Updates in Lung Cancer Treatments

2019

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COMPREHENSIVE CANCER CENTER

Disclosures

- No significant financial interests to disclose
- No significant general and obligation interests to disclose
- I will be discussing non-FDA approved indications during my presentation.

Question 1: What is your preference for molecular testing in newly diagnosed metastatic NSCLC?

1. Broad panel testing (including genes without FDA approved therapies) in **ALL** adenocarcinoma cases
2. Limited testing only for mutation targets with FDA approved therapies (EGFR, ALK, ROS1, BRAF) in **ALL** adenocarcinoma cases
3. Broad panel testing (including genes without FDA approved therapies) only in **non-smokers**
4. Limited testing only for mutation targets with FDA approved therapies (EGFR, ALK, ROS1, BRAF) only in **non-smokers**

Question 2: What is your preferred treatment for first-line therapy in treatment naïve metastatic non-squamous NSCLC patients without EGFR or ALK mutations with PD-L1 between 1-50% and no history of autoimmune disease?

1. Pembrolizumab monotherapy
2. Platinum+pemetrexed+pembrolizumab
3. Atezolizumab/bevacizumab/paclitaxel/carboplatin

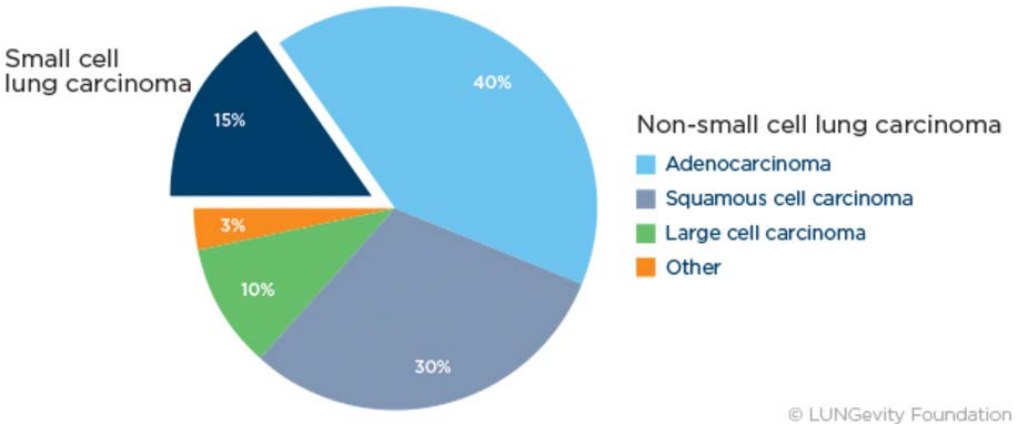
Lung Cancer

Estimated Deaths

Male		
Lung & bronchus	76,650	24%
Prostate	31,620	10%
Colon & rectum	27,640	9%
Pancreas	23,800	7%
Liver & intrahepatic bile duct	21,600	7%
Leukemia	13,150	4%
Esophagus	13,020	4%
Urinary bladder	12,870	4%
Non-Hodgkin lymphoma	11,510	4%
Brain & other nervous system	9,910	3%
All sites	**321,670**	

Female		
Lung & bronchus	66,020	23%
Breast	41,760	15%
Colon & rectum	23,380	8%
Pancreas	21,950	8%
Ovary	13,980	5%
Uterine corpus	12,160	4%
Liver & intrahepatic bile duct	10,180	4%
Leukemia	9,690	3%
Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	7,850	3%
All sites	**285,210**	

Types of Lung Cancer by Histology



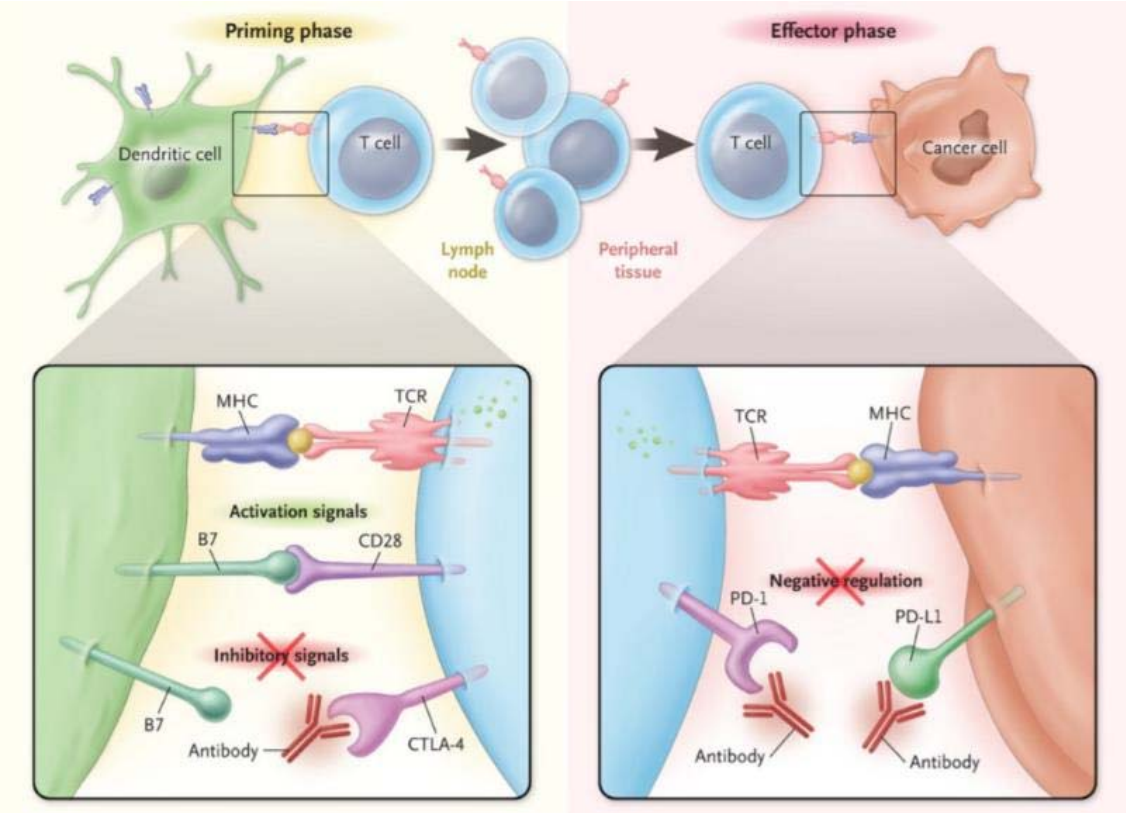
American Cancer Society, 2019

Outline

- Immunotherapy Treatment Updates
  - NSCLC
  - SCLC
- Molecular Targeted Treatment Updates
  - ROS1/NTRK
  - ALK
  - RET
  - KRAS G12C

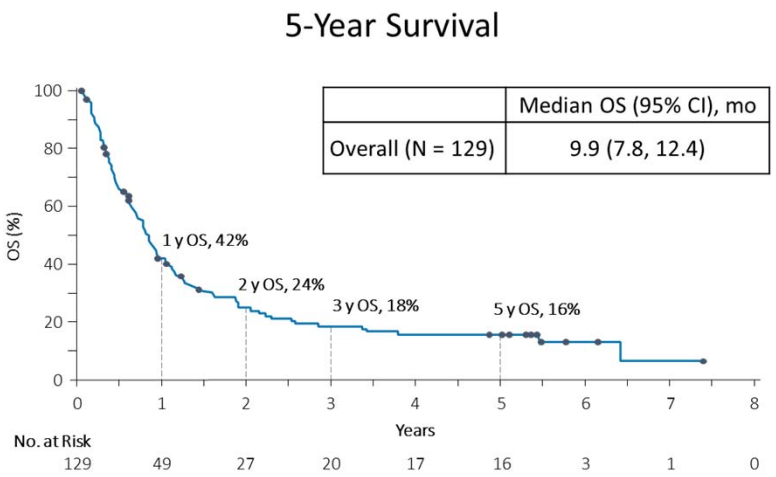
Immune Checkpoint Inhibitors

- **Immune Checkpoint Inhibitors** – Releasing the immune "brakes"
- T cell responses are regulated through a complex balance of inhibitory ("checkpoints" and activating signals
- PD-L1 (also known as B7-H1) expression in cancer cells promote tumor progression by inhibition of PD-1 expressing immune effector cells



Long term survival with Checkpoint Inhibitors

Historical rate of ~5% (per SEER 2008–2014) for advanced NSCLC prior to Immunotherapy



OS by PD-L1 TPS.

	n	Median OS (95% CI), mo	36-mo OS rate, %	60-mo OS rate, %
Treatment-naive	101*	22.3 (17.1–32.3)	37.0	23.2
- TPS ≥50%	27	35.4 (20.3–63.5)	48.1	29.6
- TPS 1%–49%	52	19.5 (10.7–26.3)	27.5	15.7
Previously treated	449†	10.5 (8.6–13.2)	20.9	15.5
- TPS ≥50%	138	15.4 (10.6–18.8)	30.4	25.0
- TPS 1%–49%	168	8.5 (6.0–12.6)	16.9	12.6
- TPS <1%	90	8.6 (5.5–10.6)	11.1	3.5

CA209-003: Nivolumab in phase I heavily pre-treated NSCLC patients

5-yr OS update (Gettinger et al. JCO 2018)

5-yr OS (n=129): 16%

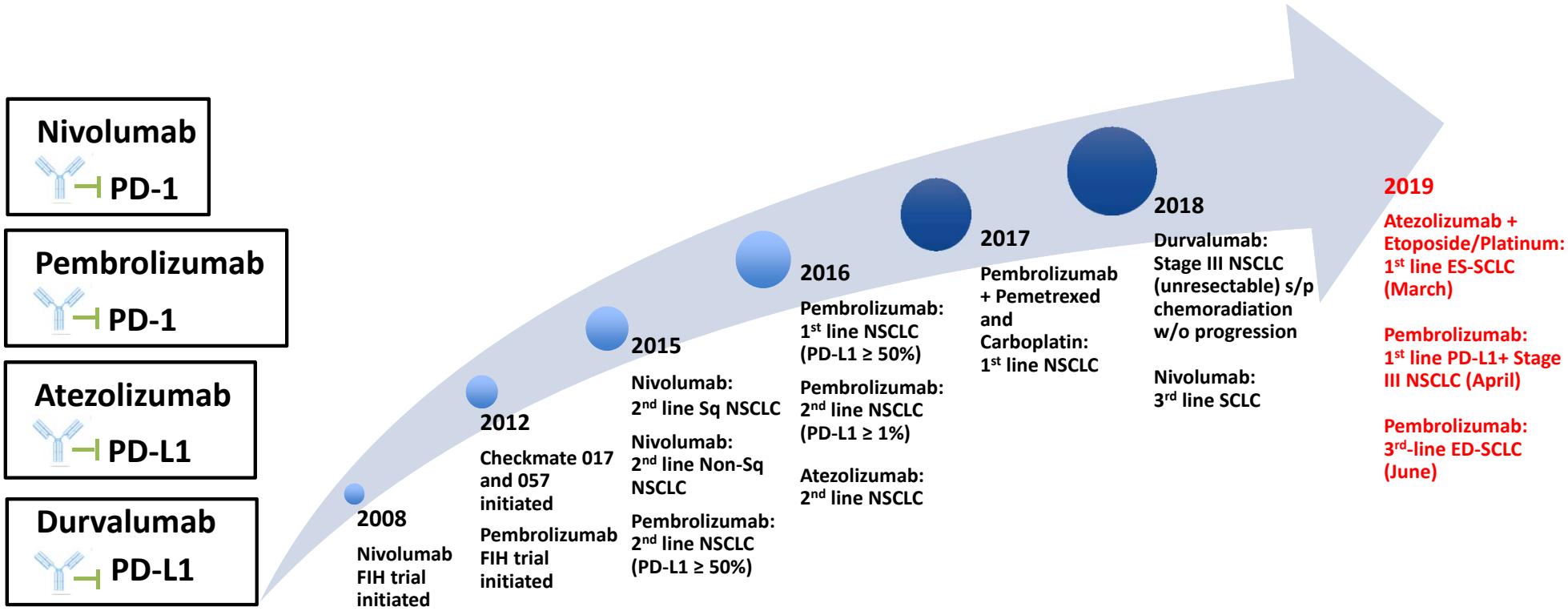
KEYNOTE-001: Pembrolizumab Phase Ib study

5-yr OS update (Garon et al. ASCO 2019)

5-yr OS in treatment naïve (n=101): 23.2%
5-yr OS in previously treated (n=449): 15.5%

Gettinger et al. JCO 2018. Garon et al. ASCO 2019

FDA approved Checkpoint Inhibitors in Lung Cancer

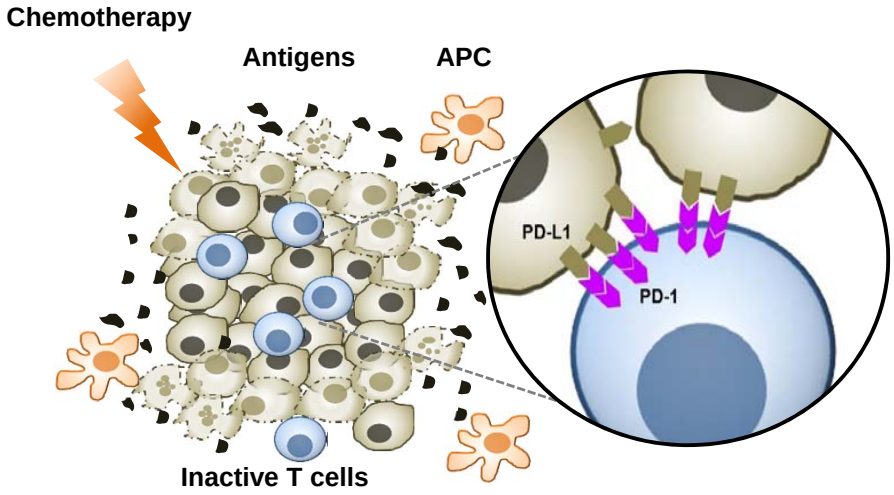


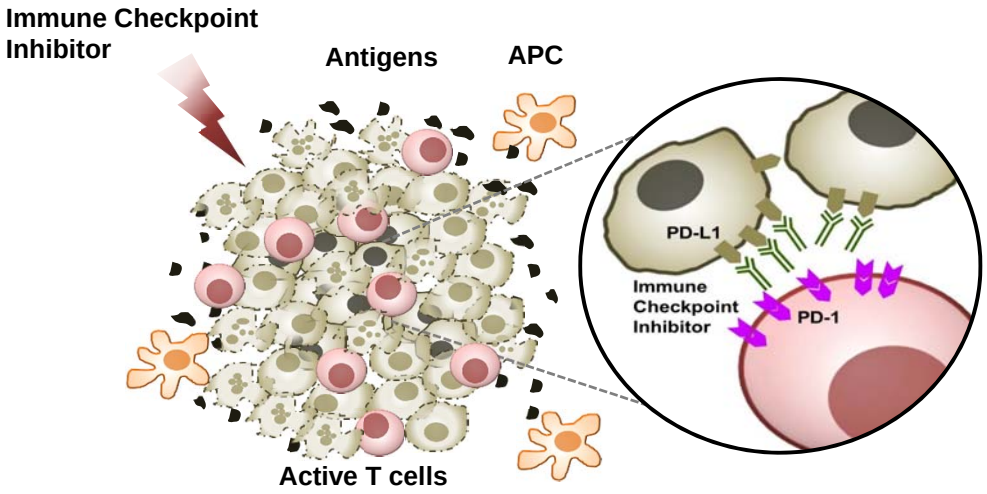
First Line Immunotherapy Options for NSCLC

- **KEYNOTE 024** – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 50%
- **KEYNOTE 042** – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 1%
- **KEYNOTE 189** – Pembrolizumab + Platinum/Pemetrexed vs. Chemotherapy alone in advanced non-squamous NSCLC
- **IMPOWER 150** – Atezolizumab + Carbo/Paclitaxal (+Bev) vs. Chemotherapy (+Bev) in advanced non-squamous NSCLC
- **KEYNOTE 407** – Pembrolizumab + Carbo/(nab) Paclitaxol vs. Chemotherapy in advanced squamous cell lung cancer

Chemotherapy-IO combinations

- Chemotherapy induces immunogenic cell death and modulate immunogenicity of tumor cells
  - enhancing tumor antigen presentation, upregulating of co-stimulatory molecule but down-regulation of co-inhibitory molecule, T cell activation, and reducing MDSC/Tregs in TME
- PD-1/PD-L1 inhibition restores tumor specific T cell immunity and reversal of immune suppression leads to deeper and more durable antitumor response

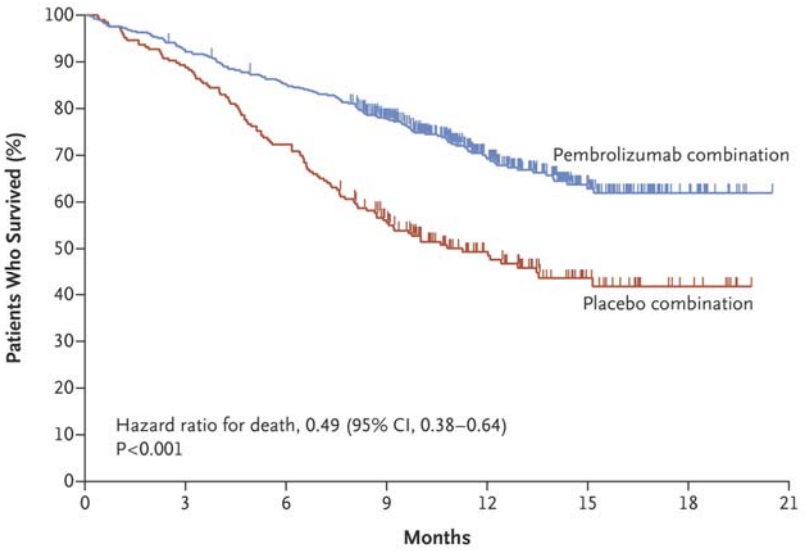




Adapted from WCLC 2019 presentation by Myung-Ju Ahn, Modified from Shafique et al Expert Opin Biol Ther 2019;19:225

First Line ChemoImmunotherapy Options for Non-Squamous NSCLC

KEYNOTE-189



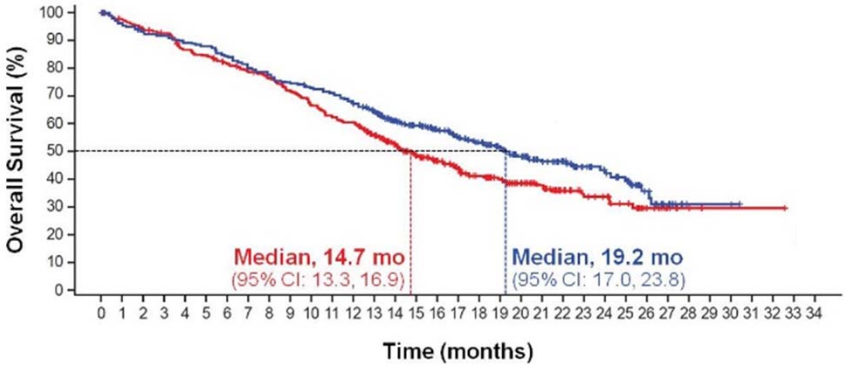
2019 ASCO OS update (Gadgeel et al.)

Pembro+Platinum/Pemetrexed **median OS 22 months vs. 10.7 months** with Chemo alone (HR 0.56, p<0.0001)

IMPower 150

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



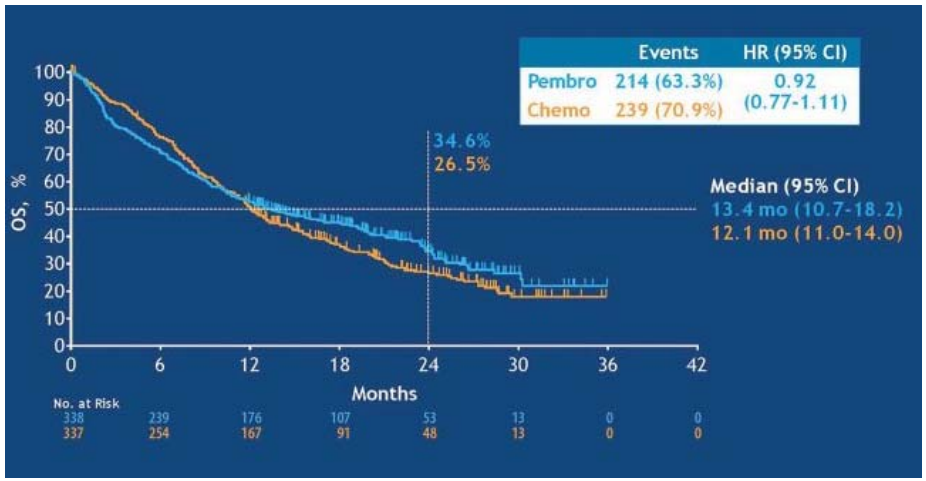
2019 ASCO OS update (Socinski et al.)

Improved PFS and OS in patients with **baseline liver mets mOS 13.3 mo vs. 9.4mo** (HR 0.52, 95% CI, 0.33-0.82).
8.9mo OS for Atezo+chemo without Bev

Ghandi et al, NEJM 2018 Socinski et al, NEJM 2018

KEYNOTE 042 – Pembrolizumab in PD-L1 ≥1%

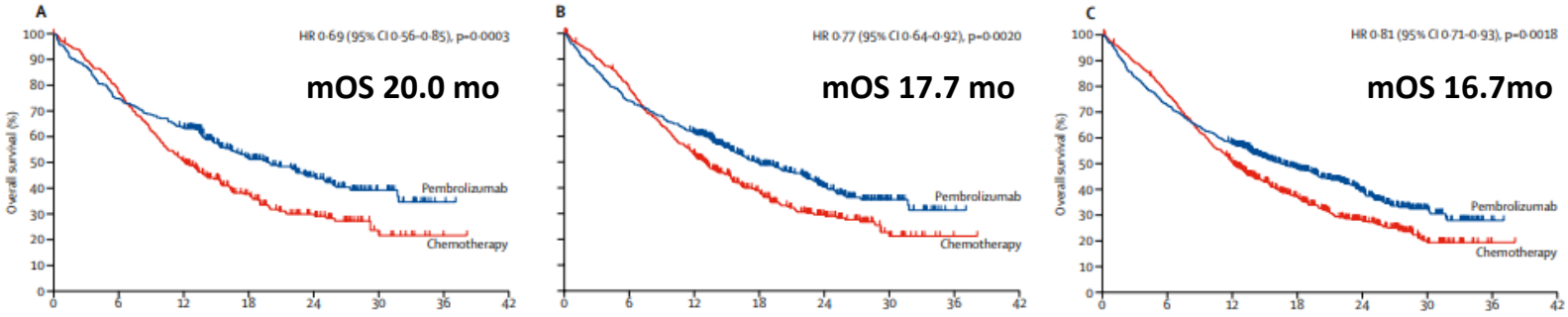
Overall Survival TPS ≥ 1-49%



Grade 3-5 AE	
Pembro	Chemo
18%	41%

Immune AE	
Pembro	Chemo
8%	1%

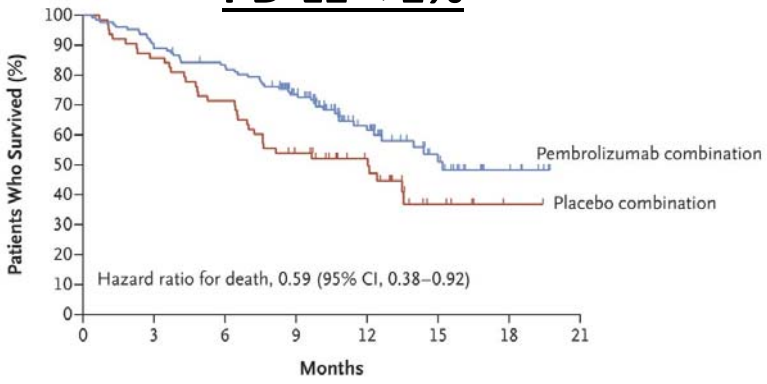
Overall Survival: **TPS ≥ 50%** **TPS ≥ 20%** **TPS ≥ 1%**



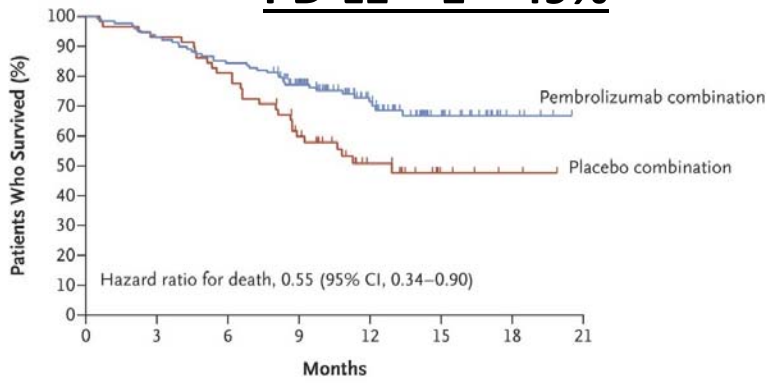
Mok et al. Lancet 2019

KEYNOTE 189 – OS by PD-L1 TPS

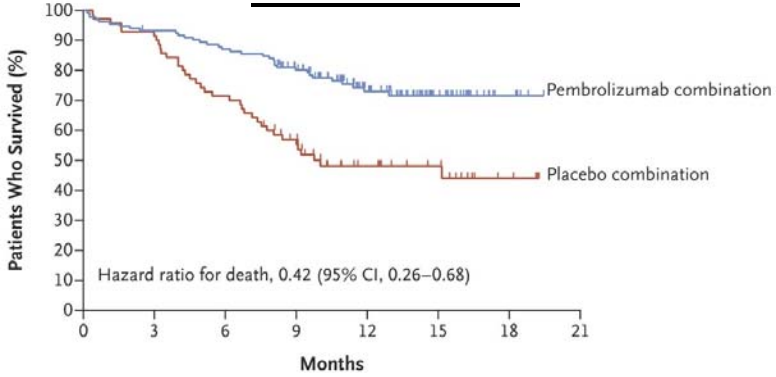
PD-L1 < 1%



PD-L1 = 1 – 49%



PD-L1 ≥ 50%



Ghandi et al. NEJM 2018

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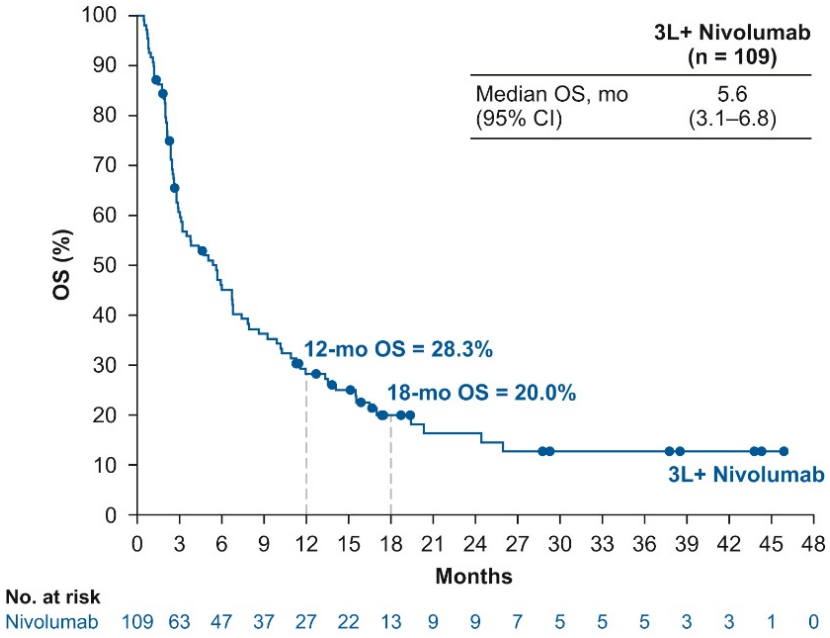
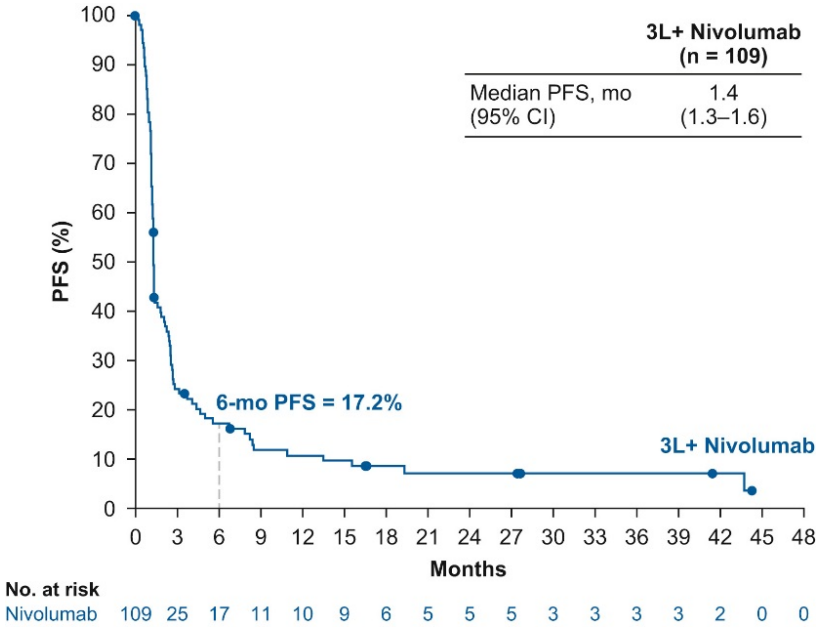
Approved Checkpoint Inhibitors in SCLC

Drug	Approved	Indication	Dose
Nivolumab	2018	Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy (**3rd line**)	240 mg Q2W
Atezolizumab + Carboplatin + Etoposide	2019	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
Pembrolizumab	2019	Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy (**3rd line**)	200 mg Q3W

- **ICI did not improve OS/PFS as Second-line in SCLC**
- **Maintenance ICI in ES SCLC did not improve survival**

CheckMate-032 – Nivolumab in 3rd Line SCLC





ORR: 11.9%

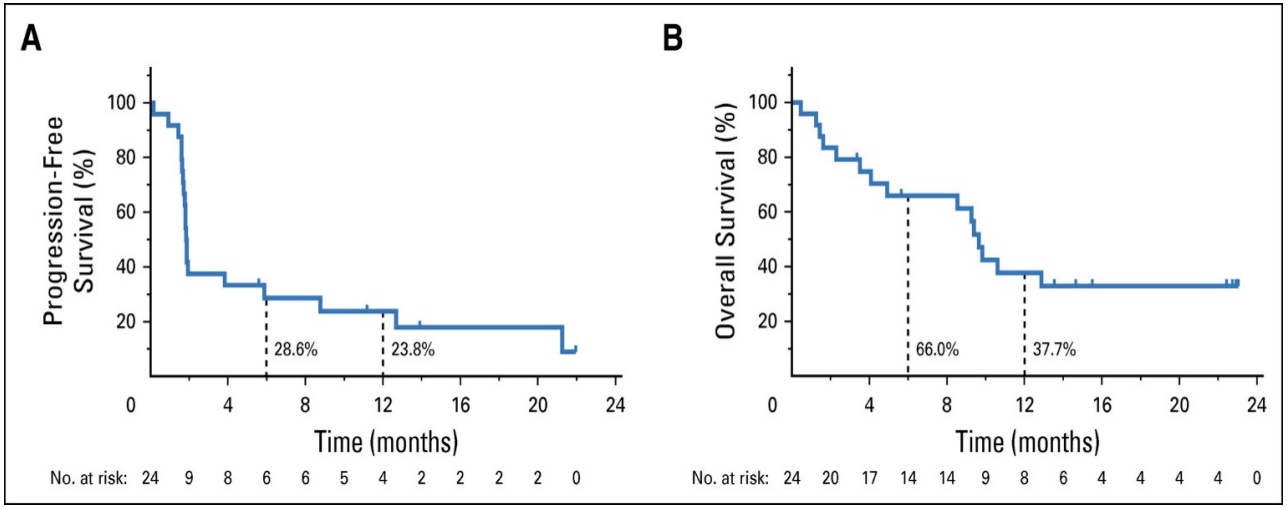
Median DOR: 17.9 mo (Range 3.0m-42.1mo)

Ready, J Thorac Oncol 2019

Pembrolizumab in 3rd Line SCLC

(KEYNOTE-028 PD-L1+ & KEYNOTE-158 PD-L1+/- combined analysis)

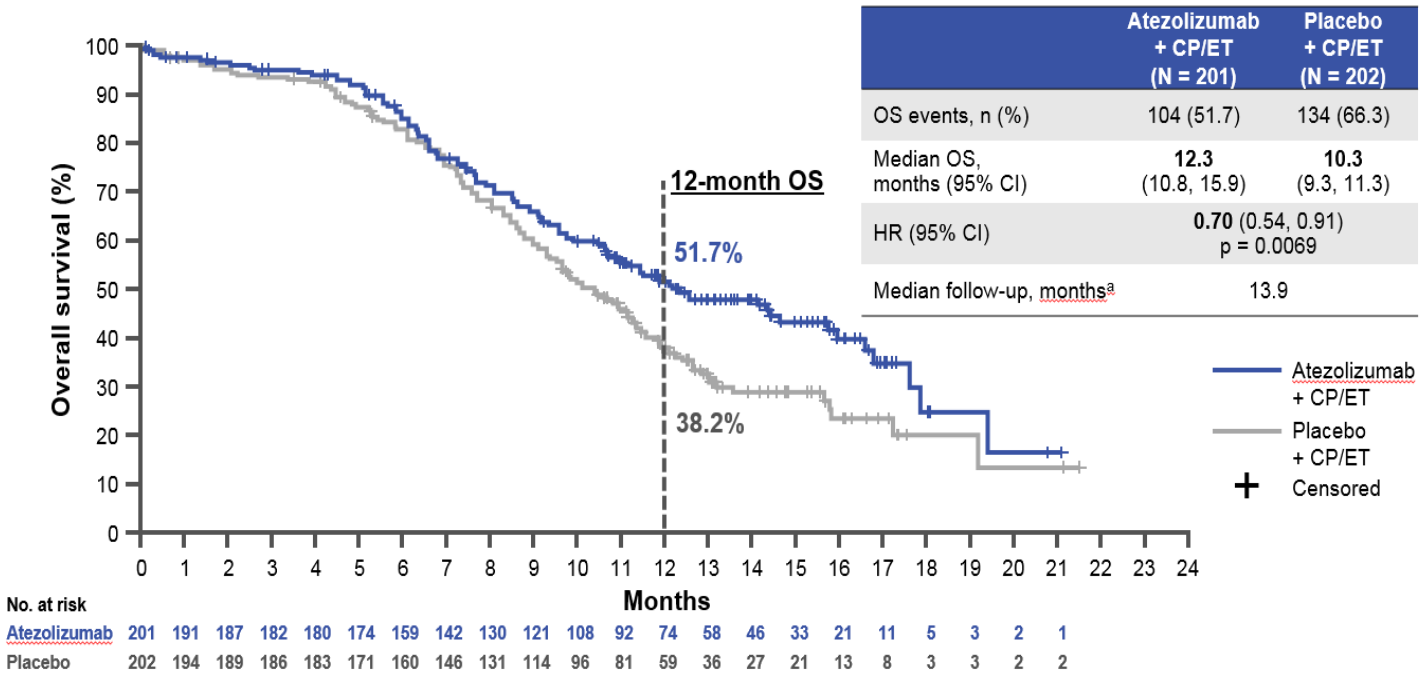
PD-L1+ (KEYNOTE-028)



ORR: 19.3% (33.3% in PD-L1+)
14/16 Responders PD-L1+
mOS: 7.7mo (9.7 in PD-L1+)

Ott, J Clin Oncol 2017.

IMPower 133
Atezolizumab + Carbo/Etoposide in ES-SCLC



	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

Horn L et al NEJM 2018

CASPIAN
Durvalumab + EP in ES-SCLC

- Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1

N=805 (randomised)

1:1:1

R

Stratified by planned platinum agent (carboplatin vs cisplatin)

Durvalumab + EP*
Durvalumab 1500 mg + EP q3w for up to 4 cycles

→ **Durvalumab**
1500 mg q4w until disease progression

EP*
q3w for up to 6 cycles‡

→ **Optional PCI‡**

Durvalumab + tremelimumab + EP*
Durvalumab 1500 mg + tremelimumab 75 mg + EP q3w for up to 4 cycles

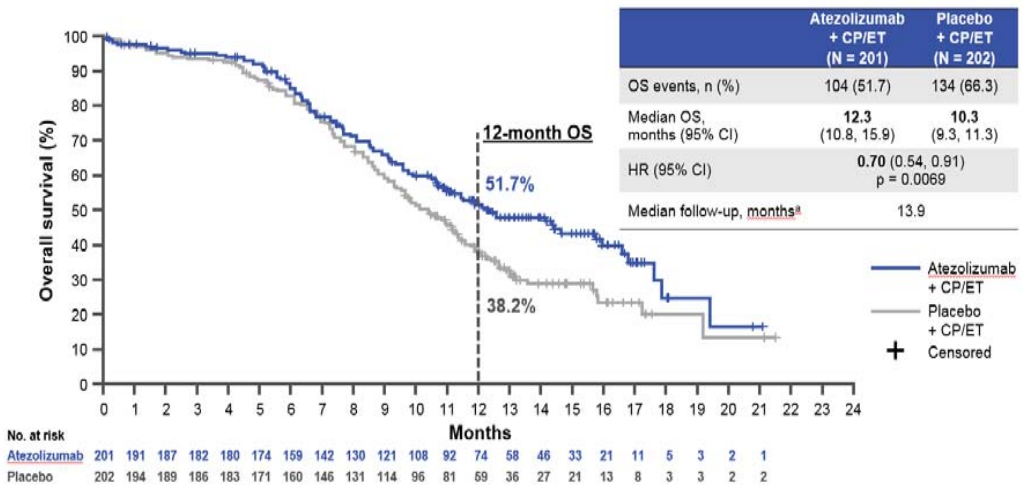
→ **Durvalumab†**
1500 mg q4w until disease progression

Primary endpoint
- OS

Secondary endpoints
- PFS
- ORR
- Safety & tolerability
- Health-related QoL

Following preplanned interim analysis by the IDMC, the durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

CASPIAN
Durvalumab + EP in ES-SCLC



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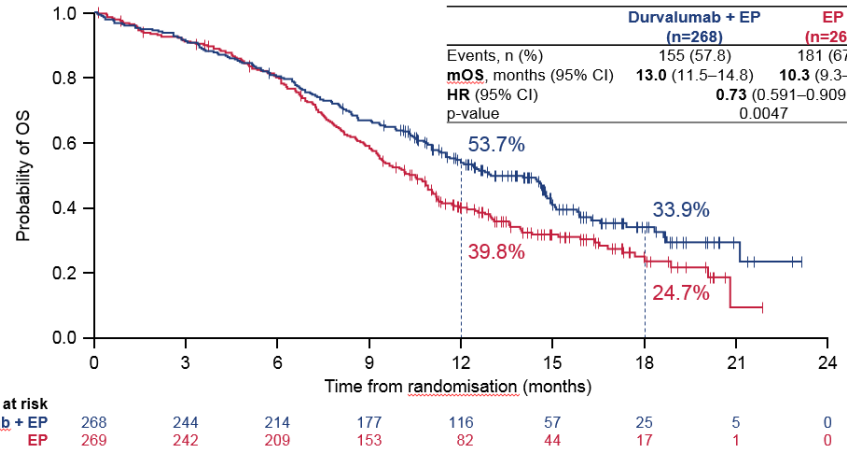
Overall Survival (Primary Endpoint)



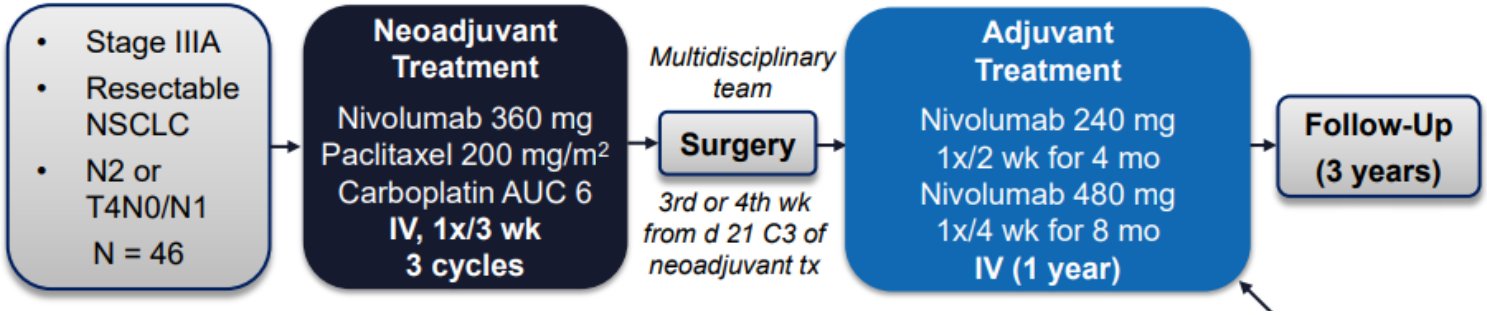
	Durvalumab + EP (n=268)	EP (n=269)
Events, n (%)	155 (57.8)	181 (67.3)
mOS, months (95% CI)	**13.0** (11.5–14.8)	**10.3** (9.3–11.2)
HR (95% CI)	**0.73** (0.591–0.909)	
p-value	0.0047	

CASPIAN and IMPower 133

	CASPIAN		IMpower 133	
	Durvalumab+EP (n=268)	EP (n=269)	Atezolizumab +EC (n= 201)	EC + placebo (n=202)
OS,m	13.0	10.3	12.3	10.3
	HR=0.73		HR=0.7	
OS at 12m,%	53.7	39.8	51.7	38.2
PFS, m	5.1	5.4	5.2	4.3
	HR=0.78		HR=0.77	
ORR, %	67.9	57.6	60.2	64.4
DOR, m	5.1	5.1	4.2	3.9
G 3/4 AEs	61.5	62.4	67.2	63.8
irAE	19.6	2.6	39.9	24.5

Neoadjuvant Immunotherapy – NADIM study

Chemo-immunotherapy for stage IIIA resectable NSCLC: single-arm, open label, multicenter phase 2 study



Pathologic response	N=41	% (CI 95%)
Major Pathological Response (MPR)	34/41	83 (68-93)
Complete Response (CR)	24/41	59 (42-74)
> 10% residual viable tumor	7/41	17 (7-32)

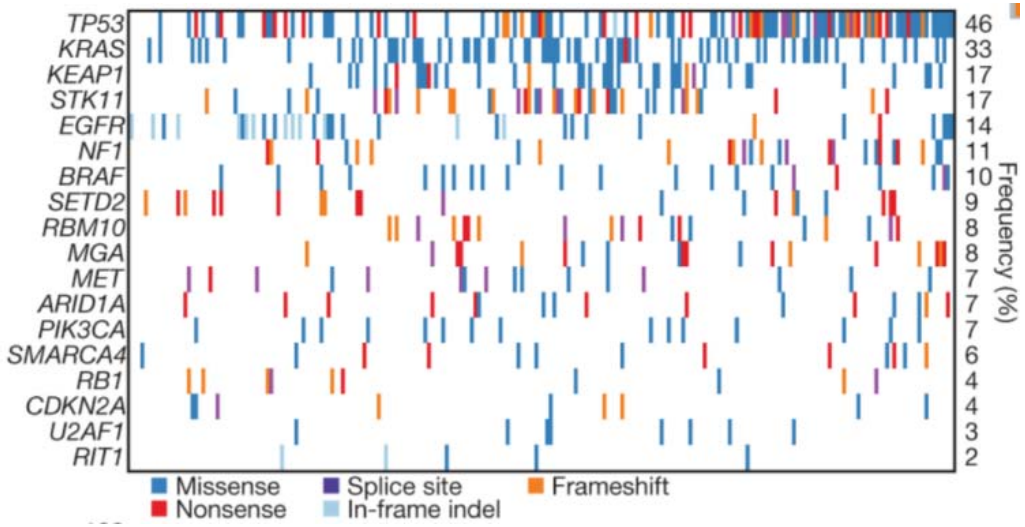
Disease progression:
1 CR
3 < MPR
2 no surgery

Pathologic response in ITT	N=46	% (CI 95%)
Major Pathological Response (MPR)	34/46	74 (60-85)
Complete Response (CR)	24/46	52 (38-66)

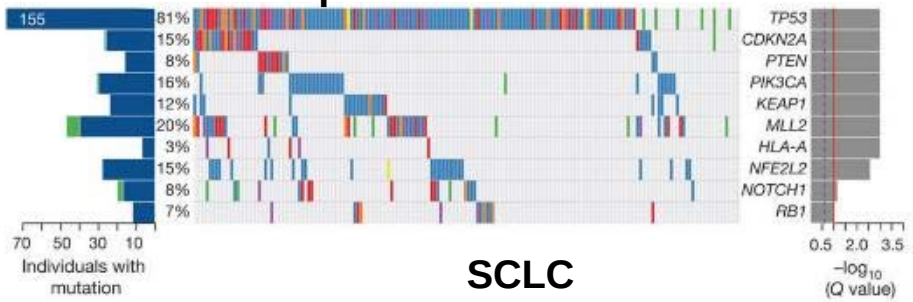
12m PFS: 96%
18m PFS: 81%

Molecular Targeted Therapy

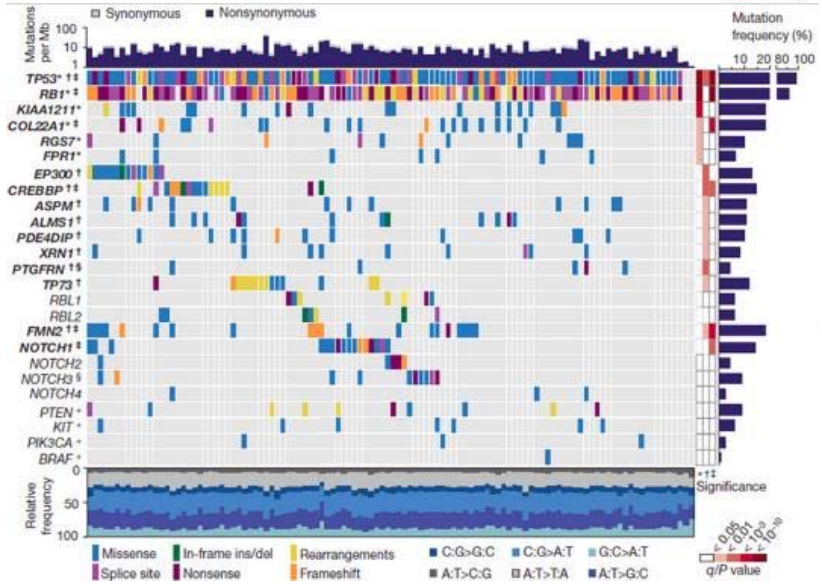
Adenocarcinoma NSCLC



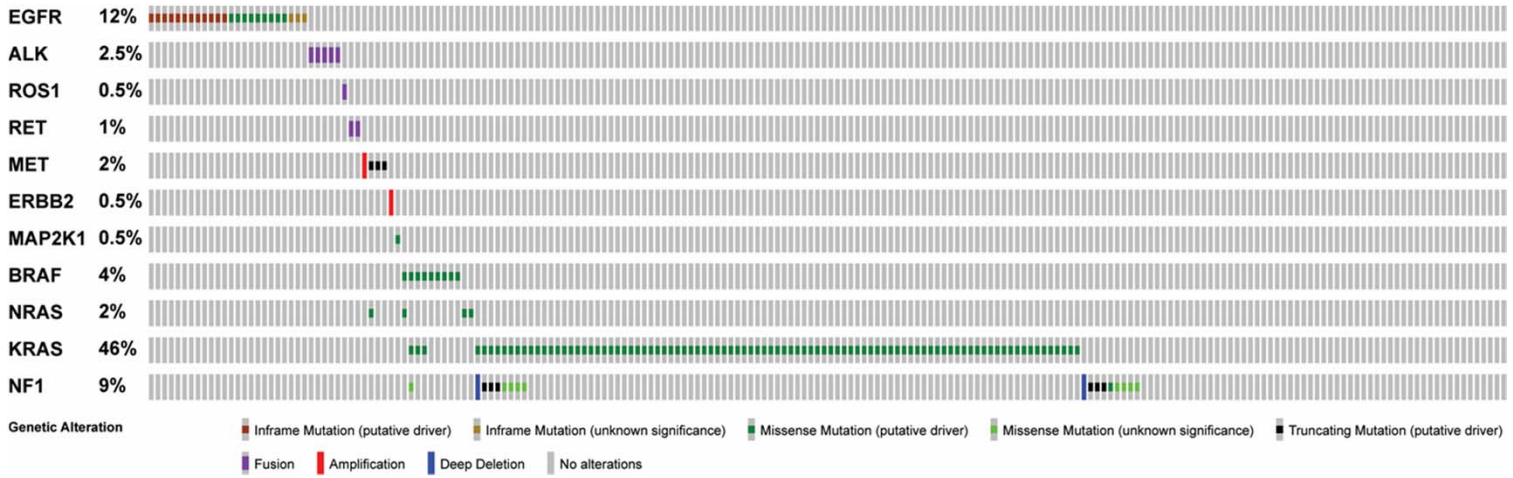
Squamous Cell NSCLC



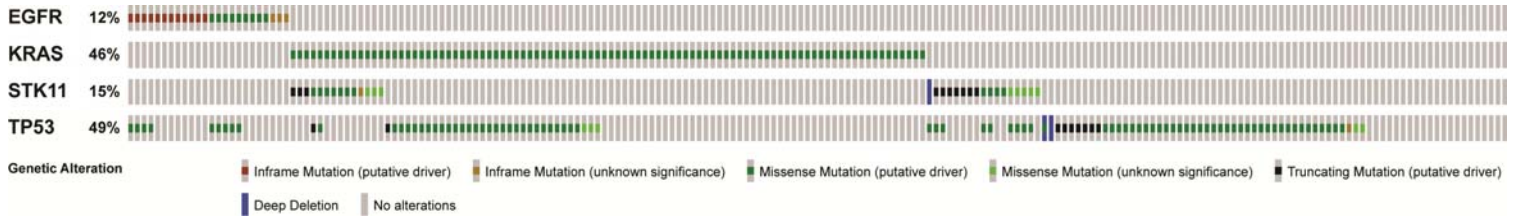
SCLC



Mutational Landscape Non-Squamous NSCLC



Mutually Exclusive MAPK Alterations



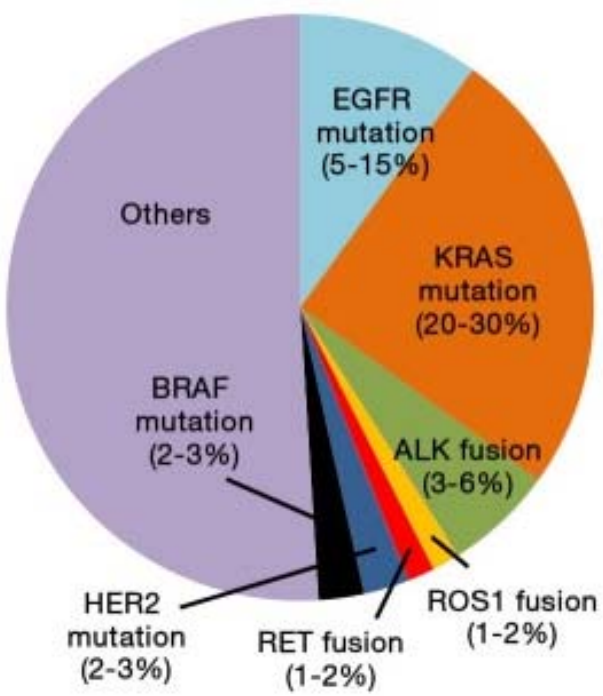
Tumor Suppressors

Recent FDA Approved Targeted NSCLC Therapies

- Jan 2018 – First line **afatinib** for EGFR+ metastatic NSCLC
- Apr 2018 – First line **osimertinib** for EGFR+ metastatic NSCLC
- Sept 2018 – First line **dacomitinib** for EGFR+ metastatic NSCLC
- Nov 2018 – second/third line **lorlatinib** in ALK+ metastatic NSCLC
- Nov 2018 – **latrotrectinib** in NTRK+ solid tumors (including NSCLC)
- Aug 2019 – **entrectinib** for NTRK+ solid tumors or ROS1+ metastatic NSCLC

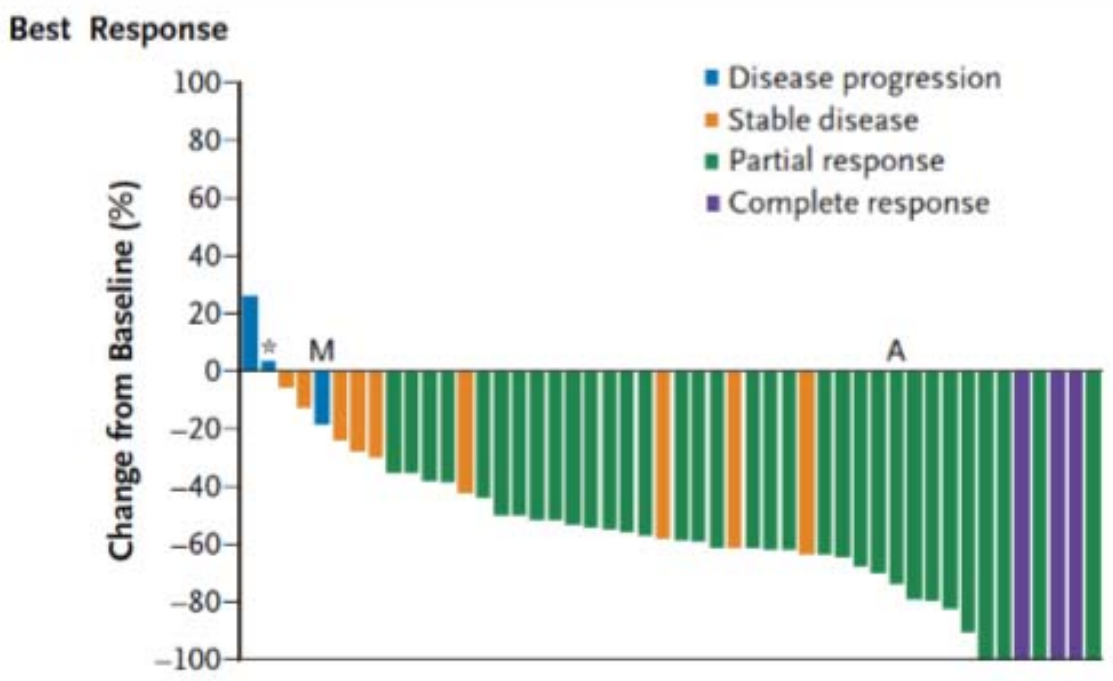
Osimertinib in EGFR+ NSCLC

RET and ROS1 Fusions in NSCLC



Kohno et al. Transl Lung Cancer Res. 2015

Crizotinib in ROS1+ NSCLC

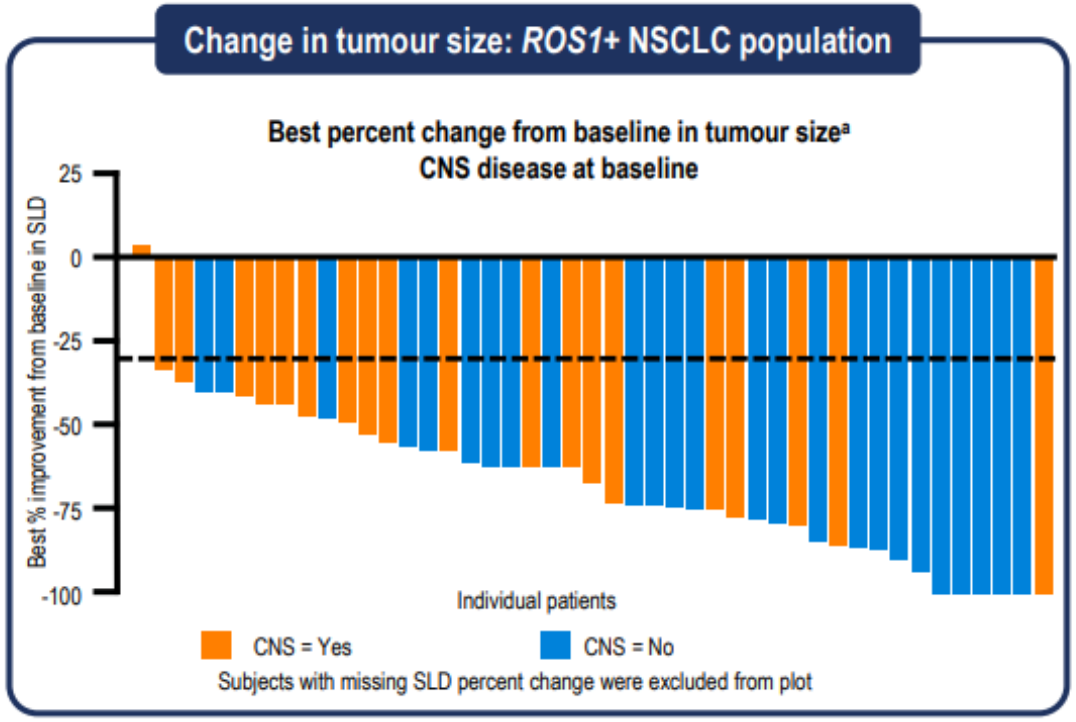


ORR: 72%
mPFS: 19.2 months

47% of patients progressing on Crizotinib have CNS progression

Shaw et al. NEJM 2014

Entrectinib in first-line ROS1+ NSCLC



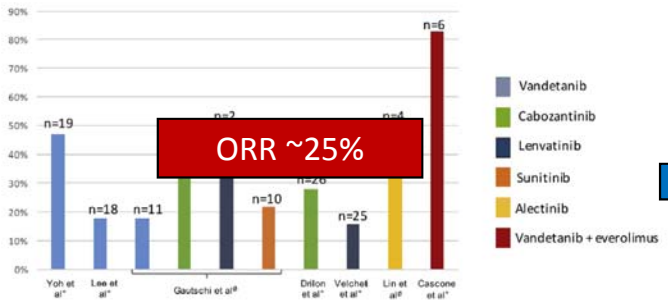
n (%)	Total (n=53)	CNS disease present at baseline† (n=23)	CNS disease absent at baseline† (n=30)
ORR[b‡] (95% CI)	**41 (77.4)** (63.8, 87.7)	**17 (73.9)** (51.6, 89.8)	**24 (80.0)** (61.4, 92.3)
CR	3 (5.7)	0	3 (10.0)
Median DoR,‡ months (95% CI)	**24.6** (11.4, 34.8)	**12.6** (6.5, NE)	**24.6** (11.4, 34.8)
Median PFS,‡ months (95% CI)	**19.0** (12.2, 36.6)	**13.6** (4.5, NE)	**26.3** (15.7, 36.6)
Median OS, months (95% CI)	NE (NE, NE)	–	–
Clinical benefit rate* (95% CI)	41 (77.4) (63.8, 87.7)	–	–

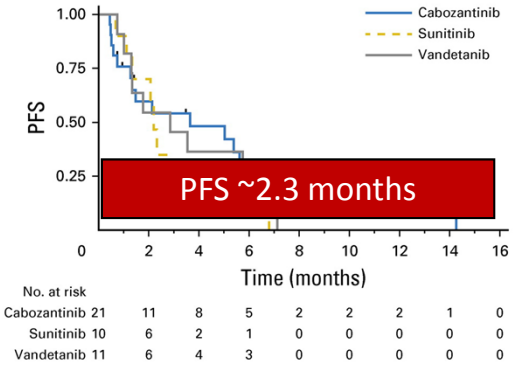
mPFS: 19.0 months

CNS ORR: 55%, CNS media DoR 12.9mo

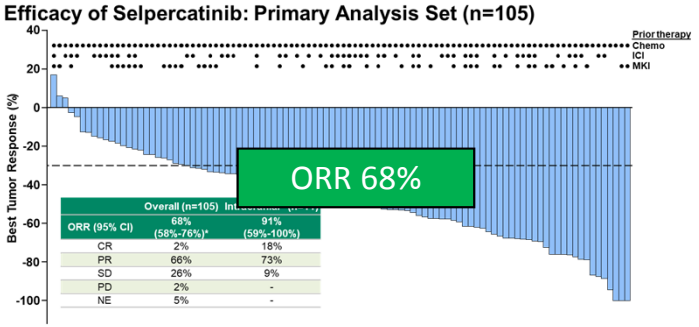
Selective RET inhibitors

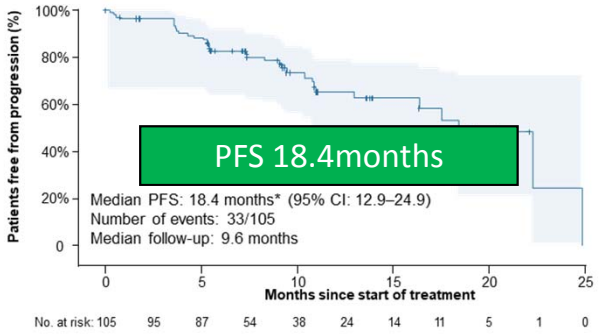
Multi-kinase Inhibitors





Selpercatinib



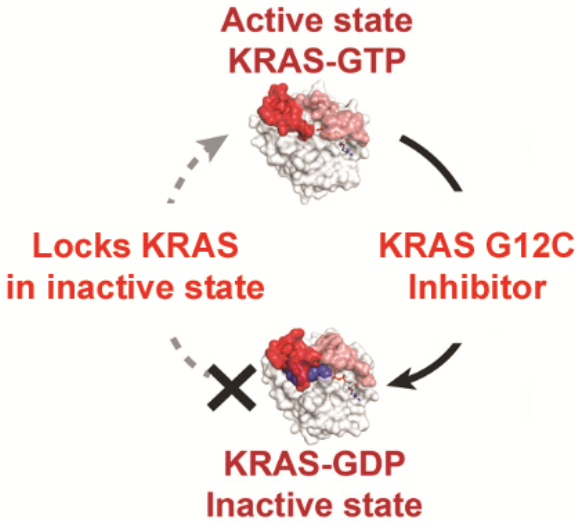


[1]Ferrara et al., JTO 2017; [2]Gautschi et al., JCO 2017,Adapted from Doebele WCLC 2019

Selective RET inhibitors

	selpercatinib[1]	pralsetinib[2]
ORR in naïve	85% (69-95)	71% (NA)
ORR in chemo-pretreated	68% (58-76)	60% (42-76)
PFS	18.4	NR
DoR	20.3	NR
Intracranial activity	91 (59-100)%	78 (NA)%
Safety (G3%)*		
HTN	14%	13%
Transaminitis	6-7%	3%
Anemia, Neutropenia	NA	7%, 13%
Drug discontinuation rate	1.7%	7%
Activity against MTC RET mutations	Yes	Yes
Tumor agnostic RET fusion activity	Yes	Yes

[1]Drilon et al., WCLC 2019; [2]Gainor et al., ASCO 2019, Adapted from Doebele WCLC 2019

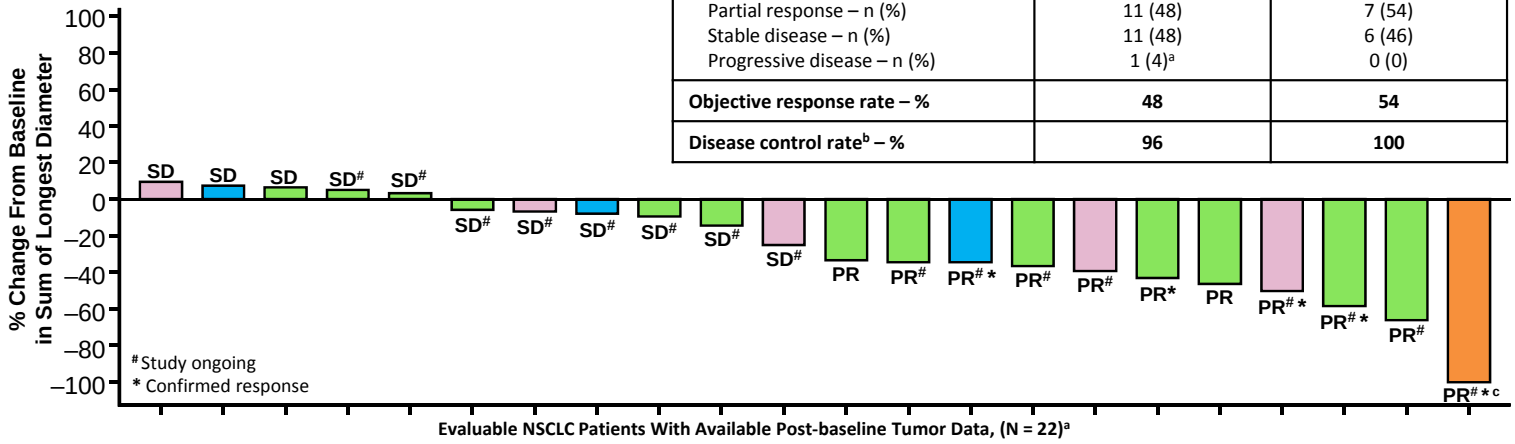


KRAS G12C Inhibitors

Irreversible Covalent inhibitors of KRAS G12C that lock oncogenic KRAS in inactive GDP bound state in clinical development

AMG 510 first in human study demonstrating promising activity

Efficacy outcomes	All evaluable patients N = 23	Evaluable patients treated with 960mg N = 13
Best overall response		
Partial response – n (%)	11 (48)	7 (54)
Stable disease – n (%)	11 (48)	6 (46)
Progressive disease – n (%)	1 (4)[a]	0 (0)
Objective response rate – %	**48**	**54**
Disease control rate[b] – %	**96**	**100**



Question 3: For a small-cell lung cancer patient who has progressed on platinum and one other therapy, which of the following is NOT an FDA-approved treatment option?

1. Atezolizumab/carboplatin/etoposide
2. Nivolumab
3. Pembrolizumab
4. Topotecan

Thank You

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