Ανοσοθεραπεία του Καρκίνου του Πνεύμονα

Ανοσοθεραπευτική αντιμετώπιση μεταστατικού ΜΜΚΠ

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Πανεπιστήμιο Αθηνών

Disclosures

Honorarium for lectures and satellite symposium : BMS, Pfizer
Consultation : Boerhinger Ingerlheim , ASTRA

Developments of I-O as 1st Line in NSCLC

A 56 y, St IV lung adeno, EGFRwt, ALK 1%.
He has HC-NGS negative for ROS1 , HER2, RET
but TMB high

A 48 y, metast (del 19) lung adeno.
Progressed after 14 months afatinib.
Re-biop ve for T790M. PD-L1 <1%

y metastatic squamous cell lungCa
D-L1 expression was 30%

Chemotherapy (2017)

Justification of the use Combination Strategies

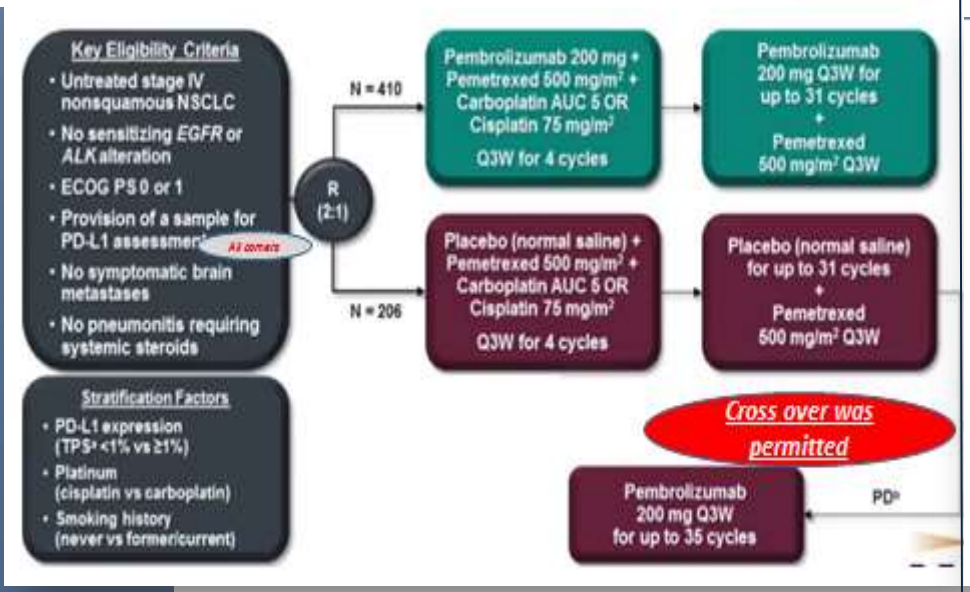
Immuno-Oncology in NSCLC

1st-line combination CT-IO

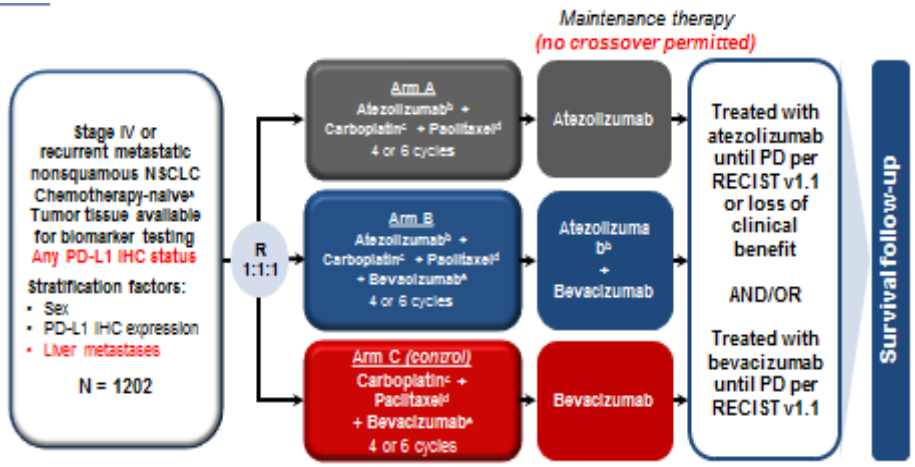
Non-Squamous

All comers

KEYNOTE 189: Trial Design



IMpower150 Study Design



[a] Patients with a sensitizing EGFR mutation or ALK translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m² IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Gandhi, AARC 2018; Gandhi, NEJM 2018

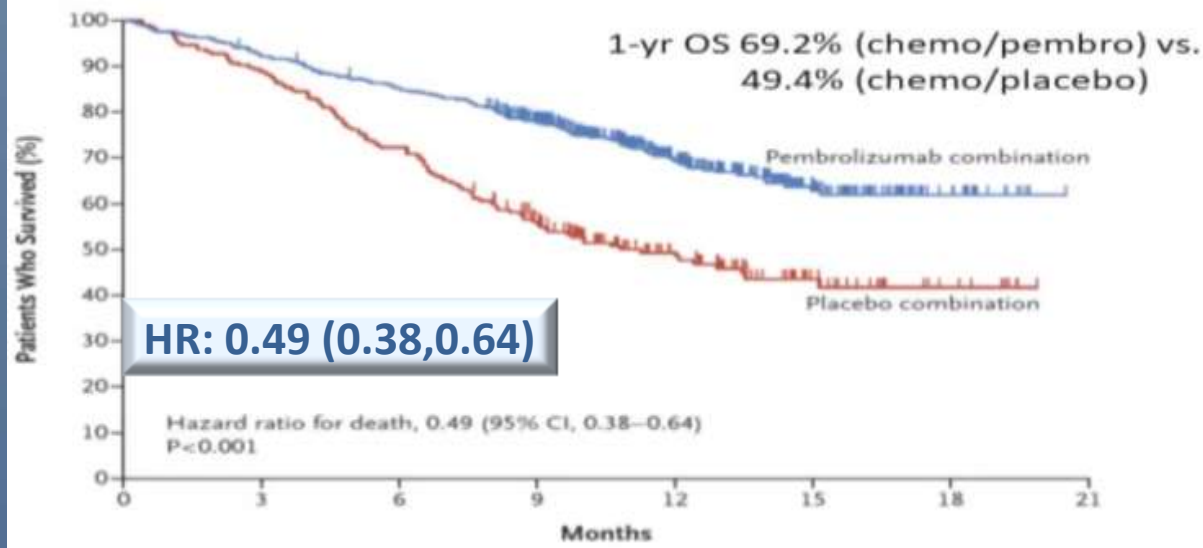
Socinski MA, et al. ASCO 2018. Abstract 9002

Immuno-Oncology in NSCLC

1st-line combination CT-IO

Non-Squamous

KEYNOTE 189: Efficacy OS



FDA APPROVAL

PD-L1 Tumor Proportion Score, %	Events /Patients	HR for Death (95% CI)
<1	84/190	0.59 (0.38, 0.92)
≥1	135/388	0.47 (0.34, 0.66)
1-49	65/186	0.55 (0.34, 0.90)
≥ 50	70/202	0.42 (0.26, 0.68)

Gandhi, AARC 2018; Gandhi, NEJM 2018

Immuno-Oncology in NSCLC
1st-line combination CT-IO

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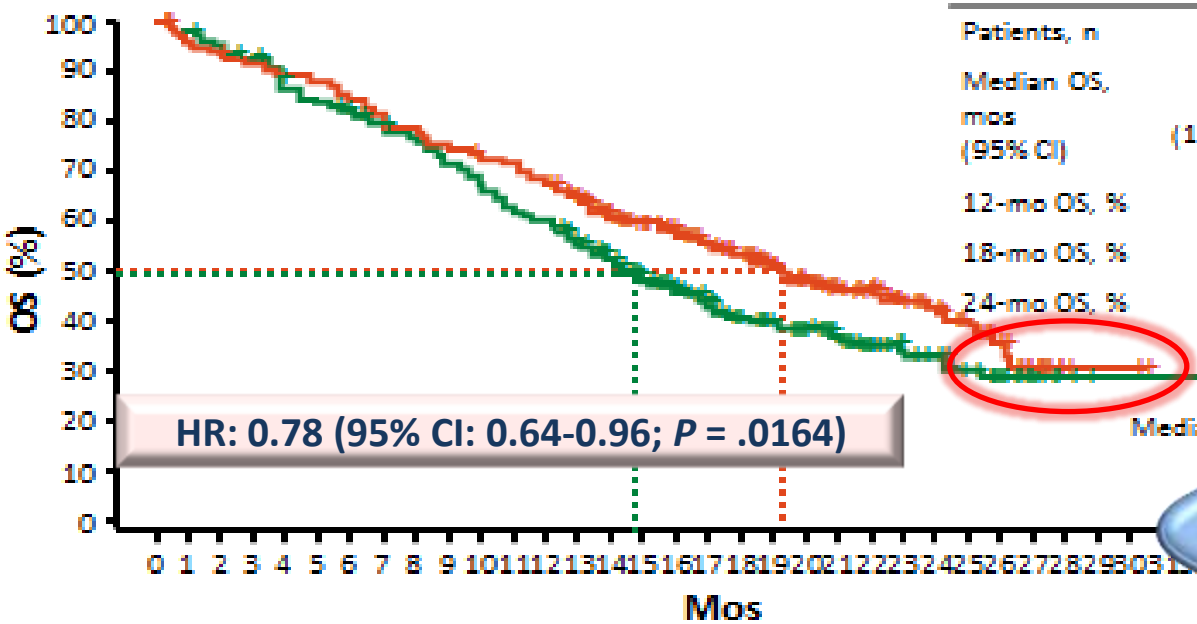
IMpower150 Efficacy OS



	Atezolb + Bev + Carbo/Pac	Bev + Carbo/Pac
Patients, n	359	337
Median OS, mos (95% CI)	19.2 (17.0-23.8)	14.7 (13.3-16.9)
12-mo OS, %	67	61
18-mo OS, %	53	41
24-mo OS, %	43	34

Median follow-up: ~ 20 mos.

FDA APPROVAL

PD-L1	HR for Death (95% CI)
High (TC3 or IC3)	0.70 (0.43, 1.13)
Low (TC1/2 or IC1/2)	0.80 (0.55, 1.15)
Negative (TC0 and IC0)	0.82 (0.62, 1.08)

Socinski MA, et al. ASCO 2018. Abstract 9002.

Immuno-Oncology in NSCLC
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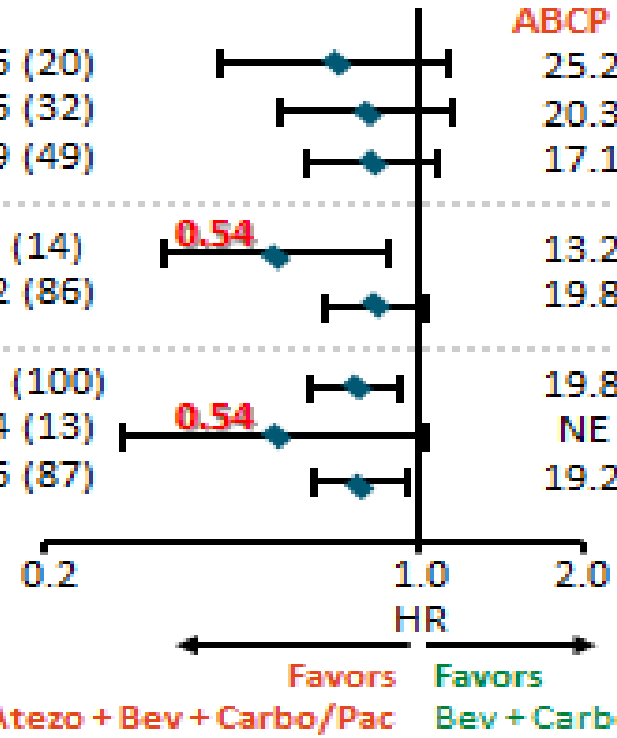
Non-Squamous

IMpower150 Efficacy OS by Subgoup

Subgroup	n (%)*	Median OS, Mos ABCP	Median OS, Mos BCP	HR
PD-L1 high (TC3 or IC3) WT	136 (20)	25.2	15.0	0.70
PD-L1 low (TC1/2 or IC1/2) WT	226 (32)	20.3	16.4	0.80
PD-L1 -ve (TC0 and IC0) WT	339 (49)	17.1	14.1	0.82
Liver metastases WT	94 (14)	13.2	9.1	0.54
No liver metastases WT	602 (86)	19.8	16.7	0.83
ITT (including *EGFR/ALK+*)	800 (100)	19.8	14.9	0.76
EGFR/ALK+ only	104 (13)	NE	17.5	0.54
ITT WT	696 (87)	19.2	14.7	0.78



*For prevalence, ITT WT (n = 696) used for PD-L1, liver metastases groups; ITT (n = 800) for rest.

Socinski MA, et al. ASCO 2018. Abstract 9002.

Immuno-Oncology in NSCLC

1st-line combination CT-IO

Squamous

KEYNOTE 407: Trial Design

- Untreated stage IV squamous NSCLC,
- ECOG PS 0/1,
- Available tumor biopsy for PD-L1 assessment,
- No brain mets
- No pneumonitis requiring systemic steroids
- (N = 559)

1:1

Pembrolizumab + Carboplatin + Paclitaxel or nab-Paclitaxel 3-wk cycles x 4 (n = 278) → Pembrolizumab up to 31 cycles

Placebo + Carboplatin + Paclitaxel or nab-Paclitaxel 3-wk cycles x 4 (n = 281) → Placebo up to 31 cycles

Stratification Factors
Stratified by PD-L1 TPS (< 1% vs ≥ 1%), taxane (paclitaxel vs nab-paclitaxel), region (east Asia vs other)

Cross over was permitted → Pembrolizumab up to 35 cycles

Primary endpoint: *PFS* by RECIST v1.1 (BICR), *OS*
Secondary endpoints: *ORR* and *DoR* by RECIST v1.1 (BICR), *safety*

Carboplatin AUC 6 Q3W, nab-paclitaxel 100 mg/m² Q1W, paclitaxel 200 mg/m² Q3W, pembrolizumab 200 mg Q3W.
*Upon confirmation of PD and safety criteria by BICR, optional crossover could occur during combination or monotherapy

IMpower131: Study Design

1st L stIV SCC NSCLC*; ECOG PS 0-1; any PD-L1 status† (N = 1021)

Stratification factors
Sex; PD-L1 expression; liver metastases

Atezolizumab 1200 mg IV Q3W + Carbo/Paclitaxel‡ for 4-6 cycles (n = 338) → Atezolizumab

Atezolizumab 1200 mg IV Q3W + Carbo/nab-Paclitaxel‡ for 4-6 cycles (n = 343) → Atezolizumab

Carbo/nab-Paclitaxel‡ for 4-6 cycles (n = 340) → BSC

Maintenance (no crossover allowed)

Until PD or loss of clinical benefit

Until PD

Coprimary endpoints: investigator-assessed *PFS* per RECIST v1.1, *OS* (ITT)

Secondary endpoints: *PFS, OS in PD-L1 subgroups*; *ORR, DoR, safety*

*Patients with *EGFR* or *ALK* aberrations must have PD or intolerance to ≥ 1 targeted tx. †PD-L1 assessed by SP142 IHC assay.
‡Carboplatin AUC 6 IV Q3W; nab-paclitaxel 100 mg/m² IV QW; paclitaxel 200 mg/m² IV Q3W.

Paz-Ares LG, et al. ASCO 2018. Abstract 105.

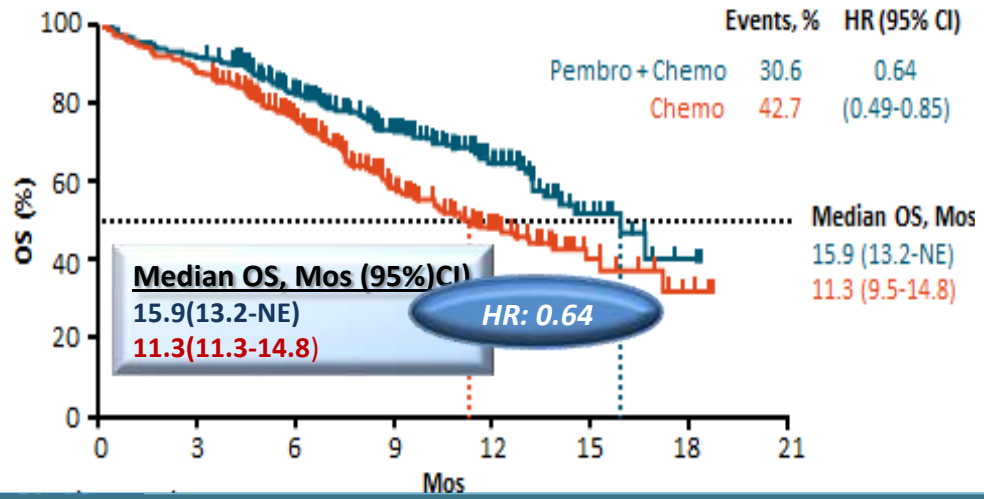
Jotte RM, et al. ASCO 2018. Abstract LBA9000.

Immuno-Oncology in NSCLC

1st-line combination CT-IO

Squamous

KEYNOTE 407: Efficacy OS



IMpower131: Efficacy OS

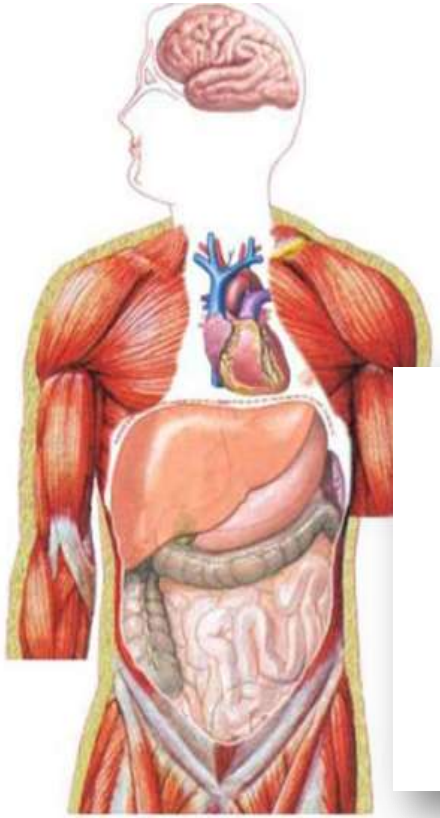
Survival by PD-L1 Expression, Mos (95% CI)	Pembro + Chemo	Chemo	HR (95% CI)
Median OS			
▪ TPS < 1%	15.9 (13.1-NE)	10.2 (8.6-13.8)	**0.61 (0.38-0.98)**
▪ TPS 1% to 49%	14.0 (12.8-NE)	11.6 (8.9-17.2)	**0.57 (0.36-0.90)**
▪ TPS ≥ 50%	NR (11.3-NE)	NR (7.4-NE)	**0.64 (0.37-1.10)**

FDA APPROVAL

Paz-Ares LG, et al. ASCO 2018. Abstract 105.

Immuno-Oncology in NSCLC

SELECT THE RIGHT PATIENT FOR EFFICACY

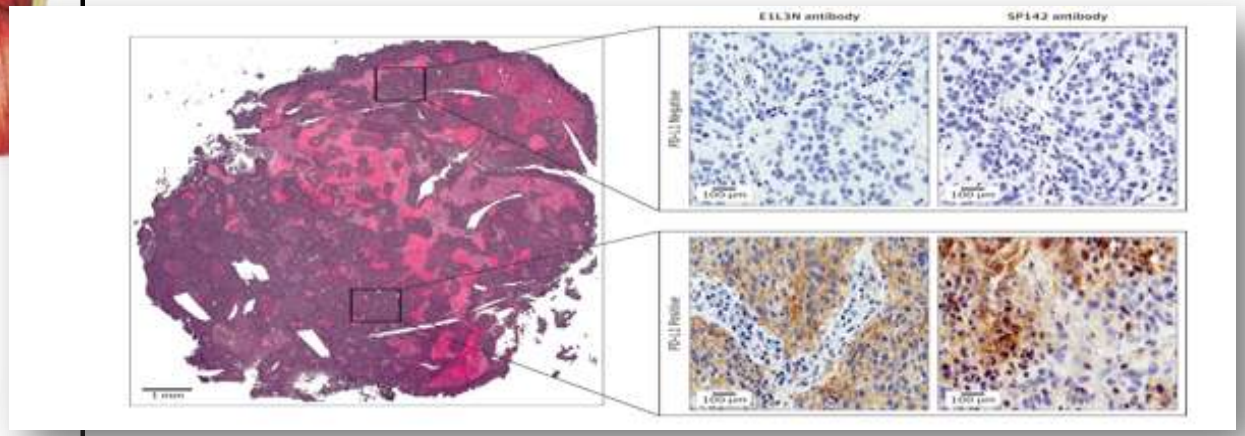


The King PD-L1

Drug	PD-L1 IHC Assay	PD-L1 scoring	Cut-offs reported in clinical trials	FDA Diagnostic Status
Nivolumab	28-8	Tumor cells	1%, 5%, 10%	Complementary
Pembrolizumab	22C3	Tumor cells (TPS)	1%, 50%	Companion
Atezolizumab	SP142	Tumor cells (TC)	1%, 5%, 50%	Complementary
		Immune cells (IC)	1%, 5%, 10%	
Durvalumab	SP263	Tumor cells	25%	Unknown
Avelumab	73-10	Tumor cells	1%, 50%, 80%	Unknown

Companion diagnosis: REQUIRED for the safe and effective use of a drug
Complementary diagnostic: NOT REQUIRED but can provide additional information
TPS: tumor proportional score; TC: staining on tumor cell; IC: staining on immune cells

Tsao MS, et al. *J Thorac Oncol.* 2017;1(1 Suppl): Abstract PL 03.03.

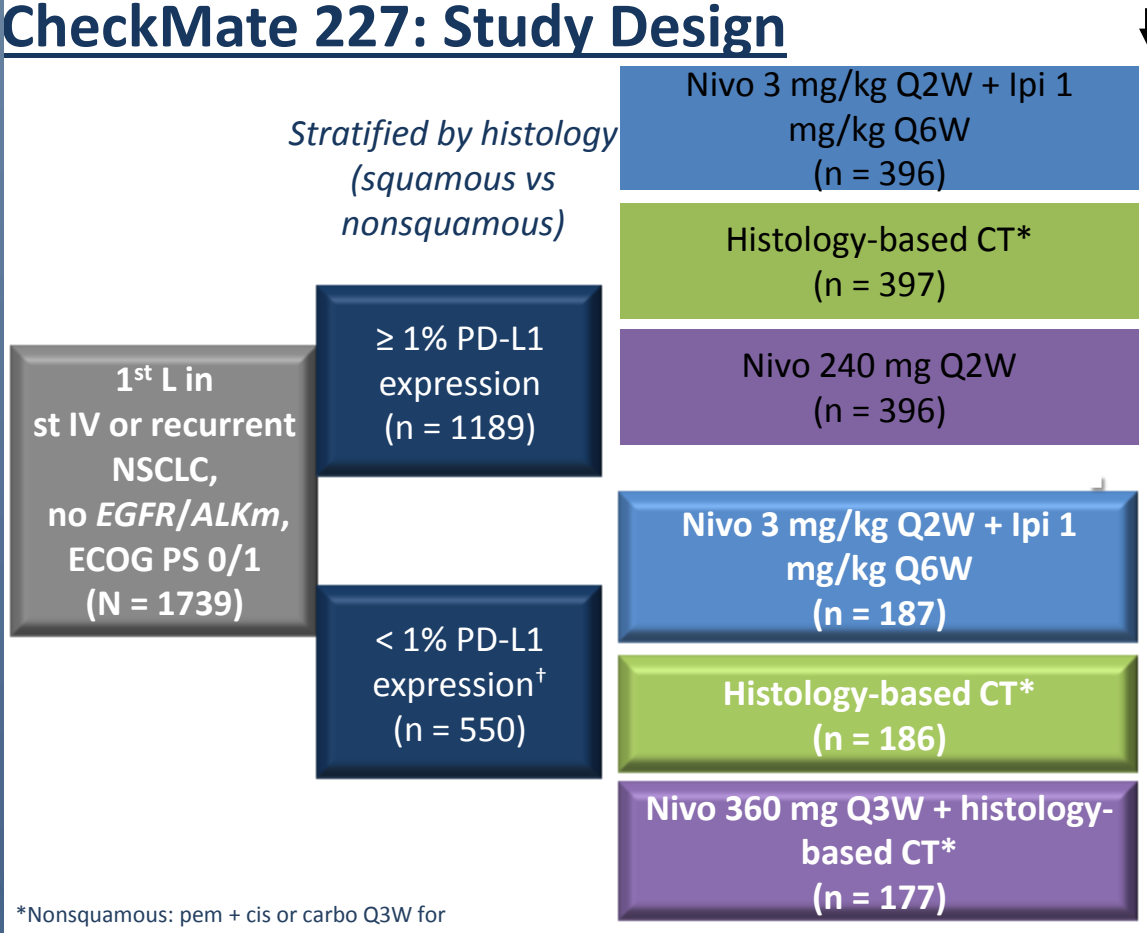


Mc Laughlin et al Jama Oncol 2016; 2: 46-54

Immuno-Oncology in NSCLC

- 2nd-line single agent IO
- 1st-line single agent IO
- **1st-line combination IO-IO**

CheckMate 227: Study Design



Coprimary endpoints: ***OS in PD-L1–selected populations, PFS in TMB-selected populations receiving nivolumab + ipilimumab vs CT***

Secondary endpoint ***(current analysis): PFS in patients with < 1% PD-L1 expression receiving nivolumab + CT vs CT***

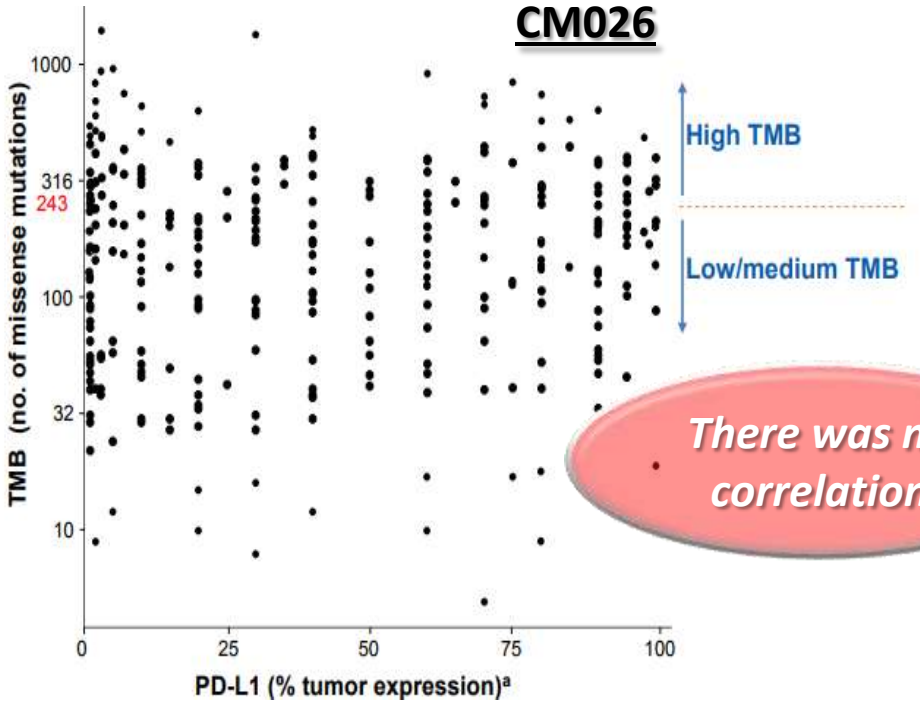
*Nonsquamous: pem + cis or carbo Q3W for ≤ 4 cycles with optional maintenance (CT: pem; nivolumab + CT: nivolumab + pem); squamous: gem + cis or carbo Q3W for ≤ 4 cycles.
†1 patient randomized as < 1% PD-L1 and subsequently determined to have ≥ 1% PD-L1 expression.

Borghaei H, et al. ASCO 2018. Abstract 9001. ClinicalTrials.gov. NCT02477826.

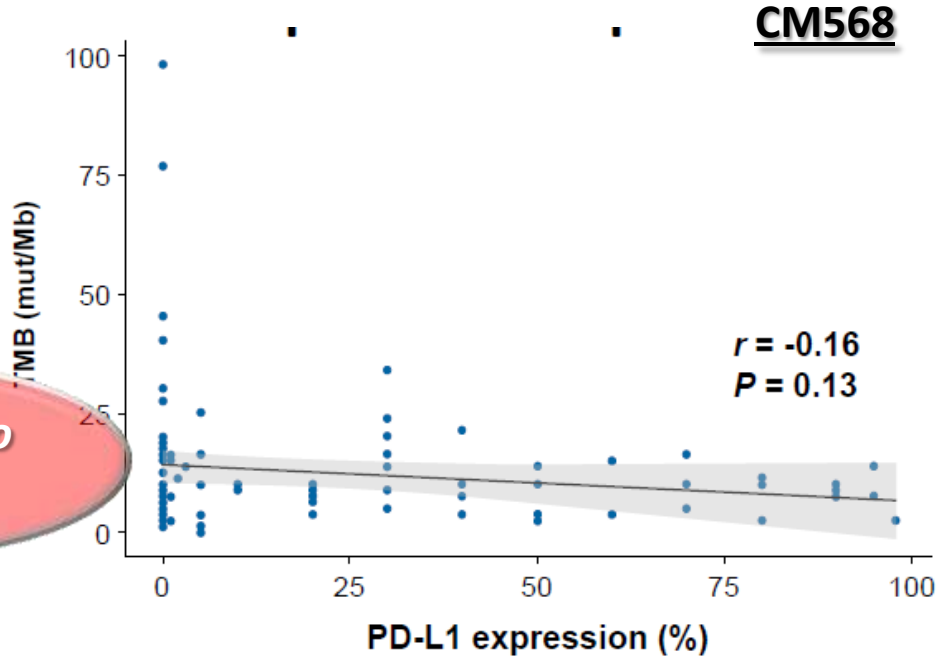
Immuno-Oncology in NSCLC

1st-line combination IO-IO

TMB and PD-L1 Expression Identify District and Independent Populations of NSCLC



There was no correlation



Peters S et al Cancer Res 2017; 77(13 Suppl): Abstract CT082

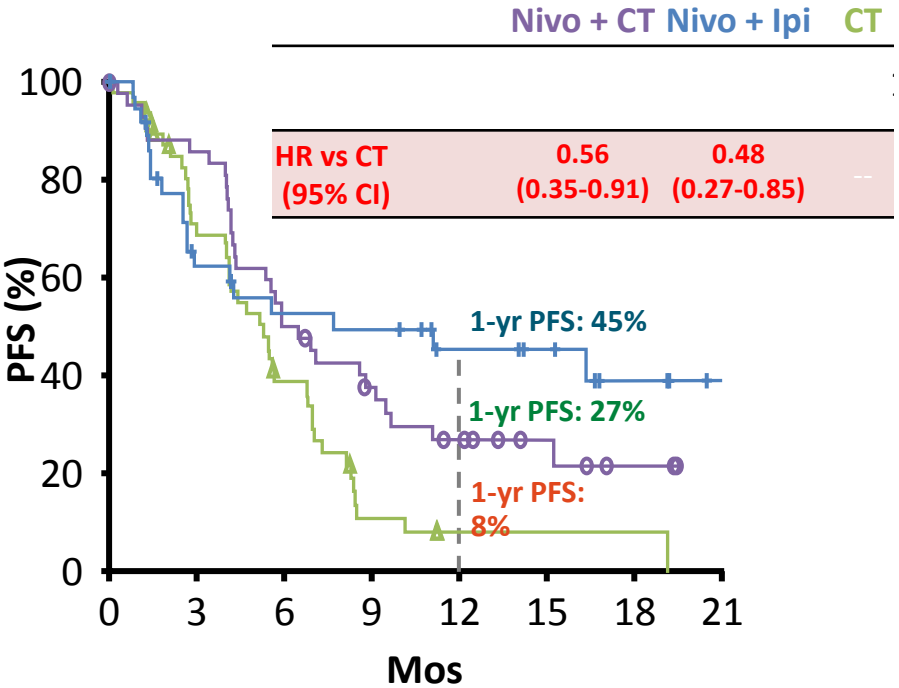
Ramalingam S, et al AACR; 2018 Abstract CT078

Immuno-Oncology in NSCLC

1st-line combination IO-IO

CheckMate 227: Exploratory Analysis of PFS by TMB in Patients With < 1% PD-L1 Expression

TMB ≥ 10 mut/Mb



Patients at Risk, n

Nivo + CT	43	36	21	14	9	5	2	0
Nivo + Ipi	38	20	16	15	10	8	4	1
CT	48	30	16	4	1	1	1	0

Borghaei H, et al. ASCO 2018. Abstract 9001.

Safety with the combination strategy

KEYNOTE 189: Safety, AEs

AE%	Pembro + CT (n=405)		Pbo+CT (n=202)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any	99.8	67.2	99.0	65.8
AE-related d/c of all trial drugs	13.8	11.9	7.9	6.9
D/c of Pembro or Pbo	20.2	15.8	10.4	8.4
Anemia	46.2	16.3	46.5	15.3
Neutropenia	27.2	15.8	24.3	11.9
Acute kidney injury	5.2	2.0	0.5	NR
Immune mediated	22.7	8.9	11.9	4.5
▪ Nephritis	1.7	1.5	0	0

- AE-related deaths: Pembro + CT, 6.7%; Pbo + CT, 5.9%

Gandhi, AARC 2018; Gandhi, NEJM 2018

IMpower150: Safety

Safety Outcome	Atezo+ Carbo/Pac (n = 400)	Atezo + Bev + Carbo/Pac (n = 393)	Bev + Carbo/Pac (n = 394)
Median dosesreceived, n (range)			
▪ Atezolizumab	10 (1-43)	12 (1-44)	NA
▪ Bevacizumab	NA	10 (1-44)	8 (1-38)
Treatment-related AE, n (%)	377 (94)	370 (94)	377 (96)
▪ Grade 3/4	172 (43)	223 (57)	191 (49)
▪ Grade 5	4 (1)	11 (3)	9 (2)
• Fatal hemorrhagic	2 (< 1)	6 (2)	3 (< 1)
Serious AE, n (%)	157 (39)	174 (44)	135 (34)
AE leading to d/c of any treatment, n (%)	53 (13)	133 (34)	98 (25)

Socinski MA, et al. ASCO 2018. Abstract 9002.

KEYNOTE-407: Safety

Summary of AE, n (%)	Pembro + Chemo (n = 278)	Chemo (n = 280)
All cause	273 (98.2)	274 (97.9)
Grade 3-5	194 (69.8)	191 (68.2)
Led to death	23 (8.3)	18 (6.4)
▪ Treatment related	10 (3.6)	6 (2.1)
Led to discontinuation		
▪ All treatment	37 (13.3)	18 (6.4)
▪ Any treatment	65 (23.4)	33 (11.8)
Immune-mediated and infusion reactions	80 (28.8)	24 (8.6)
▪ Grade 3-5	30 (10.8)	9 (3.2)
▪ Led to death	1 (0.4)	1 (0.4)

Paz-Ares LG, et al. ASCO 2018. Abstract 105.

CheckMate 227: Safety TRAE in < 1% PD-L1

Safety Outcome	Nivo + CT (n = 172)		Nivo + Ipi (n = 185)		CT (n = 183)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TRAE, %	92	52	74	25	77	35
TRAE leading to d/c, %	13	8	16	10	14	9
Median doses received, n	▪ Nivolumab Q3W: 8.5 ▪ CT Q3W: 4-7		▪ Nivolumab Q2W: 8 ▪ Ipilimumab Q6W: 3		CT Q3W: 4-7	

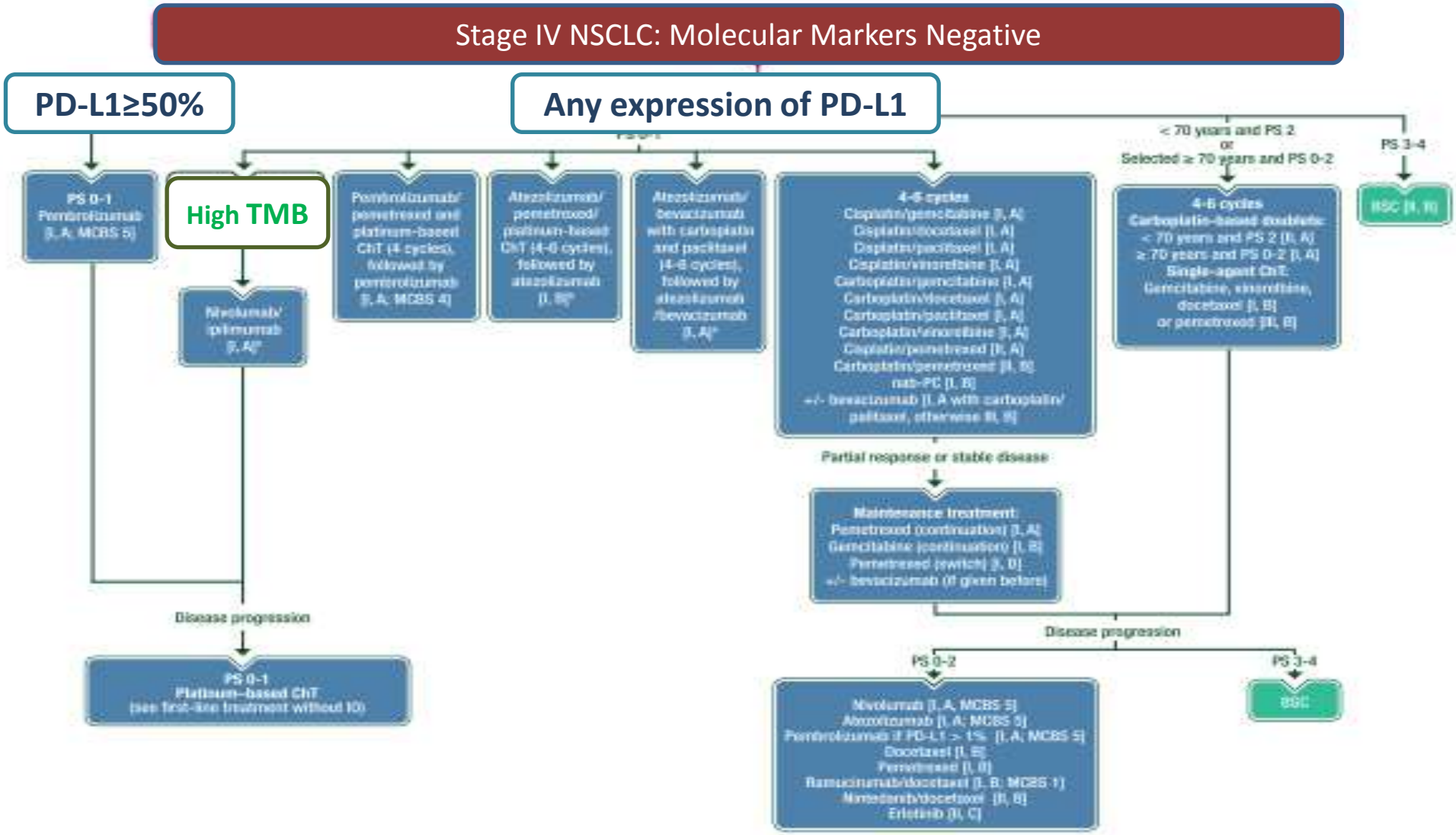
- Treatment-related deaths: nivolumab + CT, n = 4; nivolumab + ipilimumab (both arms), n = 7; CT alone (both arms), n = 6

Borghaei H, et al. ASCO 2018. Abstract 9001.

ESMO
CLINICAL PRACTICE GUIDELINES

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

D. Planchard[1], S. Popat[2], K. Kerr[3], S. Novello[4], E. F. Smit[5], C. Faivre-Finn[6], T. S. Mok[7], M. Reck[8], P. E. Van Schil[9], M. D. Hellmann[10] & S. Peters[11], on behalf of the ESMO Guidelines Committee*



Developments of I-O as 1st Line in NSCLC

A 56 y, St IV lung adeno, EGFRwt, ALK –ve, PD-L1<1%.
He has HC-NGS negative for ROS1, BRAF, cMET, HER2, RET but TMB high

- Nivo/ Ipi
- Carbo/pemetrexed /pembro
- Carboplatin /paclitaxel/bevacizumab/ atezolizumab
- Platinum doublet chemotherapy

A 48 y, metastatic EGFR+ve (del 19) lung adeno.
Progressed (unequivocal) after 14 months afatinib.
Re-biopsy was negative for T790M. PD-L1 <1%

- Carboplatin/Paclitaxel/Bev/Atezo
- Platinum doublet chemotherapy

A 75 y metastatic squamous cell lungCa
PD-L1 expression was 30%

- Carbo/(nab-)Paclitaxel/Pembro
- Platinum doublet chemotherapy

Immuno-Oncology in NSCLC

Messages Considerations

- For 1st line therapy, in patients with PD-L1 ≥ 50% Pembro monotherapy is still a strong option. Combination therapies have not yet proved to be superior in that population.
- Second-line therapy selection after combination as a front-line treatment is important
- Combination I-O are related to higher rates of toxicity
- Immunotherapy should be part of the precision medicine algorithm, not a panacea

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