CARCINOMA POLMONARE:
QUALI NOVITÀ NEL 2022?

20 Maggio 2022

IRCCS "Sacro Cuore - Don Calabria"
Negrar di Valpolicella
Sala Perez

Terapia di 1 linea: opzioni attuali e prospettive terapeutiche

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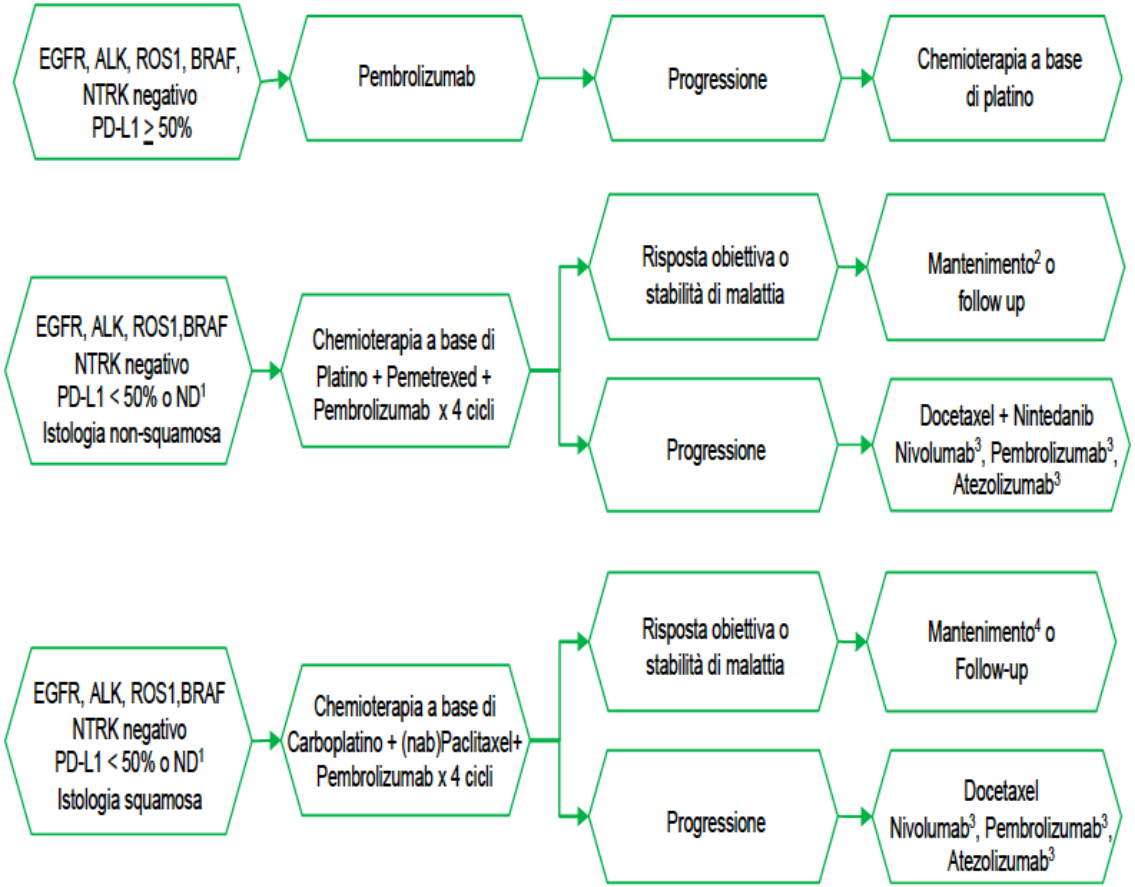
Disclosures

- **Advisory Boards / Honoraria / Speakers' fee / Consultant for**:
  - MSD
  - Astra-Zeneca
  - BMS
  - Roche
  - Boehringer Ing.

LG AIOM 2021


EGFR, ALK, ROS1, BRAF, NTRK negativo PD-L1 ≥ 50%
Pembrolizumab
Progressione
Chemioterapia a base di platino
EGFR, ALK, ROS1,BRAF NTRK negativo PD-L1 < 50% o ND[1] Istologia non-squamosa
Chemioterapia a base di Platino + Pemetrexed + Pembrolizumab x 4 cicli
Risposta obiettiva o stabilità di malattia
Mantenimento[2] o follow up
Progressione
Docetaxel + Nintedanib Nivolumab[3], Pembrolizumab[3], Atezolizumab[3]
EGFR, ALK, ROS1,BRAF NTRK negativo PD-L1 < 50% o ND[1] Istologia squamosa
Chemioterapia a base di Carboplatino + (nab)Paclitaxel+ Pembrolizumab x 4 cicli
Risposta obiettiva o stabilità di malattia
Mantenimento[4] o Follow-up
Progressione
Docetaxel Nivolumab[3], Pembrolizumab[3], Atezolizumab[3]

Agenda

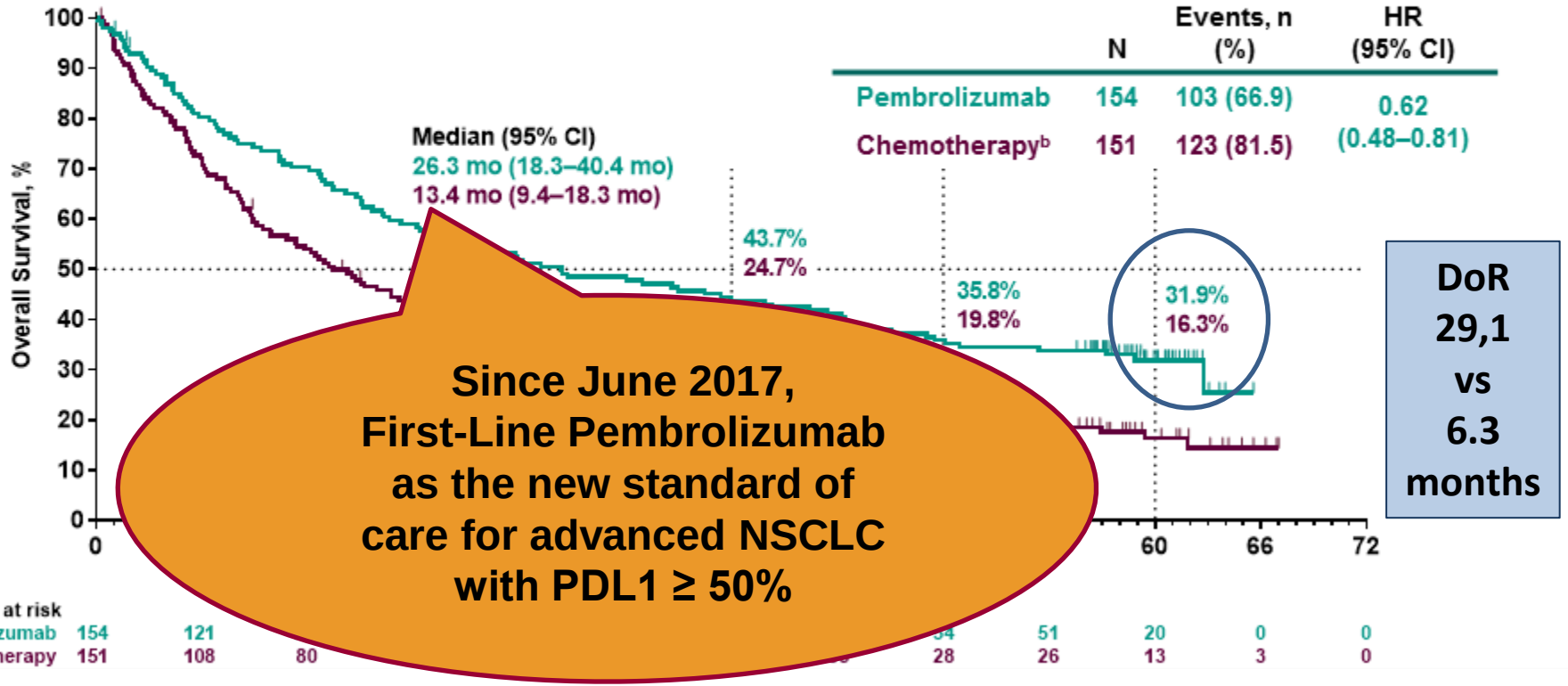
PDL1 >50%

- Pembro o Atezo ?
- In futuro, cemiplimab ?
- Nuove associazioni ?

PDL1 < 50%

- CT+Pembro o CT+Ipi-Nivo ?

KEYNOTE 024 – 5-YEAR (60 months) OS UPDATE



Since June 2017, First-Line Pembrolizumab as the new standard of care for advanced NSCLC with PDL1 ≥ 50%

DoR 29,1 vs 6.3 months

Reck M. et al J Clin Oncol. 2019 Mar 1;37(7):537-546

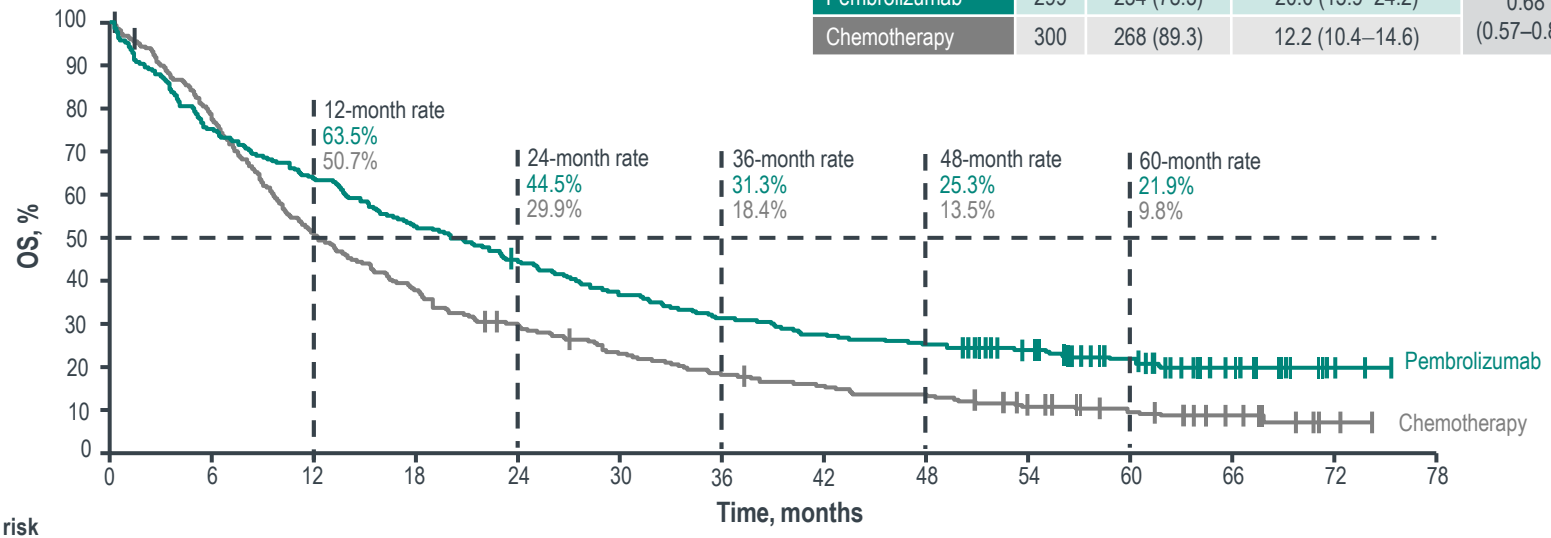
Brahmer J, *et al*. ESMO Congress 2020

NSCLC Studies: 1L Monotherapy Phase 3 Trials

DEMOGRAPHIC, CLINICAL AND BIOLOGICAL RCT FACTORS	IMPOWER110		EMPOWERLUNG 1		KEYNOTE 024		KEYNOTE 042	
	ATEZO	CHEMO	CEMIP	CHEMO	PEMBRO	CHEMO	PEMBRO	CHEMO
AGE ≥ 65y	44.9%	56.1%	45%	48%	54%	54%	44%	46%
SEX (FEMALE)	26.2%	34.7%	12%	18%	40.3%	37.1%	29.4%	29%
ECOG PS 1	67.3%	60.2%	73%	73%	35.7%	35.1%	68.9%	70%
H. SQUAMOUS	25.2%	23.5%	43%	43%	18.8%	17.2%	38%	39.1%
NEVER SMOKER	8.4%	15.3%	N/A	N/A	3.2%	12.4%	22.3%	22%
BRAIN METS	N/A	N/A	12%	12%	11.7%	6.6%	5.5%	5%
CROSSOVER	NOT PERMITTED		PERMITTED (74% ITT)**		PERMITTED (66%)		NOT PERMITTED	
TEST	SP142***		22C3		22C3		22C3	
1° ENDPOINT	OS		OS/PFS		PFS		OS	
GRADE 3-5 IMPNEUMOM	0.7%	0%	1%	1%	2.6%*	0.7%*	3.3%	0.2%

KEYNOTE-042: 5-year Update of OS in Patients With PD-L1 TPS ≥50% (Primary Hierarchical End Point)

	N	Events, n (%)	mOS, months (95% CI)	HR (95% CI)
Pembrolizumab	299	234 (78.3)	20.0 (15.9–24.2)	0.68 (0.57–0.81)
Chemotherapy	300	268 (89.3)	12.2 (10.4–14.6)	



No. at risk

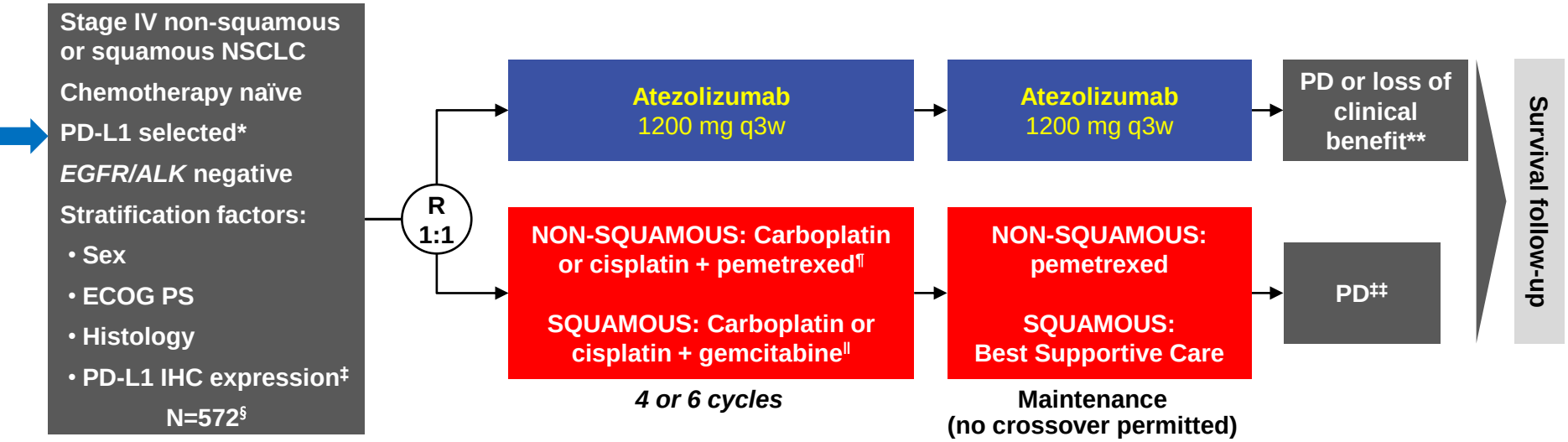
Pembrolizumab	299	224	190	157	132	109	93	82	75	56	37	16	2	0
Chemotherapy	300	231	151	113	87	66	53	44	38	25	17	9	2	0

Median follow-up for the ITT population = 61.1 months (range: 50.0–75.5 months). Data cutoff: April 28, 2021.

[a]Primary endpoint was met at the interim analysis: TPS ≥50%, *P*=0.0003.

de Castro et al. Presented at SITC 2021. Abstract 363.

IMpower110: atezolizumab monotherapy versus chemotherapy in PD-L1 selected, first-line NSCLC

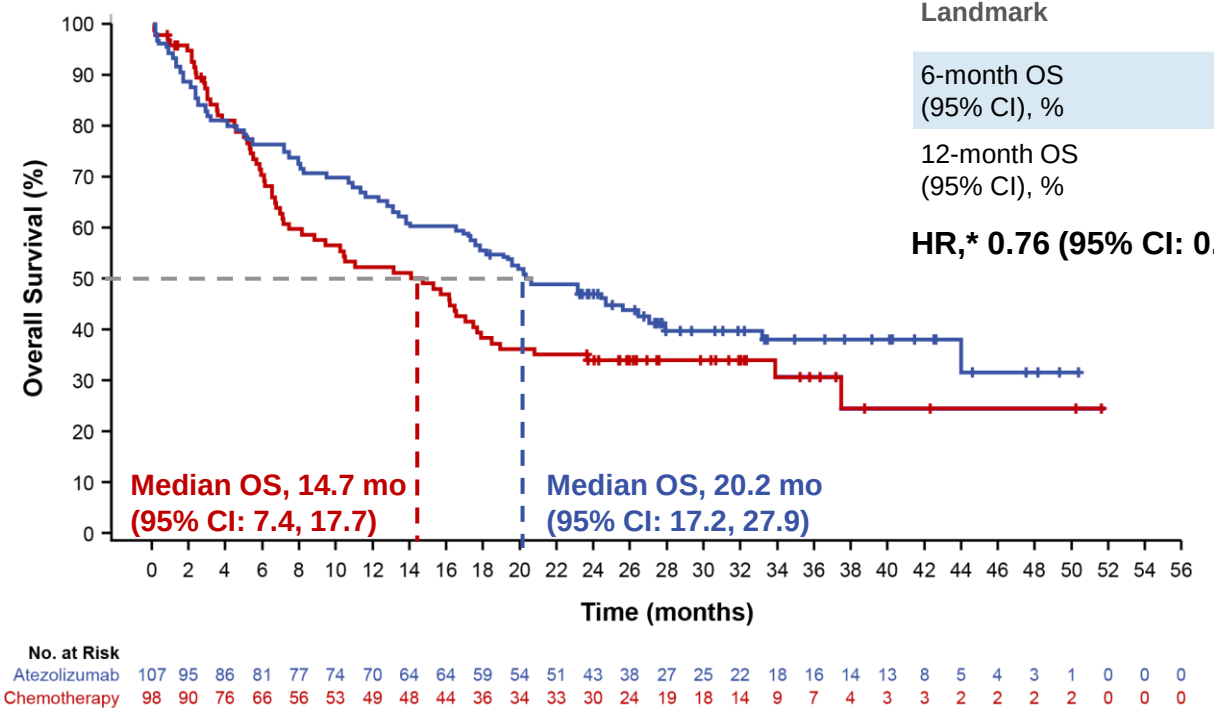


1 Primary endpoint
- OS in WT population (excluding patients with *EGFR*+/*ALK*+ NSCLC)

2 Key secondary endpoints
- PFS (investigator-assessed)
- ORR
- DOR (per RECIST v1.1)

Spigel, et al. ESMO 2019 (Abs LBA78)
Herbst, et al. N Engl J Med 2020

IMpower110: OS in the TC3 or IC3 subgroup after longer follow up



Landmark	Arm A (atezo) n=107	Arm B (chemo) n=98
6-month OS (95% CI), %	76.5 (68.5, 84.6)	70.4 (61.2, 79.6)
12-month OS (95% CI), %	66.1 (57.1, 75.1)	52.3 (42.2, 62.4)

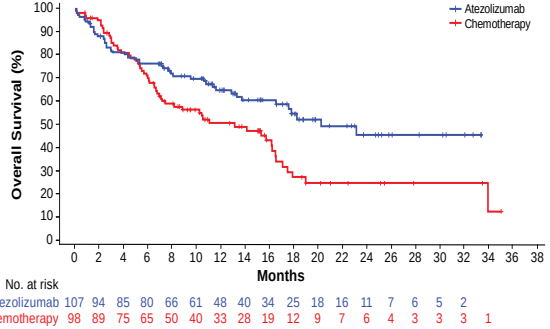
HR,* 0.76 (95% CI: 0.54, 1.09)

Median follow-up, 31.3 mo (range, 0–52)

Herbst, et al. WCLC 2020 (Abs FP13.03)
Jassem et al; JTO 2021

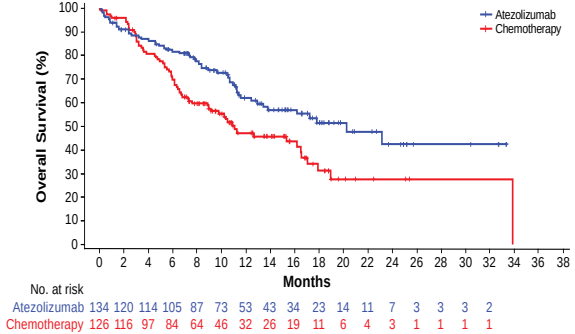
IMpower110: OS in PD-L1–high subgroup with 22C3 and SP263

SP142 (TC3 or IC3-WT)*



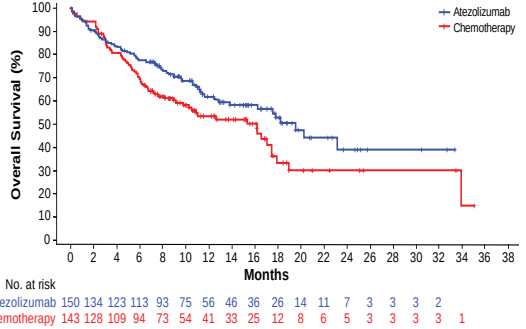
	Atezo (n=107)	Chemo (n=98)
mOS, mo	20.2	13.1
HR (95% CI)‡	0.59 (0.40, 0.89)	

22C3 BEP-WT (TPS ≥50%)*



	Atezo (n=134)	Chemo (n=126)
mOS, mo	20.2	11.0
HR (95% CI)§	0.60 (0.41, 0.86)	

SP263 BEP-WT (TC ≥50%)*

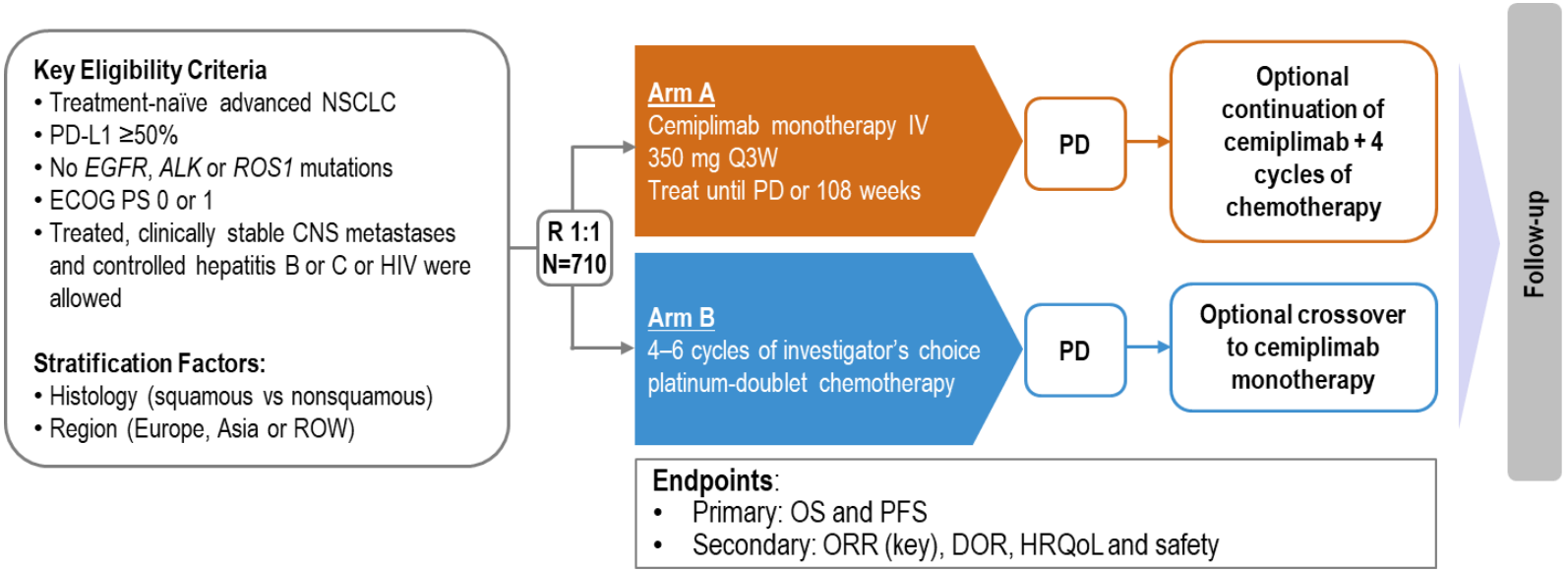


	Atezo (n=150)	Chemo (n=143)
mOS, mo	19.5	16.1
HR (95% CI)§	0.71 (0.50, 1.00)	

*SP142 TC1/2/3 or IC1/2/3-WT (n=554); 22C3 BEP-WT (n=534); SP263 BEP-WT (n=546)
‡Stratified
§Unstratified

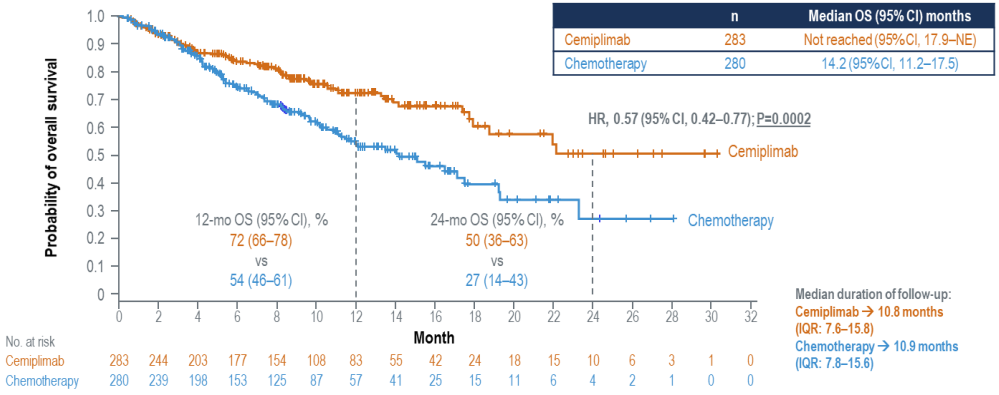
Herbst, et al. ESMO IO 2019 (Abs LBA1)
Herbst, et al. N Engl J Med 2020

EMPOWER-Lung 1: Study Design and Endpoints



OS and PFS by IRC: PD-L1 of at Least 50% (N=563)

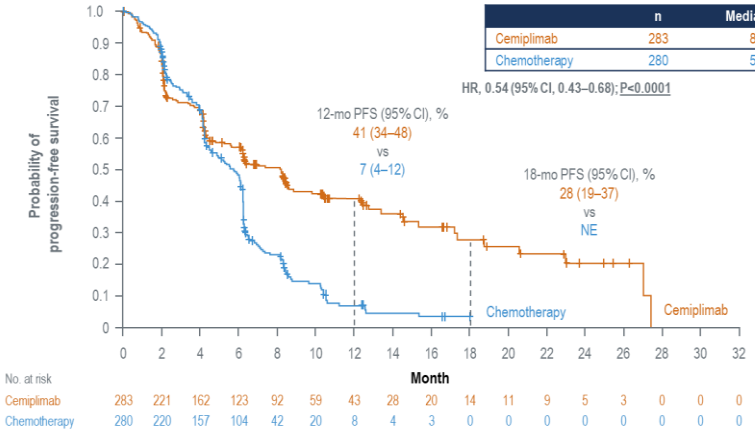
Overall survival



	n	Median OS (95% CI) months
Cemiplimab	283	Not reached (95% CI, 17.9–NE)
Chemotherapy	280	14.2 (95% CI, 11.2–17.5)

Median duration of follow-up:
Cemiplimab → 10.8 months (IQR: 7.6–15.8)
Chemotherapy → 10.9 months (IQR: 7.8–15.6)

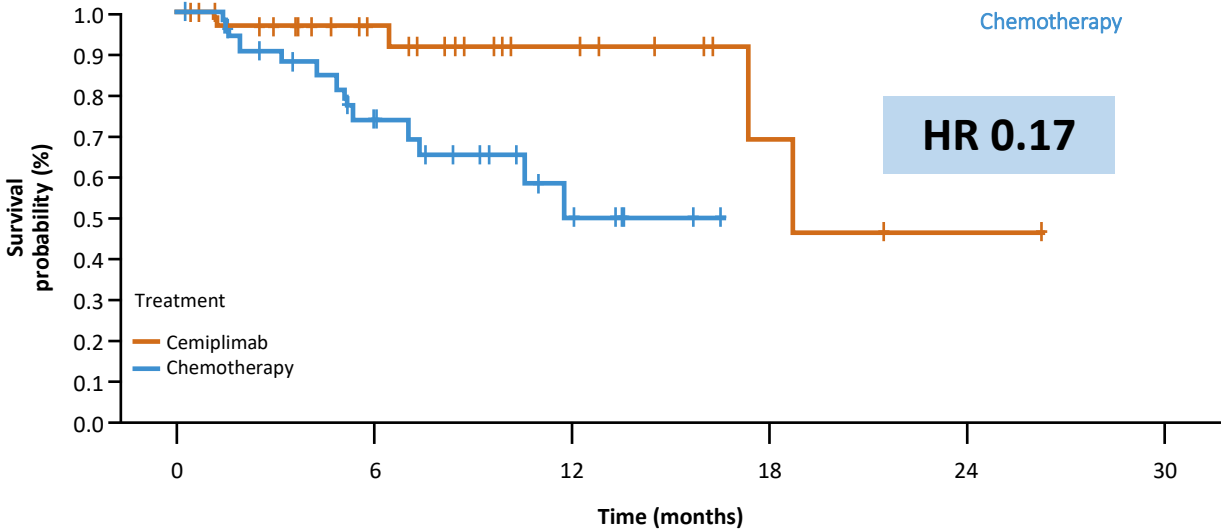
Progression free survival



	n	Median PFS (95% CI) months
Cemiplimab	283	8.2 (95% CI, 6.1–8.8)
Chemotherapy	280	5.7 (95% CI, 4.5–6.2)

mOS not reach

Kaplan-Meier Estimation of Overall Survival



HR 0.17

	No. of patients	Median OS, months (95% CI)
Cemiplimab	34	18.7 (17.3–NE)
Chemotherapy	34	11.7 (7.0–NE)

HR, 0.17 (95% CI, 0.04–0.78) *P*=0.0091*

- A total of 68 of the 563 (12.1%) patients had treated and clinically stable brain metastases at time of randomization

Number at risk

Cemiplimab	34	20	10	3	1	0
Chemotherapy	34	18	6	0	0	0

*Nominal *P*-value.
CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; NE, not evaluable; OS, overall survival.

Take home messages 1°L monoterapia PDL1 >50%

- Pembrolizumab attualmente è ancora lo standard.
- Atezolizumab ha dimostrato una OS NON superiore a Pembro ma comparabile, seppur con la difficoltà di un confronto tra studi con popolazioni diverse
- Per Atezo è attiva la cessione farmaco a prezzo simbolico fino alla pubblicazione in Gazzetta. Verosimilmente rimborsabilità a giugno 2022
- Possibilità di modulare i ricicli di terapia sia per Pembro (3w e 6w) sia per Atezo (2w, 3w e 4w)
- Dati molto promettenti sia di efficacia che di tollerabilità per cemiplibam. Rimborsabilità in estate ?
- In considerazione della competizione….Come e quanto cambieranno i costi di ICI ?

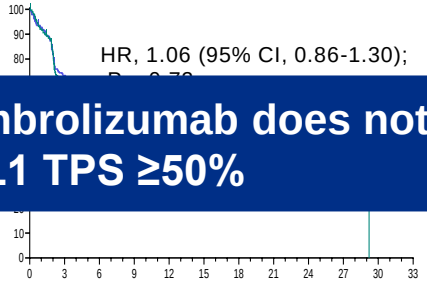
Keynote 598: Efficacy of Pembro-Ipi vs Pembro in PD-L1 expression ≥ 50% NSCLC patients

Summary of Response

	Pembro-Ipi N = 284	Pembro-Pbo N = 284
ORR, % (95% CI)	45.4% (39.5-51.4)	45.4% (39.5-51.4)
Best response, n (%)		
SD	70 (24.6%)	73 (25.7%)
PD		

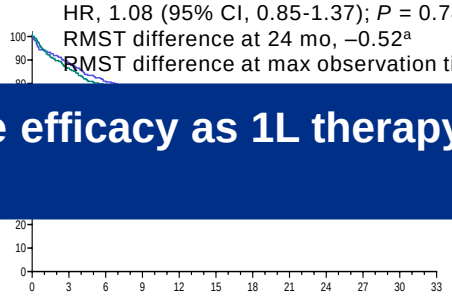
PFS by BICR

	Median (95% CI)
Pembro-Ipi	8.2 mo (6.0-10.5)
Pembro-Pbo	8.4 mo (6.3-10.5)



OS by BICR

	Median (95% CI)	RMST at 24 mo	RMST at Max Time
	21.4 mo (16.6-NR)	16.09 mo	18.76 mo
	21.9 mo (18.0-NR)	16.61 mo	19.32 mo

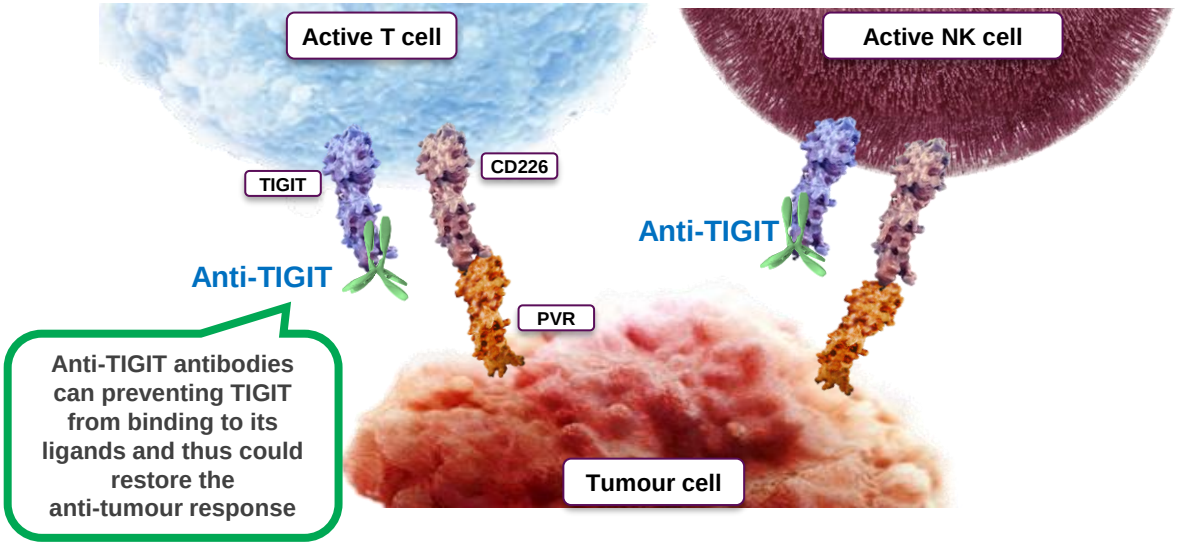


- **Adding ipilimumab to pembrolizumab does not improve efficacy as 1L therapy for stage IV NSCLC with PD-L1 TPS ≥50%**

Combo immunotherapy associates with greater toxicity and higher discontinuation rate

Boyer M, WCLC2020, Abstract 4248

Blocking TIGIT-mediated T cell inhibition may help reinitiate the anti-tumour immune response



Manieri et al. Trends Immunol 2017

CITYSCAPE: randomised Phase II study of tiragolumab + atezolizumab in PD-L1+ patients with NSCLC

Stratification factors
- PD-L1 TPS (1–49% vs ≥50%)
- Histology (non-squamous vs squamous)
- Tobacco use (yes vs no)

Co-primary endpoints
- ORR and PFS

Key secondary endpoints
- Safety, DOR, OS

Exploratory endpoints
- Efficacy analysis by PD-L1 status, PROs

Primary analysis[1]
- Cut-off date of 30 June 2019
- Median follow-up of 5.9 months

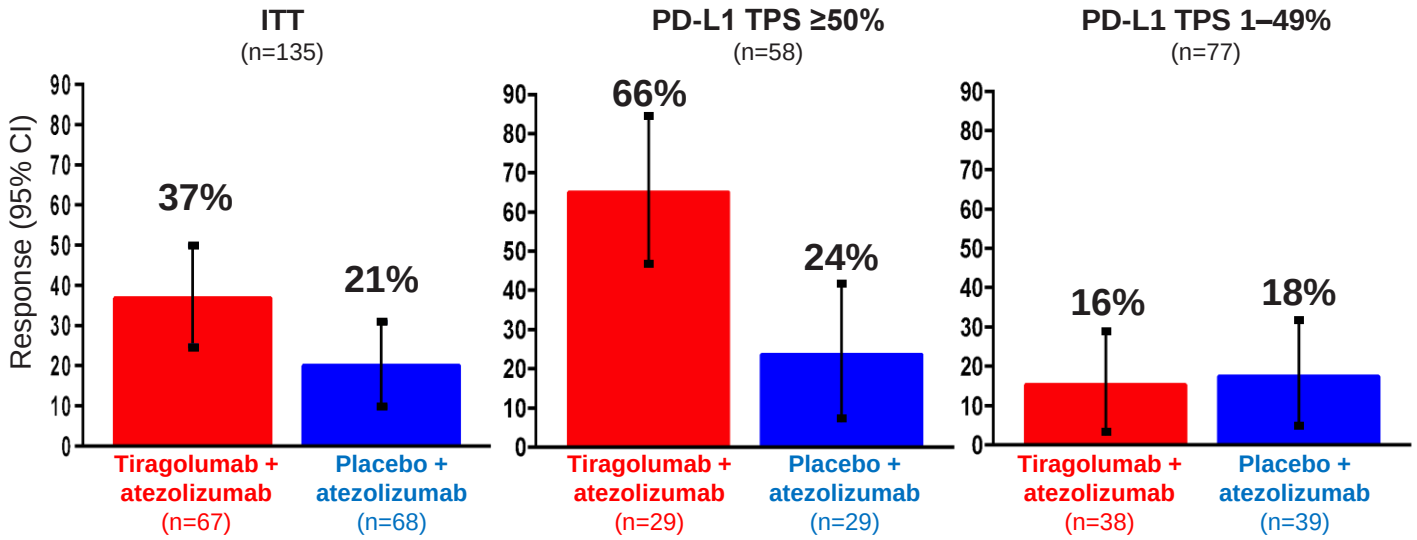
Updated analysis
- Follow-up performed to assess safety and efficacy
- Cut-off date of 16 August 2021
- Median follow-up of 30.4 months

1. Rodriguez-Abreu et al. ASCO 2020

DOR, duration of response; IHC, immunohistochemistry; ORR, confirmed overall response rate; OS, overall survival; PD, progressive disease PFS, progression-free survival; PROs, patient-reported outcomes; Q3W, every 3 weeks; TPS, tumour proportion score

ORR (updated analysis)

Median follow-up: 10.9 months



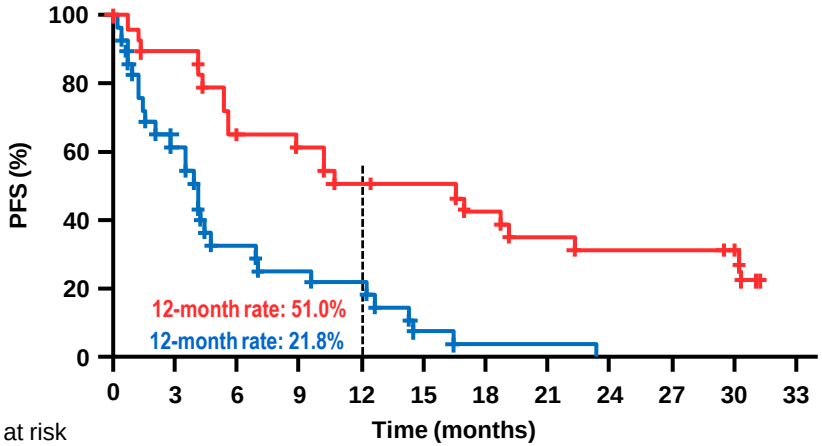
ORR benefit was pronounced in the high PD-L1 expression population (TPS ≥50%) but no additional benefit was observed in the TPS 1–49% population

Updated analysis data cutoff: 02 Dec 2019.

PD-L1 >50% subgroups (58pts)

PFS

	Events n (%)	Median PFS, months (95% CI)	PFS HR (95% CI)	ORR, %	Median DOR, months (95% CI)
Tira + atezo	21 (72.4)	16.6 (5.5–22.3)	0.29* (0.15–0.53)	69.0	15.7 (9.1–NE)
Placebo + atezo	28 (96.6)	4.1 (2.1–6.8)		24.1	8.2 (5.6–10.4)

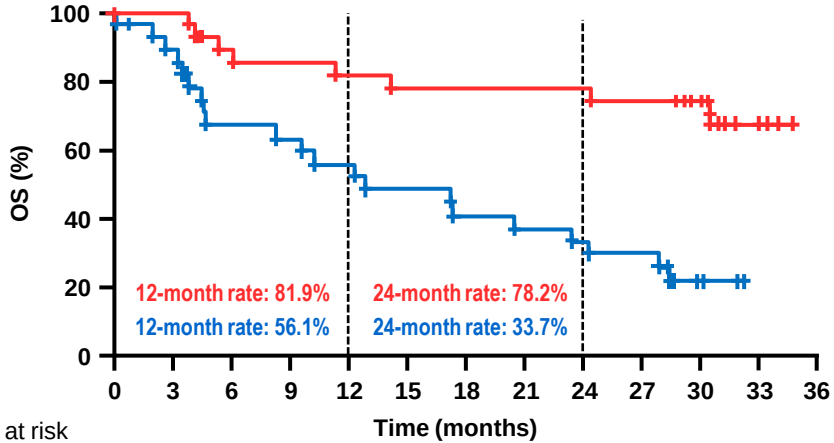


No. at risk

T + A	29	26	19	17	14	13	11	9	8	8	7	NE
P + A	29	17	9	7	6	2	1	1	NE	NE	NE	NE

OS

	Events n (%)	Median OS, months (95% CI)	HR (95% CI)
Tira + atezo	8 (27.6)	NE (30.3–NE)	0.23* (0.10–0.53)
Placebo + atezo	21 (72.4)	12.8 (4.7–24.2)	

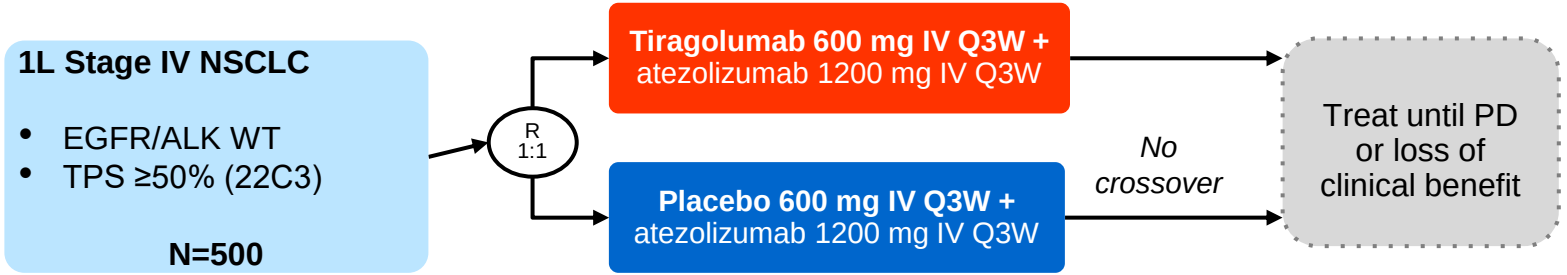


No. at risk

T + A	29	29	24	23	22	21	21	21	21	20	15	4	NE
P + A	29	25	18	17	15	13	11	10	9	8	3	NE	NE

SKYSCRAPER-01 (GO41717): tiragolumab + atezolizumab in PD-L1 TPS ≥50% 1L NSCLC

Phase III, double-blind study in 1L PD-1L-selected patients with NSCLC



Stratification factors
- ECOG (0 versus 1)
- Histology (NSQ versus SQ)
- Geographic region (Asian versus non-Asian)

Co-primary endpoints:
- OS in ITT
- PFS in ITT

Secondary endpoints:
- ORR, DOR, Landmark OS/PFS, PK/ADA, PRO, safety

SKYSCRAPER-01 (GO41717)

Press Release Roche 11.05.2022

- The study **did not meet its co-primary endpoint of PFS**
- The other co-primary endpoint of overall survival was immature and the study will continue until the next planned analysis
- The tiragolumab development programme continues as planned in non-small cell lung cancer and other cancer types
- A numerical improvement was observed in both co-primary endpoints.

MK-7684A-003 Study Design

Study Population

- Stage IV NSCLC
- PD-L1 TPS ≥1%
- No prior systemic treatment for stage IV disease
- *EGFR*-, *ALK*-, or *ROS1*-directed therapy not indicated
- ECOG PS 0 or 1
- No untreated or unstable brain metastasis
- Measurable disease per RECIST v1.1

Stratification factors

- ECOG PS: 0 vs 1
- PD-L1 TPS: 1%–49% vs ≥50%
- Region: East Asia vs non East Asia

N = 598
1:1

MK-7684A
(co-formulation of vibostolimab 200 mg with pembrolizumab 200 mg) IV Q3W
(35 cycles[a])

Pembrolizumab 200 mg IV Q3W
(35 cycles[a])

ON GOING

Agenda

PDL1 >50%

- Pembro o Atezo ?
- In futuro, cemiplimab ?
- Nuove associazioni ?

PDL1 < 50%

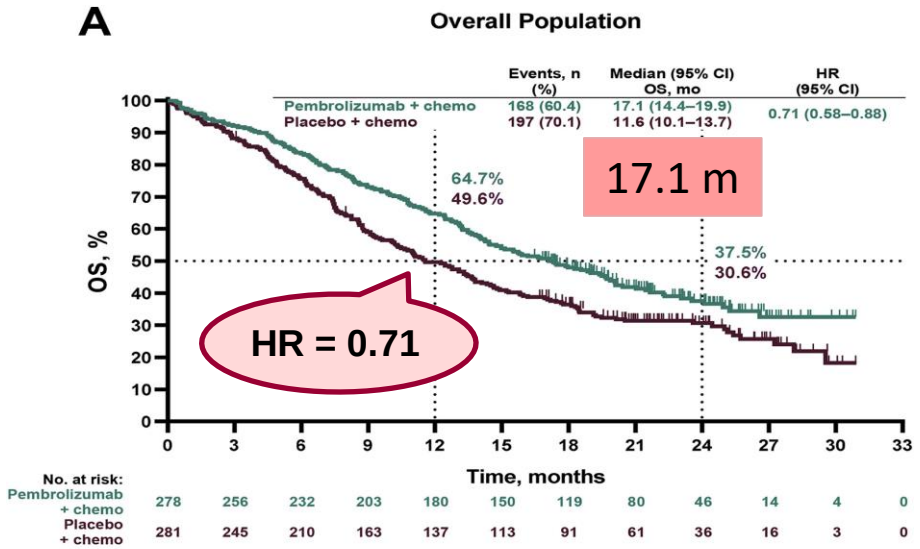
- CT+Pembro o CT+Ipi-Nivo ?

Gold standard attuale

KEYNOTE-407

Platinum + Taxane +/- Pembrolizumab

SQUAMOUS NSCLC



Paz-Ares L, et al. J Thor Oncol 2020

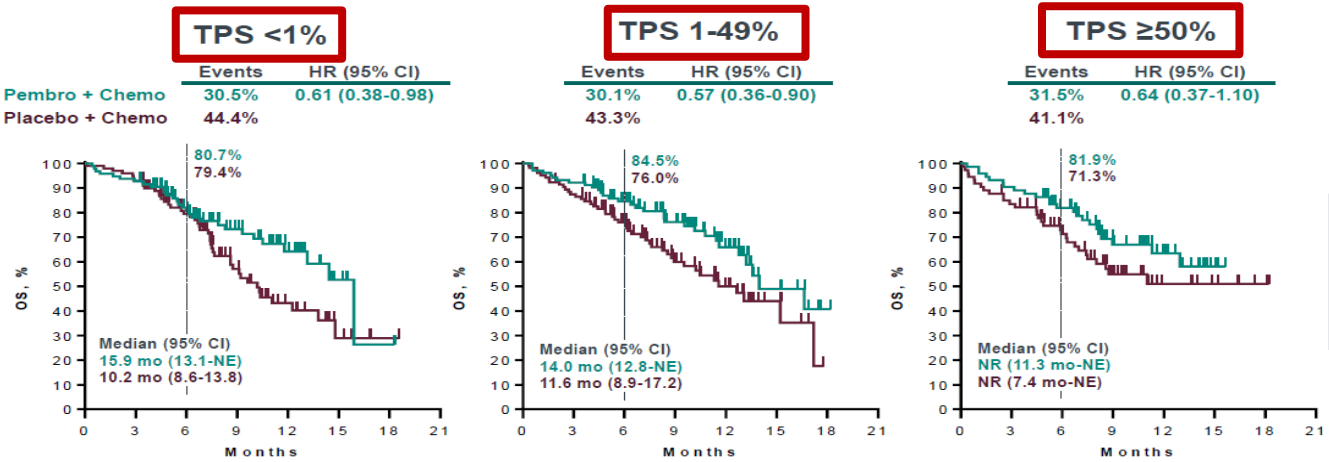
KEYNOTE-189

Platinum + pemetrexed +/- Pembrolizumab

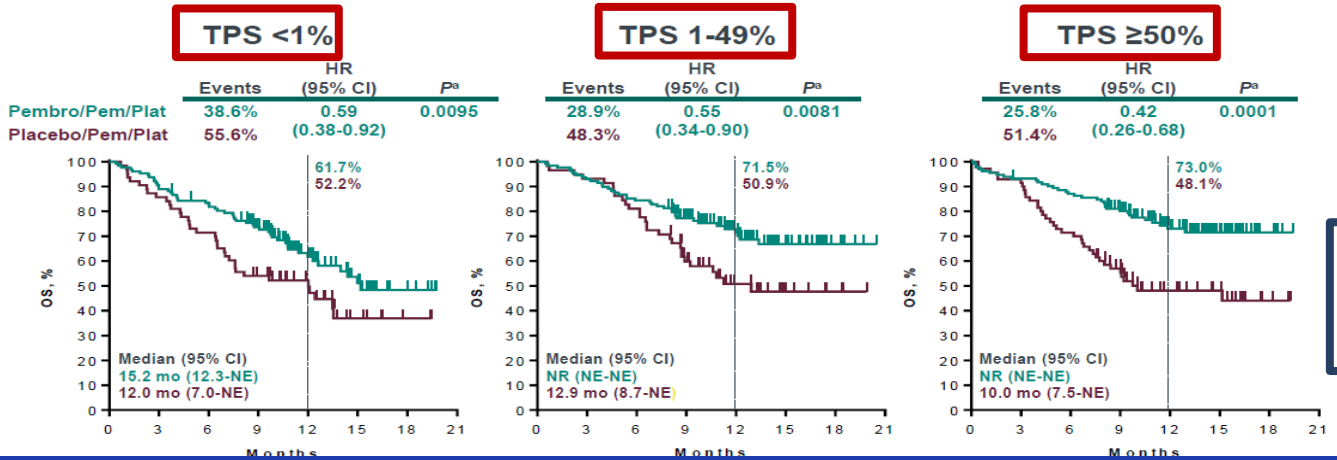
NON-SQUAMOUS NSCLC

Gray J.E. WCLC 2021 4-year FW

OS benefit across all PDL1 subgroups



KEYNOTE-407, SQ NSCLC



KEYNOTE-189, nonSQ NSCLC

CheckMate 9LA Study Design

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

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

R 1:1

NIVO 360 mg Q3W + IPI 1 mg/kg Q6W + Chemo[c] Q3W (2 cycles[d])

Post-Induction
NIVO 360 mg Q3W + IPI 1 mg/kg Q6W

Chemo[c] Q3W (4 cycles)

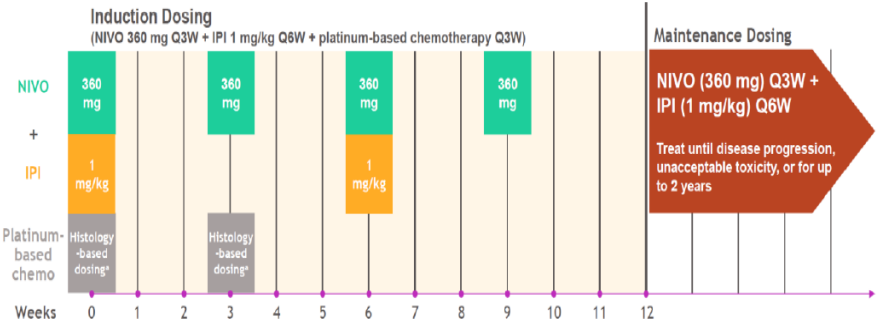
Optional
Pemetrexed maintenance (NSQ histology)

Treatment until disease progression, unacceptable toxicity, OR for 2 years for NIVO + IPI

Primary endpoint
- OS

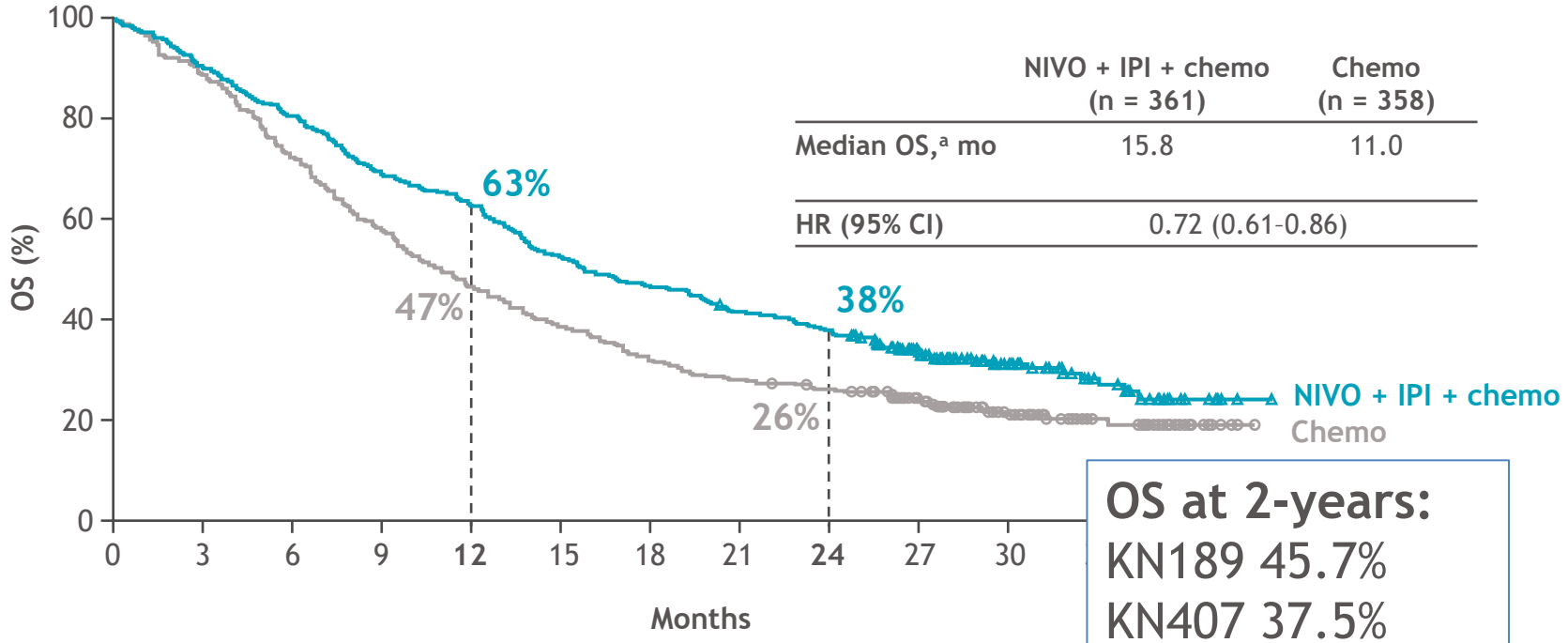
Secondary endpoints
- PFS by BICR[d]
- ORR by BICR[d]
- Efficacy by tumor PD-L1 expression

Exploratory endpoint
- Safety



	KN 189		KN 407		9LA	
	CT+ Pembro	CT	CT+ Pembro	CT	CT+ Nivo-Ipi	CT
Age (median)	65	64	65	65	65	65
PS1 %	31	31	74	68	68	68
Brain mets %	18	17	-	-	18	16
Never smokers	12	12	8	7	13	14
PDL1 < 1%	31	31	34	35	40	39

2-year update: OS in ITT population



	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS,[a] mo	15.8	11.0
HR (95% CI)	0.72 (0.61-0.86)	

OS at 2-years:
KN189 45.7%
KN407 37.5%

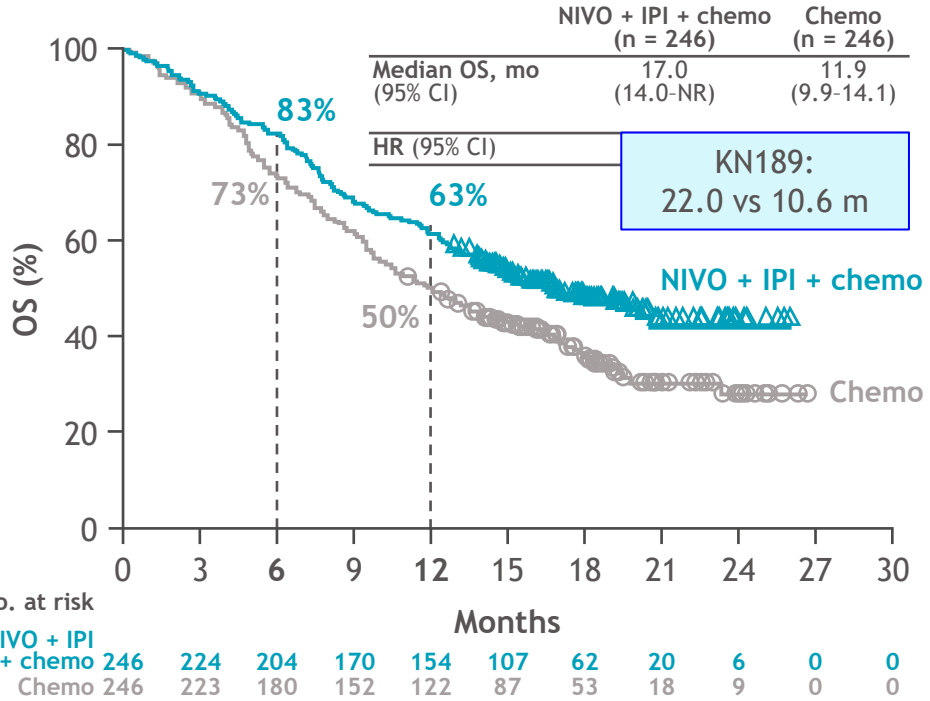
No. at risk

NIVO + IPI + chemo	361	326	292	250	227	191	170	150	137	95	50	23	7	0
Chemo	358	319	260	208	168	139	115	102	93	69	40	18	8	0

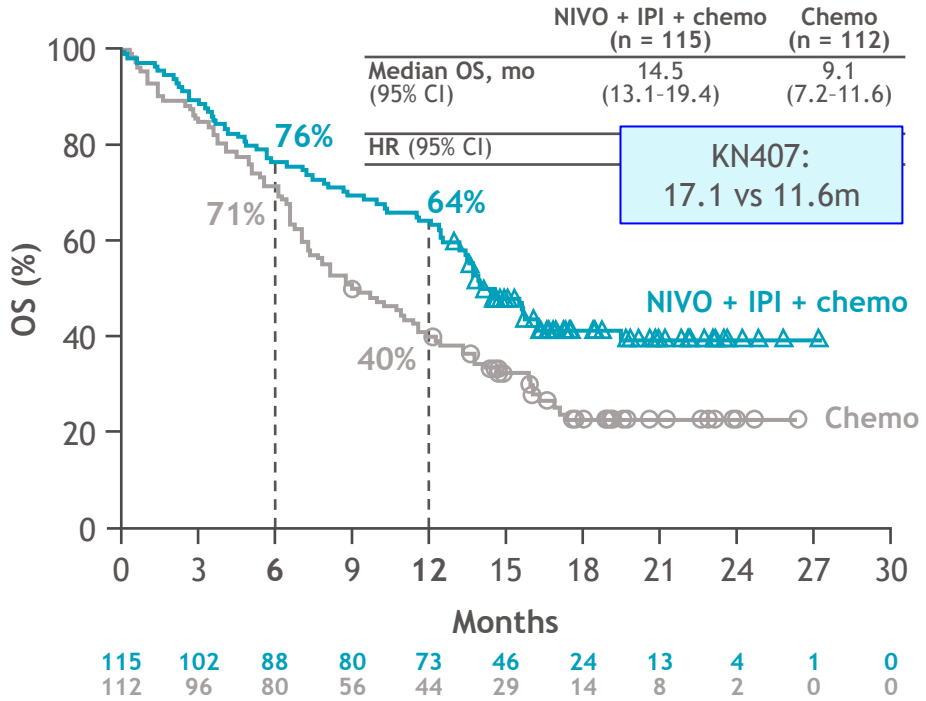
Reck M. ASCO 2021

Overall survival by histology

NSQ NSCLC[a]



SQ NSCLC[b]



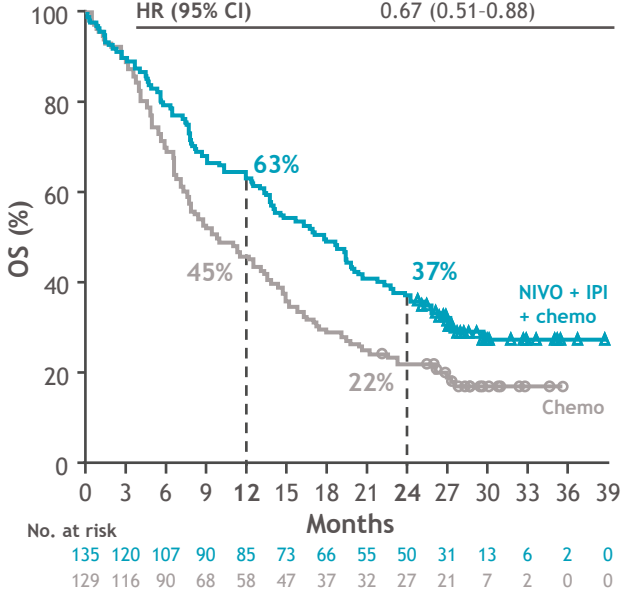
Minimum follow-up: 12.7 months.

Paz-Ares L., Lancet Oncol 2021

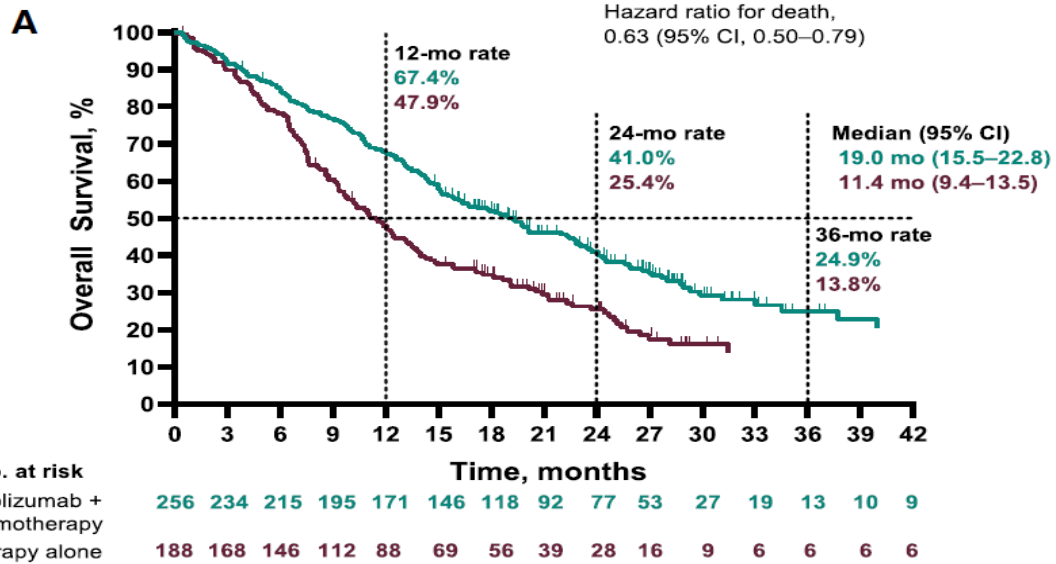
PD-L1 < 1%: efficacy outcomes

OS 9LA

	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
Median OS,[b] mo	17.7	9.8
HR (95% CI)	0.67 (0.51-0.88)	

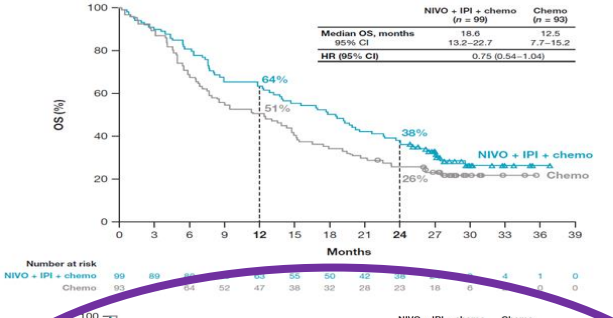


Pooled analysis KN189-407-021G, PD-L1 negativi

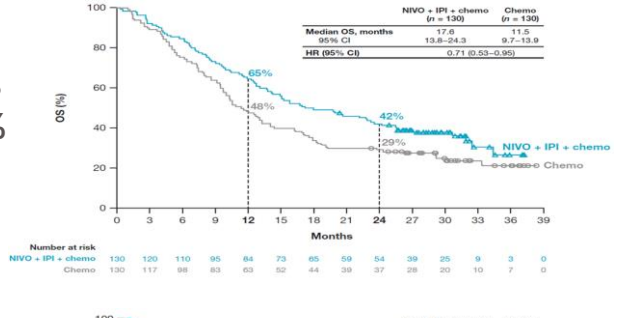


Overall survival (by histology and by PD-L1)

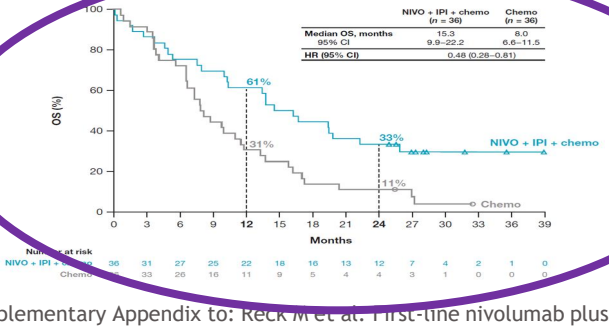
Non-squamous and PD-L1 <1%



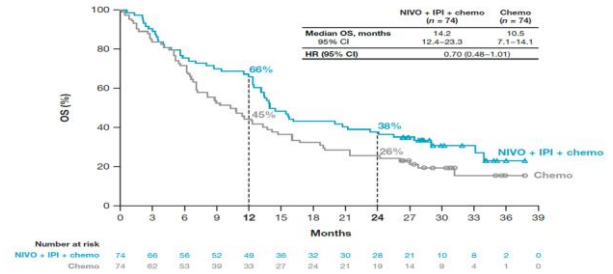
Non-squamous and PD-L1 ≥1%



Squamous and PD-L1 <1%



Squamous and PD-L1 ≥1%

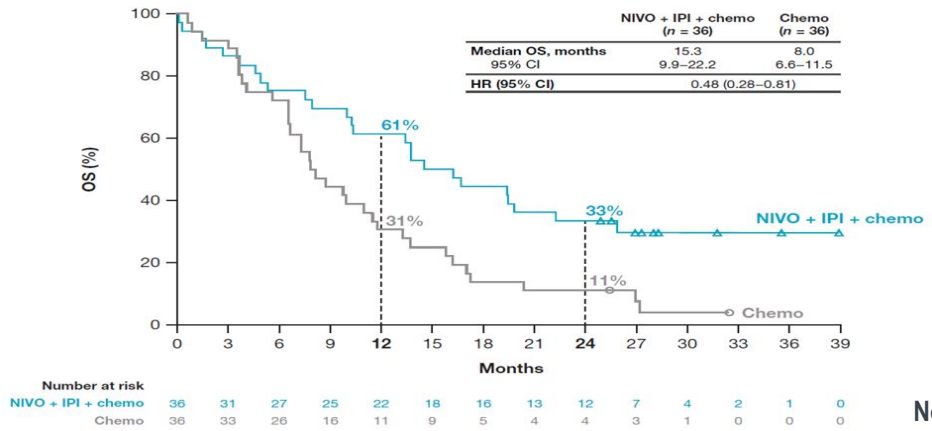


Adapted from Supplementary Appendix to: Reck M et al. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update. ESMO Open 2021

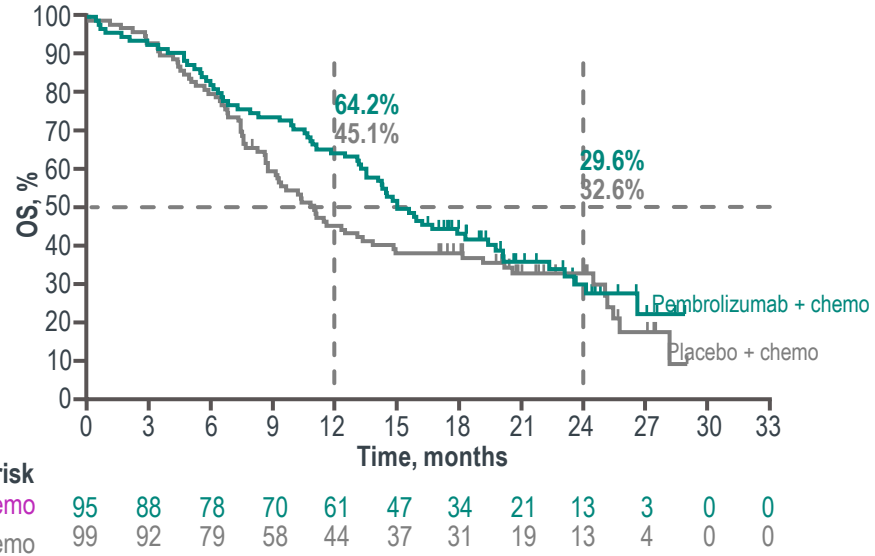
Overall survival (by histology and by PD-L1)

Squamous and PD-L1 <1%

9LA



KN407



Studio	Fase	Braccio sperimentale	Braccio standard	End point primario
Pagathor	II	Pembro+SAR444245 (IL2 pegilata)	-	PFS
Orient 11 (NSQ)	III	CT+Sintilimab	CT	PFS
Orient 12 (SQ)	III	CT+Sintilimab	CT	PFS
LEAP 006 (NSQ)	III	CT+pembro+lenvatinib	CT-IO	PFS e OS
KEYLYNK 006 (mantenimento) NSQ	III	Pembro+olaparib	Pembro+pemetrexed	PFS e OS
KEYLYNK 008 (mantenimento) SQ	III	Pembro+olaparib	Pembro	PFS e OS
MK-7684A-003	III	MK768 (anti-TIGIT + Pembro)	Pembro	PFS e OS

Conclusioni

- La schedula del 9LA è più articolata: sarà necessario un rodaggio in pratica clinica.

- Il braccio standard del 9LA, sola CT, in realtà non è più lo standard attuale indipendentemente da istologia ed espressione di PD-L1. Sarà necessario attendere un follow-up più lungo per valutare un eventuale effetto memoria di IPI

- Sarebbe interessante poter confrontare, in futuro, in uno studio di «real life» i risultati degli schemi KN189, KN407 e 9LA

Conclusioni

- 2 cicli CT convertono i tumori freddi in caldi
- In vitro gli effetti immunomodulatori di pemetrexed e paclitaxel sono ridotti dalla combinazione con il platino.
- Se l'ICI possa essere combinata ad uno schema *platinum-free* è ancora da definire con studi futuri
- Questo è il concetto della «CHEMO-REFORM»[1] : ICI associata a monoCT (senza platino), platino da solo, basse dosi di CT (metronomica)

1. Deng H. Transl Lung Cancer 2021;10(4):1924

CARCINOMA POLMONARE:
QUALI NOVITÀ NEL 2022?

20 Maggio 2022

IRCCS "Sacro Cuore - Don Calabria"
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Terapia di 1 linea: opzioni attuali e prospettive terapeutiche

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