Lung Cancer UPDATES
ASCO HIGHLIGTHS
03-07 JUNIO 2022
Chicago, IL

Iniciativa científica de GECP lung cancer research

Innovaciones inmunoterapia CPNCP avanzado

Manuel Cobo
H RU Málaga

Inmunoterapia en CPNCP avanzado Líneas sucesivas

2022 ASCO ANNUAL MEETING

Cabozantinib Plus Atezolizumab or Cabozantinib Alone in Patients With Advanced Non-Small Cell Lung Cancer Previously Treated With an Immune Checkpoint Inhibitor: COSMIC-021 Study Cohorts 7 and 20

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Abstract 9005

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COSMIC-021 Study Design for NSCLC Cohorts

Key Eligibility Criteria

- Stage IV non-squamous NSCLC with radiographic progression on or after one prior ICI for metastatic disease
- ≤2 prior lines of systemic anticancer therapy*
- Patients with known *EGFR*, *ALK*, *ROS1*, or *BRAF* V600E tumor mutations excluded

→ **Cohort 7†**: Cabozantinib 40 mg QD PO + Atezolizumab 1200 mg Q3W IV (N=80)

→ **Cohort 20‡**: Cabozantinib 60 mg QD PO (N=30)

→ Tumor assessment per RECIST v1.1 by investigator every 6 weeks for the first year and every 12 weeks thereafter

Primary endpoint:	ORR per RECIST v1.1 by investigator
Secondary endpoint:	Safety (AEs, SAEs, AESIs)
Exploratory endpoints:	DOR, PFS per RECIST v1.1 by investigator, OS

*Prior treatment with platinum-based chemotherapy was not required. †Patients were initially enrolled to cohort 7 (n=35). Following an initial assessment of clinical activity, subsequent patients were randomized between cohorts 7 and 20. ‡Patients in cohort 20 may receive combination therapy after radiographic disease progression per RECIST v1.1 by the investigator.
SAEs, serious adverse events; AESIs, adverse events of special interest

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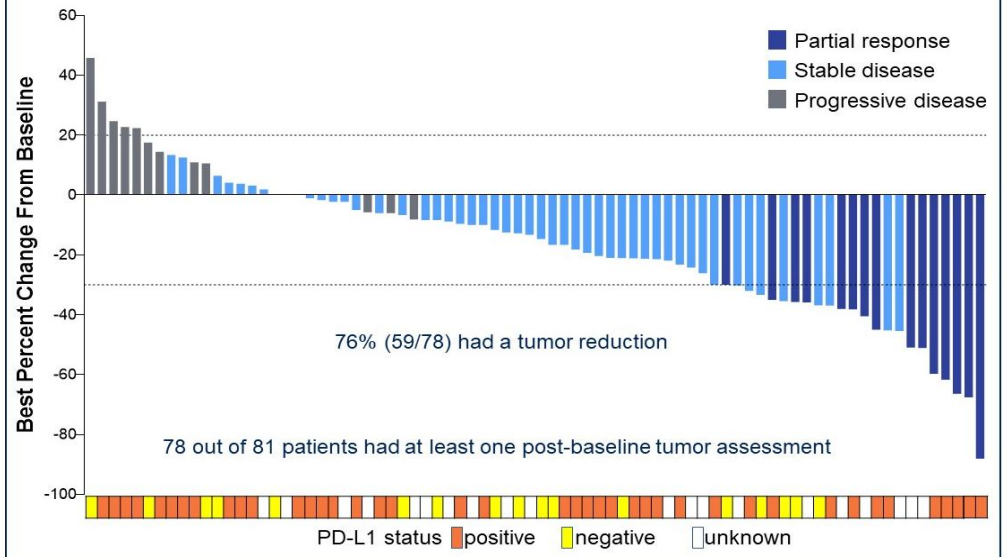
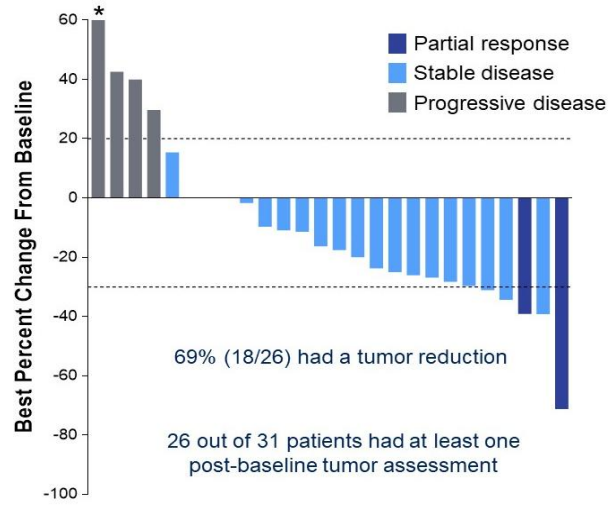
	Cabozantinib + Atezolizumab (N=81)				Cabozantinib (N=31)*
	All patients (N=81)	PD-L1 <1% (n=19)	PD-L1 ≥1% (n=41)	PD-L1 unknown (n=21)	
ORR, n (%)	**15 (19)**	2 (11)	8 (20)	5 (24)	**2 (6)**
Best overall response, n (%)					
Complete response	**0**	0	0	0	**0**
Partial response	**15 (19)**	2 (11)	8 (20)	5 (24)	**2 (6)**
Stable disease	**50 (62)**	12 (63)	25 (61)	13 (62)	**18 (58)**
Progressive disease	**13 (16)**	3 (16)	8 (20)	2 (10)	**6 (19)**
Missing / not evaluable	**3 (4)**	2 (11)	0	1 (5)	**5 (16)**
Disease control rate, n (%)	**65 (80)**	14 (74)	33 (80)	18 (86)	**20 (65)**
PFS, mo (95% CI)	**4.5 (3.5–5.6)**	4.0 (2.6–5.6)	4.7 (2.7–5.6)	5.4 (2.9–10.9)	**3.4 (1.4–5.6)**
Median DOR, mo (95% CI)	**5.8 (4.2–6.9)**	3.4 (2.6–NE)	6.5 (3.5–NE)	6.2 (4.2–NE)	**10.6 (6.3–NE)†**
OS, mo (95% CI)	**13.8 (7.2–15.7)**	6.8 (5.1–15.4)	10.4 (5.9–17.1)	17.4 (9.4–NE)	**9.4 (4.5–11.7)**

Cabozantinib + Atezolizumab



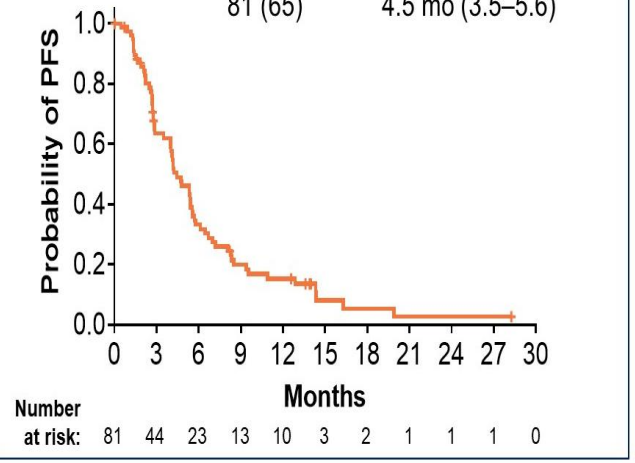
Cabozantinib



*One patient had an increase of 160%

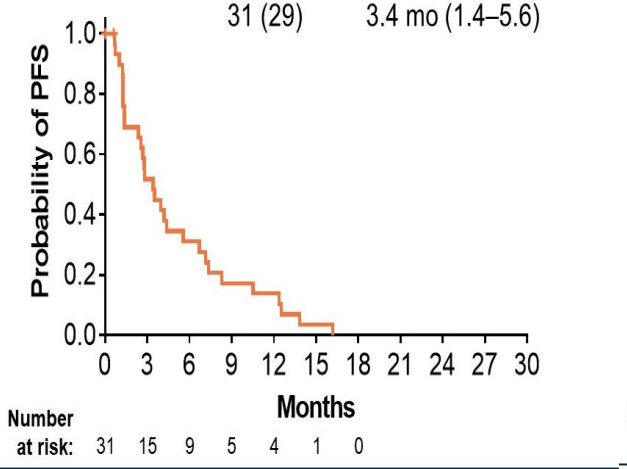
Cabozantinib + Atezolizumab

N (events)	Median (95% CI), mo
81 (65)	4.5 mo (3.5–5.6)



Cabozantinib

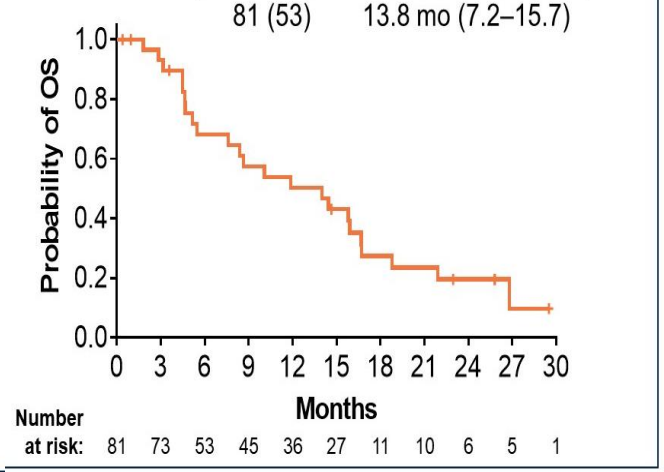
N (events)	Median (95% CI), mo
31 (29)	3.4 mo (1.4–5.6)



Median PFS (95% CI):
- 4.0 mo (2.6–5.6) for PD-L1 negative
- 4.7 mo (2.7–5.6) for PD-L1 positive
- 5.4 mo (2.9–10.9) for PD-L1 unknown

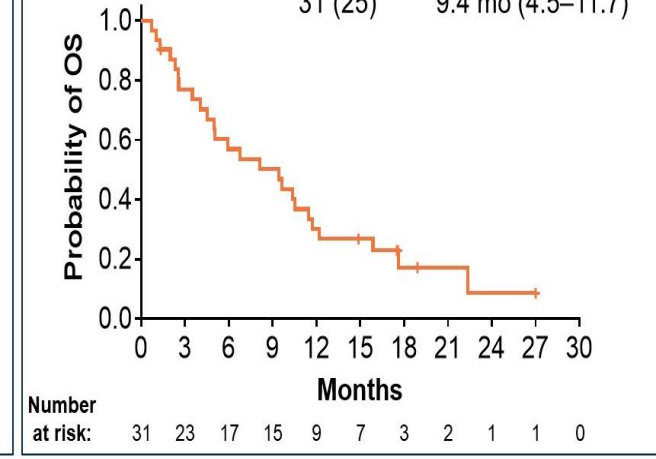
Cabozantinib + Atezolizumab

N (events)	Median (95% CI), mo
81 (53)	13.8 mo (7.2–15.7)



Cabozantinib

N (events)	Median (95% CI), mo
31 (25)	9.4 mo (4.5–11.7)



Median OS (95% CI):
- 6.8 mo (5.1–15.4) for PD-L1 negative
- 10.4 mo (5.9–17.1) for PD-L1 positive
- 17.4 mo (9.4–NE) for PD-L1 unknown

Seguridad

	Cabozantinib + Atezolizumab (N=81)	Cabozantinib* (N=31)
Patients on study treatment at data cut-off, n (%)	6 (7)	2 (6)
Duration of exposure, median (range), months		
Cabozantinib + Atezolizumab†	5.2 (0.3–28.8)	4.8 (0.7–19.4)
Cabozantinib	5.2 (0.3–28.8)	4.8 (0.7–19.4)
Atezolizumab	4.6 (0–28.0)	1.6 (0–11.8)
AEs leading to cabozantinib dose reductions, n (%)	32 (40)	18 (58)
AEs leading to cabozantinib dose hold, n (%)	60 (74)	25 (81)
AEs leading to atezolizumab dose delay, n (%)	41 (51)	2 (6)
Discontinuation due to TRAEs, n (%)		
Cabozantinib	11 (14)	3 (10)
Atezolizumab	8 (10)	1 (3)
Either	13 (16)	3 (10)
Both	5 (6)	1 (3)

	Cabozantinib + Atezolizumab (N=81)		Cabozantinib (N=31)†	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAE, n (%)	81 (100)	43 (53)	31 (100)	22 (71)
Diarrhea	36 (44)	1 (1)	16 (52)	3 (10)
Decreased appetite	30 (37)	1 (1)	11 (35)	1 (3)
Fatigue	29 (36)	4 (5)	11 (35)	2 (6)
Nausea	28 (35)	2 (2)	15 (48)	2 (6)
Asthenia	24 (30)	5 (6)	12 (39)	3 (10)
Constipation	21 (26)	0	5 (16)	0
Pyrexia	20 (25)	0	2 (6)	0
AST increased	19 (23)	2 (2)	9 (29)	0
Hypertension	19 (23)	5 (6)	10 (32)	7 (23)
Vomiting	19 (23)	0	9 (29)	1 (3)
ALT increased	17 (21)	3 (4)	10 (32)	1 (3)
PPE	17 (21)	3 (4)	6 (19)	0
Hypomagnesemia	16 (20)	1 (1)	5 (16)	0
Weight decreased	16 (20)	3 (4)	4 (13)	2 (6)
Pneumonitis	3 (4)‡	0	0	0
Gastric ulcer hemorrhage	0	0	1 (3)§	0

	Cabozantinib + Atezolizumab‡ (N=81)		Cabozantinib§ (N=31)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any adverse events of special interest (AESI), n (%)	59 (73)	21 (26)	23 (74)	4 (13)
Rash	34 (42)	7 (9)	12 (39)	2 (6)
Hepatitis (lab abnormalities)	28 (35)	5 (6)	14 (45)	1 (3)
Pancreatitis	14 (17)	5 (6)	2 (6)	0
Hypothyroidism	13 (16)	0	8 (26)	0
Colitis	3 (4)	1 (1)	2 (6)	1 (3)
Hyperthyroidism	3 (4)	0	0	0
Pneumonitis	3 (4)	0	0	0
Hepatitis (diagnosis)	2 (2)	1 (1)	2 (6)	0
Infusion-related reactions	2 (2)	1 (1)	0	0

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NCT03971474

Overall survival from a phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non-small cell lung cancer previously treated with immunotherapy—Lung-MAP non-matched sub-study S1800A

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Stratified by 1) PD-L1 expression, 2) histology, 3) intent to receive ramucirumab in standard of care arm

Primary endpoint: OS

Secondary endpoints: RR, DCR, DoR, PFS, Toxicities

ARM A
Investigator's Choice Standard of Care
docetaxel + ramucirumab; docetaxel; gemcitabine; pemetrexed (nonSCC only)

Randomization

R (1:1)
N= 130

ARM B
Pembrolizumab
200 mg Q3W for up to 35 cycles
+
Ramucirumab
10 mg/kg Q3W

Key eligibility: 1) Previously received both PD-1 or PD-L1 inhibitor therapy and platinum-based doublet chemotherapy either sequentially or combined, with PD on at least 84 days after initiation of ICI and platinum-based doublet therapy; 2) ECOG 0-1; 3) all patients met eligibility to receive ramucirumab

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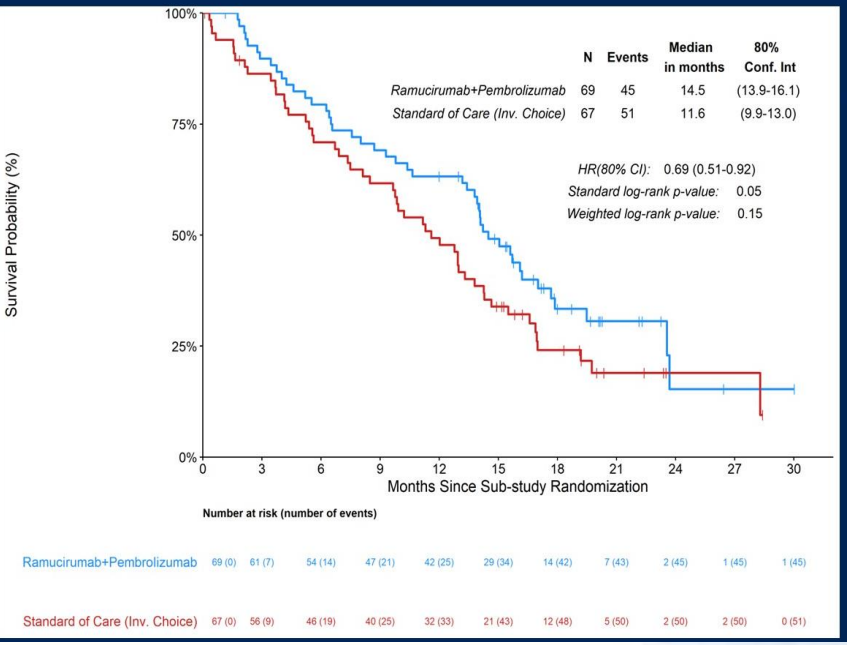
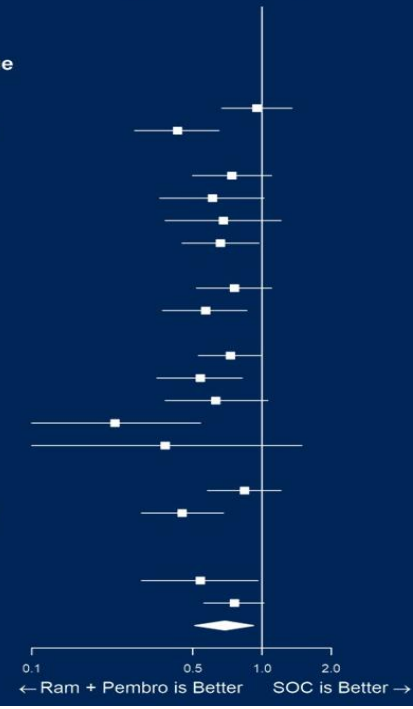
Overall survival

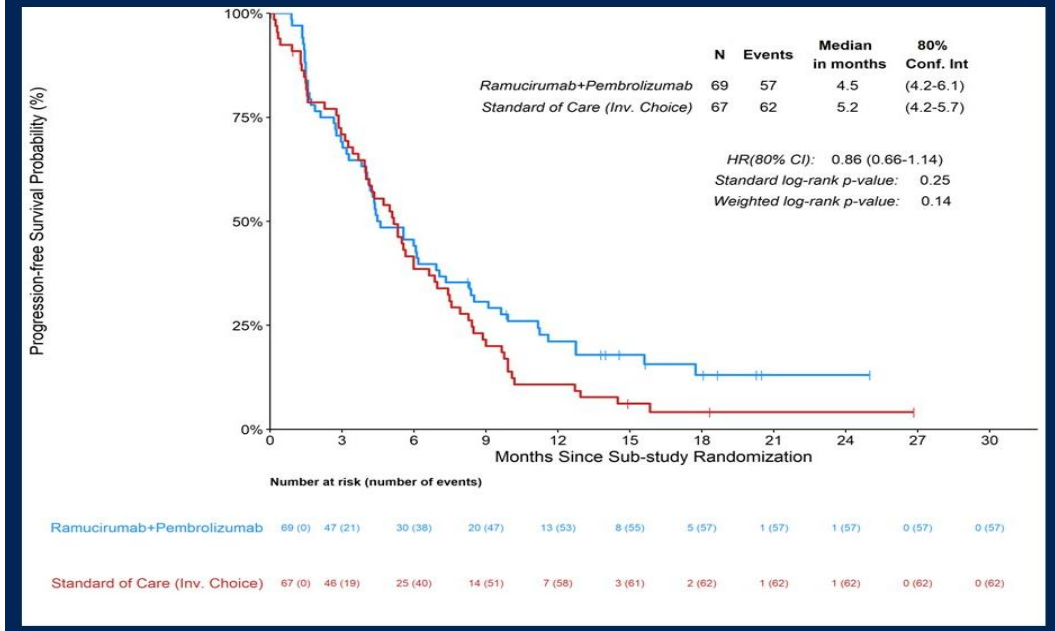


- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

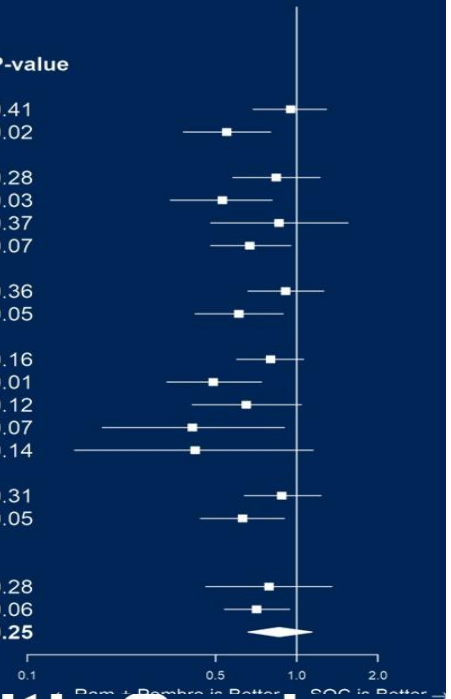
Standard of care therapy received:
- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

	Ram+ Pembro Events/N	SOC Events/N	HR (80% CI)	P-value
HISTOLOGY				
Non-Squamous	27/40	27/39	0.95 (0.67,1.35)	0.43
Squamous/Mixed	18/29	24/28	0.43 (0.28,0.65)	0.005
PD-L1				
PD-L1 0	21/29	21/26	0.74 (0.50,1.10)	0.16
PD-L1 1-49	11/21	15/22	0.61 (0.36,1.02)	0.11
PD-L1 50+	8/12	12/16	0.68 (0.38,1.21)	0.20
PD-L1 1+	19/33	27/38	0.66 (0.45,0.97)	0.08
TMB				
TMB <10	23/32	28/38	0.76 (0.52,1.10)	0.17
TMB 10+	18/33	20/25	0.57 (0.37,0.86)	0.04
BIOMARKER				
TP53	31/48	35/48	0.73 (0.53,1.00)	0.10
CDKN2A	18/27	21/24	0.54 (0.35,0.82)	0.03
KRAS	12/21	13/16	0.63 (0.38,1.06)	0.13
STK11	4/7	10/10	0.23 (0.10,0.54)	0.01
KEAP1	1/3	7/10	0.38 (0.10,1.49)	0.18
PRIOR TREATMENT				
IO+CHEMO COMBO	20/32	32/42	0.84 (0.58,1.21)	0.27
CHEMO->IO	25/36	18/23	0.45 (0.30,0.68)	0.006
PERFORMANCE STATUS				
PS 0	15/23	8/9	0.54 (0.30,0.96)	0.08
PS 1	30/46	43/58	0.76 (0.56,1.02)	0.12
OVERALL	**45/69**	**51/67**	**0.69 (0.51,0.92)**	**0.05**

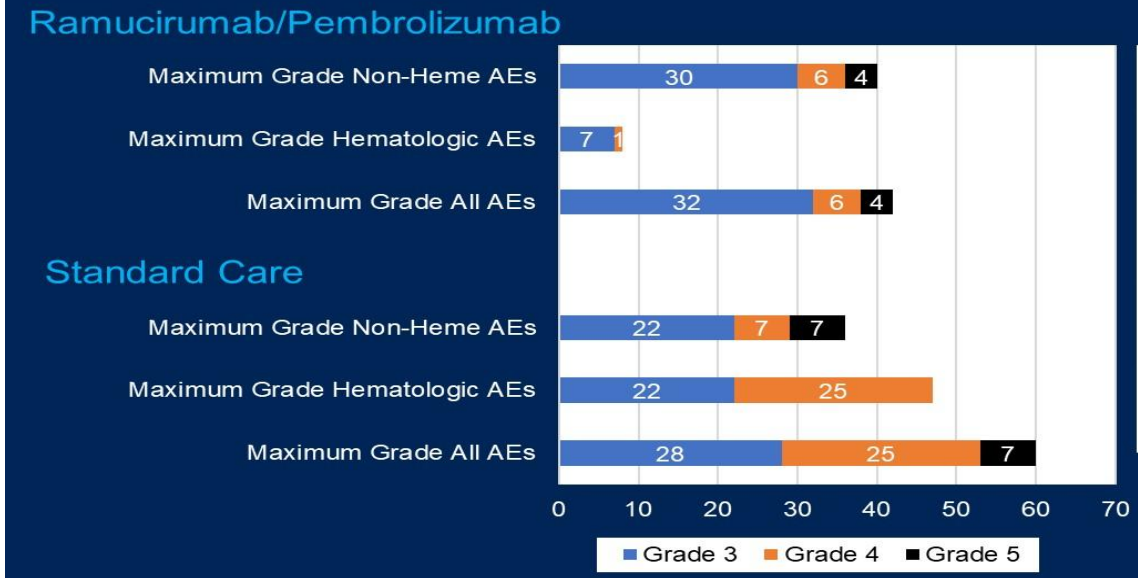


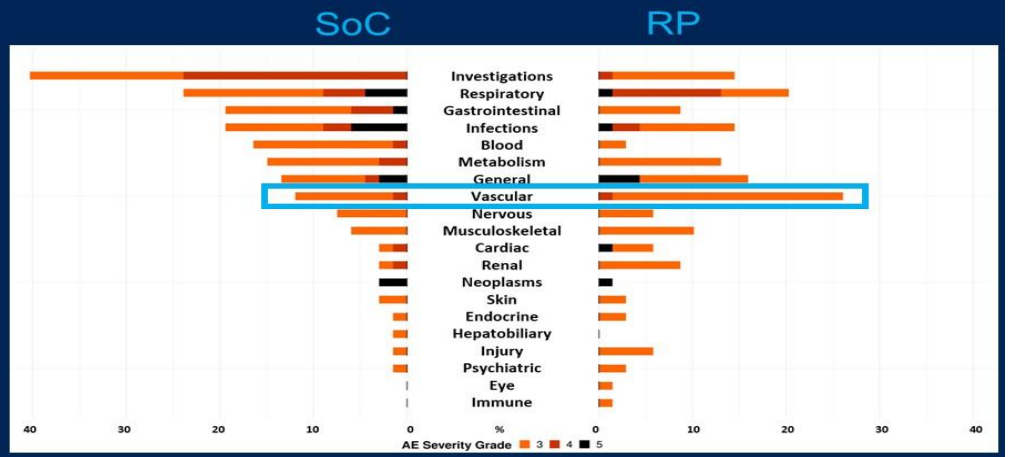


	Ram+ Pembro Events/N	SOC Events/N	HR (80% CI)	P-value
HISTOLOGY				
Non-Squamous	34/40	34/39	0.95 (0.69,1.29)	0.41
Squamous/Mixed	23/29	28/28	0.55 (0.38,0.80)	0.02
PD-L1				
PD-L1 0	27/29	25/26	0.84 (0.58,1.22)	0.28
PD-L1 1-49	16/21	22/22	0.53 (0.34,0.81)	0.03
PD-L1 50+	8/12	12/16	0.86 (0.48,1.55)	0.37
PD-L1 1+	24/33	34/38	0.67 (0.48,0.95)	0.07
TMB				
TMB <10	29/32	36/38	0.91 (0.66,1.26)	0.36
TMB 10+	24/33	23/25	0.61 (0.42,0.89)	0.05
BIOMARKER				
TP53	39/48	43/48	0.80 (0.60,1.06)	0.16
CDKN2A	22/27	24/24	0.49 (0.33,0.74)	0.01
KRAS	16/21	15/16	0.65 (0.41,1.04)	0.12
STK11	5/7	10/10	0.41 (0.19,0.90)	0.07
KEAP1	2/3	10/10	0.42 (0.15,1.15)	0.14
PRIOR TREATMENT				
IO+CHEMO COMBO	26/32	40/42	0.88 (0.64,1.23)	0.31
CHEMO->IO	31/36	21/23	0.63 (0.44,0.90)	0.05
PERFORMANCE STATUS				
PS 0	21/23	8/9	0.79 (0.46,1.35)	0.28
PS 1	36/46	54/58	0.71 (0.54,0.94)	0.06
OVERALL	**57/69**	**62/67**	**0.86 (0.66,1.14)**	**0.25**



Safety summary—Percentage of patients with Grade 3-5 AEs





- Grade ≥3 TRAEs: 42% on RP; 60% on SOC
- Nine (31%) Grade 3–5 irAEs on RP

First report of safety/tolerability and preliminary antitumor activity of CAN-2409 in inadequate responders to immune checkpoint inhibitors for stage III/IV NSCLC

Charu Aggarwal, Andrew Haas, Sarah W. Gordon, Ranee Mehra, Peter M Lee, Christine M. Bestvina, Fabien Maldonado, Vamsidhar Velcheti, Roy S. Herbst, Susan D. Bell, Rachael Gillmor, Andrea G. Manzanera, Christopher J. Matheny, Estuardo Aguilar-Cordova, Laura K. Aguilar, Francesca Barone, Paul Peter Tak, Daniel Sterman

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Abstract # 9037

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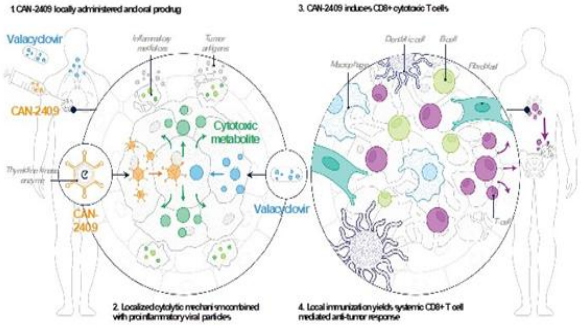
CAN-2409 Mechanism of action



Stage III/IV Non-resectable NSCLC with inadequate response to ICI

N=96 (32 per cohort)

CAN-2409 and valacyclovir (2 courses)

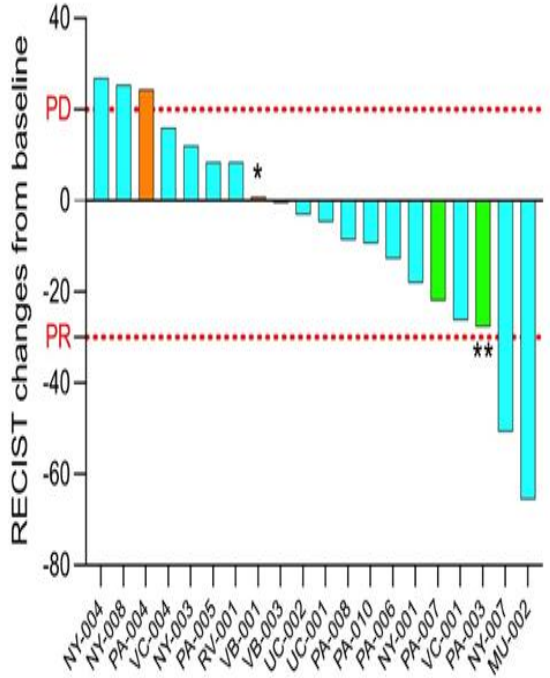
with standard of care: Anti-PD-1/PD-L1 +/- chemotherapy

- Cohort 1 Stable Disease (>18 wks ICI)
- Cohort 2 Progressive Disease (>18 wks ICI)
- Cohort 3 Refractory Disease (>9 wks ICI)

Primary Endpoints
- Response by RECIST Criteria
- Safety

Secondary Endpoints
- Overall survival
- Progression free survival
- Quality of life
- Immunological biomarkers
- Response by iRECIST and itRECIST (Exploratory)

Best responses RECIST central read



Efficacy Measures

Cohort	Completed 12-week treatment	PR	SD	PD	DCR	DoR for PR (w)	DoR for SD (w)
1	2	1**	1	0	50%	24.1+	26.9
2	16	2	12	2	87.5%	26.7-37.9+	5.4+ - 50.4+
3	2	0	0	2*	0%	n/a	n/a

PR= partial response; SD= stable disease; PD= progressive disease; DCR = disease control rate
DoR PR= weeks from PR to progression
DoR SD=weeks from SD to progression
+ongoing response
*PD by local read; **PR by local read

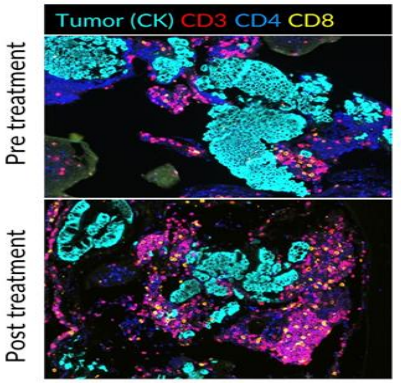
** Patients were considered evaluable if they completed both courses of CAN-2409 followed by valacyclovir*

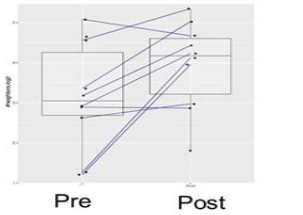
Most frequent treatment related AEs* (n=35)

SOC/Adverse Event (>10%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total patients (n=35)
General disorders and administration site conditions				
Chills	4 (11)			4 (11)
Fatigue	8 (22)	4 (11)		12 (33)
Injection site reaction	4 (11)			4 (11)
Pyrexia	6 (17)		2 (6)	7 (20)
Investigations				
Blood creatinine increased	4 (11)	1 (3)		4 (11)

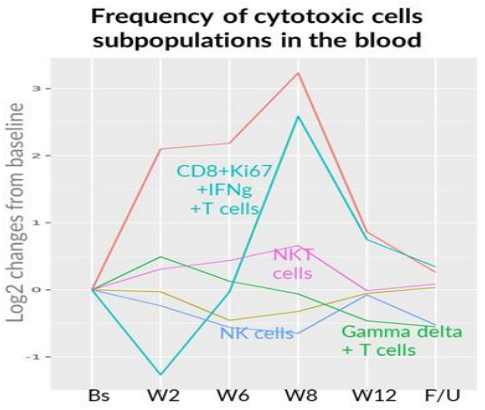
** Patients were included in the safety population if they were treated with at least one CAN-2409 injection*

CAN-2409 increases local and systemic frequency of cytotoxic T cells





Frequency of T cells in 100um radius distance from cancer cells p=0.0149



Biomarcadores e inmuno

2022 ASCO ANNUAL MEETING

FDA

Outcomes of 1L therapy in patients with advanced NSCLC according to *KRAS* mutation status & PD-L1 expression: FDA pooled analysis

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Study Therapy	Interpretation of Response	ORR		Median OS, mo		
		KRASwt	*KRASm*	*KRASwt*	*KRASm*	
ICI alone	***KRASwt* < *KRASm*** (n=127) (n=30)	29%	57%	15	28	Herbst et al Ann. Oncol. 2019
ICI+chemo	***KRASwt* ≈ *KRASm*** (n=145) (n=59)	48%	41%	23	21	Gadgeel et al Ann. Oncol. 2019

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12 Randomized 1L Trials of ICI+Chemo, ICI Alone, or Chemo Alone Arms Submitted for Marketing Approval

N = 8888

***KRAS* mutation status reported**
N = 1430 (16%)

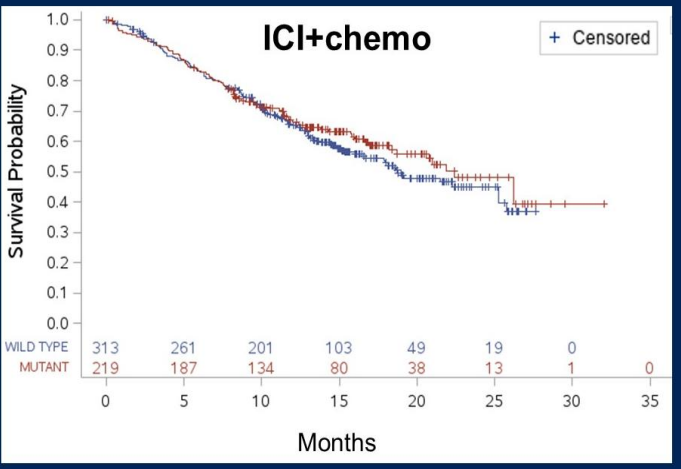
	KRASwt N = 875 (61%)	*KRASm* N = 555 (39%)	*KRAS G12C* N = 157 (11%)
PD-L1 TPS, %			
Negative (<1%)	40	36	37
Low (1-49%)	32	32	32
High (≥50%)	27	31	31
Treatment Arm, %			
ICI+Chemo	35	39	37
ICI alone	27	24	29
Chemo alone	36	36	34

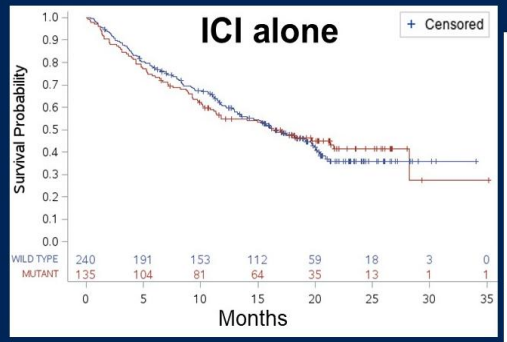
Results: ORR according to *KRAS* status

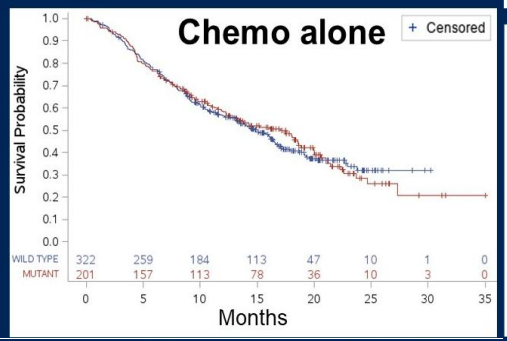
Similar response rate between patients with *KRASwt* & *KRASm* NSCLC

	ORR (95% CI)		
	KRASwt N=875	***KRASm*** N=555	***KRAS G12C*** N=157
ICI+Chemo	**51%** (46, 57)	**46%** (39, 53)	**47%** (33, 60)
ICI alone	**33%** (27, 40)	**37%** (29, 46)	**33%** (20, 49)
Chemo alone	**32%** (33, 60)	**33%** (20, 49)	44% (31, 59)

Results: Kaplan Meier curves of OS by *KRAS* status

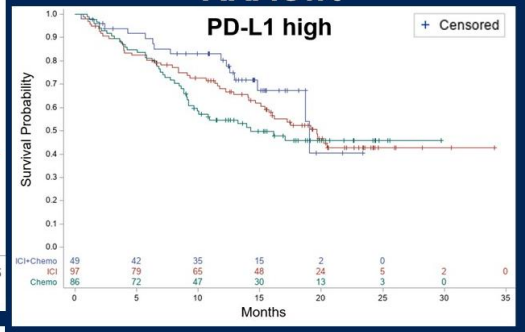


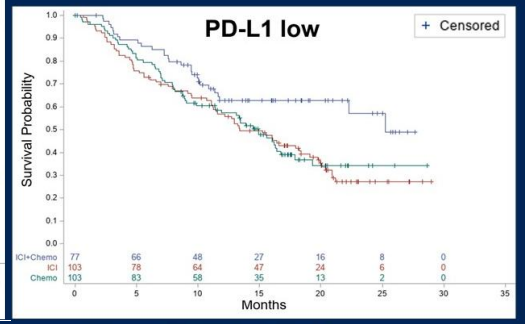




Results: OS by PD-L1 status

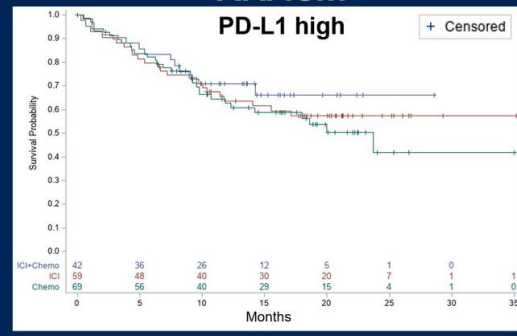
KRASwt

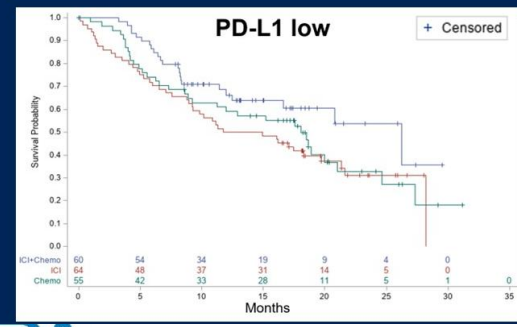




Treatment
- ICI+Chemo
- ICI
- Chemo

KRASm





OS Results: KRAS mutated vs. wildtype in PD-L1 negative

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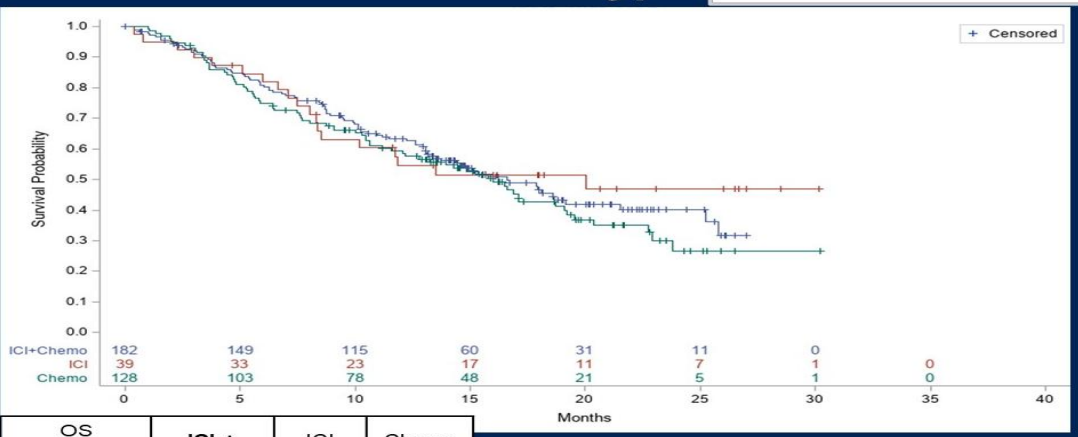
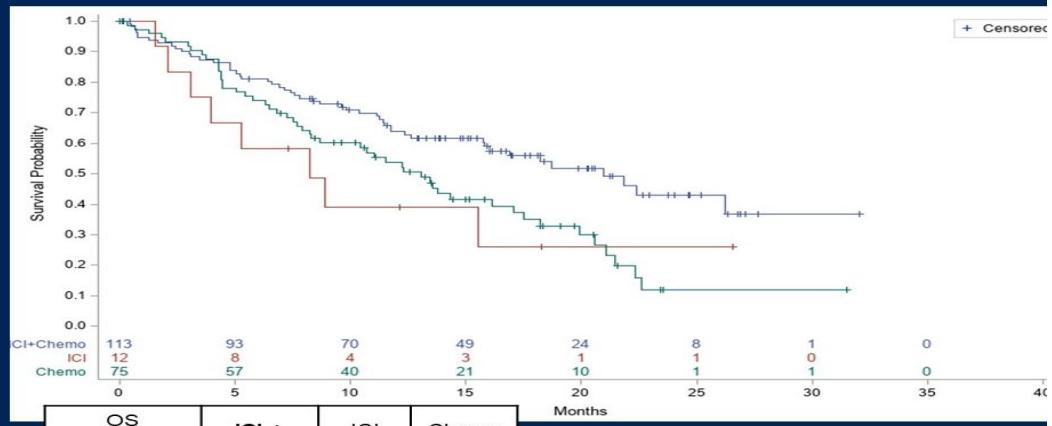
KRAS wildtype — Treatment: ICI+Chemo, ICI, Chemo — **KRAS mutant**



OS landmark rates	ICI + Chemo	ICI alone	Chemo alone
12mos	**63**	55	59
24mos	**40**	47	27



OS landmark rates	ICI + Chemo	ICI alone	Chemo alone
12mos	**64**	39	54
24mos	**43**	26	12

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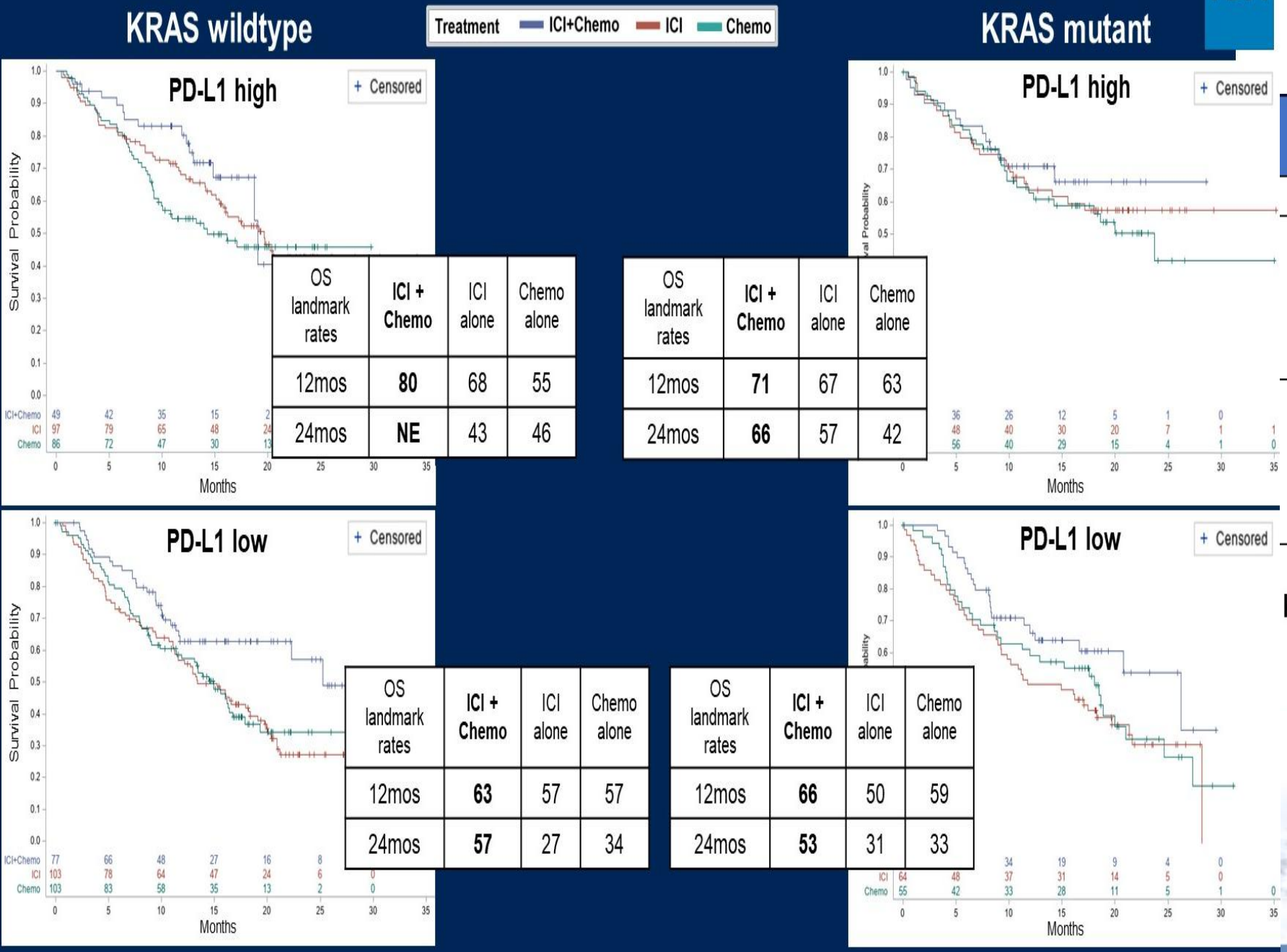
Results: Kaplan Meier curves of OS by PD-L1 status



OS landmark rates	ICI + Chemo	ICI alone	Chemo alone
12mos	**80**	68	55
24mos	**NE**	43	46

OS landmark rates	ICI + Chemo	ICI alone	Chemo alone
12mos	**71**	67	63
24mos	**66**	57	42

OS landmark rates	ICI + Chemo	ICI alone	Chemo alone
12mos	**63**	57	57
24mos	**57**	27	34

OS landmark rates	ICI + Chemo	ICI alone	Chemo alone
12mos	**66**	50	59
24mos	**53**	31	33

	Median OS, months (95% CI)		
	ICI+Chemo	**ICI alone**	Chemo alone
KRASwt n=875	**18.7** (16.0, 25.2) n=313	**16.4** (13.4, 19.7) n=240	14.9 (12.2, 16.6) n=322
	HR 0.87 (95% CI: 0.46, 1.67)		
KRASm n=555	**22.4** (18.2, NE) n=219	**16.2** (11.1, NE) n=135	17.1 (12.3, 18.9) n=201
	HR 0.74 (95% CI: 0.37, 1.49)		
KRAS G12C n=157	**20.8** (11.3, NE) n=58	**11.8** (8.2, NE) n=45	17.5 (10.7, 21.1) n=54
	HR 0.93 (95% CI: 0.59, 1.48)		

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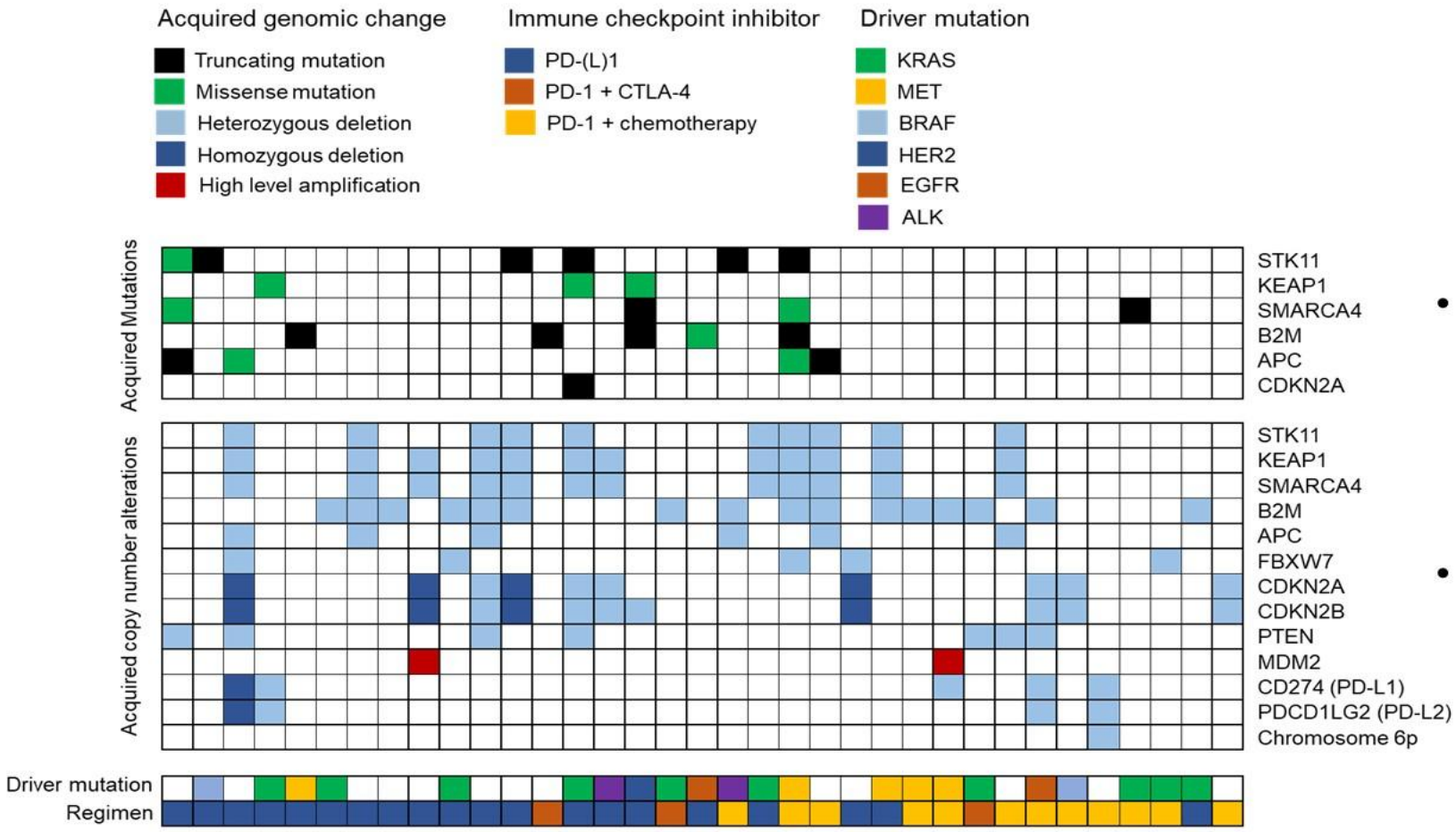
Abstract 9021: Genomic correlates of acquired resistance to PD-(L)1 blockade in patients with advanced NSCLC (Ricciuti et al)



- Acquired loss-of function mutations in *STK11* and *B2M* were detected in 9.1% (6/66) and 7.5% (5/66) of patients at the time of acquired resistance
- No such mutations identified in chemotherapy or EGFR TKI comparison arms

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Digital quantification of lymphocytic infiltration on routine H&E images and immunotherapy response in non-small cell lung cancer

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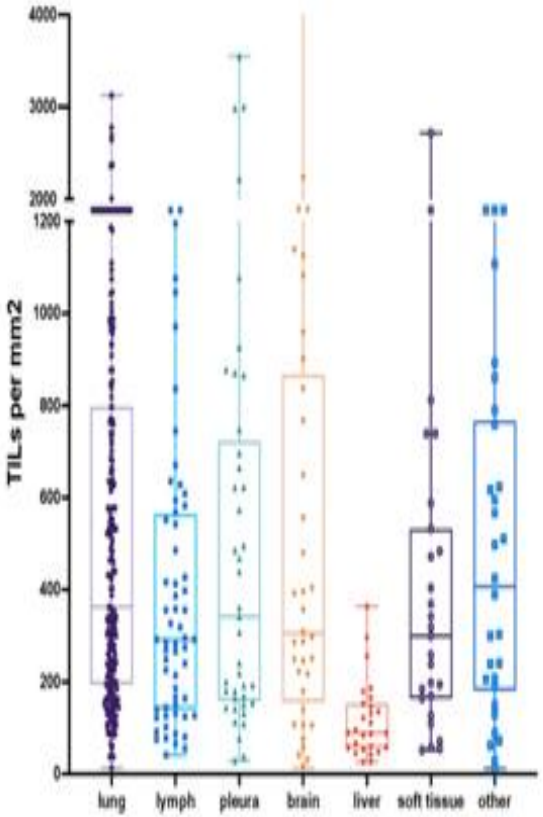
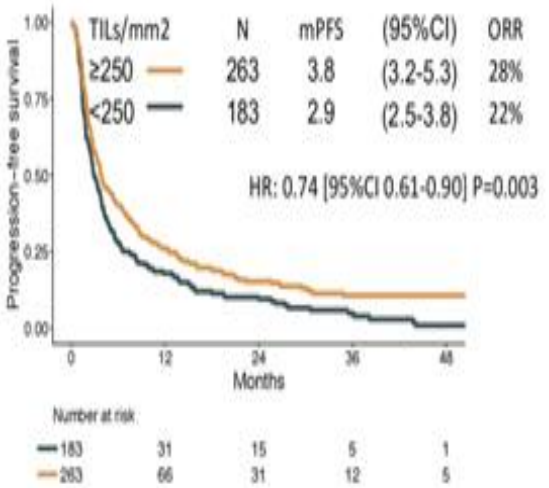
9066

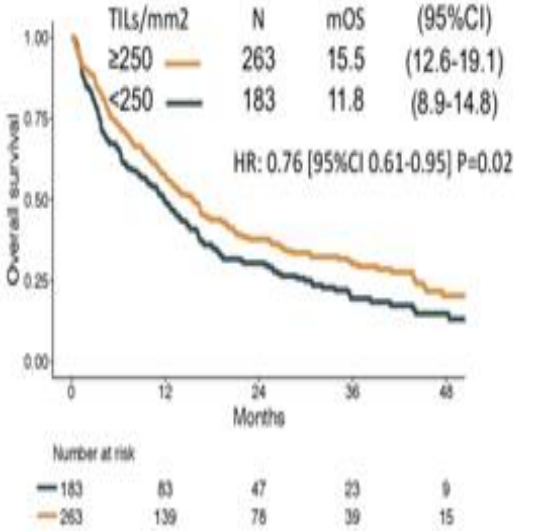
TILs distribution across different tissue sites



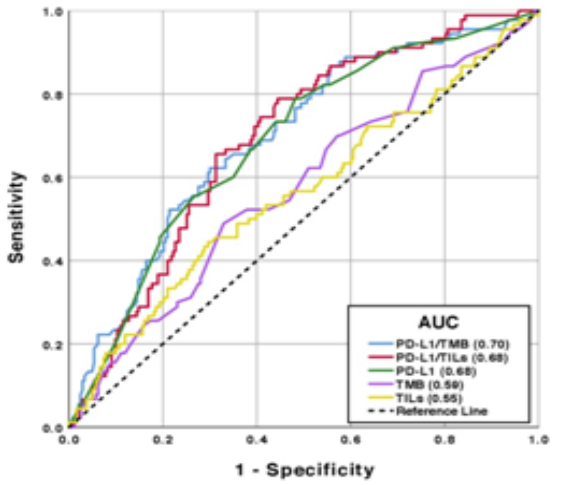
	lung	lymph	pleura	brain	liver	soft tissue	other
median	363	292	342	306	90	300	407
range	13-3125	41-1266	29-3553	13-4282	26-364	52-2717	12-1342

PFS and OS to ICIs



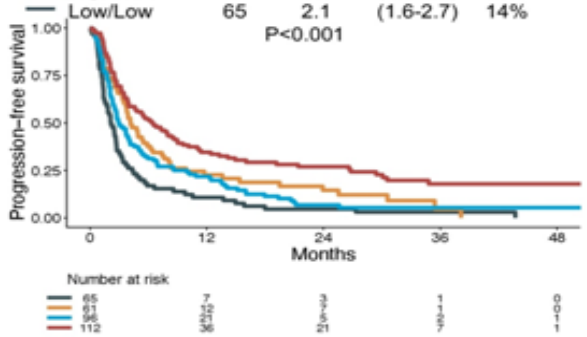


Predictive performance of biomarkers

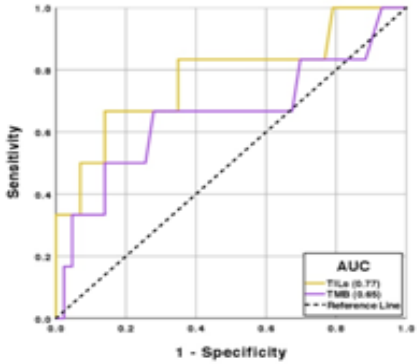


TILs/PD-L1	N	mPFS	(95%CI)	ORR
High/High	112	6.4	(4.6-9.0)	40%
Low/High	61	4.2	(3.4-6.4)	34%
High/Low	96	2.9	(2.5-4.1)	16%
Low/Low	65	2.1	(1.6-2.7)	14%

P<0.001

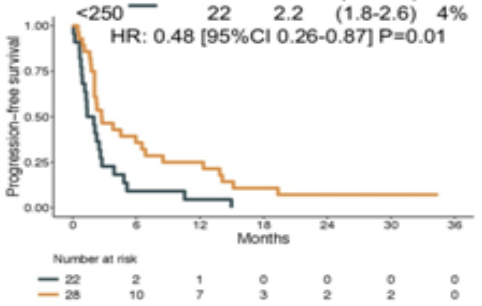


TILs vs TMB in PD-L1 negative subset



TILs/mm2	N	mPFS	(95%CI)	ORR
≥250	28	2.7	(0.7-4.7)	18%
<250	22	2.2	(1.8-2.6)	4%

HR: 0.48 [95%CI 0.26-0.87] P=0.01



TMB/Mb	N	mPFS	(95%CI)	ORR
≥10	20	2.1	(1.9-2.2)	20%
<10	29	2.3	(1.5-3.1)	7%

HR: 0.76 [95%CI 0.55-1.65] P=0.8