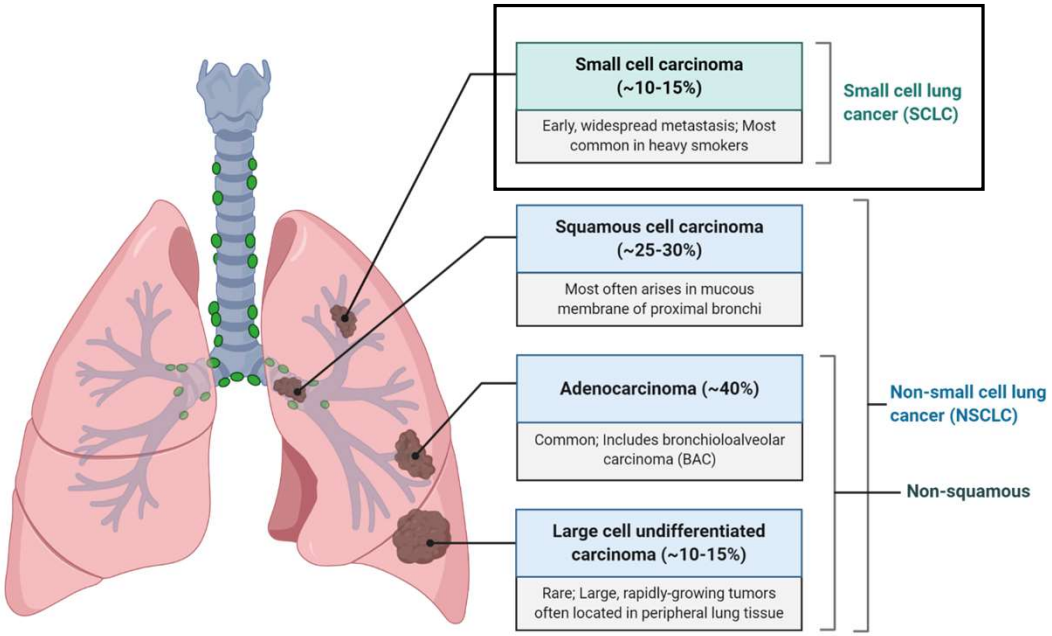
Antonia, N Engl J Med 2017.
Gray, J Thorac Oncol 2020.

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



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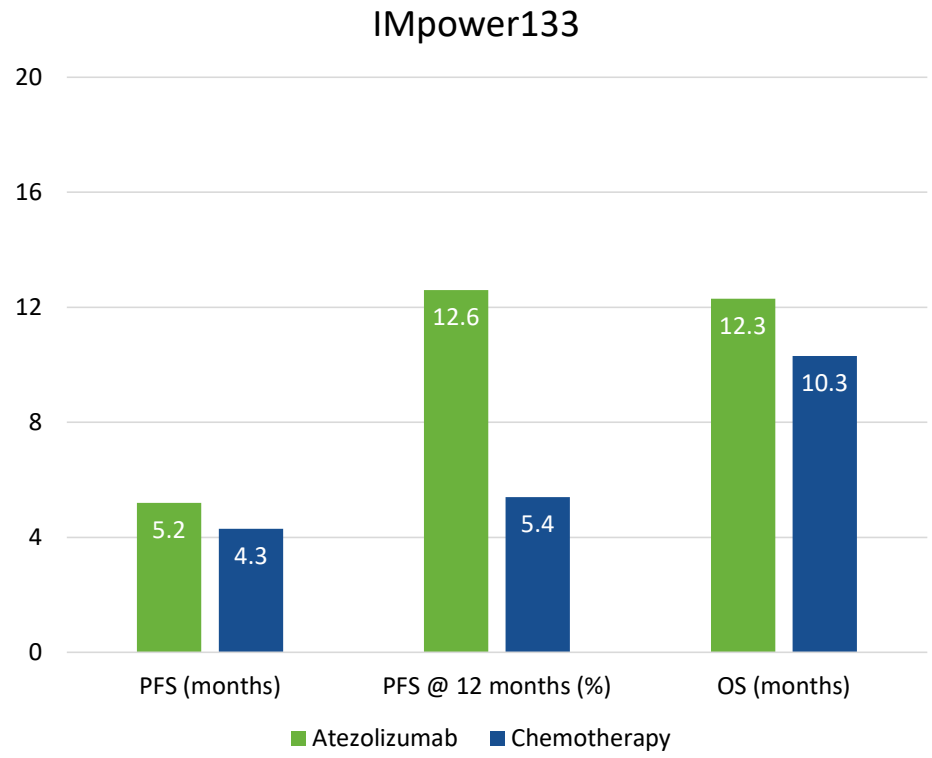
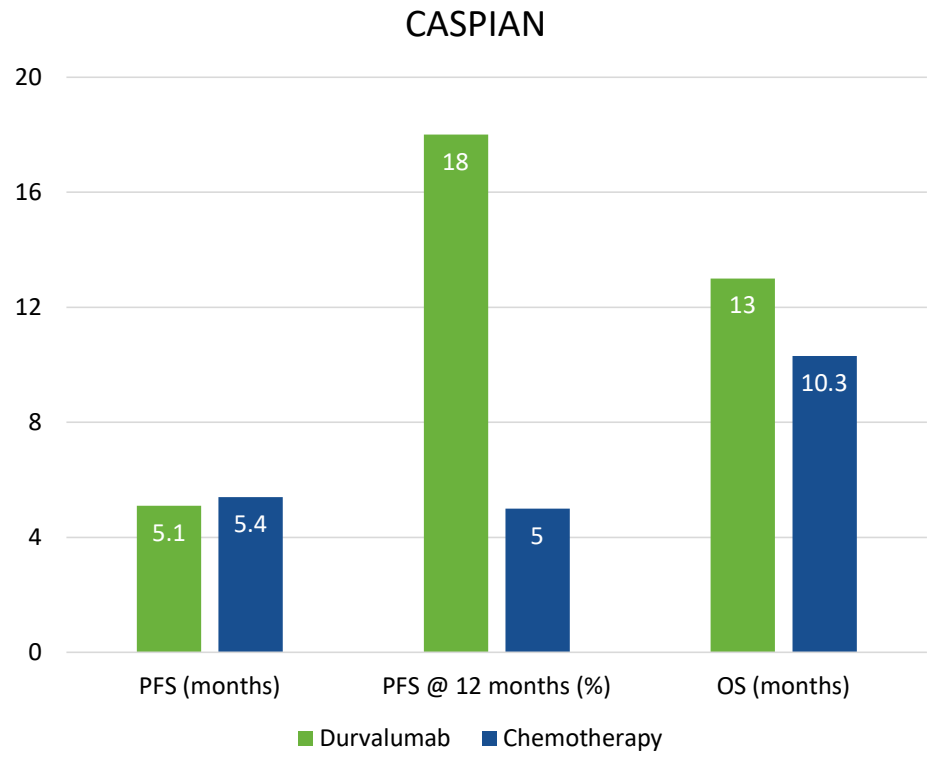
Approved checkpoint inhibitors in SCLC

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
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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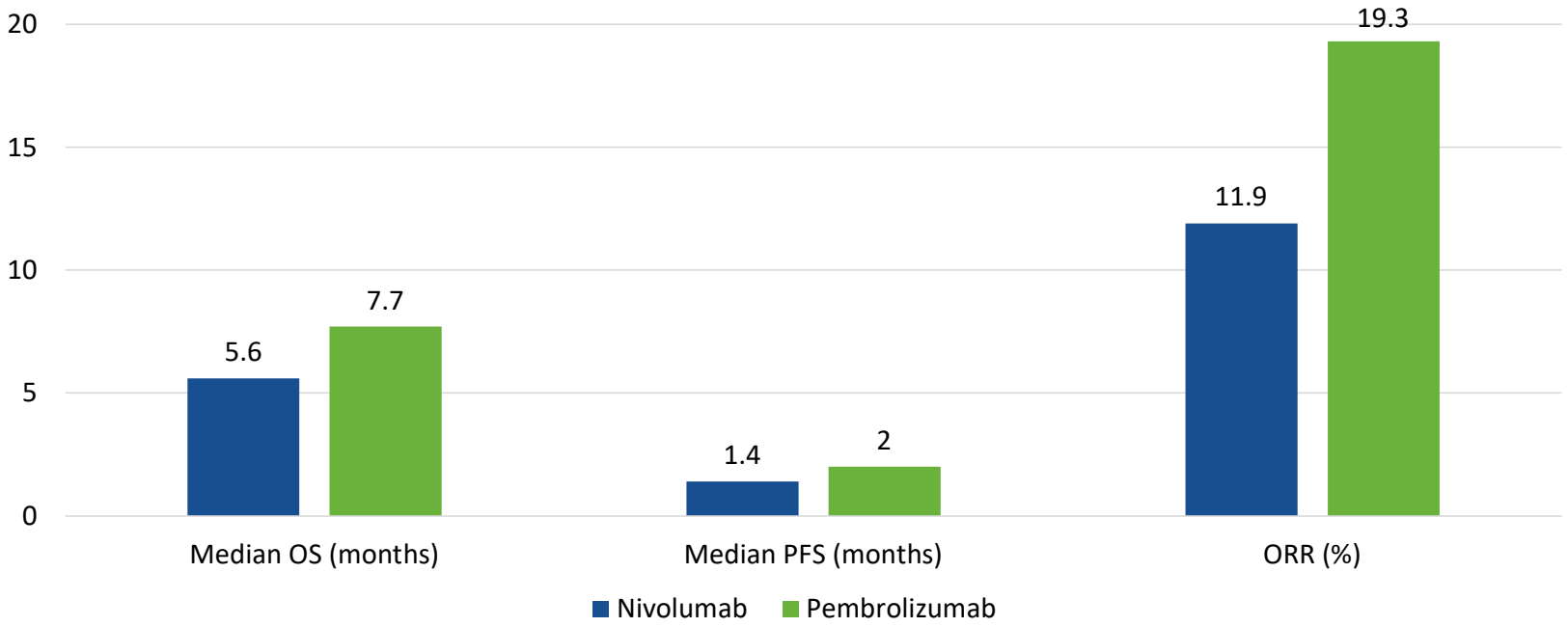
Later-line ICIs in SCLC



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

Outline

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  - 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

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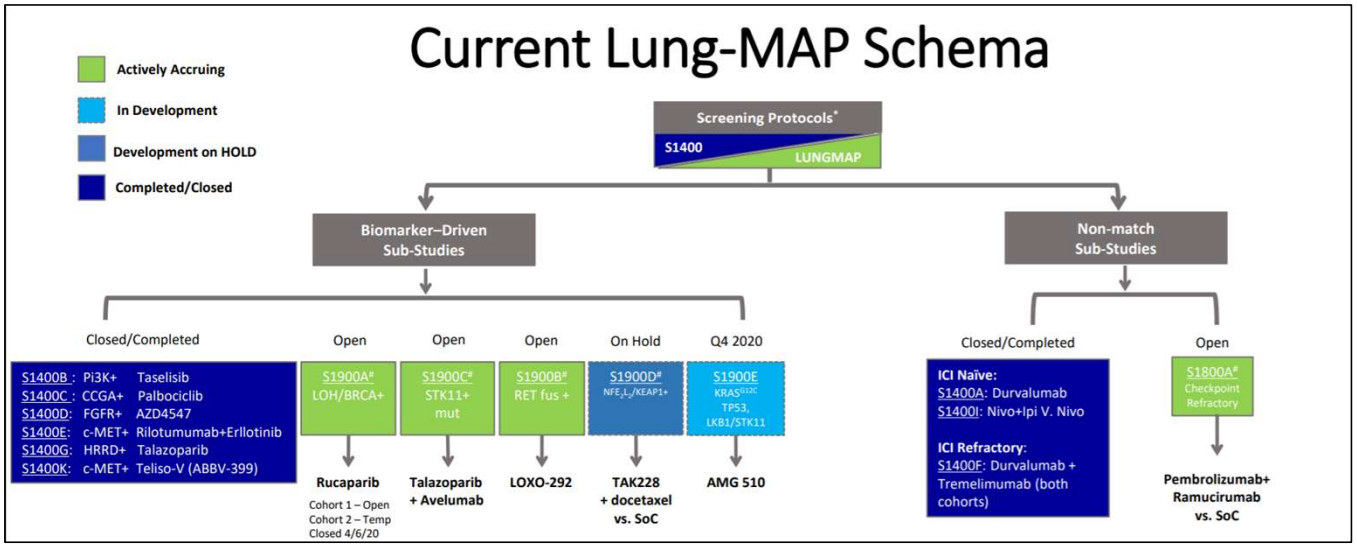

Lung-map.org

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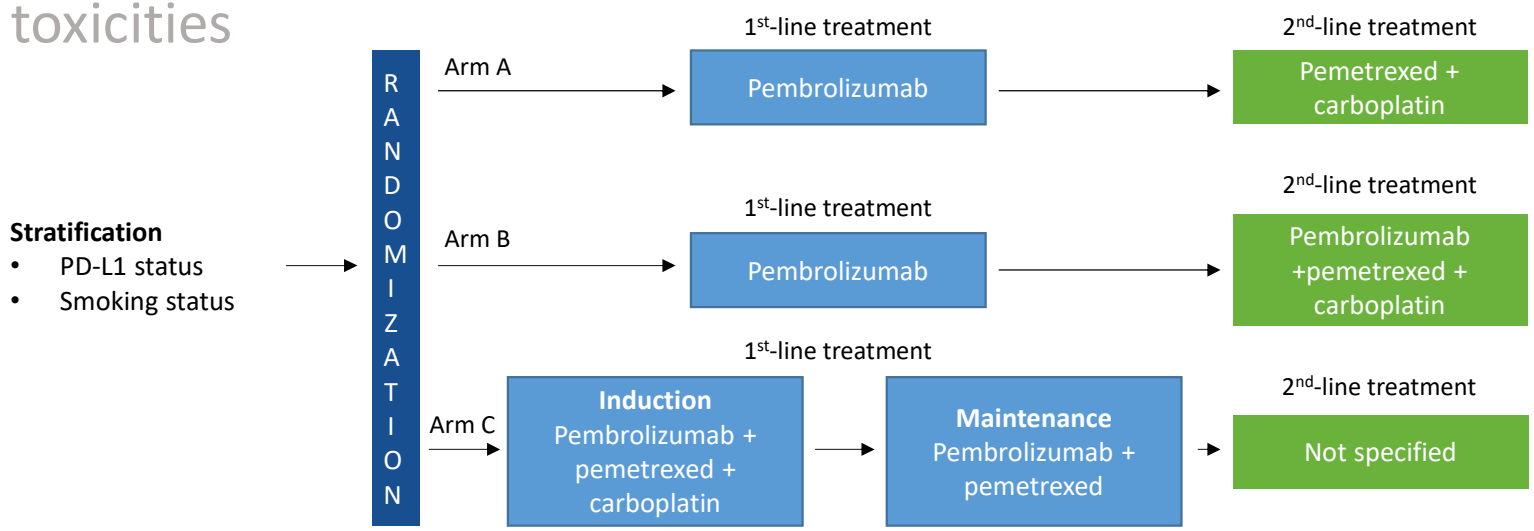
In development: answering outstanding questions

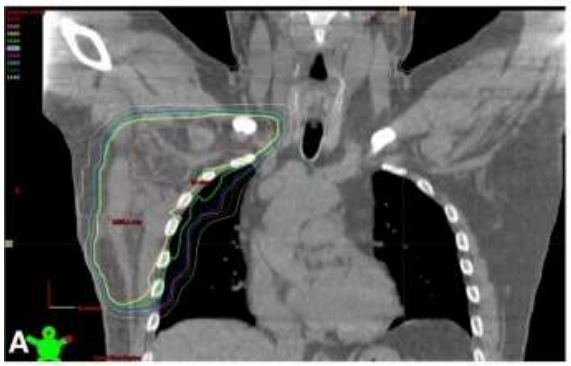
- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities



INSIGNIA trial

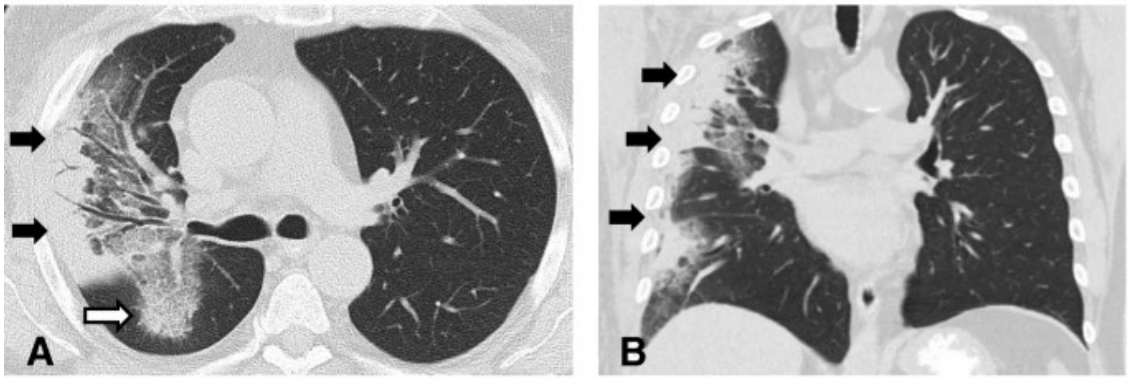
In development: answering outstanding questions

- 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

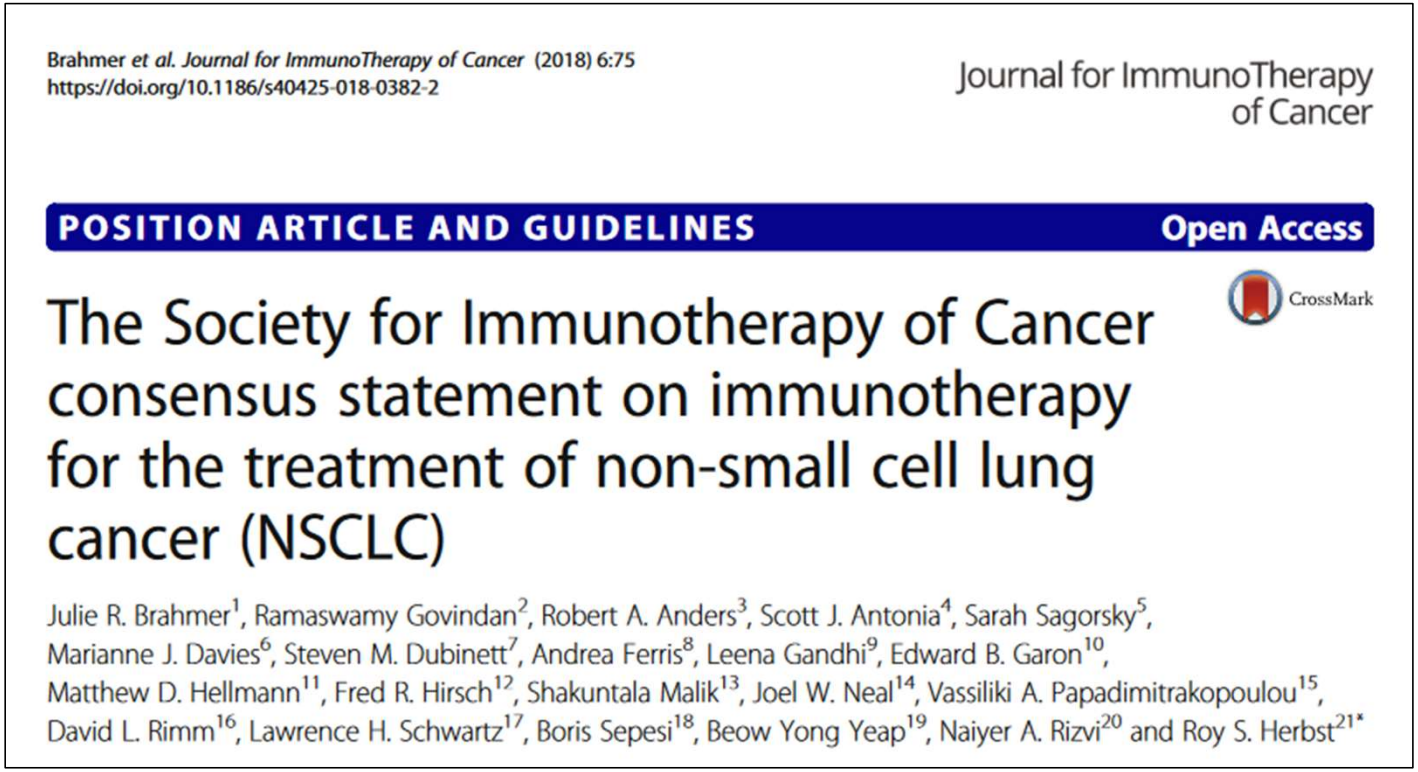


Schoenfeld, J Immunother Cancer 2019.

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

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*]

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Case Studies

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Case Study 1

- 59 year old female is diagnosed with stage IIIA NSCLC and is treated with definitive chemotherapy and radiation with weekly carboplatin and paclitaxel. Her scans post treatment show a very nice partial response. She is started on Durvalumab Consolidation therapy. After 5 months of therapy she presents with mild SOB, no hypoxia noted. CT scan shows bilateral infiltrates/ GGOs.
  1. What would you do?
     1. Consult pulmonary
     2. Initiate high dose steroids
     3. Initiate antibiotics

Continue Case Study 1

- Patient's workup rules out infection, Bronchoscopy and BAL suggests checkpoint induced pneumonitis. Patient is started on 1mg/kg po prednisone, with clinical improvement.
  - How long would you continue steroids?
    1. 2 weeks
    2. 4 weeks
    3. 12 weeks
    4. Continue current dose until symptoms are back to baseline, then start slow taper

Case Study 2

- 64 year old never smoker is diagnosed with stage IVB adenocarcinoma of the lung after presenting with rib pain. She has a RLL lung mass, mediastinal lymphadenopathy and three bony mets including a rib lesion. Her PDL1 expression by TPS is 50%. What would you do?
  1. Start her on pembrolizumab alone
  2. Start her on carboplatin and pemetrexed
  3. Start her on carboplatin and pemetrexed and pembrolizumab
  4. Await mutational analysis and rule out driver mutations prior to initiating therapy

Case Study 2 Continued

- What are the potential risks of initiating a checkpoint inhibitor prior to a targeted treatment?
  1. Lower response rate
  2. Potential increased toxicities, including -itis
  3. No risk

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Thank you for your attention

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