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.

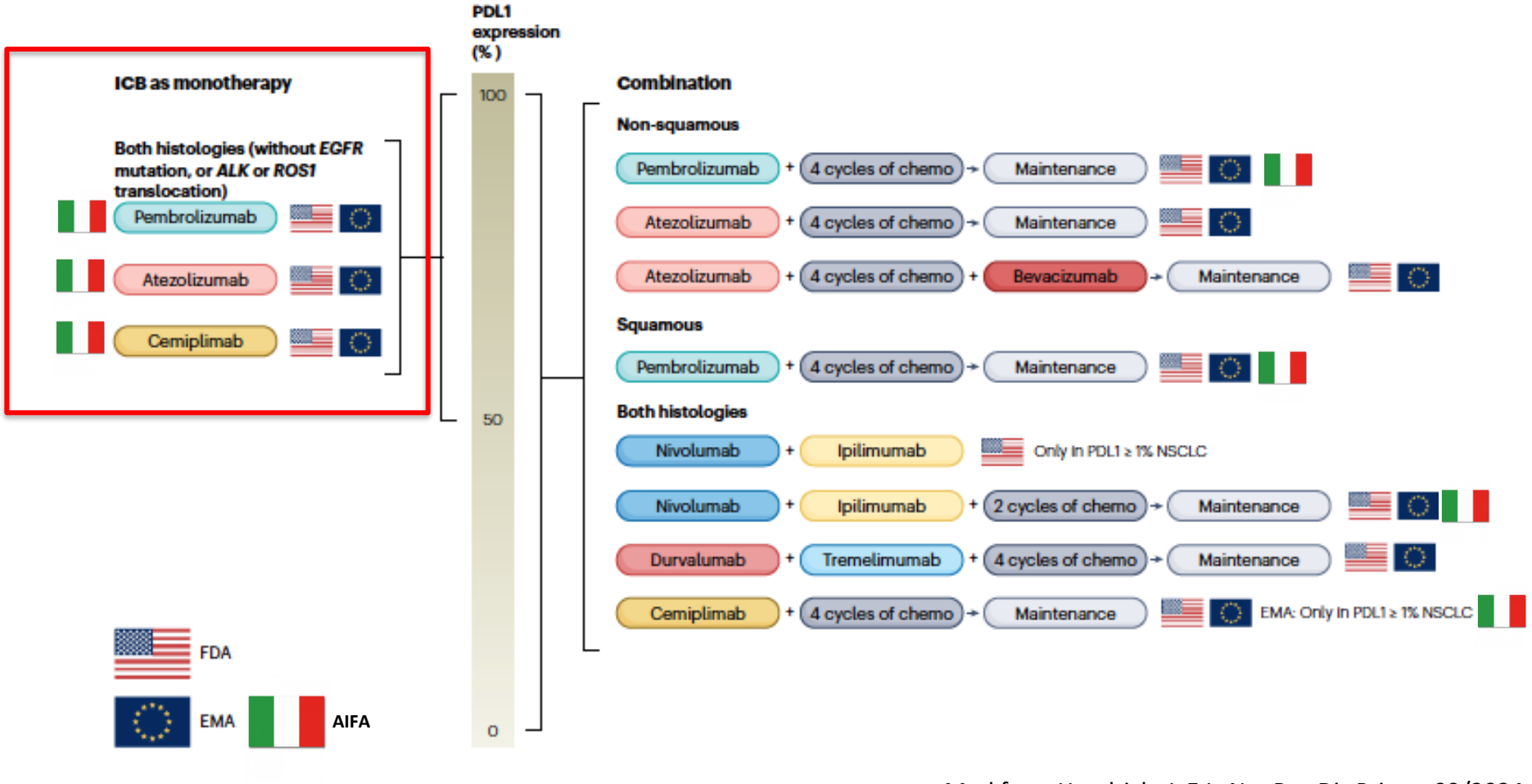
Agenda

PDL1 >50%

- Pembro, Atezo o cemiplimab ?
- Nuove formulazioni
- Ivonescimab

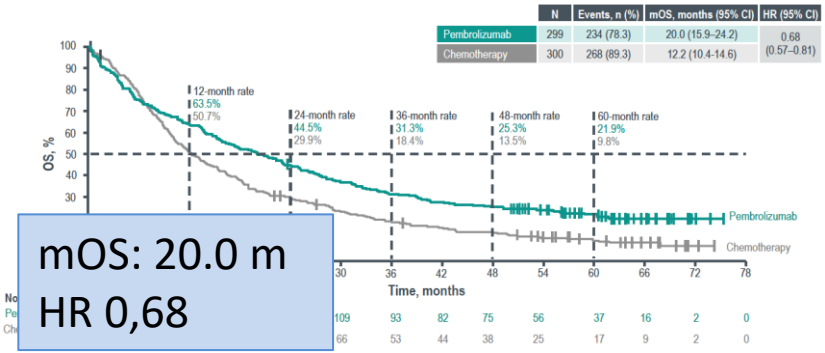
PDL1 < 50%

- CT+Pembro o CT + Cemiplimab o CT+Ipi-Nivo ?
- Dati sui PDL1 <1%
- Prospettive furure (ADC, LAG3, vaccini ecc)



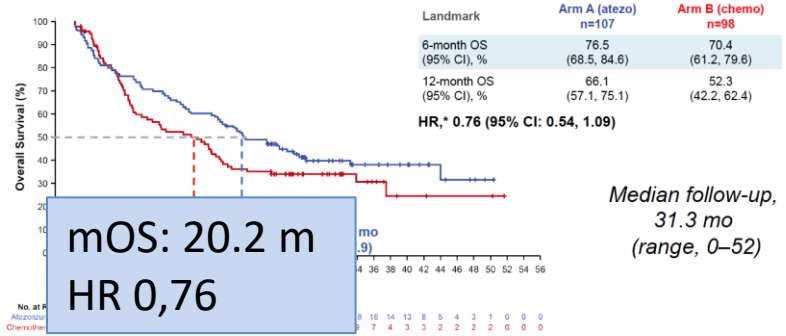
Mod from Hendricks L.E.L. Nat Rev Dis Primer 09/2024

KEYNOTE-042: 5-year Update of OS – PDL1 > 50%



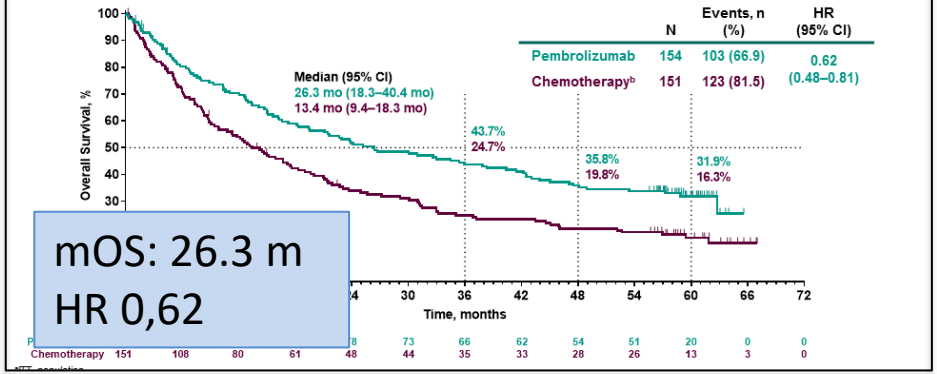
mOS: 20.0 m
HR 0,68

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



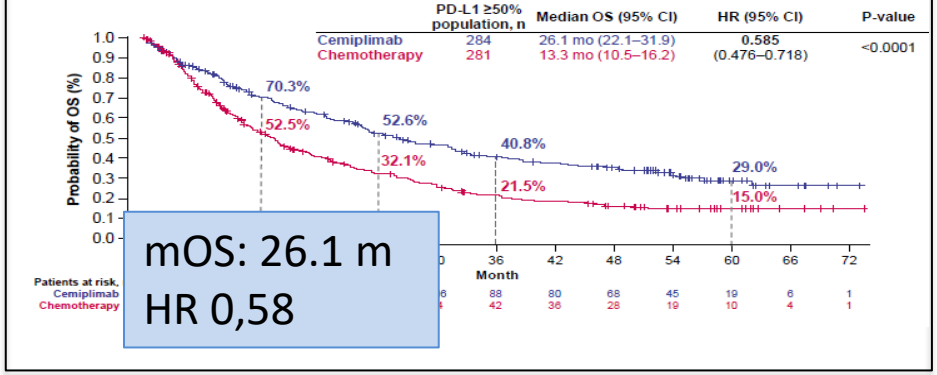
mOS: 20.2 m
HR 0,76

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



mOS: 26.3 m
HR 0,62

EMPOWER – Lung 1: 5-year Update of OS – PDL1 > 50%



mOS: 26.1 m
HR 0,58

EMPOWER-Lung-1

Key eligibility criteria
- Treatment-naive advanced NSCLC
- PD-L1 ≥50%
- No *EGFR*, *ALK* or *ROS1* mutations
- ECOG performance status 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

Stratification factors
- Histology (squamous vs non-squamous)
- Region (Europe, Asia or ROW)

Endpoints
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL and safety

R 1:1

Arm A
Cemiplimab monotherapy
350 mg IV Q3W
Treat until Progressive Disease or 108 weeks

Progressive Disease

Optional continuation of cemiplimab + 4 cycles of chemotherapy

Arm B
4–6 cycles of investigator's choice chemotherapy

Progressive Disease

Optional crossover to cemiplimab monotherapy

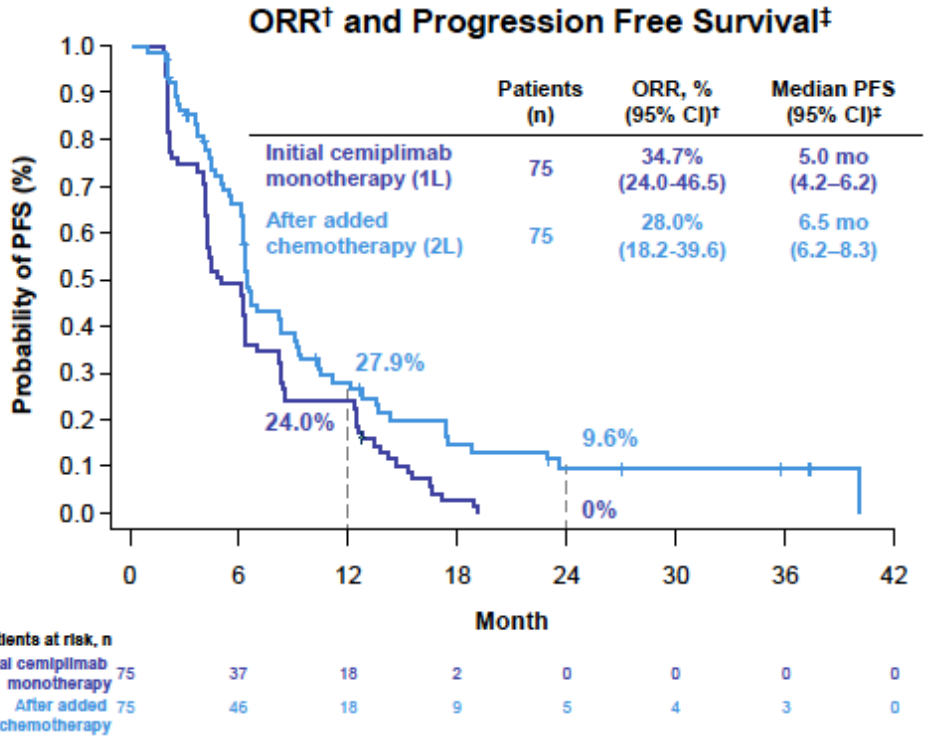
Follow-up

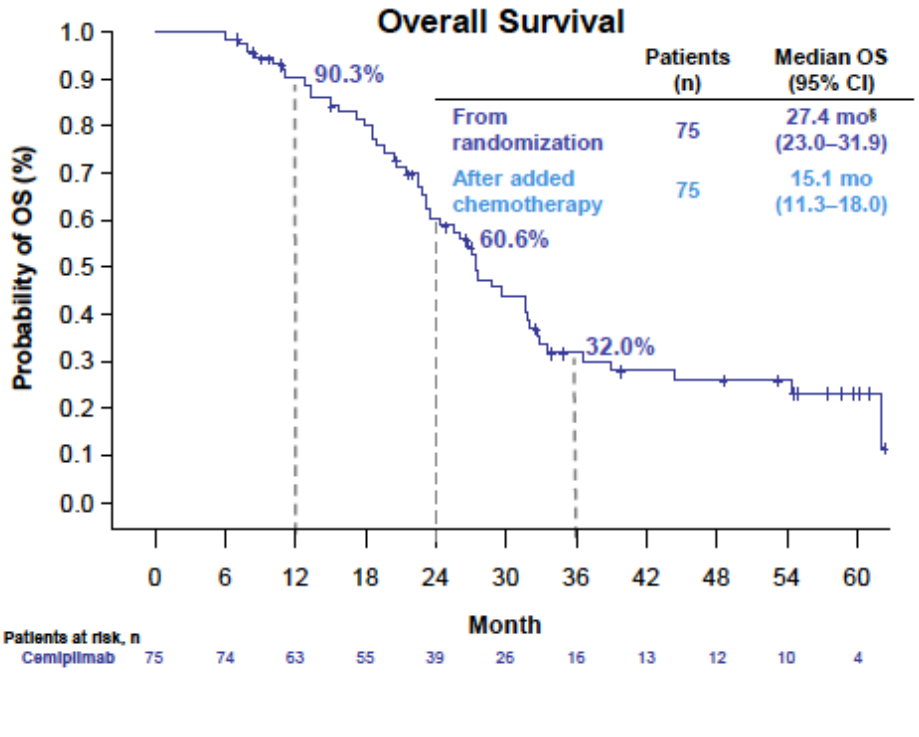
ITT (N=712†)

PD-L1 ≥50% population (N=565†)
PD-L1 testing by 22C3 assay performed per instructions for use

Here we report data per cutoff of 4 March 2022
Median time from randomisation to data cutoff: 37.1 months (range: 24.0– 56.5)

Cemiplimab with addiction of chemotherapy beyond progression



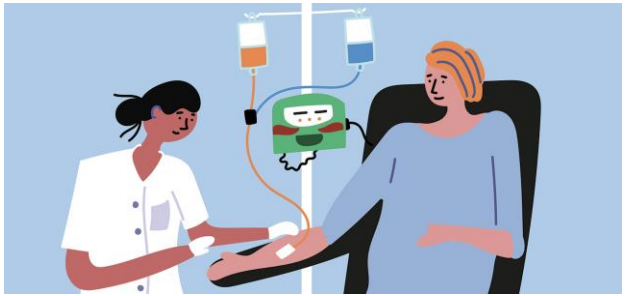


Una nuova strategia ? Potenziamento di una prima linea….NON approvato AIFA

Impatto psicologico della via di somministrazione

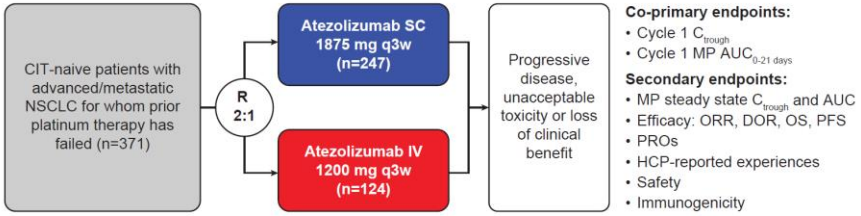
…. allora non sono così grave

…. insomma potevo stare peggio

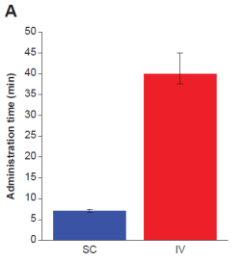


…. sono proprio messo male !!

IMscin001 (Part 2) – Ph 3



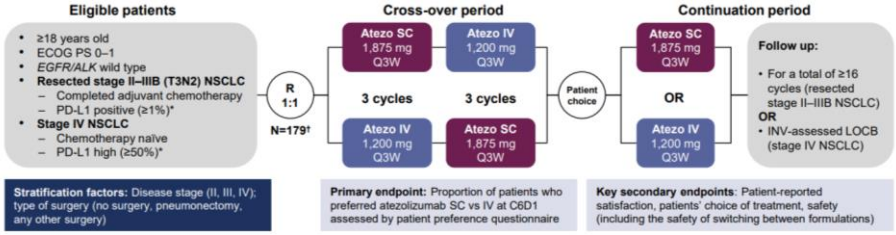
Efficacy was similar between arms

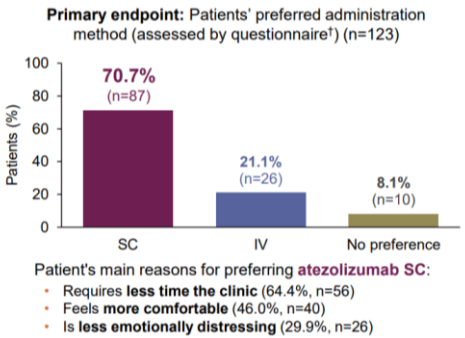


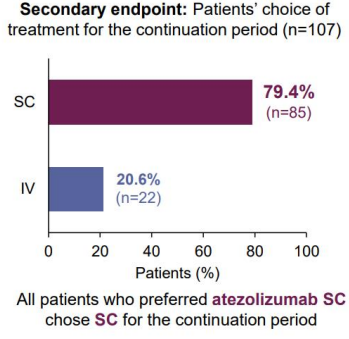
The median administration time:

- **7.1 minutes** for atezolizumab SC
- 40 minutes for atezolizumab IV

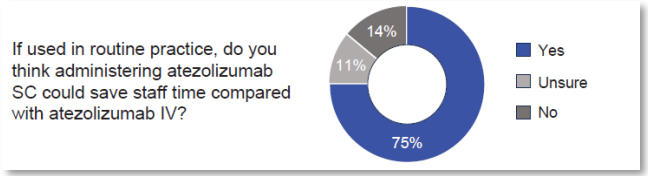
IMscin002 – Ph 2







HCP-reported experiences



Burotto et al Annals of Oncology 2023, volume 34, Issue 8 (693-702)

Come fare la scelta terapeutica ? Opinione personale

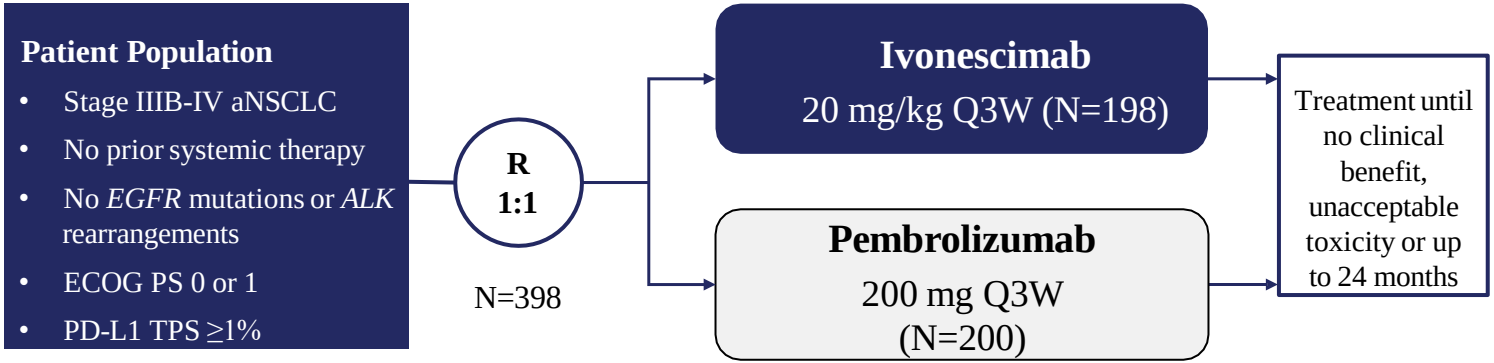
	Pembrolizumab	Atezolizumab	Cemiplimab
Dati OS a 3-5 anni	++	++	+++
Esperienza d'uso	+++	++	+
Modulazione intervallo ricicli	++	++	-
Modulazione via somministrazione	-	+	-
Tossicità	+	+	+
Indicazione St. IIIB	-	-	+
Costi	+	++	+

Prezzo s.c. ?

HARMONi-2 (AK112-303) Study Design

Ivonescimab (AK112) is a novel bispecific antibody against PD-1 and VEGF

A randomized, double-blind, phase 3 study[a]



Stratification

- Clinical stage (IIIB/C vs. IV)
- Histology (SQ vs. non-SQ)
- PD-L1 TPS (≥50% vs. 1-49%)

Endpoints

Primary: PFS by blind IRRC per RECIST v1.1
Secondary: OS, PFS assessed by INVs, ORR, DoR, TTR and safety
Exploratory: QoL

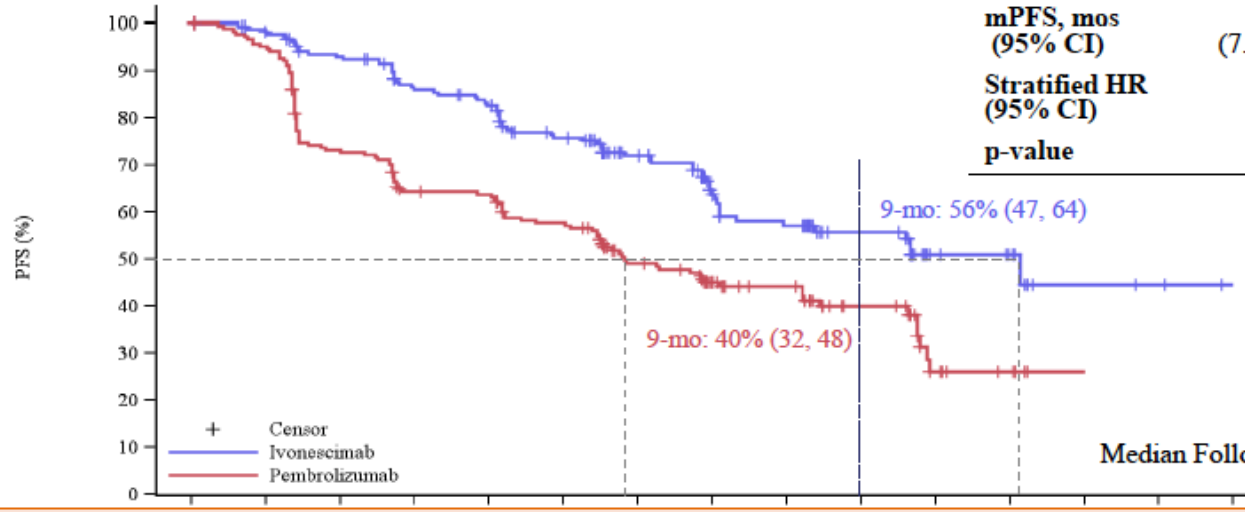
Potential issues

-relevance of pembro monotherapy as comparator for TPS 1-49%
-all China enrollment

[a] Pa

Primary endpoint: PFS per IRRC

	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	11.14 (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	0.51 (0.38, 0.69)	
p-value	<0.0001	



KN042 mPFS 5.4 m
IM110 mPFS 5.8 m

PFS benefit is striking, with almost doubling of mPFS.

Ivonescimab	198(0)	189(3)	175(13)	156(26)	148(32)	128(44)	99(50)	68(60)	59(67)	38(68)	14(71)	11(71)	3(72)	2(72)	0(72)
Pembrolizumab	200(0)	187(9)	141(52)	121(69)	119(70)	103(81)	74(95)	53(101)	45(102)	25(106)	9(112)	5(112)	0(112)		

Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 months improvement in mPFS.

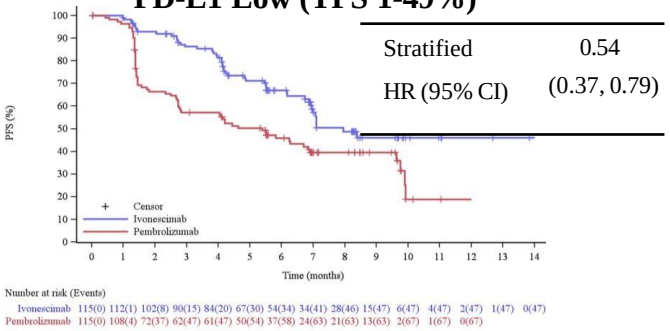
Abbreviations: mPFS, median progression-free survival; IRRC, independent radiology review committee; mo, month; NE, not estimable; HR: hazard ratio; CI, confidence interval.

Key PFS Subgroup Analyses

PD-L1 expression

NSCLC Histology

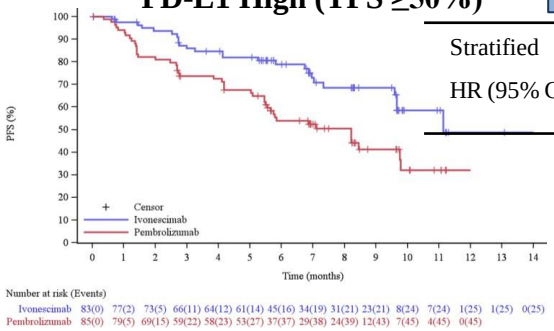
PD-L1 Low (TPS 1-49%)



Stratified HR (95% CI): 0.54 (0.37, 0.79)

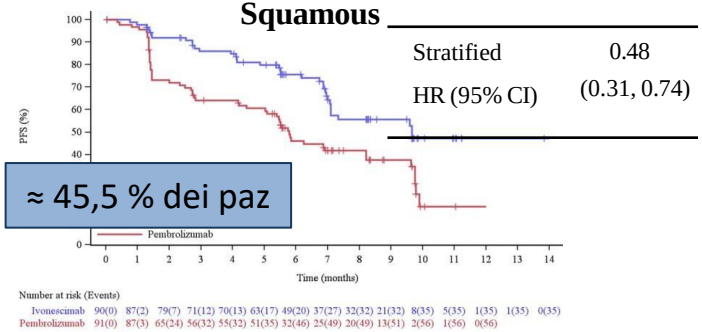
PD-L1 High (TPS ≥50%)

≈ 42% dei paz



Stratified HR (95% CI): 0.46 (0.28, 0.75)

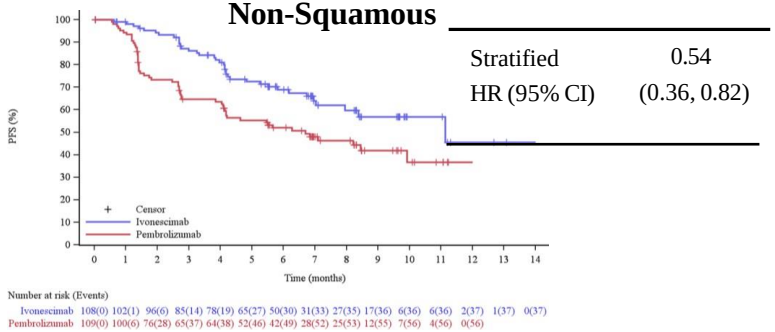
Squamous



≈ 45,5 % dei paz

Stratified HR (95% CI): 0.48 (0.31, 0.74)

Non-Squamous

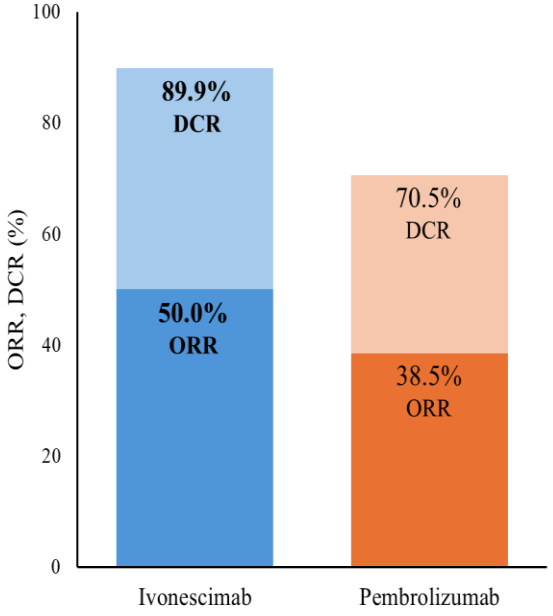


Stratified HR (95% CI): 0.54 (0.36, 0.82)

Ivonescimab showed meaningful improvement in PFS vs. pembrolizumab in patients with both low and high PD-L1, with squamous or non-squamous advanced NSCLC.

Abbreviations: PFS, progression-free survival; PD-L1, programmed death ligand 1; TPS, tumor proportion score; HR: hazard ratio; CI, confidence interval; NSCLC, non-small cell lung

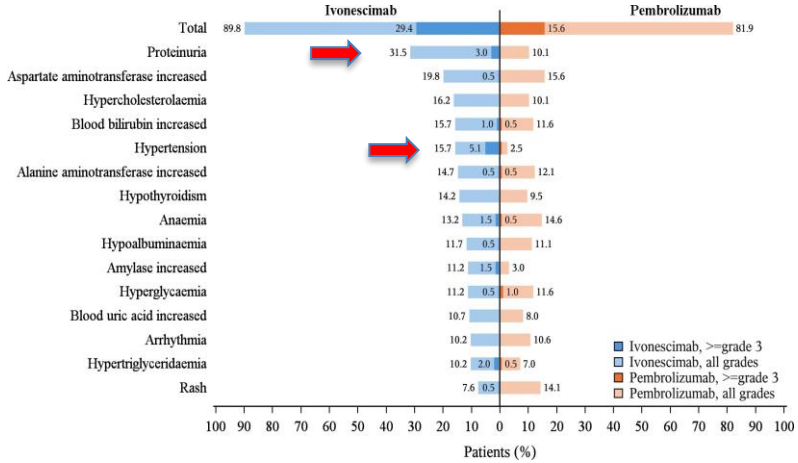
ORR, DCR and DoR per IRRC

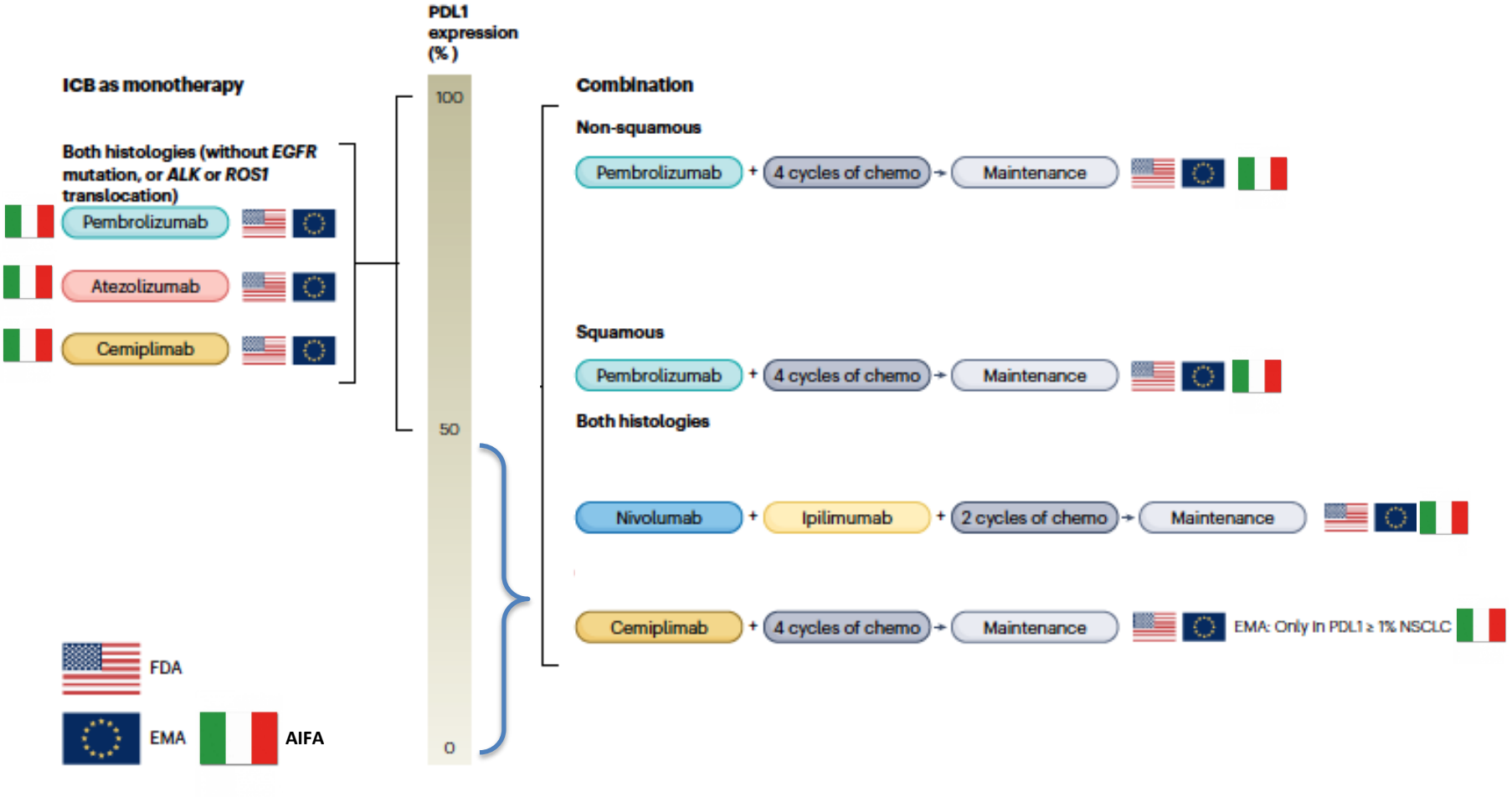


TRAEs

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
TRAEs (all grades)	177 (89.8)	163 (81.9)
Grade≥3	58 (29.4)	31 (15.6)
Serious TRAEs	41 (20.8)	32 (16.1)
Leading to discontinuation	3 (1.5)	6 (3.0)
Leading to death	1 (0.5)	2 (1.0)

Gr≥3 TRAEs almost doubled although no increase in TRAE leading to discontinuation or death





Mod from Hendricks L.E.L. Nat Rev Dis Primer 09/2024

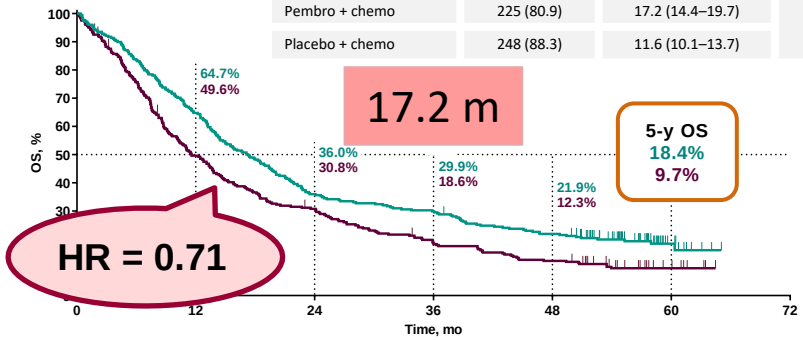
CT + Pembrolizumab

KEYNOTE-407

Platinum + Taxane +/- Pembrolizumab

SQUAMOUS NSCLC

	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85)
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	



	278	180	100	83	60	10	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

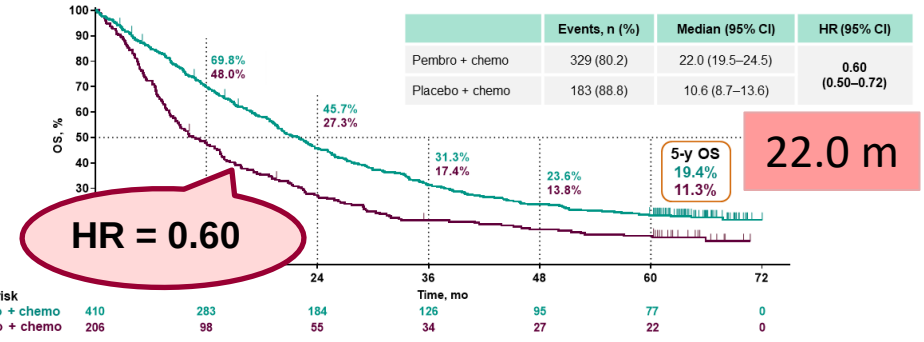
Novello S. ESMO 2022

KEYNOTE-189

Platinum + pemetrexed +/- Pembrolizumab

NON-SQUAMOUS NSCLC

	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	



	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

aplan-Meier estimate. Data cutoff date: March 8, 2022.

Garassino M, ESMO 2022

CT + Cemiplimab

Phase 3 Study of Cemiplimab Plus CT in Patients With Advanced NSCLC (Study 16113; EMPOWER-Lung 3 [Part 2]) - NCT03409614[1]

EMPOWER-Lung 3 is a two-part, double-blind, placebo-controlled, randomised Phase 3 study

Key Eligibility Criteria

- Treatment-naïve stage IIIB/C* or IV NSCLC (non-squamous or squamous†)
- Any PD-L1 expression‡
- No *EGFR*, *ALK* or *ROS1* aberrations
- ECOG PS 0 or 1
- Adequately treated, clinically stable CNS metastases§

Stratification Factors:

- PD-L1 expression (<1% vs 1–49% vs ≥50%)
- Histology (squamous vs non-squamous)

R 2:1
N=466

Arm A
Cemiplimab 350 mg Q3W + investigators' choice platinum-doublet CT Q3W (4 cycles)‖

Treat until RECIST 1.1-PD, unacceptable toxicity, or up to 108 weeks¶

Arm B
Placebo Q3W + investigator's choice platinum-doublet CT Q3W (4 cycles)‖

Treat until RECIST 1.1-PD, unacceptable toxicity, or up to 108 weeks¶

Primary endpoint

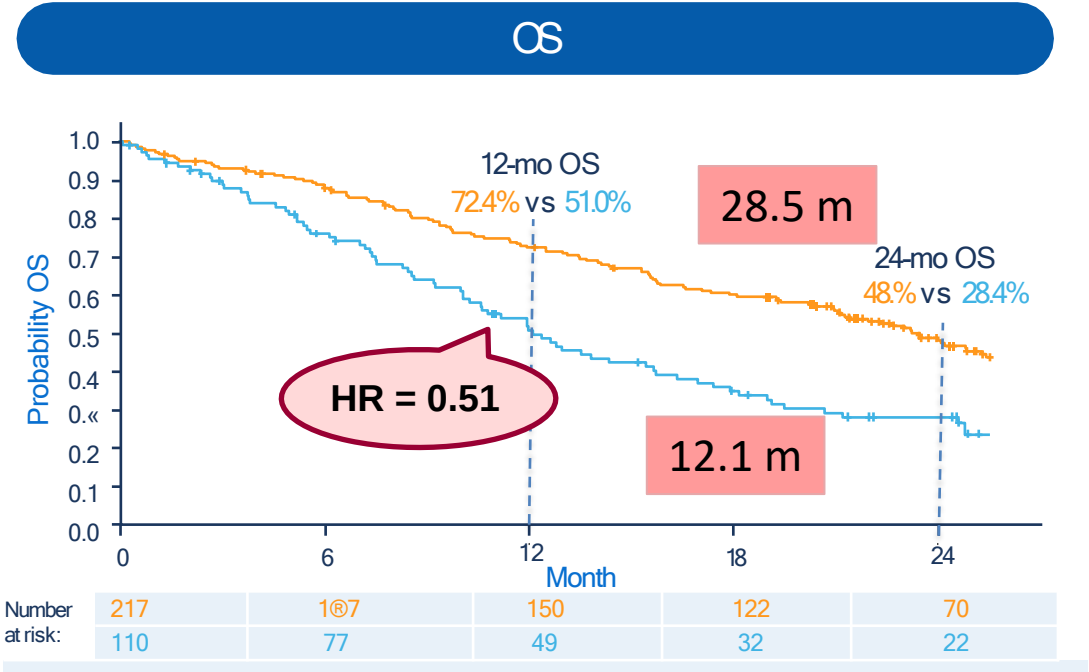
- OS

Secondary endpoints

- PFS#, ORR#, DOR#, safety, PK, PROs, and immunogenicity

CT + Cemiplimab

Empower Lung 3: PD-L >1% - 2 y FW



Per PDL1 <1%
HR 0.94

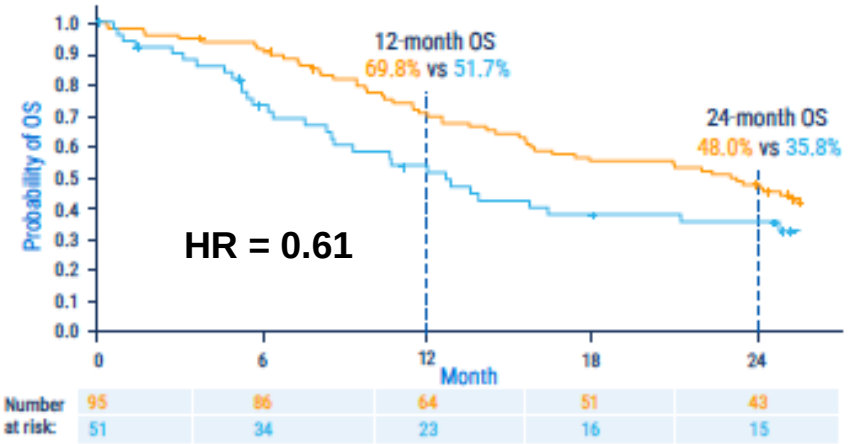
Da luglio 2024 rimborsato CT+Cemiplimab per **PDL1 1-49%**

Nell'ITT (anche PDL1 < 1%) HR 0.65, mOS 21,1 m

CT + Cemiplimab

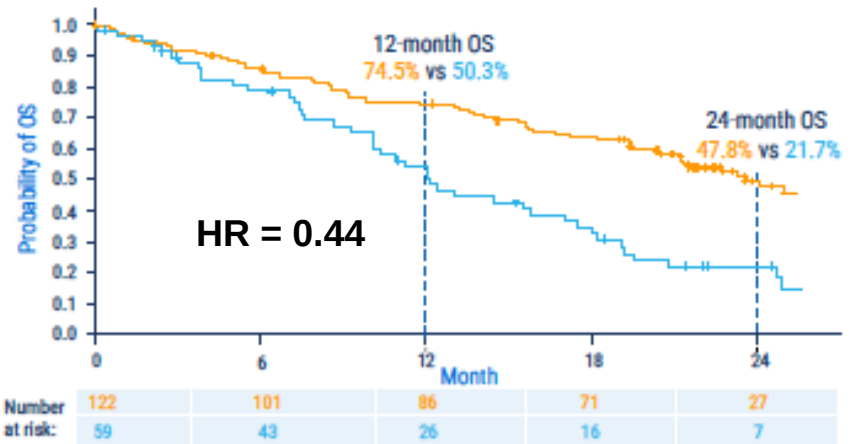
Empower Lung 3: PD-L >1% - 2 y FW

Squamous NSCLC



	Cemiplimab + CT (n=95)	Placebo + CT (n=51)
Median OS, months (95% CI)	23.2 (15.7–28.0)	12.6 (8.3–21.2)
HR (95% CI); *P* value	0.61 (0.40–0.94); *P*=0.0241*†	

Non-squamous NSCLC



	Cemiplimab + CT (n=122)	Placebo + CT (n=59)
Median OS, months (95% CI)	23.5 (20.2–NE)	12.1 (10.0–17.0)
HR (95% CI); *P* value	0.44 (0.30–0.66); *P*<0.0001*†	

CheckMate 9LA Study Design[a]

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)

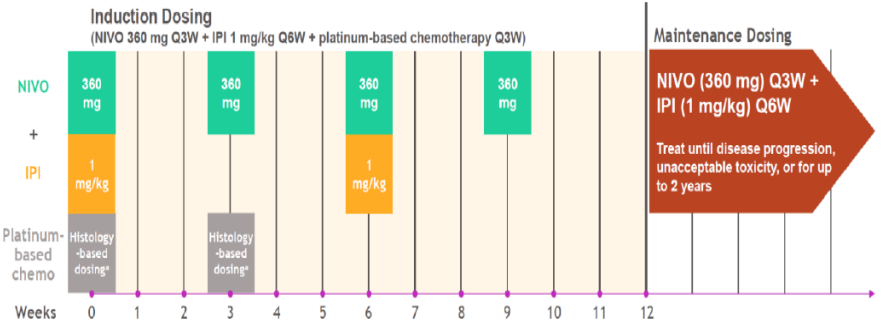
Optional
Pemetrexed maintenance (NSQ histology)

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

Primary endpoint
- OS

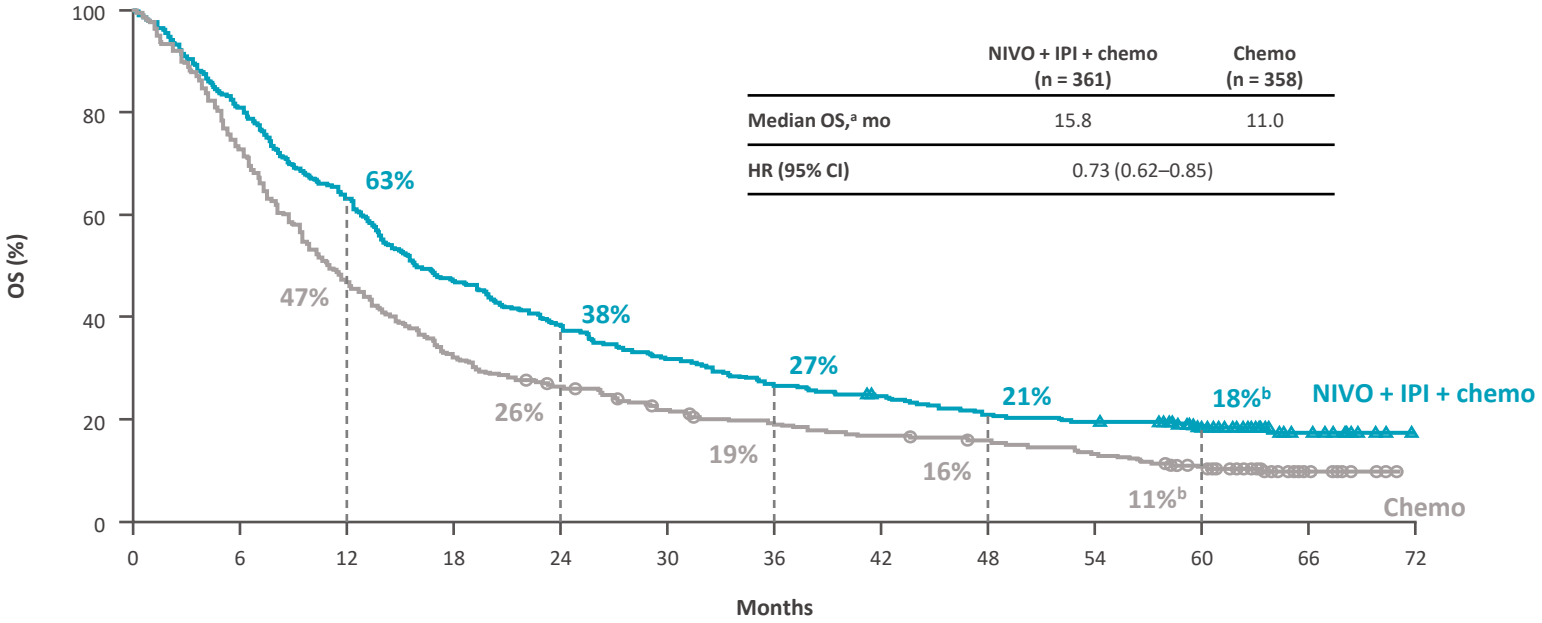
Secondary endpoints
- PFS by BICR[d]
- ORR by BICR[d]
- Efficacy by tumor PD-L1 expression

Exploratory endpoint
- Safety



CheckMate 9LA Study
OS in all randomized patients
(5-year clinical update)

A. All randomized



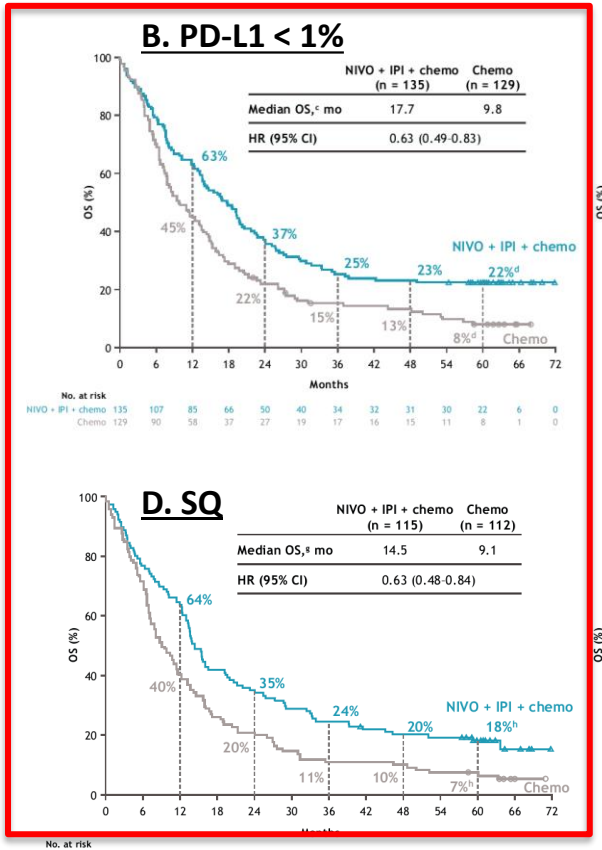
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS,[a] mo	15.8	11.0
HR (95% CI)	0.73 (0.62–0.85)	

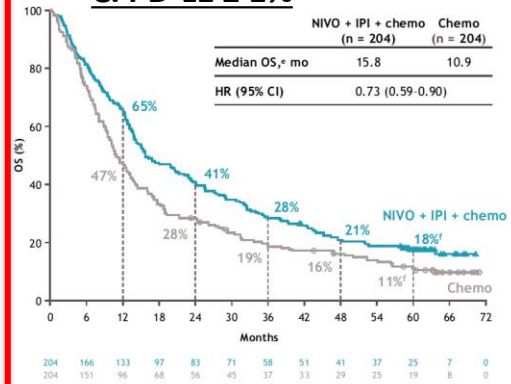
No. at risk

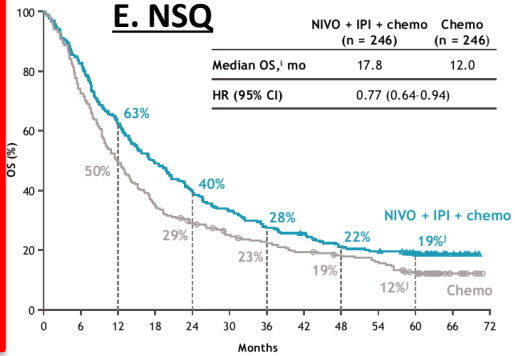
NIVO + IPI + chemo	361	292	227	170	138	115	96	87	74	69	48	13	0
Chemo	358	260	168	115	93	74	63	55	50	42	30	9	0

CheckMate 9LA Study

OS in subgoups

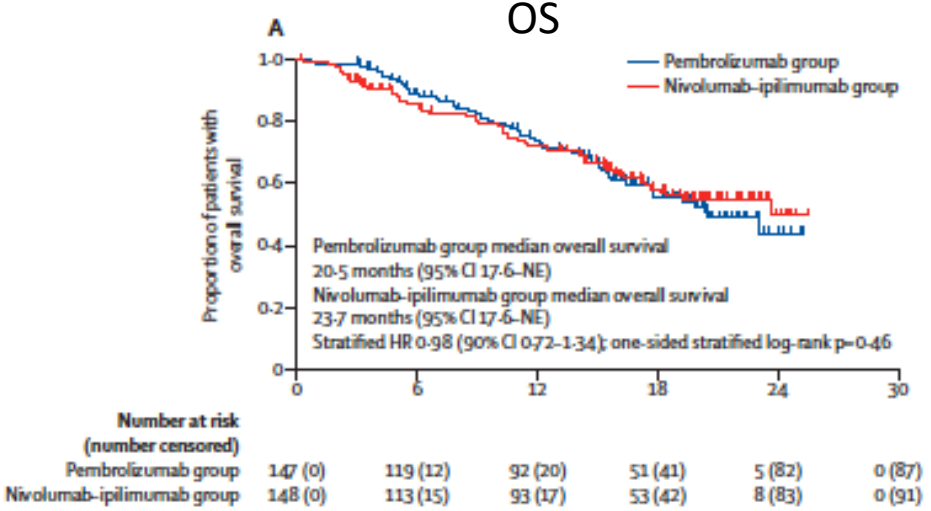






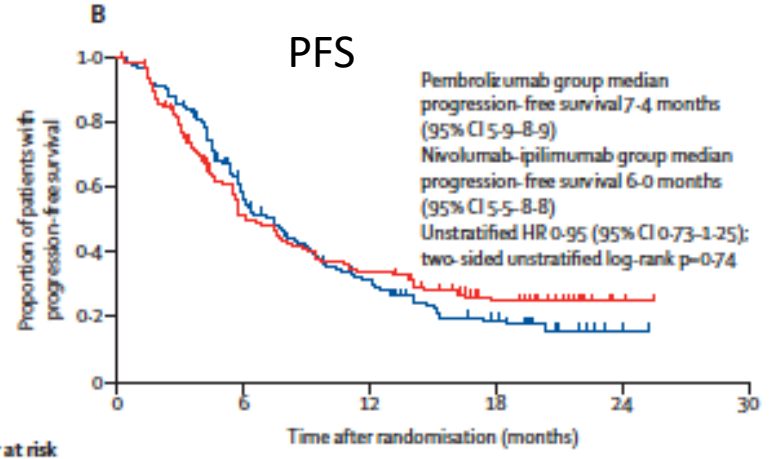
CT + pembrolizumab vs CT + nivolumab-ipilimumab in aNSCLC in Japan (JCOG2007): an open-label, multicentre, randomised, phase 3 trial

OS



Number at risk (number censored)						
Pembrolizumab group	147 (0)	119 (12)	92 (20)	51 (41)	5 (82)	0 (87)
Nivolumab-ipilimumab group	148 (0)	113 (15)	93 (17)	53 (42)	8 (83)	0 (91)

PFS

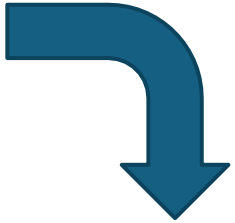


Number at risk (number censored)						
Pembrolizumab group	147 (0)	77 (9)	38 (15)	18 (21)	1 (36)	0 (37)
Nivolumab-ipilimumab group	148 (0)	67 (14)	43 (15)	21 (27)	2 (46)	0 (48)

Shiraishi Y., Lancet Respir Med 2024 Aug 16:

How could we raise the bar higher?

Novel Immunotherapies



Novel agents

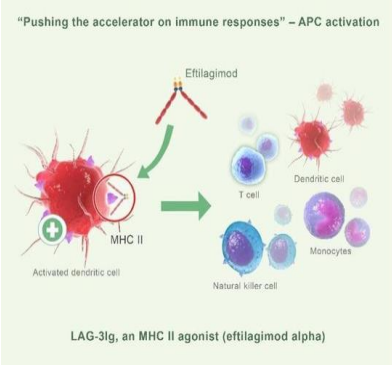
- Novel targets
- Cell based therapy
- Cancer vaccine
- Oncolytic virus

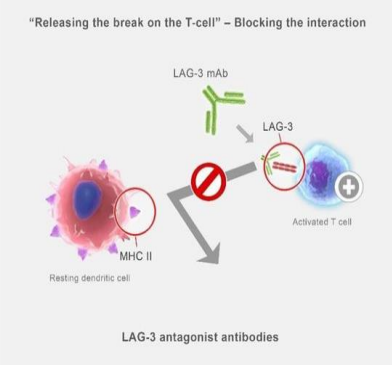
Novel combinations

- ICI+Chemo
- ICI+antiangiogenic drug
- ICI+TKI
- ICI+novel agents

Wen-Zhao Zhong WCLC 2024 ES 22.05

LAG-3 as a treatment target for lung cancer





- LAG-3 is an immune checkpoint receptor protein found on effector T-cells and Tregs that can inhibit regulation of T-cell activation, proliferation, and homeostasis[1]
- LAG-3 binds to MHC class II molecules on APCs; during prolonged exposure to an antigen in the TME, upregulated LAG-3 desensitizes T-cells and causes a loss of their effector function[2,3]
- In preclinical studies, LAG-3 inhibition restored T-cell effector function[4]

Trial	Compound	Sponsors	Phase	Population	Sample size	Intervention
KEYNOTE-495/KeyImPaCT	Favezelimab (LAG3 mAb)	MSD	II	Untreated mNSCLC	318	Pembro+Favezelimab vs Pembro+Lenvatinib vs Pembro+Quavonlimab
KEYNOTE-B98	Favezelimab (LAG3 mAb)	MSD	Ib/II	ES-SCLC	80	MK-1308A (Quavonlimab+ Pembro) vs MK-1308A+Lenvatinib vs MK- 1308A+MK-4830 vs MK-4280A
TACTI-002	Eftilagimod Alpha(Soluble LAG3)	Immutep	II	Stage IIIb/IV NSCLC	189	Efti+Pembro followed byPembro
FRACTION-Lung	Relatlimab (BMS-986016) (LAG3 mAb)	BMS	II	mNSCLC	295	Nivo vs Nivo+Dasatinib vs Nivo+Relatlimab vs Nivo+IPI vs Nivo+BMS-986205
NCT01968109	Relatlimab (BMS-986016) (LAG3 mAb)	BMS	I/II	Solid tumor (including NSCLC)	1499	Relatlimab vs Relatlimab+Nivo vs BMS-986213
NCT02460224	LAG525 (LAG3 mAb)	Novartis	I/II	Solid tumor (including NSCLC)	490	LAG525±PDR001
NCT03365791	LAG525 (LAG3 mAb)	Novartis	II	Solid tumor (including NSCLC) and	76	PDR001+LAG525
CITRINO	TSR-033 (LAG3 mAb)	Tesaro	I	Treated and unresectable or metastatic NSCLC	111	TSR-033±dostarlimab
NCT04140500	RG-6139 (PD-1×LAG3 BiAb)	Roche	I	Untreated or treated mNSCLC	320	RO7247669
DUET-4	XmAb®22841 (CTLA-4×LAG3 BiAb)	Xencor	I	Solid tumor (including NSCLC、 SCLC)	242	XmAb®22841±Pembro

1. Bhagwat BJ et al. Immunol Methods. 2018;456:7-14. 2. Pardoll DM. Nat Rev Cancer. 2012;12(4):252-64. 3. Workman CJ et al. J Immunol. 2002;169(10):5392-95. 4. Grosso JF et al. J Clin Invest. 2007;117(11):3383-92. 5. Puhr HC, Ilhan-Mutlu A. ESMO Open. 2019;4:e000482.

KEYNOTE-495/KeyImPaCT (NCT03516981)

ongoing biomarker-directed, adaptively randomized phase 2 study

Key Eligibility Criteria

- Age ≥18 years
- Confirmed diagnosis of advanced NSCLC
- No prior systemic therapy for advanced disease
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1
- *EGFR*/*ROS1*/*ALK*/*BRAF*–negative tumors

Tumor biomarker screening

- $Tcell_{inf}GEP^{a}$
- TMB^{b}

Biomarker subgroups

- **Group I (n = 66)** $Tcell_{inf}GEP^{low}$ TMB^{low}
- **Group II (n = 66)** $Tcell_{inf}GEP^{low}$ TMB^{high}
- **Group III (n = 66)** $Tcell_{inf}GEP^{high}$ TMB^{low}
- **Group IV (n = 90)** $Tcell_{inf}GEP^{high}$ TMB^{high}

Randomization 1:1:1

Adaptive randomization to pembrolizumab-based combination

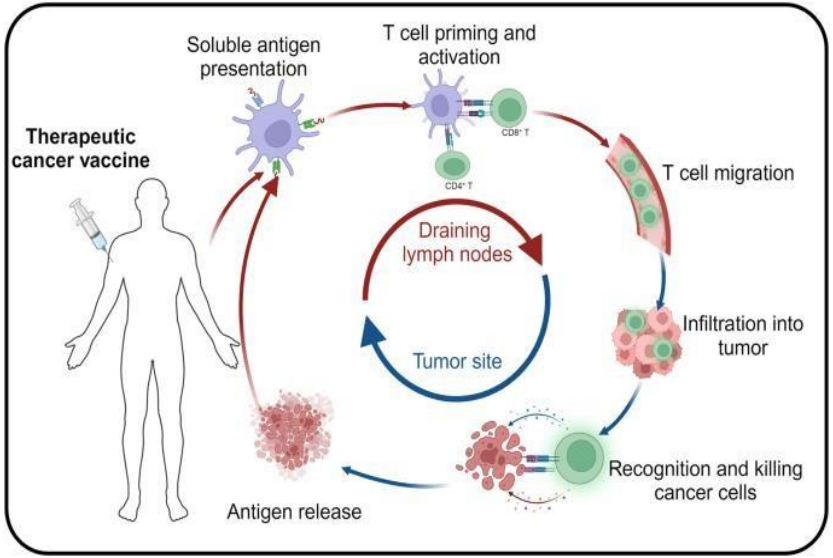
- Pembrolizumab 200 mg Q3W + Lenvatinib (TKI) 20 mg QD
- Pembrolizumab 200 mg Q3W + Quavonlimab (anti–CTLA-4) 75 mg Q6W
- Pembrolizumab 200 mg Q3W + Favezelimab (anti–LAG-3) 200 or 800 mg Q3W[c]

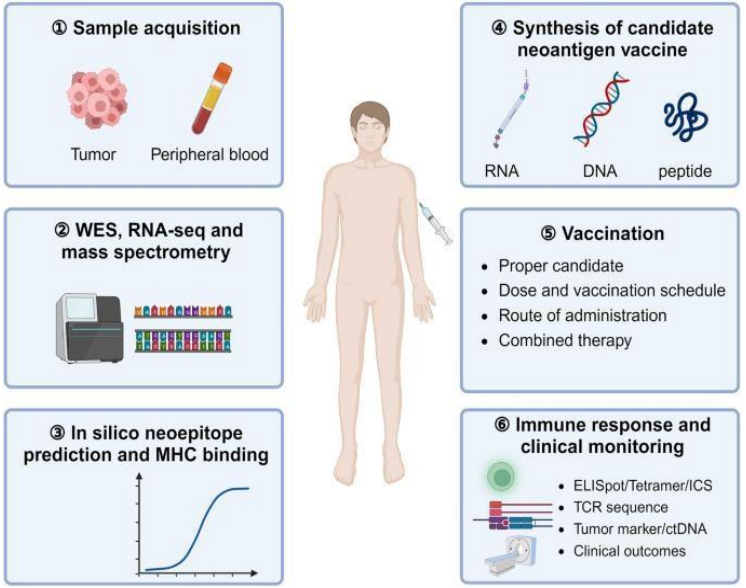
ORR, PFS, OS, safety, and follow-up

[a]The cutoff of −0.16 used to define high and low.
[b]The cutoff of 175 mut/exome (equivalent to 10 mut/Mb on FoundationOne®CDx) was used to define high and low.
[c]The initial prespecified dose was 200 mg but was changed to 800 mg based on emerging data.

Mechanism of Cancer vaccine

- Rationale: initiate or amplify adaptive anti-tumor immune responses by introducing tumor antigens





Each patient has a unique vaccine.

W.Z Zhong| Novel Immunotherapies WCLC 2024

Select ongoing NSCLC vaccine studies

	Treatment	Antigen	Phase	Setting
KEYNOTE-603 (NCT03313778)	mRNA	Personalized neoantigen	I	Adjuvant
INTerpath-002 (NCT06077760)	mRNA + pembrolizumab	Personalized neoantigen	Randomized III	Adjuvant
LuCa-MERIT-1 (NCT05142189)	mRNA +/- cemiplimab or docetaxel	Multiple tumor associated antigens	I	1L metastatic or with progressive disease
EMPOWERVAX Lung 1 (NCT05557591)	mRNA + cemiplimab	Multiple tumor associated antigens	Randomized II	1L metastatic
NCT05254184	Long peptide + ipilimumab/nivo	KRAS-mut	Pilot	1L metastatic
mRNA-4359-P101 (NCT06077760)	mRNA +/- pembrolizumab	PD-L1/IDO1	I/II	ICI-refractory (or 1L metastatic; expansion)
STEMVAC (NCT05242965)	DNA + alimta/pembro	Cancer stem cell related (CD105, YB1, SOX2, CDH3, MDM2)	Randomized II	1L metastatic on maintenance therapy
NCT05950139	Long peptide	ALK resistance mutations	Pilot	Metastatic with stable disease on TKI

Take home messages 1°L PDL1 <50%

- CT-ICI è lo standard. Non esiste una chiara superiorità di uno schema di combinazione rispetto all'altro.
- E' necessario selezionare i pazienti su base clinica condividendo la scelta con i pazienti stessi
- Sono in corso numerosi studi che stanno esplorando altre modalità di stimolazione del sistema immunitario ed altri target, ma attualmente nessuno utilizzabile in pratica clinica.
- Sfruttiamo al massimo le opportunità di inserimento dei pazienti in studi clinici.

Grazie per l'attenzione

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