Immunotherapy for the Treatment of Lung Cancer`

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Disclosures

- Consulting Fees: AstraZeneca, Boehringer Ingelheim
- Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents: Genentech
- I will be discussing non-FDA approved indications during my presentation.

Lung cancer

- 80-85% non-small cell lung cancer (NSCLC)
- 10-15% small cell lung cancer (SCLC)

Estimated Deaths

Male			Female		
Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All sites	321,670		All sites	285,210	

American Cancer Society

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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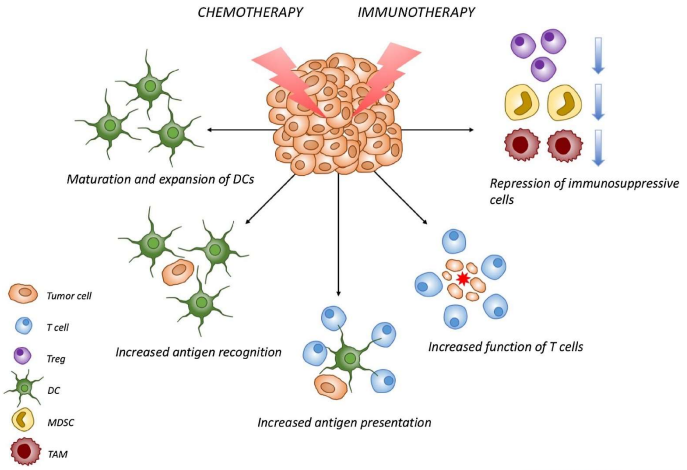
Immunomodulatory Effects of Chemotherapy



Leonetti, etl al., Molecular basis and rationale for combining immune checkpoint inhibitors with chemotherapy in NSCLC Drug Res Updates 46 (2019)

Treatment Algorithm for First Line Advanced NSCLC

Histology	NonSquamous NSCLC				
Mutation/PDL1	Oncogenic Driver	PDL1 neg	PDL1 >1-49%		PDL1 High (>50%)
First Line	First Line TKI	Chemo/IO	Chemo/IO	Pembro Or Nivo/Ipi	Pembro or Atezo

Treatment Naïve Regimens: Competing Strategies in NSCLC

- **Single Agent Immunotherapy in First-line NSCLC**
  - **KEYNOTE 024** – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 50%
  - **KEYNOTE 042** – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 1%
  - **IMPOWER-110**-Atezolizumab vs Chemo in PDL1>50%
- **Chemo-Immunotherapy in First-line NSCLC**
  - Pembrolizumab: KN-21G, KN-189, KN407 (SCC)
  - Atezolizumab: IMPOWER-150, IMPOWER-133
  - Nivolumab + Ipilimumab +platinum-doublet (2 cycles): CM-9LA
- **Combination Immune Checkpoint Blockade in First-line**
  - **CHECKMATE 227** – Ipilimumab + Nivolumab vs. Chemotherapy in advanced NSCLC -high TMB

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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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

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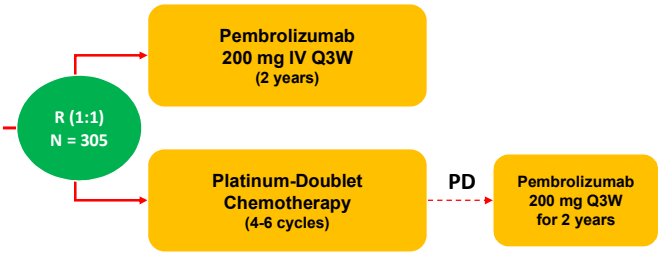
KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 Positive (≥ 50%)

NSCLC Study Design (NCT021427389)

Key Eligibility Criteria

- ***Untreated*** stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

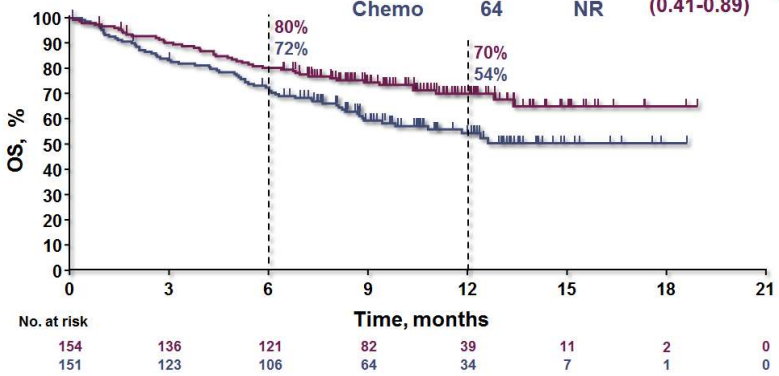


Reck M et al, ESMO 2016, NEJM 2016

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

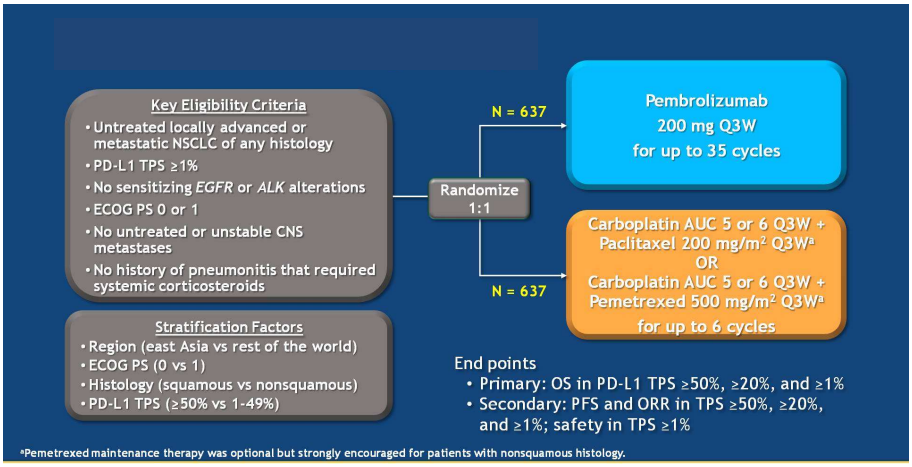
Overall Survival

	Events, n	Median, mo	HR (95% CI)	P
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



Reck M et al, ESMO 2016, NEJM 2016

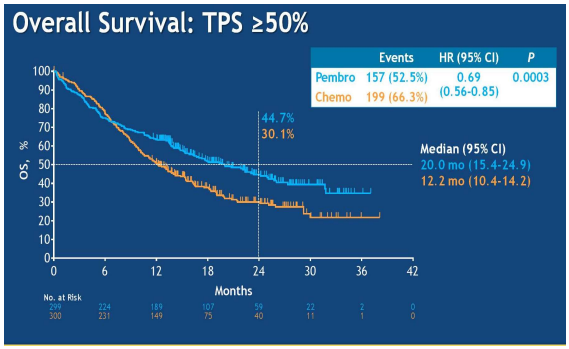
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC

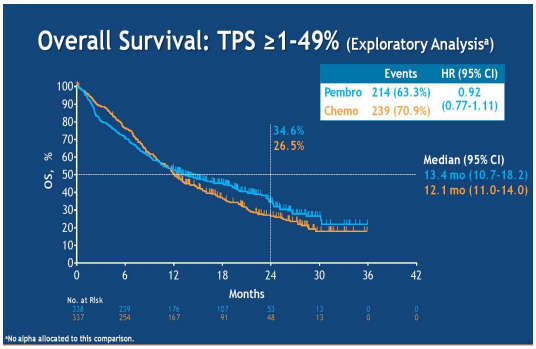


Lopes et al, ASCO 2018

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

Overall Survival

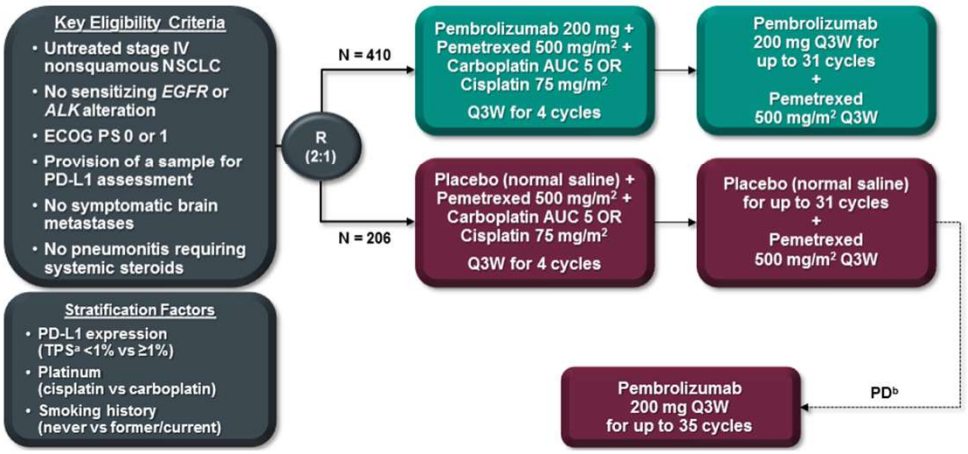




Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%

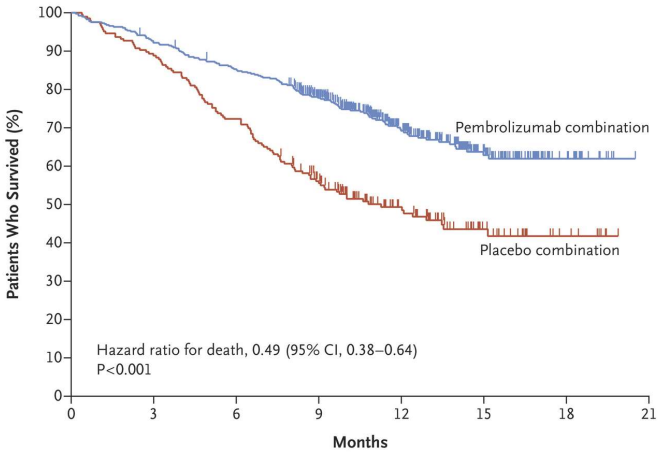
Lopes et al, ASCO 2018

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



Ghandi et al, NEJM 2018

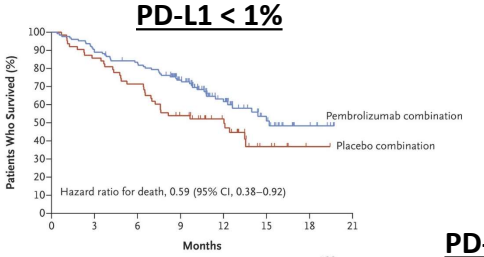
KEYNOTE-189: Pembrolizumab/Platinum /Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC



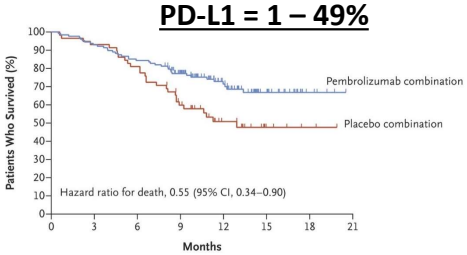
Ghandi et al, NEJM 2018

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

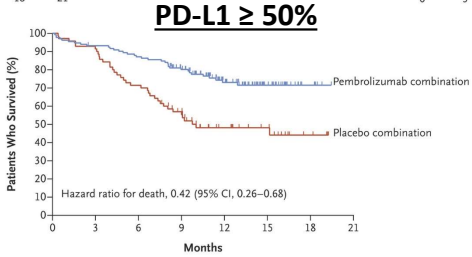
PD-L1 < 1%



PD-L1 = 1 – 49%

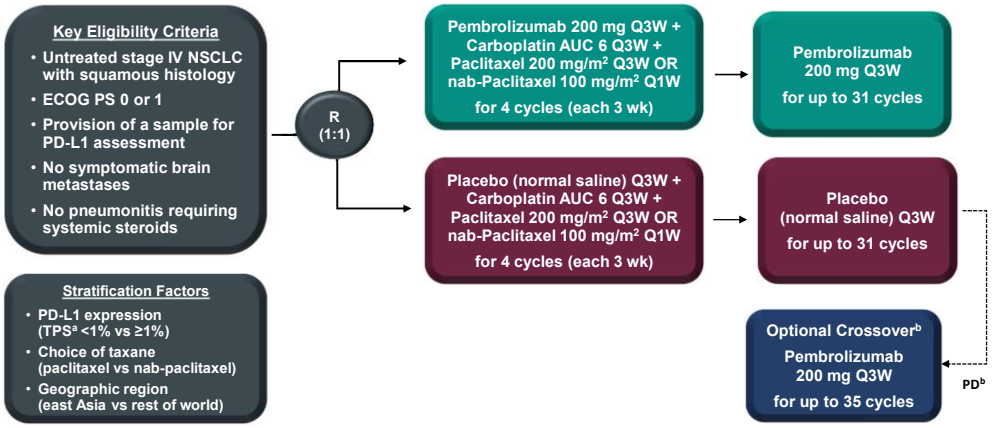


PD-L1 ≥ 50%



Ghandi et al, NEJM 2018

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

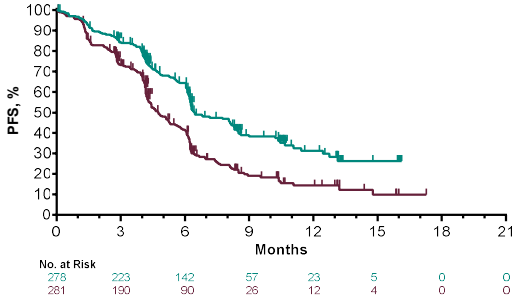


Paz-Ares et al, ASCO 2018

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

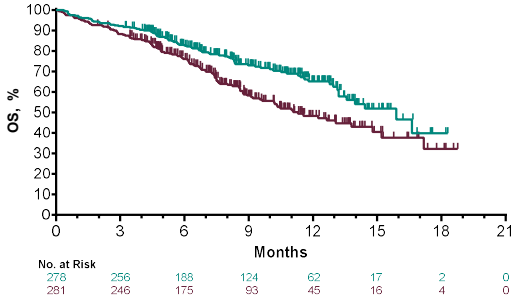
PFS (RECISTv1.1, BICR)

	Events	HR (95% CI)	*P*
Pembro + Chemo	54.7%	0.56 (0.45-0.70)	<0.0001
Placebo + Chemo	70.1%		



Overall Survival

	Events	HR (95% CI)	*P*
Pembro + Chemo	30.6%	0.64 (0.49-0.85)	0.0008
Placebo + Chemo	42.7%		



Paz-Ares et al, ASCO 2018

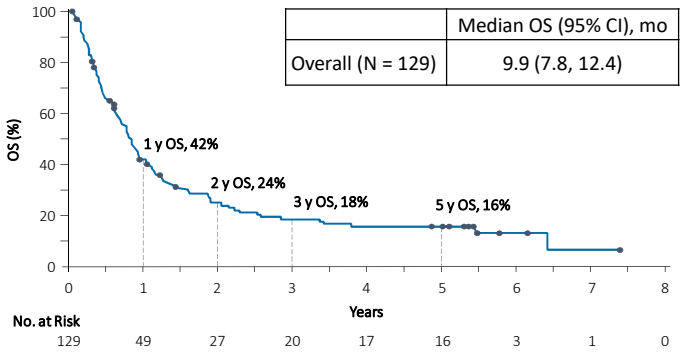
CA209-003: Nivolumab in Heavily-pretreated Advanced NSCLC (NCT00730639)

Phase 1, 5-Year Update

- First report of long-term survival rate in patients with metastatic NSCLC treated with an immune checkpoint inhibitor
- According to the National Cancer Institute's SEER data, 5-year survival rate for patients with advanced NSCLC is 4.9%

5-Year Survival

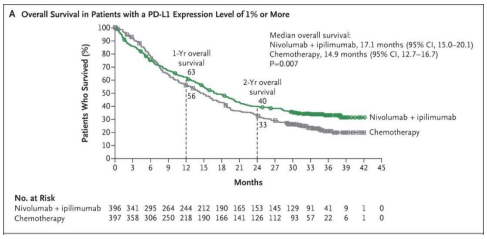
	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

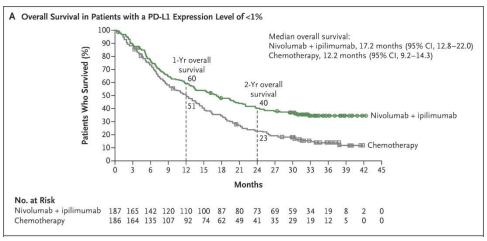


Gettinger et al. JCO 2018
Brahmer et al, AACR 2017
NCI SEER data, Lung and Bronchus Cancer, 2014

CheckMate 227

- Primary endpoint: OS in PD-L1 ≥ 1% (tumor cells)
  - Nivo/ipi: 17.1 months
  - Chemo: 14.9 months
- Longer duration of response with nivo/ipi over chemo
- Benefit of nivolumab + ipilimumab seen regardless of PD-L1 status in this study





Hellmann, NEJM 2019.

CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo

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

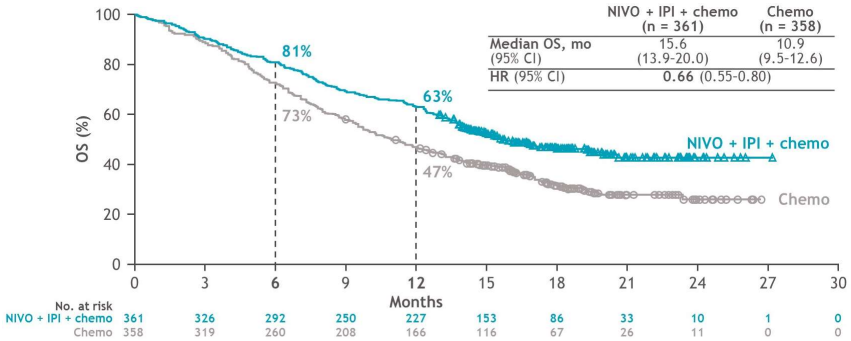
Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

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.

Reck M et al, ASCO 2020.

CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo

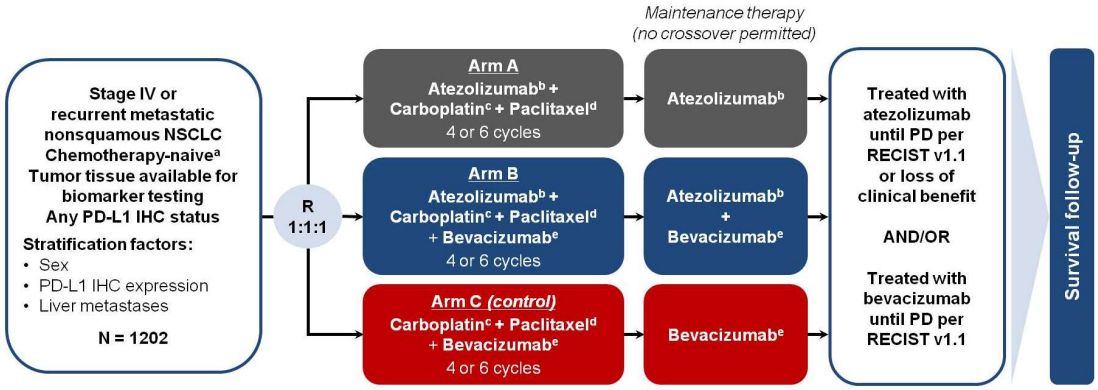


	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	0.66 (0.55-0.80)	

	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.

IMPOWER 150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/ Bevacizumab in Advanced Non-Squamous NSCLC

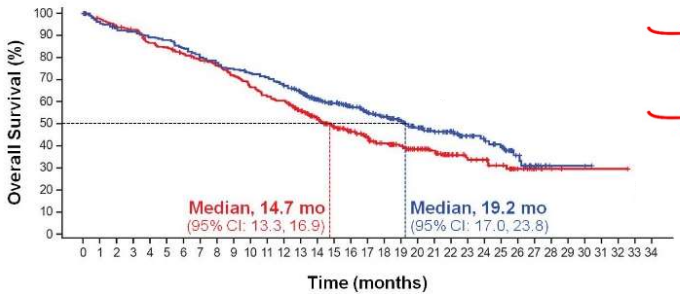


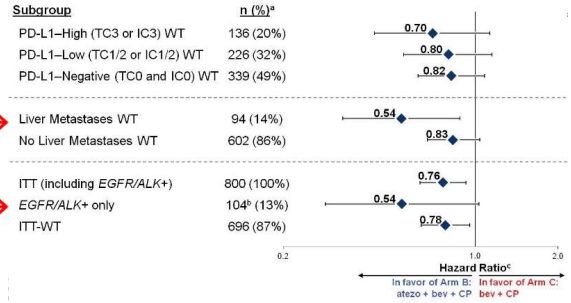
Socinski et al, NEJM 2018

IMPOWER 150: 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

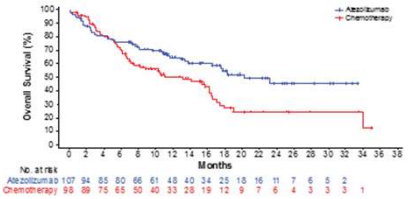




Socinski et al, NEJM 2018

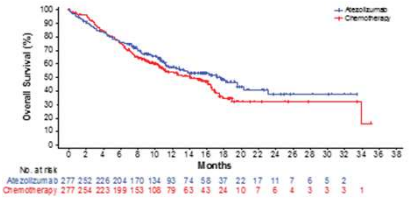
IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

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]

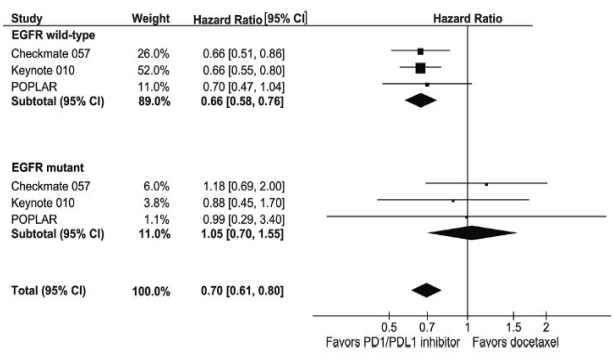


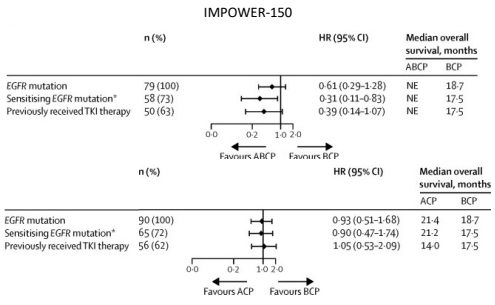
	Atezo (n = 277)	Chemo (n = 277)
mOS, mo	17.5	14.1
HR[b] (95% CI)	0.83 (0.65, 1.07)	

Herbst, ESMO-IO 2019.

Is there a Role for Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

Meta-Analysis: CM-057, KN-010, POPLAR; IMPOWER-150



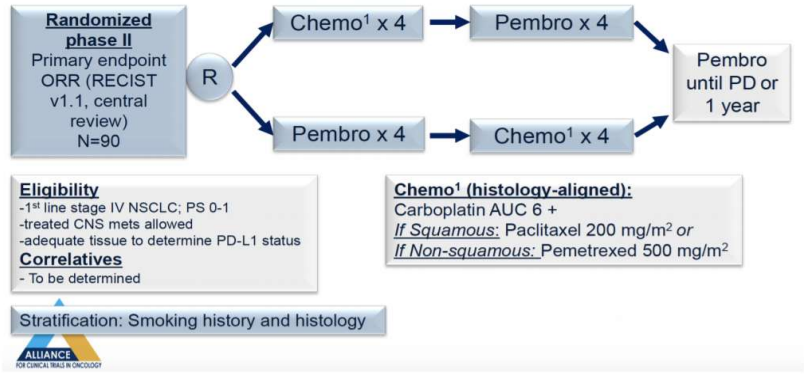


Immune Checkpoint Inhibitors alone are not active in EGFR+ lung cancer

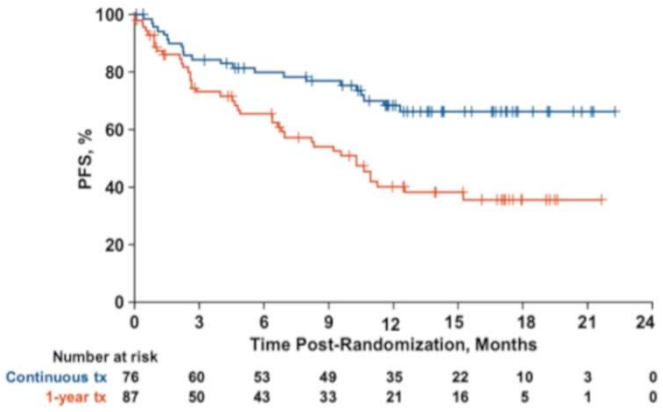
CK Lee et al., JTO 2016
M Reck et al., Lancet Resp Med 2019

Optimal Sequence of Immunotherapy

Optimal Sequencing of Pembrolizumab (MK-3475) and Standard Platinum-based Chemotherapy in First-Line NSCLC (AFT-09)



Duration of Therapy
CM-153: 1 year vs ongoing nivo in 2nd line

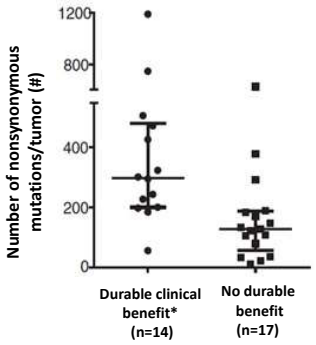


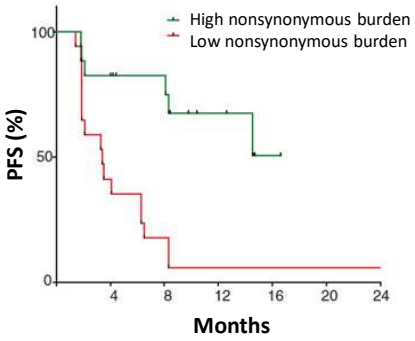
Next step: Do first-line NSCLC patients benefit from continued immunotherapy > 1 year

Spigel et al, *ESMO* 2018

Tumor Mutational Burden (TMB) may Determine Sensitivity to PD-1 Blockade in NSCLC

In two independent cohorts, higher nonsynonymous tumor mutational burden (TMB) was associated with improved objective response, durable clinical benefit, and PFS.





*Partial or stable response lasting > 6 mo

Rizvi N et al, Science, 2015

Severe Immune side effects in sequential osimertinib->PDL1

Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib Hellmann, *Annals of Oncology*, Volume 30, Issue 5, May 2019

- Case review of patients treated w EGFR and Immunotherapy who developed grade 3-4 toxicity
- Fifteen percent (6 of 41) of all patients treated with sequential PD-(L)1 blockade followed later by osimertinib developed a severe irAE.
- Severe irAEs were most common within 3 months of prior PD-(L)1 blockade, median onset 20 days after osimertinib
- No severe irAEs among patients treated w osimertinib followed by PDL1, or PDL1 followed by other EGFR-TKIs (afatinib or erlotinib)

LOCALLY ADVANCED NSCLC

Unresectable Stage III Lung Cancer

PACIFIC (NCT02125461): Durvalumab after chemoradiotherapy in Stage III NSCLC

Patients with locally advanced unresectable NSCLC (Stage III) in a consolidation setting

Absence of progression following at least 2 cycles of platinum-based chemotherapy concomitant with radiation therapy

(Randomization after chemoradiotherapy completion)

R 2:1
N=709

Durvalumab (n=473)
IV 10 mg/kg Q2W
≤12 months

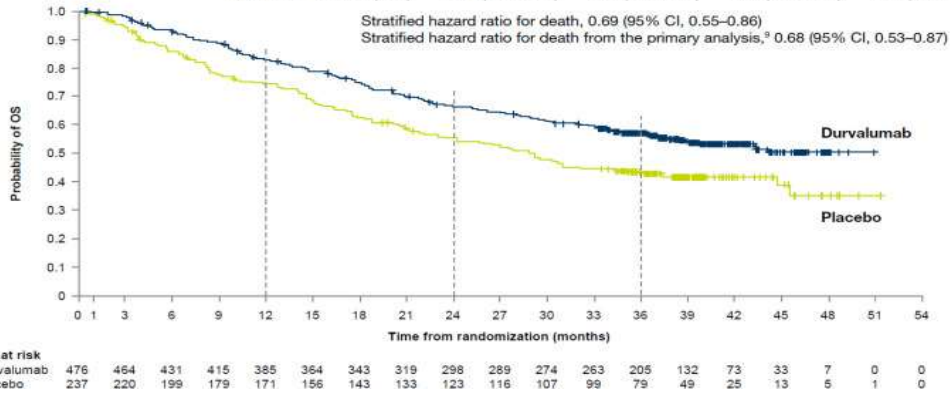
Placebo (n=236)
IV Q2W

Antonia et al, NEJM 2018

PACIFIC (NCT02125461): Durvalumab after chemoradiotherapy in Stage III NSCLC

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.4)
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.9)

Stratified hazard ratio for death, 0.69 (95% CI, 0.55–0.86)
Stratified hazard ratio for death from the primary analysis,[3] 0.68 (95% CI, 0.53–0.87)



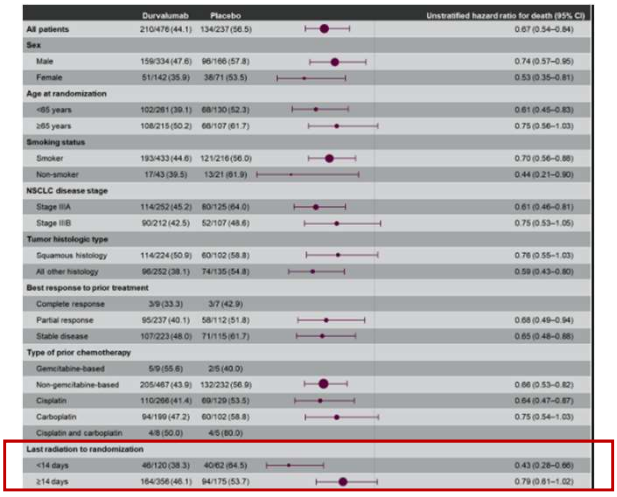
No. at risk

Durvalumab	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1	0

Gray J, et al. JTO 2019
Antonia et al, NEJM 2018

PACIFIC: Updated 3yr Subgroup Analysis

- Better response in pts started <14 days from radiation
- Retrospective series show that this is difficult
  - Emory (median time to treatment 35 days)
  - EORTC survery (54.1% within 6 weeks, 21% within 14 days)



Concurrent Chemorads + Immunotherapy trials

Trial	PHASE	N	REGIMEN
KEYNOTE 799	II	216	CRT+ Pembro followed by Pembro CRT followed by Pembro
CM- 73L	III	1400	CRT+ Nivolumab followed by Nivo/Ipi CRT+ Nivolumab followed by Nivolumab CRT followed by Durvalumab
PACIFIC 2	III	328	CRT+ Durvalumab followed by Durvalumab CRT followed by placebo
EA 5181	III	660	CRT + Durvalumab followed by Durvalumab CRT followed by Durvalumab

SMALL CELL LUNG CANCER

Small cell lung cancer

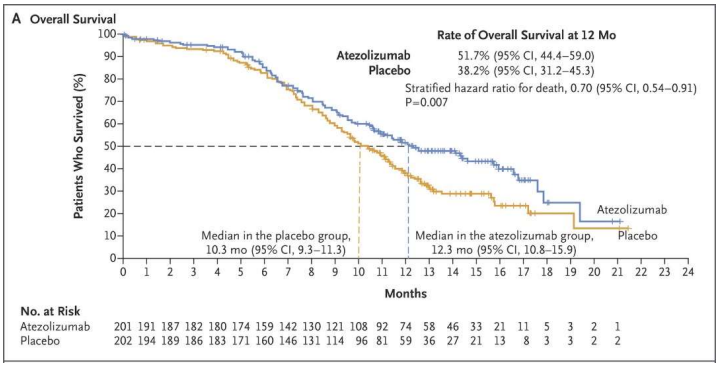
- 10-15% of lung cancers
- Almost exclusively former/current smokers
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

Approved checkpoint inhibitors in SCLC

Drug	Indication	Dose
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 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

IMpower133: Atezolizumab + chemo in 1st-line SCLC

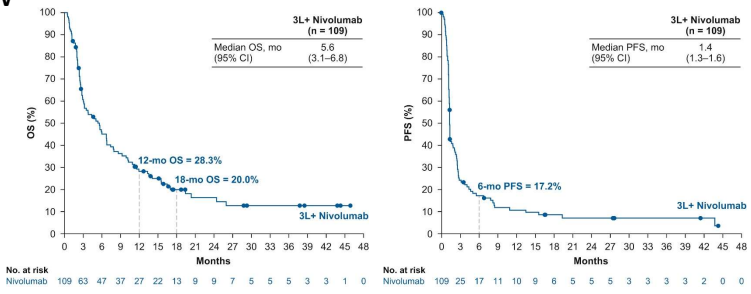
- Induction phase: four 21-day cycles of carboplatin and etoposide + atezolizumab (1200 mg once per cycle) or placebo
- Maintenance phase: either atezolizumab or placebo
- @13.9 mo:
  - mOS = 12.3 vs 10.3 mo
  - mPFS = 5.2 vs 4.3 mo



Horn, NEJM 2018.

CheckMate-032: Nivolumab in 3rd line SCLC

- Nivolumab in SCLC with progression on platinum chemotherapy and another therapy
- Nivolumab 3 mg/kg Q2W
- @28.3 months:
  - ORR: 11.9%
  - mDOR: 17.9 months

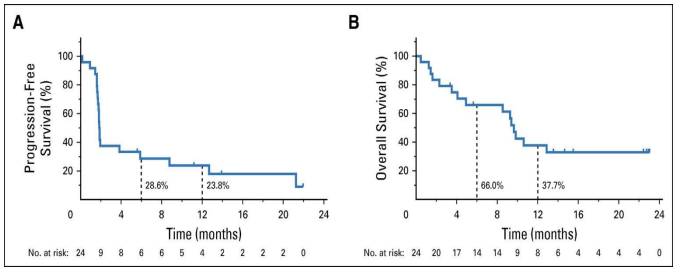


Ready, J Thorac Oncol 2019

Pembrolizumab in 3rd-line SCLC

- KEYNOTE-028: PD-L1+ only (Cohort C1)
- KEYNOTE-158: PD-L1 +/- (Cohort G)
- Combined analysis:
- ORR: 19.3%
  - 2 CR, 14 PR
  - 14/16 responders were PD-L1+
  - 9/16 responders had response ≥18 mo.
- mOS: 7.7 months

PD-L1+ (KEYNOTE-028)



Ott, J Clin Oncol 2017.

Conclusions

- New standard for advanced lung cancer is chemotherapy +ICI or an ICI as first therapy.
- For oncogenic driven tumors, treatment should be directed to the appropriate TKI, ICI can be administered in selected cases
- Patients w unresectable Stage III should receive -durvalumab as consolidation within 42 days of radiation.
- Predictive biomarkers beyond PDL1 expression are still lacking

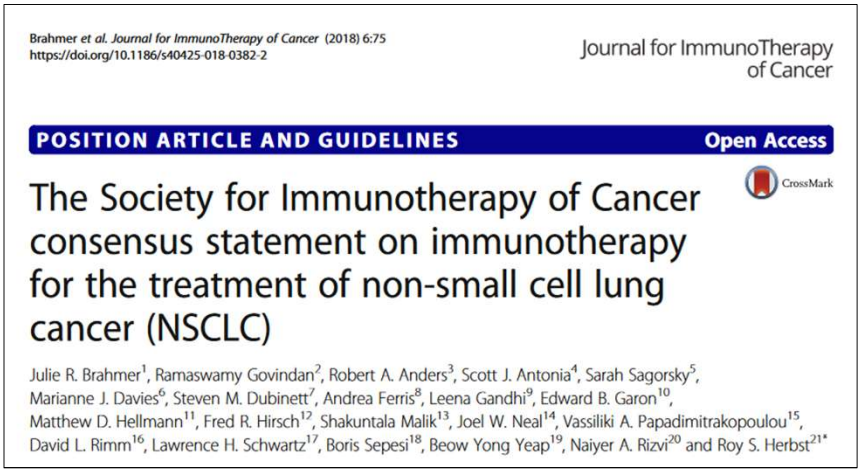
Immunotherapy for mesothelioma

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

#LearnACI

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)

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Case Studies

Case Study 1

76 year old M former heavy smoker (ECOG PS 0) presents w cough, increasing SOB. PET CT reveals Left upper lobe lung mass SUV 13 w associated bulky mediastinal adenopathy Clinical stage cT2N2M0. EBUS+ poorly diff adenocarcinoma, PDL1 expression>50%, TMB>30, EGFR/ALK/ROS wildtype

1. What is the best therapy for this patient?
   A. Single agent pembrolizumab
   B. Neoadjuvant immunotherapy followed by surgery and radiotherapy
   C. Induction carboplatin/paclitaxel followed by concurrent chemoradiotherapy followed by durvalumab
   D. Concurrent chemoradiotherapy followed by durvalumab

Case Study 1

- Patient was treated w concurrent chemoradiotherapy w carboplatin/paclitaxel followed by durvalumab.
- After 18 cycles of durvalumab, Ct scan reveals positive response in the lung but new pancreatic mass, biopsy proven metastatic adenocarcinoma of lung origin.

2. What is the best therapy for advanced lung cancer after progression on durvalumab?
   A. Single agent chemotherapy
   B. Carboplatin/pemetrexed/pembrolizumab
   C. Nivolumab/Ipilumumab
   D. Carboplatin/paclitaxel/bevacizumab/atezoluzimab

Case Study 2

58 year old woman (light smoking history) presents w 4 month history of dyspnea, non productive cough. CT scan reveals biapical lung masses, bronchial obstruction. Pt develops acute resp distress and is admitted to hospital, bronch biopsy reveals poorly diff adenocarcinoma. Staging scans + liver and bone metastases

1. What is the best first line therapy for this patient in the acute setting?
   A. Carboplatin/pemetrexed
   B. Carboplatin/pemetrexed/pembrolizumab
   C. Single agent pembrolizumab
   D. Carboplatin/paclitaxel/bevacizumab/atezoluzimab
   E. Palliative radiation until molecular mutation analysis is back

Case Study 2

- She is admitted to the hospital, intubated for resp distress. Bronchial stent is placed. She receives 2 palliative doses of radiation while inpatient. After discharge from hospital, a plasma liquid biopsy is ordered and the patient is started on carboplatin/pemetrexed
- Liquid biopsy results come back a week later with **+ EGFR L858R mutation**

1. What is the next therapy for this patient?
   - A. Continue carboplatin/pemetrexed for four cycles
   - B. Continue carboplatin/pemetrexed, but add pembrolizumab immunotherapy
   - C. Stop chemotherapy, start EGFR TKI (osimertinib)
   - D. Carboplatin/paclitaxel/bevacizumab/atezolizumab
   - E. Palliative radiation until tumor molecular mutation analysis is back

Case Study 2

Chemotherapy is stopped and she is started on osimertinib TKI. Breathing improved.

MRI brain reveals 3 isolated subcentimeter brain metastases (2-4mm in L frontal lobe). Pt is asymptomatic.

3. What is the next best management strategy for her brain metastases?
   - A. Whole brain radiation
   - B. Continuation of osimertinib, without radiation and close monitoring
   - C. SBRT to isolated brain metastases
   - D. Change to osimertinib and bevacizumab.