LUNG CANCER UPDATES

ASCO HIGHLIGHTS

1-5 JUNIO 2018, CHICAGO

"Immunotherapy for Oncogene-Driven Non-Small Cell Lung Cancer"

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GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

REtrospective analysis of activity of ICI in NSCLC patients with different oncogene drivers

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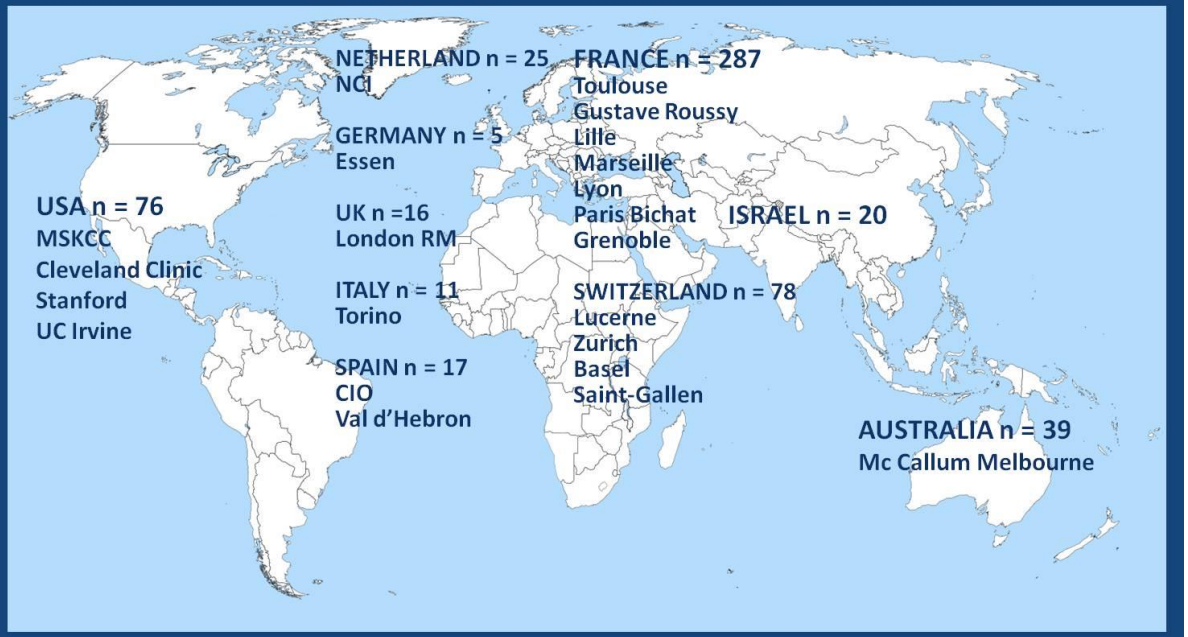
IMMUNOTARGET COHORT

Retrospective multicenter cohort

Inclusion:
- Patients with known activating mutation
- Treated with ICI monotherapy (any line)

Primary objective : PFS under ICI
Secondary objectives: RR, OS, PFS ratio
Exploratory objective : PDL1 expression

Local ethic committees



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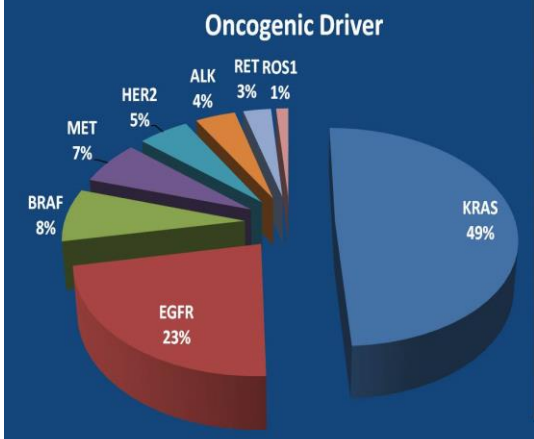
IMMUNOTARGET COHORT (n = 551)



Driver	Subgroup	%	Total
KRAS	G12C Other	42% 58%	271
EGFR	18/19/21 20/other	48% 52%	125
BRAF	V600E Other	48% 52%	43
MET	Exon 14 Other	56% 44%	36
HER2	N/A		29
ALK	N/A		23
RET	KIF5B Other	73% 27%	16
ROS1	N/A		7

IMMUNOTARGET COHORT

Driver	n	Age (median)	Sex (M/F)	Tobacco (N/S)	PDL1 (-/+)	Line of ICI (median)
KRAS	271	59	141/130	12/248	32/63	2
EGFR	125	60	48/77	78/45	18/31	4
BRAF	43	61	24/19	11/31	3/7	2
MET	36	63	21/15	8/26	5/15	2
HER2	29	62	15/14	14/13	7/8	2
ALK	23	55	12/11	10/11	4/7	4
RET	16	55	7/9	10/5	2/6	2
ROS1	7	45	5/2	5/2	0/5	2
TOTAL	551	60	274/277	148/382	71/143	3

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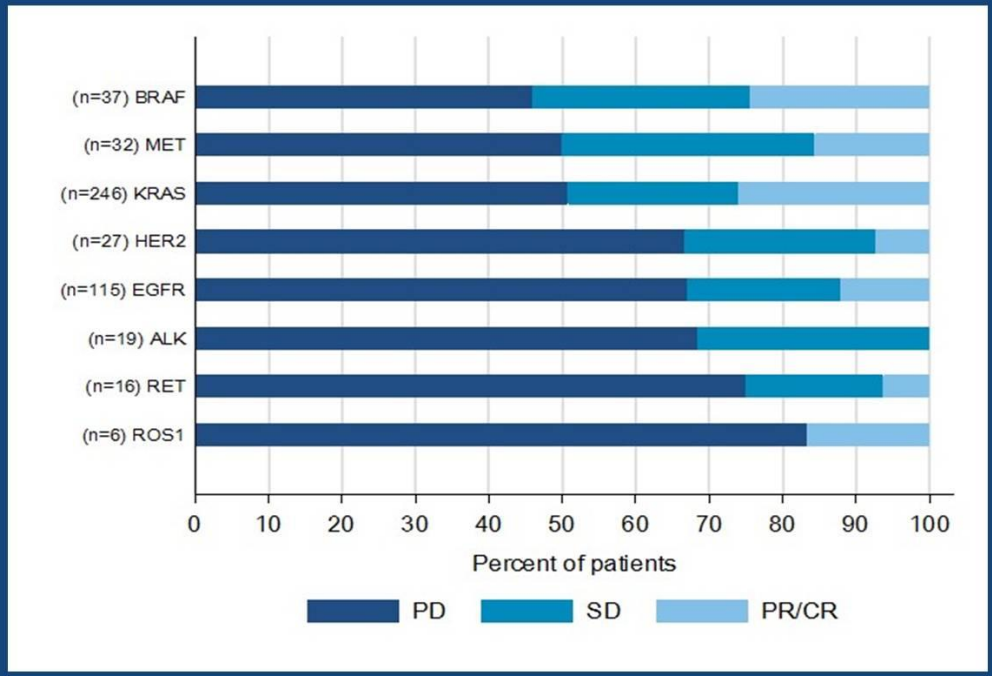
IMMUNOTARGET COHORT: Response

Driver	PD	SD	CR/PR
BRAF	46%	30%	24%
MET	50%	34%	16%
KRAS	51%	23%	26%
HER2	67%	26%	7%
EGFR	67%	21%	12%
ALK	68%	32%	0
RET	75%	19%	6%
ROS1	83%	0	17%
TOTAL	57%	24%	19%



IMMUNOTARGET COHORT: Overall Survival

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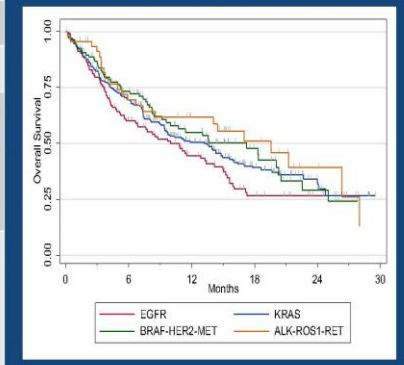
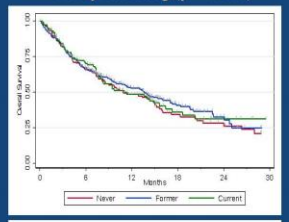
IMMUNOTARGET COHORT: Overall Survival

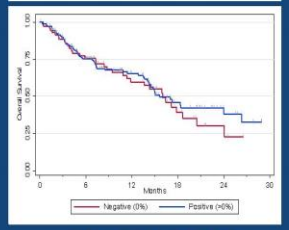
Driver	OS (months)	
KRAS	13.5	13.5
EGFR	10	10
BRAF	13.6	17,2
MET	18.4	
HER2	20.3	
ALK	17	19,5
RET	21.3	
ROS1	-	
TOTAL	13.3	

OS according to driver alteration (p = 0.25)



OS by smoking (p = 0.69)





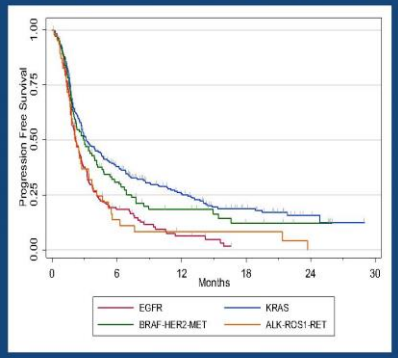
OS by PDL1 (p = 0.57)

Median follow-up 16.1 months

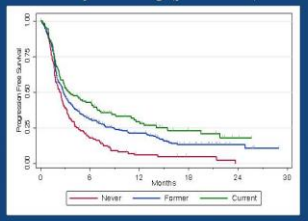
IMMUNOTARGET COHORT: PFS

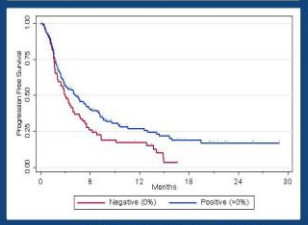
Driver	PFS (months)	
KRAS	3.2	3.2
EGFR	2.1	2.1
BRAF	3.1	2.9
MET	3.4	
HER2	2.5	
ALK	2.5	2.2
RET	2.1	
ROS1	-	
TOTAL	2.8	

PFS according to driver alteration (p < 0.001)



PFS by smoking (p < 0.001)





PFS by PDL1 (p = 0.02)

Median follow-up 16.1 months

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Conclusion

Driver	n	RR	PFS	OS	Impact (+/X) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	16.1					Outcome consistent with registration trial for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	X	Could be considered in PDL1 + after TKIs exhaustion
BRAF	43	24%	3.1	13.6	X	+	X	NA	Could be considered in smokers
MET	36	16%	3.4	18.4	NA	X	NA	X	Could be considered after conventionnal treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17	X	X	X	NA	Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3					
ROS1	7	17%	-	-					

CONCLUSION

- ✓ Large dataset of ICI in NSCLC with known driver mutation
- ✓ Outcome of patients treated with ICI monotherapy is consistent with ICI registration trials but inferior to the one observed with targeted therapies. ICI should thus be considered only after exhaustion of targeted therapy.
- ✓ Selection of patient can be guided in some cases by smoking or PDL1 expression but new biomarkers are needed in this setting
- ✓ Due to the high heterogeneity of efficacy in each subgroup, aimed trials should be conducted
- ✓ Combination of chemotherapy + immunotherapy +/- antiangiogenic agents (as demonstrated in recent trials [2,3]) should be more efficient than single-agent checkpoint blockade and should be further investigated.
- ✓ Our cohort is still open for enrollment to collect information.

Response and Durability of Checkpoint Blockade in Never- or Light-Smokers with NSCLC and High PD-L1 Expression

Justin F. Gainor[1], Hira Rizvi[2], Elizabeth Jimenez Aguilar[3], Ferdinandos Skoulidis[4], Beow Y. Yeap[1], Sara Khosrowjerdi[1], Meghan Mooradian[1], Christine Lydon[3], Danyon Anderson[1], Brett W. Carter[4], Megan Tenet[2], Jennifer L. Sauter[2], Subba Digumarthy[1], John V. Heymach[4], Mari Mino-Kenudson[1], Alice T. Shaw[1], Mark M. Awad[3], Matthew D. Hellmann[2]

[1]Massachusetts General Hospital, [2]Memorial Sloan Kettering Cancer Center, [3]Dana-Farber Cancer Institute, [4]MD Anderson Cancer Center

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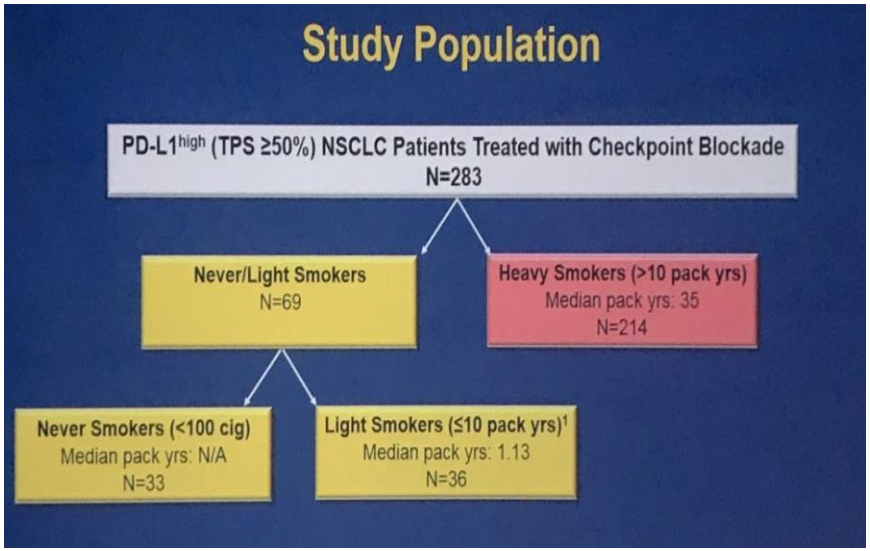
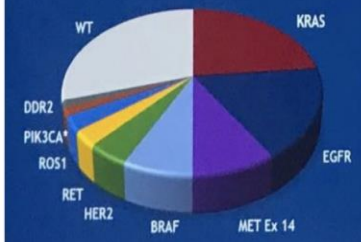
Study Population

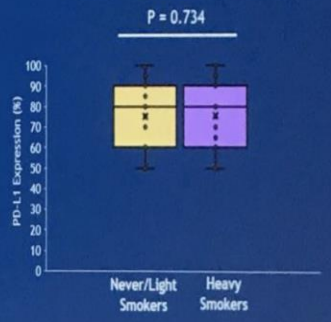


Molecular Characteristics of Never/Light Smokers

Distribution of Oncogenic Driver Mutations in Never/Light Smoking Cohort (N=68)^

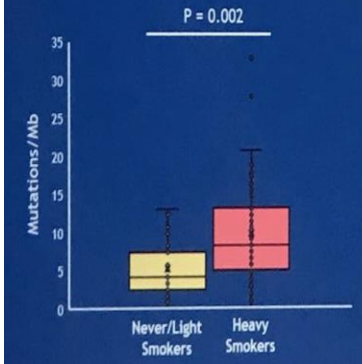


PD-L1 Expression in Never/Light Smoking versus Heavy Smoking Cohort



*Genotyping unavailable in 1 patient.
†Two additional patients had PIK3CA mutations co-occurring with a KRAS (N=1) and BRAF V600E mutation (N=1)
15/32 (16%) never smokers had KRAS mutations.

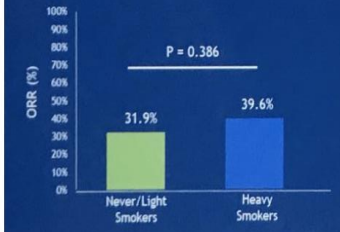
Tumor Mutation Burden Based Upon Smoking Status



Tumor Mutation Burden (Mut/Mb)	Never/Light Smokers* N=23	Heavy Smokers N=55	P value
Median	4.1	8.2	0.002
Range	0-12.3	0-33	

*Median TMB was similar (4.1) between never and light smokers.

Response to Checkpoint Blockade By Smoking Status Among PD-L1^{high} NSCLC Patients

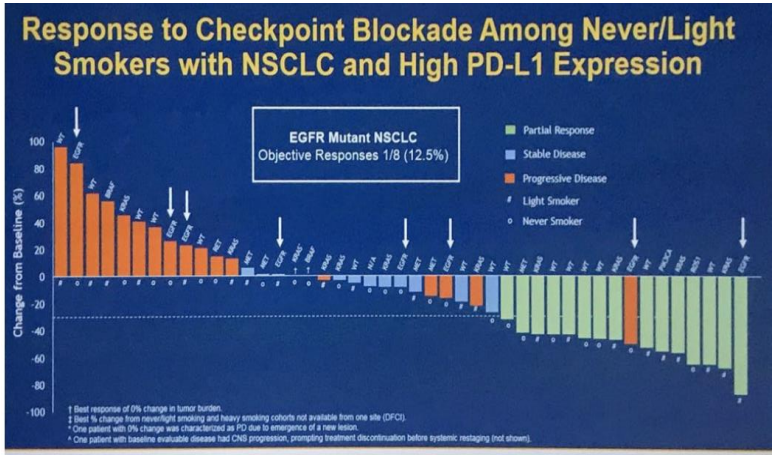


Best Response by RECIST v1.1
Among Patients with Evaluable Disease

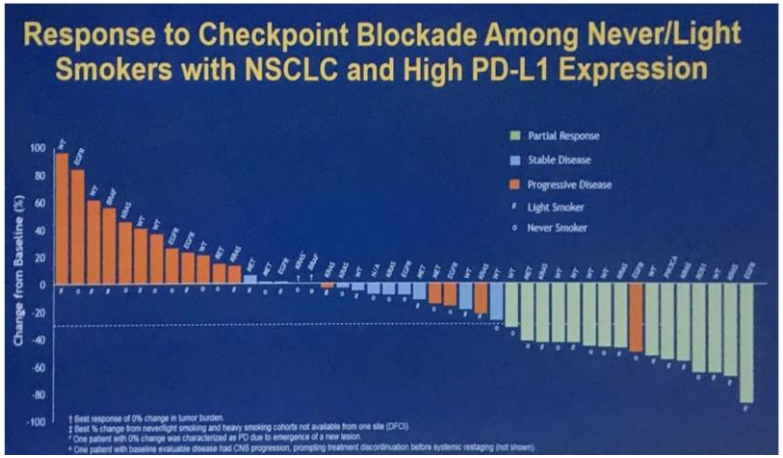
Best response, n (%)	Never/Light Smokers N=47	Heavy Smokers N=134
Complete response	0 (0)	4 (2.9)
Partial response	15 (31.9)	49 (36.6)*
Stable disease	13 (27.7)	47 (35.1)
Progressive disease	19 (40.4)	34 (25.4)

*Includes 3 unconfirmed partial responses
#ORR among 24 never smokers with measurable disease was 25%

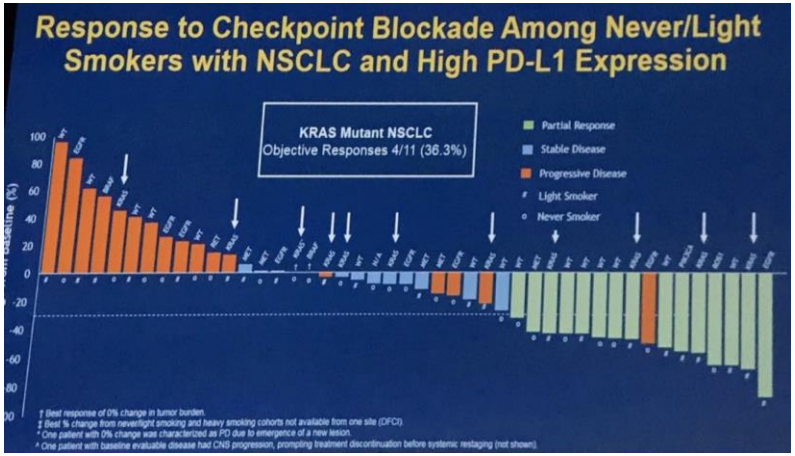
Response to Checkpoint Blockade Among Never/Light Smokers with NSCLC and High PD-L1 Expression



Response to Checkpoint Blockade Among Never/Light Smokers with NSCLC and High PD-L1 Expression



Response to Checkpoint Blockade Among Never/Light Smokers with NSCLC and High PD-L1 Expression



- PD-L1 inhibition was associated with an ORR of **32%** among never/light smokers with high PD-L1 expression, although **shorter DOR** compare to patients with more significant tobacco exposure (TMB could be the reason for this difference?

- Light smokers are a heterogeneous group of patients that may respond to IO, and PD-L1 helps as a predictive biomarker

- Further work is needed in order to define who is getting the strongest benefit…