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Immunotherapy for the Treatment of Lung Cancer

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Disclosures

- **Advisory Committees** – AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Catalyst, EMD Serono, Foundation Medicine, Hengrui Therapeutics, Genentech, GSK, Guardant Health, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sanofi, Seattle Genetics, Spectrum, Takeda.
  Research Support – AstraZeneca, GlaxoSmithKline, Spectrum.
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- I will be discussing non-FDA approved indications during my presentation.

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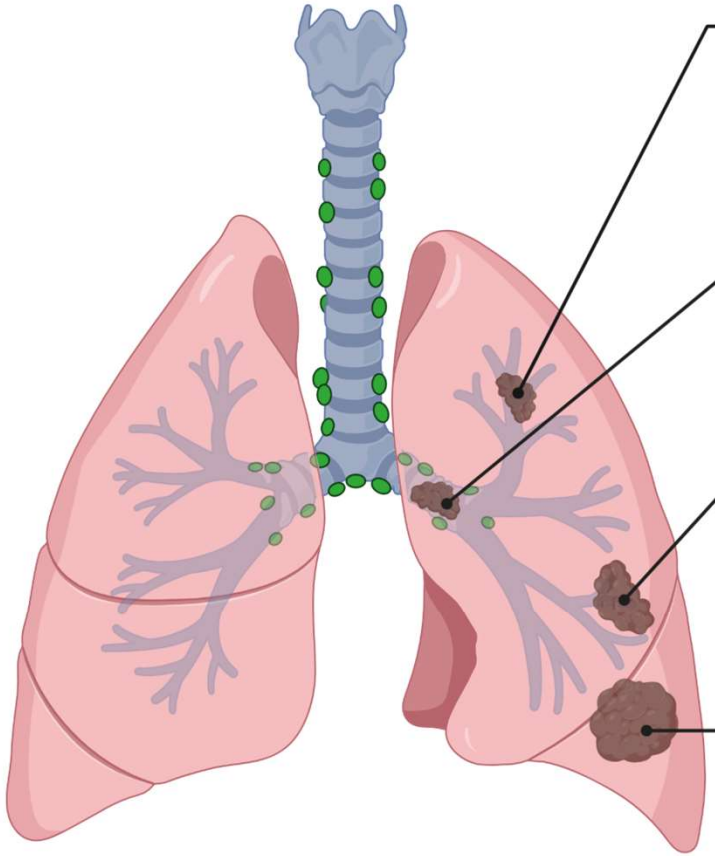
Lung cancer



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

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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

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GM1

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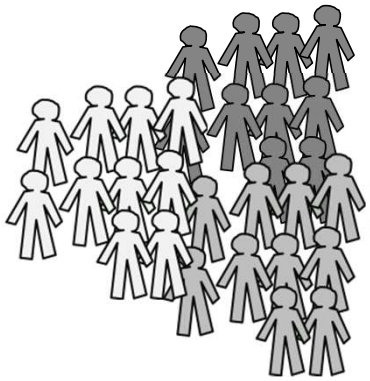
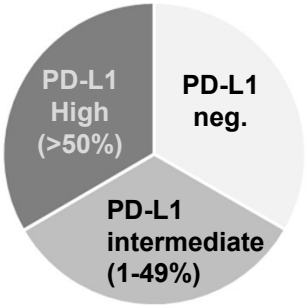
Treatment of metastatic NSCLC

NSCLC

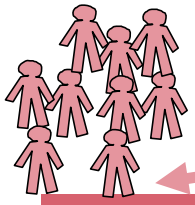
Driver negative: the immune pie (60%)

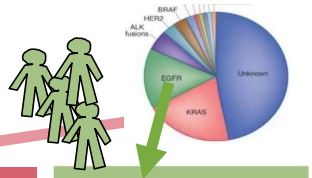


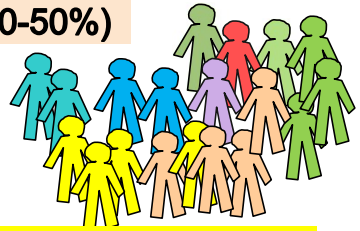


PD-L1 neg/intermediate	PD-L1 high
1.chemo+IMT 2. Pembro 3. Ipi/Nivo	1. pembro 2. chemo+IMT

Driver positive: the genomic pie (40-50%)







- KRAS mutant (20-29%)
  - KRAS LKB1mut
  - KRAS TP53mut
  - KRAS CDKN2A
  - KRAS G12C
  - KRAS G12D
  - KRAS G12V
  - KRAS Codon 13,61,etc
- EGFR mutant (12-15%)
  - **Classical** (L858R, ex19del)
  - **Classic Resistance** (T790M)
  - **Exon 20/atypicals**
- EML4-ALK (4%)
- HER2 mutant (2%)
- MET ex14 (3%)
- RET fusion (1%)
- BRAF mutant (3%)
- ROS1 mutant (1%)
- NTRK mutant (1%)
- Other thin slices (1-3%) NRG fusions, etc

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Slide 5

GM1 NEW SLIDE

Guijarro Munoz,Irene, 12/8/2020

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

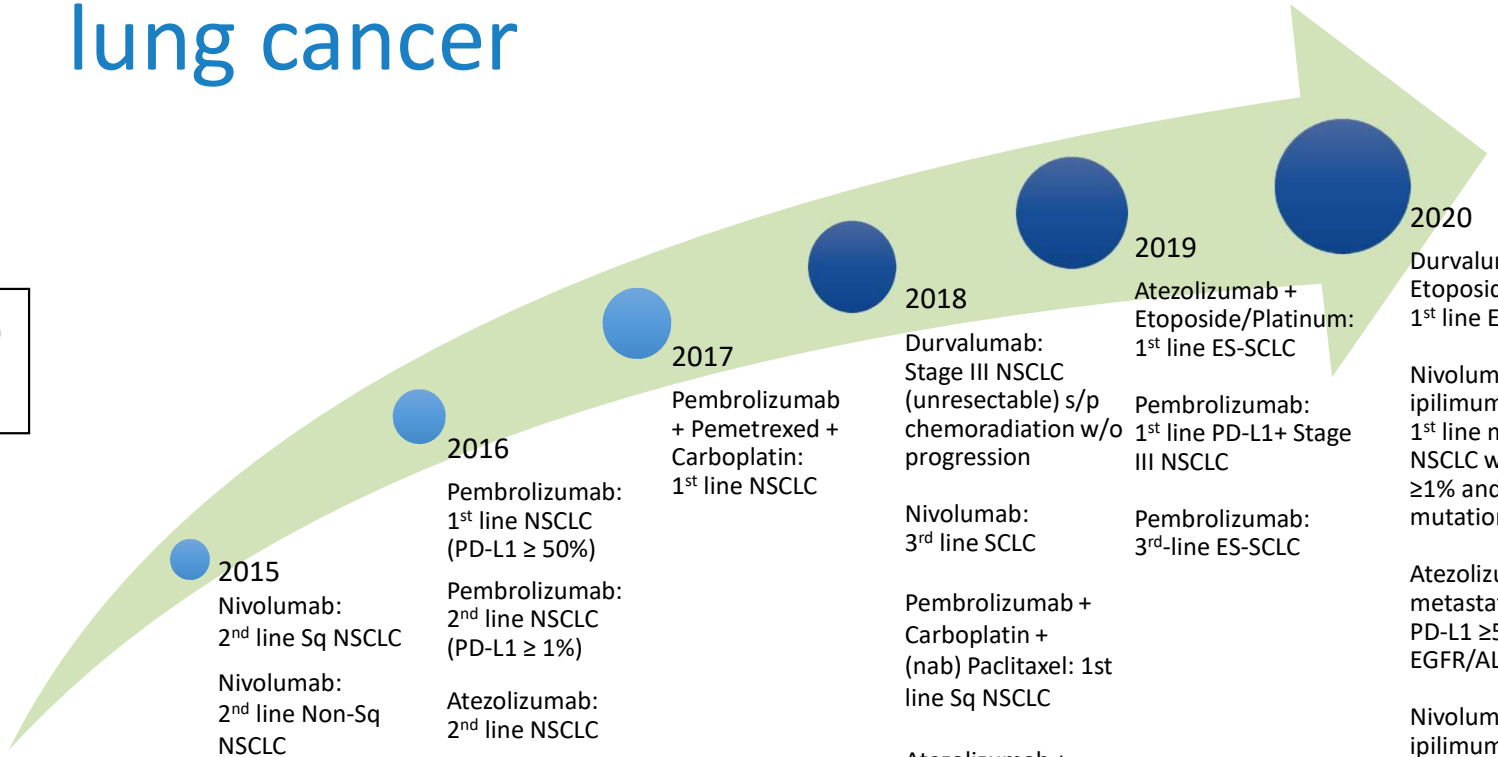
Nivolumab — **PD-1**

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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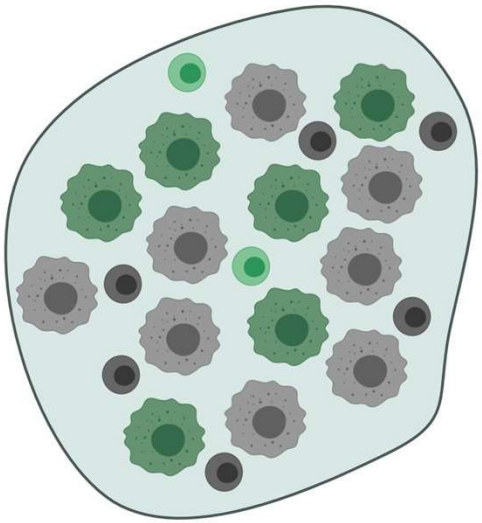
Brief aside: PD-L1 TPS vs CPS

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

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



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

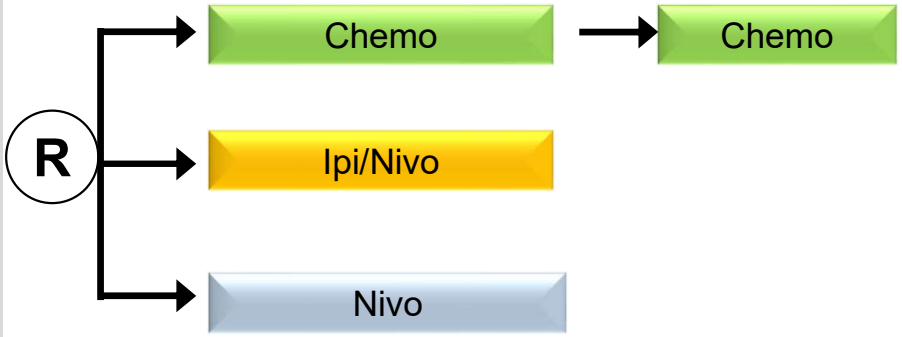
PD-L1-selected	PD-L1-unselected
Nivolumab + ipilimumab *CheckMate 227*	Nivolumab + ipilimumab + platinum-doublet *CheckMate 9LA*
Pembrolizumab *KEYNOTE-024, -042*	Pembrolizumab + chemotherapy *KEYNOTE-189, -407*
Atezolizumab *IMpower110*	Atezolizumab + bevacizumab + chemotherapy *IMpower150*
	Atezolizumab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

GM2

Checkmate-227: randomized phase III of nivo and nivo combinations

1L nonsquamous NSCLC
N=1202

Primary endpoint:
- OS
- PFS (by ICR)
  - Adjusted to: PFS (by IRC) in pts with high mutational burden (≥10 mut/mb)



Hellman et al, AACR 2018; Hellman et al, NEJM 2018

1L, first-line; BMS, Bristol-Myers Squibb; chemo, chemotherapy; ipi, ipilumumab; nivo, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RP3, randomized phase 3.

1. CT.Gov. Accessed Mar 2, 2018. 2. https://news.bms.com/press-release/bms/pivotal-phase-3-checkmate-227-study-demonstrates-superior-progression-free-survival. Accessed Mar 2, 2018.

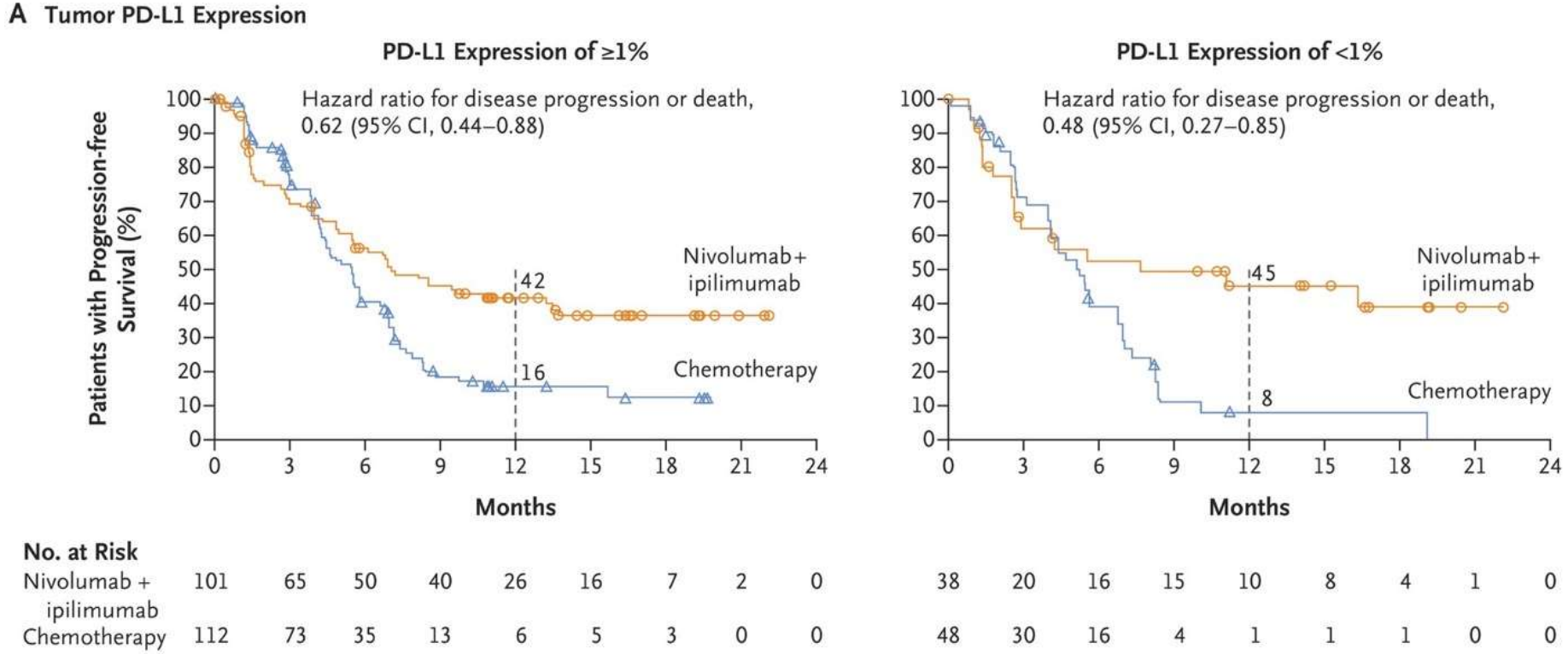
Slide 12

GM2 NEW

Guijarro Munoz,Irene, 12/8/2020

GM3

Ipi/nivo is prolongs PFS compared with chemo in TMB-high NSCLC, regardless of PD-L1 level



Hellman et al, NEJM, 2018

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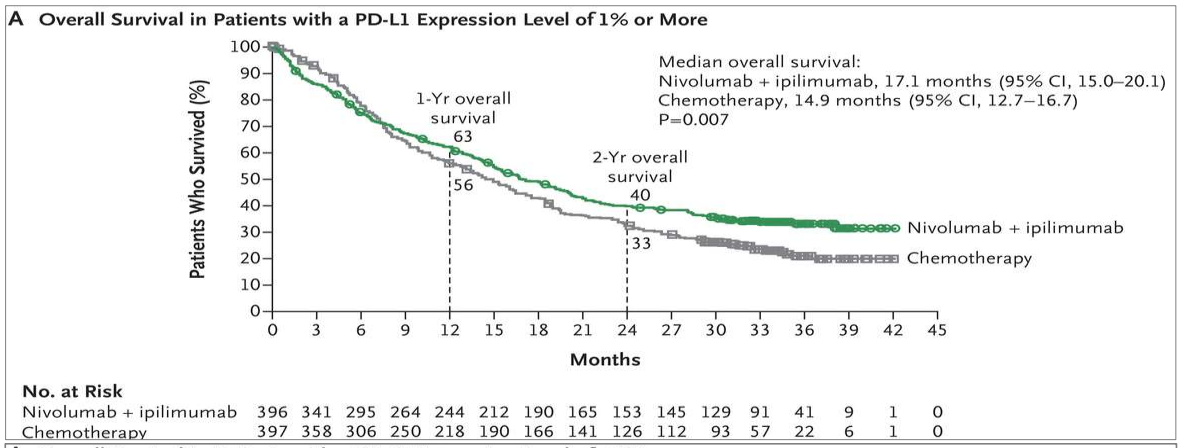
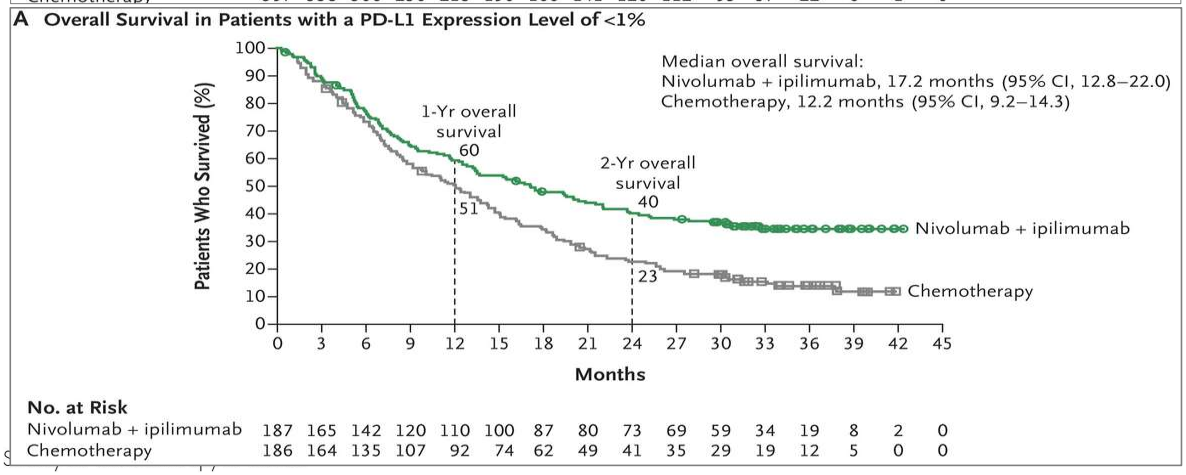
GM3 NEW SLIDE

Guijarro Munoz,Irene, 12/8/2020

GM4

Updated results: Ipi/nivo is prolongs OS compared with chemo regardless of PD-L1 level





PD-L1 expression level of 1% or more:

mOS was **17.1** months (95% CI, 15.0 to 20.1) with nivo plus ipi and **14.9** months (95% CI, 12.7 to 16.7) with chemo

PD-L1 expression level of less than 1%:

17.2 months (95% CI, 12.8 to 22.0) with nivo plus ipi and **12.2** months (95% CI, 9.2 to 14.3) with chemo

Hellman et al, NEJM, 2019

Slide 14

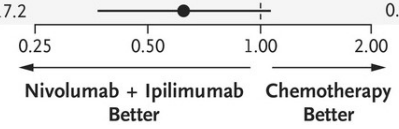
GM4 NEW SLIDE

Guijarro Munoz,Irene, 12/8/2020

GM5

Ipi/nivo treatment resulted in a longer duration of OS independent of the PD-L1 level or TMB

Subgroup	No. of Patients	Median Overall Survival (months): Nivolumab + ipilimumab (N=583)	Median Overall Survival (months): Chemotherapy (N=583)	Unstratified Hazard Ratio for Death (95% CI)
Randomized Groups				
PD-L1				
All randomized	1166	17.1	13.9	0.73 (0.64–0.84)
<1%	373	17.2	12.2	0.62 (0.49–0.79)
≥1%	793	17.1	14.9	0.79 (0.65–0.96)
Subgroup Analyses				
PD-L1				
1–49%	396	15.1	15.1	0.94 (0.75–1.18)
Tumor mutational burden				
Low, <10 mut/Mb	380	16.2	12.6	0.75 (0.59–0.94)
High, ≥10 mut/Mb	299	23.0	16.4	0.68 (0.51–0.91)
PD-L1 and tumor mutational burden (mut/Mb) combined				
PD-L1 <1%				
Tumor mutational burden <10	111	15.5	13.0	0.69 (0.46–1.05)
Tumor mutational burden ≥10	86	20.4	11.2	0.51 (0.30–0.87)
PD-L1 ≥1%				
Tumor mutational burden <10	269	16.2	12.1	0.78 (0.59–1.02)
Tumor mutational burden ≥10	213	24.4	18.1	0.77 (0.54–1.09)
PD-L1 ≥50%				
Tumor mutational burden <10	125	18.1	8.1	0.67 (0.44–1.03)
Tumor mutational burden ≥10	111	NR	17.2	0.63 (0.37–1.07)



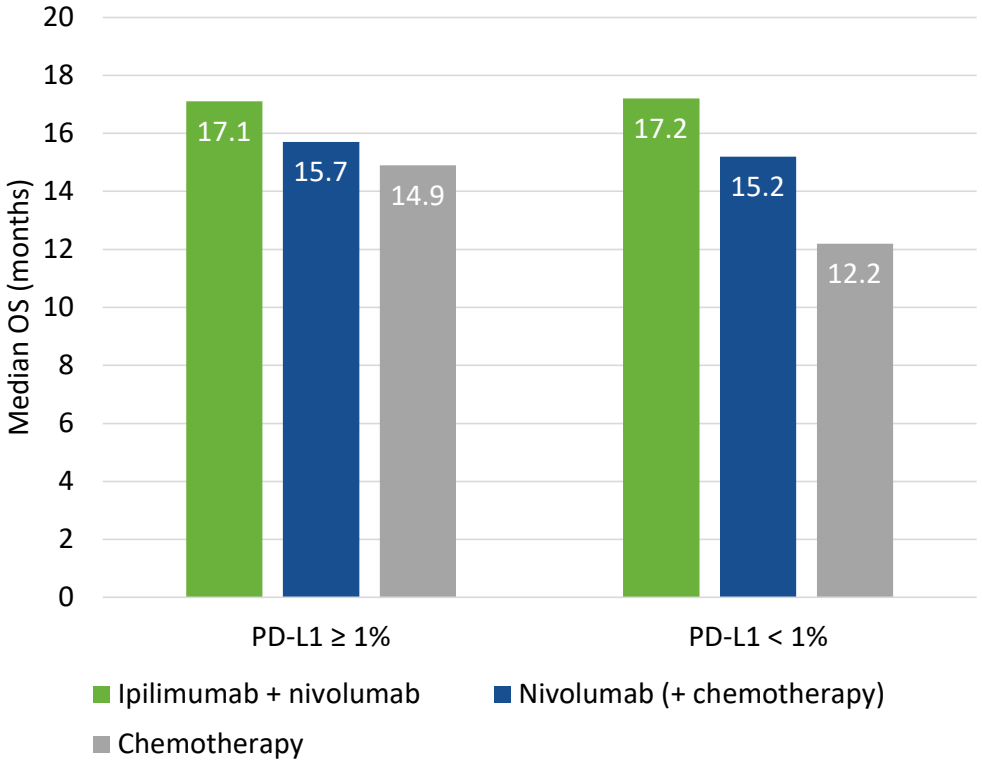
Hellman et al, NEJM, 2019

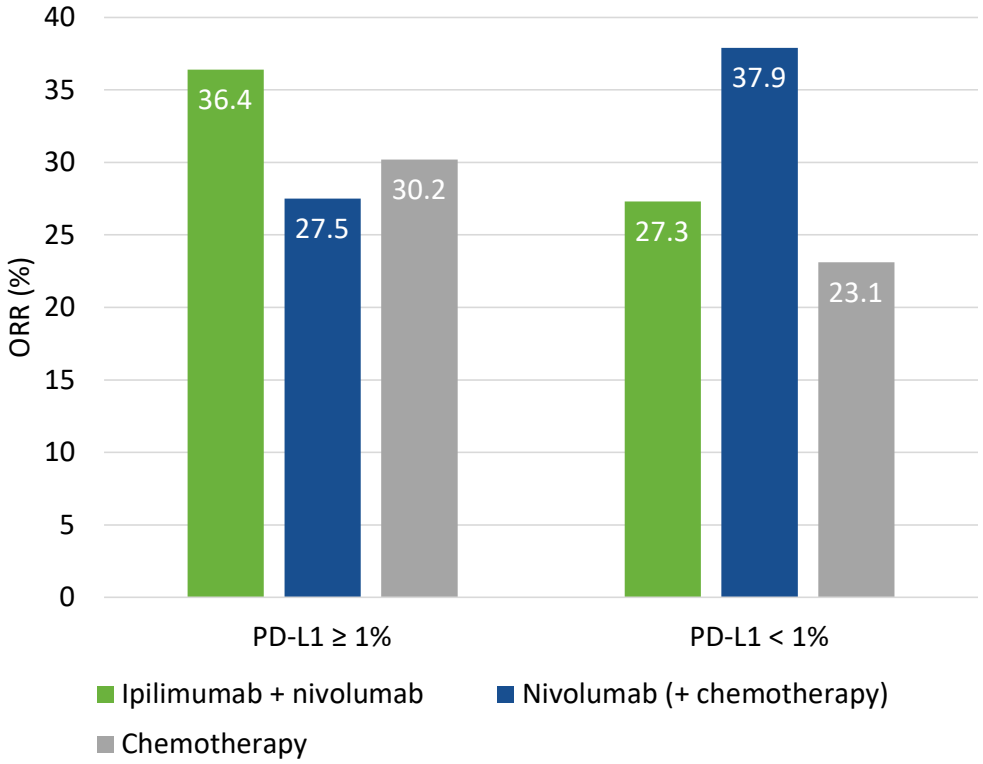
Slide 15

GM5 NEW SLIDE

Guijarro Munoz,Irene, 12/8/2020

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





Ramalingam, ASCO 2020.

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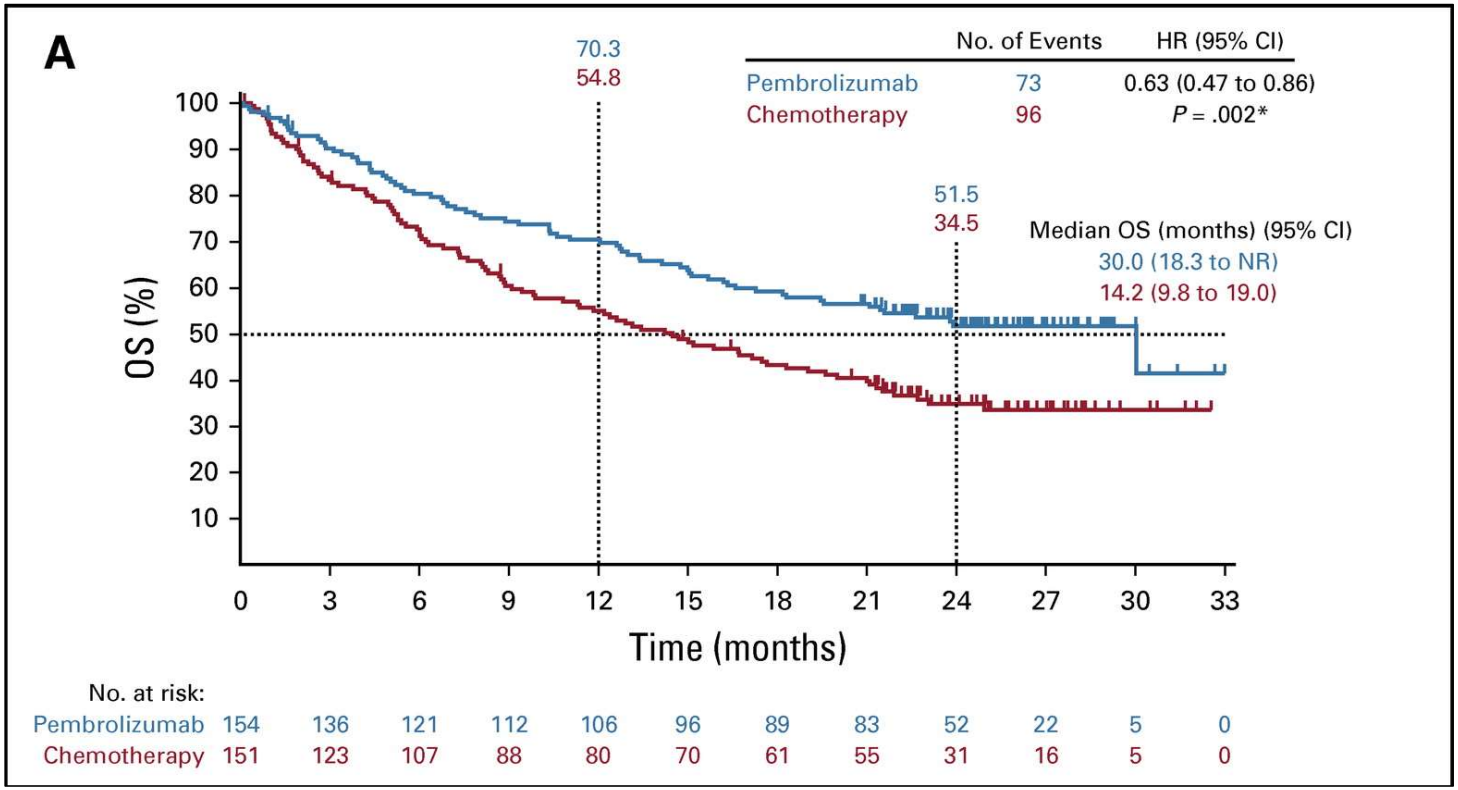
KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 50% NSCLC



Reck, J Clin Oncol 2019.

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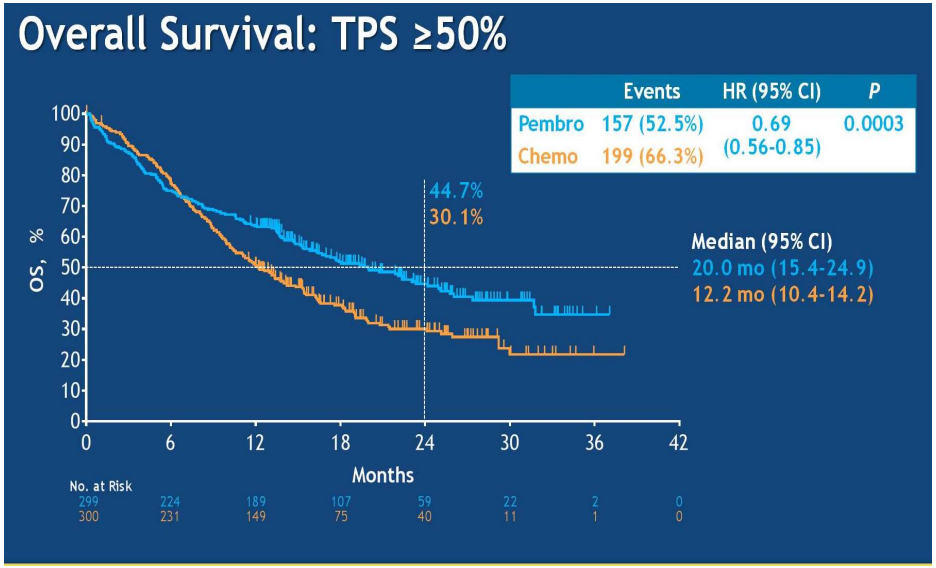
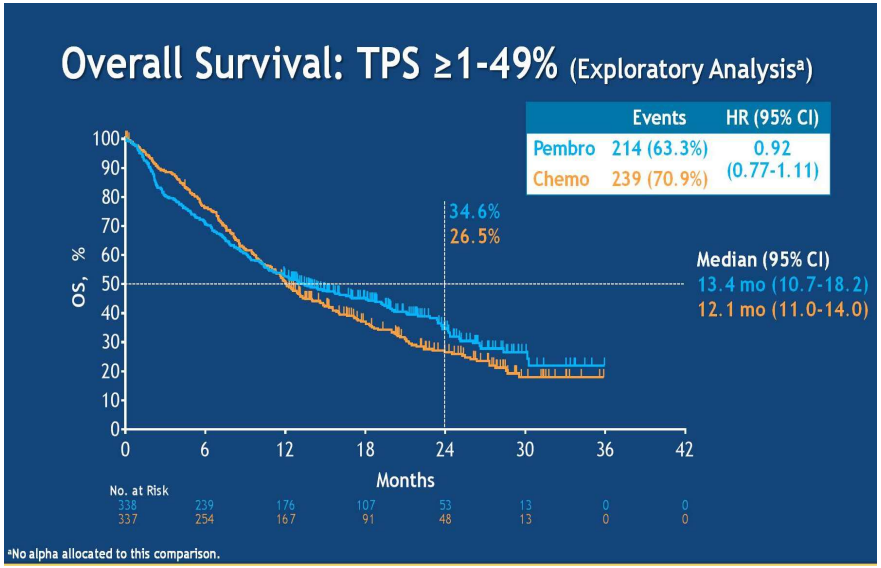
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC





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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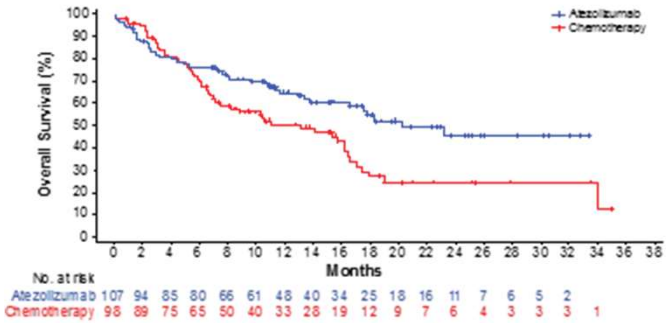
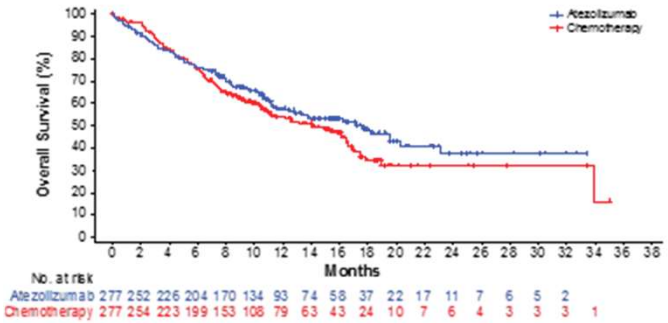
IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

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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GM6

CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo study design

Key Eligibility Criteria
- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)

N = 719
R 1:1

n = 361
NIVO 360 mg Q3W + **IPI** 1 mg/kg Q6W
+
Chemo[d] Q3W (2 cycles)

n = 358
Chemo[d] Q3W (4 cycles)
with optional pemetrexed maintenance (NSQ)

Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.
Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]**NSQ**: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Presented By Martin Reck at ASCO 2020

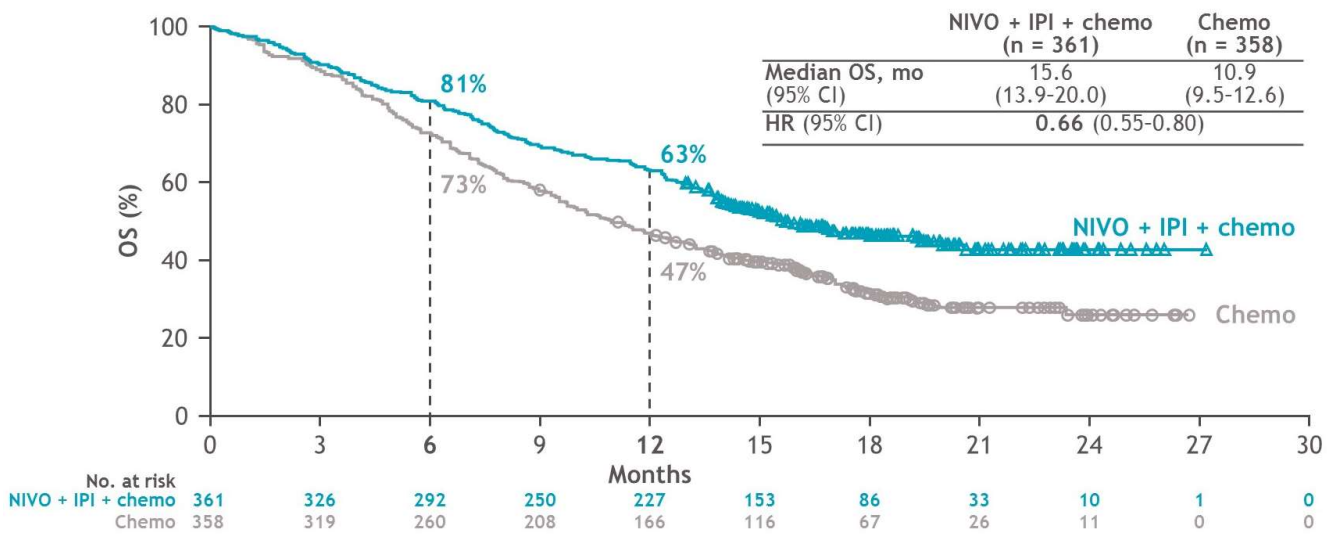
Slide 21

GM6 NEW SLIDE

Guijarro Munoz,Irene, 12/8/2020

CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo

The 9LA regimen improves OS (HR 0.66), PFS, ORR



	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)

May 26 2020: US FDA approves the 9LA regimen for all metastatic 1L NSCLC with wt EGFR/ALK, regardless of PD-L1 levels.

Reck M et al, ASCO 2020.

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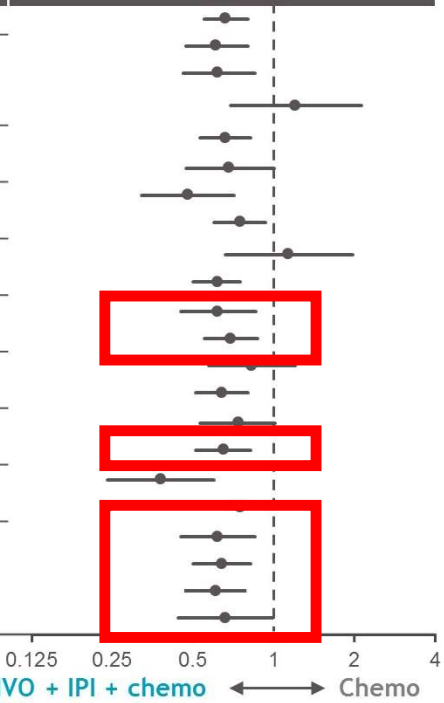
GM7

Checkmate 9LA study: OS subgroup analysis

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.6	10.9	0.66[a]
< 65 years (n = 354)	15.6	10.7	0.61
65 to < 75 years (n = 295)	19.4	11.9	0.62
≥ 75 years (n = 70)	8.5	11.5	1.21
Male (n = 504)	14.1	9.8	0.66
Female (n = 215)	19.4	15.8	0.68
ECOG PS 0 (n = 225)	NR	15.4	0.48
ECOG PS 1 (n = 492)	13.6	9.7	0.75
Never smoker (n = 98)	14.1	17.8	1.14
Smoker (n = 621)	15.6	10.4	0.62
Squamous (n = 227)	14.5	9.1	0.62
Non-squamous (n = 492)	17.0	11.9	0.69
Liver metastases (n = 154)	10.2	8.1	0.83
No liver metastases (n = 565)	19.4	12.4	0.64
Bone metastases (n = 207)	11.9	8.3	0.74
No bone metastases (n = 512)	20.5	12.4	0.65
CNS metastases (n = 122)	NR	7.9	0.38
No CNS metastases (n = 597)	15.4	11.8	0.75
PD-L1 < 1% (n = 264)	16.8	9.8	0.62
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64
PD-L1 1-49% (n = 233)	15.4	10.4	0.61
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66



Minimum follow-up: 12.7 months.

[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55-0.81).

Presented By Martin Reck at ASCO 2020

Slide 23

GM7 NEW SLIDE

Guijarro Munoz,Irene, 12/8/2020

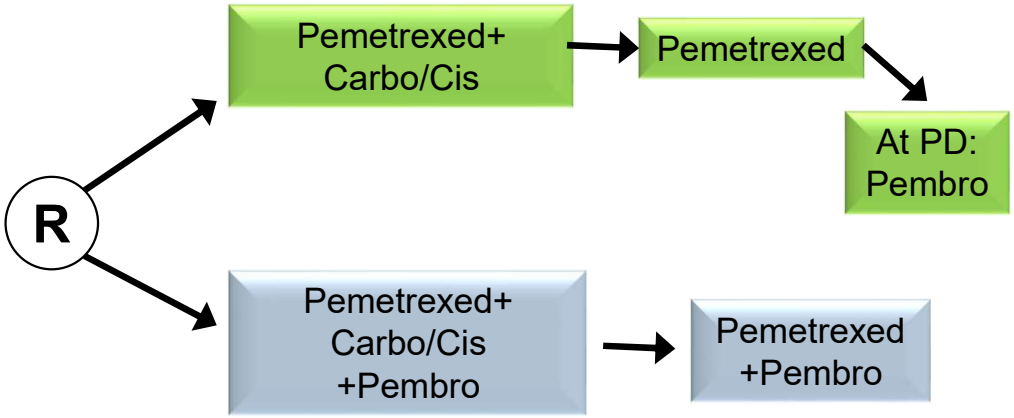
GM8

Keynote-189: RP3 of pemetrexed/platinum +/- pembro in non-squamous NSCLC (EGFR, ALK wt)

1L nonsquamous NSCLC
N=570, 2:1 randomization
Primary endpoint: PFS, target HR 0.7
Secondary: OS, ORR

Stratification:
PD-L1 prop score (<1% vs ≥1%), smoking status, cis vs carbo

- EGFR, ALK WT
- No active CNS metastases



1L, first-line; ALK, anaplastic lymphoma kinase; Carbo, carboplatin; Cis, cisplatin; CNS, central nervous system; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; PFS, progression-free survival; RP3, randomized phase 3; WT, wild type.
https://www.businesswire.com/news/home/20180116005680/en/Mercks-KEYTRUDA-pembrolizumab-Significantly-Improved-Survival-Progression-Free. Accessed Mar 2018.

Gandhi L NEJM 2018

Slide 24

GM8 NEW SLIDE

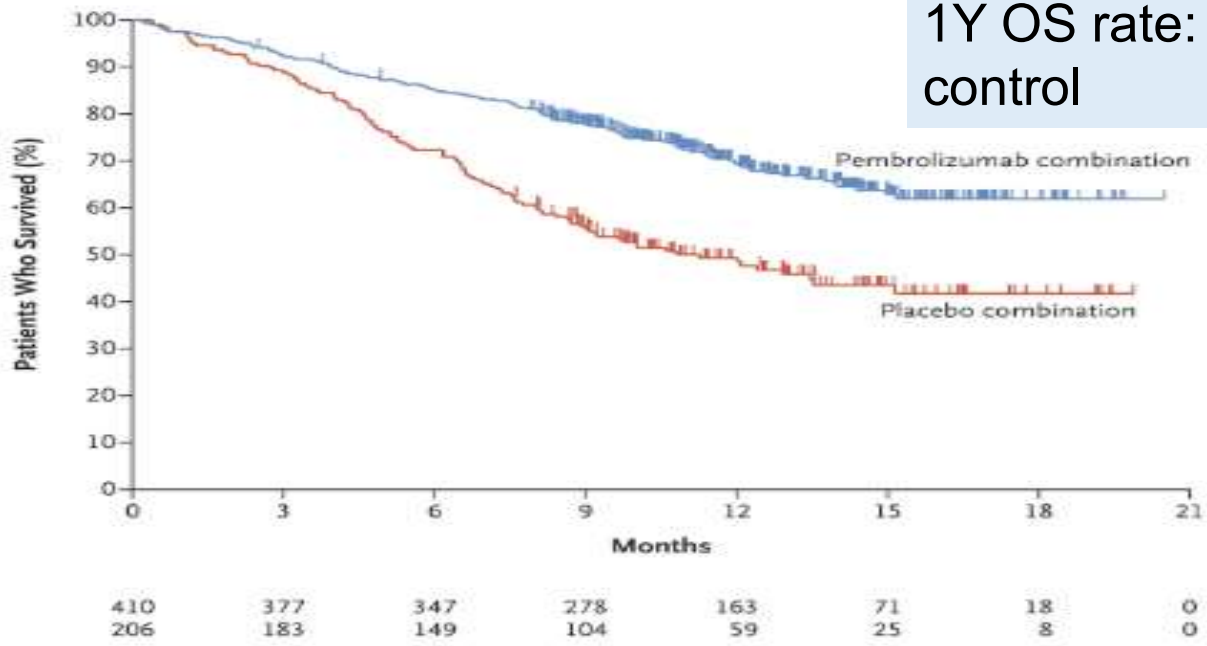
Guijarro Munoz,Irene, 12/8/2020

GM9

Keynote-189: RP3 of pemetrexed/platinum +/- pembro in non-squamous NSCLC (EGFR, ALK wt)

OS HR 0.49 (P<0.001, CI 0.38 to 0.64)

1Y OS rate: 69% pembro vs 49% control



Gandhi L NEJM 2018

Bottom line: pembro prolongs OS when added to chemo and is a new standard for non-squamous NSCLC regardless of PD-L1 level (EGFR, ALK negative)

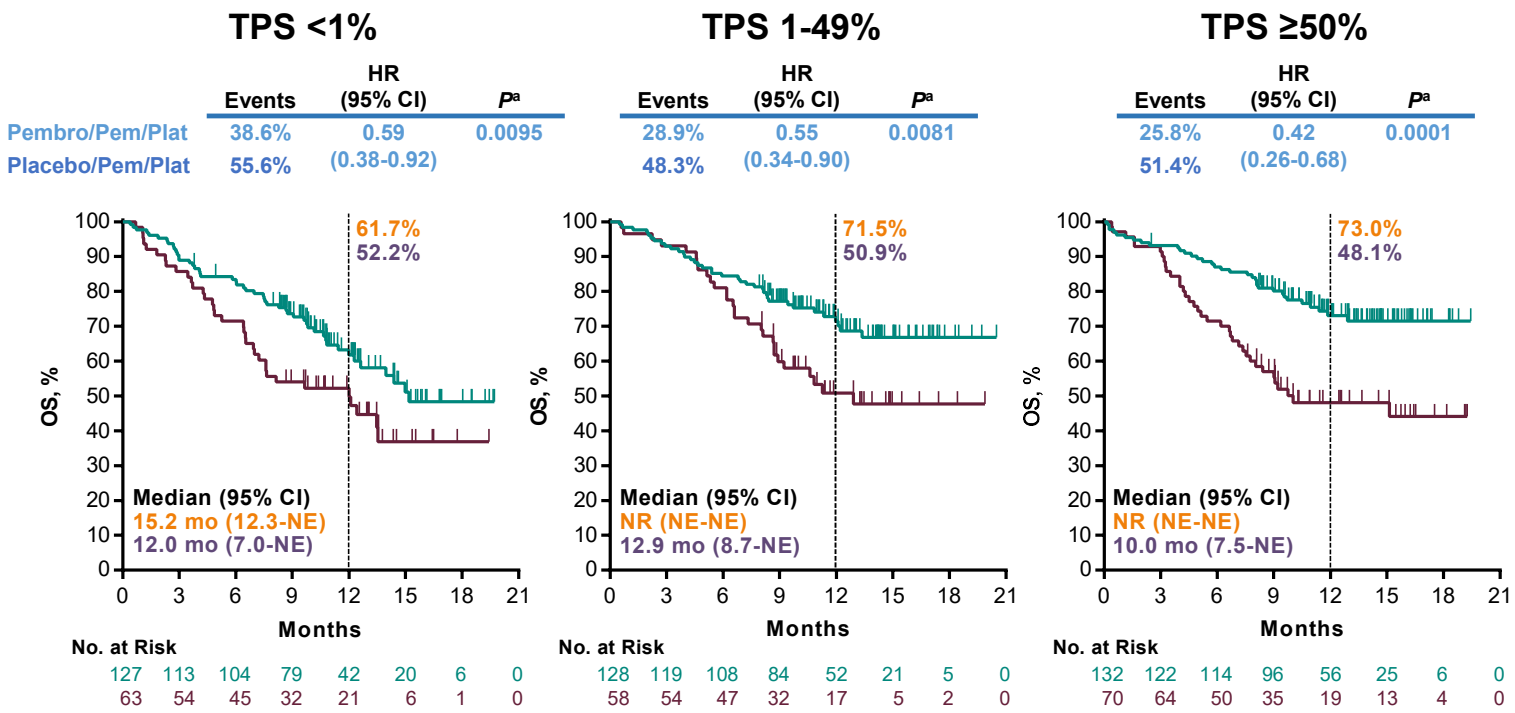
Slide 25

GM9 NEW SLIDE

Guijarro Munoz,Irene, 12/8/2020

GM10

Keynote 189: OS benefit across PD-L1 subgroups



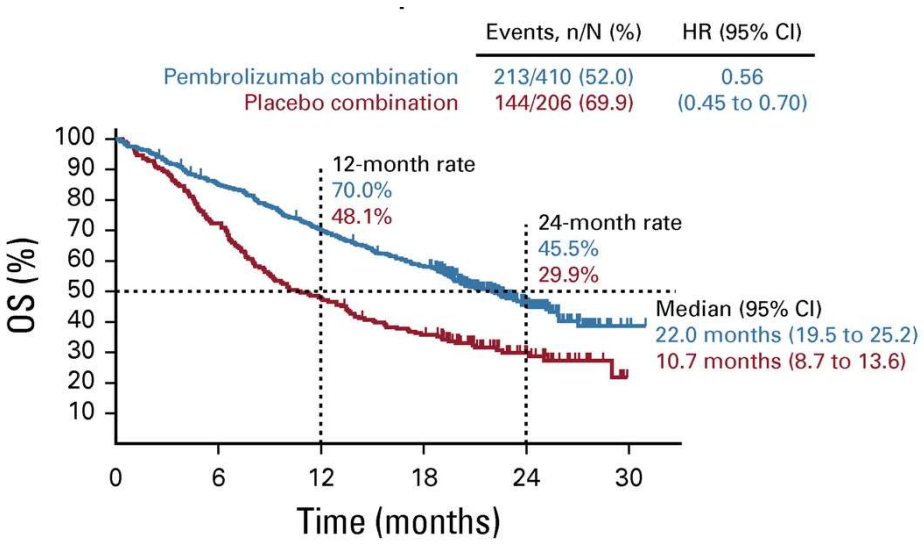
- [a]Nominal and one-sided. Data cutoff date: Nov 8, 2017.

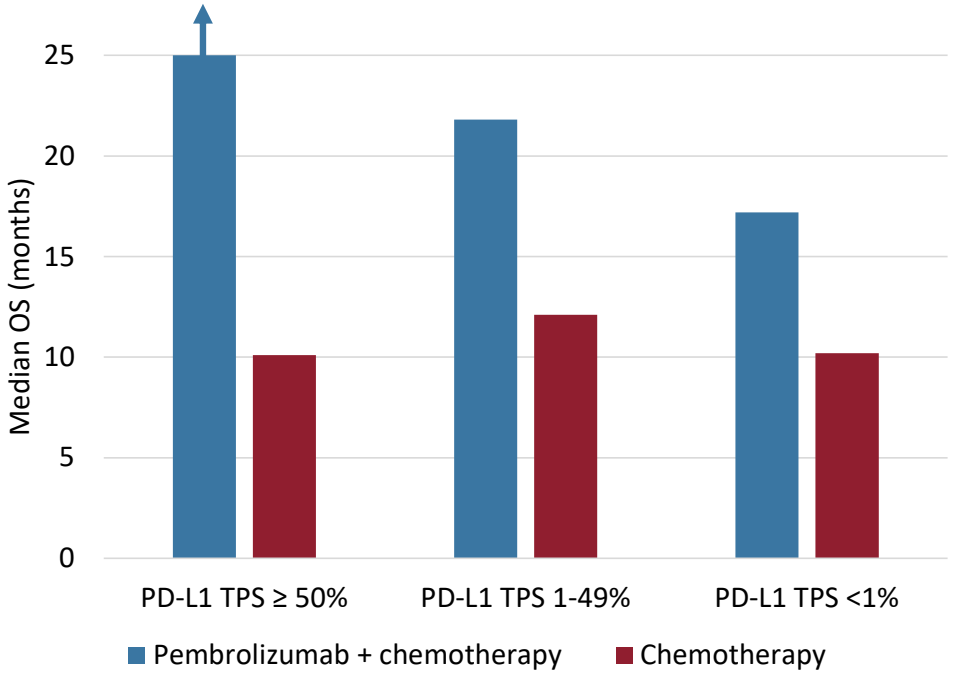
Gandhi et al, AACR 2018; Gandhi et al, NEJM 2018

Slide 26

GM10 Guijarro Munoz,Irene, 12/8/2020

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





Gadgeel, J Clin Oncol 2020.

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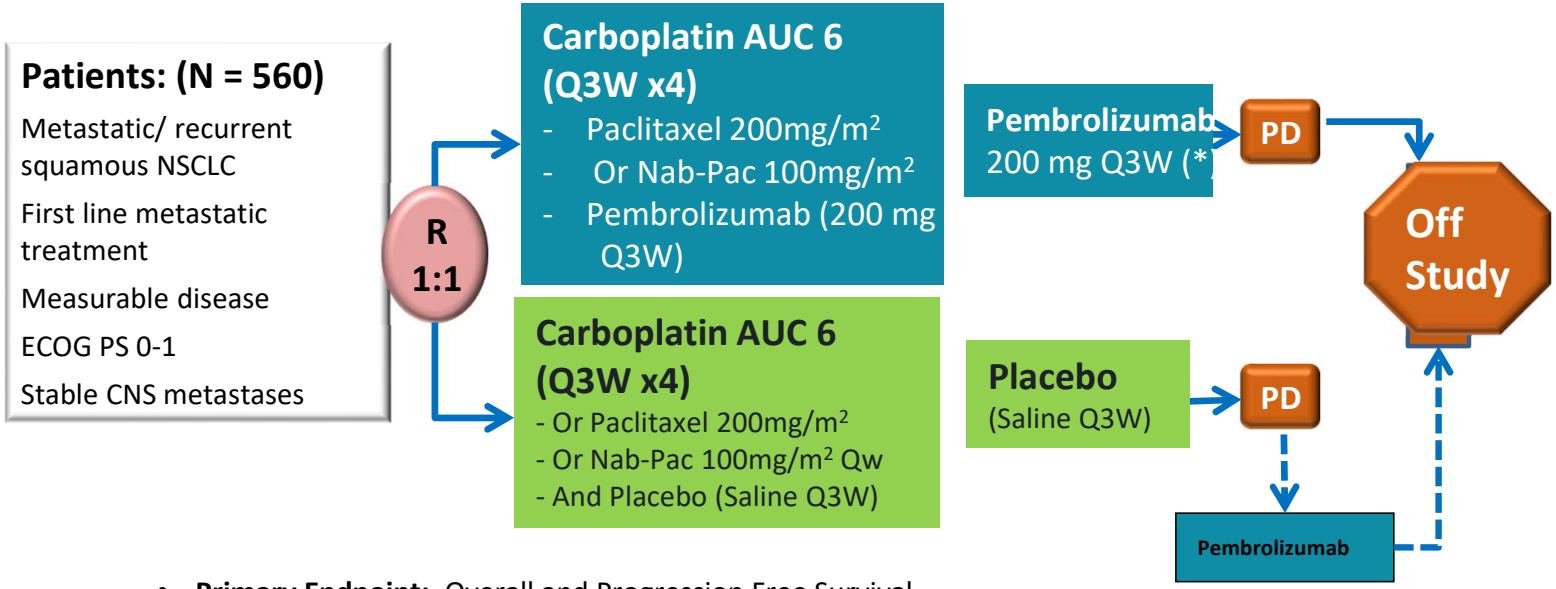
KEYNOTE 407 (Squamous NSCLC)
First line pembrolizumab + chemotherapy (carboplatin + paclitaxel/nab-paclitaxel) combination study

NEW



- **Primary Endpoint:** Overall and Progression Free Survival
- **Secondary Endpoints:** ORR, AE
- **Exploratory Endpoints:** QoL

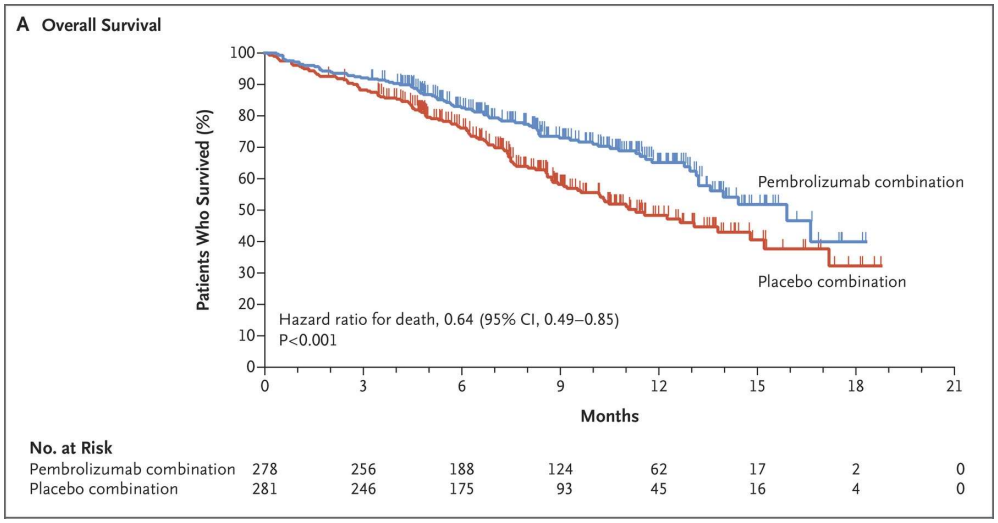
Stratify:
PD-L1 TPS score: ≥1% vs <1%
Paclitaxel vs nab-paclitaxel

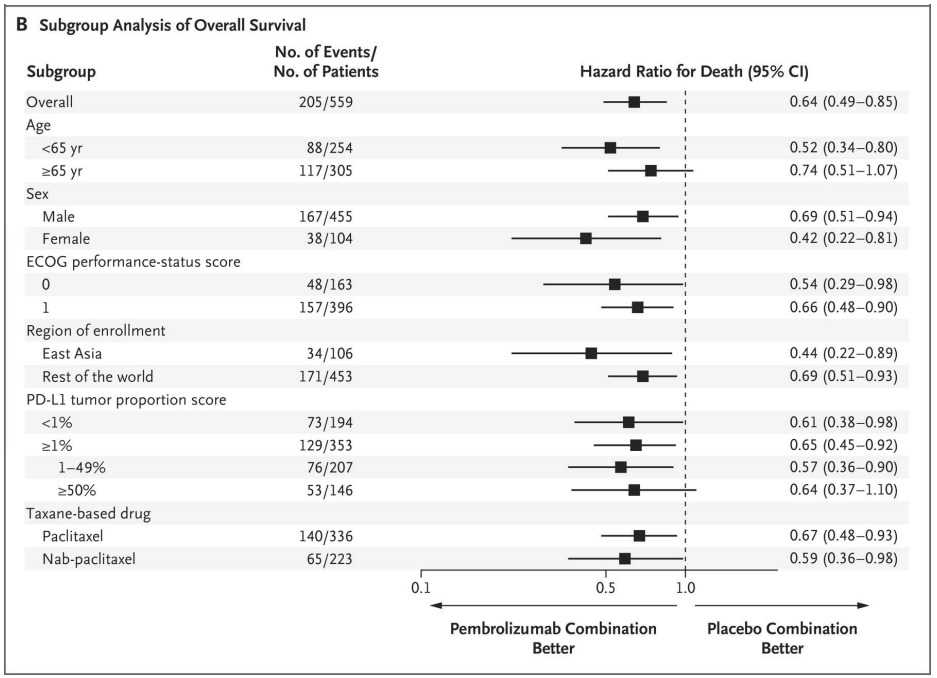
Paz-Ares NEJM 2018

* Up to 2 years

AE, adverse event; AUC, area under the curve; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PD-L1, programmed death-ligand; Q3W, every 3 weeks; QoL, quality of life.

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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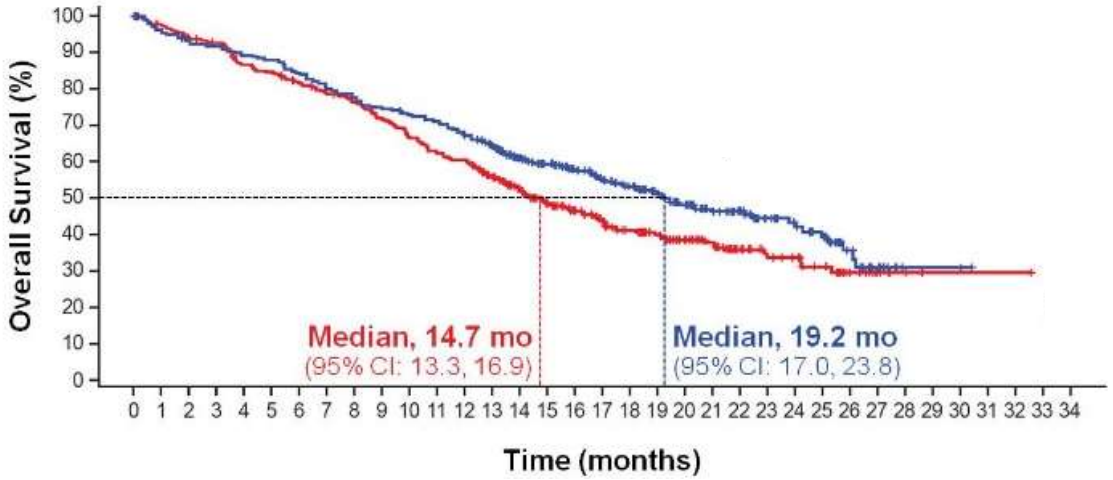
EE15

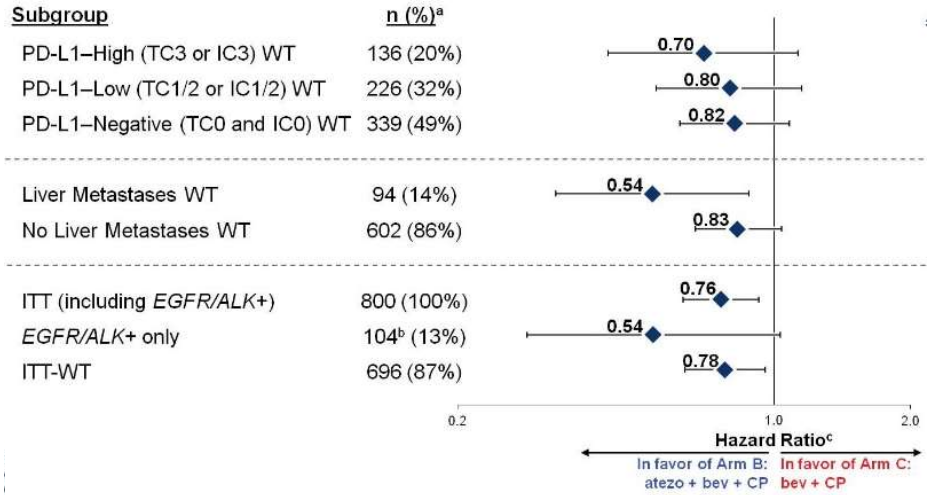
sitc Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

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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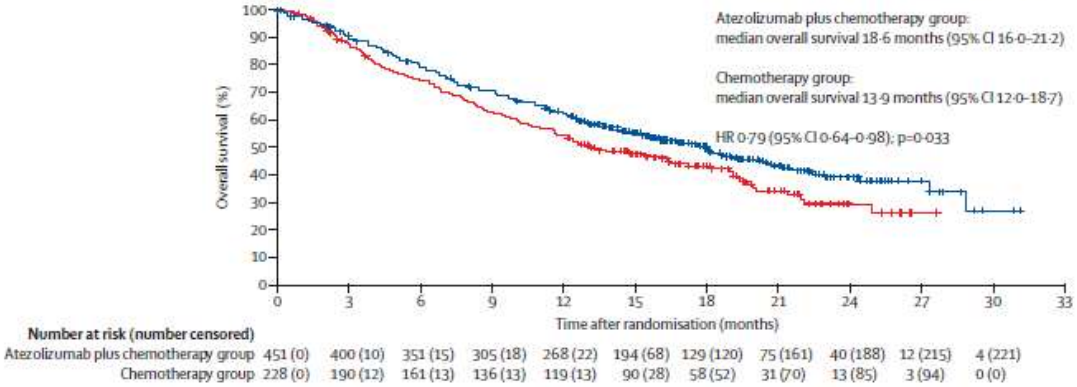
Slide 30

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

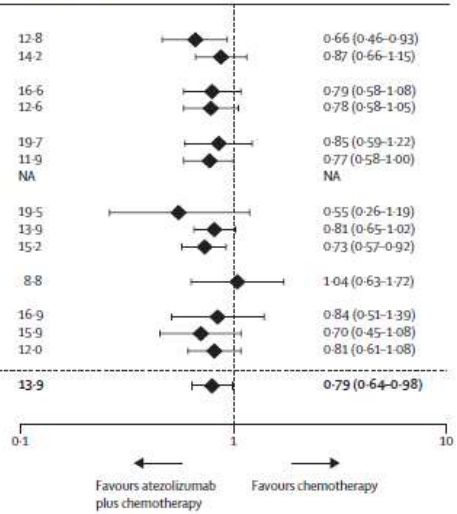
Emily Ehlerding, 7/27/2020

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

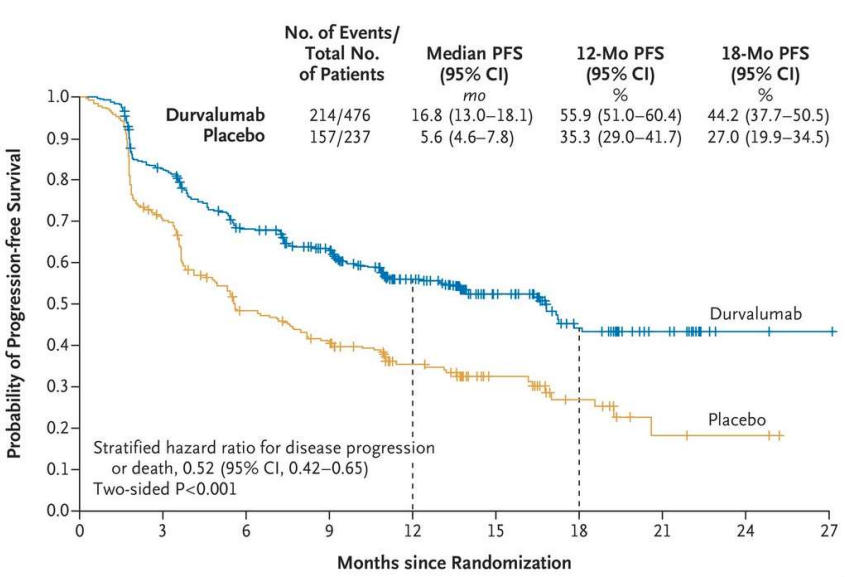
Study	Treatment arms	ORR	Median PFS (months)	Median OS (months)
CheckMate 017 and CheckMate 057	Nivolumab	19%	2.56	11.1
	Docetaxel	11%	3.52	8.1
KEYNOTE-010 (PD-L1 TPS ≥ 1%)	Pembrolizumab	18%	4.0	12.7
	Docetaxel	9%	4.0	8.5
OAK	Atezolizumab	14%	2.8	13.8
	Docetaxel	13%	4.0	9.6

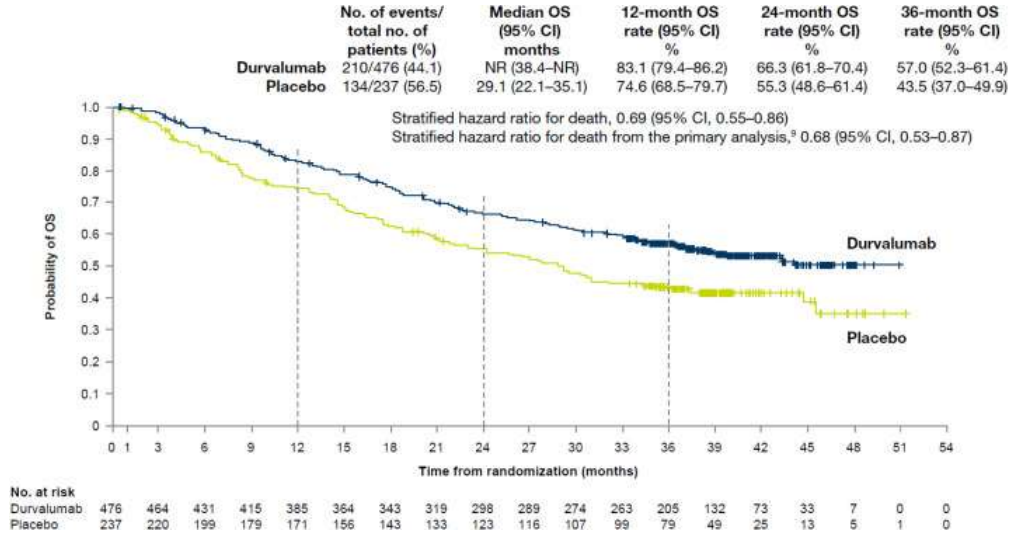
Vokes, Ann Oncol 2018.
Herbst, Lancet 2016.
Fehrenbacker, J Thorac Oncol 2018.

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.

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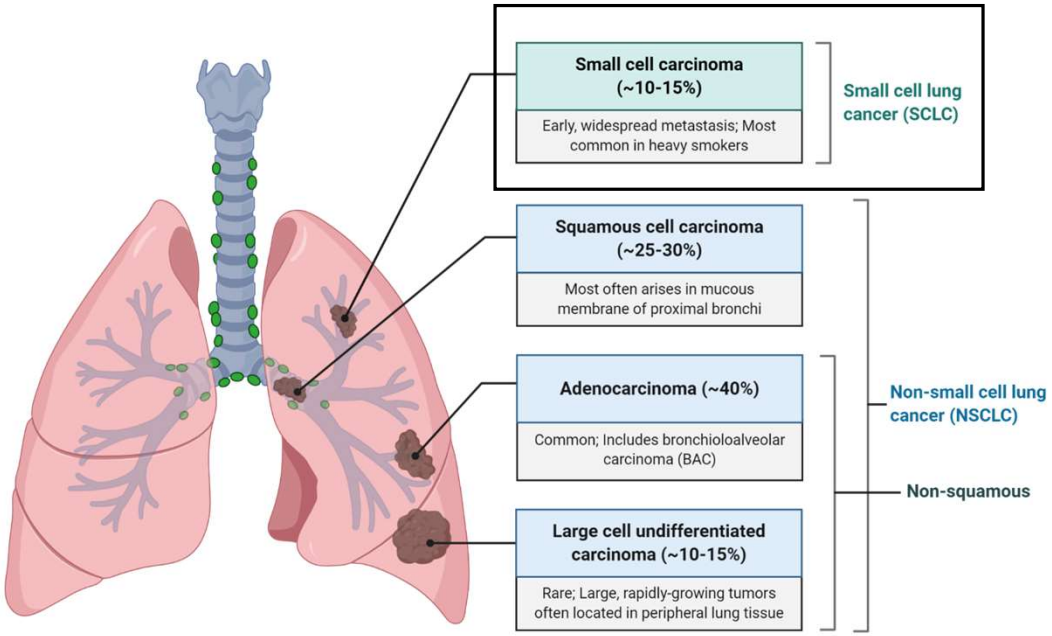
Outline

- 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

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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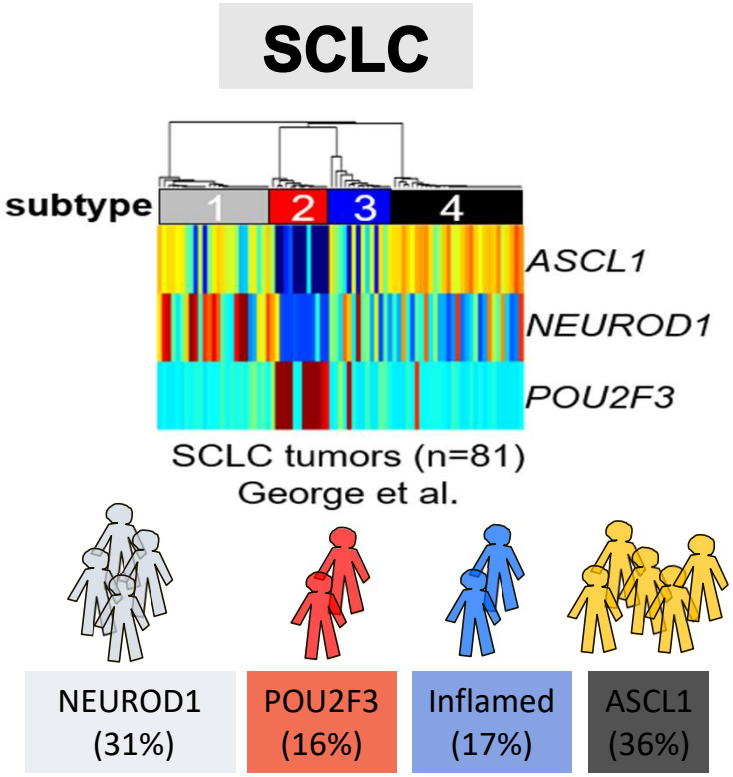
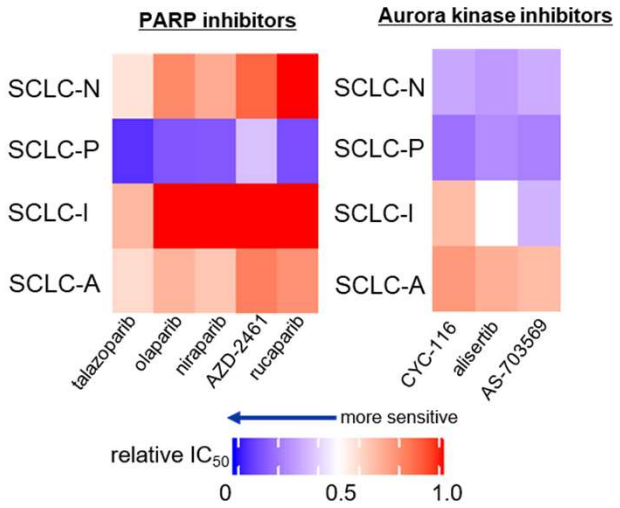
GM11

New advances in the treatment of small cell lung cancer (SCLC)



The four new targetable subgroups of SCLC showed differential response to drugs



New clinical trials testing aurora kinase inhibitors in SCLC (PI: Byers/Gay)

Gay et al Cancer Cell In press

Slide 38

GM11 NEW SLIDE

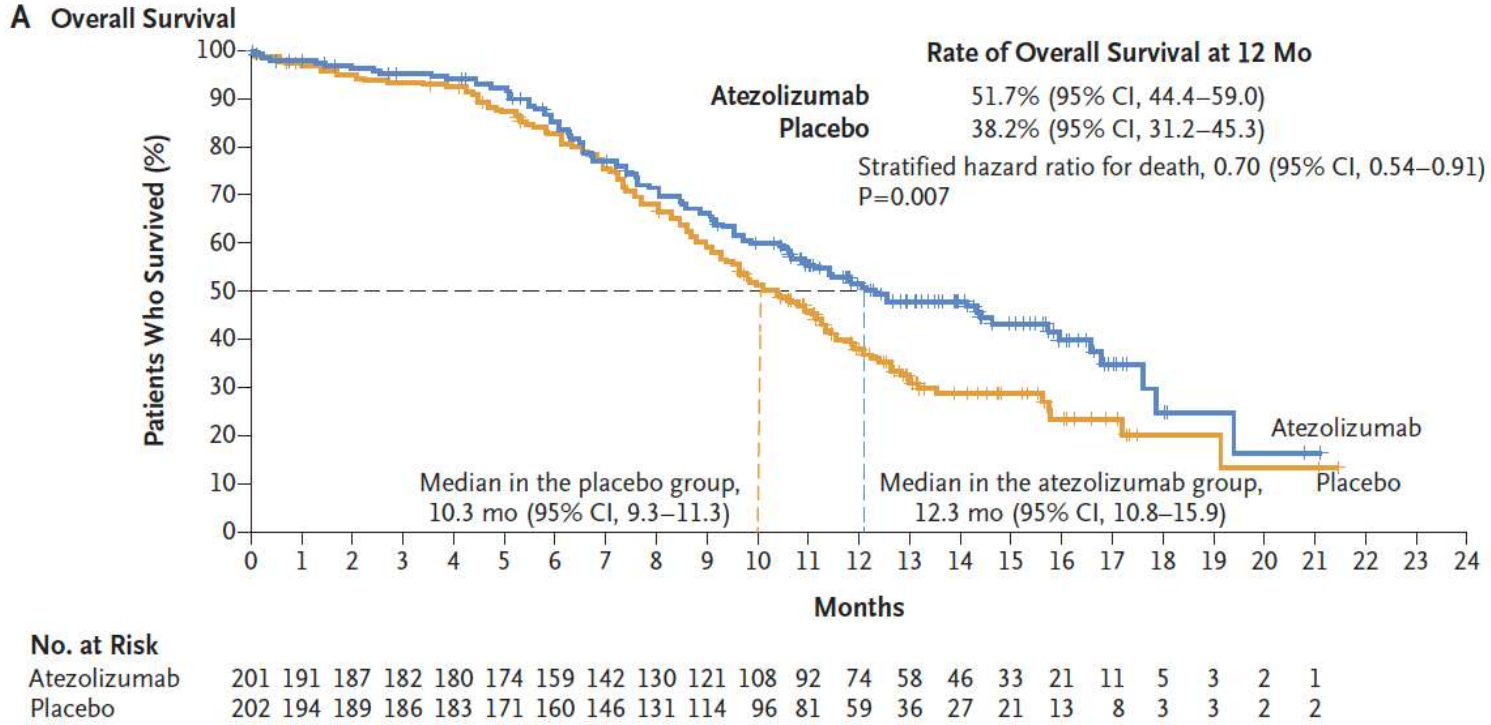
Guijarro Munoz,Irene, 12/8/2020

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

GM12

Impower 133: the addition of atezolizumab to carbo/etoposide prolongs OS in ES SCLC



First immunotherapy drug (or targeted agent) to improve OS in ES SCLC in RP3 trial!

Horn et al, NEJM 2018

Slide 40

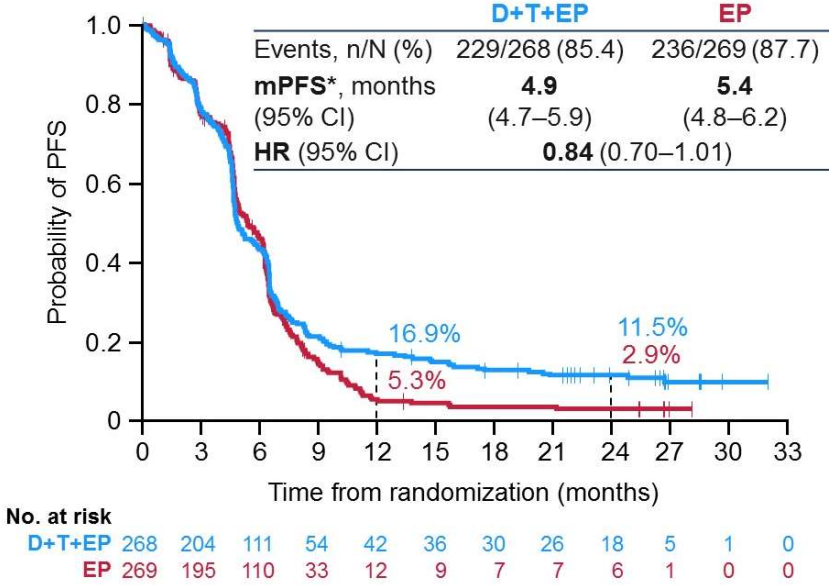
GM12 NEW SLIDE

Guijarro Munoz,Irene, 12/8/2020

GM13

Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): phase III CASPIAN study

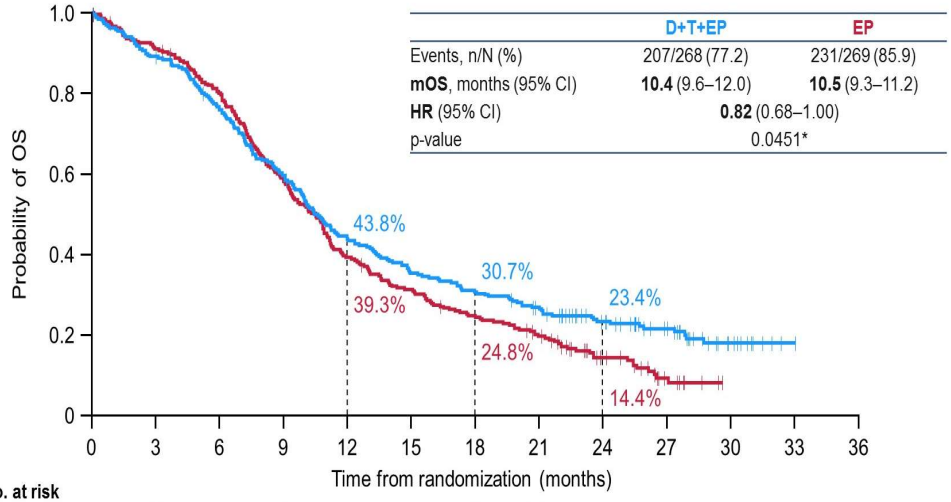
PFS



	D+T+EP	EP
Events, n/N (%)	229/268 (85.4)	236/269 (87.7)
mPFS*, months (95% CI)	**4.9** (4.7–5.9)	**5.4** (4.8–6.2)
HR (95% CI)	**0.84** (0.70–1.01)	

No. at risk												
D+T+EP	268	204	111	54	42	36	30	26	18	5	1	0
EP	269	195	110	33	12	9	7	7	6	1	0	0

Overall Survival: D+T+EP vs EP (Primary Endpoint)



	D+T+EP	EP
Events, n/N (%)	207/268 (77.2)	231/269 (85.9)
mOS, months (95% CI)	**10.4** (9.6–12.0)	**10.5** (9.3–11.2)
HR (95% CI)	**0.82** (0.68–1.00)	
p-value	0.0451*	

No. at risk												
D+T+EP	268	238	200	156	114	92	80	67	47	30	11	1	0
EP	269	243	212	156	104	82	64	48	24	8	0	0	0

Presented By Luis Paz-Ares ASCO 2020

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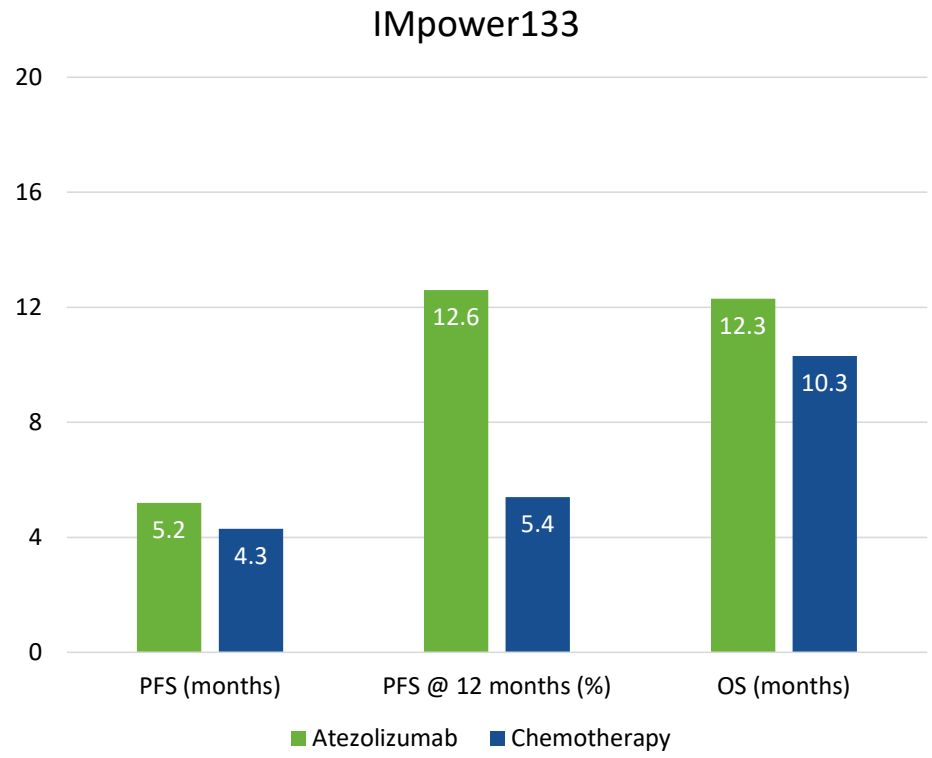
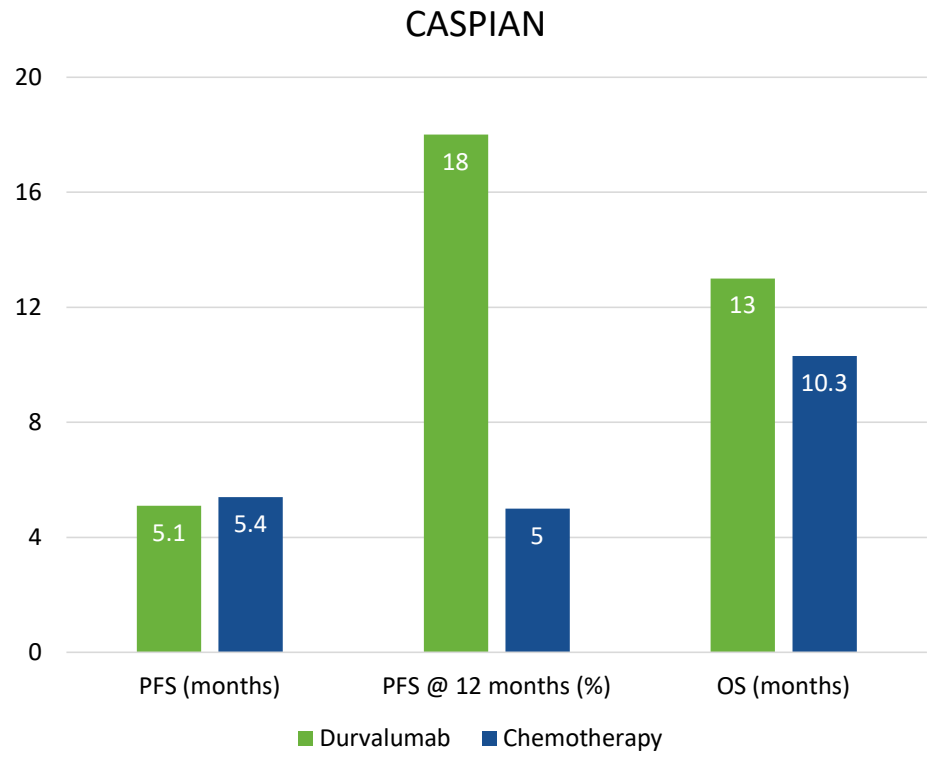
Slide 41

GM13 Guijarro Munoz,Irene, 12/8/2020

Front-line ICIs in SCLC





Huang, J Hematol Oncol 2020.

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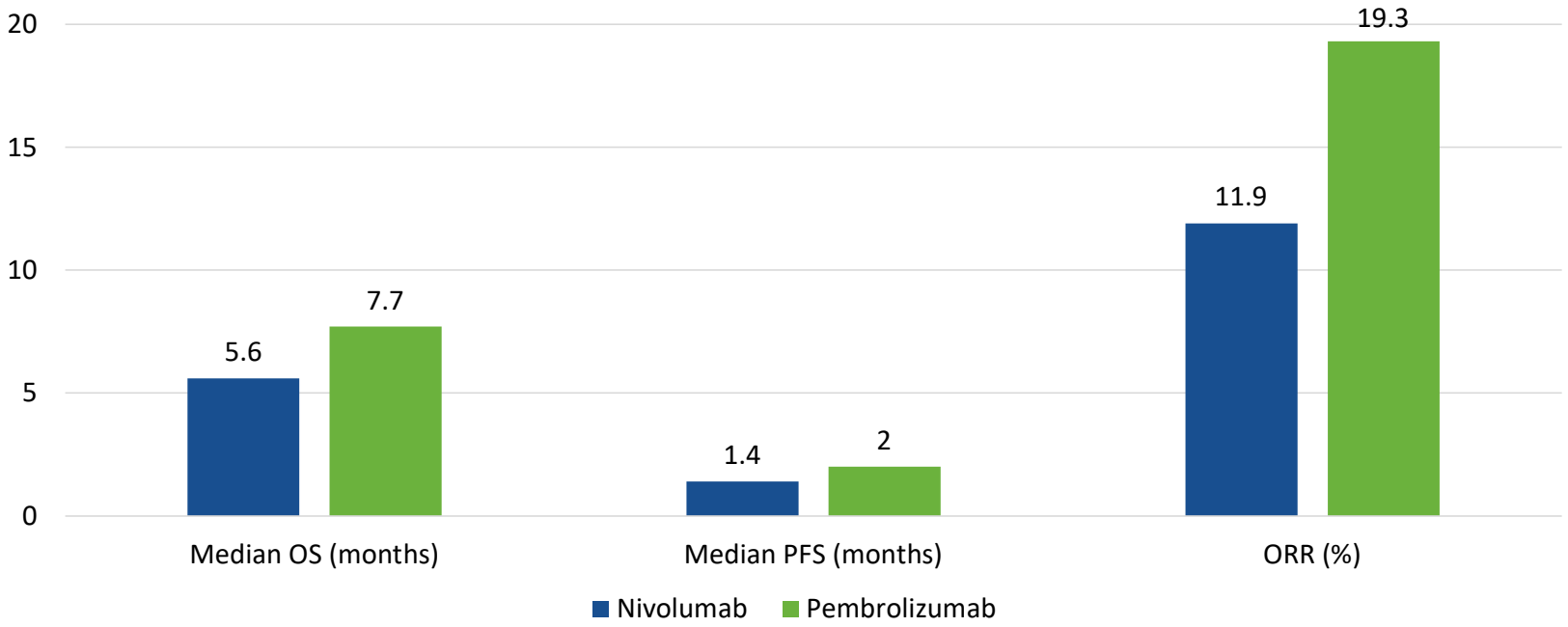
Later-line ICIs in SCLC



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

Outline

- 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

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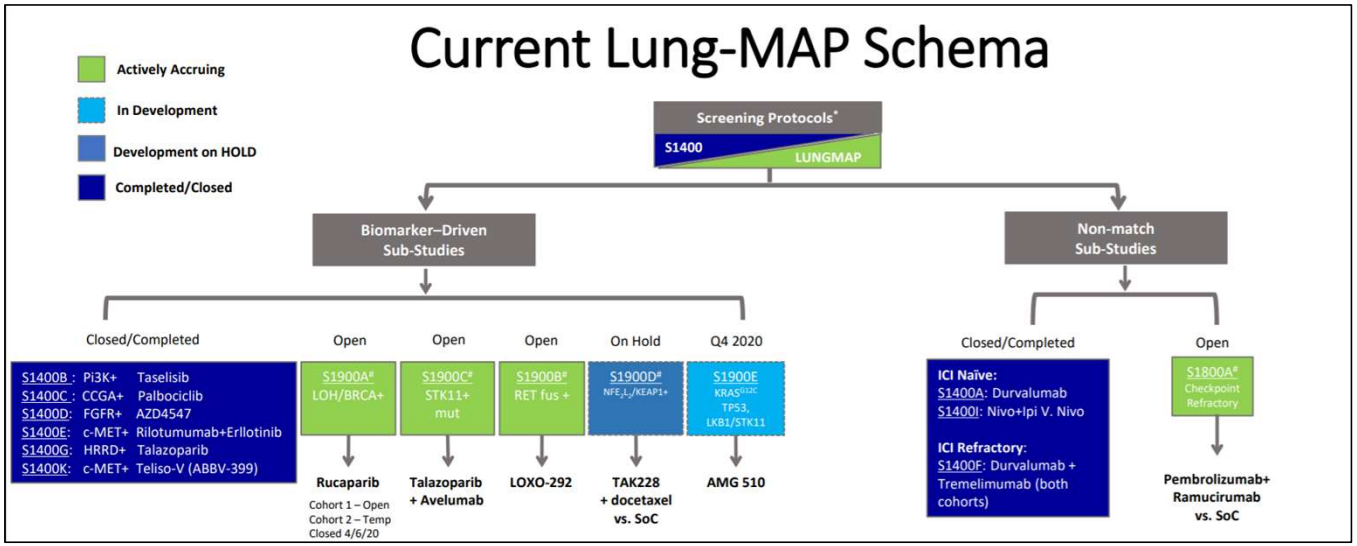
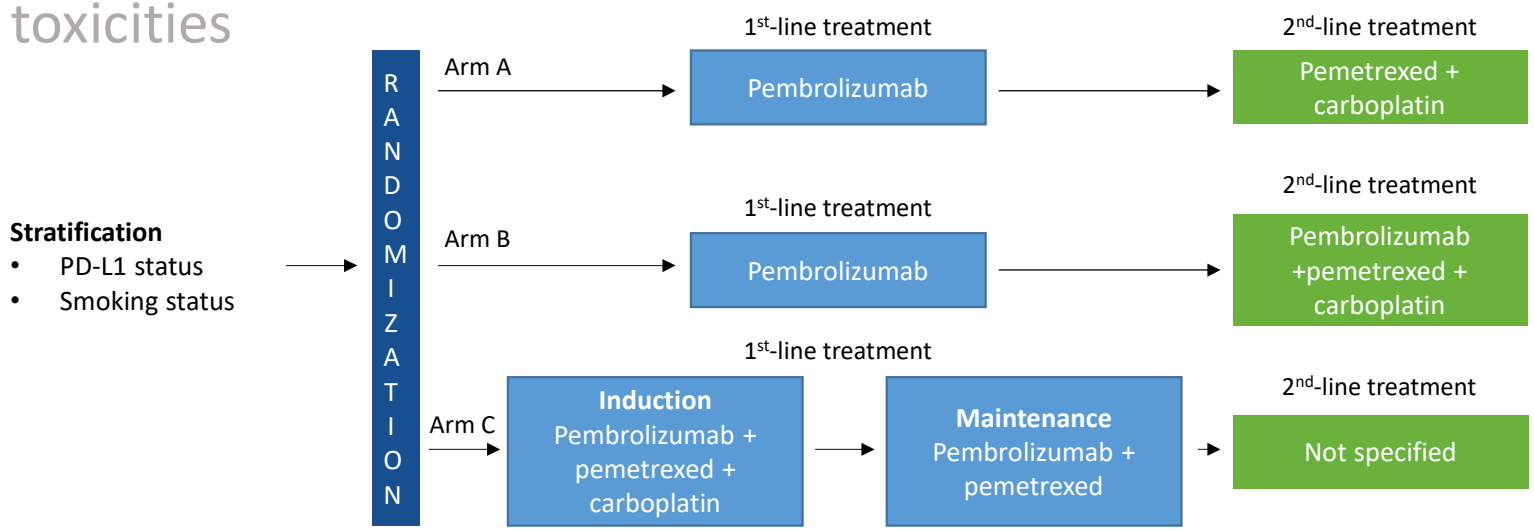


Lung-map.org

#LearnACI

In development: answering outstanding questions

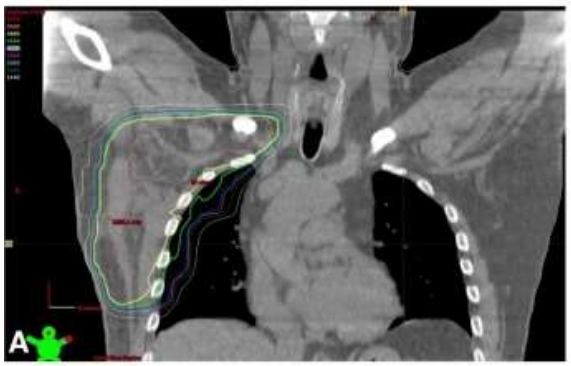
- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities



INSIGNIA trial

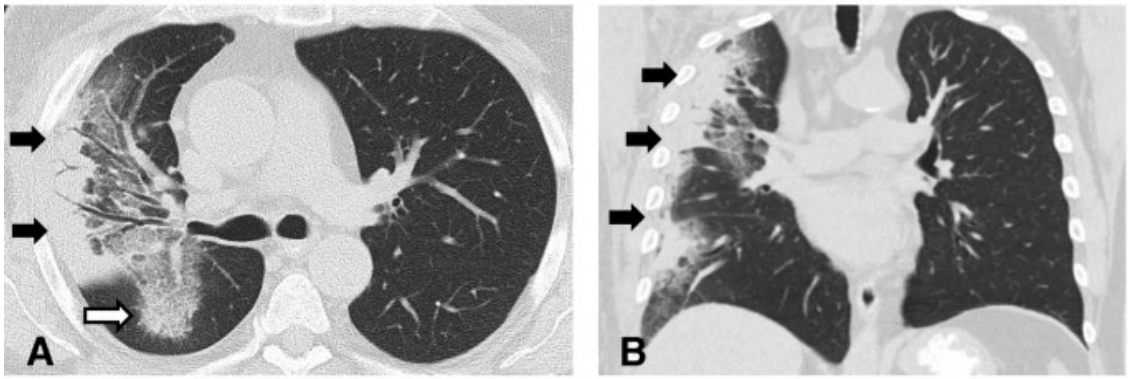
In development: answering outstanding questions

- 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

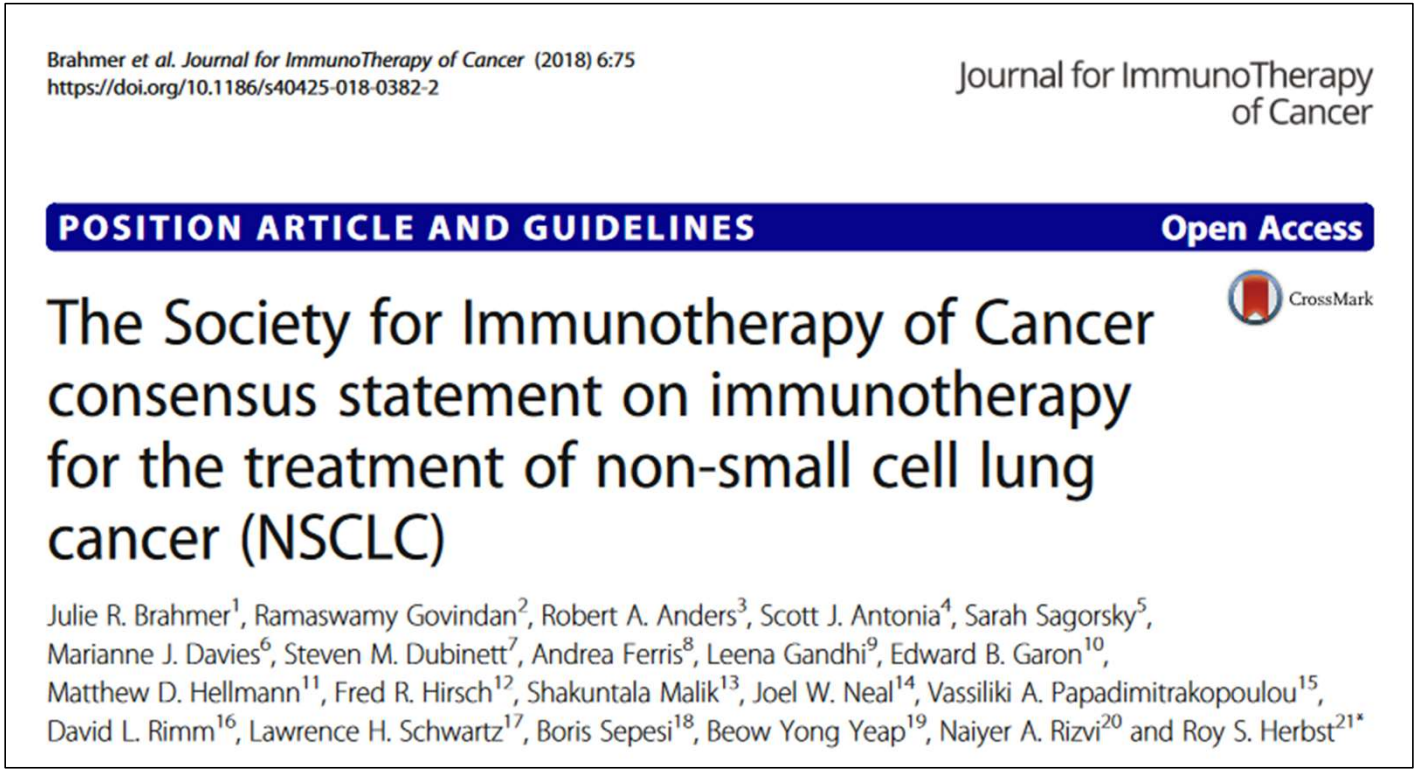


Schoenfeld, J Immunother Cancer 2019.

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*]

Case Study 1

- A 60 year old man with a 15 packyear history of smoking in his twenties presents with two episodes of hemoptysis (~10cc) and is found to have metastatic lung adenocarcinoma with multiple liver and bone metastases.
- MRI brain shows a 6mm lesion in the right frontal lobe. He is neurologically asymptomatic.
- His PDL1 is 0%. He is eager to initiate treatment.

1. Which of the following do you recommend?
   A. Initiate treatment with carboplatin/pemetrexed/pembrolizumab (KN189)
   B. Initiate treatment with ipilumumab/nivolumab (CM 227)
   C. Await results of molecular profiling of EGFR, ALK, and other driver oncogenes.
   D. Initiate treatment with chemotherapy alone.

Case Study 1

- He is found to be EGFR and ALKwt and have a KRAS G12V mutation.

2. Which of the following regimens would you recommend?
   A. Pembrolizumab.
   B. Ipilumumab and nivolumab (CM 227)
   C. carboplatin/pemetrexed/pembrolizumab (KN189)
   D. Carboplatin/pemetrexed/ipilumumab/nivolumab (9-LA)
   E. Carboplatin/paclitaxel/atezolizumab/bevacizumab.

Case Study 1

He states that his highest priority is to minimize the amount of chemotherapy he receives.

2. Which of the following approved regimens do you recommend?

A. Pembrolizumab.
B. Ipilumumab and nivolumab (CM 227)
C. carboplatin/pemetrexed/pembrolizumab (KN189)
D. Carboplatin/pemetrexed/ipilumumab/nivolumab (9-LA)
E. Carboplatin/paclitaxel/atezolizumab/bevacizumab.

Case Study 2

- A 70 year old man with a history of Hodgkin's disease treated with mantle field radiotherapy in 1970, and 10 packyear smoking, presents with stage 3A squamous lung cancer with a 4.5 cm primary and multiple ipsilateral mediastinal LNs involved (T2N2M0). He is EGFR and ALK wt, PD-L1 20%. He has been told that he cannot receive additional RT to his lungs or mediastinum.

1. Which of the following regimens are approved in this setting?
   A. Durvalumab (Pacific regimen)
   B. Pembrolizumab
   C. Ipilumumab/nivolumab (Checkmate 227)
   D. Carboplatin/paclitaxel/ipilumumab/nivolumab (9-LA regimen)