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

Society for Immunotherapy of Cancer

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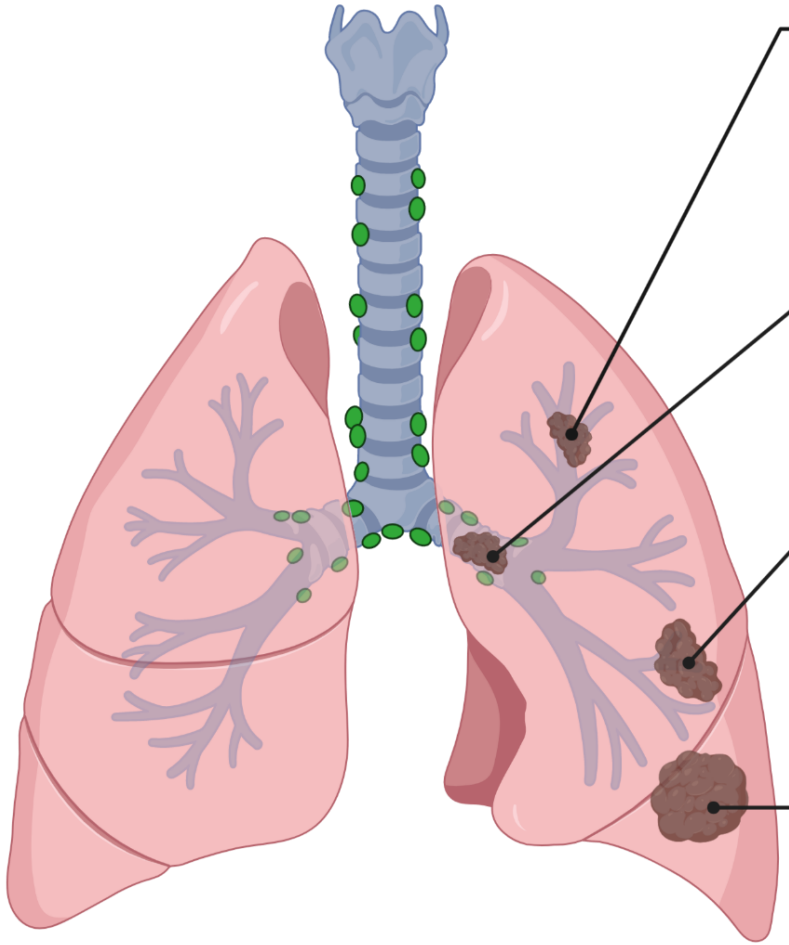
Disclosures

- Contracted Research: Merck Sharp & Dohme, Mirati Therapeutics, AstraZeneca, Blueprints Medicine, Lilly
- I will be discussing non-FDA approved indications during my presentation.

Epidemiology of Lung Cancers



Small cell carcinoma (~10-15%)
Early, widespread metastasis; Most common in heavy smokers

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

Small cell lung cancer (SCLC)

Non-small cell lung cancer (NSCLC)

Non-squamous

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Treatment options for NSCLC

Local disease (stage I and II)

- Surgery or SBRT
- Post surgery platinum CTX

Stage III unresectable disease

- Concurrent CTX + RT then IO (durvalumab)

Metastatic disease

- Oral TKI for oncogene driver cancers
- Single agent immunotherapy
- CTX + IO – multiple regimens
- Combination IO
- RARE to use CTX alone

Immune checkpoint inhibitors in lung cancer

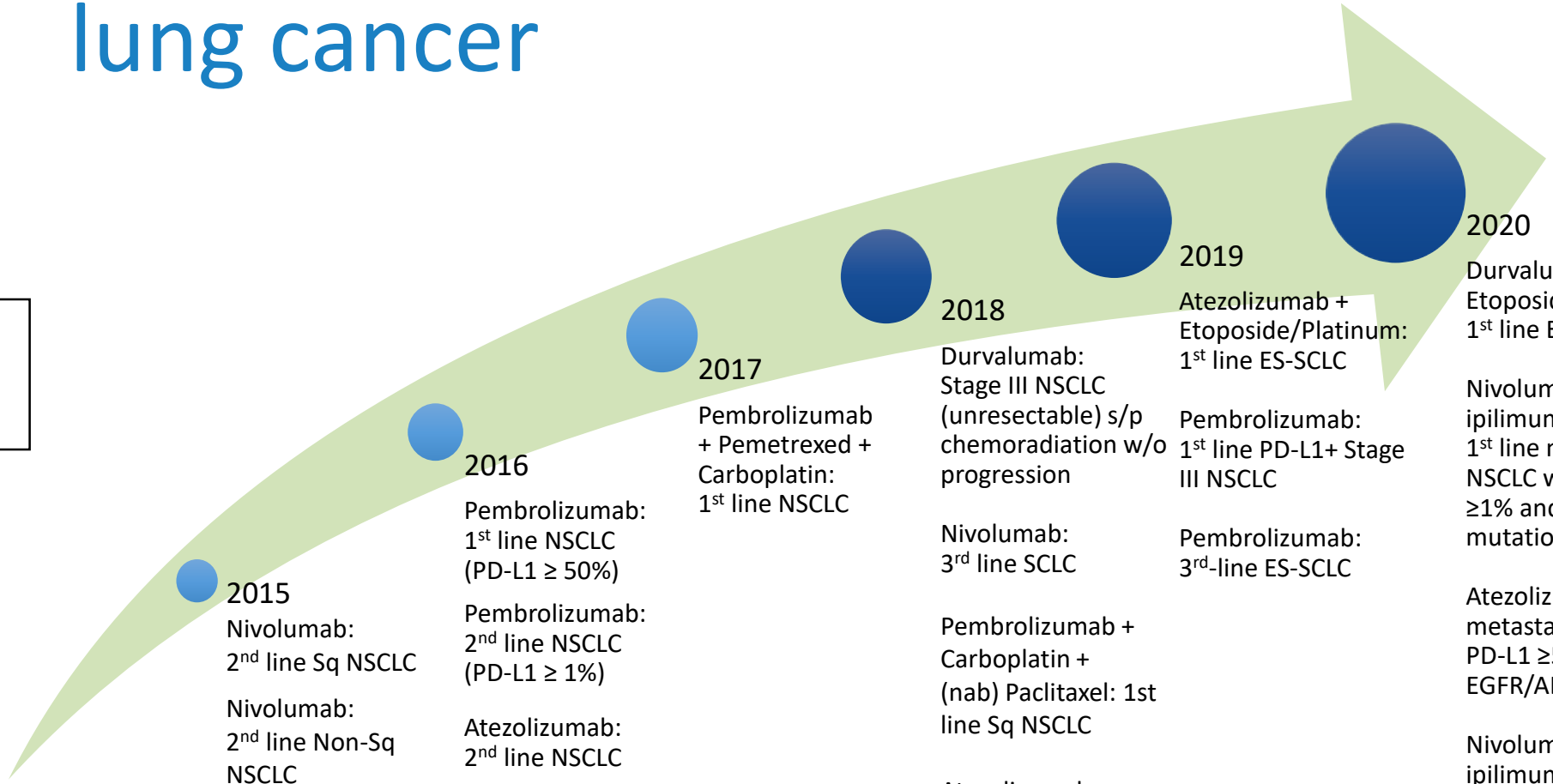
Nivolumab
PD-1

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

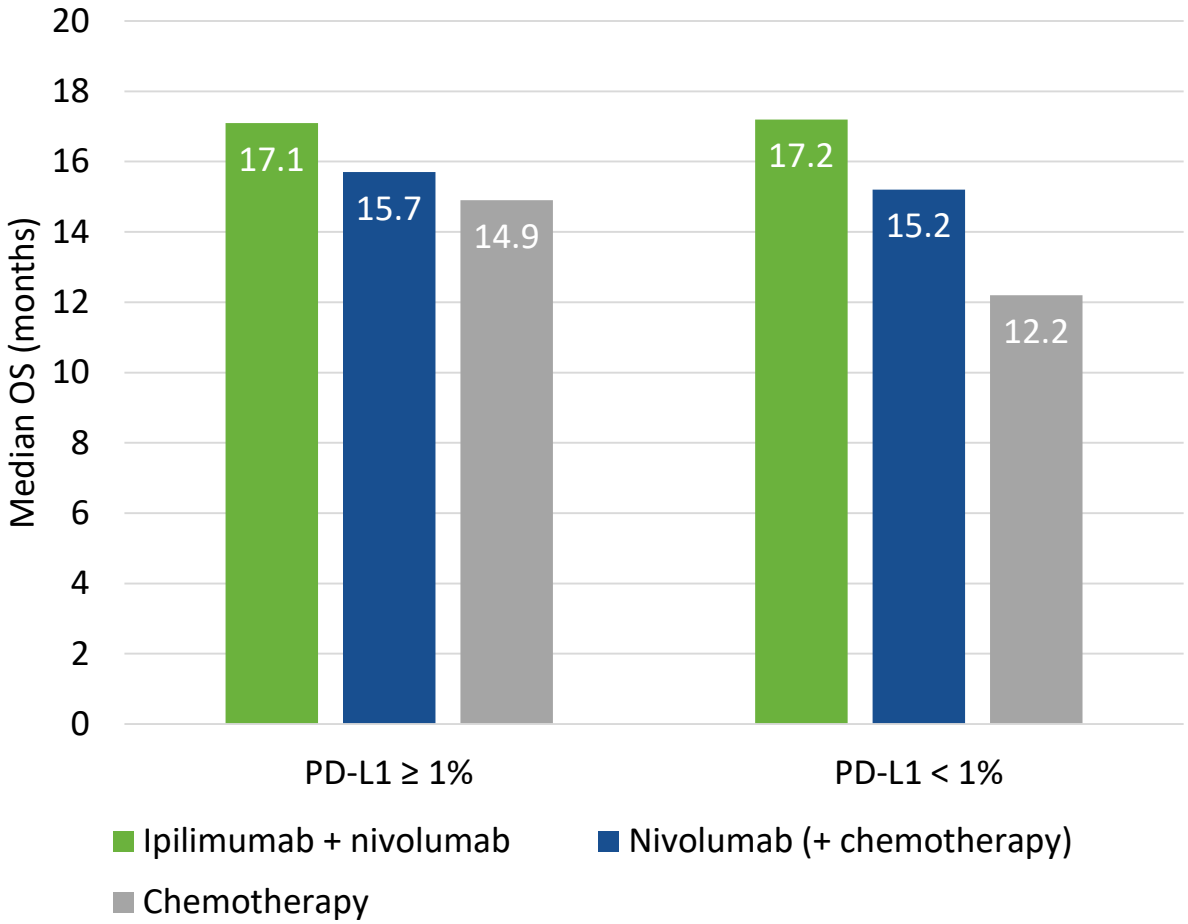
Immunotherapy for first-line treatment of metastatic NSCLC

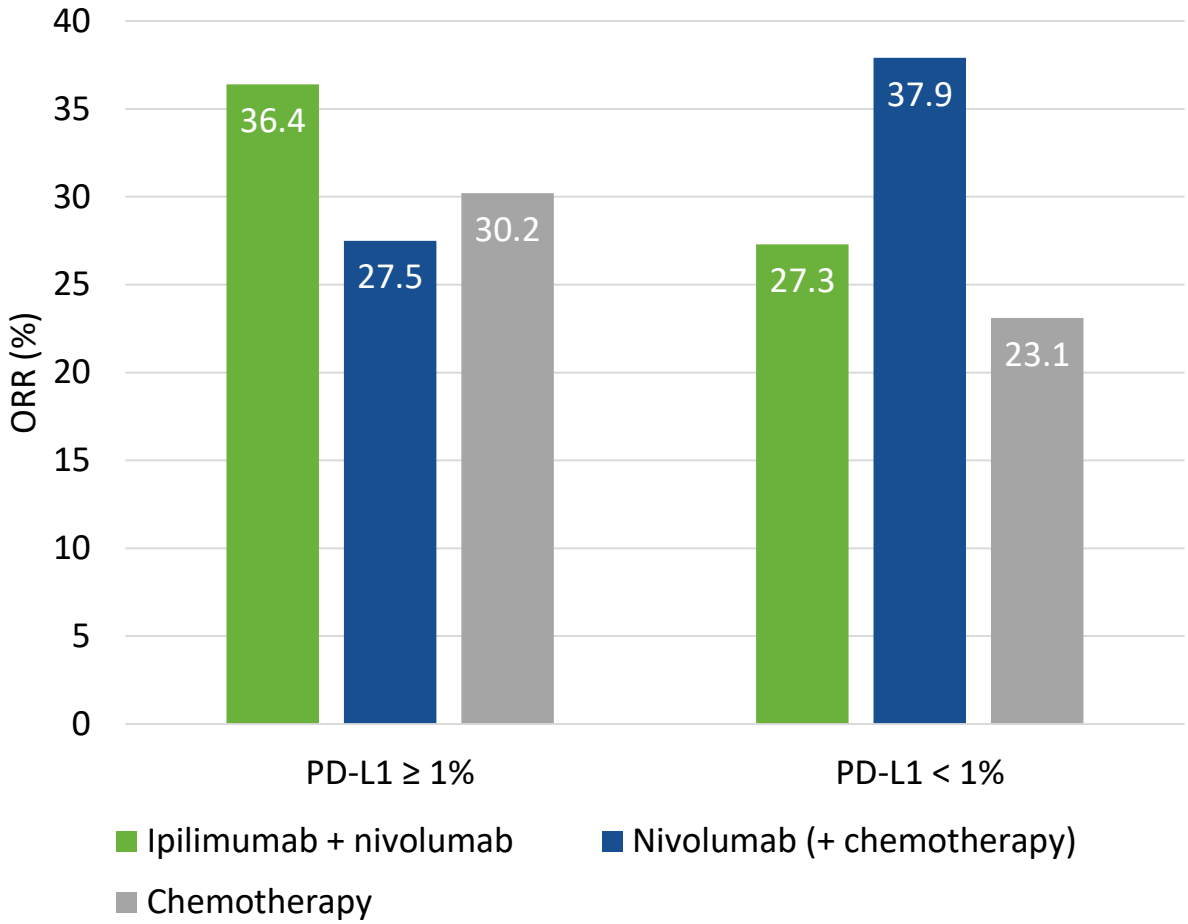
Study	Drugs	mOS	FDA Approval
KEYNOTE 024, 042	Pembrolizumab (Adeno, & SCC)	30.0 mos, 16.4 mos	October 2016, April 2019
KEYNOTE 189 (NEJM 2018)	Carboplatin, pemetrexed, pembrolizumab (Adeno only)	22.0 mos	August 2018
KEYNOTE 407 (NEJM 2019)	Carboplatin, paclitaxel, pembrolizumab (SCC only)	15.9 mos	October 2018
IMPower 150 (NEJM 2018)	Atezolizumab, bevacizumab, carboplatin, paclitaxel (ABCP, adeno only)	19.2 mos	December 2018
CHECKMATE 227 (NEJM 2018, 2020)	Ipilimumab, nivolumab (Adeno, & SCC)	17.1 mos	May 2020
CHECKMATE 9LA ASCO 2020	Ipilimumab, nivolumab, platinum doublet chemotherapy (Adeno & SCC)	15.6 mos	May 2020
IMPower 110	Atezolizumab (Adeno, & SCC)	20.2 mos	May 2020

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*

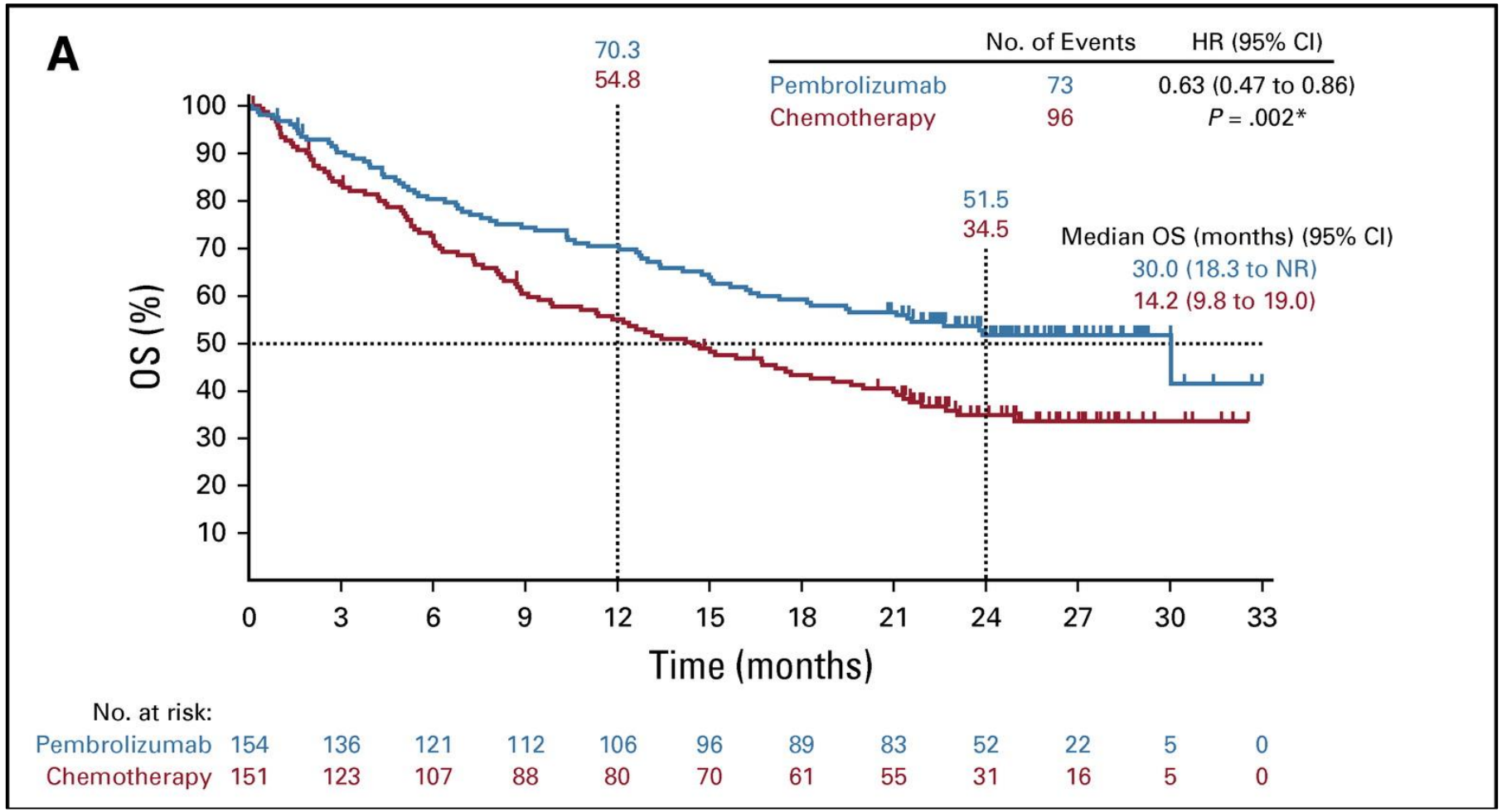
CheckMate 227: Ipilimumab + nivolumab vs chemotherapy for 1L NSCLC





Ramalingam, ASCO 2020.

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



Reck, J Clin Oncol 2019.

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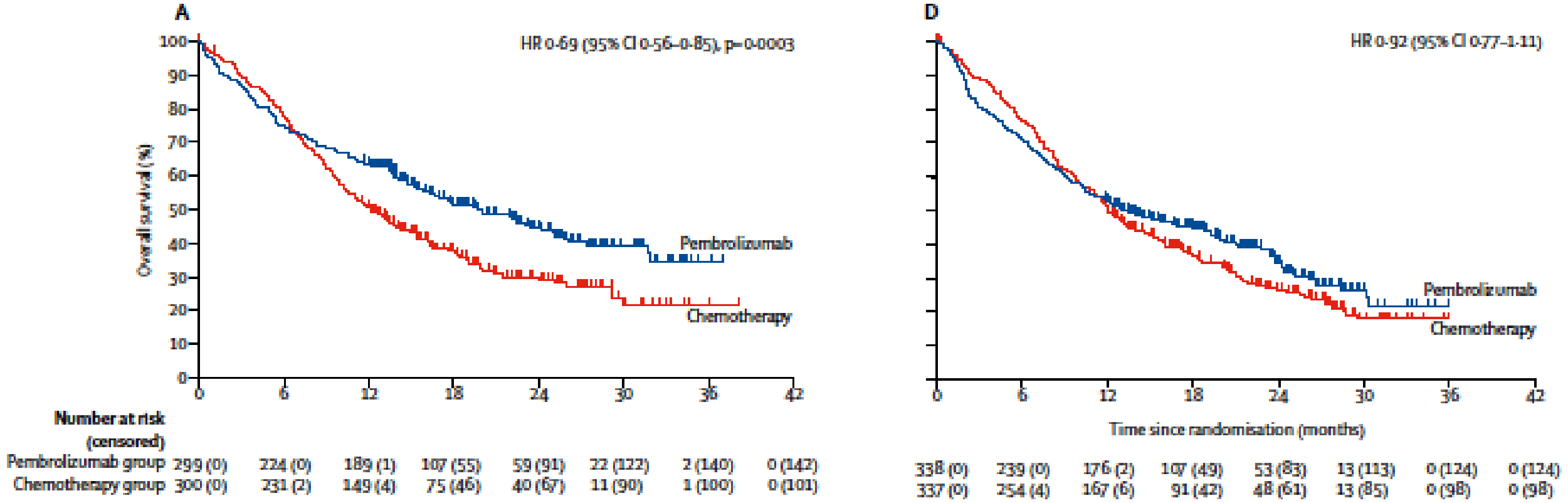
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC

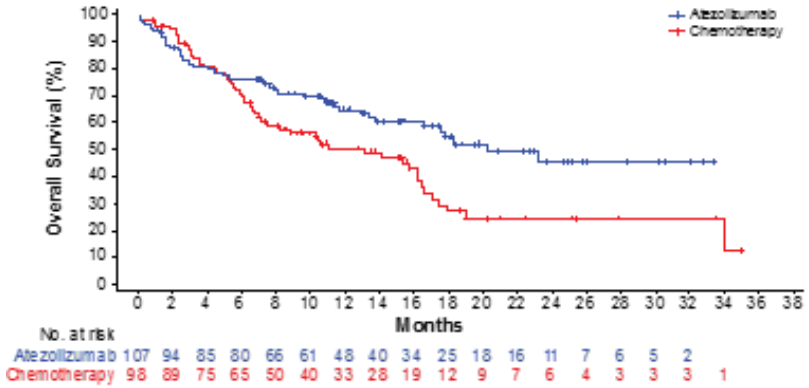


Survival benefit seemed to be driven by the TPS ≥ 50% subset (L above) with little benefit witnessed in the subset TPS = 1 - 49% (R above)

Mok et al. Lancet 2019

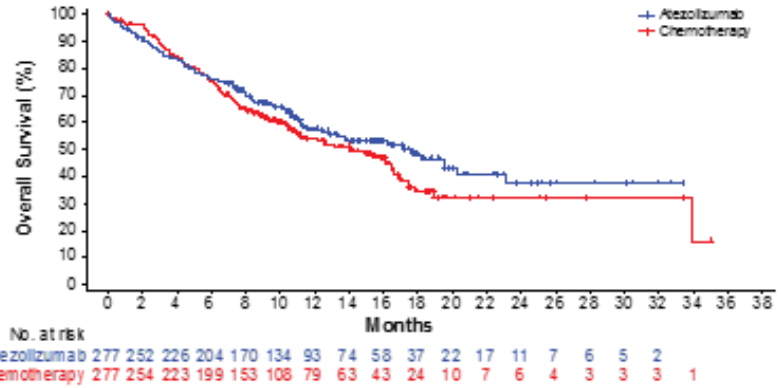
IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

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]



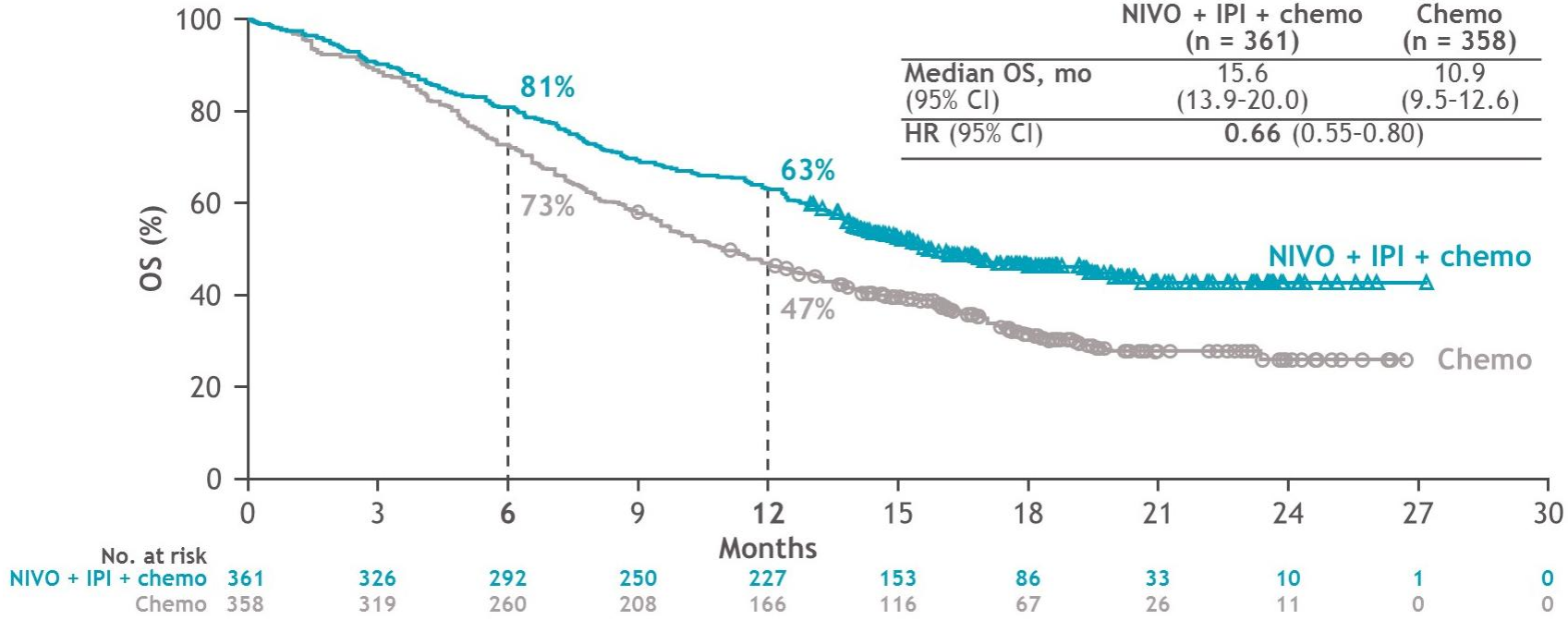
	Atezo (n = 277)	Chemo (n = 277)
mOS, mo	17.5	14.1
HR[b] (95% CI)	0.83 (0.65, 1.07)	

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

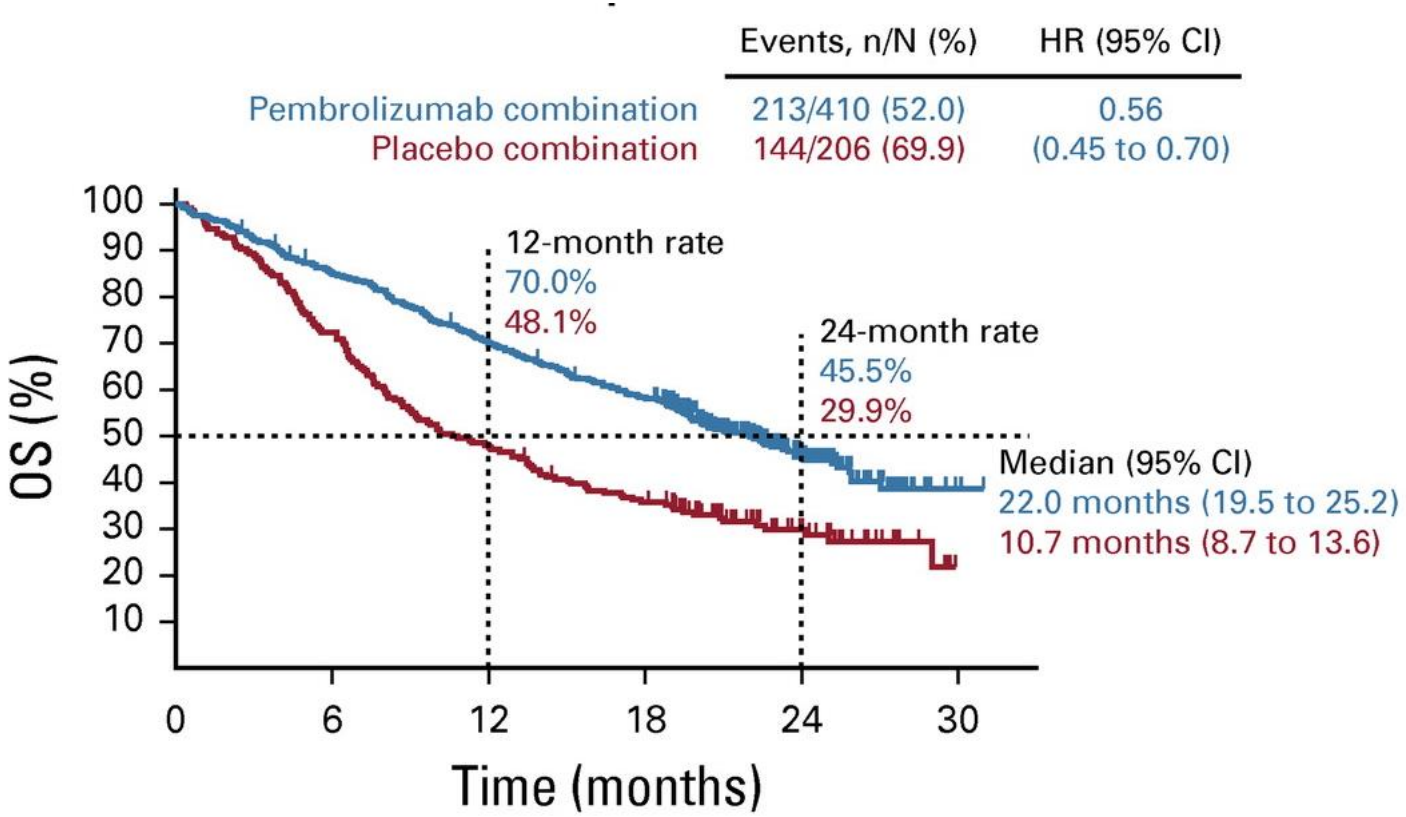


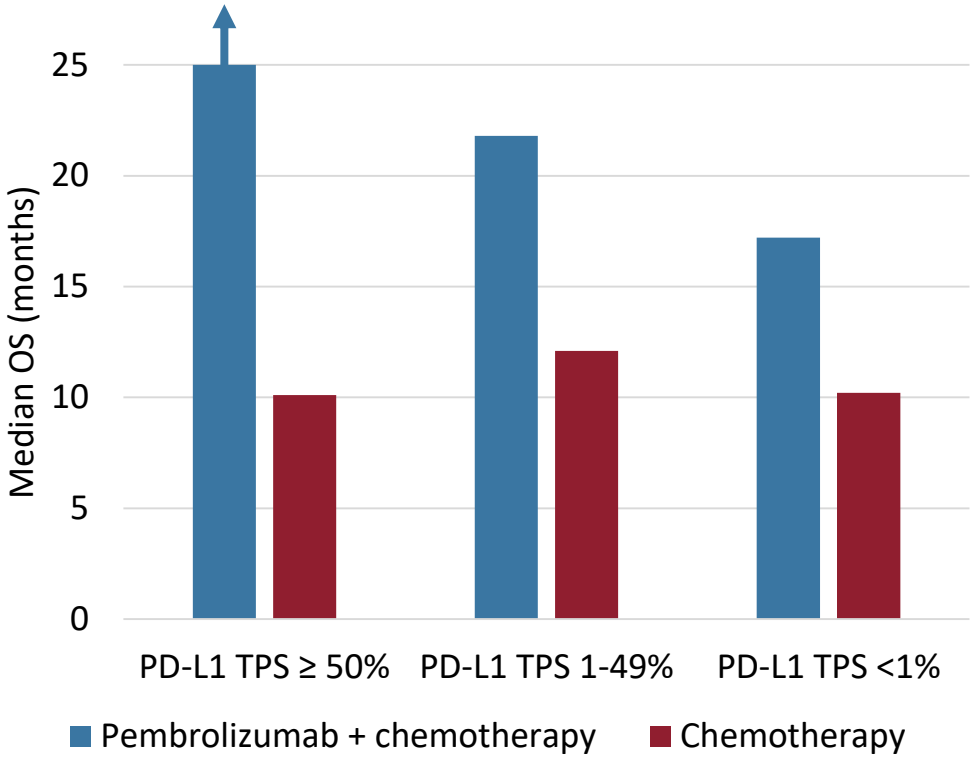
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	0.66 (0.55-0.80)	

	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.

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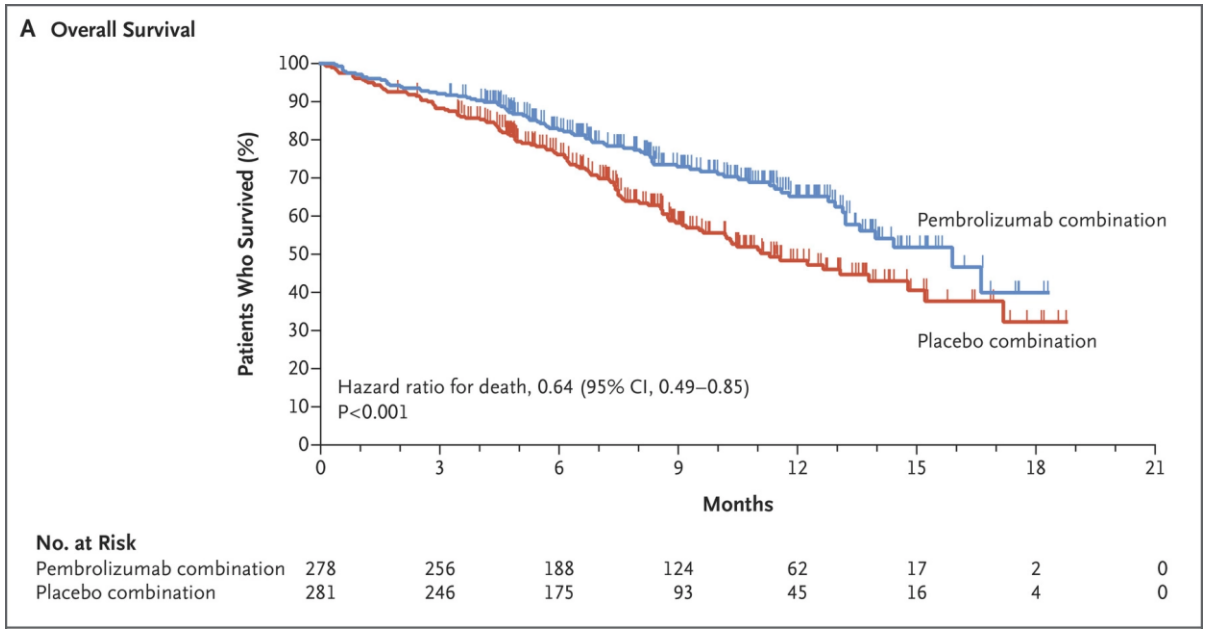
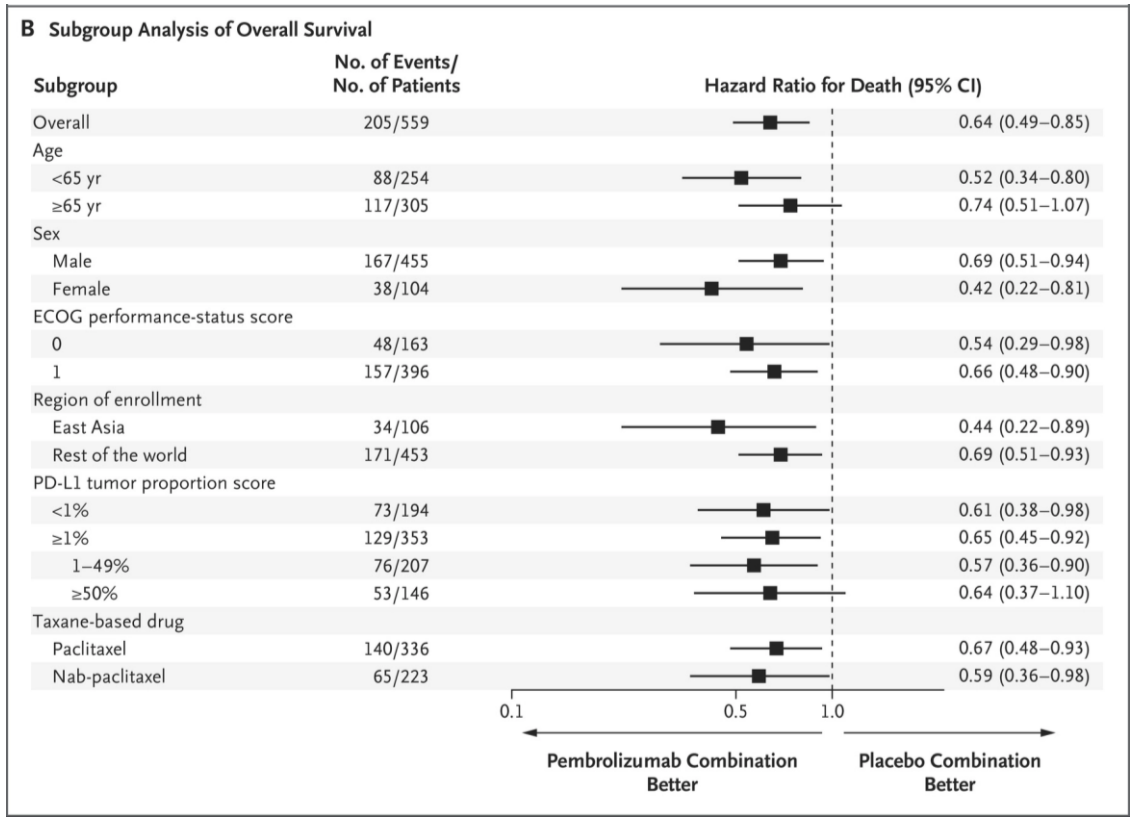
KEYNOTE-407: Pembrolizumab/Chemotherapy vs Chemotherapy Alone for Advanced Squamous-Cell NSCLC





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

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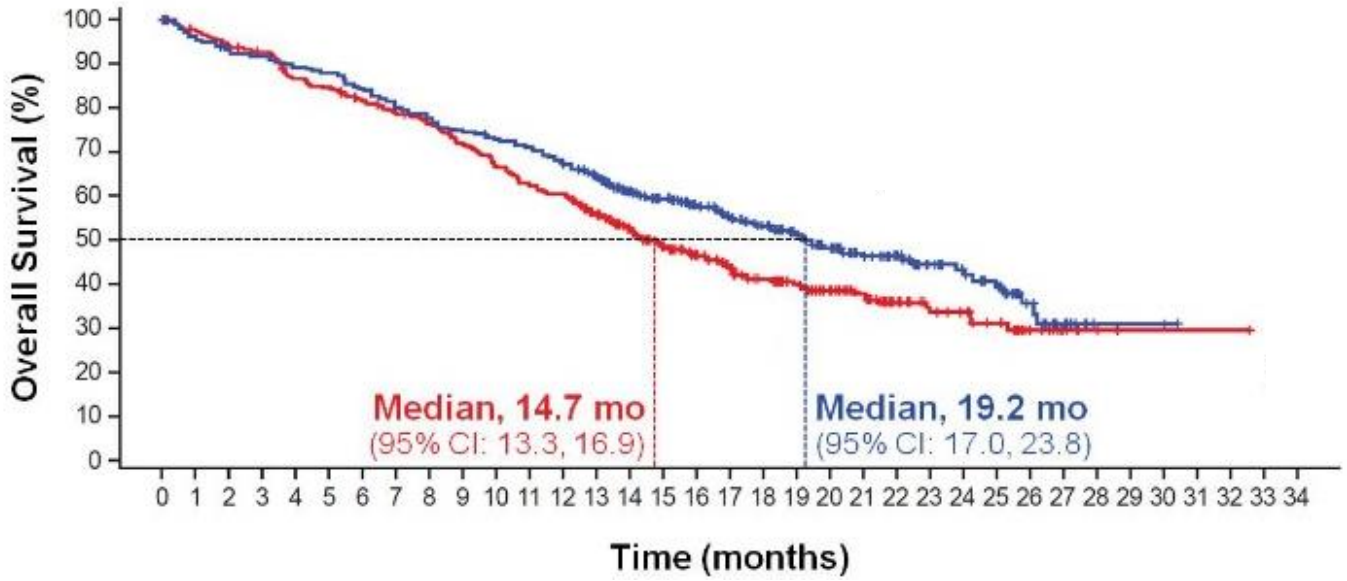
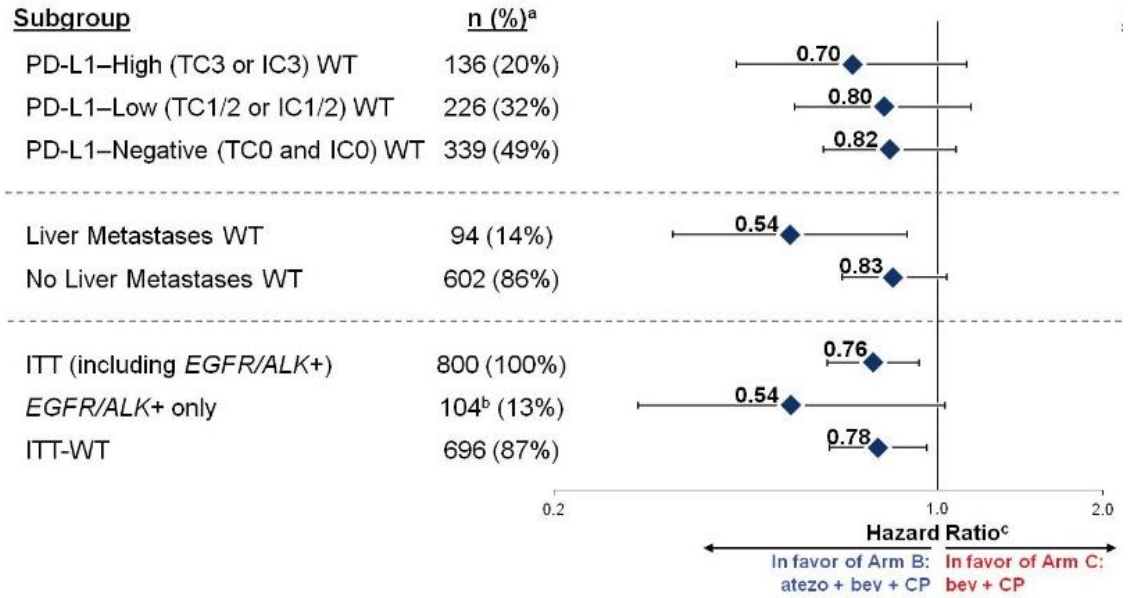
IMpower150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/ Bevacizumab in Advanced Non-Squamous NSCLC

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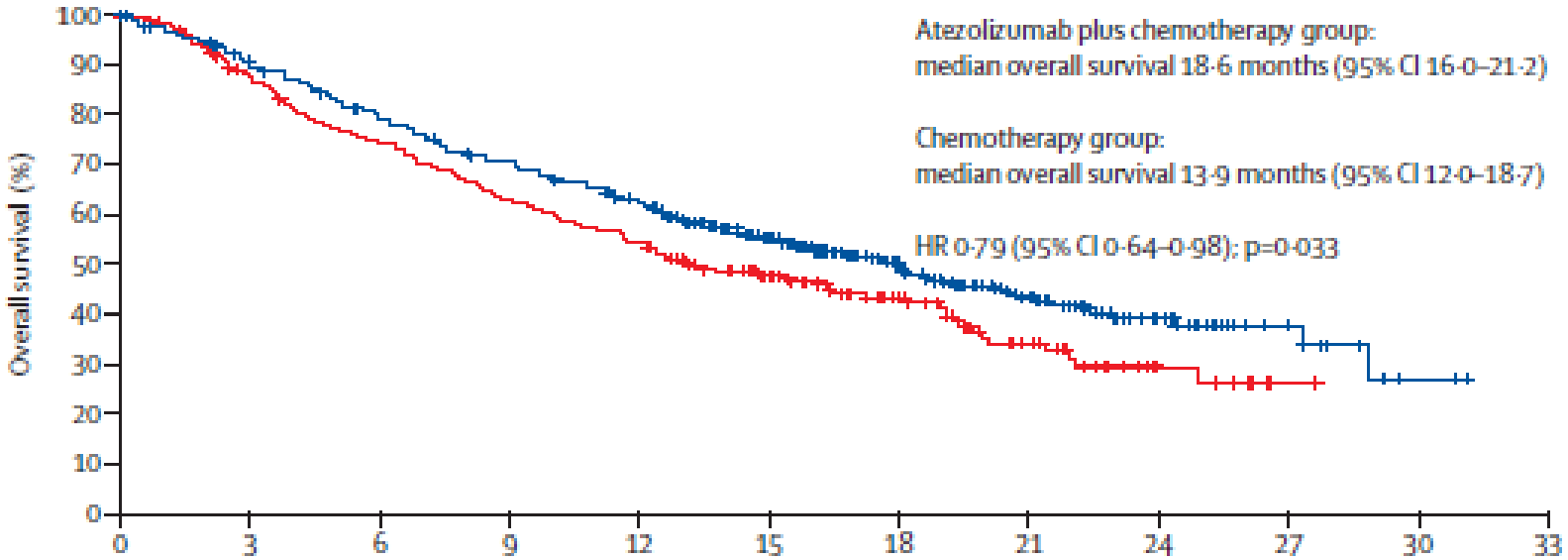
IMpower130: Atezolizumab + chemo vs chemo alone for non-squamous NSCLC

	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)



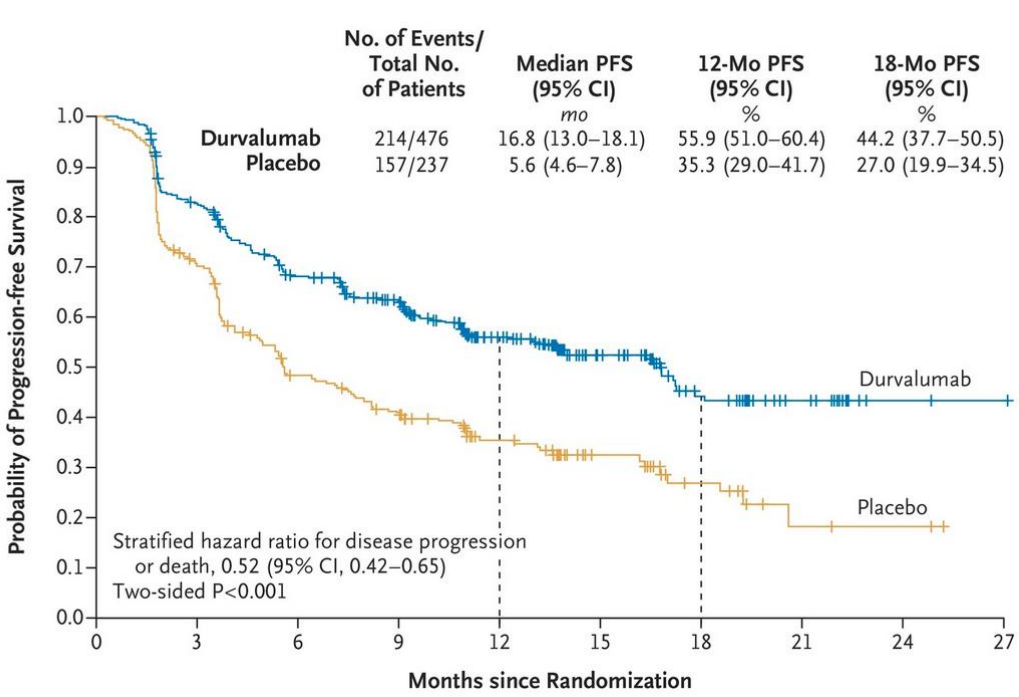
Number at risk (number censored)											
Atezolizumab plus chemotherapy group	451 (0)	400 (10)	351 (15)	305 (18)	268 (22)	194 (68)	129 (120)	75 (161)	40 (188)	12 (215)	4 (221)
Chemotherapy group	228 (0)	190 (12)	161 (13)	136 (13)	119 (13)	90 (28)	58 (52)	31 (70)	13 (85)	3 (94)	0 (0)

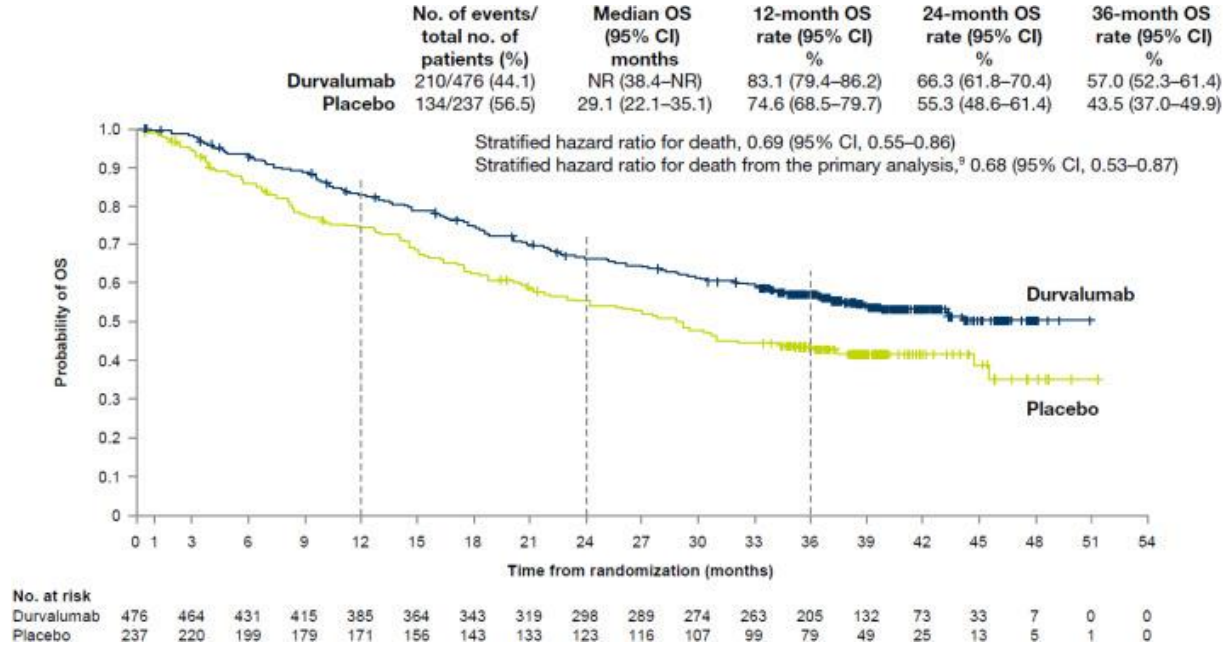
West, Lancet 2019

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





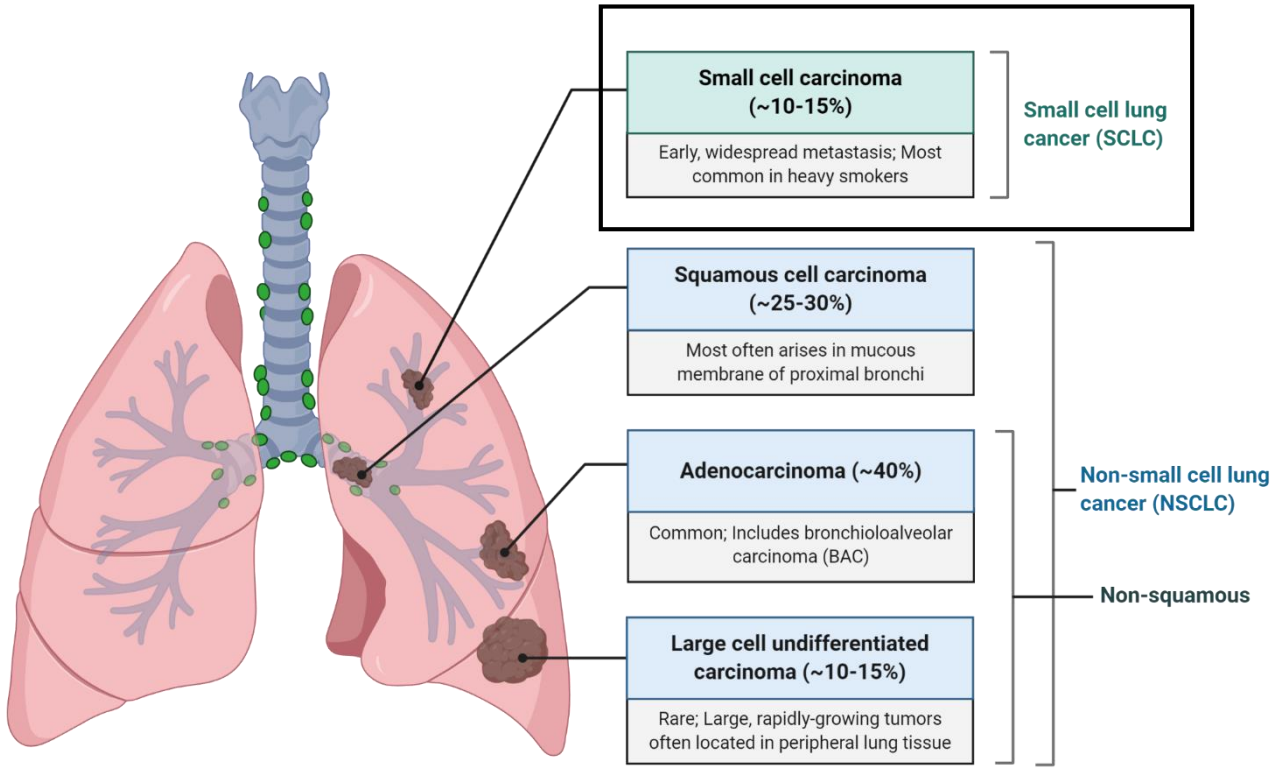
Antonia, N Engl J Med 2017.
Gray, J Thorac Oncol 2020.

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

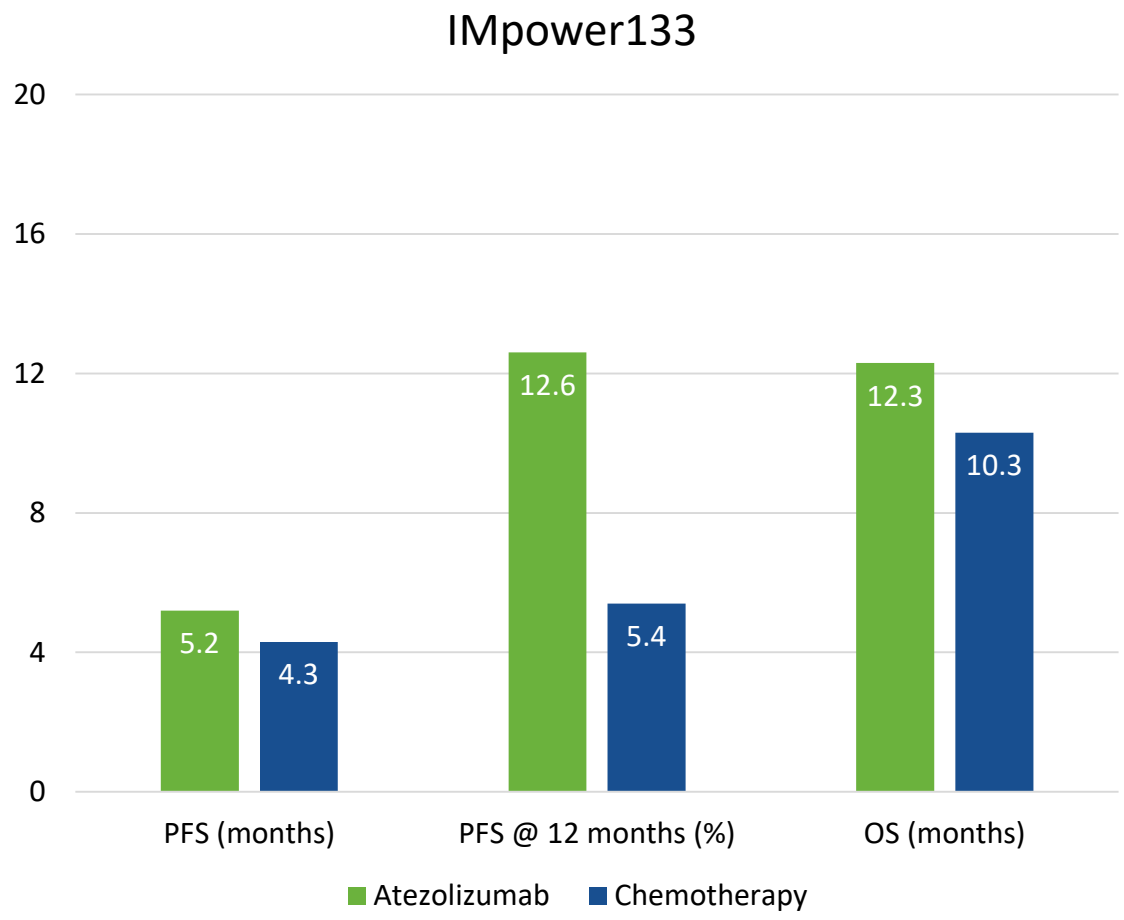
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

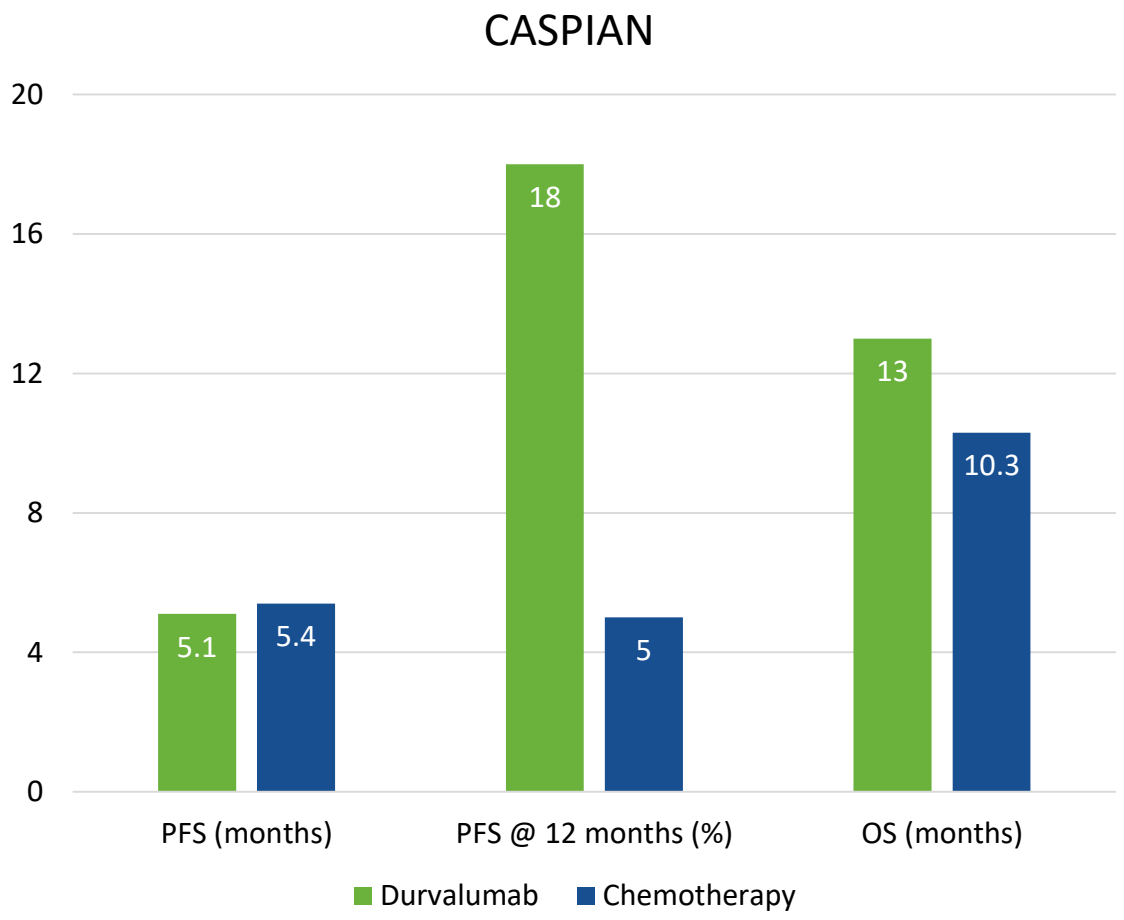


Approved checkpoint inhibitors in SCLC

Drug	Indication	Dose
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 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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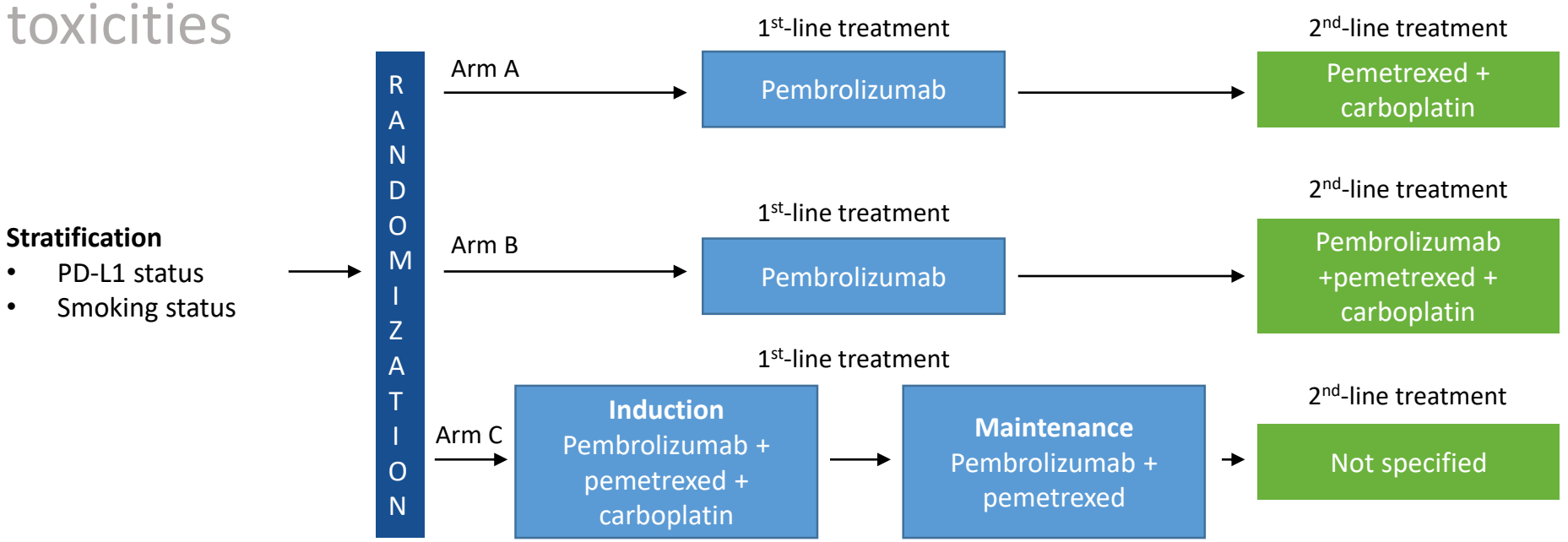
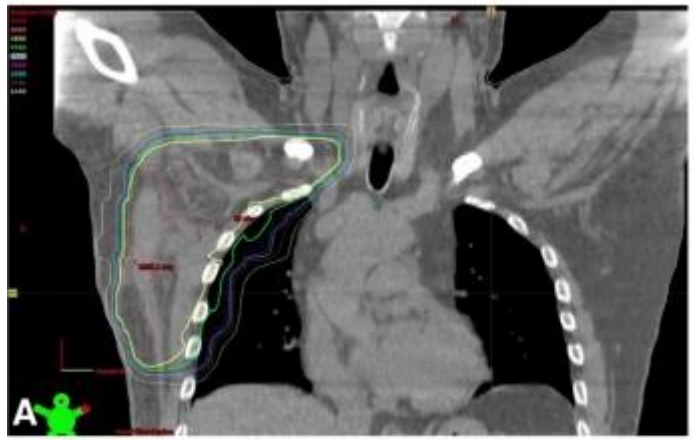


INSIGNIA trial

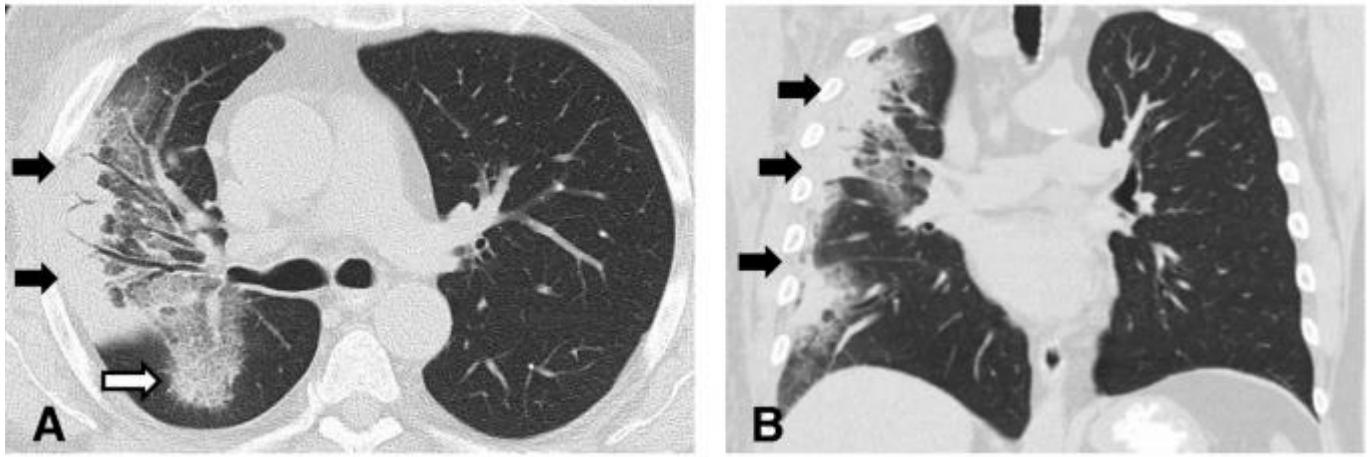
In development: answering outstanding questions

- 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

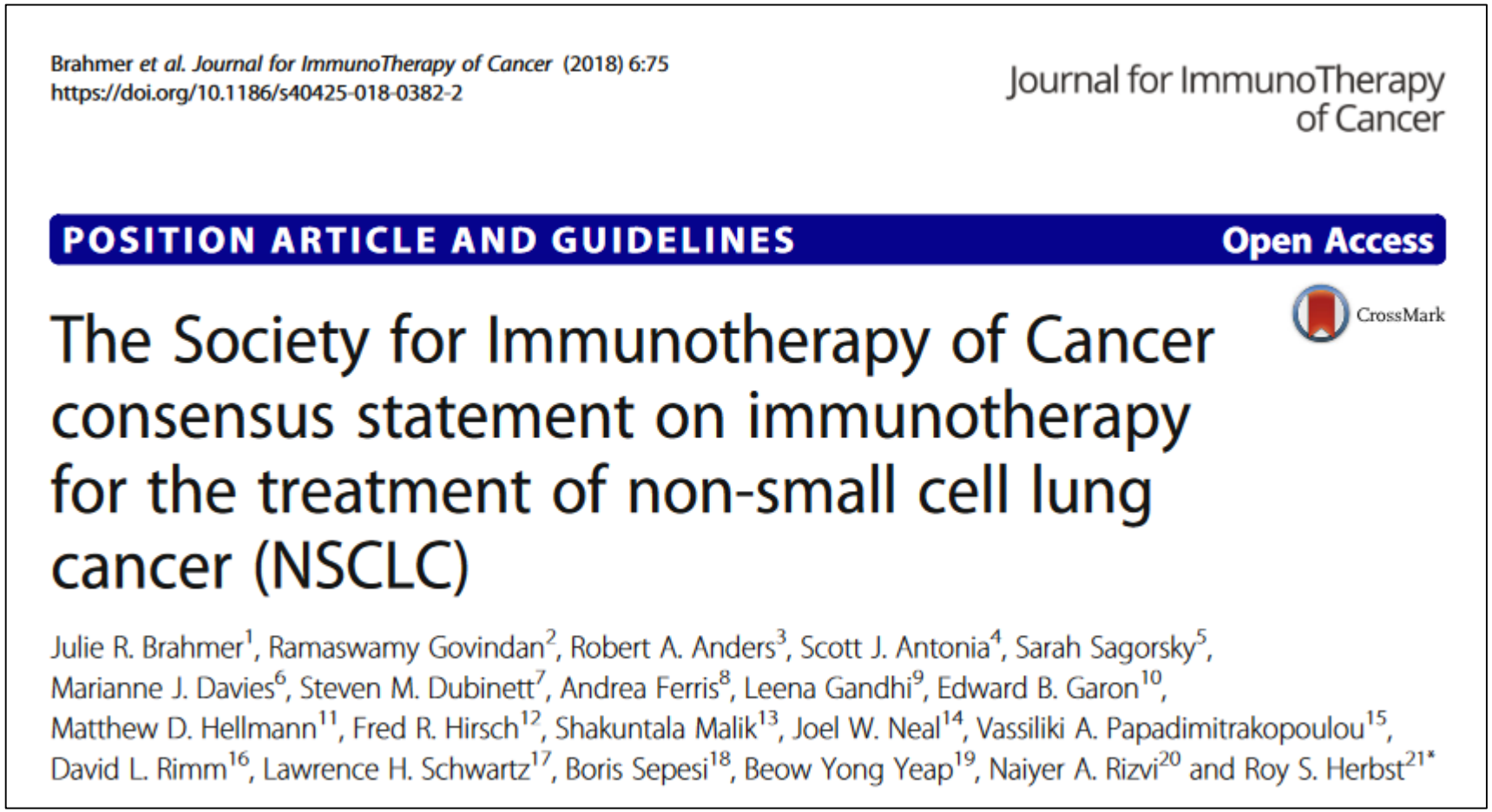
Drug	Indication	Dose
Nivolumab + ipilimumab	Frontline unresectable malignant pleural mesothelioma	Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W

- 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 options now available – with no data to guide which regimen is preferred in the 1st line setting
- PD-L1 IHC works… but is imperfect
- SCLC and MPM now have approved IO combinations (with CTX in the case of SCLC)

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 – Which Regimen?

- 59 yo F presented with bilateral “neck bumps” to her PCP.
- CT chest imaging revealed a LLL mass, bilateral supraclavicular and mediastinal LAD.
- PET/CT revealed FDG uptake in the LLL mass, lymph nodes, L adrenal, multiple skeletal muscle metastases
- L supraclavicular node biopsied – revealed lung adenocarcinoma
- Genomics: KRAS G12C
- PD-L1 IHC: 5%

Case 1 – Which Regimen(s)?

A. Pembrolizumab
B. Atezolizumab
C. Carboplatin, pemetrexed, and pembrolizumab
D. Atezolizumab, carboplatin, paclitaxel, and atezolizumab
E. Carboplatin, nab-paclitaxel, and pembrolizumab
F. Ipilimumab and nivolumab
G. Carboplatin, pemetrexed, ipilimumab, and nivolumab

Case 1 – Which Regimen(s)?

A. **Pembrolizumab**
B. Atezolizumab
C. **Carboplatin, pemetrexed, and pembrolizumab**
D. **Atezolizumab, carboplatin, paclitaxel, and atezolizumab**
E. Carboplatin, nab-paclitaxel, and pembrolizumab
F. **Ipilimumab and nivolumab**
G. **Carboplatin, pemetrexed, ipilimumab, and nivolumab**

Case 1 – Which Regimen?

- Started carboplatin, pemetrexed, and pembrolizumab – she was diagnosed in July 2018
- Completed 2 years of therapy in August 2020
- In remission without evidence of disease recurrence as of January 2021

Case 2 – What now?

- 66 yo female diagnosed with stage III NSCLC, adenocarcinoma, EGFR/ALK/KRAS wt in 2014
- Underwent resection followed by cisplatin + pemetrexed adjuvant therapy x 4 cycles
- Developed progressive L chest wall pain in 2018
- Imaging showed numerous bone lesions and LNs
- EBUS/bronchoscopy performed – revealed lung adenocarcinoma
- Genomics: pan negative (only p53 +)
- PD-L1: 80%

Case 2 – What now?

- Palliative RT performed to L rib (20Gy)
- Pembrolizumab initiated in April 2018
- Marked clinical and radiographic response by July 2018
- January 2020 she developed an enlarging L axillary LN – PET/CT showed no other evidence of disease
- L axillary node biopsied: lung adenocarcinoma

What would you do next?

Case 1 – Which Regimen(s)?

A. Change to docetaxel
B. Lymph node dissection
C. Radiation therapy to the LN
D. Add chemotherapy to pembrolizumab
E. Change to ipilimumab, nivolumab, carboplatin, and pemetrexed

Case 1 – Which Regimen(s)?

A. Change to docetaxel

B. Lymph node dissection

C. Radiation therapy to the LN

D. Add chemotherapy to pembrolizumab

E. Change to ipilimumab, nivolumab, carboplatin, and pemetrexed

Case 1 – Which Regimen(s)?

- Underwent LN dissection since there was no evidence of distant recurrent disease
- Continued pembrolizumab without progression – remains on as of March 2021

Illustrates the growing need to understand how to treat patients with metastatic disease at progression.