Lung Cancer UPDATES
ASCO HIGHLIGTHS
29-31 MAYO 2020

Iniciativa científica de:
GECP lung cancer research

Cáncer de pulmón no microcítico: enfermedad avanzada. Inmunoterapia

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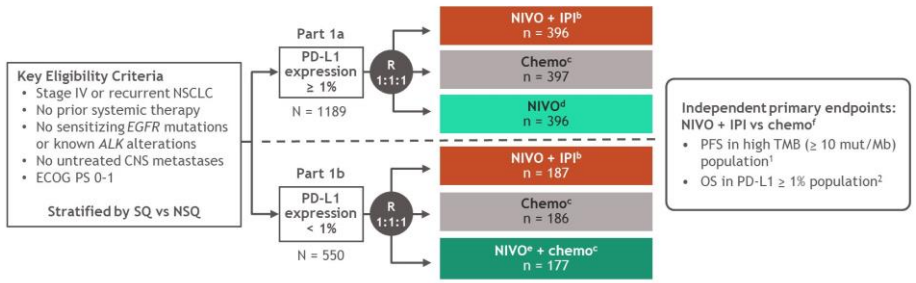
Combinacion Anti-PD-1 + Anti-CTLA4 / CheckMate 227

CheckMate 227[a] Part 1 study design

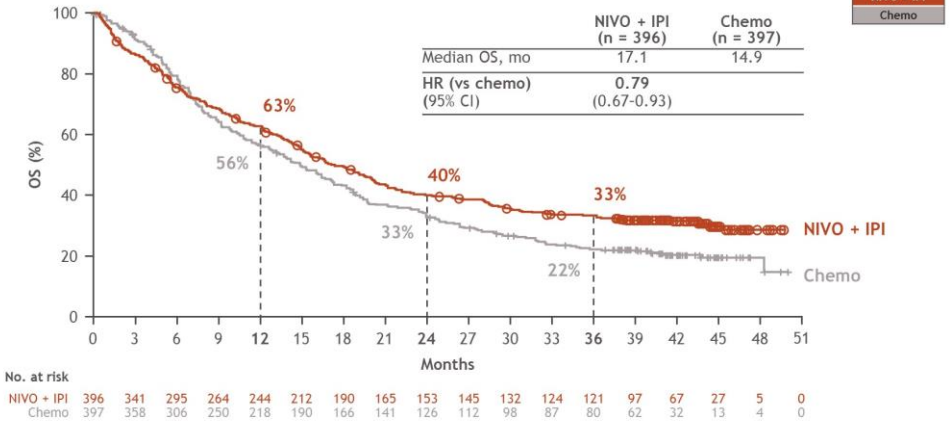


Database lock: February 28, 2020; minimum / median follow-up for OS: 37.7 months / 43.1 months.

Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy; [a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]NSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; SQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]Both endpoints were met; results were previously reported.

1. Hellmann MD, et al. *N Engl J Med* 2018;378(22):2093-2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381(21):2020-2031.

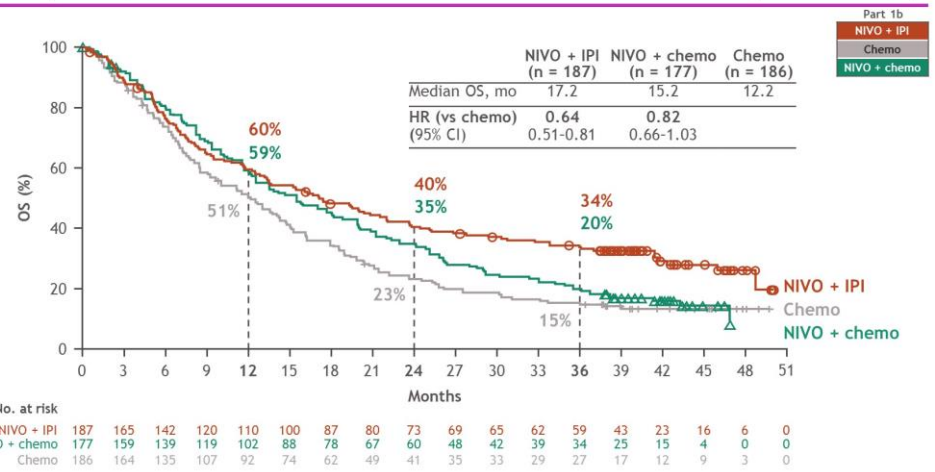
3-year update: OS with NIVO + IPI vs chemo (PD-L1 ≥ 1%)



Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Among patients who were alive at 3 years, subsequent systemic therapy was received by 35% in the NIVO + IPI arm and 76% in the chemo arm; subsequent immunotherapies were received by 13% and 71%, respectively, and subsequent chemotherapy was received by 28% and 30%, respectively.

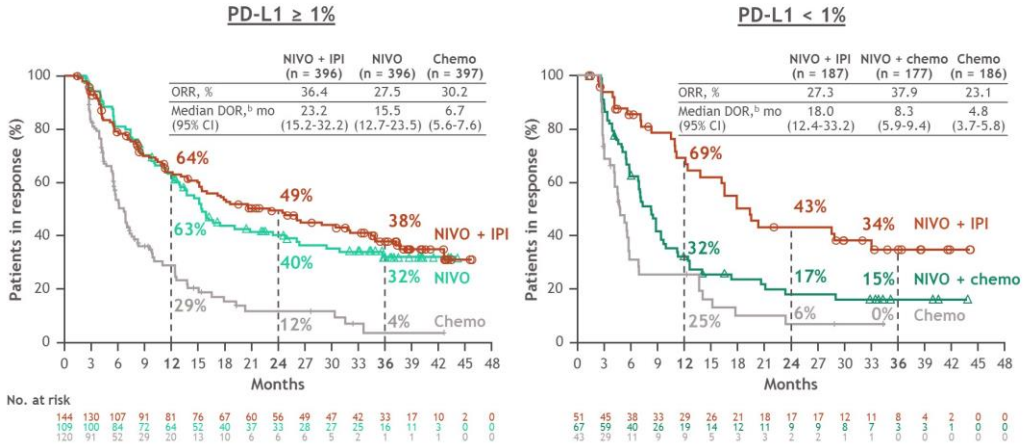
3-year update: OS with NIVO + IPI vs Chemo vs NIVO + Chemo (PD-L1 < 1%)



Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Among patients who were alive at 3 years, subsequent systemic therapy was received by 49% in the NIVO + IPI arm, 38% in the NIVO + chemo arm, and 78% in the chemo arm; subsequent immunotherapies were received by 12%, 12%, and 74%; and subsequent chemotherapy was received by 46%, 35% and 33%, respectively.

3-year update: ORR[a] and DOR[a] among patients with PD-L1 ≥ 1% or < 1%



Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), NIVO (240 mg Q2W), and NIVO (360 mg Q3W) + chemo. [a]ORR and DOR were assessed by blinded independent central review; [b]DOR was reported for responders only in each treatment arm.

Combinación Anti-PD-1 + Anti-CTLA4 + QT x 2 vs QT x 4: CheckMate 9LA

CheckMate 9LA study design[a]

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

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

N = 719, R 1:1

- n = 361: **NIVO** 360 mg Q3W + **IPI** 1 mg/kg Q6W + **Chemo**[d] Q3W (2 cycles)
- n = 358: **Chemo**[d] Q3W (4 cycles) with optional pemetrexed maintenance (NSQ)

Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

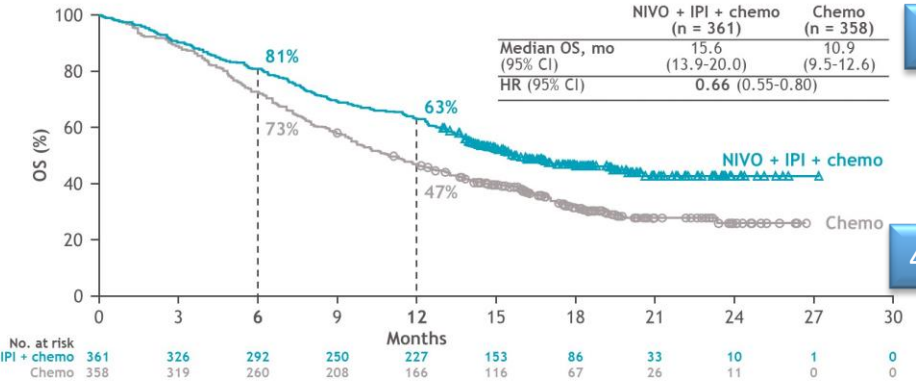
Primary endpoint
- OS

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

Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.
Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Primary endpoint (updated): Overall survival[a]



	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	0.66 (0.55-0.80)	

No. at risk											
NIVO + IPI + chemo	361	326	292	250	227	153	86	33	10	1	0
Chemo	358	319	260	208	166	116	67	26	11	0	0

Minimum follow-up: 12.7 months.

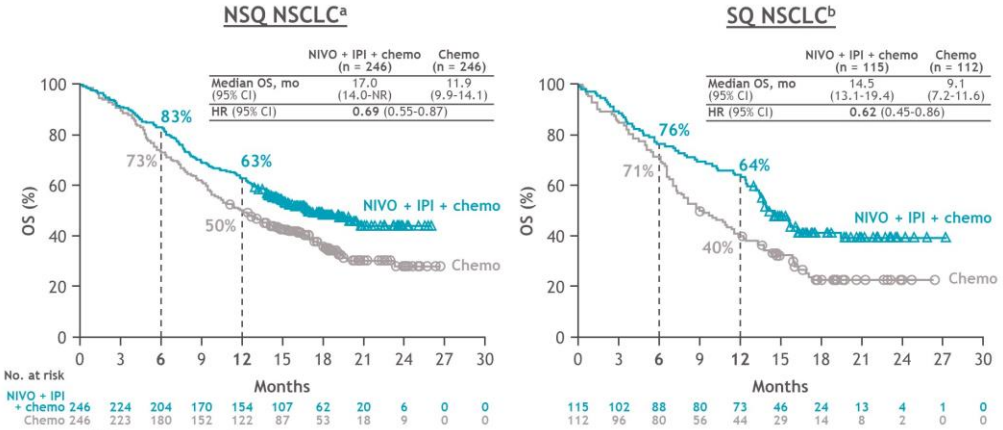
[a]Patients remaining in follow-up were censored on the last date they were known to be alive; 47% of patients in the NIVO + IPI + chemo arm and 32% of patients in the chemo arm were censored. Subsequent systemic therapy was received by 31% of patients in the NIVO + IPI + chemo arm and 40% in the chemo arm; subsequent immunotherapy was received by 5% and 30%, and subsequent chemotherapy by 29% and 22%, respectively. Among patients with BICR-confirmed disease progression on study, subsequent systemic therapy was received by 40% in the NIVO + IPI + chemo arm and 44% in the chemo arm; subsequent immunotherapy was received by 7% and 34%, and subsequent chemotherapy by 38% and 24%, respectively

Minimal f-u: 12.7 m

69% Non-Squamous

45% Pem Maintenance

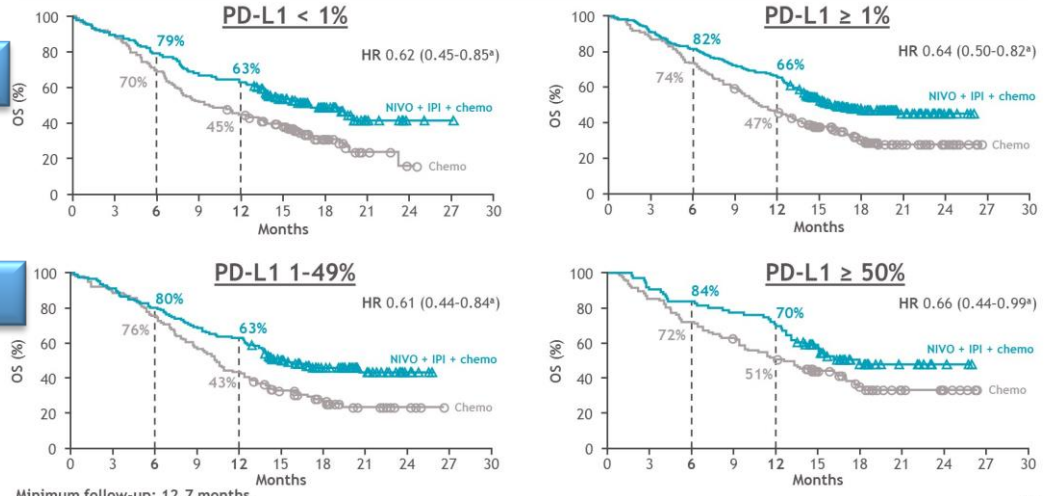
Overall survival by histology



Minimum follow-up: 12.7 months.

[a]Subsequent systemic therapy was received by 30% of patients in the NIVO + IPI + chemo arm and 39% of patients in the chemo arm; subsequent immunotherapy was received by 6% and 28%, and subsequent chemotherapy by 29% and 22%, respectively; [b]Subsequent systemic therapy was received by 31% of patients in the NIVO + IPI + chemo arm and 44% of patients in the chemo arm; subsequent immunotherapy was received by 4% and 35%, and subsequent chemotherapy by 30% and 24% of patients, respectively

Overall survival by PD-L1 expression level



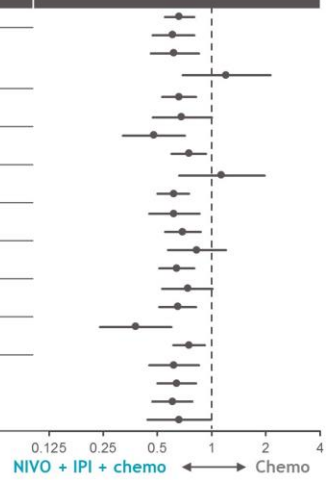
Minimum follow-up: 12.7 months.

[a]95% CI.

Combinación Anti-PD-1 + Anti-CTLA4 + QT x 2 vs QT x 4: CheckMate 9LA

Overall survival subgroup analysis

Subgroup	Median OS, mo		Unstratified HR	Unstratified HR (95% CI)
	NIVO + IPI + chemo n = 361	Chemo n = 358		
All randomized (N = 719)	15.6	10.9	0.66[a]	
< 65 years (n = 354)	15.6	10.7	0.61	
65 to < 75 years (n = 295)	19.4	11.9	0.62	
≥ 75 years (n = 70)	8.5	11.5	1.21	
Male (n = 504)	14.1	9.8	0.66	
Female (n = 215)	19.4	15.8	0.68	
ECOG PS 0 (n = 225)	NR	15.4	0.48	
ECOG PS 1 (n = 492)	13.6	9.7	0.75	
Never smoker (n = 98)	14.1	17.8	1.14	
Smoker (n = 621)	15.6	10.4	0.62	
Squamous (n = 227)	14.5	9.1	0.62	
Non-squamous (n = 492)	17.0	11.9	0.69	
Liver metastases (n = 154)	10.2	8.1	0.83	
No liver metastases (n = 565)	19.4	12.4	0.64	
Bone metastases (n = 207)	11.9	8.3	0.74	
No bone metastases (n = 512)	20.5	12.4	0.65	
CNS metastases (n = 122)	NR	7.9	0.38	
No CNS metastases (n = 597)	15.4	11.8	0.75	
PD-L1 < 1% (n = 264)	16.8	9.8	0.62	
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64	
PD-L1 1-49% (n = 233)	15.4	10.4	0.61	
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66	



Minimum follow-up: 12.7 months.
[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55-0.81).

CheckMate 9LA: NIVO + IPI + 2 cycles of chemo in 1L NSCLC

Safety summary of TRAEs

TRAE,[a] %	NIVO + IPI + chemo (n = 358)		Chemo (n = 349)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE	92	47	88	38
TRAEs leading to discontinuation of any component of the regimen	19	16	7	5
Serious TRAEs	30	25.4	18	15
Treatment-related deaths[b]	2		2	

- Median (range) duration of therapy was 6.1 (0-23.5) months and 2.4 (0-24.0) months for NIVO + IPI + chemo versus chemo, respectively
- Most common any-grade TRAEs (≥ 15%) were nausea, anemia, asthenia and diarrhea

Minimum follow-up: 12.2 months.
[a]Includes events reported between first dose and 30 days after last dose of study drug; [b]Treatment-related deaths in the NIVO + IPI + chemo arm (n = 7; 1 for each event) were due to acute renal failure due to chemotherapy, thrombocytopenia, pneumonitis, hepatic toxicity, hepatitis, diarrhea, sepsis, and acute renal insufficiency; treatment-related deaths in the chemo arm (n = 6; 1 for each event) were due to sepsis, anemia, pancytopenia, respiratory failure, pulmonary sepsis, and febrile neutropenia (1 grade 5 AE was reported [sudden death due to fall] as potentially treatment-related but cause of death was recorded as unknown).

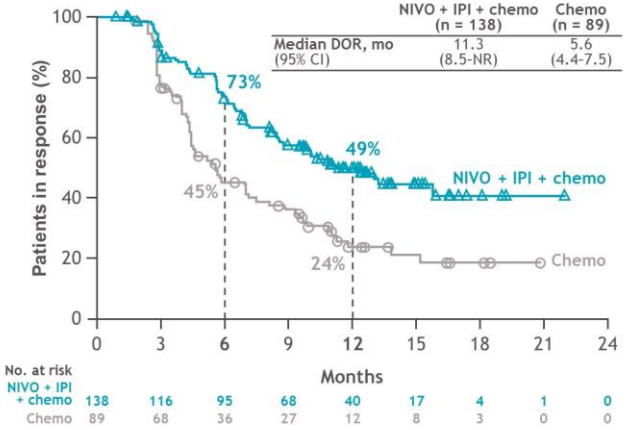
CheckMate 9LA: NIVO + IPI + 2 cycles of chemo in 1L NSCLC

Overall response rate per BICR and duration of response

Response rates

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	138 (38)	89 (25)
Odds ratio (95% CI)	1.9 (1.4-2.6)	
BOR, n (%)		
CR	8 (2)	4 (1)
PR	130 (36)	85 (24)
SD	164 (45)	185 (52)
PD	32 (9)	45 (13)
DCR, n (%)	302 (84)	274 (76)

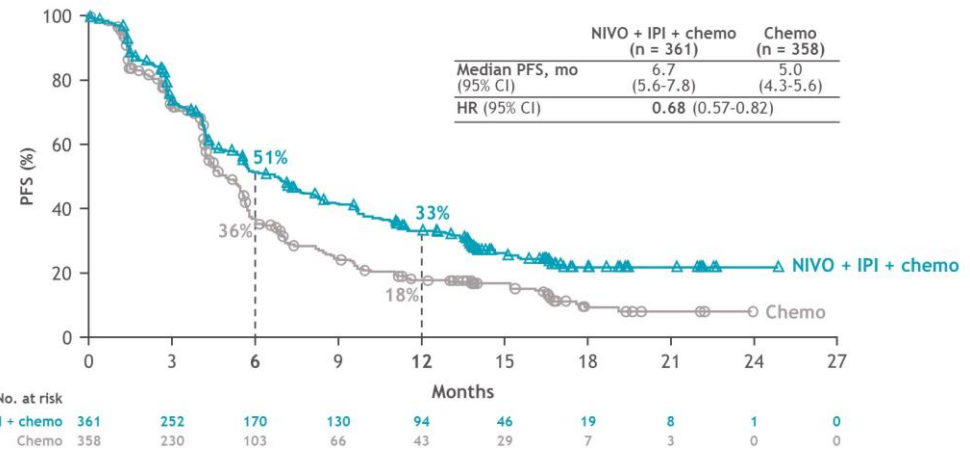
Duration of response



Minimum follow-up: 12.2 months.

CheckMate 9LA: NIVO + IPI + 2 cycles of chemo in 1L NSCLC

Progression-free survival per BICR[a]



Minimum follow-up: 12.2 months.
[a]Patients who did not progress or die were censored on the date of their last evaluable tumor assessment; those who did not have any study tumor assessments and did not die were censored on their date of randomization; patients without reported progression who went on to receive palliative local therapy or subsequent anti-cancer therapy were censored on the date of their last evaluable tumor assessment prior to starting either therapy.

Combinación Anti-PD-L1 + Anti-CTLA4 +/- QT: CCTG BR.34

CCTG BR.34 Schema

An international, multicenter, prospective 2-arm randomized trial

Metastatic squamous or non-squamous NSCLC:
- Stage IVA (high risk) or IVB*
- No prior chemotherapy for Stage IV
- EGFR wild type, ALK fusion negative**
- ECOG PS 0 or 1
- Adequate organ function
- No prior autoimmune disease
- No untreated CNS metastases
- Measurable disease (RECIST 1.1)

Stratification factors:
- Squamous versus non-squamous
- Stage IVA vs B
- Never vs current vs former smoker

RANDOMIZED 1:1

ARM 1 Durvalumab + Tremelimumab

Durvalumab 1500 mg IV + Tremelimumab 75 mg IV q28 days x 4 then Durvalumab 1500 mg IV until Disease Progression

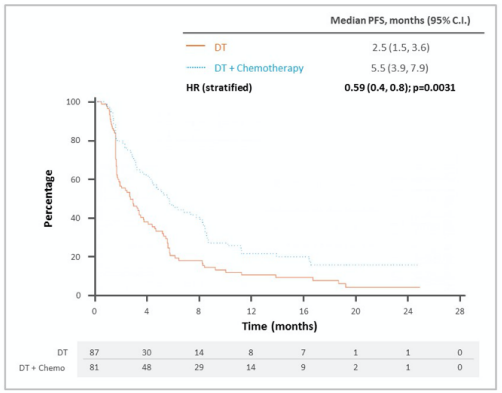
Crossover between treatment arms not permitted

ARM 2 Durvalumab + Tremelimumab + Chemotherapy

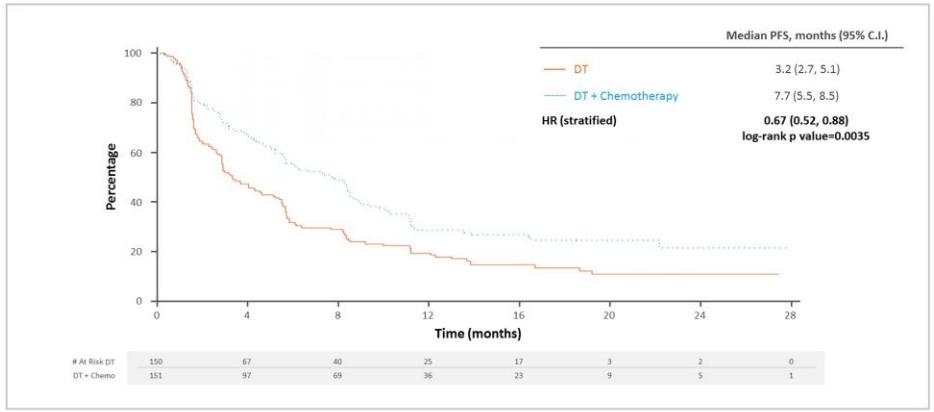
Durvalumab 1500 mg IV + Tremelimumab 75 mg IV + Platinum Doublet Chemotherapy# IV q21 days x 4, then Durvalumab 1500 mg alone (squamous) or plus Pemetrexed 500 mg/m^2 IV (non-squamous) q28 days until Disease Progression

*Stage IVA patients were initially required to have ≥5% weight loss in previous 3 months, elevated LDH or poorly differentiated histology; American Joint Committee on Cancer TNM 8th edition; **EGFR, ALK testing performed locally; #patients received either cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL*min IV q21 days x 4, plus gemcitabine (1000-1250 mg/m^2 – squamous) IV day 1 and day 8 q 21 days x 4, or pemetrexed (500 mg/m^2 - nonsquamous) IV q21 days x 4 then q28 days until progression

Patients with bTMB < 20 mutations/Mb



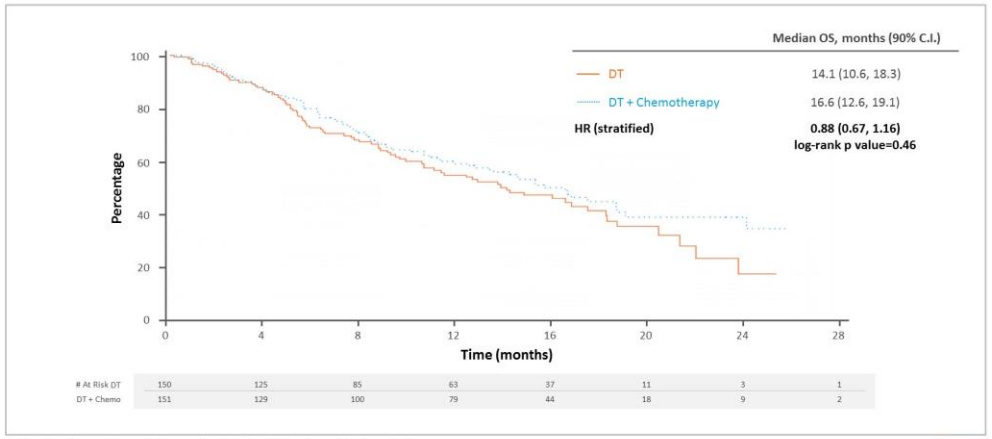
Progression-Free Survival



DT: durvalumab + tremelimumab; PFS: progression-free survival; CI: confidence interval; HR: hazard ratio

Canadian Cancer Trials Group / Groupe canadien des essais sur le cancer ASCO 2020: Presented by N. Leighl

Overall Survival by Treatment Arm



DT: durvalumab + tremelimumab; OS: overall survival; CI: confidence interval; HR: hazard ratio

Canadian Cancer Trials Group / Groupe canadien des essais sur le cancer ASCO 2020: Presented by N. Leighl

- Phase III: 301 p
- 18% Squamous
- 9% Never smokers
- PD-L1 >50%: 19%
- bTMB >20MB: 23%
- 2nd line systemic Tx: 16 vs 47%

Adverse Events (AE)

Rate of AE – no. (%)	Durvalumab + Tremelimumab (N=149)	Durvalumab + Tremelimumab + Chemotherapy (N=148)
Any Grade≥3 AE	105 (70)	121 (82)
Grade≥3 AE attributed to protocol therapy*	18 (12)	21(14)
Serious AE**	84 (56)	102 (69)
SAE requiring high dose steroid initiation#	38 (26)	37 (25)
AE leading to treatment discontinuation*	21 (14)	34 (23)
AE leading to death*##	3 (2)	5 (3)

* Attributed at least possibly, probably or definitely to protocol therapy
** AEs requiring high dose steroid initiation were deemed serious. SAE related to cancer progression were excluded.
# 44 and 48 SAE were reported in DT and DT + chemotherapy arms respectively
Fatal events in the DT arm included pneumonitis (1), pneumonitis and concurrent sepsis (1), death not otherwise specified (1). In the DT + chemotherapy arm, these included pneumonitis (1), functional decline (1), gastric perforation (1), acute kidney injury and pneumonia (1), death not otherwise specified (1).

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Atezolizumab +/- Tiragolumab (Anti-TIGIT Ab): CITYSCAPE Trial

CITYSCAPE Study Design

1L Stage IV NSCLC
- *EGFR/ALK* wild-type
- Tumor PD-L1 TPS ≥ 1% by 22C3 IHC by local or central assay

N=135

R 1:1

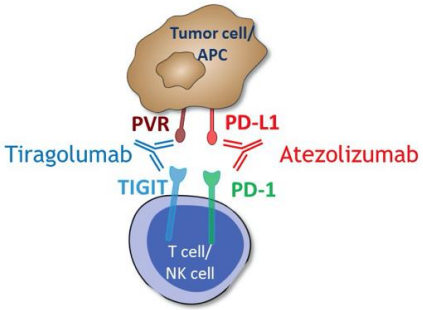
- Tiragolumab 600 mg IV q3w + Atezolizumab 1200 mg IV q3w
- Placebo 600 mg IV q3w + Atezolizumab 1200 mg IV q3w

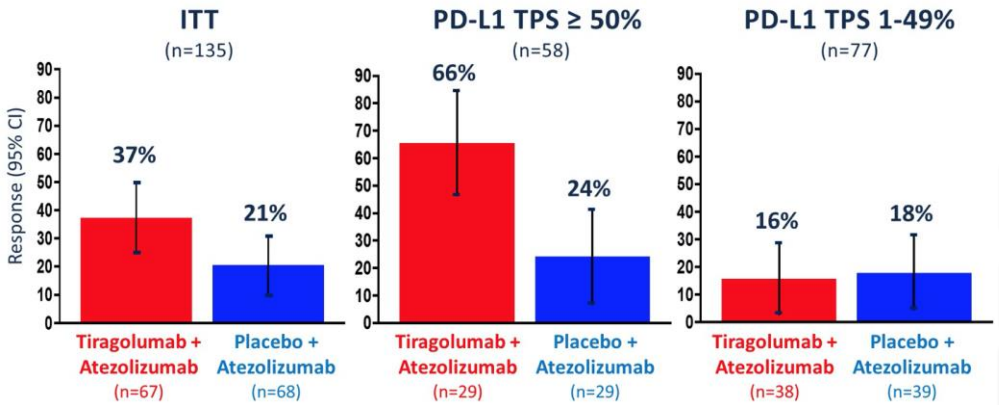
No crossover

PD or loss of clinical benefit

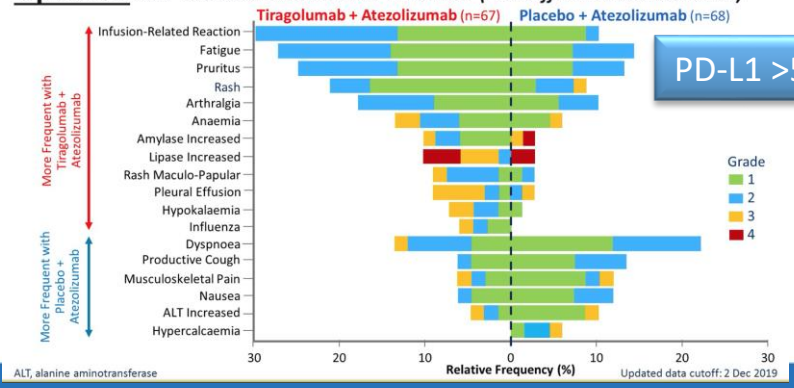
Stratification Factors:
- PD-L1 TPS (1-49% vs ≥ 50%)
- Histology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

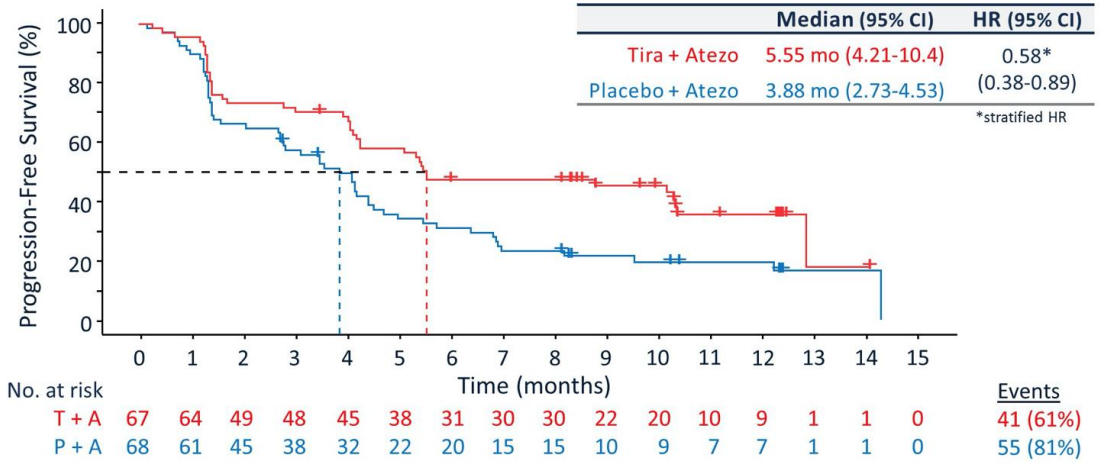
- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety,** DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

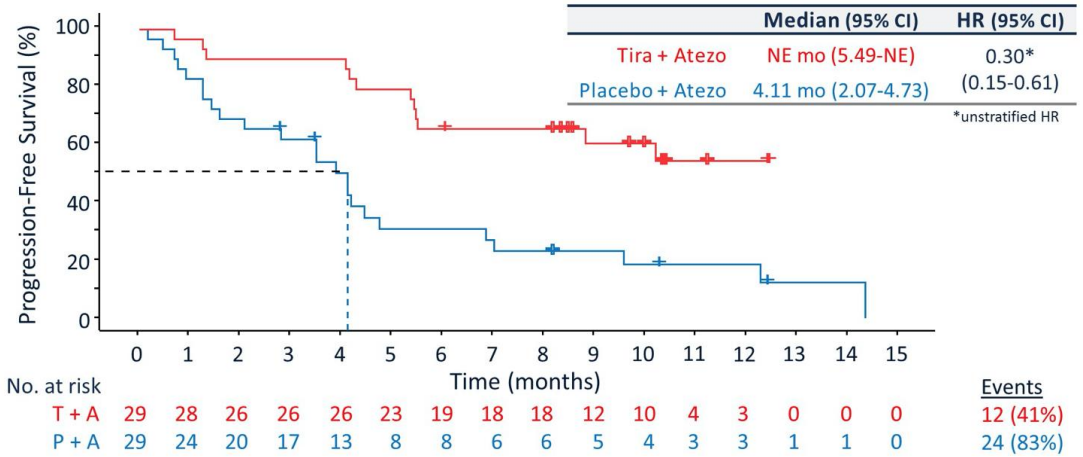




- Phase II: 135 p
- Male: 71 vs 58%
- Asian: 34 vs 27%
- Non-Squam: 60%
- PD-L1 >50%: 43%

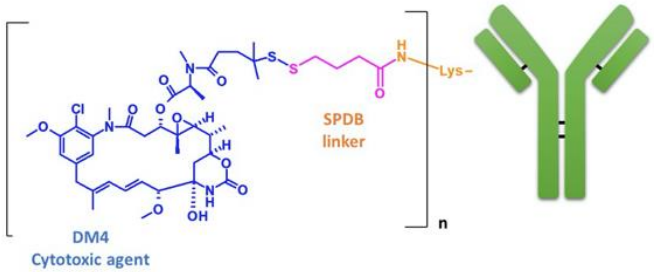






SAR408701 ADC directed to CEACAM5

Structure of SAR408701



Humanized antibody: Specific for **CEACAM5**

Cytotoxic agent: Maytansinoid **DM4** (inhibits tubulin polymerization)

SPDB linker: Cleavable inside cells

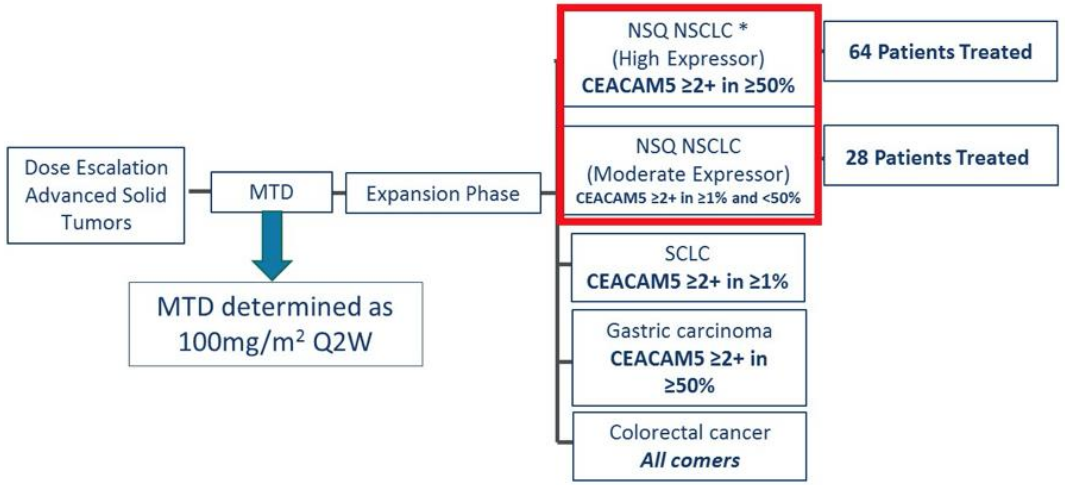
Overall Population

Response, n (%)	High expressors (n = 64)	Moderate expressors (n = 28)
ORR [95% CI]	13 (20.3%) [12.27-31.71]	2 (7.1%) [1.98-22.65]
Confirmed PR	13 (20.3%)	2 (7.1%)
SD	28 (43.8%)	15 (53.6%)
DCR	41 (64.1%)	17 (60.7%)
PD	21 (32.8%)	10 (35.7%)
NE	2 (3.1%)	1 (3.6%)

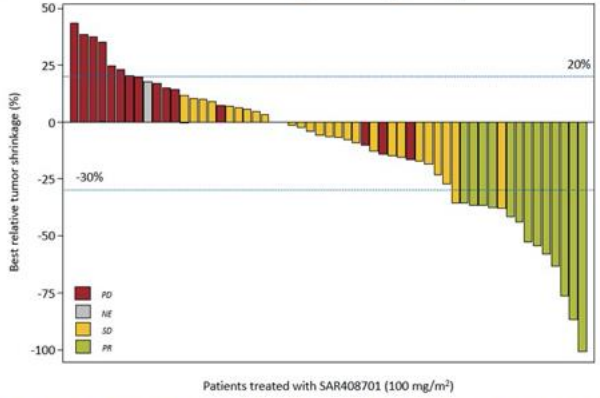
Preferred Term	SAR408701 100 mg/m² Q2W (n=92)	
	All Grades, n (%)	Grade ≥3, n (%)
Any class, TEAEs ≥ 10%	92 (100%)	47 (51.1%)
Corneal AE (Keratopathy/Keratitis)	35 (38.0%)	10 (10.9%)
Asthenia	34 (37.0%)	4 (4.3%)
Peripheral neuropathy (SMQ*)	25 (27.2%)	1 (1.1%)
Diarrhea	21 (22.8%)	1 (1.1%)
Dyspnea	20 (21.7%)	10 (10.9%)
Decreased appetite	19 (20.7%)	0
Cough	14 (15.2%)	0
Nausea	12 (13.0%)	1 (1.1%)
Arthralgia	10 (10.9%)	0
Constipation	10 (10.9%)	0

Dyspnea was the most frequent serious TEAE, reported in 5 (5.4%) patients, all as a symptom of progressive disease.

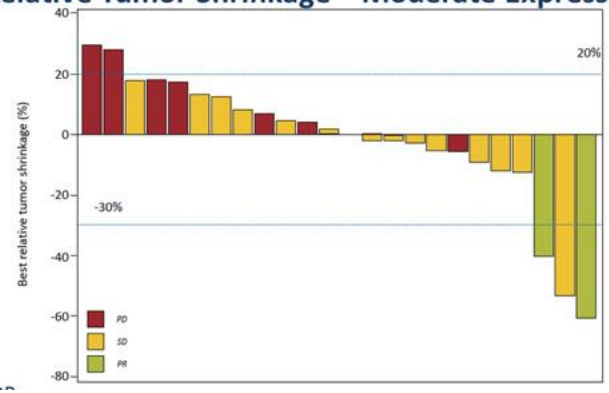
A first-in-human study for the evaluation of the safety, PK and antitumor activity of SAR408701 in patients with advanced solid tumors (NCT02187848)



Best Relative Tumor Shrinkage – High Expressor Cohort



Best Relative Tumor Shrinkage – Moderate Expressor Cohort



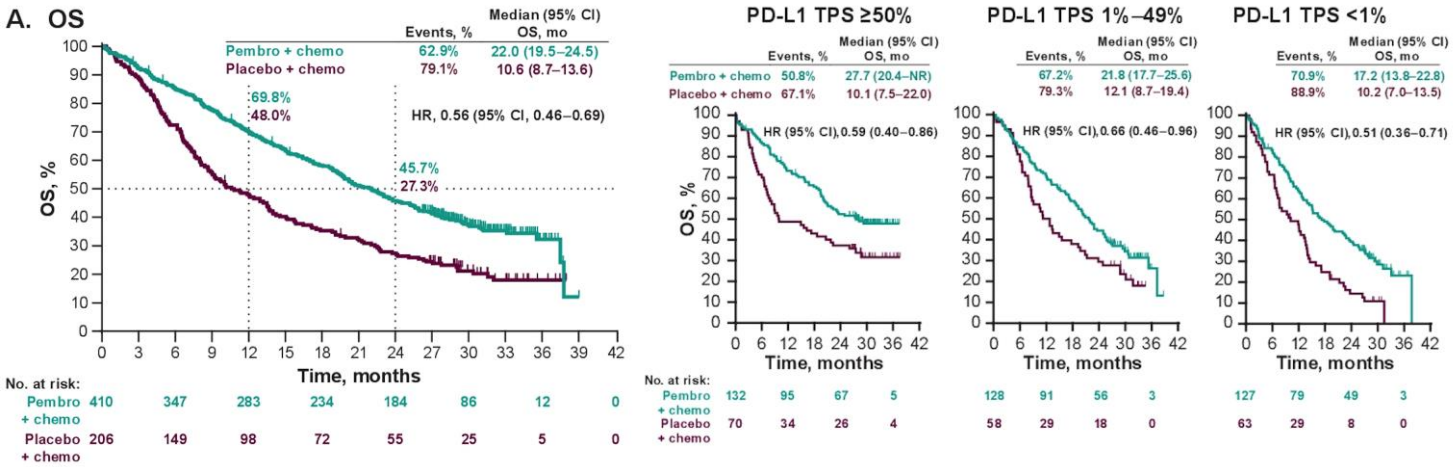
61% antitubulin agents

75% Anti PD-1/PD-L1

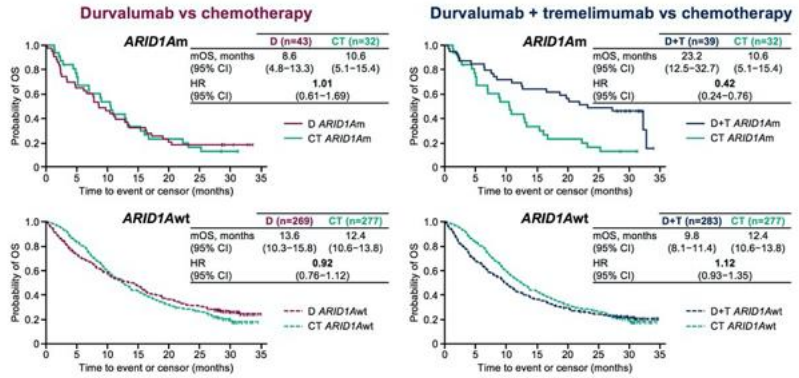
Median DOR High Express 5.6 months (2-24.6 m)

27 patients (42%) > 10 cycles

Predictive factors?: **PD-L1,** TMB, ARID1A….



MYSTIC TRIAL

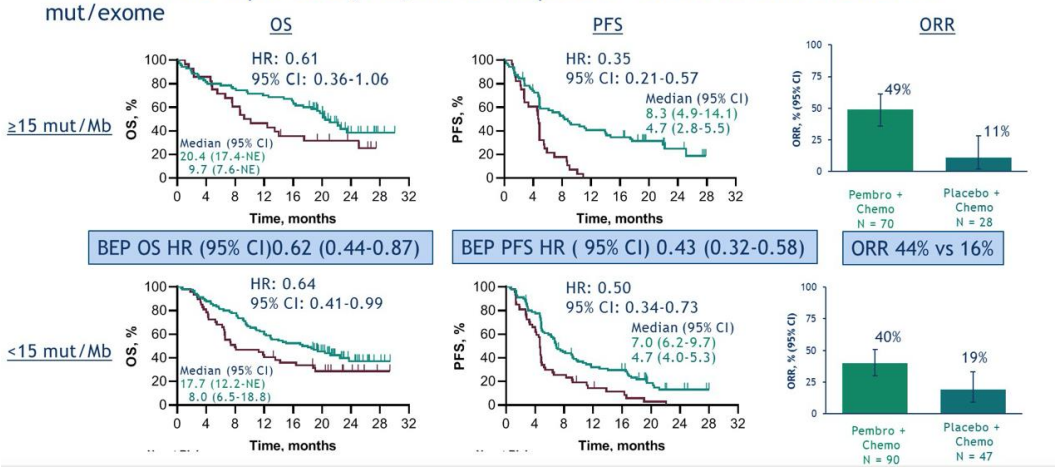


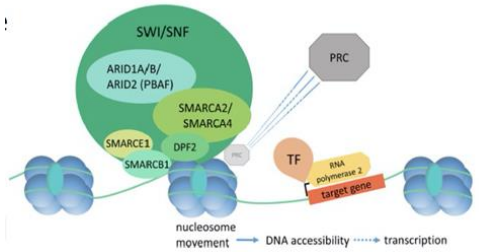
Rizvi et al. OA04.07, WCLC 2019

ARID1A mutations were predictive of benefit of PD-L1/CTLA 4 combination but not PD-L1 monotherapy

Clinical Utility of Prespecified bTMB Cutpoint of 15 mut/Mb

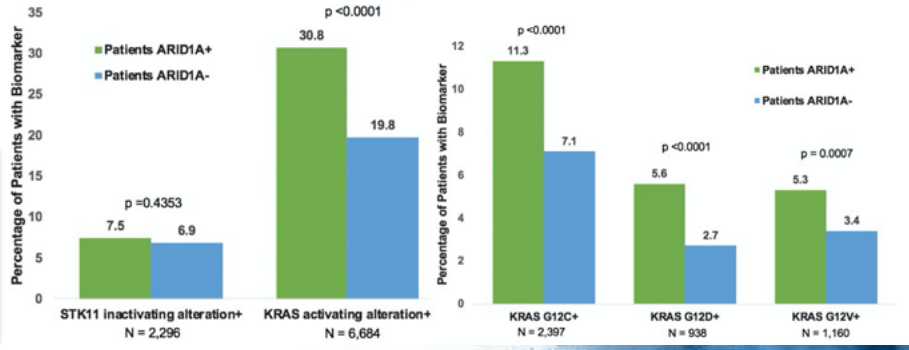
- Pembro + chemo improved OS, PFS, and ORR vs placebo + chemo for bTMB ≥15 and <15 mut/exome





Results

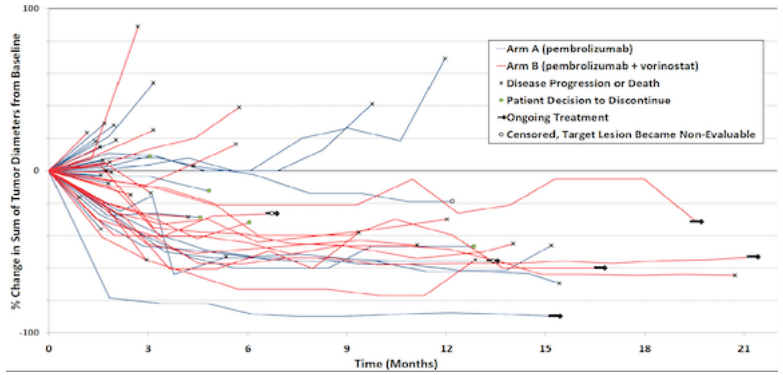
- 33,086 NSCLC patients with ≥1 ctDNA alteration detected
- 1,298 patients (3.9%) had (f)ARID1A mutation
- Samples with (f)*ARID1A* mutations had a significantly higher median number of alterations per sample 6 vs 3 (p<0.0001)
- (f)*ARID1A* mutations were associated with a different co mutation patters than ARID1A wt.

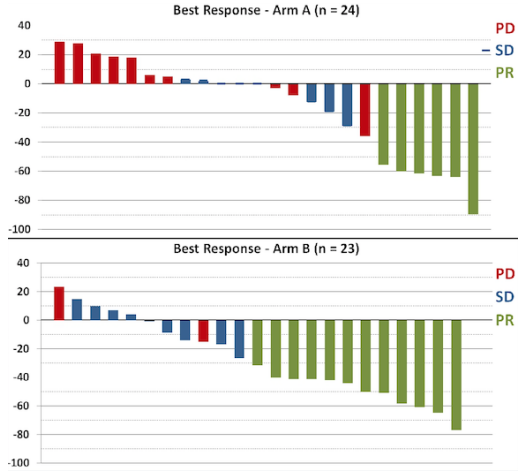


Other potential predictive factors: ctDNA (9525), SWI/SNF complex (9531), CAF/CD8 (9536), PD-L1 proportion score (9539), Blood immunoprofile (9545), Plasma cfDNA (9588), Serum Amyloid (9598)

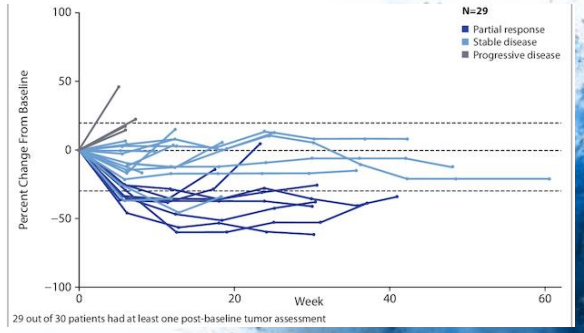
Combinaciones

- ✓ Tislelizumab +/- CT in Squamous Cell (9554): Increase ORR and PFS
- ✓ Pembrolizumab + Abemaciclib (9562): ORR 25% KRASmut and PD-L1+; 8% Squam
- ✓ Pembrolizumab +/- Pegilodecakin (9563): No improvement ORR, PFS, OS in PD-L1 >50%)
- ✓ Pembrolizumab +/- Vorinostat (9567): PR: 52 vs 25%

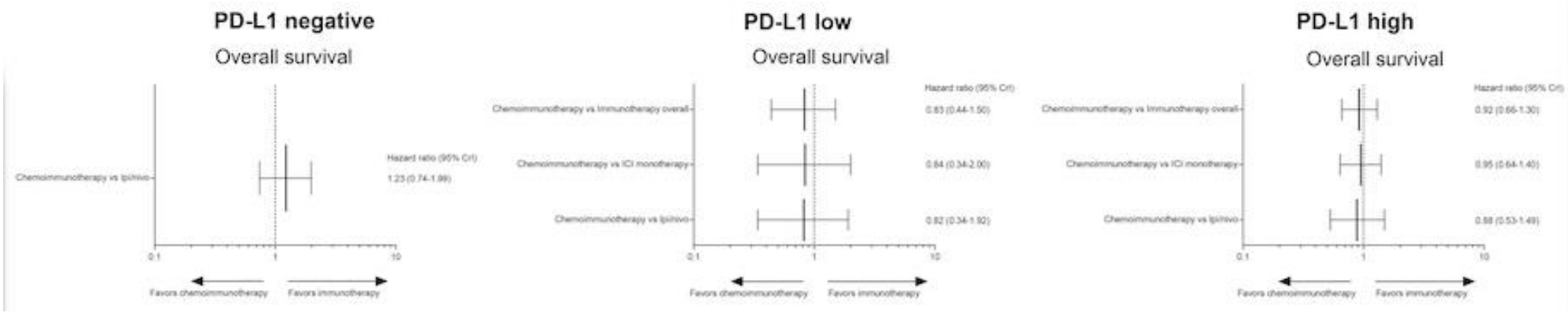




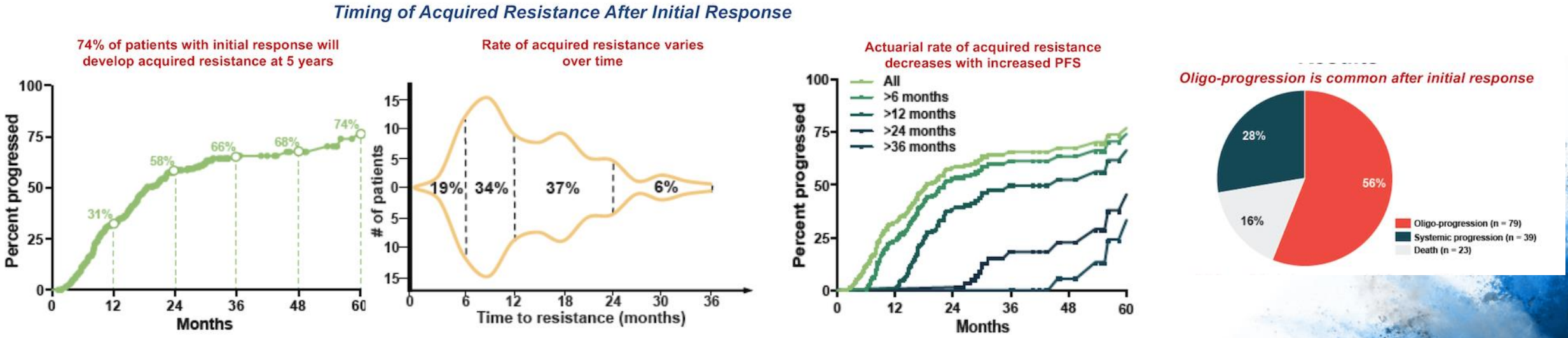
- ✓ Atezolizumab + Cabozantinib in 2nd line (9610): ORR 27%, DCR 82%



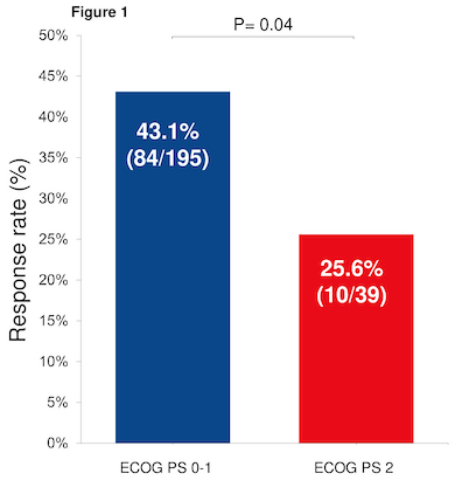
Network metanalysis IT vs IT+CT

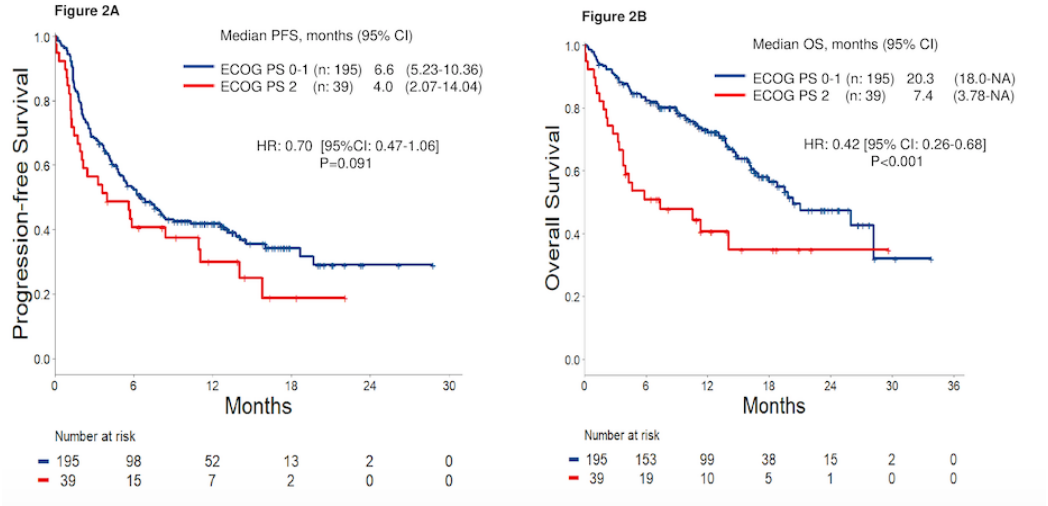


Acquired resistance

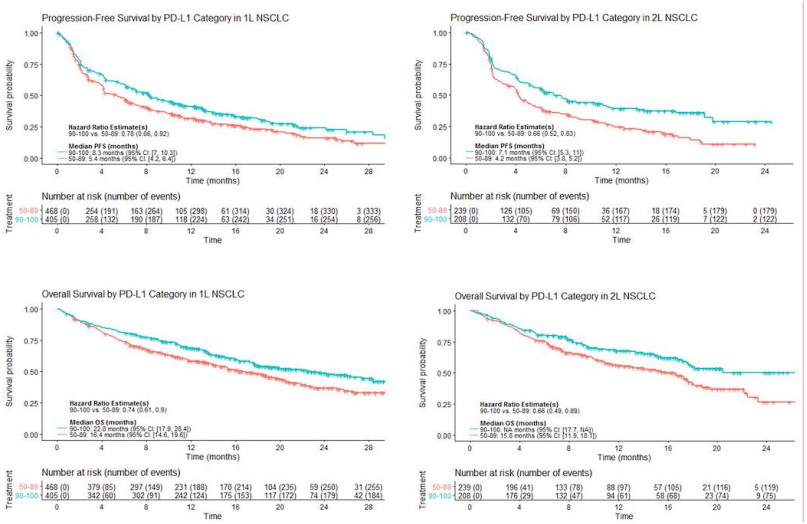


PD-L1 > 50% and Poor PS





ICIs outcome in PD-L1 > 90% vs 50-89%



1st line:
PFS: 8.3 vs 5.4 m HR 0.78
OS: 22.8 vs 16.4 m HR 0.75

2ndt line:
PFS: 7.1 vs 4.2 m HR 0.66
OS: NR vs 15.8 m HR 0.66