Iniciativa científica de:

GECP lung cancer research

LUNG CANCER UPDATES

ASCO HIGHLIGHTS

31 MAYO - 4 JUNIO 2019

Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

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Biomarcadores

Dra. Ana Laura Ortega

Día 2

Con la colaboración de:

Bristol-Myers Squibb
illumina
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Biomarcadores en inmunoterapia: neoadyuvancia

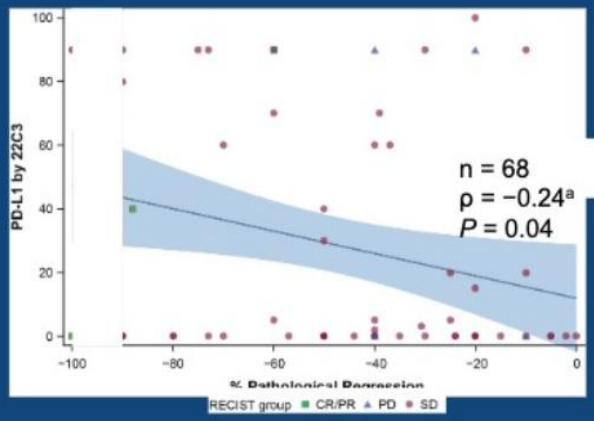
Biomarkers for Personalization of Neoadjuvant Immunotherapy

- Neoadjuvant trials are ideal settings for exploring potential biomarkers
- Currently lack biomarkers to personalize neoadjuvant immunotherapy
  - PDL1 IHC is only semi-quantitative
  - TMB variably correlates with response
  - ctDNA? Under investigation
- Ideal biomarkers would identify if patients:
  1. Have micrometastatic disease
  2. Will respond to neoadjuvant treatment

Biomarcadores en inmunoterapia: neoadyuvancia

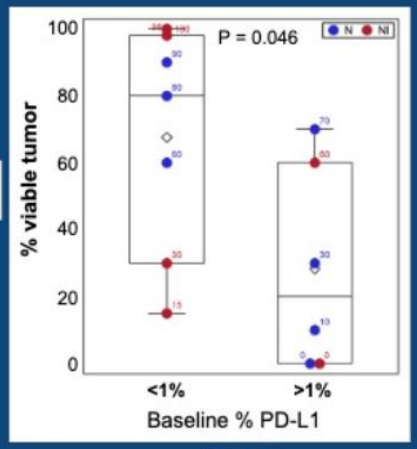
PD-L1 Expression

LCMC3



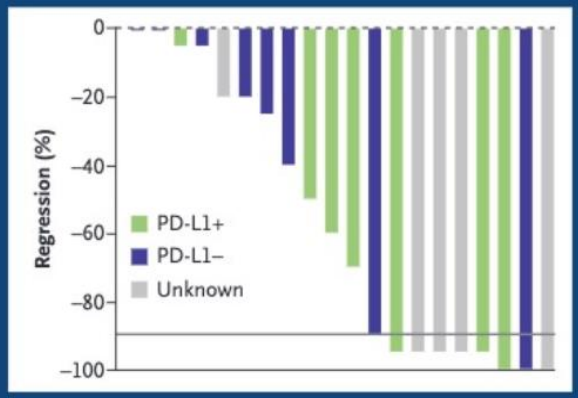
PD-L1+
MPR: 8/11 (73%)
No MPR: 26/57 (46%)

NEOSTAR



PD-L1+
MPR: 3/3 (100%)
No MPR: 3/10 (30%)

Forde et al.



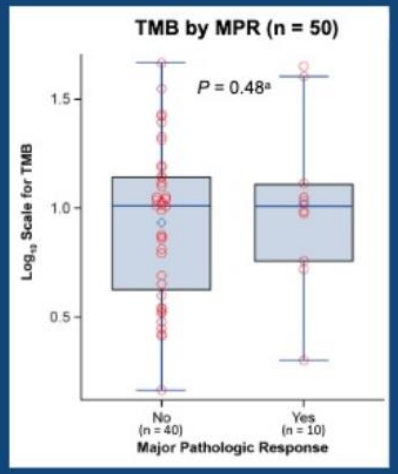
PD-L1+
MPR: 3/5 (60%)
No MPR: 4/10 (40%)

PD-L1 is associated with pathologic regression but responses in positive and negative tumors

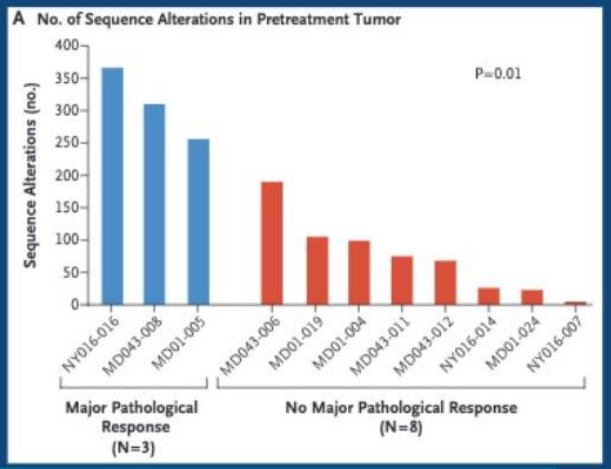
Biomarcadores en inmunoterapia: neoadyuvancia

Tumor Mutation Burden (TMB)

LCMC3



Forde et al.

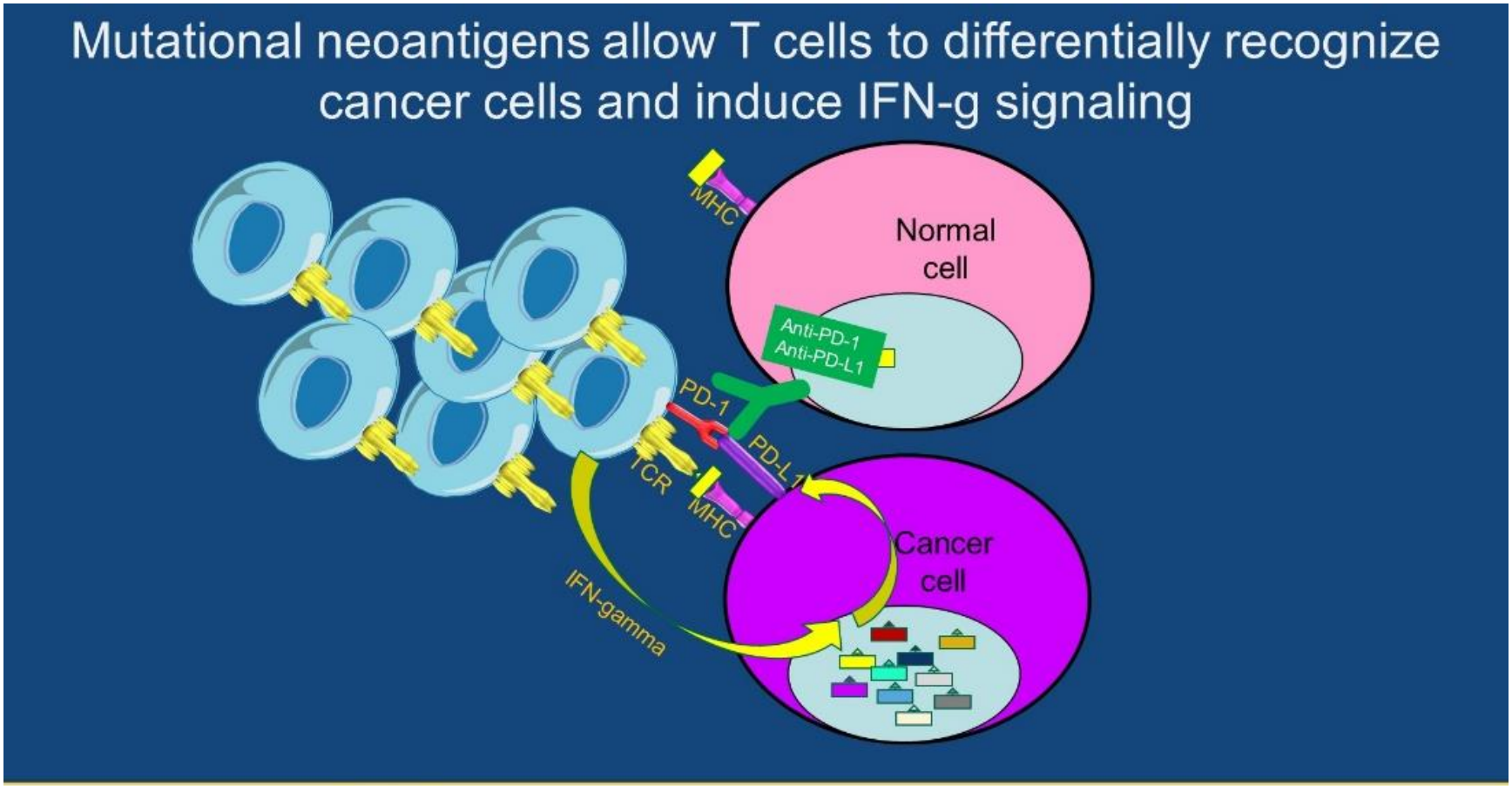


Association of TMB with MPR remains unclear

Association of *STK11/LKB1* genomic alterations with lack of benefit from the addition of pembrolizumab to platinum doublet chemotherapy in non-squamous non-small cell lung cancer

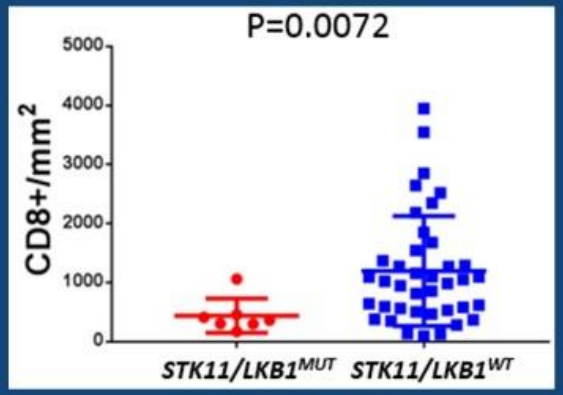
Ferdinandos Skoulidis, Kathryn C. Arbour, Matthew D. Hellmann, Pradnya D. Patil, Melina E. Marmarelis, Mark M. Awad, Joseph C. Murray, Jessica Hellyer, Justin F. Gainor, Anastasios Dimou, Christine M. Bestvina, Catherine A. Shu, Jonathan W. Riess, Collin M. Blakely, Chad V. Pecot, Laura Mezquita, Fabrizio Tabbó, Matthias Scheffler, Vassiliki Papadimitrakopoulou, John V. Heymach

Biomarcadores en inmunoterapia: STK11/LKB1



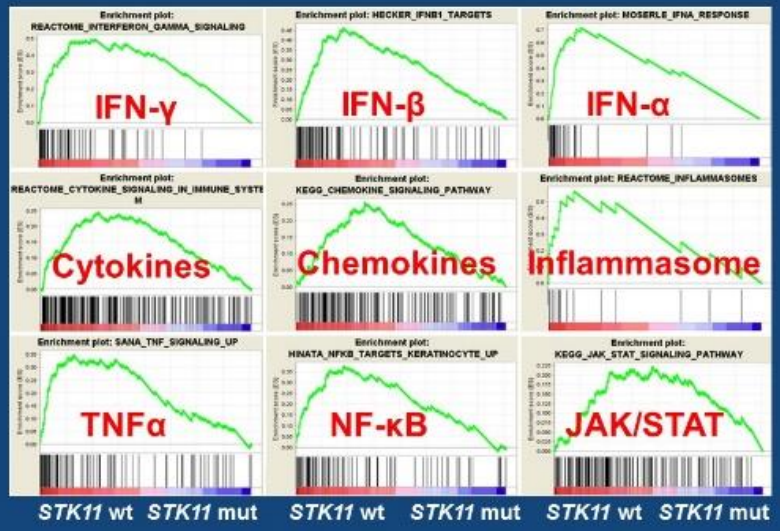
Biomarcadores en inmunoterapia: STK11/LKB1

Low densities of infiltrating CD8+ T cells and IFN signaling in *STK11/LKB1* mutant or deficient lung cancers



PROSPECT cohort

Skoulidis F et al, *Cancer Discovery*, 2018



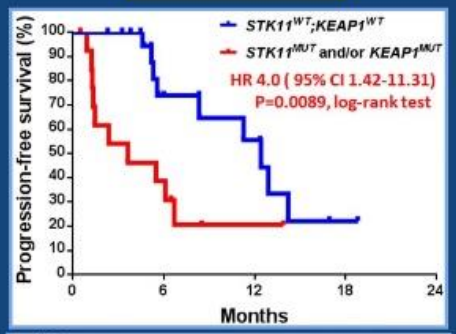
LUACs in the TCGA cohort

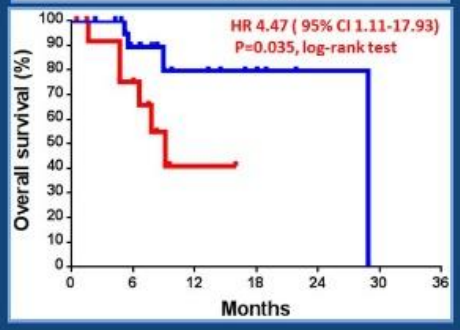
Skoulidis F et al, *AACR*, 2018

Biomarcadores en inmunoterapia: STK11/LKB1

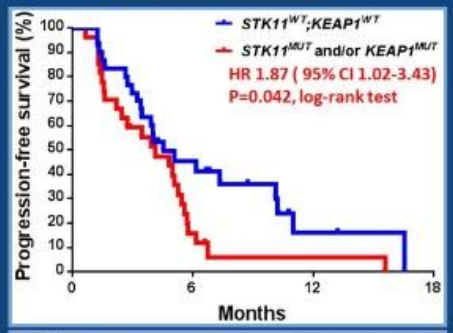
STK11 and/or *KEAP1* genomic alterations are associated with inferior clinical outcomes with PCP in TMB-High non-squamous NSCLC

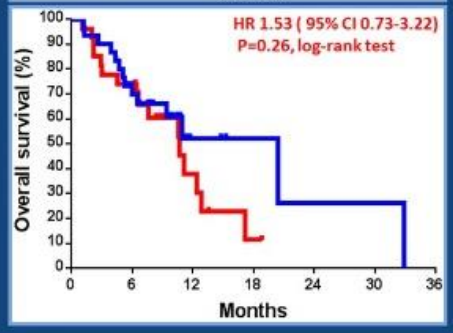
TMB HIGH





TMB LOW



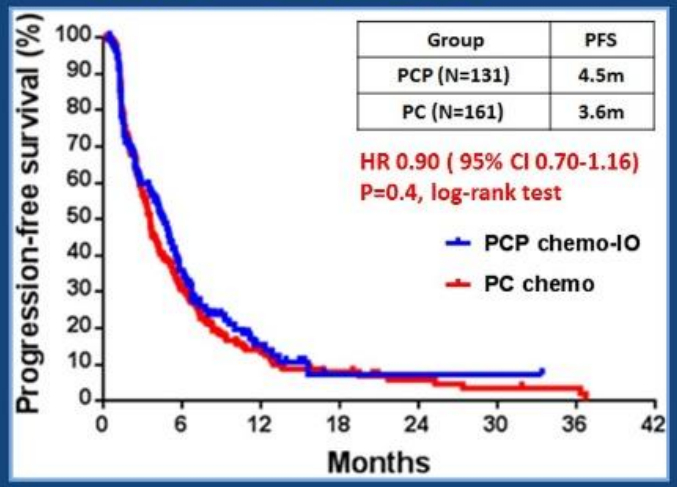


TMB definitions:
- High≥ 8.58 Mut/Mb
- Low <8.58 Mut/Mb (WES equivalent of FMI 10Mut/Mb)

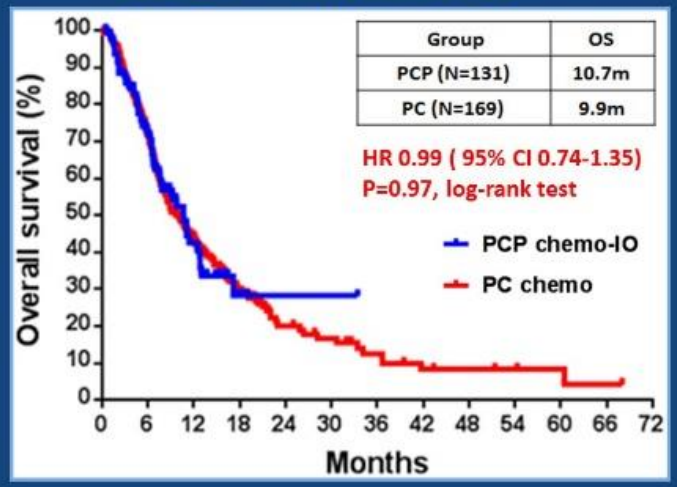
Biomarcadores en inmunoterapia: STK11/LKB1

Lack of benefit from addition of pembrolizumab to CP chemotherapy in *STK11* and/or *KEAP1*-mutant non-squamous NSCLC

STK11^{MUT} and/or *KEAP1*^{MUT}



STK11^{MUT} and/or *KEAP1*^{MUT}



Conclusions

- *STK11* and/or *KEAP1* alterations define a prevalent (~25%) subgroup of patients with NSCLC with an unmet need for novel strategies to establish effective antitumor immunity (final conclusion from the presentation by Dr. Skoulidis)

- The definition of recurrent genetic events in cancer resulting in lower activity of PD-1 blockade therapies, and the understanding of their mechanism, may allow better personalization of therapy and defining certain contexts for rationally designed combination therapies

Biomarcadores en inmunoterapia: CPNCP avanzado

LUNG CANCER UPDATES
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31 MAYO - 4 JUNIO 2019

Memorial Sloan Kettering Cancer Center

Molecular correlates of PD-L1 expression in patients with non-small cell lung cancer

Hira Rizvi, Chaitanya Bandlamudi, Adam J. Schoenfeld, Jennifer L. Sauter, Kathryn C. Arbour, Amanda Beras, Jacklynn V. Egger, Marc Ladanyi, Mark T.A. Donoghue, Charles M. Rudin, Barry S. Taylor, Matthew D. Hellmann

Memorial Sloan Kettering Cancer Center, New York, NY

Abstract # 9018

Background

- PD-L1 expression is the only FDA-approved predictive biomarker for patients with NSCLC treated with immune checkpoint inhibitors.
- The impact of tumor molecular phenotype on tumor PD-L1 expression is not known.
- Somatic mutations and copy number alterations may associate with distinct patterns of PD-L1 expression in patients with NSCLC.

Methods

- Patients with lung adenocarcinomas in whom PD-L1 testing and targeted next-generation sequencing (MSK-IMPACT) were performed on the same tissue sample.
- PD-L1 expression was determined by IHC using the E1L3N antibody clone and categorized as PD-L1 high (≥50%), intermediate (1-49%), or negative (<1%).
- Tumor mutation burden (TMB, high ≥20mut/Mb; intermediate ≥8mut/Mb and <20mut/Mb; low <8mut/Mb), individuals genes and pathways, whole genome duplication (WGD), and aneuploidy (fraction of genome altered (FGA)) were evaluated using MSK-IMPACT.
- Tumor purity was estimated by thoracic pathologists.
- To limit false discovery, associations with individual genes were considered significant for p values <0.05 and q values <0.15.
- A cohort of NSCLC patients (n = 638) were used to assess outcomes to anti-PD-(L)1 blockade therapy.

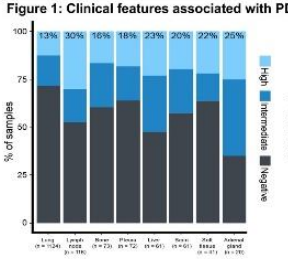
Patient characteristics

PD-L1 expression	High (n = 245)		Intermediate (n = 284)		Negative (n = 1056)	
N = 1586	No.	%	No.	%	No.	%
Age (median, range)	67	(30-93)	67	(25-92)	68	(27-89)
Gender						
Female	154	63	170	60	678	64
Male	91	37	114	40	379	36
Smoking status						
Ever	185	76	196	69	730	69
Never	60	24	88	31	327	31
Procedure						
Biopsy	164	67	167	59	534	51
Resection	81	33	118	41	523	49
Sample type*						
Primary	136	56	181	64	789	75
Metastatic	109	44	103	36	268	25

*p < 0.001

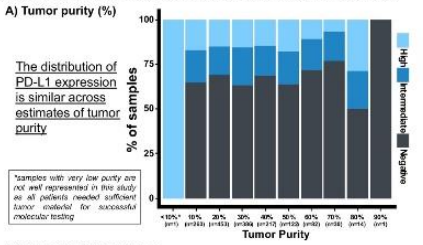
Results

Figure 1: Clinical features associated with PD-L1 sub-groups



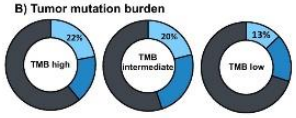
The distribution of PD-L1 expression varies modestly by the site of tissue

Figure 2: Molecular features associated with PD-L1 sub-groups

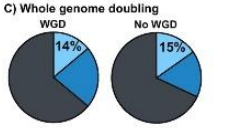


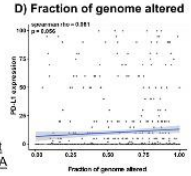
The distribution of PD-L1 expression is similar across estimates of tumor purity

*samples with very low purity are not well represented in this study as all patients needed sufficient tumor material for successful molecular testing



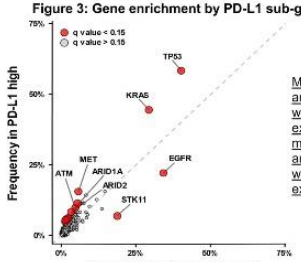
PD-L1 expression is modestly increased in patients with high tumor mutational burden





PD-L1 expression does not associate with WGD or FGA

Figure 3: Gene enrichment by PD-L1 sub-groups



Mutations in *KRAS* and *TP53* associate with high PD-L1 expression, while mutations in *EGFR* and *STK11* associate with negative PD-L1 expression

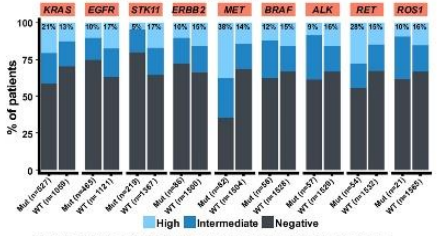
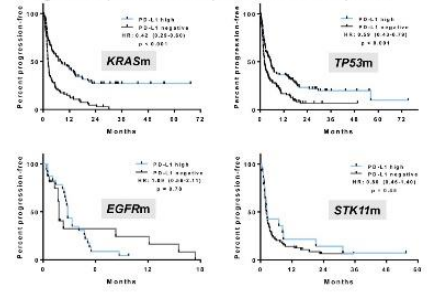
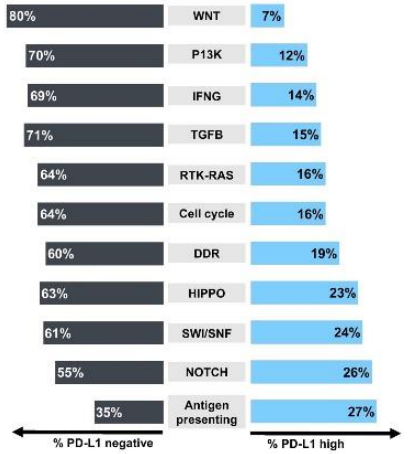


Figure 4: Impact of PD-L1 expression on PD-1 responses



Results

Figure 5: Pathway enrichment by PD-L1 sub-groups



Alterations in the NOTCH and Antigen presenting pathways positively associate with PD-L1 high expression. Alterations in the WNT signaling pathway negatively associate with PD-L1 high expression

Conclusions

- PD-L1 negative expression is more common in tissue from primary compared to metastatic sites of disease. PD-L1 high expression modestly varies across sites of tissue.
- Although TMB and PD-L1 are independent as continuous variables, there is a slight enrichment in PD-L1 positivity in patients with high TMB.
- Individual genes and pathways are associated with differential expression of PD-L1.
  - Mutations in KRAS associate with PD-L1 high expression.
  - Mutations in EGFR and STK11 associate with negative PD-L1 expression.
- Building on these associations, mechanistic studies are needed to determine causal relationships between the molecular phenotype and immunologic phenotype of tumors.

Biomarcadores en inmunoterapia: CPNCP avanzado

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Spatial and Temporal Heterogeneity of PD-L1 and its Impact on Benefit from Immune Checkpoint Blockade in Non-Small Cell Lung Cancer (NSCLC)

Lingzhi Hong[1], Marcelo V. Negrao[2], Seyedeh Dibaji[2], Alexandre Reuben[1], Emily B. Roarty[1], Ferdinandos Skoulidis[1], Kyle G. Mitchell[3], Carl M. Gay[1], Tina Cascone[1], Hai T Tran[1], Lauren Byers[1], Boris Sepesi[3], Waree Rinsurongkawong[1], Jeff Lewis[2], Don L. Gibbons[1], Vassiliki Papadimitrakopoulou[1], Bonnie S. Glisson[1], George R. Blumenschein Jr[1], P. Andrew Futreal[4], Ignacio I. Wistuba[5], Jack A. Roth[3], Stephen G. Swisher[3], George Simon[1], J. Jack Lee[2], John V. Heymach[1], Jianjun Zhang[1]

[1]Department of Thoracic / Head and Neck Medical Oncology, [2]Department of Biostatistics, [3]Department of Thoracic and Cardiovascular Surgery, [4]Department of Genomic Medicine, [5]Department of Translational Molecular Pathology, University of Texas MD Anderson Cancer center, Houston, TX

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Background

- Therapies with immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1) receptor, and its ligand (PD-L1) have revolutionized the treatment of non-small cell lung cancer (NSCLC).
- At present, PD-L1 tumor proportion score (TPS) was approved predictive biomarker treatment selection with for ICIs in NSCLC. However, 55% of PD-L1 positive advanced NSCLC patients will not benefit from ICIs.
- Spatial and temporal heterogeneity of PD-L1 expression have been identified in various studies.

Objectives

To determine whether PD-L1 expression varies in tumor specimens from different anatomic sites and/or at different times of disease course and whether these differences impact the predictive value of PD-L1 to ICIs.

Methods

- A total of 1398 NSCLC patients from MD Anderson Lung Cancer GEMINI database who had PD-L1 test were queried.
- PD-L1 IHC 22C3 pharmDx assay was most commonly used (87%).
- In this cohort, 398 metastatic NSCLC patients treated with single-agent ICIs or combination therapy were eligible for the outcome analysis.

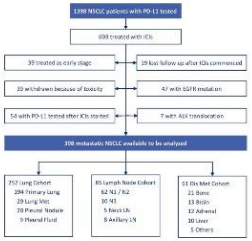

Fig 1. Flow chart of the patients enrolled in this study.

Results

PD-L1 was associated with clinicopathological characteristics in NSCLC

Tab 1. Summary of demographic and clinical characteristics associated with PD-L1 expression in NSCLC

		PD-L1 expression N (%)					
		1% cutoff			50% cutoff		
	N (%)	0	1-100%	P	0-49%	50%-100%	P
All	1398	381(34.6)	917(65.4)		1186(79.1)	212(20.9)	
Median age, years (range)	66.2 [24.8 94.7]	66.7[27.8-94.7]	65.7[24.8-88.1]	0.055	66.4[27.8-94.7]	65.7[24.8-88.1]	0.911
Gender	1398			0.008			0.785
Male	610(49.0)	209(40.1)	376(54.9)		546(79.4)	141(20.6)	
Female	713(51.0)	272(38.1)	441(61.9)		522(76.8)	153(21.2)	
Age	1398			0.315			0.701
<=65	643(46.0)	258(40.1)	385(59.9)		513(79.5)	132(20.5)	
>65	755(54.0)	323(42.8)	432(57.2)		595(78.8)	160(21.2)	
Tobacco	1398			0.580			0.806
Never	354(25.4)	140(39.5)	214(60.5)		252(82.5)	62(17.5)	
Current/former	1040(74.6)	439(42.2)	601(57.8)		810(77.9)	230(22.1)	
Specimen	1398			0.722			0.025
Surgical case	341(17.2)	130(43.2)	137(56.8)		204(84.6)	37(15.4)	
Biopsy	929(66.5)	380(41.9)	549(58.1)		735(78.7)	198(21.3)	
Pleural fluid	37(2.6)	13(35.1)	24(64.9)		28(75.7)	9(24.3)	
FNA	191(13.7)	75(39.3)	116(60.7)		149(74.9)	48(25.1)	
Tissue*	1328			<0.001			<0.001
Fresh	1007(76.0)	361(37.8)	626(62.2)		779(76.5)	237(23.5)	
Archival	318(24.0)	169(53.1)	149(46.9)		275(86.5)	43(13.5)	
Treatment**	1398			0.555			0.964
Yes	517(36.6)	221(43.2)	293(56.8)		405(79.1)	107(20.9)	
No	896(63.6)	360(40.6)	529(59.4)		703(79.1)	185(20.9)	
Localization	1398			0.011			0.009
Lung***	917(67.9)	339(42.2)	542(57.8)		734(79.2)	194(20.7)	
LN	259(18.5)	92(36.1)	163(63.9)		198(77.6)	57(22.4)	
Liver	43(3.0)	14(34.1)	27(65.9)		26(63.4)	15(36.6)	
Adrenal	33(2.2)	9(29.0)	22(71.0)		23(71.0)	9(29.0)	
Brain	47(3.4)	24(51.1)	23(48.9)		42(89.4)	5(10.6)	
Bone	68(4.9)	39(57.4)	29(42.6)		61(89.7)	7(10.3)	
Other	191(1.3)	84(2.1)	115(9.9)		148(73.7)	52(26.3)	
Pathology****	1398			0.007			0.485
Adeno	1085(77.9)	481(44.3)	604(55.7)		871(80.5)	214(19.7)	
SCC	252(18.1)	88(34.9)	164(65.1)		197(78.2)	55(21.8)	
NSCC/NOS	29(1.9)	10(1.1)	19(68.9)		21(77.8)	6(22.2)	
Adeno/SCC	12(0.9)	2(16.7)	10(83.3)		5(41.7)	7(58.3)	
Sarcomatoid	19(1.1)	3(18.8)	13(81.3)		7(43.8)	9(56.3)	

- *Tissues were classified into fresh (tested in <=30 days) or archival (>90 days)
- **any treatment before biopsy
- ***including 64 pleural nodules and 37 pleural fluid
- ****P-value reflects comparison between adeno and SCC pathologies

Results

PD-L1 was associated with molecular characteristics in lung adenocarcinoma

Tab 2. The relationship of PD-L1 expression and molecular characteristics in lung adenocarcinoma patients

		PD-L1 expression N (%)					
		1% cutoff			50% cutoff		
	N (%)	0	1-100%	P	0-49%	50%-100%	P
EGFR	994			0.346			0.013
Negative	736(74.0)	315(42.8)	421(57.2)		578(78.5)	158(21.5)	
Positive	258(26.0)	134(45.9)	142(55.1)		221(85.7)	37(14.3)	
ALK	879			0.051			0.021
Negative	834(94.9)	359(43.0)	475(56.2)		674(80.8)	160(19.2)	
Positive	45(5.1)	13(24.4)	34(75.6)		30(66.7)	15(33.3)	
BRAF	785			0.199			0.456
Negative	779(98.6)	312(42.9)	443(57.1)		624(88.6)	110(15.4)	
Rearrangement	13(1.4)	2(18.2)	9(81.8)		8(72.7)	3(27.3)	
MET	582			0.094			0.002
Negative	472(81.1)	220(46.6)	252(53.4)		404(85.6)	68(14.4)	
Amplification	110(18.9)	35(31.5)	71(64.5)		83(75.5)	20(26.4)	
RET	655			0.690			0.036
Negative	610(97.6)	263(42.6)	357(57.5)		517(82.6)	108(17.4)	
Positive	15(2.4)	5(33.3)	10(66.7)		9(60.0)	6(40.0)	
ERBB2	833			0.076			0.012
Negative	697(98.5)	261(44.7)	446(65.3)		652(92.0)	145(18.0)	
Mutation	12(1.5)	2(16.7)	10(83.3)		6(50.0)	6(50.0)	
ROS1	841			0.272			0.248
Negative	555(66.0)	258(42.9)	317(57.1)		455(82.0)	100(18.0)	
Positive	286(34.0)	134(46.9)	152(53.1)		220(78.7)	61(21.3)	
TERT	765			<0.001			<0.001
Negative	681(89.0)	279(41.0)	402(59.0)		548(98.5)	115(19.5)	
Positive	84(11.0)	66(76.2)	18(23.8)		81(96.4)	3(3.6)	

PD-L1 varies at different anatomic sites.

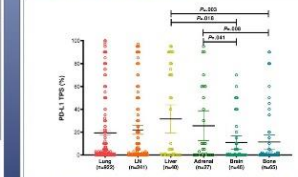

Fig 2. PD-L1 tumor proportion score (TPS) stratified by biopsy sites. LN: Lymph Node

Results

Temporal heterogeneity impacts the predictive value of PD-L1 on ICI treatment

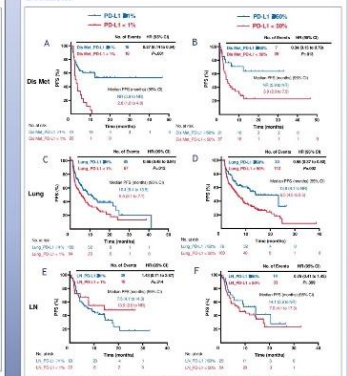

Fig 3. KM curves of PFS in metastatic NSCLC by different biopsy sites associated with PD-L1 expression TPS at 1% cutoff (A,C,E) and 50% cutoff (B,D,F). (A,B): Distant Metastasis. (C,D): Lung. (E,F): Lymph Node.

PD-L1 changes over time with or without treatment

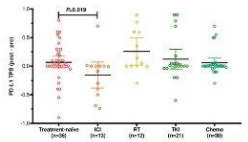

Fig 4. Changes of PD-L1 TPS in NSCLC patients treated with anticancer treatment. PD-L1 TPS (post-pre)= TPS of second biopsy - TPS of first biopsy.

Results

Temporal heterogeneity impacts the predictive value of PD-L1 on ICI treatment

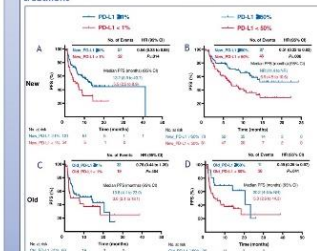

Fig 5. KM curves of PFS in metastatic NSCLC by different time points associated with PD-L1 expression TPS at 1% cutoff (A,C) and 50% cutoff (B,D). (A,B): New biopsy: was defined as that the biopsy was obtained within 90 days before initiating ICI treatment and patients did not receive other therapy between biopsy and ICI treatment.(C,D): Old biopsy: was defined as that the biopsy was obtained more than 90 days before initiating ICI treatment regardless of whether patients received other therapies between biopsy and ICI treatment.

Conclusions

- Liver and adrenal specimens had the highest PD-L1 expression, while specimens from brain and bone demonstrated the lowest expression.
- Prior treatment with ICIs is associated with lower PD-L1 expression.
- PD-L1 in LN biopsies may not be reliable to predict clinical benefit for ICIs in NSCLC.
- When PD-L1 is used to choose NSCLC patients for ICI treatment, new biopsy and PD-L1 staining should be strongly considered.

Acknowledgements

- The authors thank MD Anderson Lung Cancer GEMINI team and Advanced Non-Small Cell Lung Holistic Registry (ANCHoR) team.
- This study was supported by MD Anderson Moon Shot Program, MD Anderson Physician Scientist Program, MD Anderson Visiting Scholar Program and ANCHoR.

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Biomarcadores en inmunoterapia: CPNCP avanzado

LUNG CANCER UPDATES
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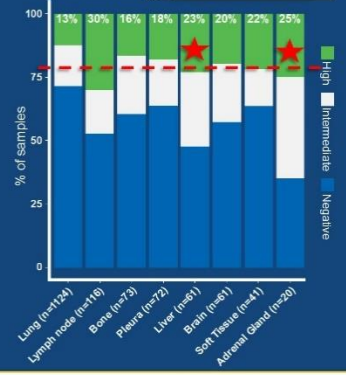
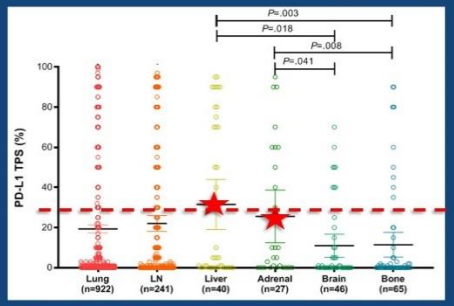
31 MAYO - 4 JUNIO 2019

PD-L1 by anatomic site varies modestly

Memorial Sloan Kettering Cancer Center



THE UNIVERSITY OF TEXAS MD Anderson Cancer Center



Is there different distribution of PD-L1 by site of diagnosis?

Memorial Sloan Kettering Cancer Center

PD-L1 expression	tot	High (n = 245)		Intermediate (n = 284)		Negative (n = 1056)	
N = 1586		No.	%	No.	%	No.	%
Sample							
Primary	1106	136	12	181	16	789	71
Mets	480	109	23	103	21	268	56

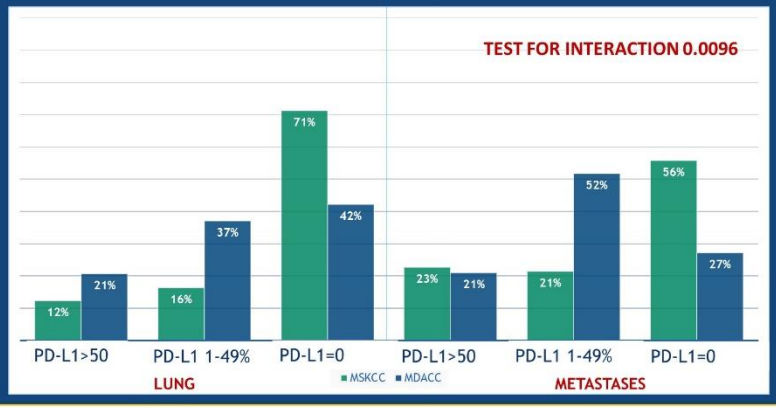
*p <0.0001

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

PD-L1 expression	tot	High (n = 287)		Intermediate (n = 577)		Negative (n = 515)	
N = 1586		No.	%	No.	%	No.	%
Sample							
Primary	937	194	21	348	37	395	42
Mets	442	93	21	229	52	120	27

*p <0.0004

Different PD-L1 distribution in MSKCC and MDACC



Memorial Sloan Kettering Cancer Center

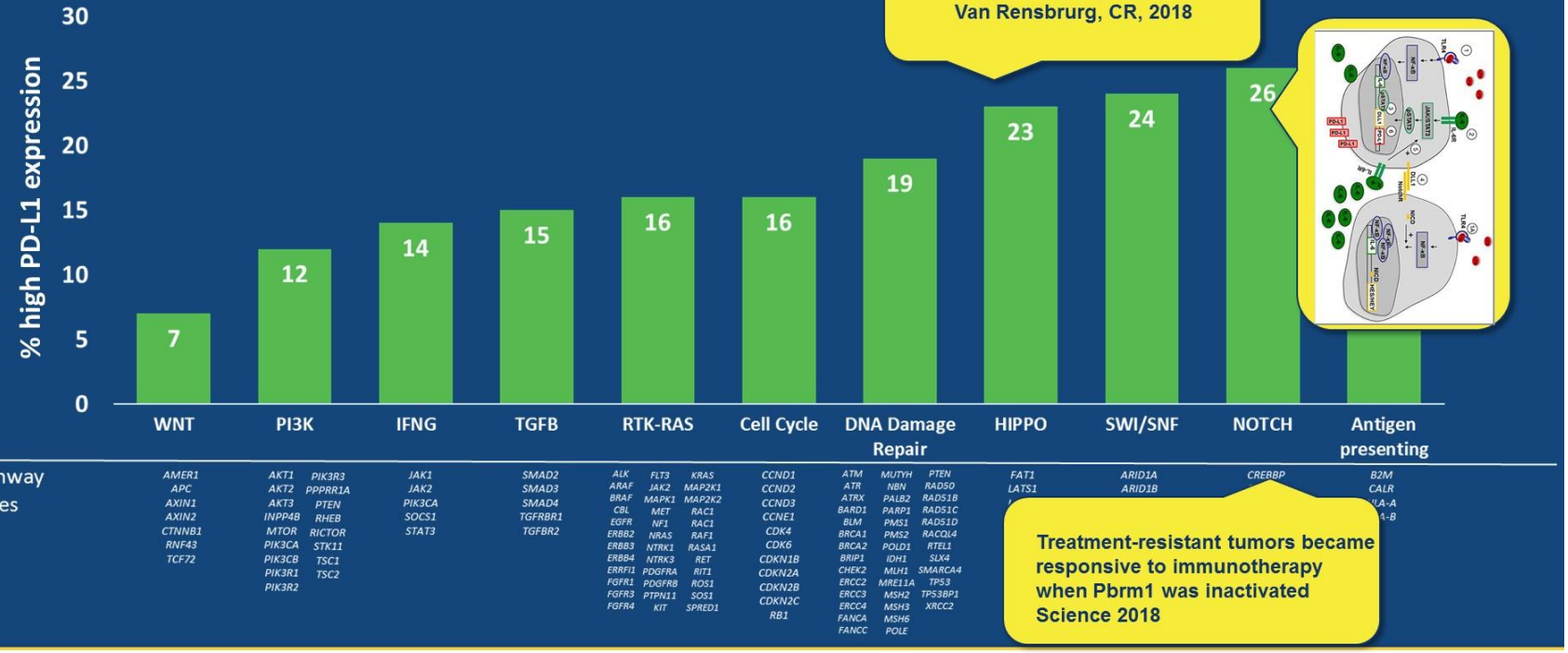
PD-L1<1% 66.6%

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

PD-L1<1% 41.2%

Biomarcadores en inmunoterapia: CPNCP avanzado

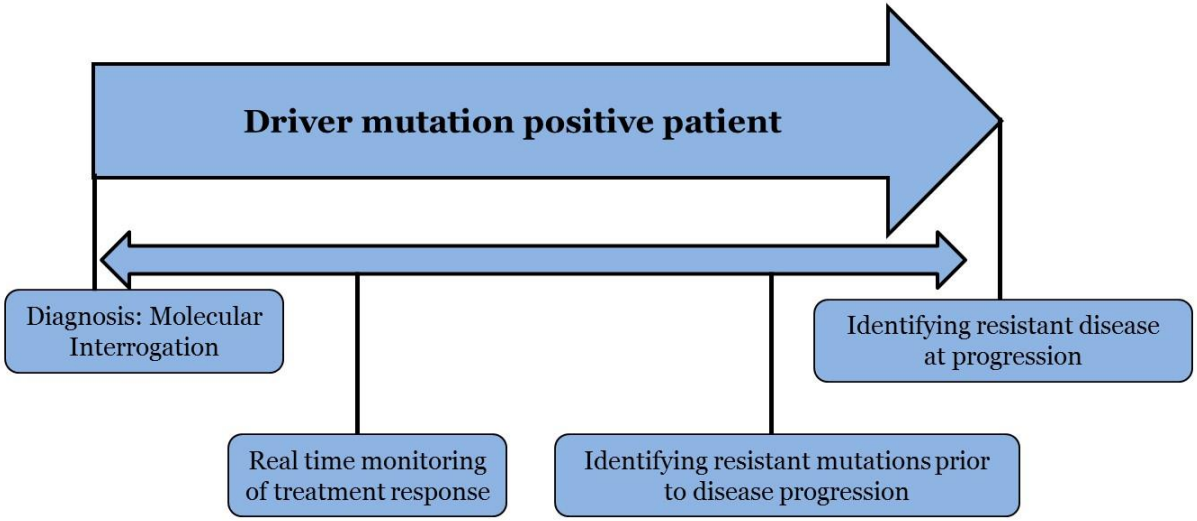
Some Pathways have role in immunoevasion



Conclusion = Immuno-Confusion

1. PD-L1 testing is the cornerstone of treatment selection
   - a lot of work still to be done
2. Molecular understanding could open-up new combination strategies and biomarkers
3. Combining bTMB plus PD-L1 could:
   - Avoid IO when useless
   - Open a new reasearch area for anti CTLA4 plus anti PD-L1 (PD-L1 neg TMB high)
   - The most discriminant cut-off when combined with PD-L1 still to be defined
4. We need TMB +/-PD-L1 data for combination of chemo+IO to design further treatment and research strategies

Plasma Interrogation: Many clinical applications



Biomarcadores en genes oncogénicos

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Early clearance of plasma EGFR mutations as a predictor of response to osimertinib and comparator EGFR-TKIs in the FLAURA trial

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Poster #9020

Introduction

- Osimertinib is a third-generation, irreversible, oral EGFR-tyrosine kinase inhibitor (TKI) that potently and selectively inhibits both EGFR-TKI sensitizing (EGFRm) and EGFR T790M resistance mutations, and has demonstrated efficacy in NSCLC central nervous system metastases.[1–5]
- In the FLAURA trial (NCT02296125), first-line treatment with osimertinib resulted in superior progression-free survival (PFS) versus comparator EGFR-TKIs in patients with previously untreated, EGFRm positive, advanced NSCLC.[3]
- Early clearance of circulating tumor DNA (ctDNA) was found to correlate with superior PFS with second-line osimertinib treatment in the AURA trials.[6,7]
- In this exploratory analysis, we investigated clinical outcomes associated with detection of plasma EGFRm at 3 or 6 weeks after start of treatment in FLAURA to determine if early ctDNA clearance predicted outcomes in patients with EGFRm positive advanced NSCLC treated with a first-line EGFR-TKI.

Methods

- In the Phase III, double-blind, randomized FLAURA trial, treatment-naïve patients with EGFRm positive (ex19del or L858R), locally advanced or metastatic NSCLC were randomized 1:1 to receive osimertinib 80 mg once daily (qd) or comparator EGFR-TKIs (gefitinib 250 mg qd or erlotinib 150 mg qd).[3]
- Tumor tissue EGFR mutation status (ex19del or L858R, alone or co-occurring with other EGFR mutations) was confirmed by central or local testing.
- Plasma ctDNA EGFR mutation analysis was conducted by droplet digital polymerase chain reaction (ddPCR; Biodesix) from samples collected at baseline, week 3, and week 6 post-osimertinib or -comparator EGFR-TKI treatment.
  - Evaluable patients had a baseline plasma sample that returned a definitive result of detectable or non-detectable plasma levels of ex19del or L858R using ddPCR.
  - The patients included in this exploratory analysis were required to have a baseline plasma sample with detectable plasma levels of ex19del or L858R using ddPCR.
- Clinical outcomes (median PFS [mPFS], objective response rate [ORR]) were investigator assessed (per RECIST 1.1) in patients with detectable EGFRm at baseline and were investigated based on clearance of plasma EGFRm at weeks 3 or 6 with hazard ratios (HRs) calculated using a Cox proportional hazards model.
  - EGFRm clearance was defined as non-detectable plasma levels of either ex19del or L858R at weeks 3 and/or 6, using ddPCR, where they were detected at baseline.
- Data cut-off for clinical outcomes: June 12, 2017.

Results

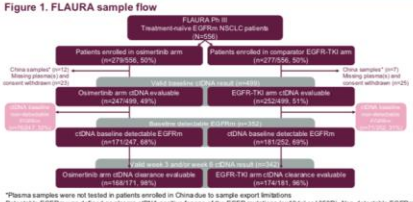
Evaluable ctDNA patient population

- In total, 556 patients were enrolled in FLAURA, of whom 489 (88%) had evaluable ctDNA at baseline, and weeks 3 and/or 6 (osimertinib arm, n=244; comparator EGFR-TKI arm, n=245) (**Figure 1**).

Patients with detectable plasma EGFRm at baseline

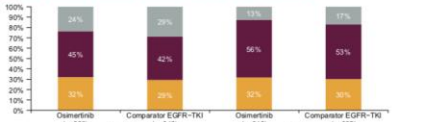
- In the evaluable ctDNA patient population, 342 (70%) patients had detectable plasma EGFRm at baseline and 147 (30%) patients did not have detectable plasma EGFRm at baseline (**Figure 1**).
- The proportion of patients with detectable plasma EGFRm at baseline was similar between treatment arms (osimertinib arm, n=168 [69%]; comparator EGFR-TKI arm, n=174 [71%]) (**Figure 1**).
- The proportion of patients who received treatment and had non-detectable and detectable plasma EGFRm at week 3 and week 6 can be seen in **Figure 2**.

Figure 1. FLAURA sample flow



*Plasma samples were not tested in patients enrolled in China due to sample export limitations
Detectable EGFRm was defined as plasma ctDNA positive for one of the EGFR mutations (ex19del or L858R). Non-detectable EGFRm was defined as plasma ctDNA negative for all primary EGFR mutations
ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; EGFRm, EGFR-TKI sensitizing mutations (ex19del or L858R); EGFR-TKI, EGFR-tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer

Figure 2. Proportions of patients with detectable and non-detectable plasma EGFRm at baseline across treatment arms in week 3 and week 6

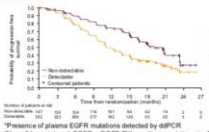


*Clearance refers to non-detectable plasma EGFR mutations, where they were detectable at baseline, using ddPCR
ddPCR, droplet digital polymerase chain reaction; EGFR, epidermal growth factor receptor; EGFRm, EGFR-TKI sensitizing mutations (ex19del or L858R); EGFR-TKI, EGFR-tyrosine kinase inhibitor

PFS based on detectable and non-detectable plasma EGFRm at baseline

- At baseline, patients with non-detectable plasma EGFRm (n=147) had longer mPFS compared to patients with detectable EGFRm (n=352) (**Figure 3**).

Figure 3. PFS in patients with detectable and non-detectable plasma EGFRm* at baseline



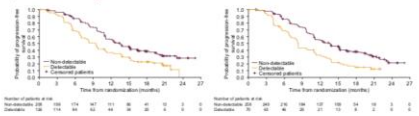
	Detectable (n=352)	Non-detectable (n=147)
Events,n (maturity,%)	238 (68)	70 (48)
mPFS, months (95% CI)	11.1 (10.8, 13.1)	19.1 (16.6, 23.4)

*Presence of plasma EGFR mutations detected by ddPCR
CI, confidence interval; EGFRm, EGFR-TKI sensitizing mutations (ex19del or L858R); mPFS, median progression-free survival

ORR and PFS analysis by clearance of plasma EGFRm

- At week 3 and week 6, 61% (n=208/342) and 75% (n=258/342), respectively, of all patients with detectable plasma EGFRm at baseline had clearance of plasma EGFRm.
- Overall, across both arms, response rates were similar, but significantly longer PFS was observed in patients with clearance of plasma EGFRm at weeks 3 and 6 compared with patients with detectable plasma EGFRm (**Figure 4**).

Figure 4. ORR and PFS based on clearance of plasma EGFRm* at a) week 3 and b) week 6 following treatment initiation



a) Clearance of plasma EGFRm at week 3

	Detectable EGFRm (n=126)	Non-detectable EGFRm (n=208)
Events,n (maturity,%)	99 (79)	128 (62)
mPFS, months (95% CI)	9.5 (7.0, 10.9)	13.5 (11.1, 15.2)
HR (95% CI); p-value	0.57 (0.4, 0.7) p<0.0001	
ORR, % (95% CI)	78 (69.5, 84.7)	87 (81.7, 91.3)

b) Clearance of plasma EGFRm at week 6

	Detectable EGFRm (n=70)	Non-detectable EGFRm (n=258)
Events,n (maturity,%)	57 (81)	165 (64)
mPFS, months (95% CI)	8.2 (5.8, 10.9)	13.5 (11.1, 15.2)
HR (95% CI); p-value	0.51 (0.4, 0.7) p<0.0001	
ORR, % (95% CI)	73 (60.9, 82.8)	88 (83.4, 91.7)

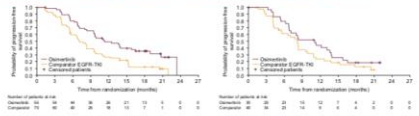
*Clearance refers to non-detectable plasma EGFR mutations, where they were detectable at baseline, using ddPCR
CI, confidence interval; ddPCR, droplet digital polymerase chain reaction; EGFR, epidermal growth factor receptor; EGFRm, EGFR-TKI sensitizing mutations (ex19del or L858R); EGFR-TKI, EGFR-tyrosine kinase inhibitor; HR, hazard ratio; mPFS, median progression-free survival; ORR, objective response rate

ORR and PFS analysis by clearance of plasma EGFRm according to treatment arm

Patients with non-clearance of plasma EGFRm at weeks 3 or 6

- In the subgroup of patients with detectable plasma EGFRm at week 3, PFS was significantly longer in patients receiving osimertinib compared with patients receiving comparator EGFR-TKIs (**Figure 5a**) and ORRs were similar.
- In the subgroup of patients with detectable plasma EGFRm at week 6, numerically longer mPFS was observed in patients receiving osimertinib compared with patients receiving comparator (**Figure 5b**) and ORRs were similar.

Figure 5. ORR and PFS in patients with detectable plasma EGFRm* at a) week 3 and b) week 6 following initiation of osimertinib or comparator EGFR-TKI



a) Detectable plasma EGFRm at week 3

	Osimertinib (n=156)	Comparator EGFR-TKI (n=70)
Events,n (maturity,%)	38 (68)	51 (67)
mPFS, months (95% CI)	11.3 (9.5, 16.5)	7.0 (5.6, 8.3)
HR (95% CI); p-value	0.50 (0.3, 0.8) p<0.001	
ORR, % (95% CI)	80 (67.6, 89.8)	76 (64.0, 85.2)
Odds ratio (95%CI) p-value	1.3 (0.6, 3.2) p=0.5319	

b) Detectable plasma EGFRm at week 6

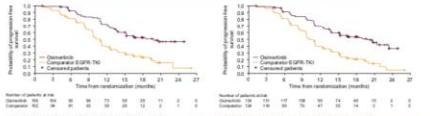
	Osimertinib (n=39)	Comparator EGFR-TKI (n=40)
Events,n (maturity,%)	23 (77)	34 (85)
mPFS, months (95% CI)	11.1 (6.8, 13.8)	8.2 (5.0, 9.6)
HR (95% CI); p-value	0.69 (0.4, 1.2) p=0.164	
ORR, % (95% CI)	73 (54.1, 87.7)	73 (56.1, 85.4)
Odds ratio (95% CI) p-value	1.0 (0.4, 3.1) p=0.9381	

*Presence of plasma EGFR mutations detected by ddPCR
CI, confidence interval; EGFR, epidermal growth factor receptor; EGFRm, EGFR-TKI sensitizing mutations (ex19del or L858R); EGFR-TKI; EGFR-tyrosine kinase inhibitor; HR, hazard ratio; mPFS, median progression-free survival; ORR, objective response rate

Patients with clearance of plasma EGFRm at weeks 3 or 6

- In patients with clearance of plasma EGFRm at weeks 3 or 6, mPFS was higher than for patients with detectable plasma EGFRm at weeks 3 or 6, irrespective of treatment arm. At both weeks 3 and 6, mPFS was longer with osimertinib treatment. ORR was similar at both weeks (**Figure 6**).

Figure 6. ORR and PFS in patients with clearance of plasma EGFRm* at a) week 3 and b) week 6 following initiation of osimertinib or comparator EGFR-TKI



a) Clearance of plasma EGFRm at week 3

	Osimertinib (n=106)	Comparator EGFR-TKI (n=128)
Events,n (maturity,%)	50 (47)	78 (76)
mPFS, months (95% CI)	19.9 (15.1, NC)	10.8 (9.7, 11.1)
HR (95% CI); p-value	0.41 (0.3, 0.6) p<0.0001	
ORR, % (95% CI)	86 (77.7, 91.9)	88 (80.4, 93.8)
Odds ratio (95%CI) p-value	0.8 (0.4, 1.8) p=0.6083	

b) Clearance of plasma EGFRm at week 6

	Osimertinib (n=134)	Comparator EGFR-TKI (n=124)
Events,n (maturity,%)	66 (49)	99 (80)
mPFS, months (95% CI)	19.8 (15.1, NC)	10.2 (9.5, 11.1)
HR (95% CI); p-value	0.40 (0.3, 0.6) p<0.0001	
ORR, % (95% CI)	86 (78.8, 91.2)	90 (83.7, 94.9)
Odds ratio (95% CI) p-value	0.7 (0.3, 1.4) p=0.2643	

*Clearance refers to non-detectable EGFR mutations, where they were detectable at baseline, using ddPCR
CI, confidence interval; ddPCR, droplet digital polymerase chain reaction; EGFR, epidermal growth factor receptor; EGFRm, EGFR-TKI sensitizing mutations (ex19del or L858R); EGFR-TKI, EGFR-tyrosine kinase inhibitor; HR, hazard ratio; mPFS, median progression-free survival; NC, non-calculable; ORR, objective response rate

Conclusions

- The early clearance of plasma EGFRm in patients with EGFRm positive, advanced NSCLC receiving first-line EGFR-TKI (osimertinib or comparator) therapy appears to be a prognostic factor for improved outcome; similar findings have been observed with second-line osimertinib treatment from the AURA trials.[6,7]
- Patients with detectable plasma EGFRm at baseline had worse PFS compared to patients with non-detectable EGFRm.
- PFS of osimertinib was superior to comparator EGFR-TKIs, regardless of clearance status.
- These data suggest that patients at higher risk of shorter time to progression or death (in the absence of progression) with first-line osimertinib could be identified early in the treatment course.
- A serial analysis at additional timepoints over the course of treatment is under way. In addition, further analysis is ongoing to investigate the mechanism underlying the high risk of early progression in patients with detectable plasma EGFRm following EGFR-TKI treatment.

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Acknowledgments

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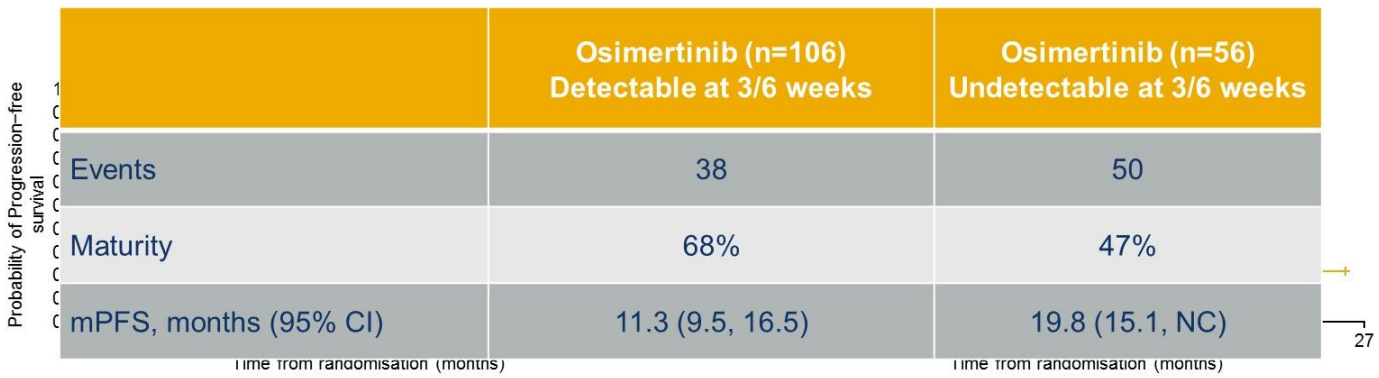
Presented at the American Society of Clinical Oncology Annual Meeting, Chicago, IL, May 31–June 4, 2019

Biomarcadores en genes oncogénicos

Abstract 9019: FLAURA plasma samples: [Platform: ddPCR; clearance]

	Osimertinib (n=106) Detectable at 3/6 weeks	Osimertinib (n=56) Undetectable at 3/6 weeks
Events	38	50
Maturity	68%	47%
mPFS, months (95% CI)	11.3 (9.5, 16.5)	19.8 (15.1, NC)



a) Clearance of plasma EGFRm at week 3

	Detectable EGFRm (n=126)	Non-detectable EGFRm (n=208)
Events,n (maturity,%)	99 (79)	128 (62)
mPFS, months (95% CI)	9.5 (7.0, 10.9)	13.5 (11.1, 15.2)
HR (95% CI); p value	0.57 (0.4, 0.7) p<0.0001	
ORR, % (95% CI)	78 (69.5, 84.7)	87 (81.7, 91.3)

b) Clearance of plasma EGFRm at week 6

	Detectable EGFRm (n=70)	Non-detectable EGFRm (n=258)
Events,n (maturity,%)	57 (81)	165 (64)
mPFS, months (95% CI)	8.2 (6.8, 10.9)	13.5 (11.1, 15.2)
HR (95% CI); p value	0.51 (0.4, 0.7) p<0.0001	
ORR, % (95% CI)	73 (60.9, 82.8)	88 (83.4, 91.7)

*Clearance refers to undetectable plasma EGFR mutations, where they were detectable at baseline, using ddPCR
CI, confidence interval; EGFR, epidermal growth factor receptor; EGFRm, EGFR-TKI sensitizing mutations (ex19del or L858R); EGFR-TKI; EGFR-tyrosine kinase inhibitor; HR, hazard ratio; mPFS, median progression-free survival

Biomarcadores en genes oncogénicos

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Early Circulating Tumor DNA Dynamics and Efficacy of Lorlatinib in Patients With Advanced *ALK*-Positive Non-Small Cell Lung Cancer

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BACKGROUND

- Lorlatinib is a selective, potent, brain-penetrant, third-generation anaplastic lymphoma kinase (ALK)/ROS1 tyrosine kinase inhibitor (TKI).[1-3]
- In an ongoing phase 1/2 study (NCT01970865), lorlatinib showed clinical activity among patients (pts) with *ALK*/*ROS1*-positive non-small cell lung cancer (NSCLC).[4,5]
- The US FDA granted lorlatinib accelerated approval for the treatment of pts with *ALK*-positive metastatic NSCLC whose disease has progressed on crizotinib and ≥1 other ALK TKI for metastatic disease or in those with disease progression on alectinib or ceritinib as the first ALK TKI for metastatic disease.[6]
- We recently showed that *ALK* mutation tumor genotyping after failure of ≥1 second-generation ALK TKI may identify pts more likely to respond to lorlatinib.[7]
- To identify other molecular response correlates, we evaluated if early circulating tumor DNA (ctDNA) dynamics can predict clinical outcomes during lorlatinib treatment among *ALK*-positive pts previously treated with ≥1 second-generation ALK TKI.

STUDY DESIGN/METHODS

- In pts enrolled in both the phase 2 portion of the ongoing phase 1/2 study and in a drug-drug interaction (DDI) sub-study (NCT01970865), plasma samples were prospectively collected for ctDNA analysis at baseline (BL), cycle 3 day 1 (C3D1, or 6 weeks) and end of treatment (EOT).
  - Plasma DNA was analyzed using Guardant360 (panel v 2.10, bioinformatics pipeline v 3.7; Guardant Health, Inc., Redwood City, CA, USA).

STATISTICAL METHODS

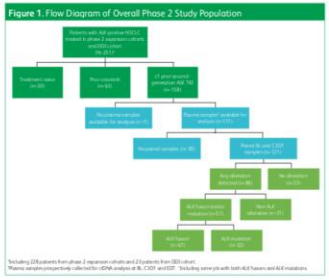
- Paired Analysis Set was defined as all patients in the intention-to-treat (ITT) analysis set who had valid paired results from at least one molecular biomarker (analyte mutation) assayed at screening and post-treatment (ie, EOT for phase 1, C3D1 and/or EOT for phase 2).
- Change in variant allele fraction (dVAF)[8] of *ALK* alterations (fusions and/or mutations) was calculated as (mean VAF_{C3D1}) – (mean VAF_{BL}); dVAF <0 indicated decreased ctDNA at C3D1.
- dVAF between BL and C3D1 was compared by paired Student's *t*-test. No adjustment was made for multiple hypotheses testing and nominal p-values are presented.
- Best overall response (BOR), progression-free survival (PFS) and overall survival (OS) were evaluated according to dVAF.

RESULTS

Patient Characteristics

- In total, 228 pts with *ALK*-positive NSCLC were enrolled into the phase 2 study and 23 were enrolled into the DDI sub-study (**Figure 1**).
  - Thirty treatment-naïve *ALK*-positive pts were excluded from this biomarker analysis.
  - The remaining 221 pts had received ≥1 prior ALK TKI; 63 pts had received crizotinib as their only prior ALK TKI and were excluded from this biomarker analysis, while 158 pts had received ≥1 second-generation ALK TKI, often with prior crizotinib.
- For pts who received ≥1 second-generation ALK TKI, sample availability for the present analysis is depicted in **Figure 1**.
  - Of 121 paired BL/C3D1 samples collected, 57 (47%) harbored a detectable *ALK* alteration at BL.

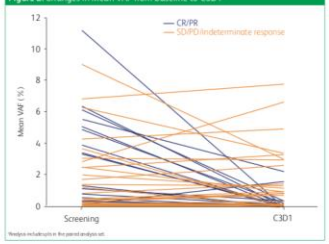
Figure 1. Flow Diagram of Overall Phase 2 Study Population



Clinical Activity

- Of the 57 pts with *ALK* fusions and/or mutations, BOR was complete response (CR)/partial response (PR) in 29 pts (51%), stable disease (SD) in 16 pts (28%) and progressive disease (PD)/indeterminate response in 12 pts (21%).
- At C3D1, mean VAF of *ALK* fusions and/or mutations was significantly decreased from BL (–1.07, P=0.0014) (**Figure 2**).

Figure 2. Changes in Mean VAF from Baseline to C3D1[a]



[a]Analysis includes pts in the paired analysis set.

- In pts with *ALK* fusion and/or mutation, mean VAF at C3D1 was significantly decreased from BL for those with BOR of CR/PR (P=0.0011, **Table 1**); mean VAF was not significantly different between BL and C3D1 among pts with SD or PD/indeterminate response as BOR (P=0.1444 and P=0.3383, respectively).
  - Among pts with no *ALK* alteration, mean VAF was not significantly different between BL and C3D1, irrespective of BOR.
  - Among pts with any alteration, mean VAF at C3D1 was significantly decreased from BL for those with BOR of CR/PR, but not for those with SD or PD/indeterminate response (P<0.0008, P=0.1628 and P=0.4834, respectively).

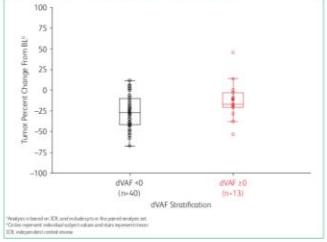
Table 1. Mean dVAF from BL to C3D1 by BOR[a]

BOR	Mutation Status		
	ALK fusion and/or mutation (N=57)	No *ALK* alteration (N=31)	Any alteration[b] (N=88)
CR/PR			
n	29	10	39
Mean dVAF	−1.84	−0.14	−1.26
P	0.0011	0.1489	0.0008
SD			
n	16	12	28
Mean dVAF	−0.74	−0.25	−0.87
P	0.1444	0.2147	0.1628
PD/indeterminate response			
n	12	9	21
Mean dVAF	0.35	−0.21	0.19
P	0.3383	0.1733	0.4834

[a]Analysis is based on EOT and includes pts in the paired analysis set.
[b]Including pts with non-*ALK* alterations.
IDR, independent central review.

- Tumor percent change from baseline, pooled across pts with *ALK* fusion and/or mutation, was reduced by 26% in pts with dVAF <0 (n=40) and only by 12% in pts with dVAF ≥0 (n=13) (P=0.0149) (**Figure 3**).

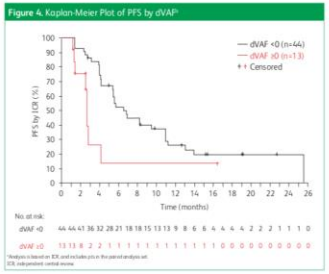
Figure 3. Tumor Percent Change from BL to C3D1 by dVAF at C3D1[a]



[a]Analysis is based on IDR, and includes pts in the paired analysis set.
[b]Circles represent individual subject values and stars represent means.
IDR, independent central review.

- In pts with *ALK* fusion and/or mutation, median PFS was 6.6 months in pts with dVAF <0 (n=44) and 2.6 months in pts with dVAF ≥0 (n=13) (HR=2.6, 95% CI: 1.2, 5.8) (**Figure 4**).

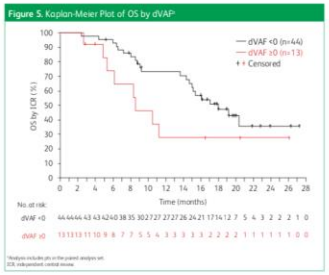
Figure 4. Kaplan-Meier Plot of PFS by dVAF[a]



[a]Analysis is based on IDR and includes pts in the paired analysis set.
IDR, independent central review.

- In pts with *ALK* fusion and/or mutation, median OS was 18.0 months in pts with dVAF <0 (n=44) and 8.6 months in pts with dVAF ≥0 (n=13) (HR 2.0, 95% CI: 0.9–4.6) (**Figure 5**).

Figure 5. Kaplan-Meier Plot of OS by dVAF[a]



[a]Analysis includes pts in the paired analysis set.
IDR, independent central review.

CONCLUSIONS

- Early ctDNA dynamics may predict lorlatinib efficacy in *ALK*-positive metastatic NSCLC, with decreased ctDNA dVAF at 6 weeks associated with response and longer PFS and OS.
- Further studies are needed to validate these findings and to determine whether early intervention based on dynamic ctDNA monitoring may improve outcome.

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PLAIN-LANGUAGE SUMMARY

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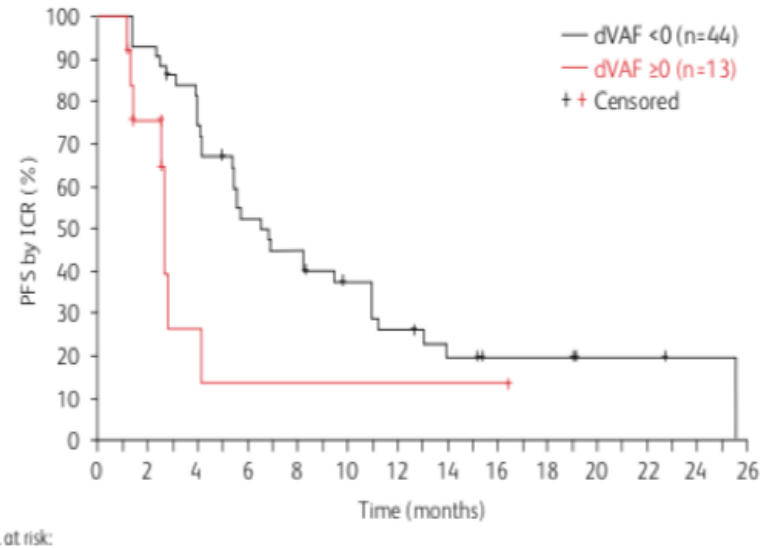
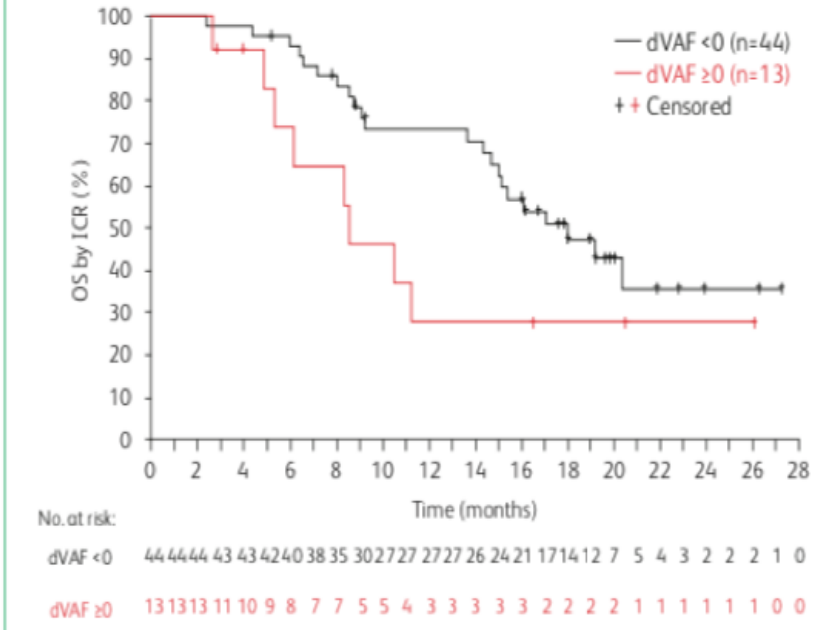
Figure 4. Kaplan-Meier Plot of PFS by dVAF[a]



[a]Analysis is based on ICR, and includes pts in the paired analysis set.
ICR, independent central review.

Figure 5. Kaplan-Meier Plot of OS by dVAF[a]



[a]Analysis includes pts in the paired analysis set.
ICR, independent central review.

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Dra. Ana Laura Ortega

Día 2

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