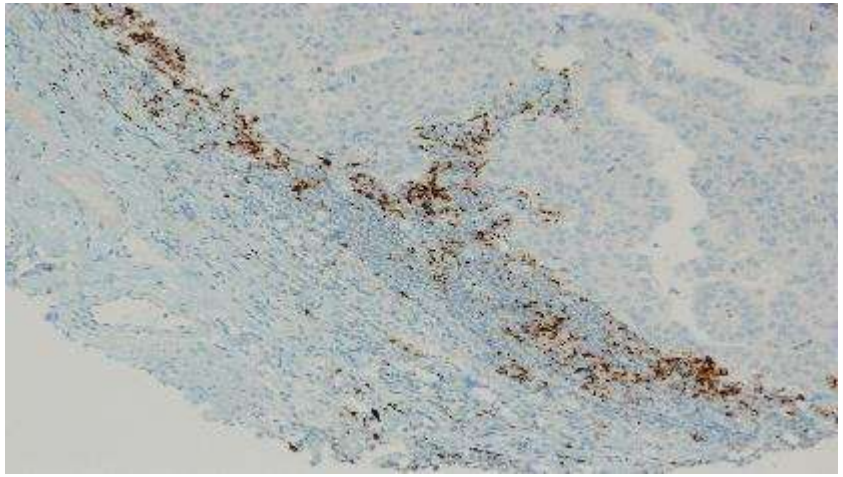
GUIÓN

1. Conceptos básicos en PD-L1
2. ¿En qué muestras?
3. **Novedades técnicas (TMB)**
4. Impacto clínico
5. Retos

PROBLEMAS

- Una prueba diferente para cada fármaco no es práctico
  - Cantidad limitada de tejido, tiempo, coste
- Sólo una prueba para todos los fármacos no es práctico
  - Diferentes plataformas, características , guías…
  - Cada fármaco tiene diferente respuesta basado en química, biología y diferencias en los anticuerpos monoclonales
- Peligroso para los pacientes si:
  - Ausencia de una validación clínica y analítica
- Nuevas pruebas más “objetivas” con posibilidad de monitorización (Biopsia líquida)



REVIEW ARTICLE

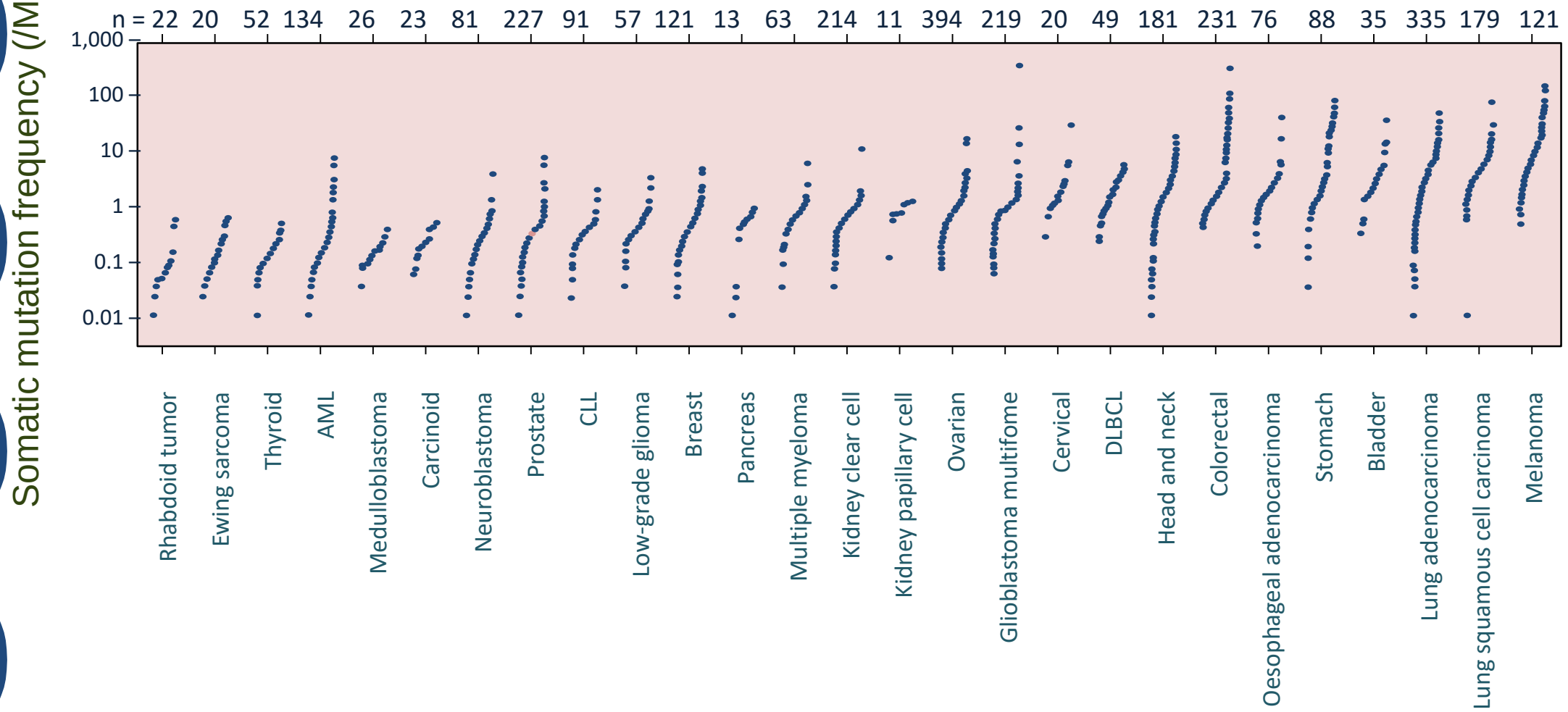
Assessing Tumor-Infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from the International Immuno-Oncology Biomarkers Working Group: Part 2: TILs in Melanoma, Gastrointestinal Tract Carcinomas, Non–Small Cell Lung Carcinoma and Mesothelioma, Endometrial and Ovarian Carcinomas, Squamous Cell Carcinoma of the Head and Neck, Genitourinary Carcinomas, and Primary Brain Tumors

Shona Hendry, MBBS,† Roberto Salgado, MD,‡§ Thomas Gevaert, MD,‖¶*

(*Adv Anat Pathol* 2017;00:000–000)

- El infiltrado CD3, CD8 está asociado con mejor pronóstico
- El infiltrado Treg, FOXP3 está asociado con peor pronóstico
  - No existen criterios claros para la cuantificación de los TILs
  - Estromales? Intraepiteliales? Estructuras linfoides terciarias?
- ¿Citología?
- Tras el tratamiento los niveles de linfocitos CD8+ PD1+ en sangre son indicadores asimismo de respuesta

CARGA MUTACIONAL (TMB) COMO FACTOR SELECTIVO



Companion Diagnostic, Pharmacogenomic, and Cancer Biomarkers

Molecular Cancer Therapeutics

Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers

Aaron M. Goodman[1,2,3], Shumei Kato[1,2], Lyudmila Bazhenova[1], Sandip P. Patel[1], Garrett M. Frampton[4], Vincent Miller[4], Philip J. Stephens[4], Gregory A. Daniels[1], and Razelle Kurzrock[1,2]

0.024). Higher TMB predicts favorable outcome to PD-1/PD-L1 blockade across diverse tumors. Benefit from dual checkpoint blockade did not show a similarly strong dependence on TMB.
Mol Cancer Ther; 16(11); 2598–608. ©2017 AACR.

- Mutaciones no sinónimas por megabase (codificante)
  - Baja: 1-5 mutaciones / mb (50%)
  - Intermedia: 6-19 mutaciones / mb (40%)
  - Alta: >20 mutaciones / mb (10%)

		Baja	Media	Alta	
Age	<60 years	78 (52%)	67 (59%)	11 (29%)	**0.0014**
	≥60 years	73 (48%)	46 (41%)	27 (71%)	
Response	CR/PR	45 (30%)	23 (20%)	22 (58%)	**0.0001** (OR 5.38; 95% CI, 2.44–11.58)[f]
	SD or PD	106 (70%)	90 (80%)	16 (42%)	**0.0001** (OR 0.19; 95% CI, 0.09–0.41)[f]
PFS	Median (months)	4.6	3.3 (2.98)	12.8 (0.34)	<**0.0001** (HR 0.34; 95% CI, 0.23–0.50)[f]
OS	Median (months)	25.4	16.3 (3.03)	Not reached (median f/u of 10.5 mos)	**0.0036** (HR 0.33, 95% CI, 0.19–0.58)[f]

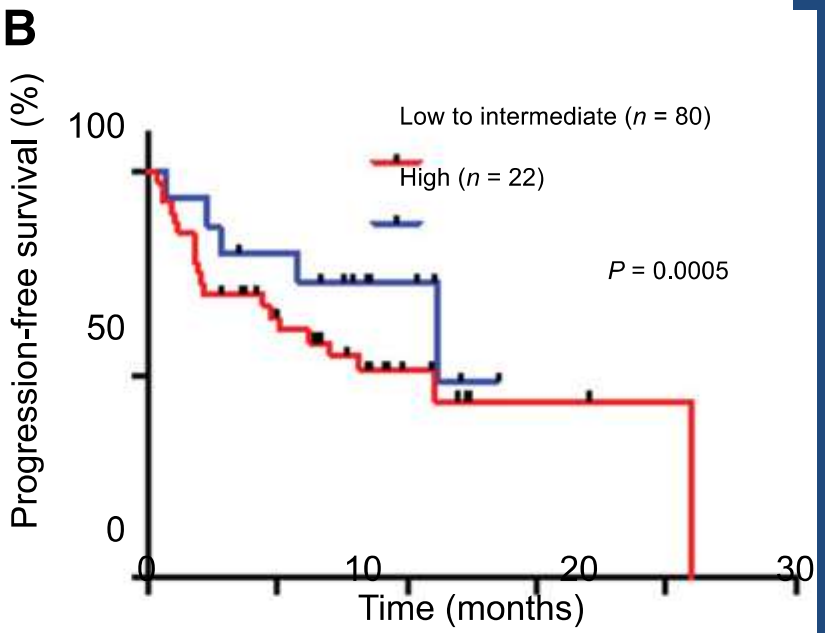
Companion Diagnostic, Pharmacogenomic, and Cancer Biomarkers

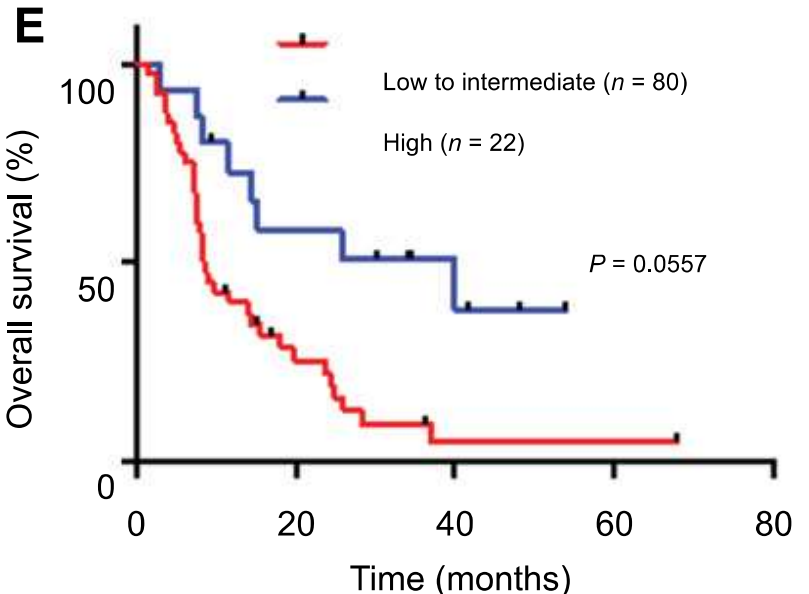
Molecular Cancer Therapeutics

Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers

Aaron M. Goodman[1,2,3], Shumei Kato[1,2], Lyudmila Bazhenova[1], Sandip P. Patel[1], Garrett M. Frampton[4], Vincent Miller[4], Philip J. Stephens[4], Gregory A. Daniels[1], and Razelle Kurzrock[1,2]

- Se usó terapia combinada antiPD-1/PD-L1 y anti CTLA4 en 17 pacientes (melanoma) con buena respuesta
  - En estos pacientes el TMB no era diferente en los respondedores y no respondedores
  - No estratifica pacientes
- *De forma no sorpresiva, TMB no es un predictor perfecto de respuesta a fármacos anti PD-1/PD-L1*
  - Un 4,3% (2/46) con baja TMB respondieron
  - Un 54,5% (12/22) con alta TMB no tuvieron respuesta objetiva



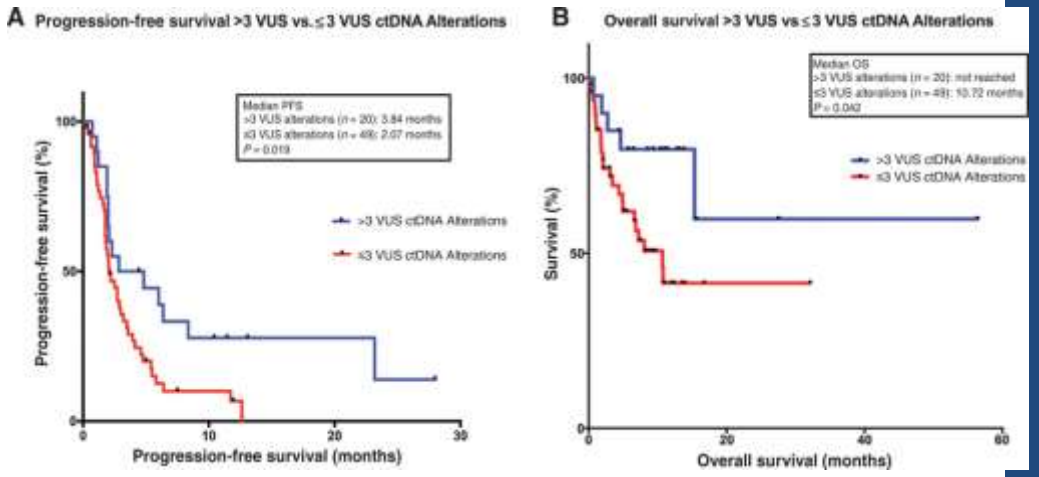


Clinical Cancer Research

Hypermutated Circulating Tumor DNA: Correlation with Response to Checkpoint Inhibitor–Based Immunotherapy

Yulian Khagi[1], Aaron M. Goodman[1,2], Gregory A. Daniels[3], Sandip P. Patel[1], Assuntina G. Sacco[3], James M. Randall[3], Lyudmila A. Bazhenova[3], and Razelle Kurzrock[1]

Conclusions: Given the association of alteration number on liquid biopsy and checkpoint inhibitor–based immunotherapy outcomes, further investigation of hypermutated ctDNA as a predictive biomarker is warranted. *Clin Cancer Res; 23(19); 5729–36. ©2017 AACR.*



Oncomine Immune Response Research Assay

Analyze the immune pathway and low-expressing genes
from your clinical research samples with as little as 10 ng FFPE RNA

Table 1. Oncomine Immune Response Research Assay content includes 395 genes across 36 functional annotation groups. These groups are comprised of genes associated with lymphocyte regulation, cytokine signaling, lymphocyte markers, checkpoint pathways, and tumor characterization.

Functional annotation group	No. of genes
Adhesion, migration	14
Antigen presentation	3
Antigen processing	19
Apoptosis	4
B cell marker	11
B cell receptor signaling	3
Checkpoint pathway	30
Chemokine signaling	10
Cytokine signaling	15
Dendritic cell	7
Dendritic cell, macrophage	6
Drug target	21
Helper T cells	8
Housekeeping	11
Innate immune response	11
Interferon signaling	8
Leukocyte inhibition	2
Leukocyte migration	5
Lymphocyte activation	2
Lymphocyte development	3
Lymphocyte infiltrate	48
Macrophage	5
Myeloid marker	7
Neutrophil	5
NK activation	8
NK cell marker	4
PD-1 signaling	9
Proliferation	10
T cell differentiation	2

Functional annotation group	No. of genes
T cell receptor signaling	6
T cell regulation	9
TCR coexpression	19
Tumor antigen	17
Tumor marker	27
Type I interferon signaling	8
Type II interferon signaling	23

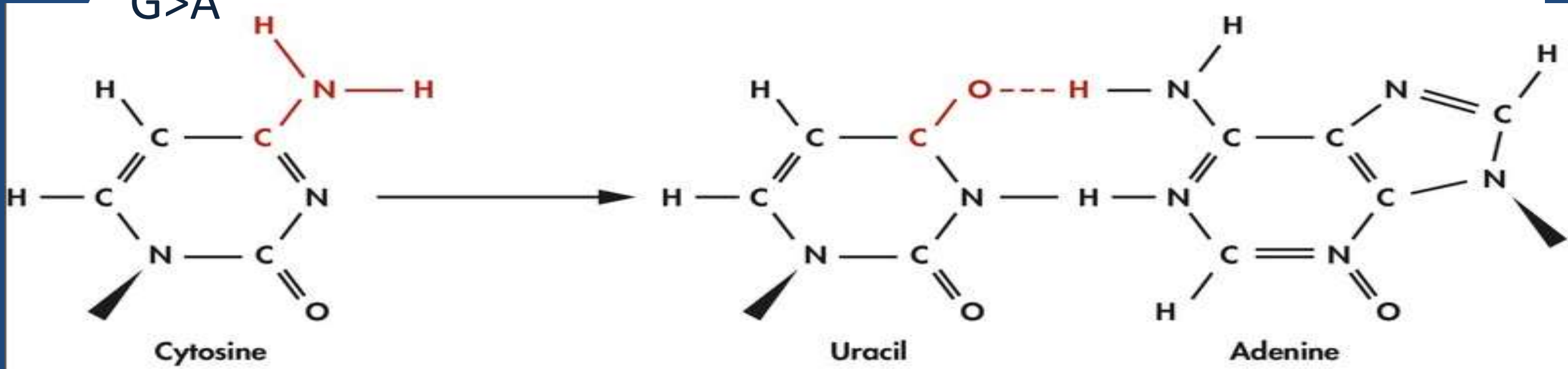
"Analyzing results from the Oncomine Immune Response Research Assay, we found some interesting results with fold changes comparing research samples with up- and down-regulated genes. The targeted NGS assay approach proved informative for our team."

Wissam Hamou, PhD
Staff Scientist
Department of Genetics
and Genomic Sciences
Icahn School of Medicine at Mount Sinai

ThermoFisher SCIENTIFIC

DESAMINACIÓN DE CITOSINAS

- En las muestras fijadas en formol la desaminación de citosinas da lugar a falsos apareamientos
- En las reacciones de secuenciación puede aparecer como C>T ó G>A



Locus	Genes	Amino Acid ...	Genotype	Ref	Type	Coverage	Allele Ratio
chr13:32913422	BRCA2	p.Glu1644Lys	G/A	G	SNV	299	G=0.9765, A=0.0235
chr13:32913309	BRCA2	p.Ser1606Phe	C/T	C	SNV	495	C=0.9758, T=0.0242
chr13:32912984	BRCA2	p.Gly1498Ser	G/A	G	SNV	237	G=0.9747, A=0.0253
chr13:32912765	BRCA2	p.Asp1425Asn	G/A	G	SNV	552	G=0.9746, A=0.0254
chr13:32912735	BRCA2	p.Glu1415Lys	G/A	G	SNV	552	G=0.9728, A=0.0272
chr13:32912546	BRCA2	p.Asp1352Asn	G/A	G	SNV	517	G=0.9768, A=0.0232
chr13:32912468	BRCA2	p.Ala1326Thr	G/A	G	SNV	183	G=0.9617, A=0.0383
chr13:32912394	BRCA2	p.Thr1301Ile	C/T	C	SNV	174	C=0.9713, T=0.0287
chr13:32911914	BRCA2	p.Thr1141Ile	C/T	C	SNV	335	C=0.9672, T=0.0328
chr13:32911752	BRCA2	p.Thr1087Ile	C/T	C	SNV	166	C=0.9759, T=0.0241
chr13:32911628	BRCA2	p.Glu1046Lys	G/A	G	SNV	215	G=0.9581, A=0.0419
chr13:32911598	BRCA2	p.Glu1036Lys	G/A	G	SNV	530	G=0.9698, A=0.0302
chr13:32911589	BRCA2	p.Asp1033Asn	G/A	G	SNV	531	G=0.9755, A=0.0245
chr13:32911579	BRCA2	p.Met1029Ile	G/A	G	SNV	316	G=0.962, A=0.038
chr13:32911085	BRCA2	p.Glu865Lys	G/A	G	SNV	169	G=0.9704, A=0.0296
chr13:32910878	BRCA2	p.Asp796Asn	G/A	G	SNV	333	G=0.967, A=0.033
chr13:32910695	BRCA2	p.Ala735Thr	G/A	G	SNV	528	G=0.9754, A=0.0246
chr13:32910435	BRCA2	p.Ser648Leu	C/T	C	SNV	572	C=0.9755, T=0.0245
chr13:32906964	BRCA2	p.Ser450Phe	C/T	C	SNV	319	C=0.9718, T=0.0282
chr13:32905059	BRCA2	p.Val229Met	G/A	G	SNV	435	G=0.9655, A=0.0345
chr13:32903797	BRCA2	p.?	C/T	C	SNV	258	C=0.9729, T=0.0271
chr13:32903735	BRCA2	p.?	C/T	C	SNV	260	C=0.9692, T=0.0308
chr13:32903680	BRCA2	p.?	A/G	A	SNV	239	A=0.9749, G=0.0251
chr13:32900663	BRCA2	p.Glu182Lys	G/A	G	SNV	455	G=0.967, A=0.033
chr13:32900590	BRCA2	p.?	G/A	G	SNV	419	G=0.9737, A=0.0263
chr13:32899367	BRCA2	p.?	C/T	C	SNV	179	C=0.9609, T=0.0391
chr13:32899221	BRCA2	p.Val108Ile	G/A	G	SNV	999	G=0.976, A=0.024
chr13:32899193	BRCA2	p.?	G/A	G	SNV	288	G=0.9722, A=0.0278
chr13:32899158	BRCA2	p.?	G/A	G	SNV	288	G=0.9549, A=0.0451
chr13:32893246	BRCA2	p.Glu34Lys	G/A	G	SNV	302	G=0.9669, A=0.0331
chr13:32893179	BRCA2	p.?	G/A	G	SNV	298	G=0.9732, A=0.0268
chr13:32890587	BRCA2	p.?	C/T	C	SNV	980	C=0.9765, T=0.0235

1 2 100 items per page

GUIÓN

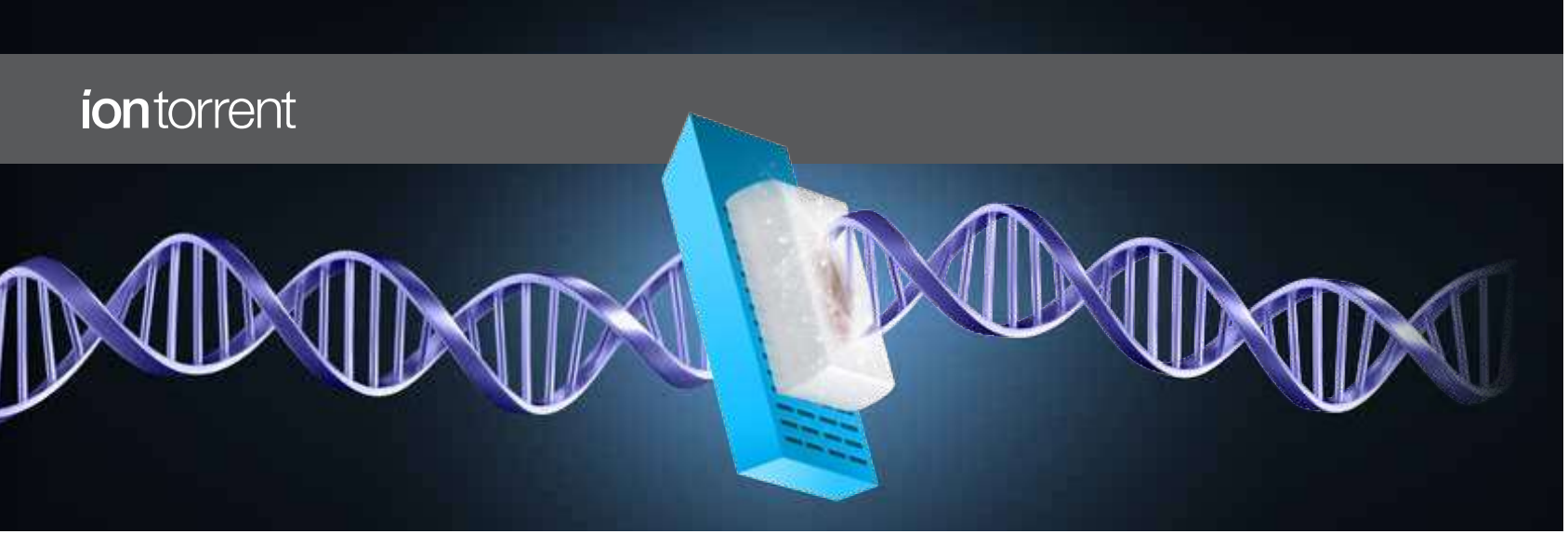
1. Conceptos básicos en PD-L1
2. ¿En qué muestras?
3. Novedades técnicas (TMB)
4. **Impacto clínico**
5. Retos

5º CONGRESO Oncología Farmacia
23-25 noviembre 2017

Héctor Cristóbal Gutiérrez, Cristina Garay Sarría, Virginia Martínez Callejo, María Ochagavía Sufrategui, Ana Mª García de la Paz, José Javier Gómez Román, Pilar García-Berbel, Almudena García Castaño, Marta Valero Domínguez

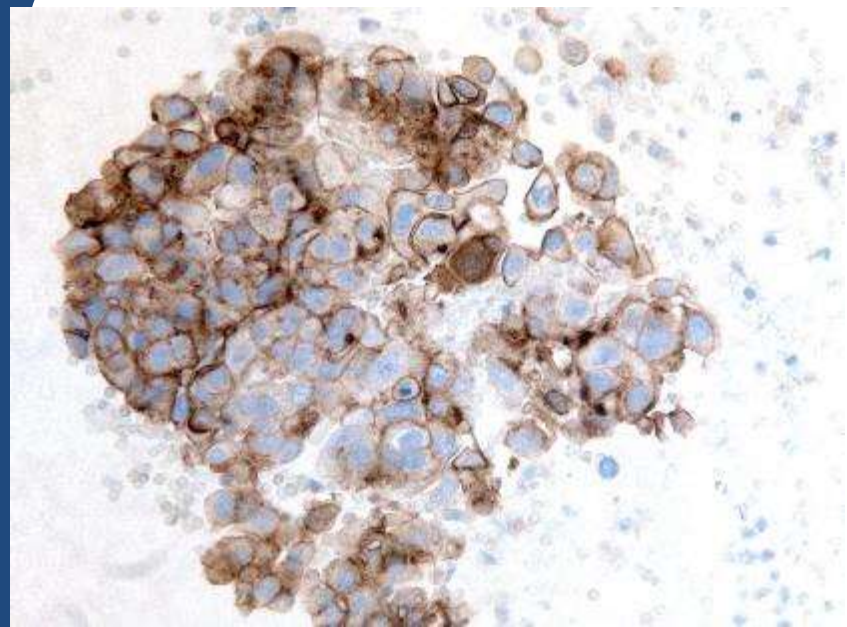
IMPACTO CLÍNICO

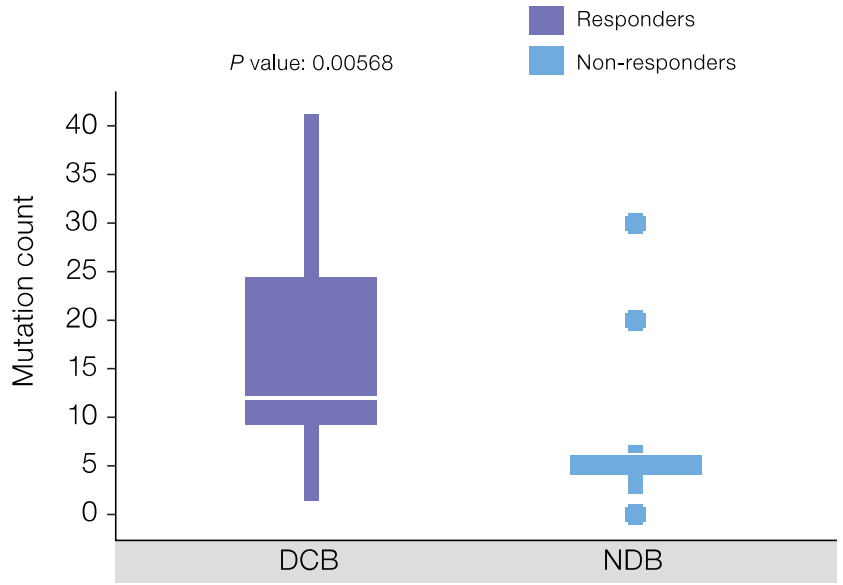
- 31 pacientes (21 varones), con media de edad de 65 años (49-78), con ECOG 0 (19 pacientes), ECOG 1 (11) y ECOG 2 (1)
- Adenocarcinoma (16) y carcinoma epidermoide (15)
- Estadio IV (27), IIIB (2) y IIIA (2).
- Presentaban metástasis pulmonares (17), óseas (11), ganglionares (8), pleurales (6), suprarrenales (5), hepáticas (3), mediastínicas (3), pericardio (1) y cerebro (1)
- Nivolumab a 3 mg/kg IV cada 14 días, mediana de ciclos administrados de 6 (1-49)
  - 2ª línea en 18 pacientes (12 histología epidermoide y 6 adenocarcinoma)
  - 3ª línea en 7 (2 epidermoide y 5 adenocarcinoma)
  - 4ª línea en 4 (3 adenocarcinoma y 1 epidermoide)
  - 5ª línea en 2 (adenocarcinoma)

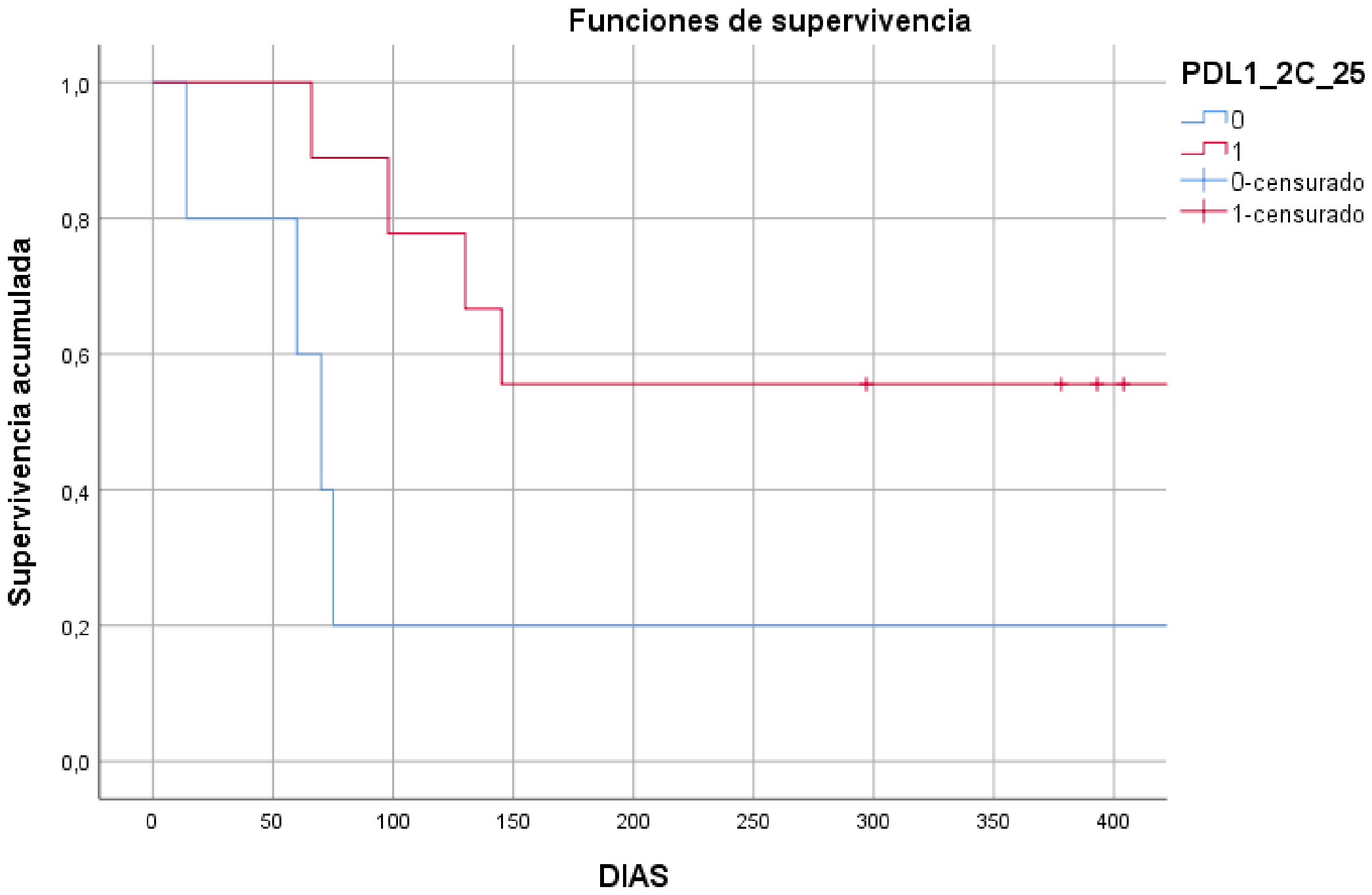


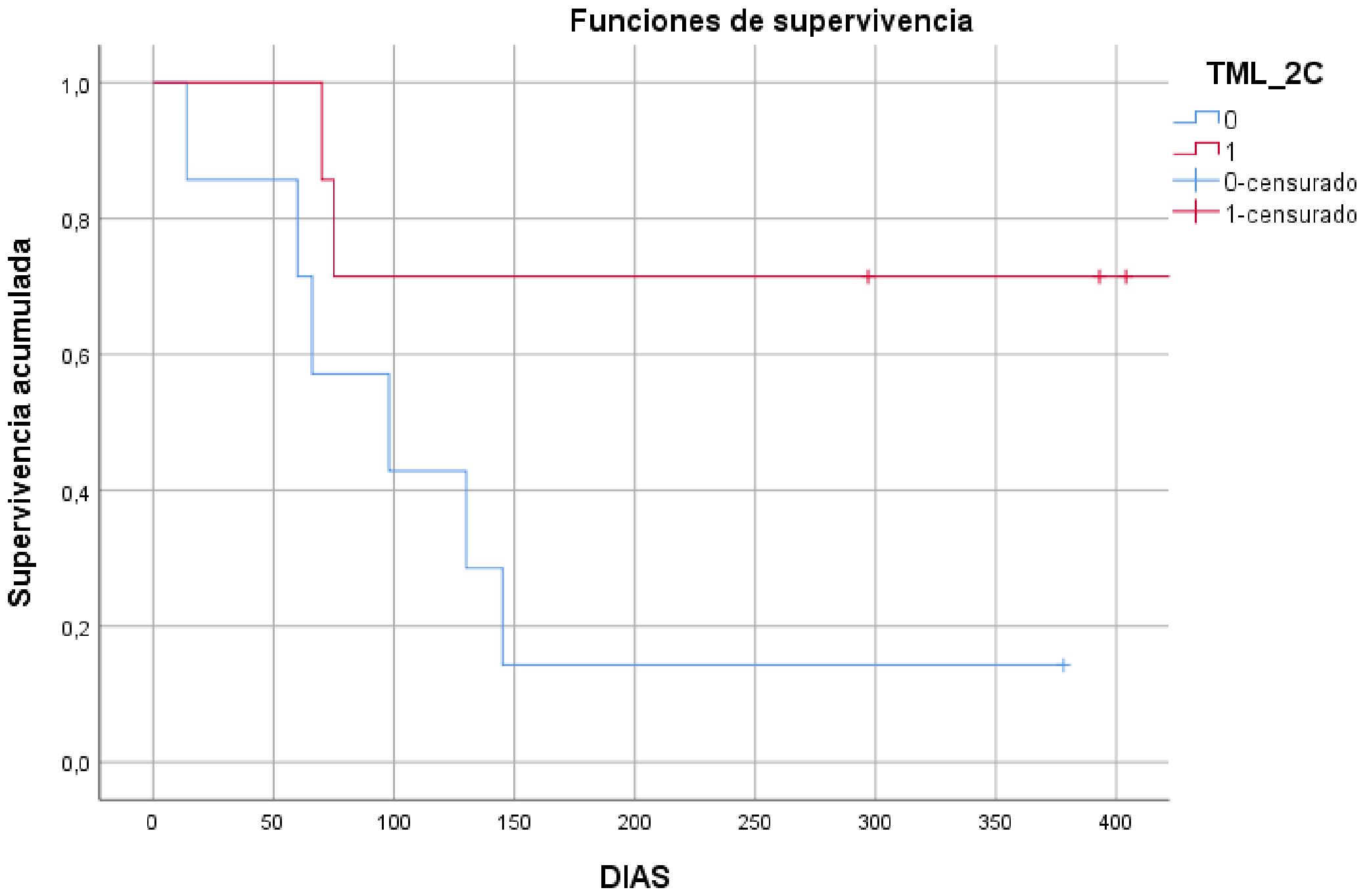
Oncomine Tumor Mutation Load Assay

An NGS assay for an emerging immuno-oncology biomarker






Funciones de supervivencia
PDL1_2C_25
0
1
0-censurado
1-censurado
Supervivencia acumulada
1,0
0,8
0,6
0,4
0,2
0,0
0
50
100
150
200
250
300
350
400
DIAS


Funciones de supervivencia
TML_2C
0
1
0-censurado
1-censurado
Supervivencia acumulada
1,0
0,8
0,6
0,4
0,2
0,0
0
50
100
150
200
250
300
350
400
DIAS

GUIÓN

1. Conceptos básicos en PD-L1
2. ¿En qué muestras?
3. Novedades técnicas (TMB)
4. Impacto clínico
5. **Retos**

ORIGINAL ARTICLE
N Engl J Med 2018;378:1976-86.
DOI: 10.1056/NEJMoa1716078

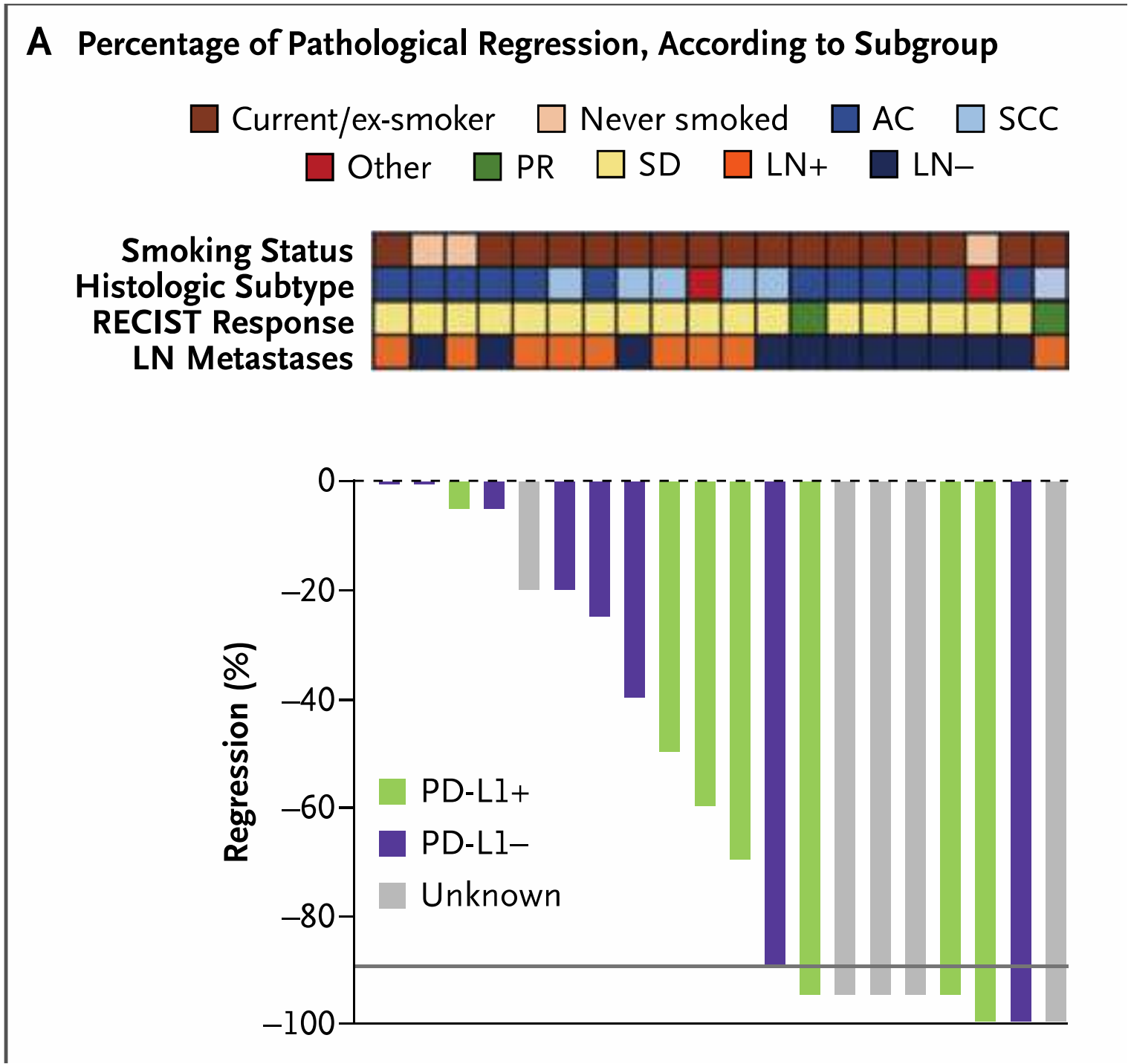
Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmar M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

resected. A major pathological response occurred in 9 of 20 resected tumors (45%). Responses occurred in both PD-L1–positive and PD-L1–negative tumors. There was a significant correlation between the pathological response and the pretreatment tumor mutational burden. The number of T-cell clones that were found in both the tumor and peripheral blood increased systemically after PD-1 blockade in eight of nine patients who were evaluated. Mutation-associated, neoantigen-specific T-cell

1

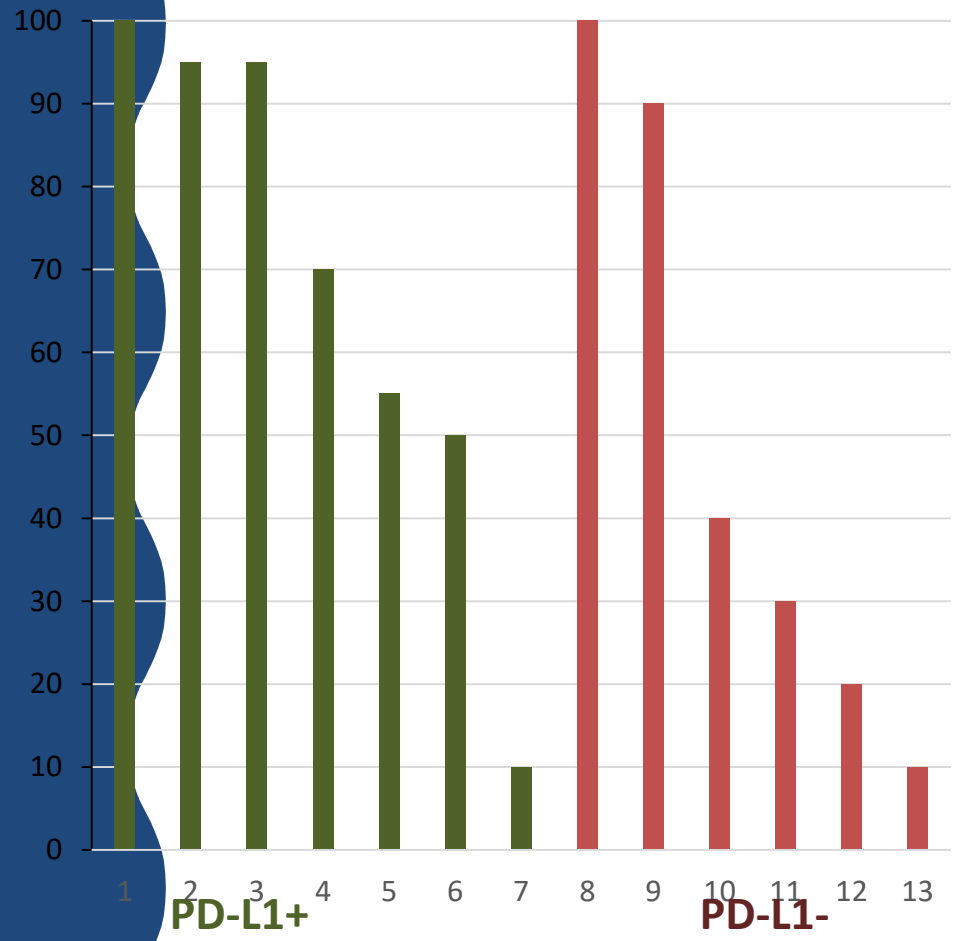
- Los casos de neoplasias localizadas tienen una supervivencia a 5 años del 50% en estadío IA al 20% de los IIIA
- La quimioterapia adyuvante mejora las cifras en un 5,4% aportando platino con toxicidad grado 3 en más del 60% de los pacientes
- El tratamiento neoadyuvante con inmunoterapia nos da la oportunidad además de estudiar los efectos sobre las células tumorales
- Dos dosis de Nivolumab previo a la cirugía
- Respuesta patológica mayor: No más de 10% de células tumorales viables
- Respuesta mayor en 9/20 (45%)
- Aparentemente los tumores crecían en el TAC (infiltración inflamatoria)

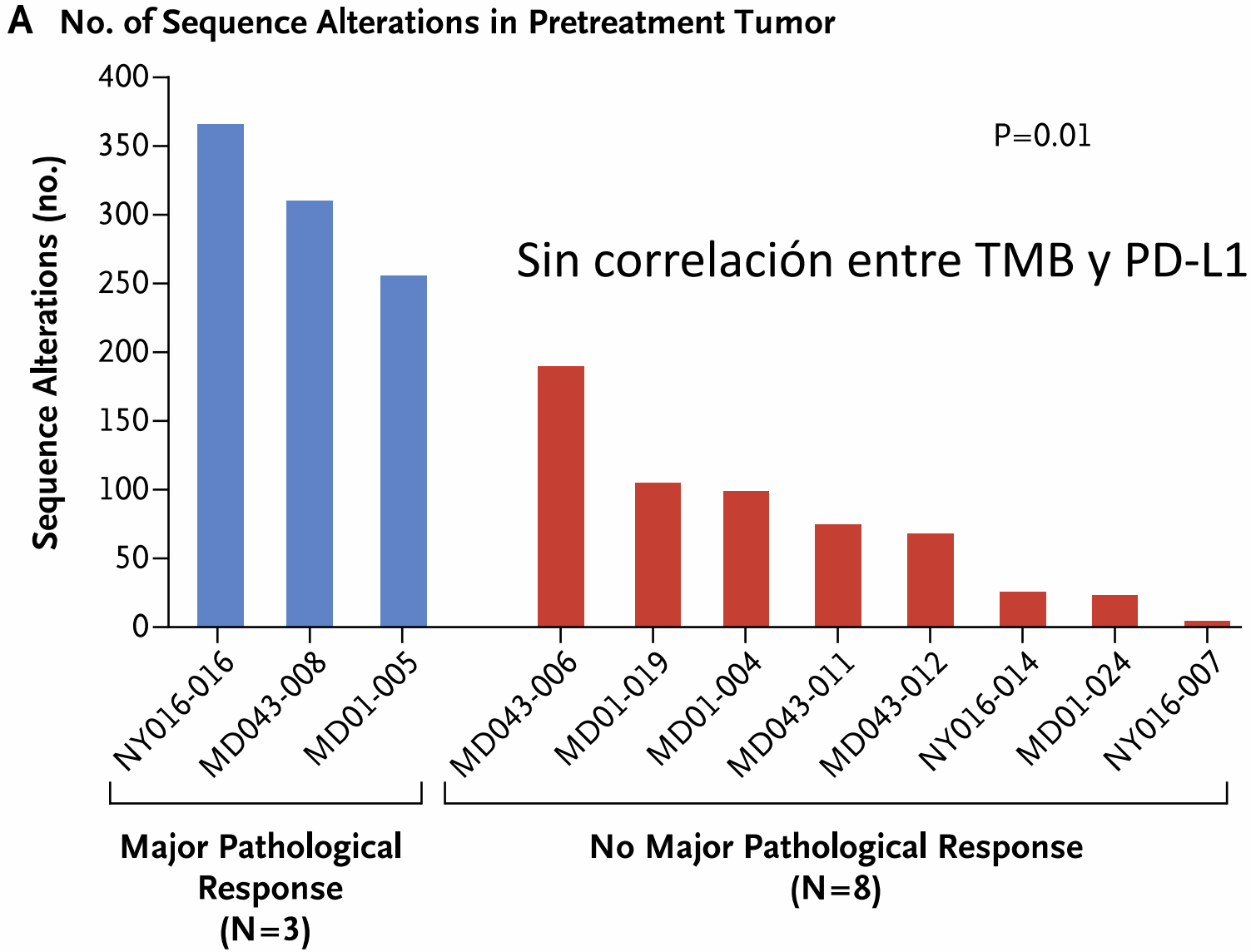

A Percentage of Pathological Regression, According to Subgroup
Current/ex-smoker
Never smoked
AC
SCC
Other
PR
SD
LN+
LN–
Smoking Status
Histologic Subtype
RECIST Response
LN Metastases
Regression (%)
0
–20
–40
–60
–80
–100
PD-L1+
PD-L1–
Unknown

Adenda Javier Gómez

Casos con tumor negativo pero células inmunes +

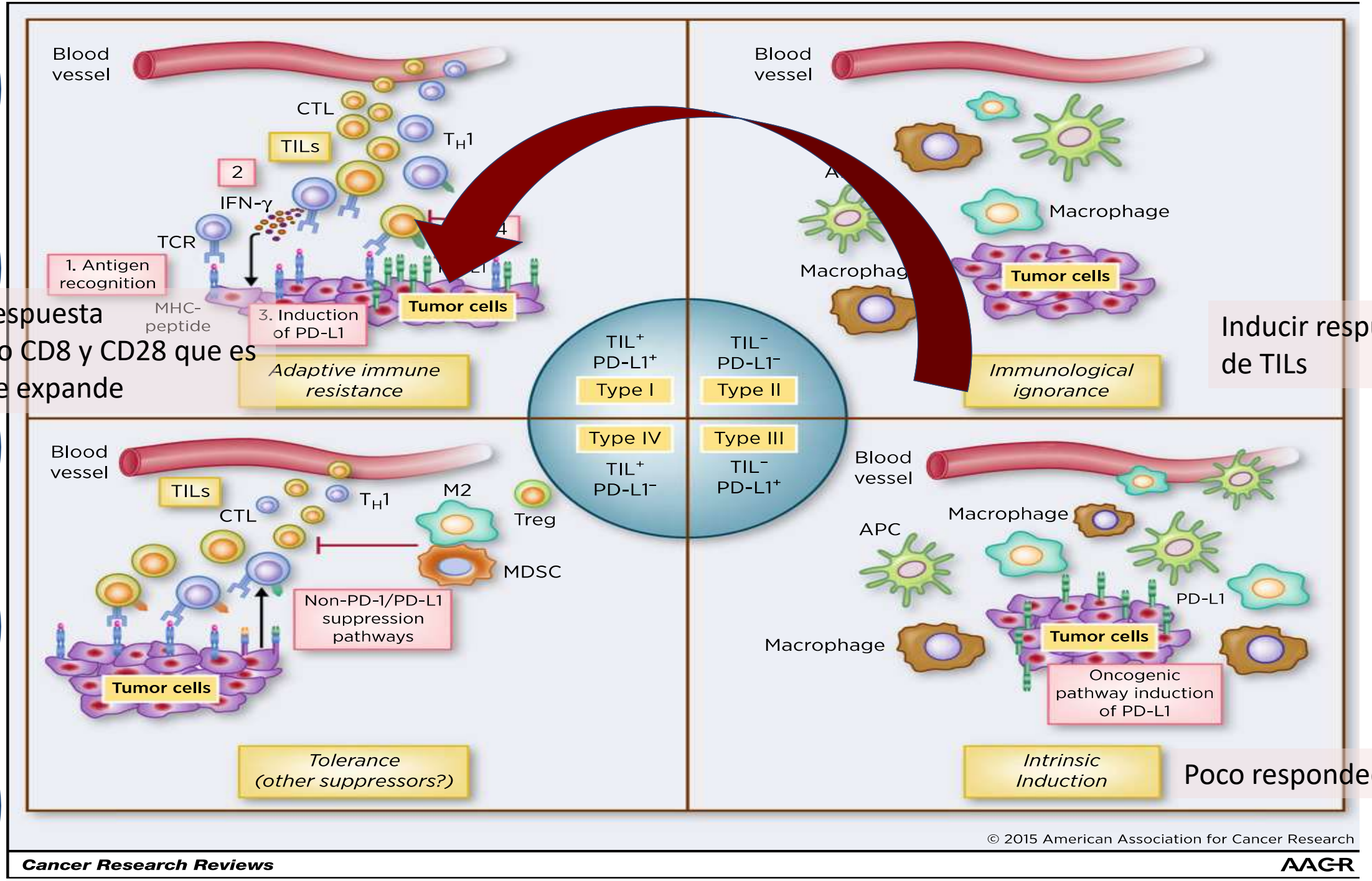
No detallan el clon (inmunofluorescencia)





2

Mejor respuesta
Infiltrado CD8 y CD28 que es el que se expande



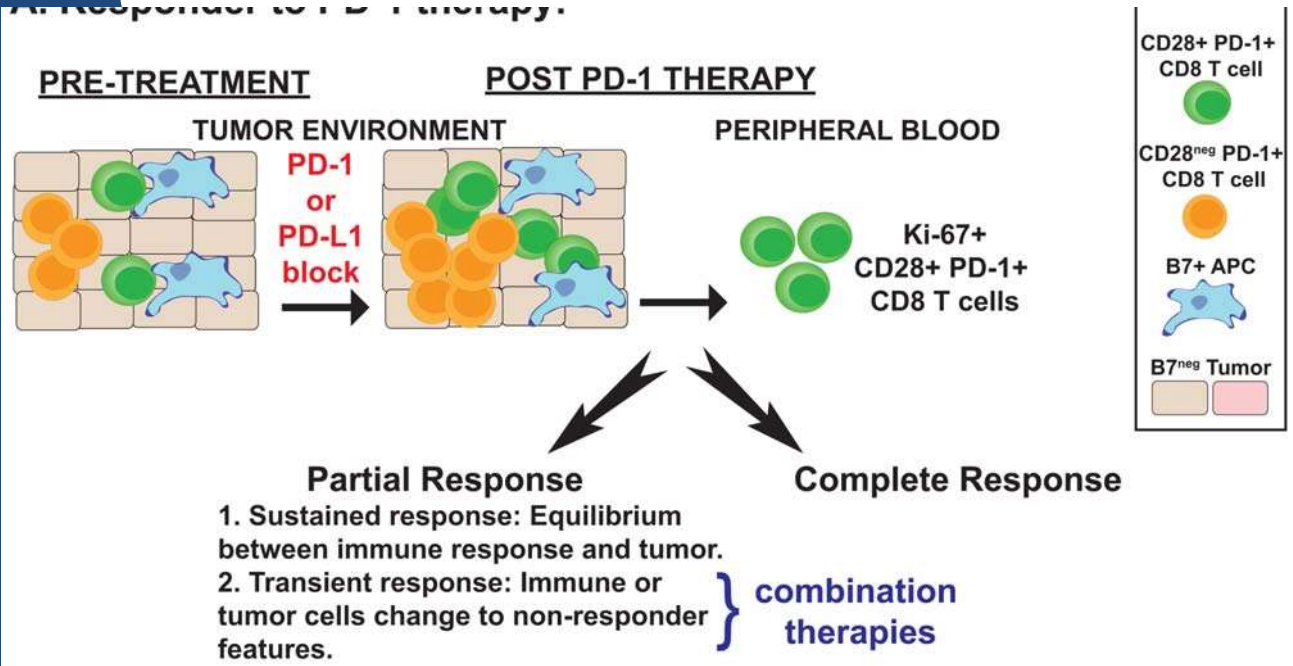
Inducir respuesta de TILs

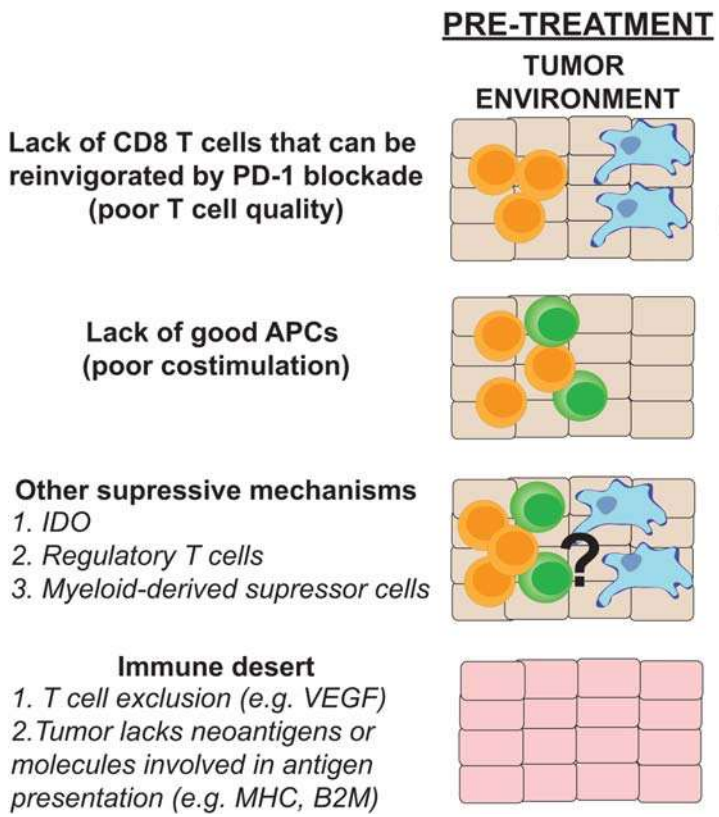
Poco respondedores

Immune Checkpoint Inhibitors in Advanced Non–Small Cell Lung Cancer

Cancer Month 00, 2017

Hazem I. Assi, MD [1]; Alice O. Kamphorst, PhD [2]; Nour M. Moukalled, MD [1]; and Suresh S. Ramalingam, MD [3]





In summary, we envisaged the possibility that integrative approaches incorporating distinct features of tumor cells and immune infiltrate in pretreatment biopsies may determine patient selection for checkpoint inhibition, and subsequent immune monitoring in peripheral blood may further guide personalized treatment decisions.

MECANISMOS DE RESISTENCIA A INMUNOTERAPIA

- Intrínsecos de las células tumorales
  - Pérdida de expresión de neoantígenos
  - Alteración en los mecanismos de presentación de antígeno (pérdida de HLA)
  - Expresión constitutiva de PD-L1
  - Mutaciones en la ruta IFNγ (JAK1/2)
- Extrínsecos a las células tumorales
  - Células T agotadas que expresan checkpoint alternativos LAG3, TIM3
  - Infiltración tumoral por células Treg, macrófagos M2 o células supresoras derivadas de línea mieloide
  - Sobreexpresión de enzimas inmunosupresores (IDO, IL10, TGFβ)

NATURE REVIEWS | CLINICAL O

Hyperprogressive disease: recognizing a novel pattern to improve patient management

https://doi.org/10.1038/s41571-018-0111-2

Stéphane Champiat[1,2], Roberto Ferrara[3], Christophe Massard[1], Benjamin Besse[2,3], Aurélien Marabelle[1,4], Jean-Charles Soria[1,2] and Charles Ferté[1]**

Published in final edited form as:
Nat Med. 2015 November ; 21(11): 1350–1356. doi:10.1038/nm.3967.

The Consensus Molecular Subtypes of Colorectal Cancer

Justin Guinney[1,*], **Rodrigo Dienstmann**[1,2,*], **Xin Wang**[3,4,*], **Aurélien de Reyniès**[5,*], **Andreas Schlicker**[6,*], **Charlotte Soneson**[7,*], **Laetitia Marisa**[5,*], **Paul Roepman**[8,*], **Gift Nyamundanda**[9,*], **Paolo Angelino**[7], **Brian M. Bot**[1], **Jeffrey S. Morris**[10], **Iris M. Simon**[8], **Sarah Gerster**[7], **Evelyn Fessler**[3], **Felipe de Sousa e Melo**[3], **Edoardo Missiaglia**[7], **Hena Ramay**[7], **David Barras**[7], **Krisztian Homicsko**[11], **Dipen Maru**[10], **Ganiraju C. Manyam**[10], **Bradley Broom**[10], **Valerie Boige**[12], **Beatriz Perez-Villamil**[13], **Ted Laderas**[1], **Ramon Salazar**[14], **Joe W. Gray**[15], **Douglas Hanahan**[11], **Josep Tabernero**[2], **Rene Bernards**[6], **Stephen H. Friend**[1], **Pierre Laurent-Puig**[16,§], **Jan Paul Medema**[3,§], **Anguraj Sadanandam**[9,§], **Lodewyk Wessels**[6,§], **Mauro Delorenzi**[7,17,§], **Scott Kopetz**[10,§], **Louis Vermeulen**[3,§], and **Sabine Tejpar**[18,§]

CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGFβ activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

Virchows Archiv
https://doi.org/10.1007/s00428-018-02517-1

REVIEW ARTICLE

Integrating histopathology, immune biomarkers, and molecular subgroups in solid cancer: the next step in precision oncology

Nicolas A. Giraldo[1] &J. David Peske[1] &Catherine Sautès-Fridman[2,3,4] &Wolf H. Fridman[2,3,4]

5

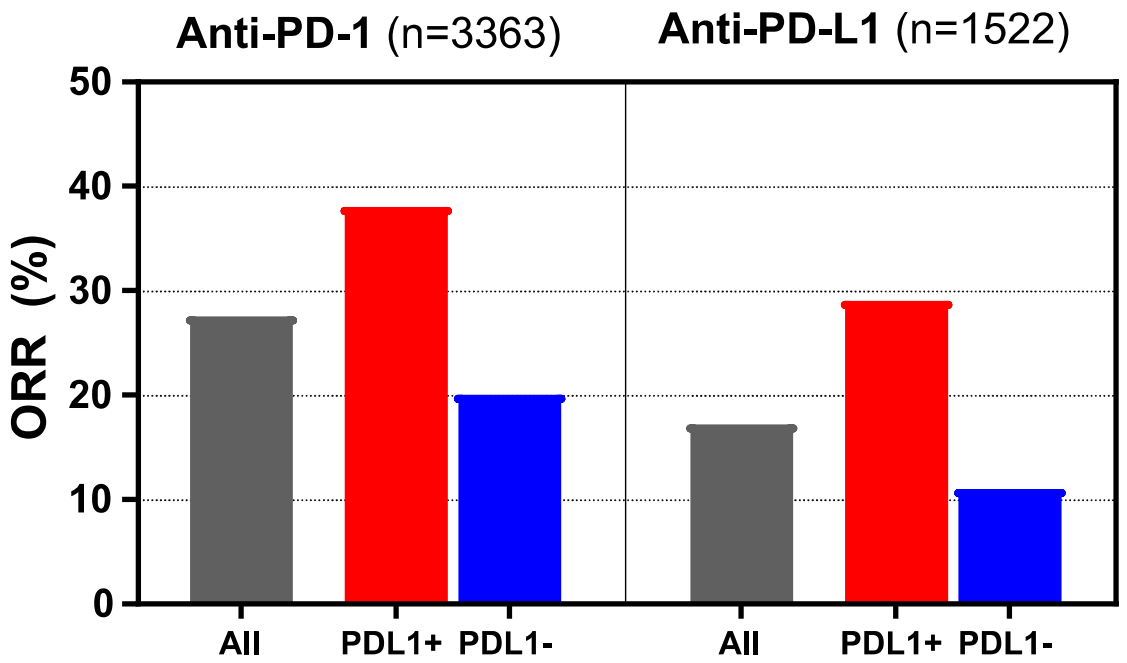


Fig. 3 ORR to anti-PD-1 or PD-L1 therapy in cancer according to the expression of PD-L1 by tumor cells. The ORR to PD-1/PD-L1 blocking agents (nivolumab, pembrolizumab, atezolizumab, or durvalumab) in 28 luding $n = 3363$ patients, stratified by PD- positivity varies from 1 to 50%). Last up-

Localización	Respuesta PD-L1+	Respuesta PD-L1-
Pulmón	30%	19%
Urotelial	27,5%	11%
Renal	24%	16%
Melanoma	53%	34%

Non–Small Cell Lung Cancer, PD-L1, and the Pathologist

Keith M. Kerr, BSc, MB, ChB, FRCPath, FRCPE; Marianne C. Nicolson, MD, FRCP

***Conclusions.*—The biology of PD-1/PD-L1 is complex, the clinical data for these drugs show considerable variation, the selection performance of the PD-L1 biomarker test is not perfect, and the existence of 4 drug/test combinations adds significantly to the problems faced. This article addresses some of the background to this therapeutic problem and discusses some of the issues ahead.**

(*Arch Pathol Lab Med.* 2016;140:249–254; doi: 10.5858/arpa.2015-0303-SA)

PD-L1 IHC is the best currently available biomarker, although it is not optimal. Given the nature of this test and


Well, in the first place,
I'm not a natural blonde.


I can never have children.


I smoke!
I smoke all the time!


MARILYN MONROE
and her bosom companions
TONY CURTIS
JACK LEMMON
BILLY WILDER
"SOME LIKE IT HOT"
RAFT O'BRIEN BROWN


Well, in the first place,
I'm not a natural blonde.

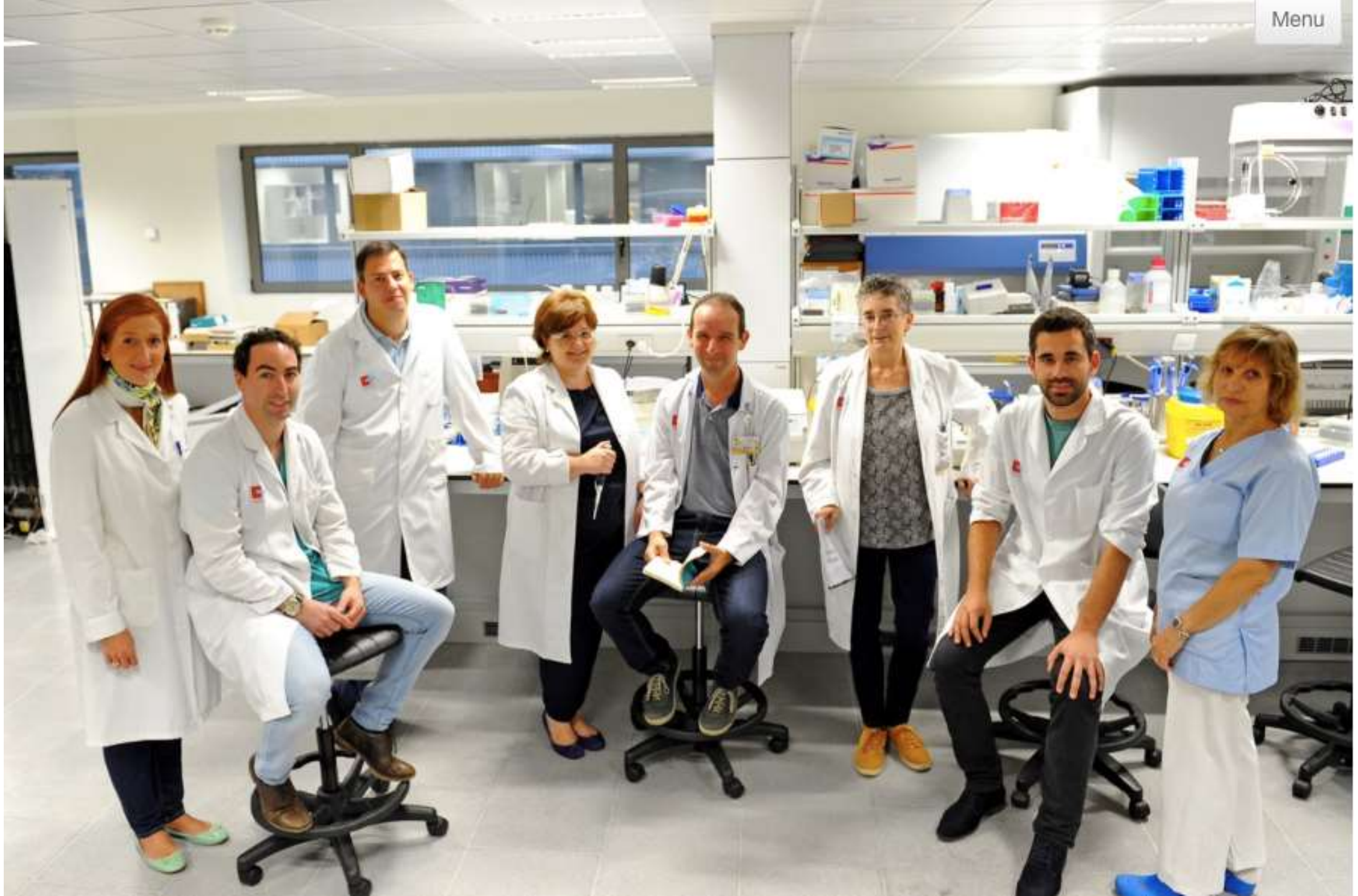

I can never have children.


I smoke!
I smoke all the time!


MARILYN MONROE
and her bosom companions
TONY CURTIS
JACK LEMMON
BILLY WILDER
"SOME LIKE IT HOT"
RAFT O'BRIEN BROWN


You don't understand, Osgood! I'm a man.


Well, nobody's perfect.


Menu

Opinion

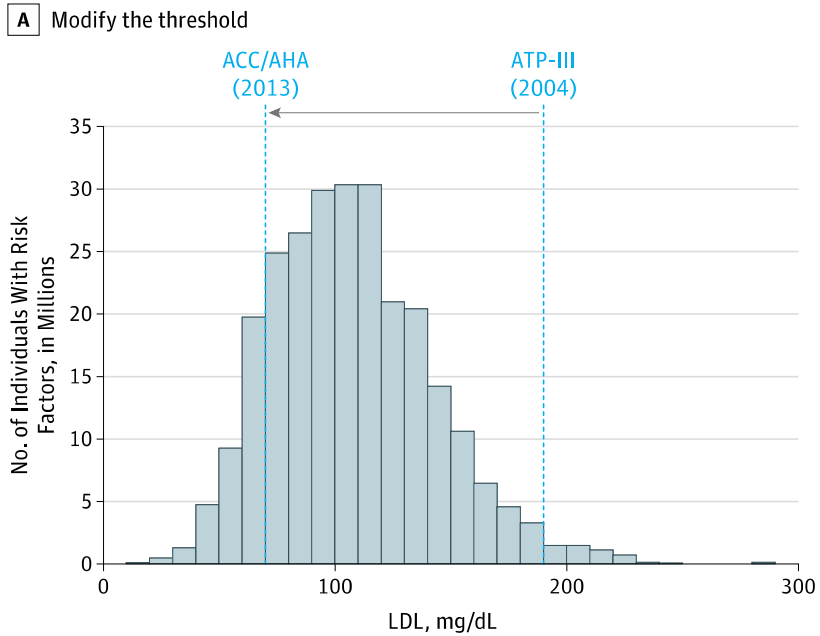
Kenneth D. Mandl, MD, MPH
Computational Health Informatics Program, Boston Children's Hospital, Boston, Massachusetts; and Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts.

VIEWPOINT

Potential Excessive Testing at Scale
Biomarkers, Genomics, and Machine Learning

JAMA Published online February 8, 2019

ments. Economic pressures, obfuscated intentionally or inadvertently, can drive increased use of biomarkers, a phenomenon that could be termed "biomarkup."



special care with regard to interpretation of biomarkers. The UK National Health Service announced a nationwide genomic medicine service, which at the outset is expected to sequence 30 000 patients per month. Geisenger an-

population. The FDA recently granted marketing authorization to 23andMe for a direct-to-consumer *BRCA1/BRCA2*

NATURE REVIEWS | CLINICAL ONCOLOGY

https://doi.org/10.1038/s41571-018-0111-2

Hyperprogressive disease: recognizing a novel pattern to improve patient management

Stéphane Champiat[1,2], Roberto Ferrara[3], Christophe Massard[1], Benjamin Besse[2,3], Aurélien Marabelle[1,4], Jean-Charles Soria[1,2] and Charles Ferté[1]**

- The evaluation of tumour biopsy samples obtained at the time of tumour growth acceleration will be key to evaluating the biological mechanisms underlying hyperprogressive disease, to interrogate the immunological nature of this phenomenon and to identify the best therapeutic strategies.

Study	Reported frequency for hyperprogressive disease	Tumour types
Champiat et al.	9% (12/131)	• Melanoma (9%; 4/45) • Urothelial carcinoma (25%; 2/8) • Colorectal carcinoma (12%; 1/8) • Lymphoma (14%; 1/7) • Ovarian carcinoma (40%; 2/5) • Cholangiocarcinoma (50%; 1/2) • Uveal melanoma (50%; 1/2)
Kato et al.	6% (6/102)	• NSCLC (8%; 3/38) • Urothelial carcinoma (ND; 1/ND) • Triple negative breast cancer (ND; 1/ND) • Endometrial carcinoma (ND; 1/ND)
Saâda-Bouzid et al.	29% (10/34)	HNSCC (all patients)
Ferrara et al.	14% (56/406)	NSCLC (all patients)

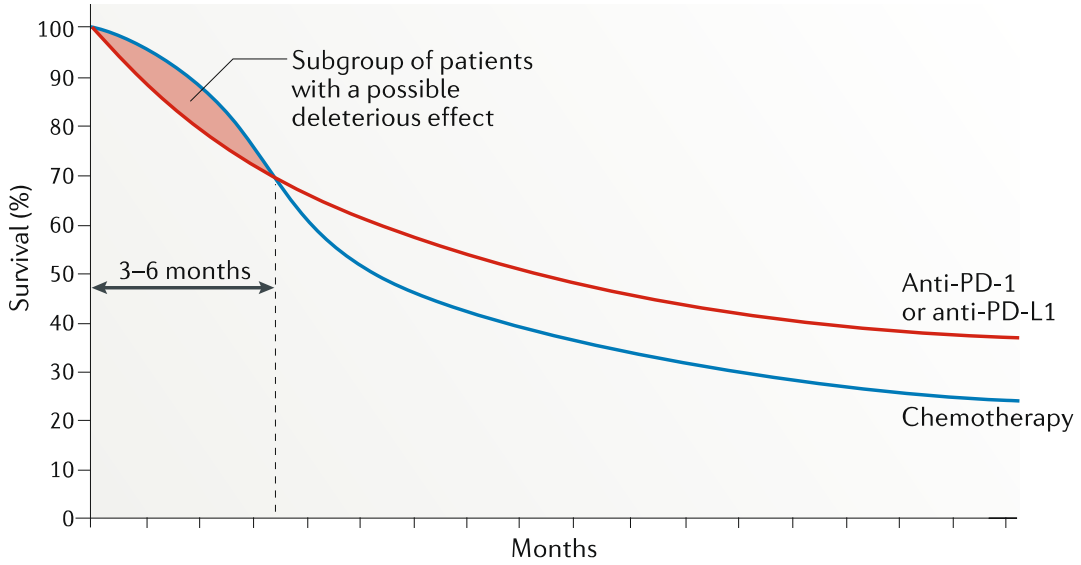


Fig. 2 | **Crossing survival curves in clinical trials.** In phase III trials comparing immune-checkpoint inhibitors with cytotoxic agents, a phenomenon can be observed whereby survival is lower in the immunotherapy arm in the early stages of the trial (initial 3–6 months after starting treatment).

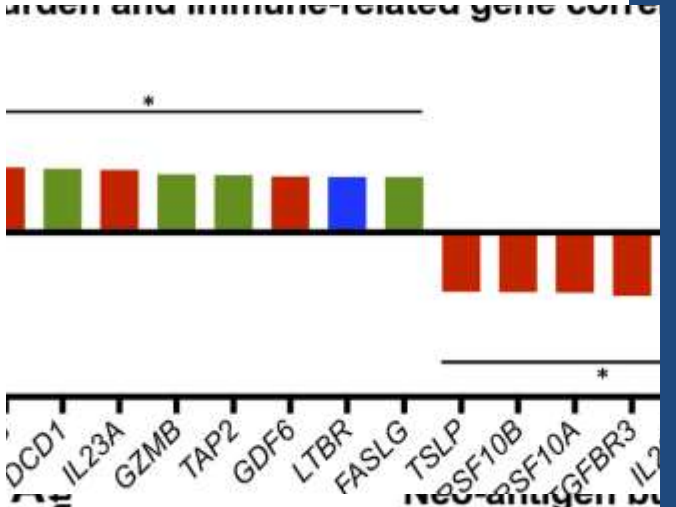
www.impactjournals.com/ oncotarget/ Oncotarget, 2018, Vol. 9, (No. 8), pp: 7949-7960

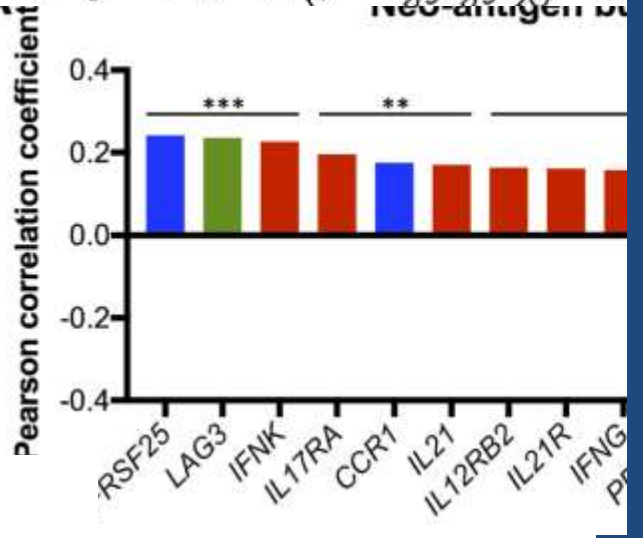
Research Paper

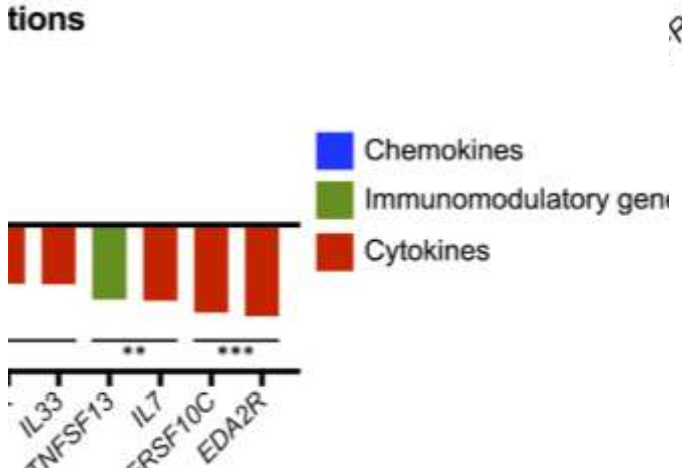
Mutations in DNA repair genes are associated with increased neo-antigen load and activated T cell infiltration in lung adenocarcinoma

Young Kwang Chae[1,2,*], Jonathan F. Anker[1,*], Preeti Bais[3], Sandeep Namburi[3], Francis J. Giles[1,2] and Jeffrey H. Chuang[3,4]

- Pacientes con Adenocarcinomas pulmonares
- Relación TMB con PD1 y PD-L1
- Tendencia al mejor pronóstico en tumores con alta TMB







PROTEÍNAS REPARADORAS

- En 2017 se aprueba el uso de Pembrolizumab para el tratamiento de tumores sólidos no resecables o metastásicos con inestabilidad de microsatélites o déficit de proteínas reparadoras de daño en ADN
- Esto se basa en defectos genéticos más que en el tejido de origen del tumor
- Es preciso desarrollar otros test de susceptibilidad y respuesta

FORMOL Y ADN

- El formol es un agente desnaturalizante irreversible porque induce enlaces covalentes con los grupos NH2 de las bases e impide su apareamiento
- El ADN desnaturalizado absorbe más luz a 260nm (hipercromicidad)
  - Muchas muestras extraídas de parafina tienen cocientes A260/A280 buenos pero no amplifican adecuadamente
  - Indica mala fijación y enlaces estables