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 ?
- Come predire soppravvivenza a lungo termine ?

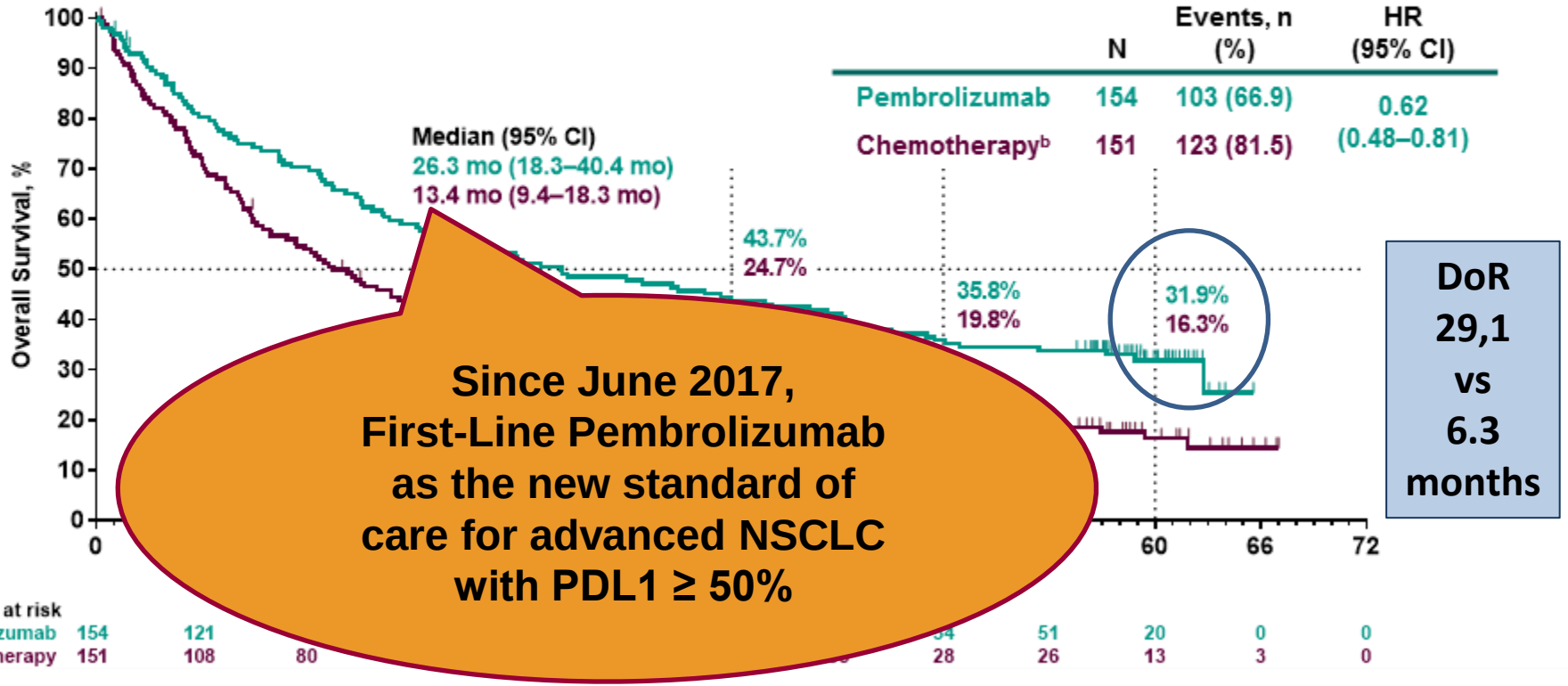
PDL1 < 50%

- CT+Pembro o CT+Ipi-Nivo ?
- Dati sui PDL1 <1%
- Possibili ruoli di mutazioni

PROSPETTIVE FUTURE

- Anticorpi coniugati con farmaci (ADC) – anti-TROP2

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

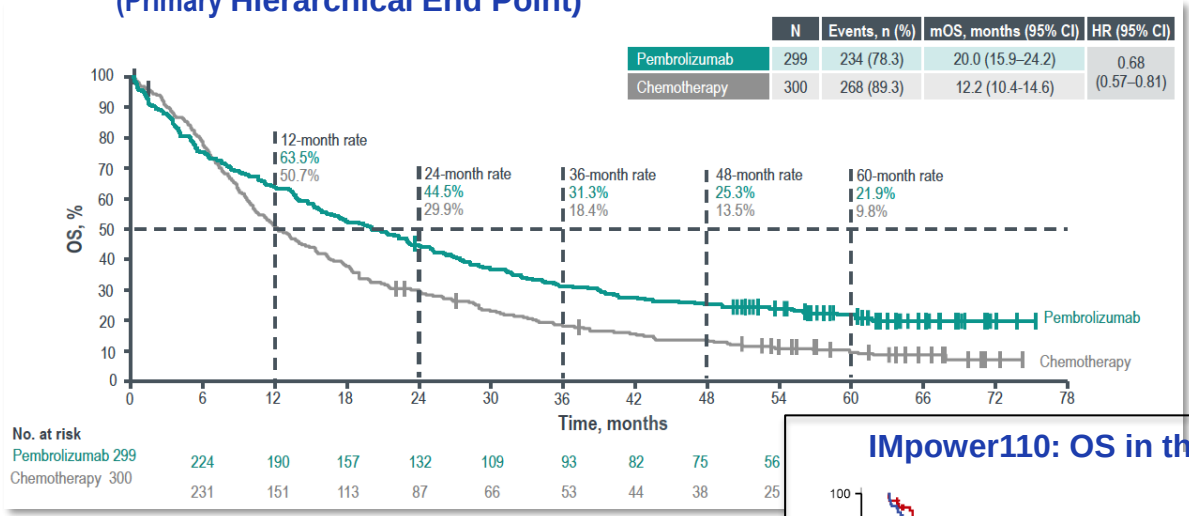
Reck M. et al J Clin Oncol. 2019 Mar 1;37(7):537-546

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%

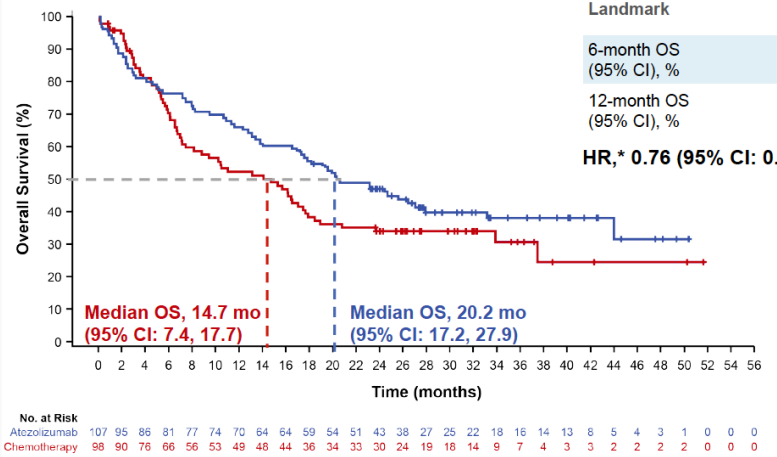
KEYNOTE-042: 5-year Update of OS in Patients With PD-L1 TPS ≥50% (Primary Hierarchical End Point)



mOS: 20.0 m
HR 0,68

mOS: 20.2 m
HR 0,76

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)

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

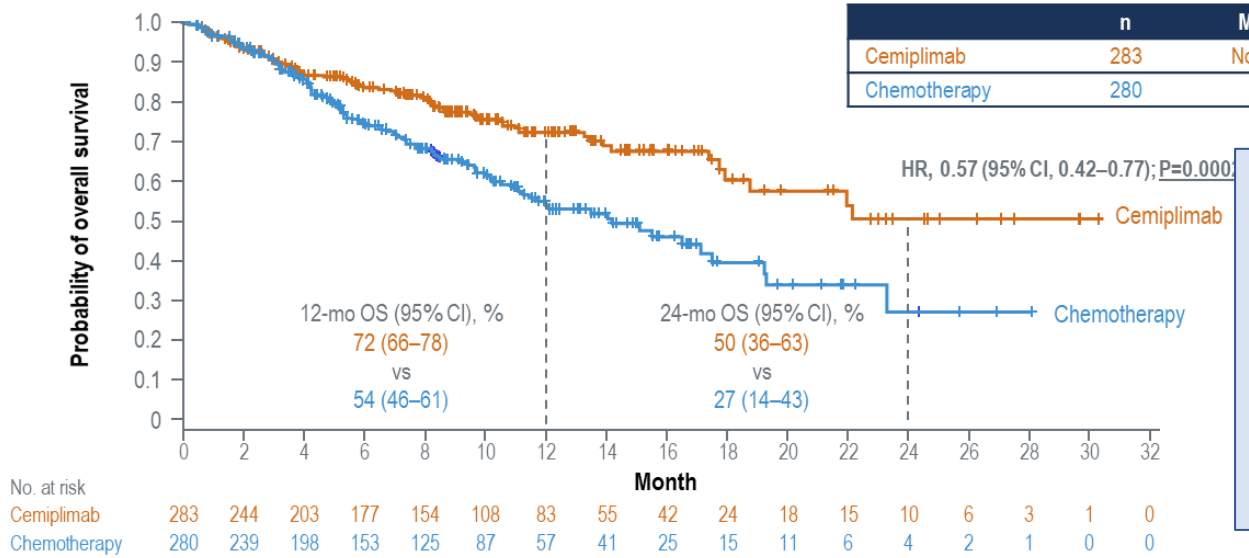
Follow-up

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)

Overall Survival by IRC: PD-L1 of at Least 50% (N=563)[1]



	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)

At 35 months' follow-up

Cemiplimab **26·1 m**

vs

Chemo **13·3 m**

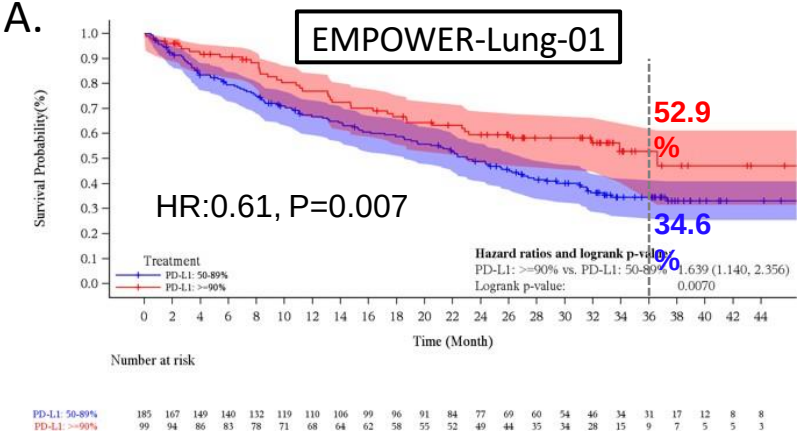
HR 0·57 (0·46-0·71)

p<0·0001

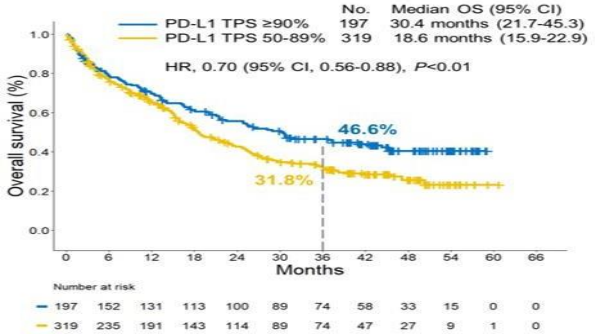
CI, confidence interval; HR, hazard ratio; IQR, interquartile range; C, IRC, independent review committee; mo, month; NE, not evaluable; OS, overall survival; PD-L1, programmed death-ligand 1.
Data cut-off date: 1 March 2020 (interim analysis #2). 1. Sezer A et al. *Lancet*. 2021;397:592–604 (including supplementary materials).
Reproduced from *The Lancet*, Vol. 397, Sezer A, et al. Cemiplimab monotherapy for first-line treatment of advanced NSCLC with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial, 592–604, Copyright (2021), with permission from Elsevier

Patients harboring NSCLC with PD-L1 TPS ≥ 90% have improved long term survival with PD-1 inhibitors

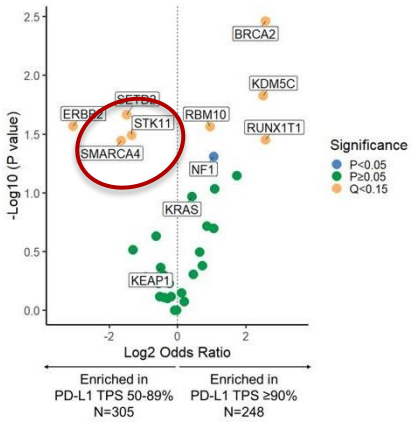
A.

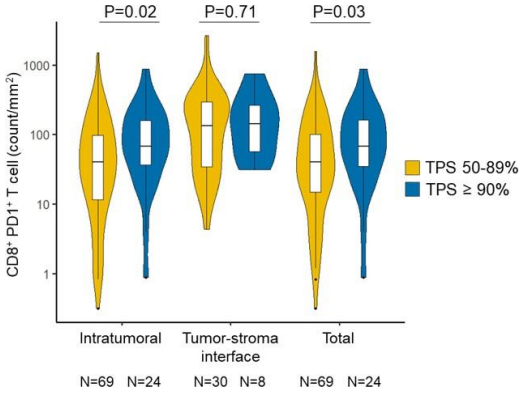


B.

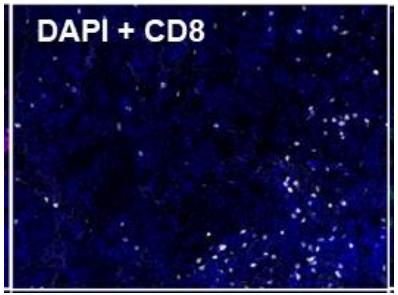


C.

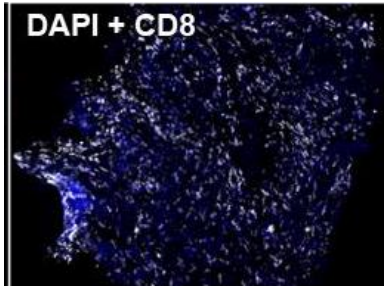




TPS 52 %



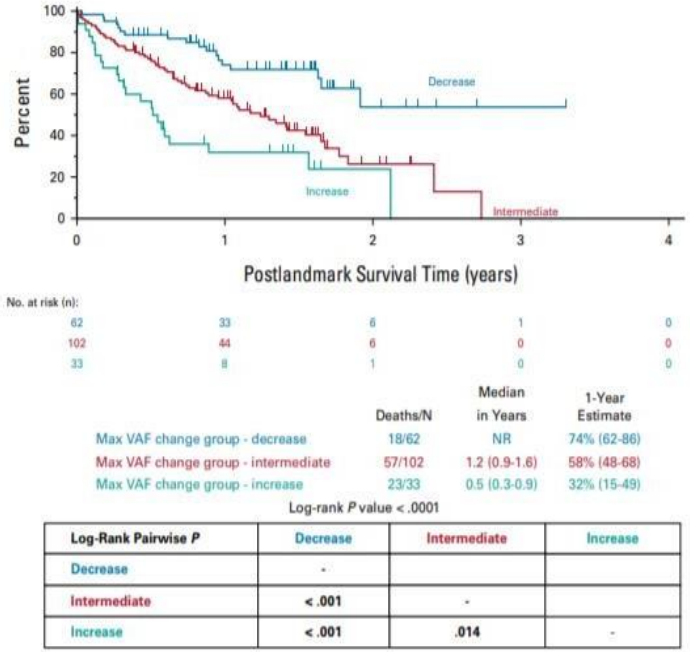
TPS 99 %



Ricciuti B et al, WCLC

Can we predict long term survival with immune checkpoint inhibitors?

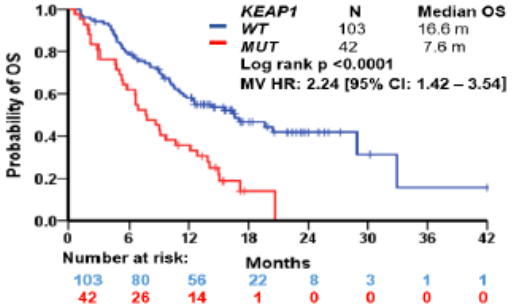
2. Dynamic changes in ctDNA

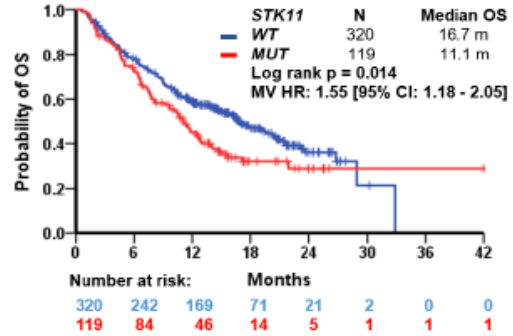


Log-Rank Pairwise *P*	Decrease	Intermediate	Increase
Decrease	-		
Intermediate	< .001	-	
Increase	< .001	.014	-

Vega DM et al, *JCO Precis Oncol*, 2022

3. Genomic co-alterations





Limited data in IO outcomes in patients bearing alterations *STK11*, *KEAP1*, *SMARCA4* etc

Skoulidis F et al., TTLC meeting, 2022

Take home messages 1°L monoterapia PDL1 >50%

- Pembrolizumab (> esperienza), atezolizumab o cemiplimab (anche St. IIIB) sono gli standard terapeutici. Studi con popolazioni non sovrapponibili

- Possibilità di modulare i ricicli di terapia sia per Pembro (3w e 6w) sia per Atezo (2w, 3w e 4w)

- Esistono alcuni paramentri che predicono una lunga sopravvivenza ?
  - ✓ forse PDL1 > 90% (< prevalenza di mutazioni di STK11/SMARCA4 ed > linfociti T CD8+PD1+)
  - ✓ forse riduzione di ctDNA
  - ✓ forse KEAP1 o STK11

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- Dati sui PDL1 <1%
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PROSPETTIVE FUTURE

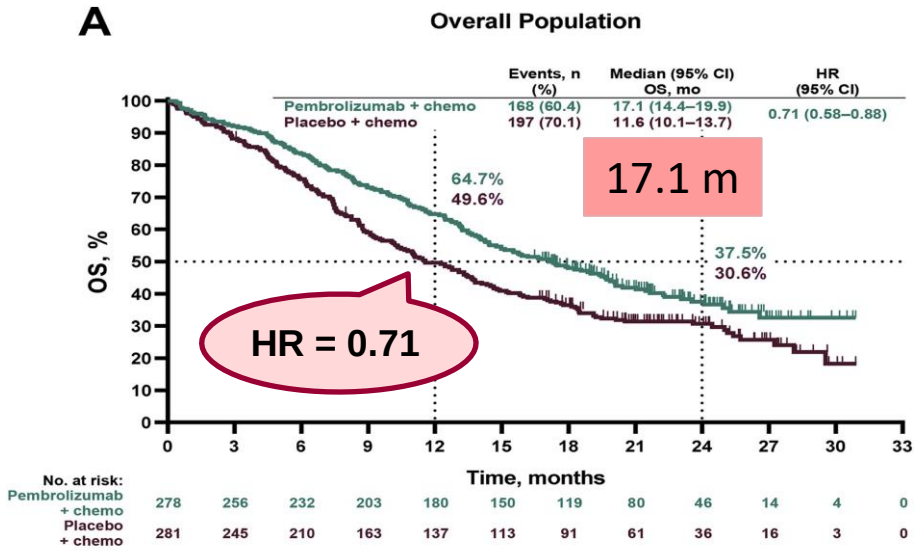
- Anticorpi coniugati con farmaci (ADC) – anti-TROP2

CT + Pembrolizumab

KEYNOTE-407

Platinum + Taxane +/- Pembrolizumab

SQUAMOUS NSCLC

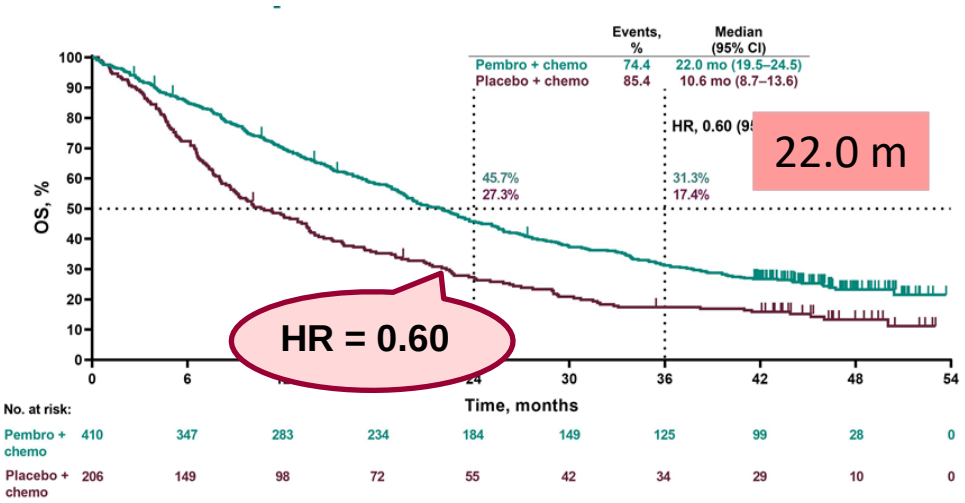


Paz-Ares L, et al. J Thor Oncol 2020

KEYNOTE-189

Platinum + pemetrexed +/- Pembrolizumab

NON-SQUAMOUS NSCLC



Gray J.E. WCLC 2021 4-year FW

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)

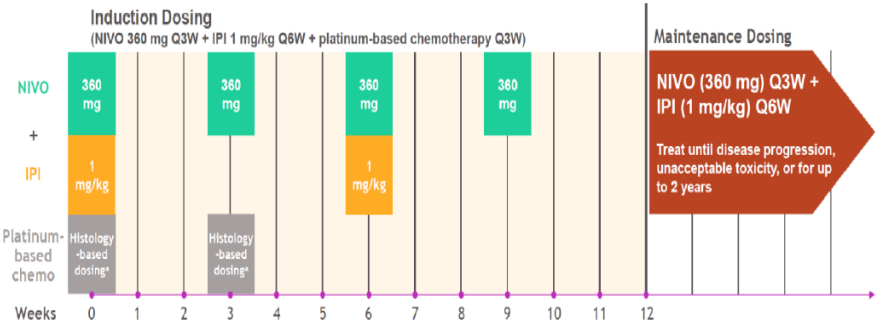
Optional
Pemetrexed maintenance (NSQ histology)

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

Primary endpoint
- OS

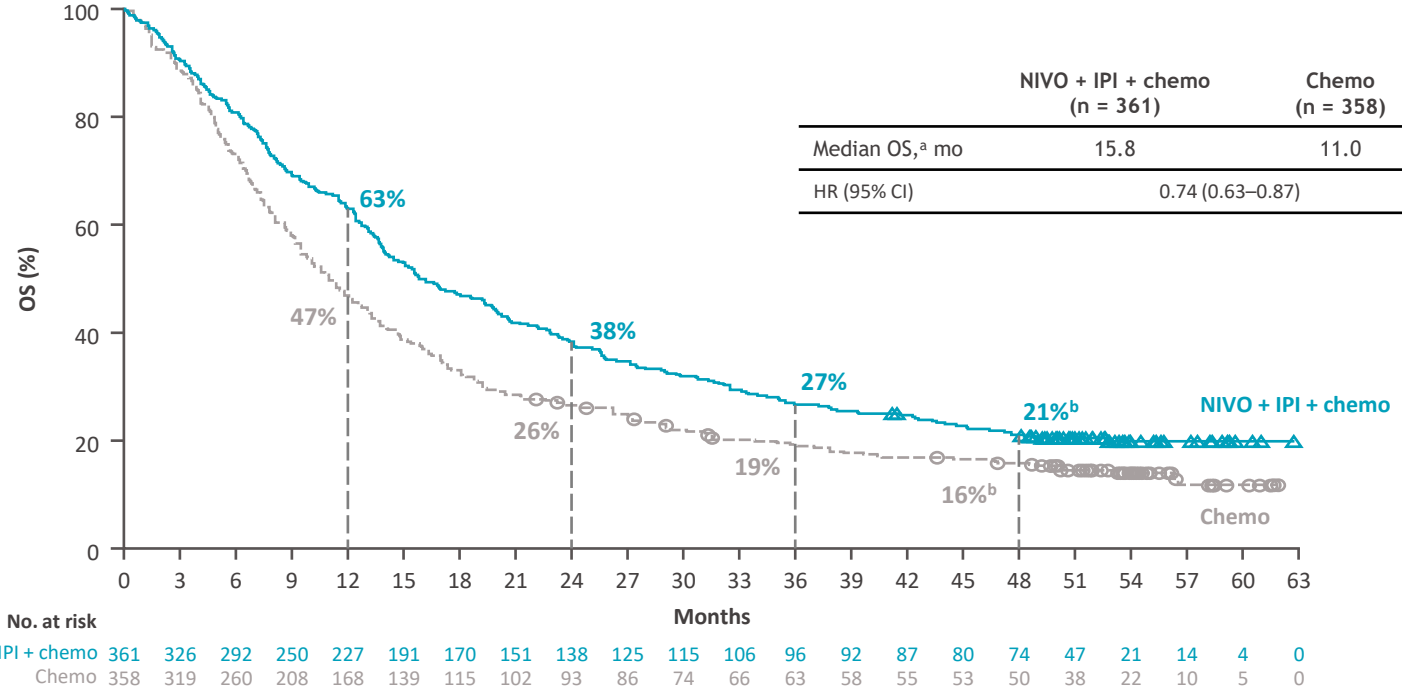
Secondary endpoints
- PFS by BICR[d]
- ORR by BICR[d]
- Efficacy by tumor PD-L1 expression

Exploratory endpoint
- Safety



OS in all randomized patients
(4-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)	0.74 (0.63–0.87)	

Database lock: February 13, 2023; minimum/median follow-up for OS: 47.9/54.5 months.
95% CIs for NIVO + IPI + chemo and chemo, respectively: [a]13.9–19.7 and 9.5–12.7; [b]17–25 and 12–20.

Frontline Chemo-Immunotherapy Regardless of PD-L1 Expression

Trial	Treatment	Histology	Median DoR	Median OS	3-yr OS	4-yr OS	5-Yr OS
Keynote 189	CT + pembrolizumab	Non-squamous	12.7 m	22.0 m	31,3%	**23.6%**	19.4%
CheckMate 9LA	CT + **ipilimumab** + nivolumab	Non-squamous	17.5 m	17.8 m	28%	**22%**	-
Poseidon	CT + **tremelimumab x5** + durvalumab	Non-squamous	16.4 m	17.2 m	31.4%	**25.1%**	-

Trial	Treatment	Histology	Median DoR	Median OS	3-yr OS	4-yr OS	5-Yr OS
Keynote 407	CT + pembrolizumab	Squamous	9.0 m	17.2 m	29,9%	**21.9%**	18.4%
CheckMate 9LA	CT_2 + **ipilimumab** + nivolumab	Squamous	10.8 m	14.5 m	24%	**20%**	-
Poseidon	CT + **tremelimumab x5** + durvalumab	Squamous	5.6 m	10.4 m	14%	**13.1%**	-

Not head-to-head comparisons

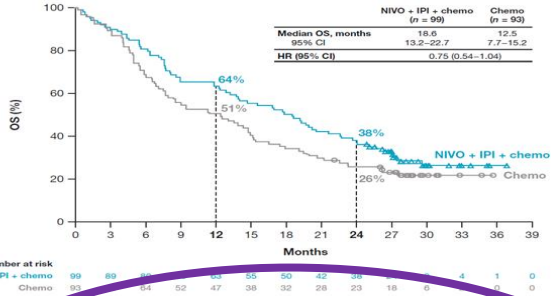
How to Select Patients for CTLA-4 Inhibition?

WCLC 2023 ES43.05 Maurice Pérol, Léon Bérard Cancer Center, Lyon France

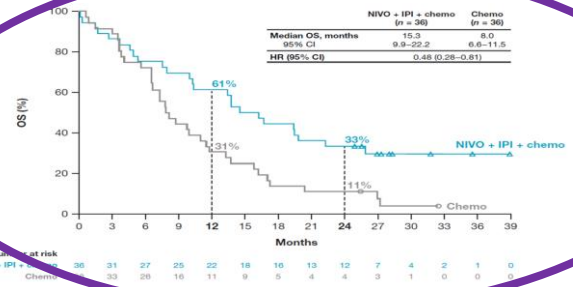
Garassino M et al., JCO 2023; Novello S et al., JCO 2023; Carbone D et al., ASCO 2023; Johnson M et al., ESMO 2022; Paz-Ares, JTO 2023

CM 9LA - Overall survival (by histology and by PD-L1)

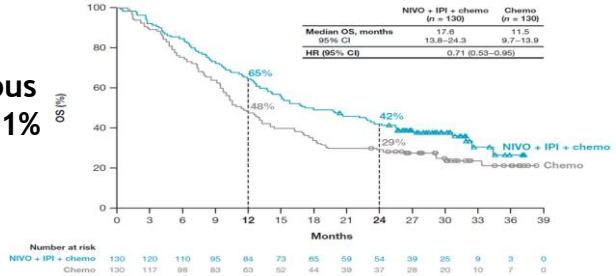
Non-squamous and PD-L1 <1%



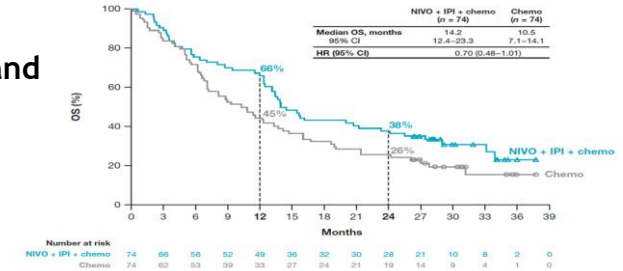
Squamous and PD-L1 <1%



Non-squamous and PD-L1 ≥1%

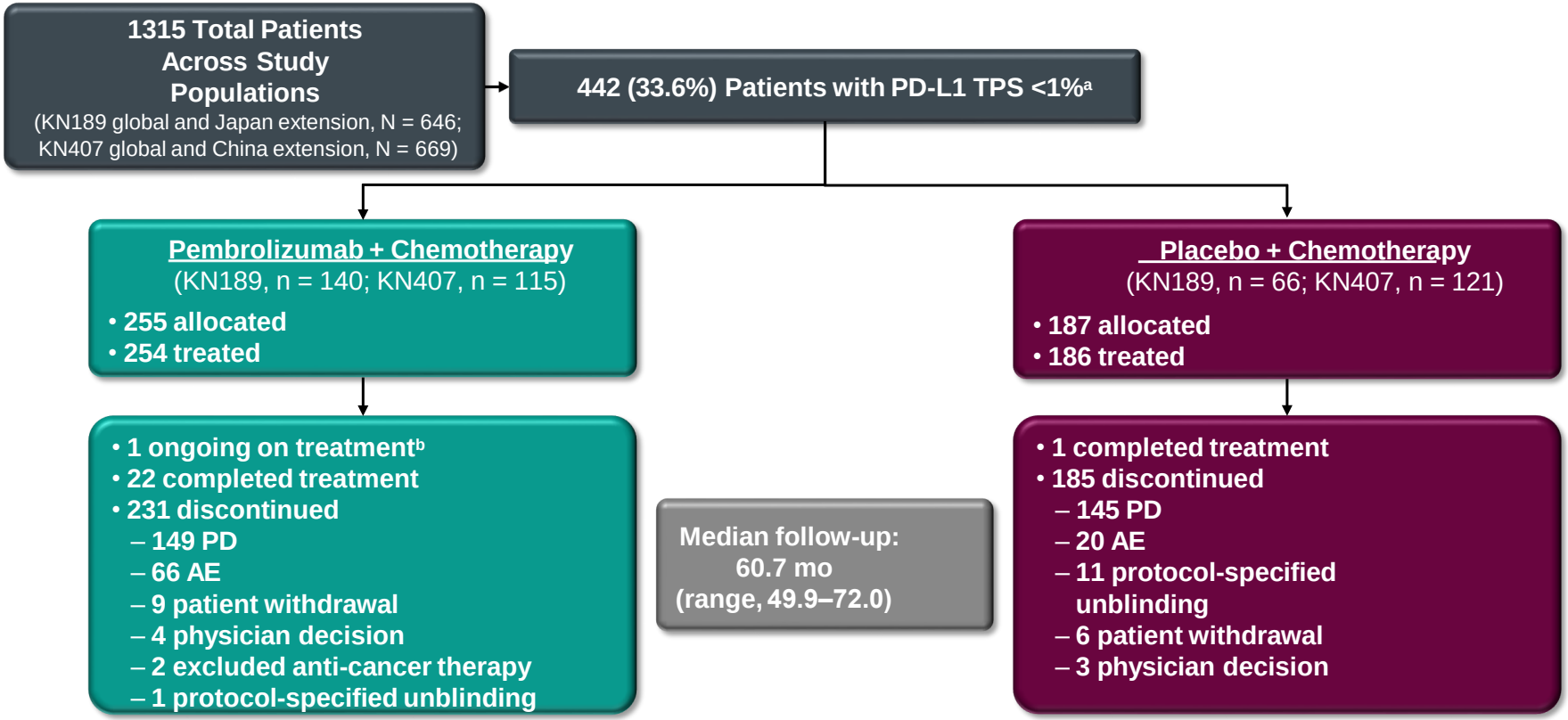


Squamous and PD-L1 ≥1%



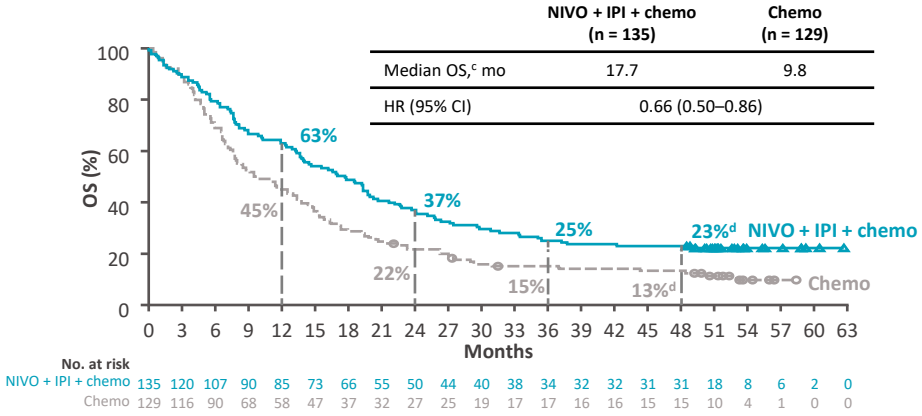
Adapted from Supplementary Appendix to: Reck M et al. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update. ESMO Open 2021

Disposition of Pooled Analysis Population



PD-L1 < 1%

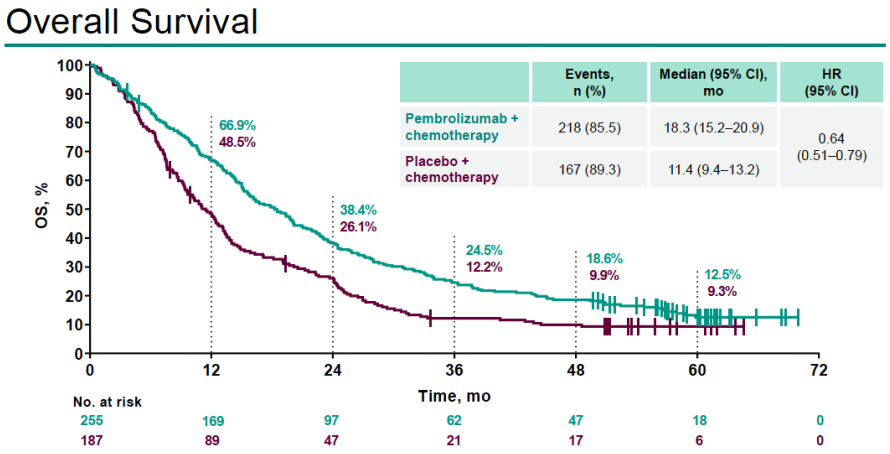
Subgroup 9LA



4-year clinical update

Carbone D. P. ASCO 2023 LBA9023

Pooled analysis CT ± Pembro



5-year survival data

Gadgeel SM WCLC 2023 OA 14.05

Which Room for Anti-CTLA-4?
PD-L1 TPS<1%

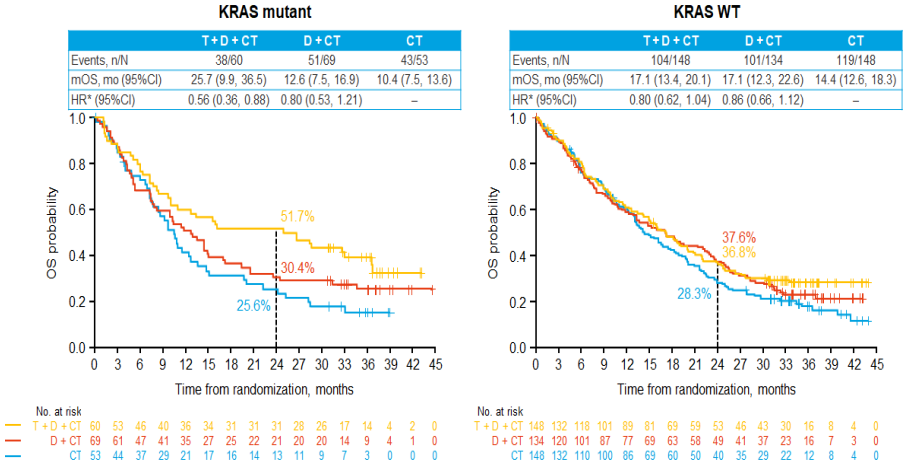
		Median PFS (months)	3-yr PFS	5-yr PFS	Median OS (months)	3-yr OS	4-yr OS	5-yr OS
Non-squamous	CheckMate 227	-	-	-	17.5	**32%**	**24%**	**19%**
	CheckMate 9LA	6.4	16%	-	18.6	25%	-	-
	Keynote 189	6.2	6.4%	2.4%	17.2	23.3%	16%	9.6%
Squamous	CheckMate 227	-	-	-	16.3	**36%**	**22%**	**18%**
	CheckMate 9LA	5.3	19%	-	15.3	25%	-	-
	Keynote 407	6.3	11.6%	7.1%	15.0	22.1%	15.8%	10.7%

Not head-to-head comparisons

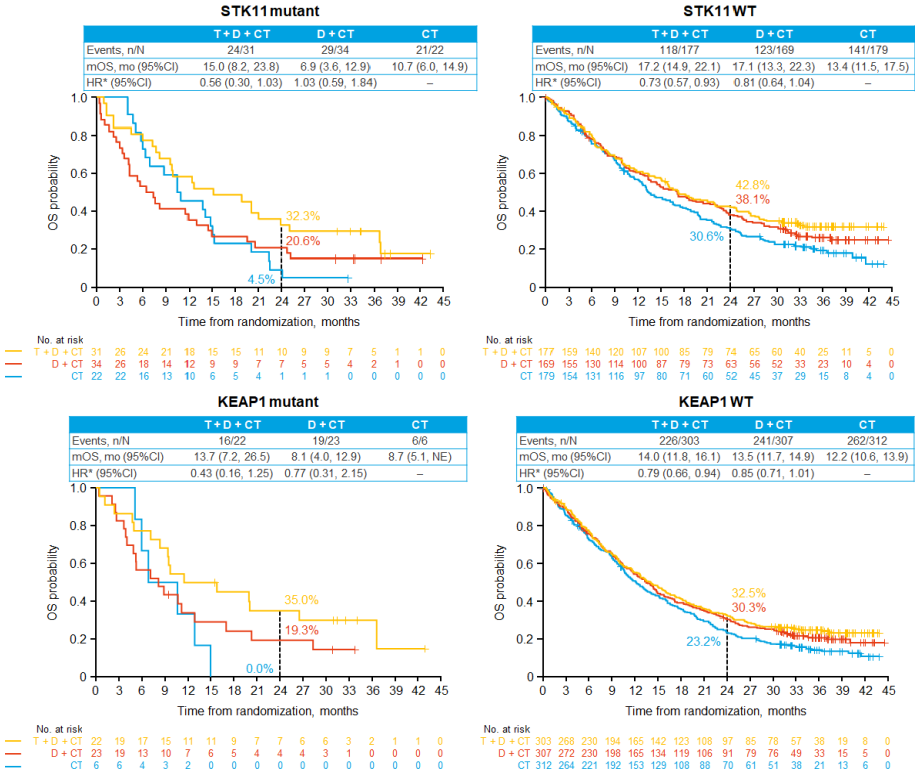
Maybe

Paz-Ares, ASCO 2022; Garassino et al., ESMO 2022; Novello et al., ESMO 2022; Gray et al., WCLC 2021; Garon, WCLC 2022; Robinson, ELCC 2021; Brahmer, JCO 2022

Association Between *KRAS/STK11/KEAP1* Mutations and Outcomes in POSEIDON



- Exploratory analyses
- Small sample size



Peters S, et al. J Thorac Oncol 2022;17(suppl):Abstr OA15.04

Take home messages 1°L PDL1 <50%

- CT+Pembrolizumab (> esperienza) e CT+Nivo-Ipi sono gli standard terapeutici.
- Non è ancora chiaro come selezionare clinicamente i pazienti che beneficiano maggiormente di uno o dell'altro schema terapeutico (PDL1 < 1% ?)
- Esistono alcune analisi esploratorie su piccole casistiche che ipotizzazano una maggior utilità di associare un anti-CTLA4 in caso di mutazioni di K-RAS o STK11 o KEAP1
- Troppi studi ME TOO.
- La nuova sfida è rendere questi trattamenti accessibili alla maggior parte dei pazienti e ridurre I costi

Agenda

PDL1 >50%

- Pembro, Atezo o cemiplimab ?
- Come predire soppravvivenza a lungo termine ?

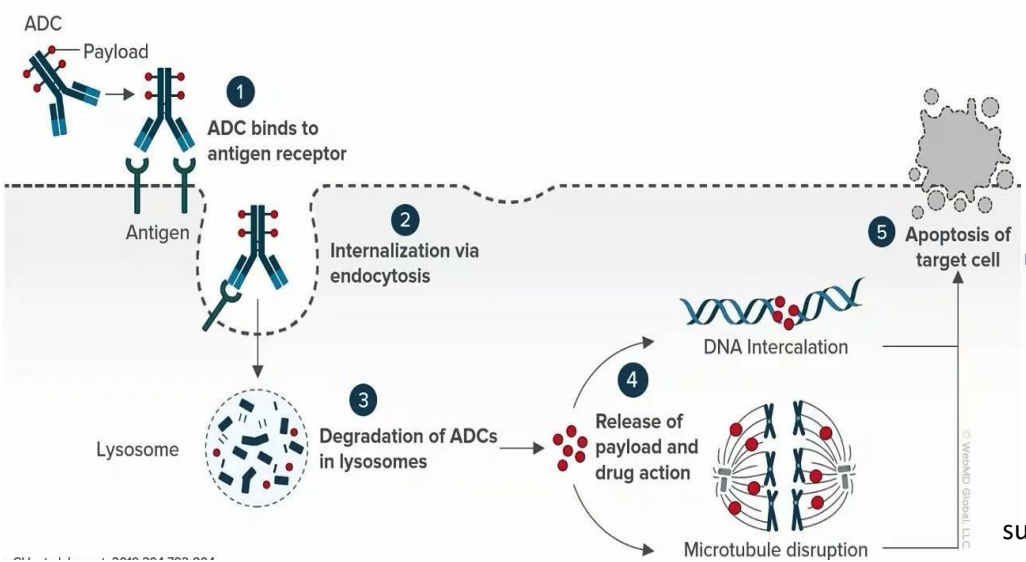
PDL1 < 50%

- CT+Pembro o CT+Ipi-Nivo ?
- Dati sui PDL1 <1%
- Possibili ruoli di mutazioni

PROSPETTIVE FUTURE

- Anticorpi coniugati con farmaci (ADC) – anti-TROP2

Mechanisms of action of ADCs



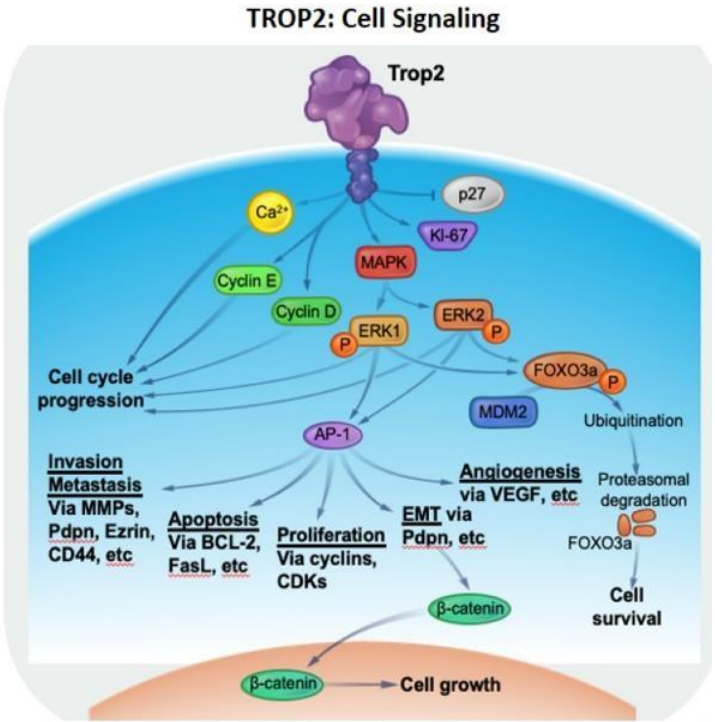
Bystander effect: killing of surrounding antigen-negative cells

- ✓ Apoptosis
- ✓ ADCC/ CDC/ ADCP
- ✓ Bystander Effect

- HER-2
- HER-3
- TROP-2
- C-MET
- CEACAM-5
- B7-H3

Chau CH et al. Lancet 2019; 394:793

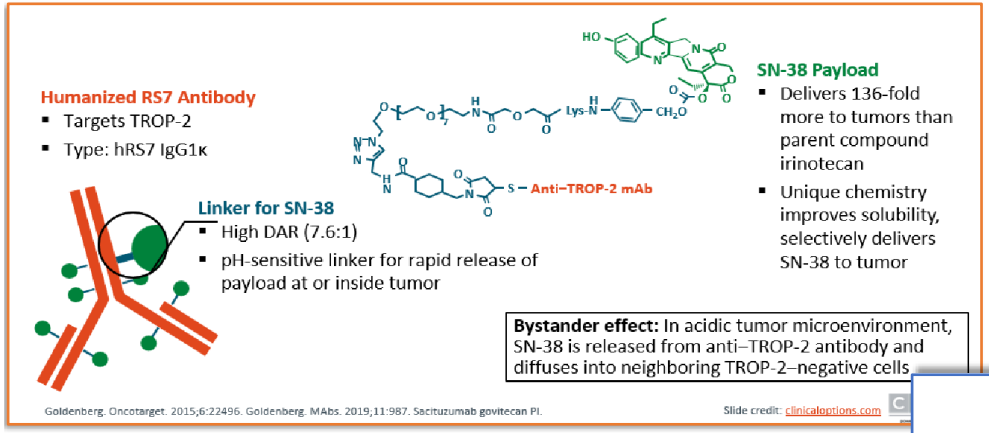
TROP-2 as a therapeutic target in NSCLC



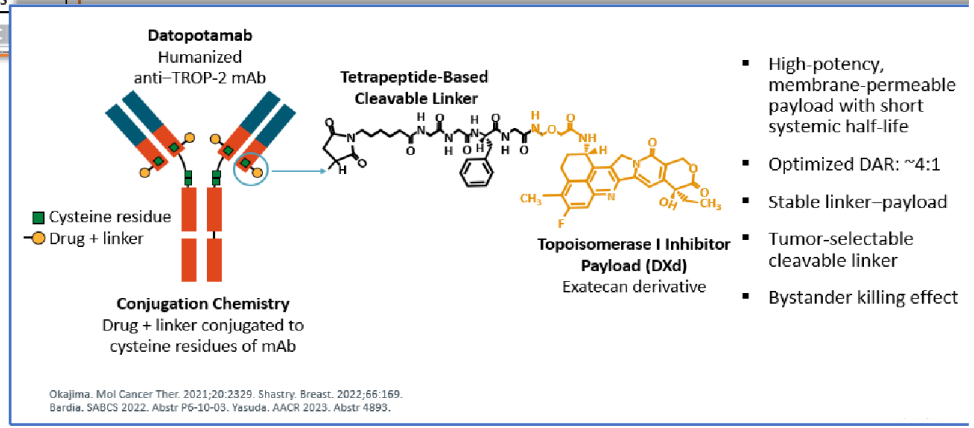
- Trophoblast cell-surface antigen 2 (TROP-2) is a transmembane glycoprotein overexpressed in solid tumors including TNBC and NSCLC, associated with poor survival
- **NSCLC overespression in 64% of AC and 75% of SCC**
- TROP-2 is an epithelial adhesion molecule and regulates stem cell marker-associated cell regeneration

TROP-2 targeted ADCs

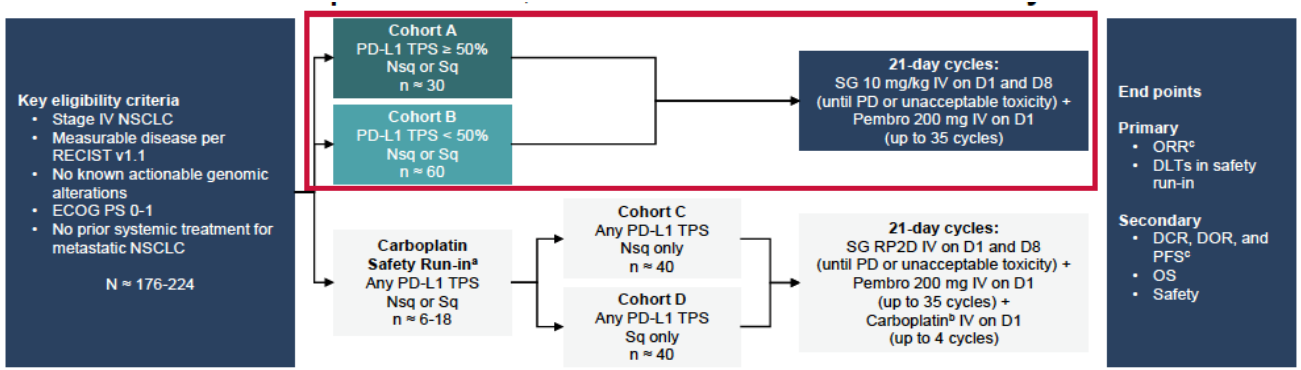
Sacituzumab Govitecan



Datopotamab Deruxtecan



EVOKE-02: An Open-Label, Multicohort Phase 2 Study, 1st Line



The safety profile of SG + Pembro was manageable and consistent with the known safety of each agent

- The most common any-grade TEAEs were diarrhea, anemia, and asthenia
- TEAEs leading to treatment discontinuation were low (18%)

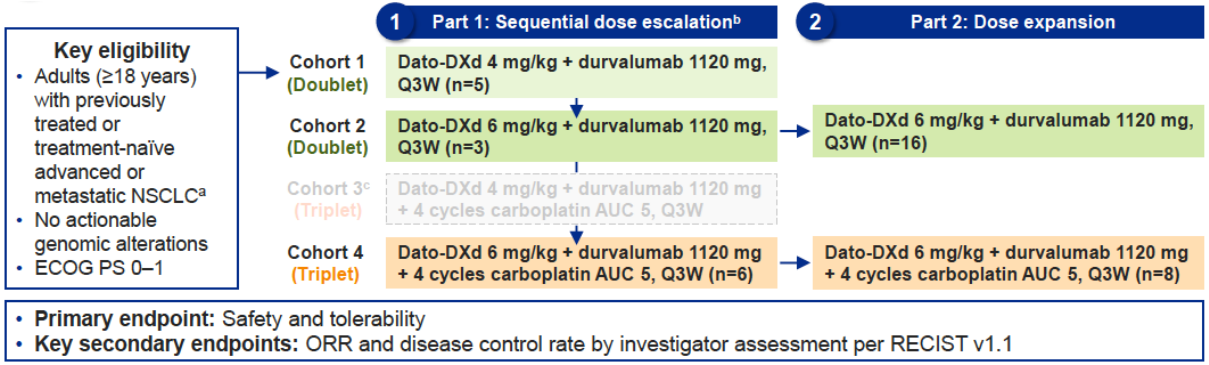
	> 50%	< 50%	
Efficacy by INV[a]	Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro n = 29	Cohort B (PD-L1 TPS < 50%) SG + Pembro n = 32	Total SG + Pembro n = 61
ORR[b] (95% CI), %	**69 (49-85)**	**44 (26-62)**	**56 (42-69)**
PR, n (%) – confirmed and unconfirmed	20 (69)	14 (44)	34 (56)
Confirmed PR, n (%)	18 (62)	12 (38)	30 (49)
SD, n (%)	5 (17)	11 (34)	16 (26)
PD, n (%)	3 (10)	2 (6)	5 (8)
DCR[c] (95% CI), %	86 (68-96)	78 (60-91)	82 (70-91)
Median DOR[d,e] (95% CI), months	NR (5.6-NR)	NR (3.5-NR)	NR (7.9-NR)
DOR rate at 6 months[d,e] (95% CI), %	88 (39-98)	88 (39-98)	87 (58-97)

KEYNOTE 189: ORR: 62.1% (TPS≥50%), 50% (TPS 1-49%), 48.3% all comers

Ongoing, open-label, global, randomized, phase 3 EVOKE-03 study: SG + Pembro versus Pembro monotherapy in 1L mNSCLC PD-L1 TPS ≥ 50%

TROPION-Lung04 Study Design

Phase 1b, multicenter, open-label, dose escalation/confirmation and expansion study



Safety

- No new safety signals
- The most frequent TEAEs were stomatitis, nausea and alopecia.
- G3 hematological tox more frequent in triplet
- 4 case of ILD

The Phase 3 AVANZAR (NCT05687266), TROPION-Lung07 (NCT05555732) and TROPION-Lung08 (NCT05215340) trials are evaluating Dato-DXd and immune checkpoint inhibitor combinations as potential 1L treatment options in patients with advanced or metastatic NSCLC

Response in patients in the 1L setting,[a] n (%)		Cohort 2 (doublet) N=14	Cohort 4 (triplet) N=13
Objective response rate (confirmed)		**7 (50.0)**	**10 (76 . 9)**
[95% CI]		[23.0, 77.0]	[46.2, 95.0]
Best objective response	Complete response	0	0
	Partial response	7 (50.0)	10 (76.9)[b]
	Stable disease	6 (42.9)	2 (15.4)
	Progressive disease	1 (7.1)	1 (7.7)
Disease control rate		**13 (92.9)**	**12 (92.3)**
[95% CI]		[66.1, 99.8]	[64.0, 99.8]

PROSPETTIVE FUTURE
Take home messages

- ✓ TROP-2 è un target interessante, frequentemente espresso nei ca. polmonari (>60% in SCC, 42-64% in AC, 20% nei neuroendocrini alto grado)

- ✓ Preliminari **segnali di attività promettenti** degli anti-TROP-2 ADCs
- ✓ **Tossicità maneggevole**
- ✓ **Manca un biomarcatore predittore di efficacia**
- ✓ **Significativa attività e buona safety quando associati con IO**

Grazie per l'attenzione

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