Lung Cancer Immunotherapy

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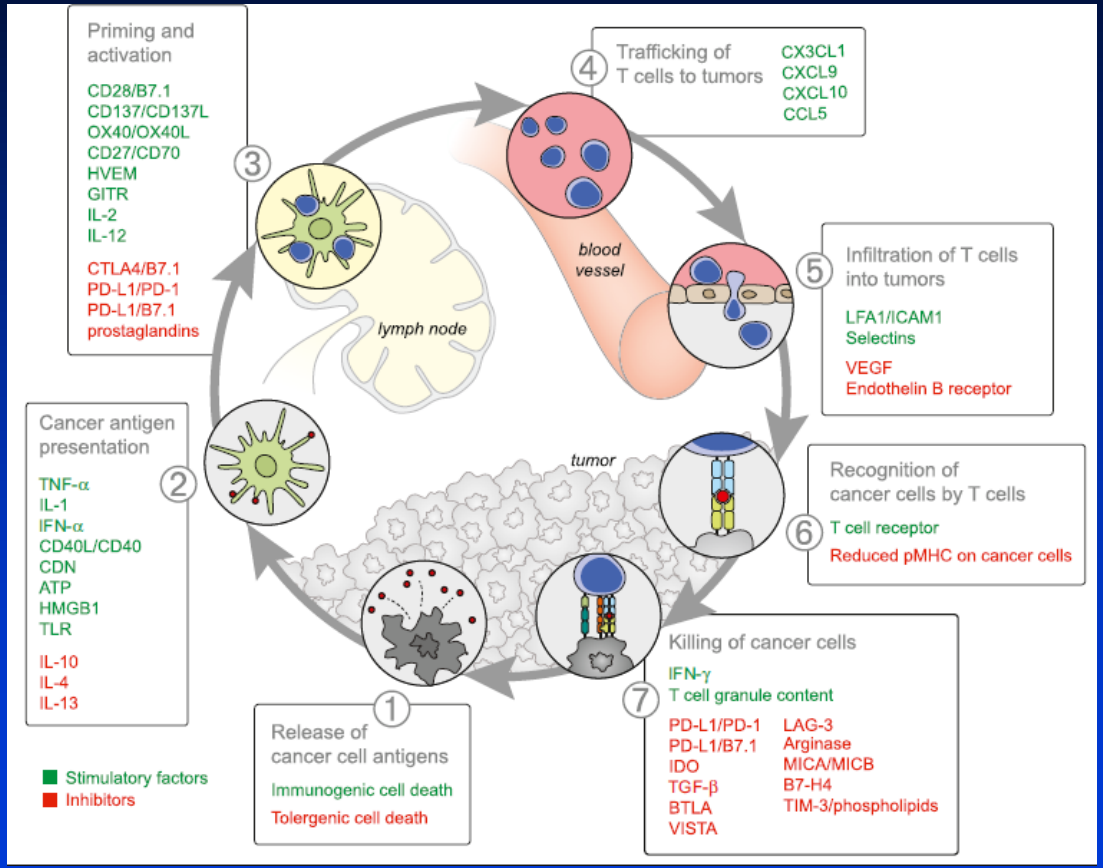
Conflict of Interest

- Honoraria for Advisory Board/Consulting
  - AstraZeneca
  - Boehringer Ingelheim
  - Eli Lilly
  - Pfizer
  - Roche
- Speaker‘s fee
  - AstraZeneca
  - Boehringer Ingelheim
- Data Safety Monitoring Board
  - Merck Sharp Dohme
  - Genmab
  - Regeneron

The Cancer-Immunity Cycle

Shen DS e& Mellman I. Immunity 2013, 39, 1



Immune checkpoint inhibitors in lung cancer

Helissey C et al. Curr Opin Oncol 2015, 27, 108

Anti-CTLA4	Anti-PD-1	Anti-PD-L1
Ipilimumab (Yervoy®)	Nivolumab (Opdivo®)	Atezolizumab (Tecentriq®)
Tremelimumab	Pembrolizumab (Keytruda®)	Durvalumab (Imfinzi®)
		Avelumab (Bavencio™)

Clinical development

Pre-treated patients	First-line therapy	Biomarkers
Single agents Combinations	Single agents Combined with platin-based CT Other combinations	PD-L1 expression; tumor mutational burden; others

Immune checkpoint inhibitors in pretreated patients with advanced NSCLC: phase 3 trials

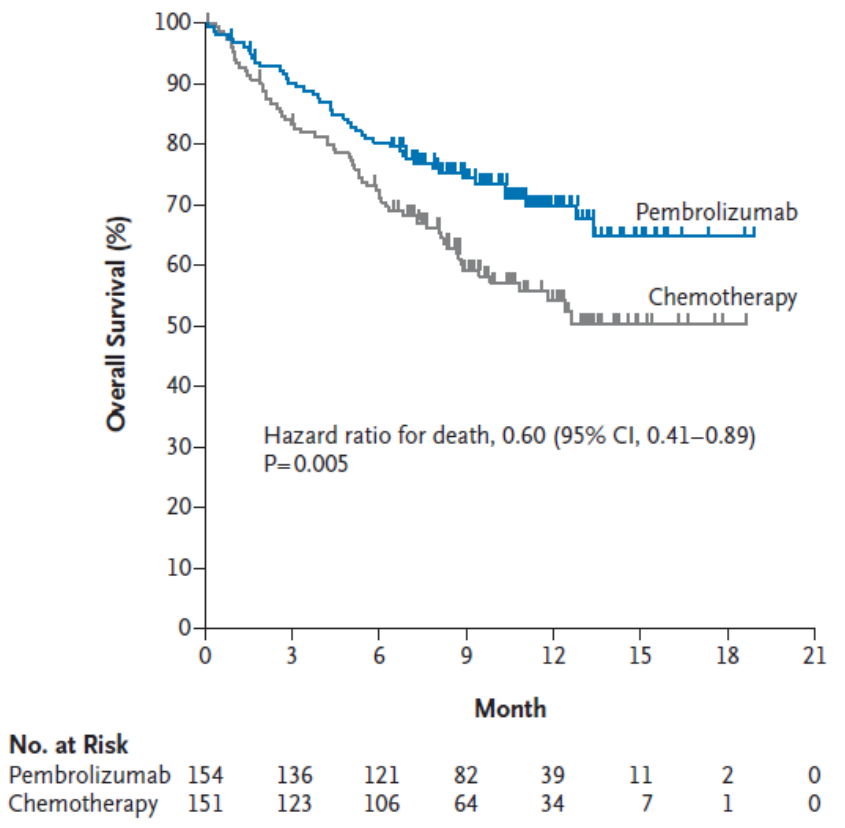
Trial	Drug	Histology / Biomarker	Survival Hazard ratio	Reference
CheckMate 017	Nivolumab *versus* docetaxel	Squamous	0.59 (0.44-0.79)	*Brahmer J et al. NEJM 2015, 373, 123*
CheckMate 057	Nivolumab *versus* docetaxel	Non-squamous	0.73 (0.59-0.89)	*Borghaei H et al. NEJM 2015, 373, 1627*
KEYNOTE-010	Pembrolizumab *versus* docetaxel	NSCLC PD-L1 ≥1%	*0.67 (0.56-0.80)* (pooled analysis)	*Herbst R et al. Lancet 2016, 387, 1540*
OAK	Atezolizumab *versus* docetaxel	NSCLC	0.73 (0.62-0.87)	*Rittmeyer A et al. Lancet 2017, 389, 255*
JAVELIN 200	Avelumab *versus* docetaxel	NSCLC	0.90 (0.72-1.12) (PD-L1 ≥1%)	*Barlesi F et al. Lancet Oncol 2018, 19, 1468*

Immune checkpoint inhibitors *versus* first-line chemotherapy in advanced NSCLC: phase 3 trials

Trial	Drug	Histology / Biomarker	Primary Endpoint	Reference
KEYNOTE-024	Pembrolizumab *versus* platin-based CT	NSCLC PD-L1 ≥50%	PFS	*Reck M et al. NEJM 2016, 375, 1823*
KEYNOTE-042	Pembrolizumab *versus* platin-based CT	NSCLC PD-L1 ≥1%	OS (≥50%, ≥20%, ≥1%)	*Mok T et al. ASCO 2018*
CheckMate 026	Nivolumab *versus* platin-based CT	NSCLC PD-L1 ≥5%	PFS	*Carbone DP et al. NEJM 2017, 376, 2415*
CheckMate 227	Nivo + ipilimumab *versus* chemotherapy	NSCLC	PFS (TMB) OS (PD-L1)	*Hellmann MD et al. NEJM 2018, 378, 2093*
MYSTIC	Durva + tremelimumab *versus* durvalumab *versus* platin-based CT	NSCLC	PFS (PD-L1≥25%) OS	*Rizvi N et al. ESMO 2018*

Pembrolizumab (200 mg) *versus* first-line chemotherapy for PD-L1-positive NSCLC: overall survival

Reck M et al. NEJM 2016, 375, 1823



Previously untreated advanced NSCLC

PD-L1 expression on at least 50% of tumor cells

HR 0.60
(95% CI 0.41-0.89)

Immune checkpoint inhibitors *versus* first-line chemotherapy in advanced NSCLC: phase 3 trials

Trial	Drug	PD-L1	Overall survival Hazard ratio (95%CI)	Reference
KEYNOTE-024	Pembrolizumab versus platin-based CT	≥50%	0.60 (0.41-0.89)	Reck M et al. NEJM 2016,375, 1823
KEYNOTE-042	Pembrolizumab versus platin-based CT	≥50% ≥20% ≥1% 1-49%*	0.69 (0.56-0.85) 0.77 (0.64-0.92) 0.81 (0.71-0.93) 0.92 (0.77-1.11)	Mok T et al. ASCO 2018

* Explorative analysis

Conclusion: Pembrolizumab monotherapy as first-line therapy only in patients with PD-L1 ≥50%

MYSTIC STUDY DESIGN

Phase 3, global, randomised, open-label, multicentre study

- Stage IV NSCLC
- All-comers population (i.e. irrespective of PD-L1 status)
- No sensitising *EGFR* mutation or *ALK* rearrangement
- ECOG PS 0/1
- Immunotherapy- and CT-naïve

N=1118 randomised

1:1:1 R

Stratified by PD-L1 TC (<25% vs ≥25%*) and histology

Durvalumab (n=374)
20 mg/kg q4w until disease progression

Durvalumab + tremelimumab (n=372)
D 20 mg/kg q4w until disease progression +
T 1 mg/kg q4w for up to 4 doses

Platinum-based chemotherapy (n=372)
- Paclitaxel + carboplatin OR
- Gemcitabine + cisplatin/carboplatin (squamous) OR
- Pemetrexed + cisplatin/carboplatin (non-squamous)†

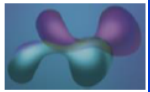
for up to 6 cycles

Primary endpoints (PD-L1 TC ≥25%*):
- PFS‡ (D+T vs CT)
- OS (D vs CT)
- OS (D+T vs CT)

Key secondary endpoints:
- PFS‡ (D vs CT; PD-L1 TC ≥25%*)
- OS (D+T vs CT; PD-L1 TC ≥1%*)
- ORR‡
- DoR
- Safety and tolerability

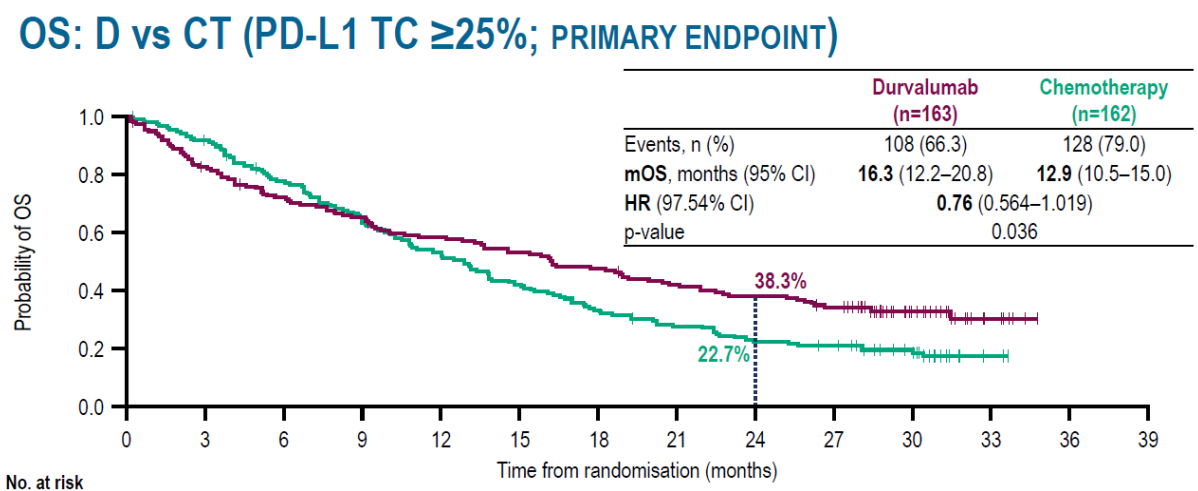
Key exploratory endpoints:
- OS by additional PD-L1 TC cutoffs
- OS by blood TMB

*Ventana PD-L1 (SP263) assay using newly acquired or archival (<3 months) tumour biopsy;
†Followed by pemetrexed maintenance therapy if eligible; ‡Blinded independent central review per RECIST v1.1
CT, chemotherapy; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group;
ORR, objective response rate; PFS, progression-free survival; PS, performance status; q4w, every 4 weeks; T, tremelimumab; TMB, tumour mutational burden



Rizvi N et al. ESMO 2018

MYSTIC: Durvalumab *versus* chemotherapy (PD-L1 ≥25%)



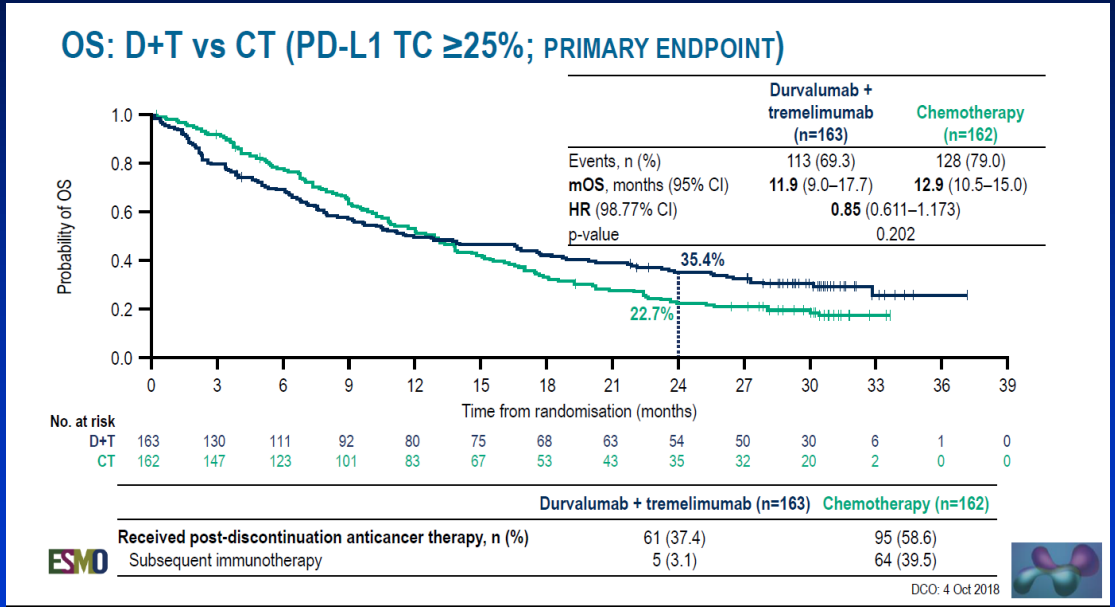
Durvalumab (20 mg/kg every 4 weeks)

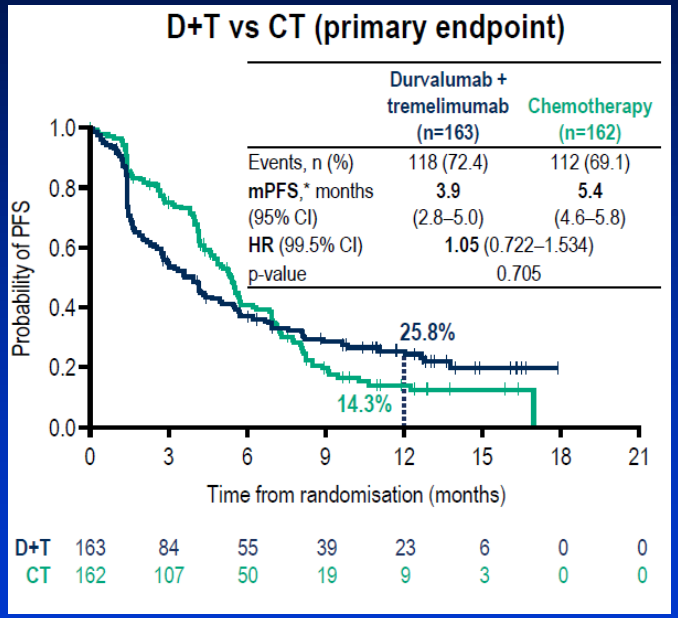
HR 0.76 (0.56-1.019)
p=0.036 (NS)

Explorative analysis in PD-L1 ≥50%:
HR 0.76 (0.55-1.038)

Rizvi N et al. ESMO 2018

MYSTIC: Durvalumab + tremelimumab *versus* cemotherapy (PD-L1 ≥25%)





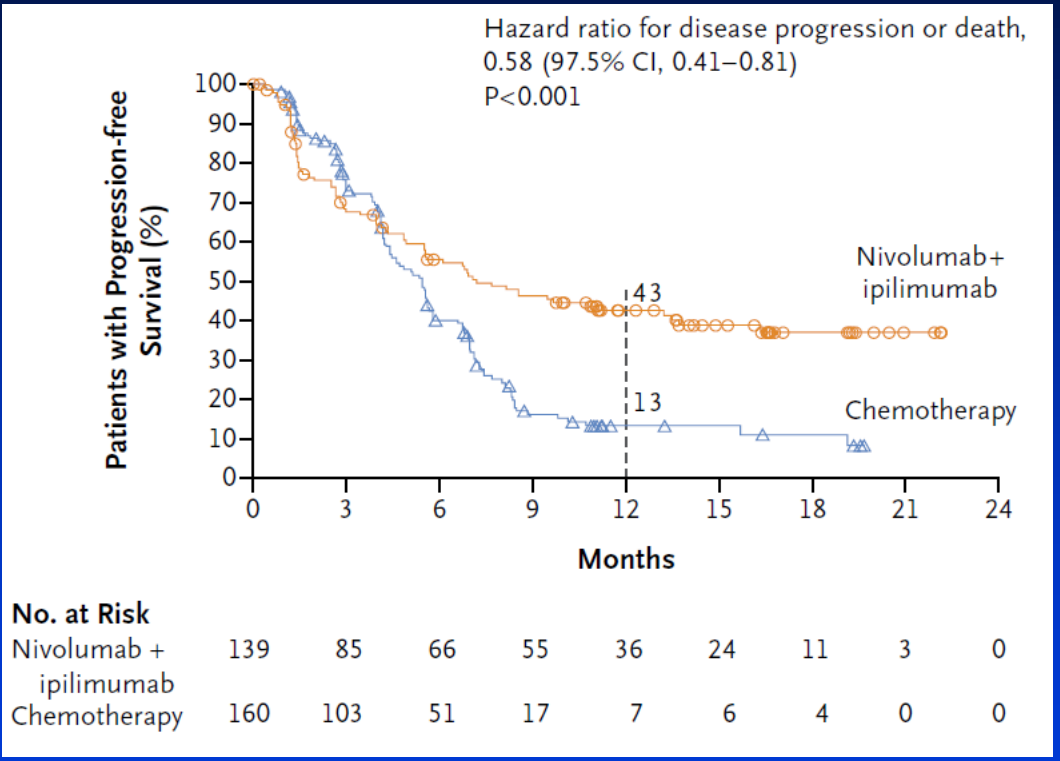
OS: HR 0.85 (0.611-1.173)

PFS: HR 1.05 (0.72-1.53)

Rizvi N et al. ESMO 2018

CheckMate-227: High tumor mutational burden

Hellmann MD et al. NEJM 2018, 378, 2093



≥10 mutations per megabase

Nivolumab + ipilimumab *versus* chemotherapy

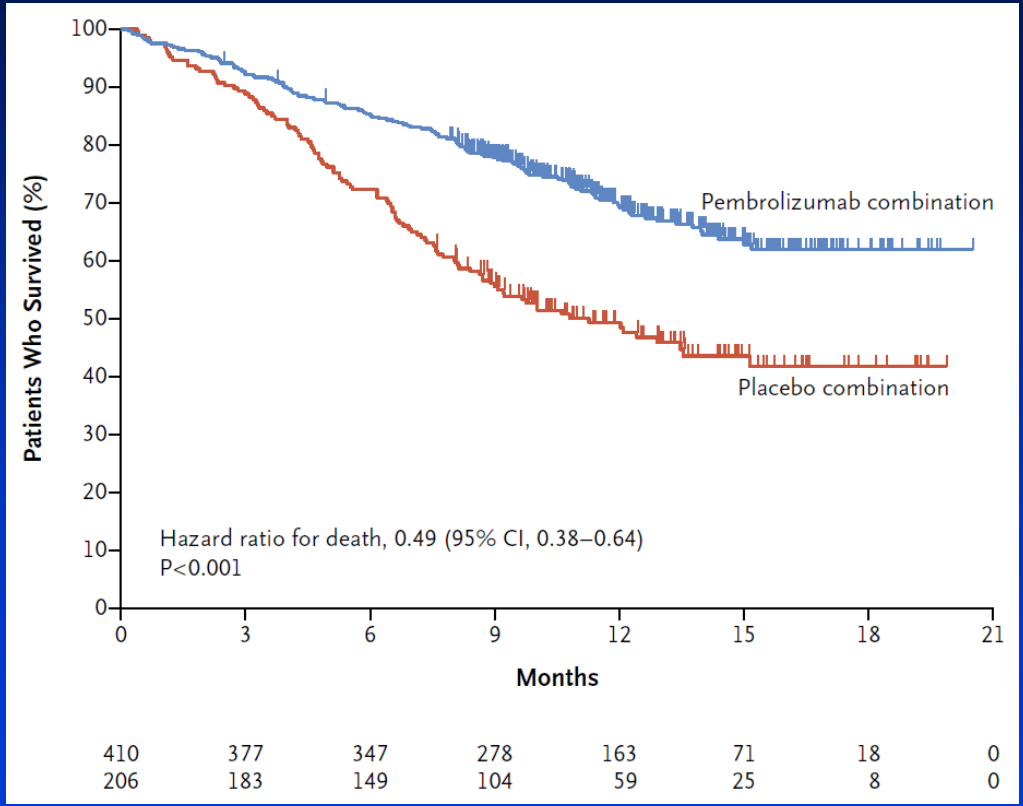
	Hazard ratio
ITT	0.58 (0.41-0.81)
PD-L1 ≥1%	0.62 (0.44-0.88)
PD-L1 <1%	0.48 (0.27-0.85)

First-line chemotherapy ± immune checkpoint inhibitors in advanced non-squamous cell NSCLC: phase 3 trials

Study	Pts.	PD-L1	Treatment	PFS HR (95%CI)	PFS median mo	Survival HR (95%CI)	Survival median mo
KEYNOTE-189	616	0-100%	CT + pembro versus CT	0.52 (0.43-0.64)	8.8 4.9	0.49 (0.38-0.64)	not reach. 11.3
IMpower150	692	0-100%	CT + bev + atezolizumab versus carbo+pacl+bev	0.62 (0.52.0.74)	8.3 6.8	0.78 (0.64-0.96)	19.2 14.7

Gandhi L et al. NEJM 2018, 378, 2078
Socinski MA et al. NEJM 2018, 378, 2288

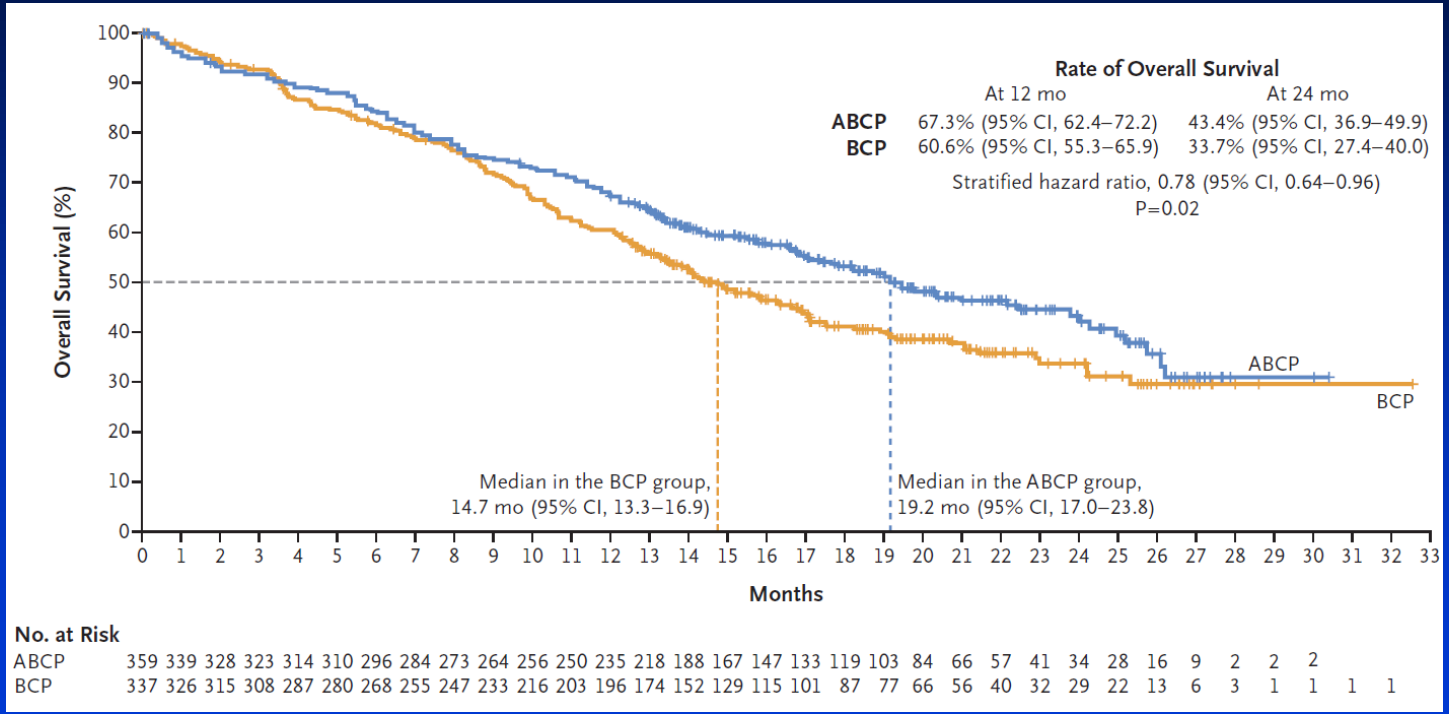
KEYNOTE-189: First-line chemotherapy ± pembrolizumab
Overall survival



PD-L1	Hazard ratio (95% CI)
All	**0.49 (0.38-0.64)**
<1%	0.59 (0.38-0.92)
≥1%	0.47 (0.34-0.66)
1-49%	0.55 (0.34-0.90)
≥50%	0.42 (0.26-0.68)

Gandhi L et al. NEJM 2018,378,2078

IMpower150: Carboplatin + nab-paclitaxel + bevacizumab ± atezolizumab
Overall survival



Socinski MA et al. NEJM 2018,378,2288

Chemotherapy ± immune checkpoint inhibitors in advanced squamous cell NSCLC: phase 3 trials

Study	Treatment	PFS HR (95%CI)	PFS median mo	Survival HR (95%CI)	Survival median mo	References
KEYNOTE-407	CT + pembrolizumab versus carbo + pacl/nab-pacl	0.56 (0.45-0.70)	6.4 4.8	0.64 (0.49-0.85)	15.9 11.3	*Paz-Ares L et al. NEJM 2018, online*
IMpower131	CT + atezolizumab versus carbo + nab-pacl	0.71 (0.60-0.85)	6.3 5.6	0.96 (0.78-1.18)	14.0 13.9	*Jotte RM et al. ASCO 2018, LBA9000*

Treatment of advanced driver-negative non-squamous NSCLC

Pirker R, January 2019

	First-line	Second-line	Third-line
All	Platin + pem + pembrolizumab	Docetaxel ± nintedanib Docetaxel ± ramucirumab	Gemcitabine, vinorelbine, erlotinib, anlotinib
	Carbo + nab-pacl + bevacizumab + atezolizumab	Docetaxel ± nintedanib Docetaxel ± ramucirumab	Gemcitabine, vinorelbine, erlotinib, anlotinib
PD-L1 ≥50%	Pembrolizumab	Platin + pemetrexed	Docetaxel ± nintedanib Docetaxel ± ramucirumab
High TMB	Nivolumab + ipilimumab	Platin + pemetrexed	Docetaxel ± nintedanib Docetaxel ± ramucirumab
All	Platin + pemetrexed	Atezolizumab, nivolumab, pembrolizumab	Docetaxel ± nintedanib Docetaxel ± ramucirumab

Treatment of advanced driver-negative squamous NSCLC

R Pirker, January 2019

	First-line	Second-line	Third-line
All	Platin-based CT + pembro	Docetaxel ± ramu; Afatinib	Afatinib, gemcitabine, vinorelbine, anlotinib
	Carbo + nab-pacl + atezolizumab	Docetaxel ± ramucirumab	Afatinib, erlotinib, gem, vinorelbine, anlotinib
PD-L1 ≥50%	Pembrolizumab	Platin-based CT	Docetaxel ± ramucirumab
High TMB	Nivolumab + ipi	Platin-based CT	Docetaxel ± ramucirumab
All	Platin-based CT	Atezo, nivo, pembro	Docetaxel ± ramucirumab
High EGFR	Platin + gem + necitumumab	Atezo, nivo, pembro	Docetaxel ± ramucirumab

MADRID 2017 ESMO congress

PACIFIC: Study Design

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

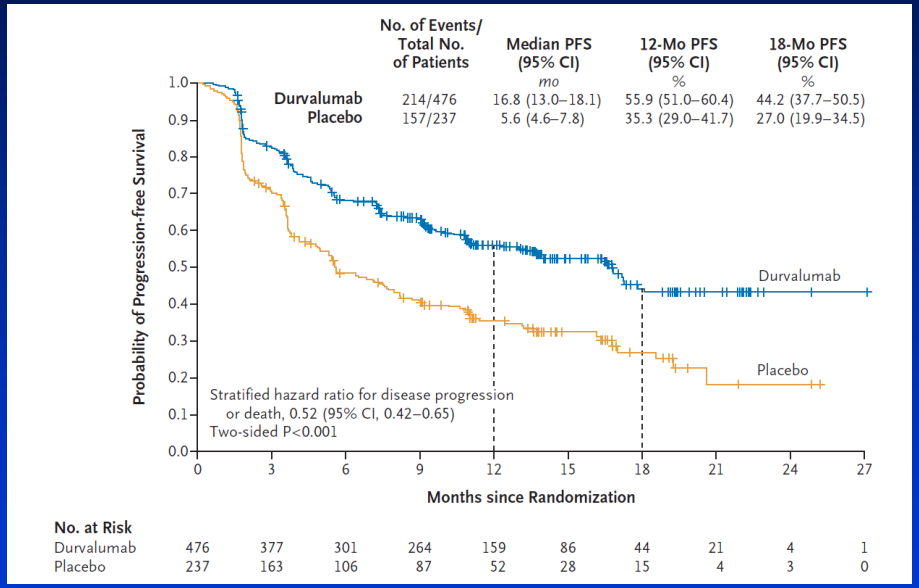
Key secondary endpoints

- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

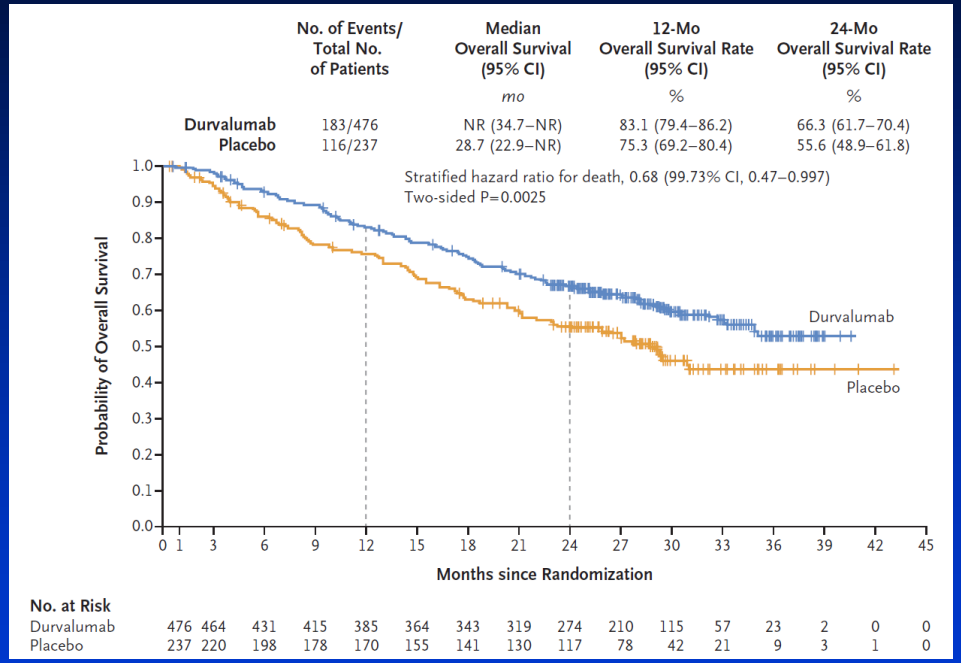
*Defined as the time from randomization (which occurred up to 6 weeks post-cCRT) to the first documented event of tumor progression or death in the absence of progression.
ClinicalTrials.gov number: NCT02125461 BICR, blinded independent central review; cCRT, concurrent chemoradiation therapy; DoR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

PACIFIC: Progression-free survival & overall survival

Antonia SJ et al. NEJM 2017, 377, 1919



HR 0.52 (95% CI 0.42-0.65)



HR 0.68 (95% CI 0.47-0.99)

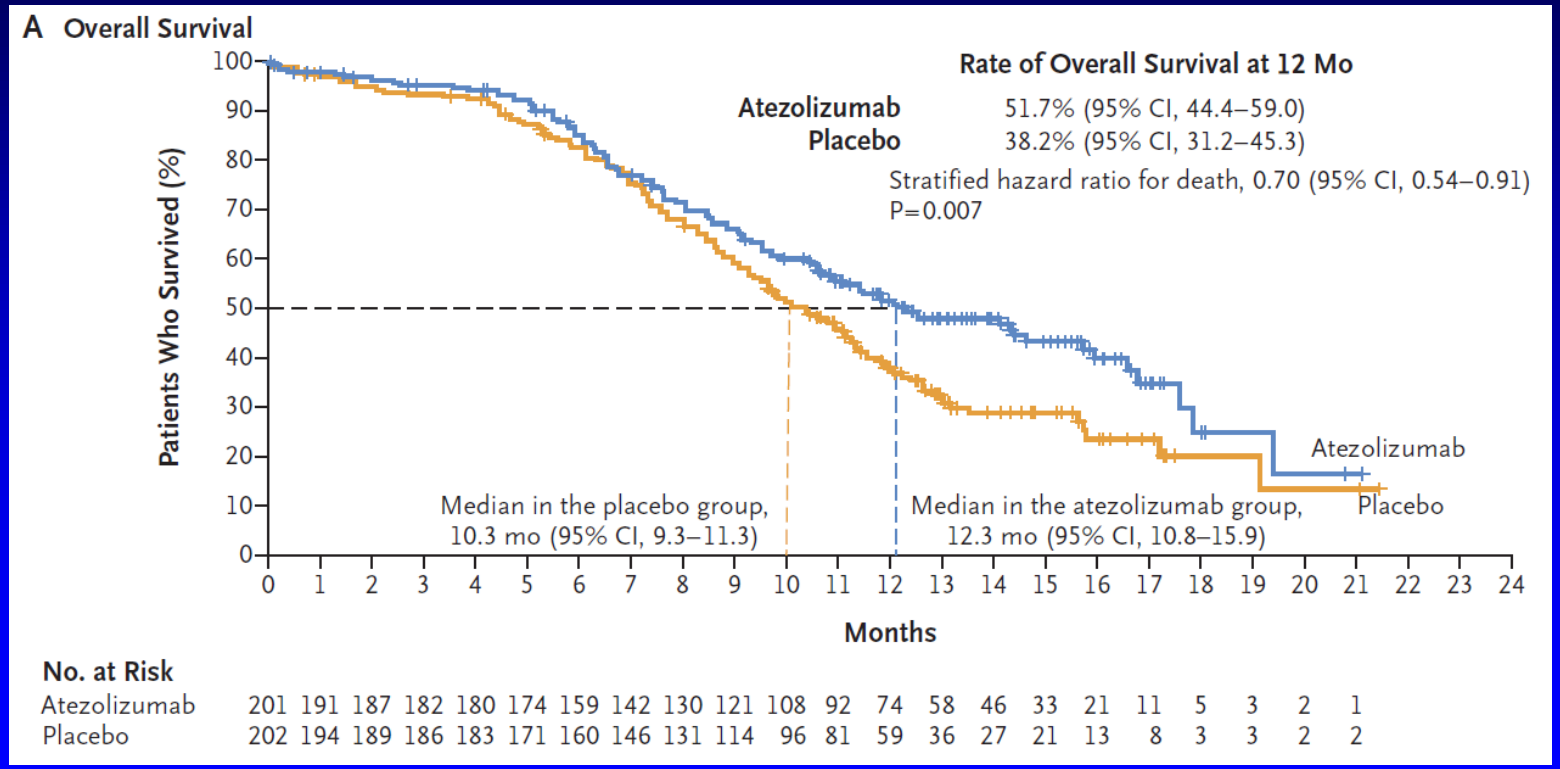
Immune checkpoint inhibitors in the adjuvant treatment of NSCLC: phase 3 trials

Study	Drug	Patients	Tumor stage	Primary Endpoint*	Trial identifier
ANVIL	Nivolumab (1 year) *versus* Observation	714	IB - IIIA	OS and / or DFS	NCT02595944 (ALCHEMIST)
PEARLS	Pembrolizumab (1 year) *versus* Placebo	1380	IB (≥4cm) - IIIA	DFS	NCT02504372 (ETOP, EORTC)
ADJUVANT BR.31	Durvalumab (1 year) *versus* Placebo	1100	IB - IIIA	DFS (PD-L1 positive; all patients)	NCT02273375 (NCIC Clinical Trials Group)

* OS overall survival DFS disease-free survival

Impower 133: First-line atezolizumab plus chemotherapy in extensive-stage SCLC

Horn L et al. NEJM, online September 25, 2018, at nejm.org



Immune checkpoint inhibitors in lung cancer
Summary

- Nivolumab, pembrolizumab & atezolizumab are established as single agents in patients with advanced NSCLC who progress after first-line chemotherapy.
- Immune checkpoint inhibitors improved outcome compared to first-line chemotherapy in advanced NSCLC.
  - Pembrolizumab in patients with PD-L1 levels ≥50%
  - Prembrolizumab or atezolizumab combined with platin-based chemotherapy in both non-squamous and squamous NSCLC.
  - Nivolumab + ipilimumab in patients with high tumor mutational burden.
- PD-L1 levels & tumor mutational load often predict degree of benefit.
- Durvalumab consolidation improved survival in NSCLC stage III.
- Adjuvant trials are ongoing in completely resected NSCLC.
- Atezolizumab added to chemotherapy improved survival in extensive disease SCLC.

Benefits of stopping smoking:
United Kingdom Million Women Study
Jha P & Peto R. NEJM 2014, 370, 60