MEDICINA DE PRECISIÓN EN EL PACIENTE ONCOLÓGICO

I[er] SIMPOSIO INTERNACIONAL de acceso a la inovación

Medicina de precisión en oncología: una necesidad estratégica.

Tania Fleitas Kanonnikoff

Noviembre 2018

VNIVERSITAT DE VALÈNCIA

Fundación Investigación Clínico de Valencia

incliva

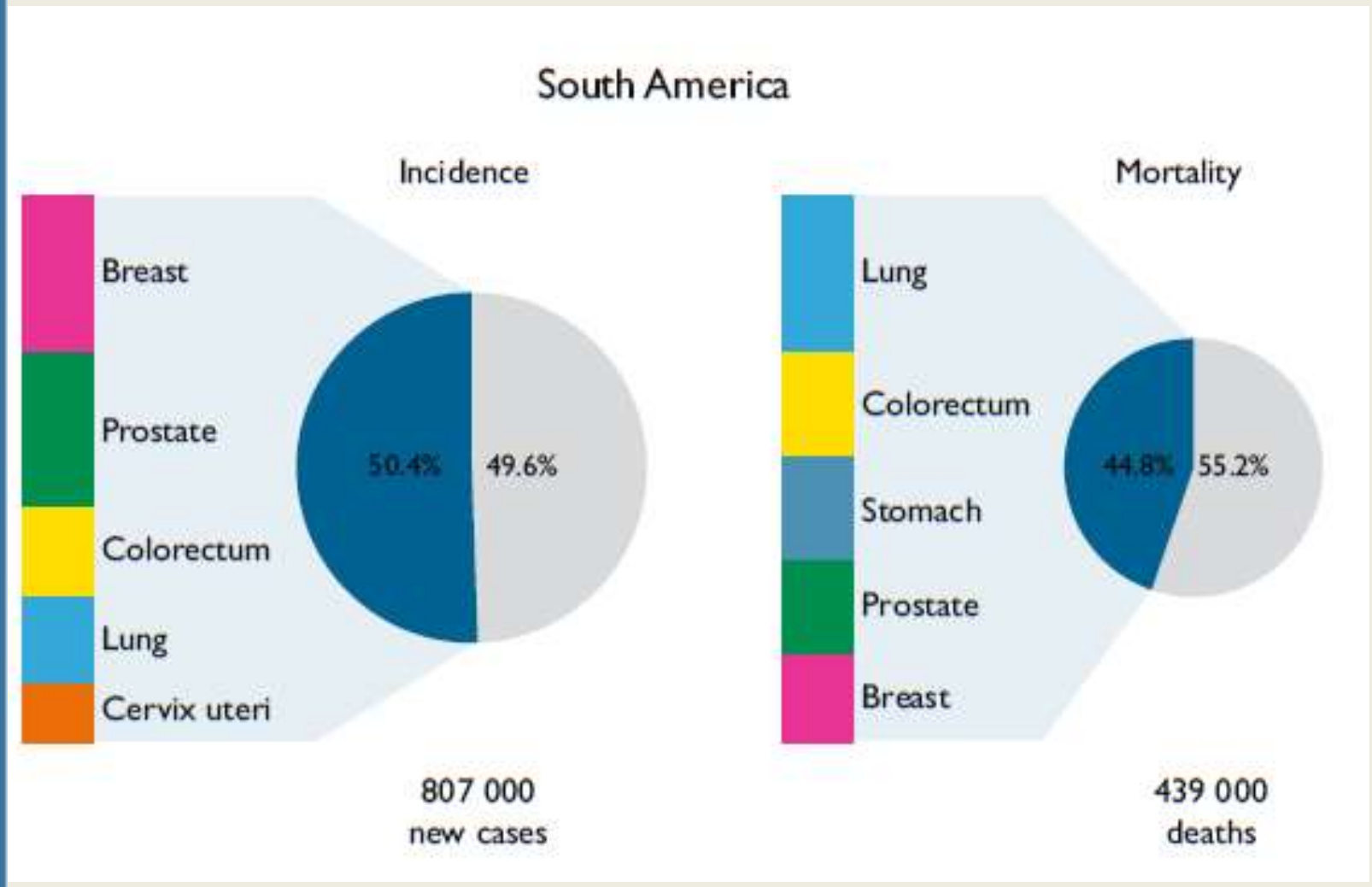
Situación del cáncer en LATAM

En 2012, se estimaron casi 1.1 millones de nuevos casos de cáncer en la región de LATAM correspondiendo a un 7,8% de los casos de cáncer en todo el mundo.

Tres cuartos de los nuevos casos se vieron en la región de América del Sur.

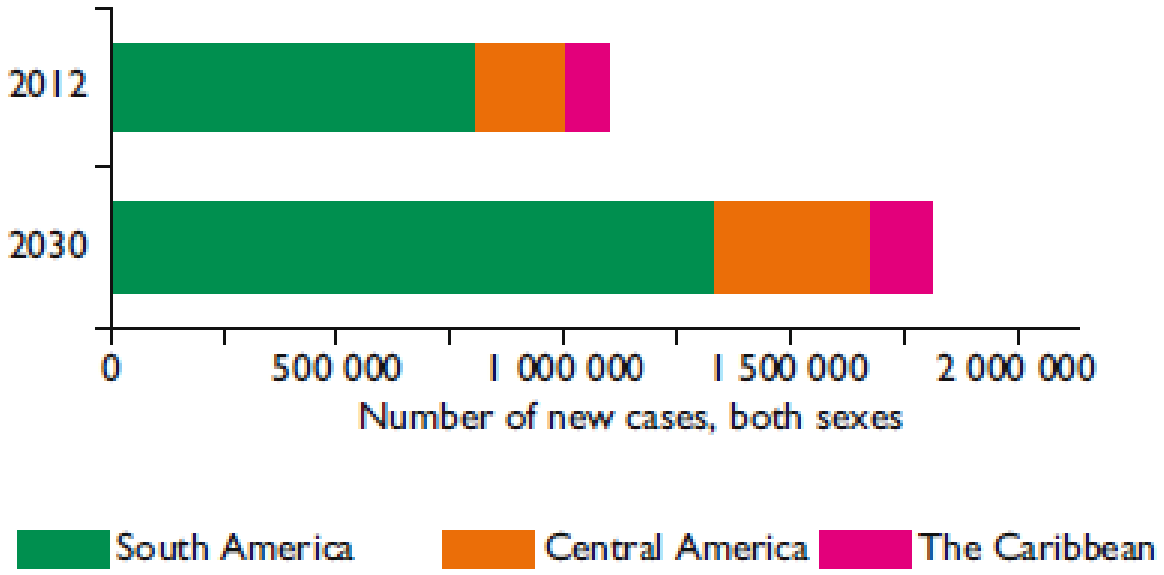
Piñeros et al. **Cancer patterns, trends and projections in Latin America and the Caribbean: a global context.**
Salud Publica Mex 2016;58:104-117.

Situación del cáncer en LATAM



Piñeros et al. **Cancer patterns, trends and projections in Latin America and the Caribbean: a global context.**
Salud Publica Mex 2016;58:104-117.

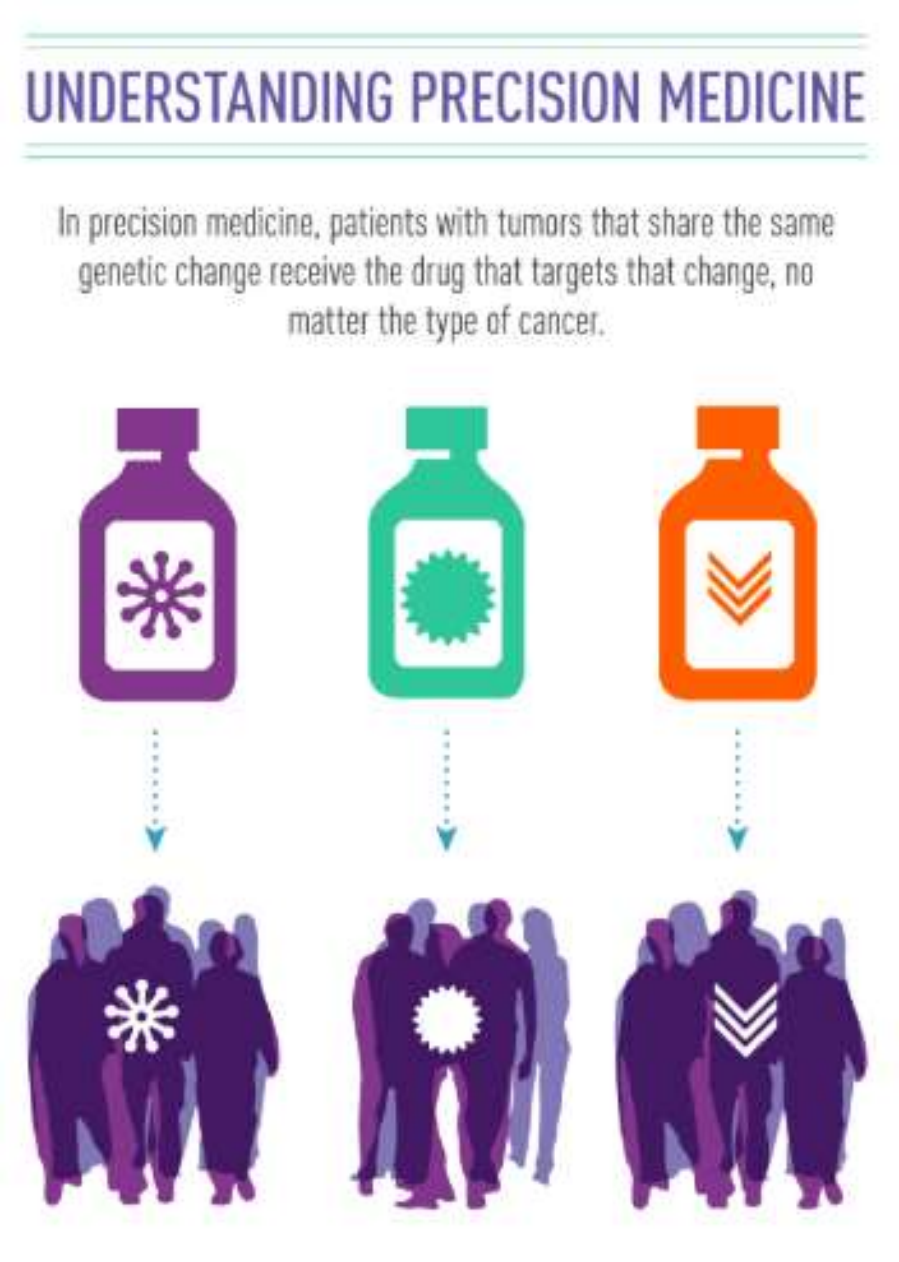
Situación del cáncer en LATAM



Source: Global 2012

FIGURE 10. PROJECTIONS OF THE CANCER INCIDENCE BURDEN IN LAC BY SUB-REGION 2012 AND 2030

Piñeros et al. **Cancer patterns, trends and projections in Latin America and the Caribbean: a global context.**
Salud Publica Mex 2016;58:104-117.



National Cancer Institute

EVOLUCION DE LOS ESTUDIOS EPIDEMIOLOGICOS

I[er] SIMPOSIO INTERNACIONAL
de acceso a la inovación

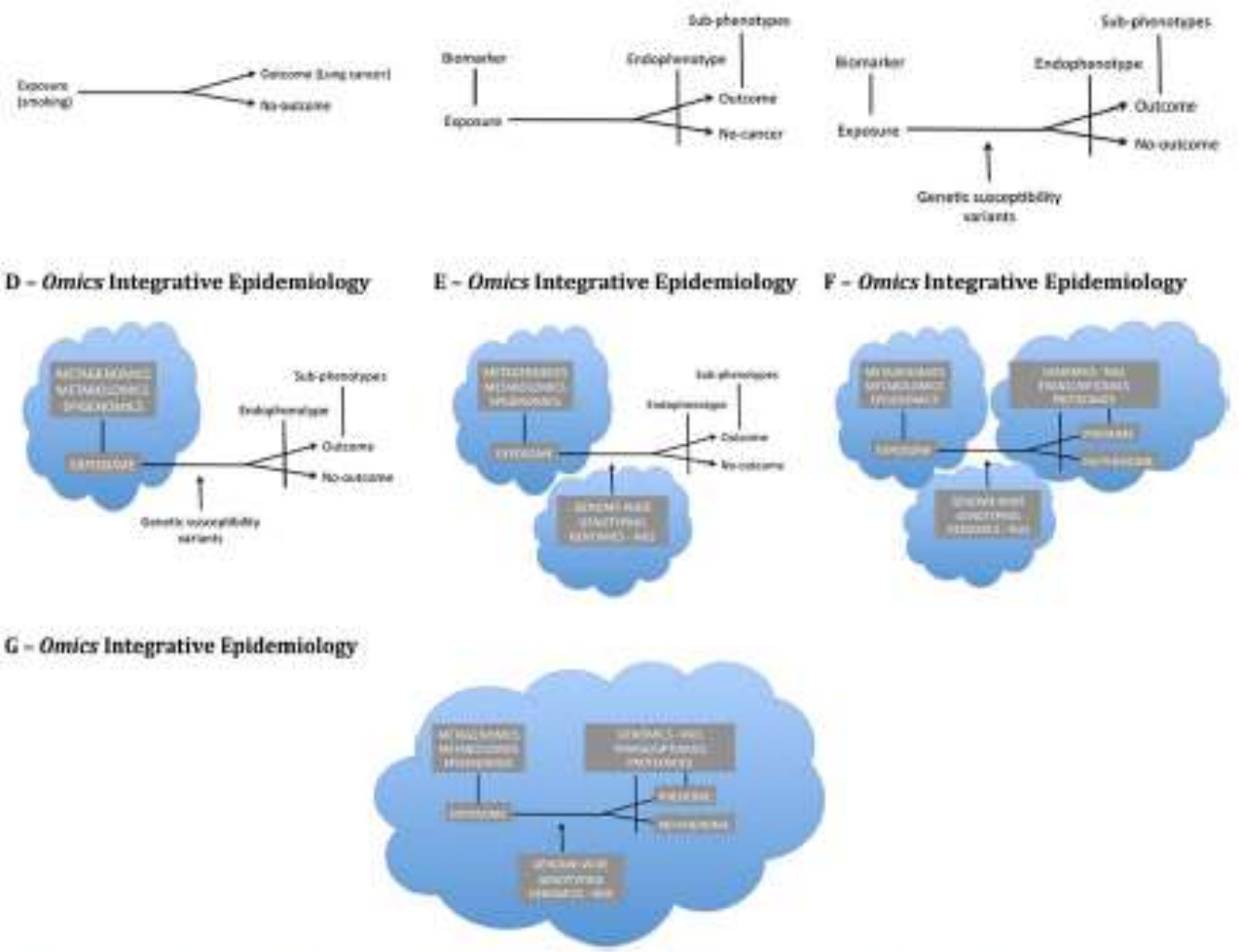


FIGURE 1 Conceptual association models applied in classical (A), molecular (B), genetic (C), and *omics* integrative epidemiology (D–G)

ESTRATEGIAS DE “PREVENCIÓN PERSONALIZADA

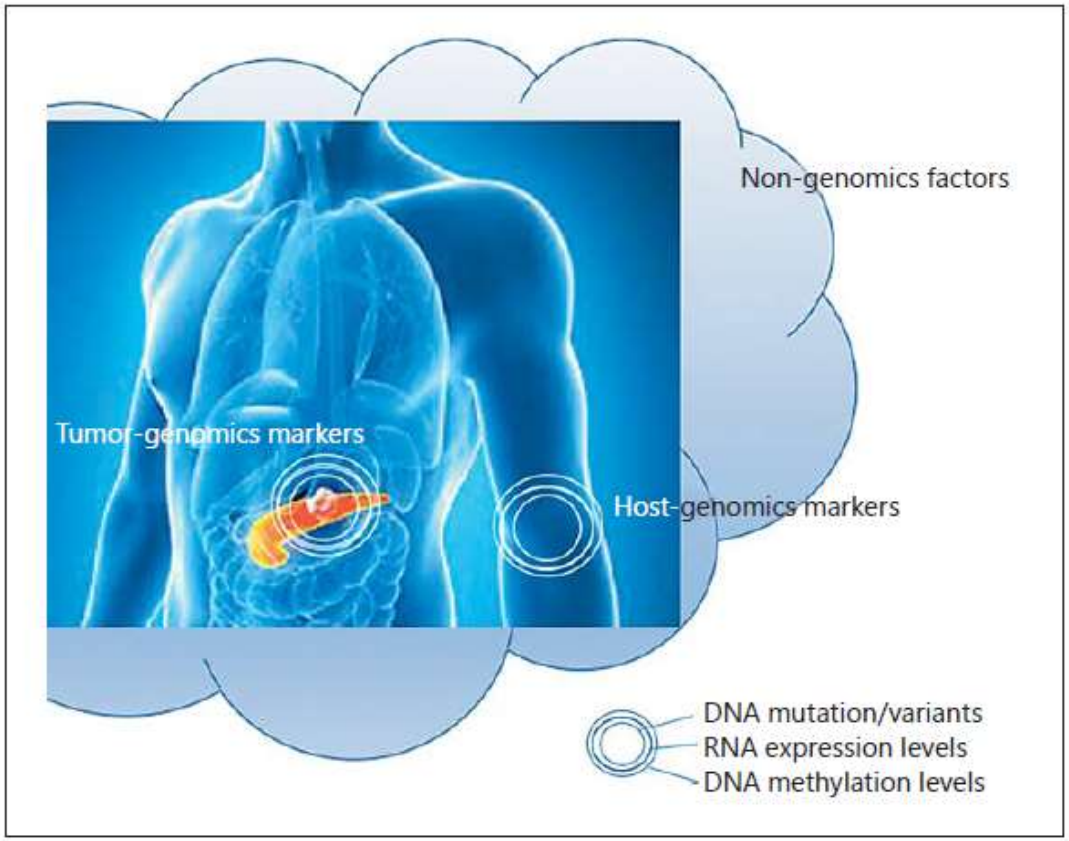
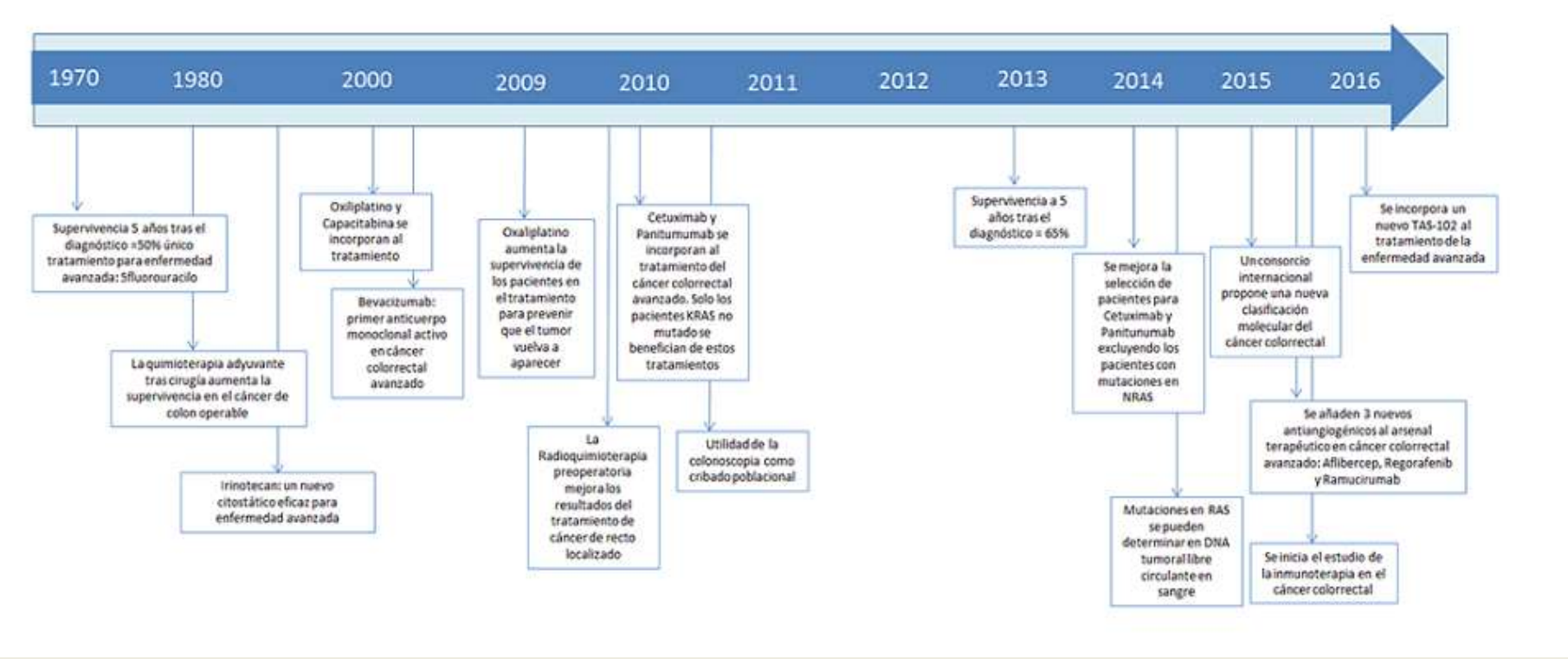
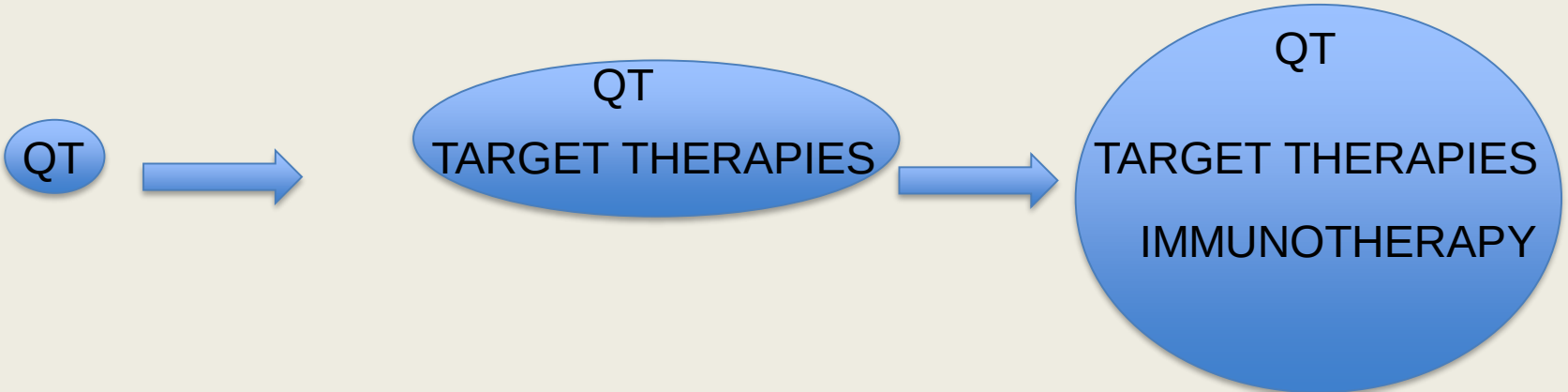


Fig. 1. The three main components in the personalized prevention scenario: the non-genomics factors, and the multilayer genomics markers at the host and tumor levels. Modified from Sebastian Kaulitzki, 3D-rendered illustration of the male pancreas; www.shutterstock.com.

EVOLUCION HISTORICA DEL CANCER COLORRECTAL



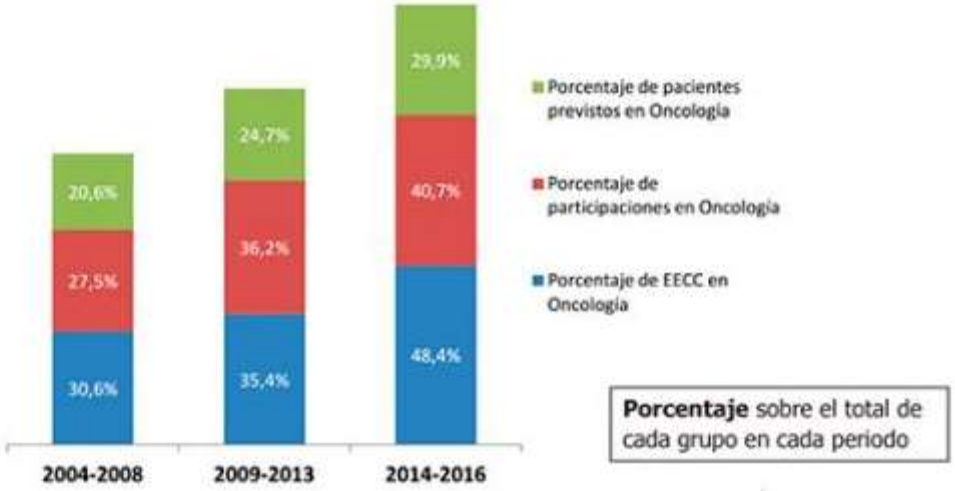


INNOVACION EN ONCOLOGÍA

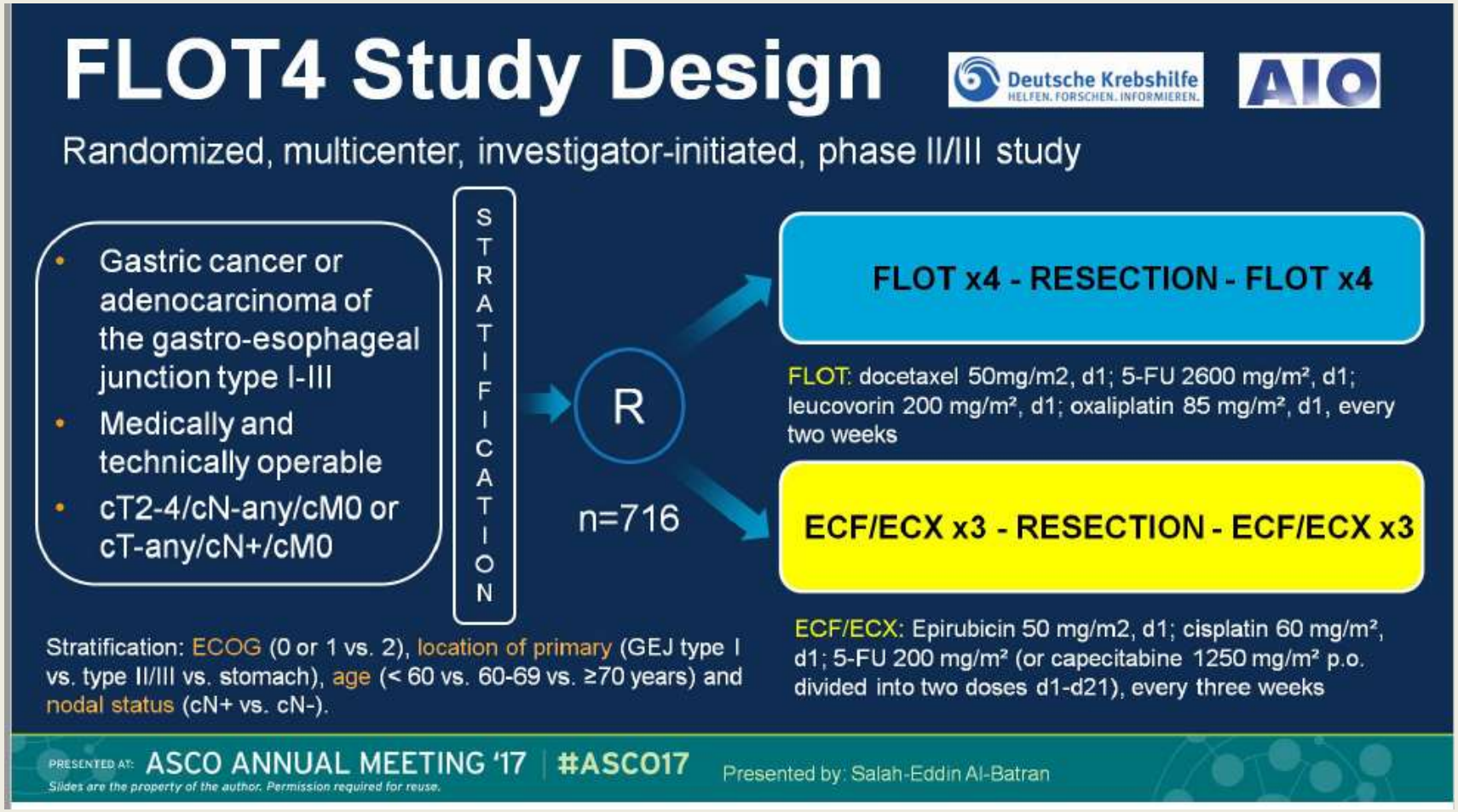
La oncología, protagonista de uno de cada tres ensayos clínicos en España

Ensayos clínicos en oncología en España (Proyecto Best)

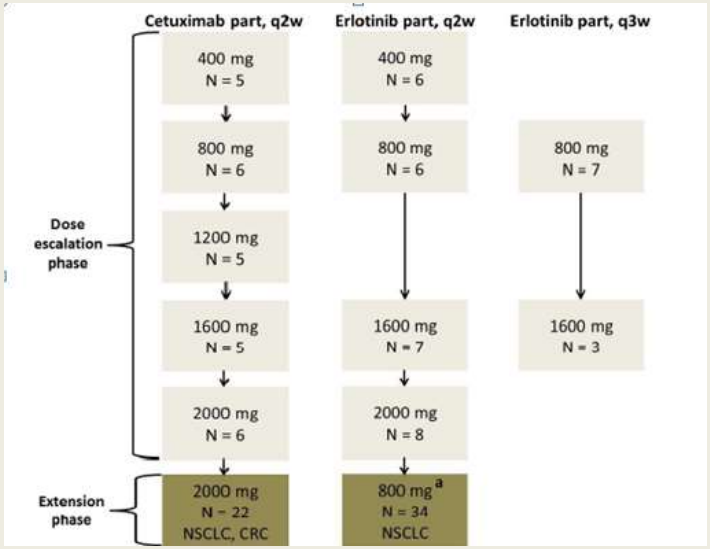
Evolución del porcentaje de los ensayos clínicos en oncología y de las participaciones de los hospitales y los pacientes en ellos, respecto del total de ensayos clínicos del conjunto de áreas terapéuticas. Periodos 2004-2008, 2009-2013 y 2014-Primer semestre 2016. Datos del Proyecto BEST (industria farmacéutica).



DISEÑO DE ENSAYO CLÍNICO FASE 3



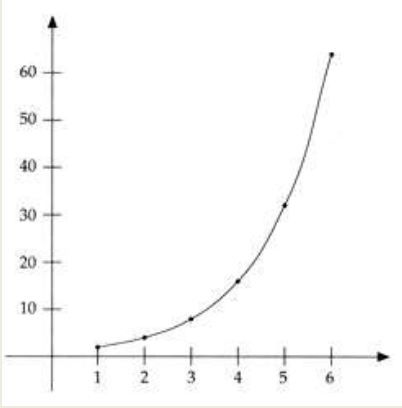
DISEÑO DE ENSAYO CLÍNICO FASE 1



Unidad de fases 1 -Incliva

Clin Cancer Res. 2017 Sep 15;23(18):5406-5415.

CÁNCER DE VEJIGA



Clinical Trials

- **GO27831 (Phase I)** atezolizumab
- **Checkmate 032 (Phase I)** 2nd line nivolumab
- **IMvigor 210 Cohort 2 (Phase II)** 2nd line atezolizumab
- **Keynote 052 (Phase II)** 1st line pembrolizumab
- **Checkmate 275 (Phase II)** 2nd line nivolumab
- **MEDI4736-1108 (Phase I/II)** 2nd line durvalumab
- **Keynote 012 (Phase IB)** 2nd line pembrolizumab
- **IMvigor 210 Cohort 1: (Phase II)** 1st line atezolizumab
- **JAVELIN (Phase I)** 2nd line avelumab
- **Keynote 045 (Phase III)** study of 2nd line pembrolizumab

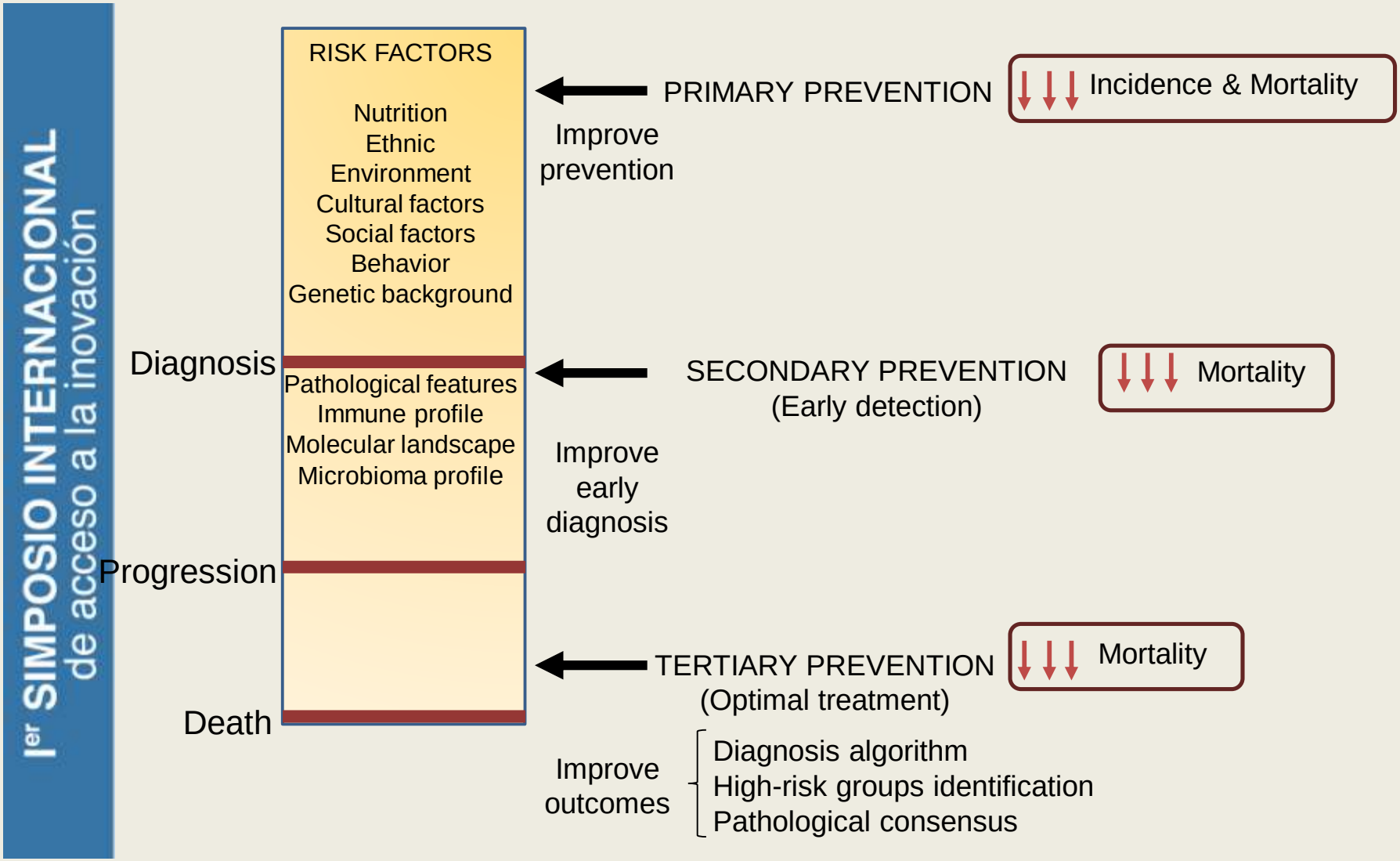
2015 2016 2017

FDA APPROVALS

- **5/18/16: atezolizumab** approved for 2nd line therapy of mUC
- **2/2/17: nivolumab** approved for 2nd line therapy of mUC
- **4/18/17: atezolizumab** accelerated approval for 1st line (Cis-ineligible patients)
- **5/1/17: durvalumab** accelerated approval for 2nd line therapy of mUC
- **5/8/17: avelumab** accelerated approval for 2nd line therapy of mUC.
- **5/8/17: pembrolizumab** approval for 2nd line therapy of mUC
- **5/18/17: pembrolizumab** accelerated approval for 1st line (Cis-ineligible patients)

Journal for ImmunoTherapy of Cancer (2017) 5:94

AIMS: integral intervention against Cancer



Adapted from Nuria Malats

Strategies for eliminating death from gastric cancer in Japan

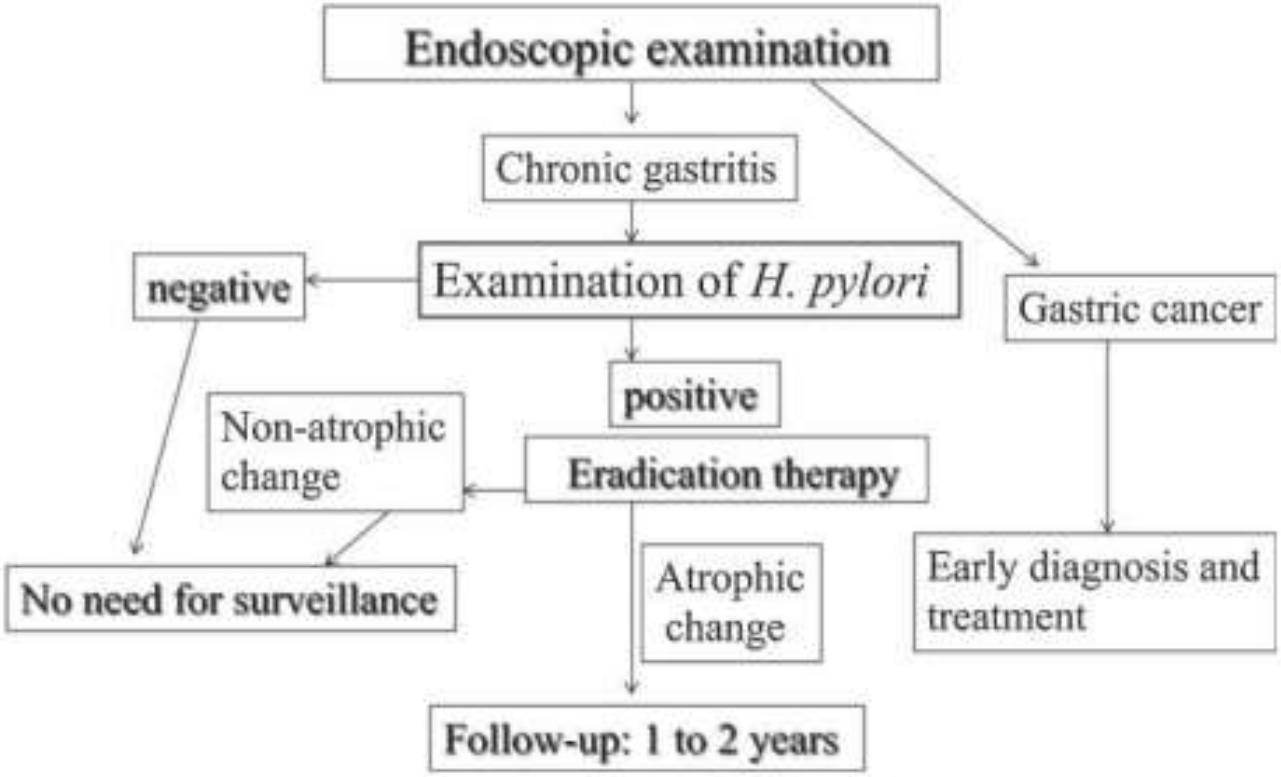


Fig. 3. Strategy for elimination of gastric cancer deaths in Japan.[5)]

Proc. Jpn. Acad., Ser. B 90 (2014)

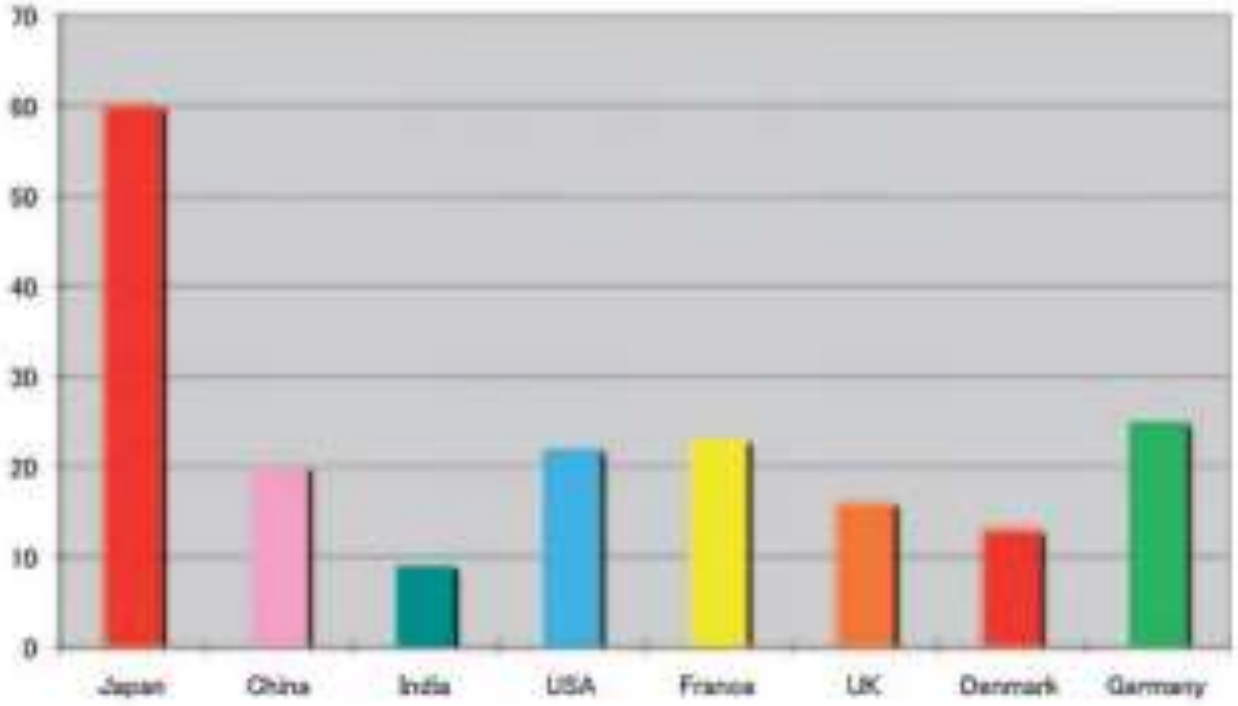


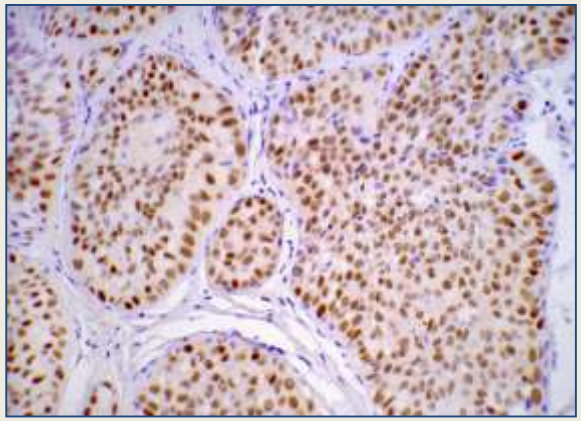
Fig. 1. Five years survival rates (%) of gastric cancer in various countries.

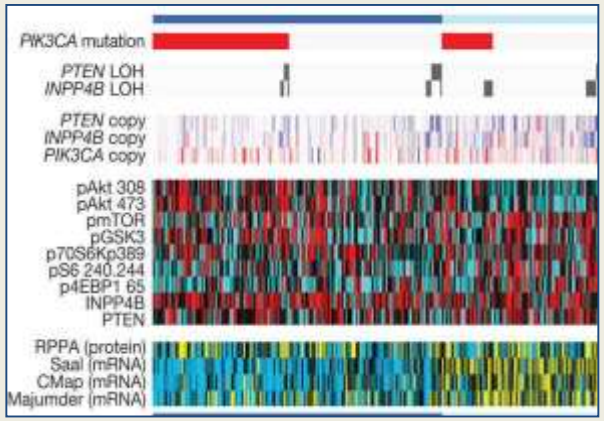
Proc. Jpn. Acad., Ser. B 90 (2014)

DIAGNOSIS EVOLUTION IN CANCER

Currently

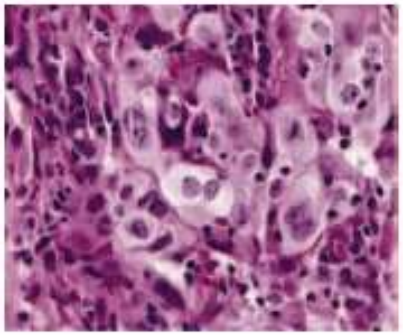
Clinical diagnosis → Pathology diagnosis → Molecular diagnosis → Personalized Oncology

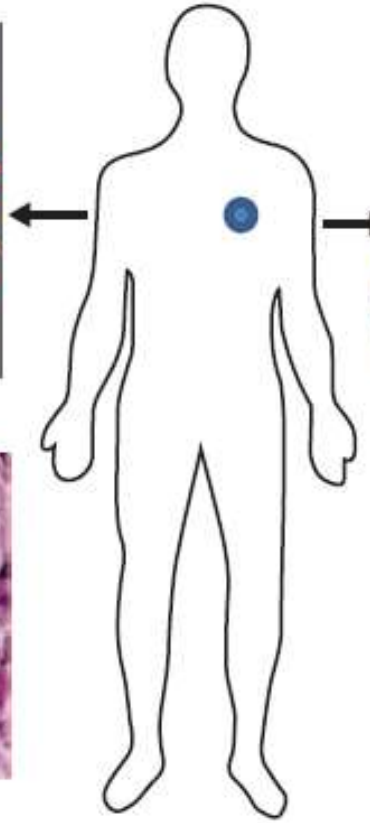




Clinical approach → Pathology approach → Molecular approach

GENOMICS DRIVEN CANCER MEDICINE

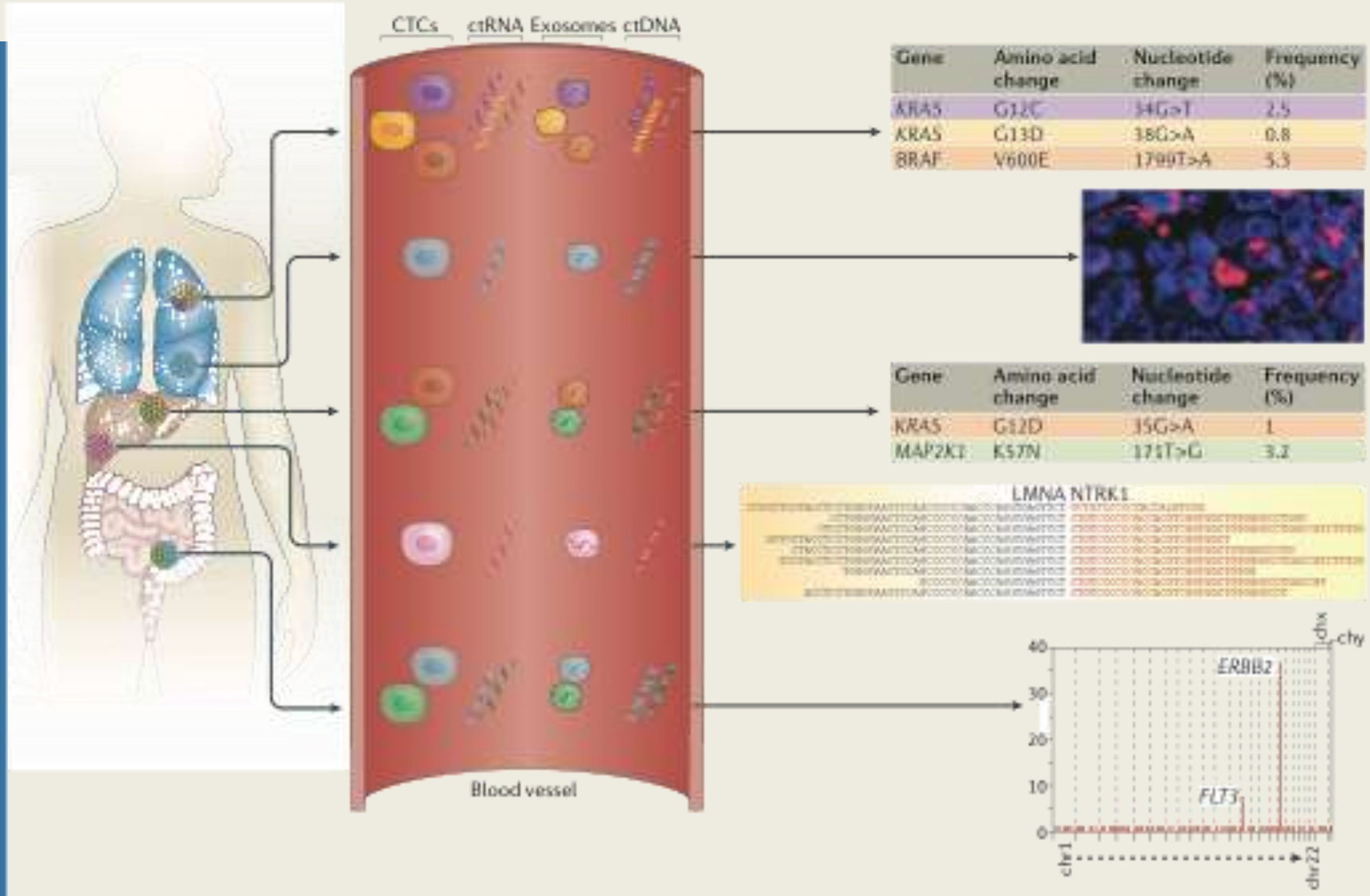




Category of Alteration
Actionable in principle Tier 1: FDA-approved drugs Tier 2: Drugs in clinical trials
Prognostic
Variants of uncertain significance (VUS)

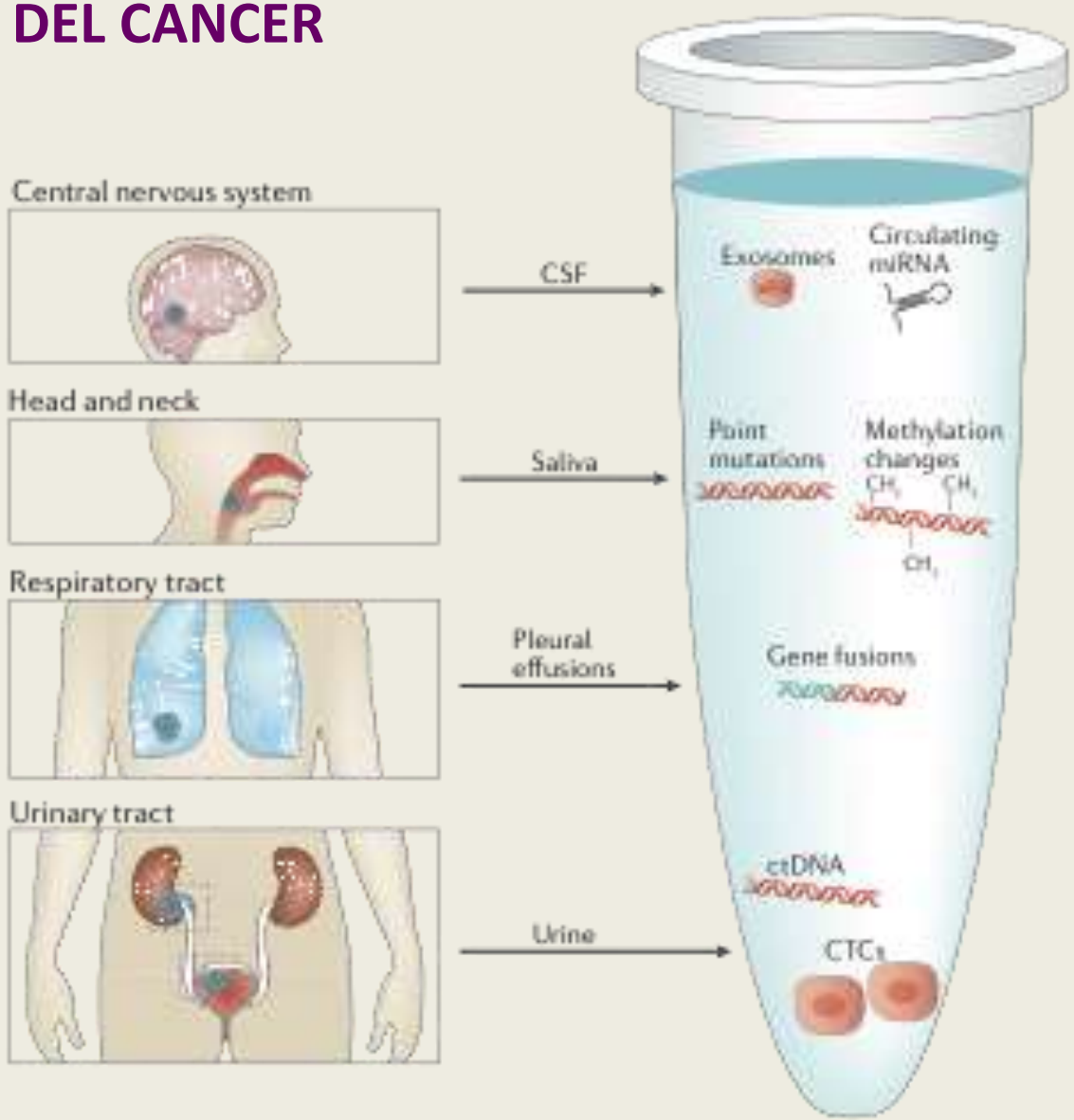
Garraway LA, Verwey J, Ballman K. J Clin Oncol 2013

LAS BIOPSIAS LIQUIDAS CAPTAN LA HETEROGENEIDAD MOLECULAR DEL CANCER



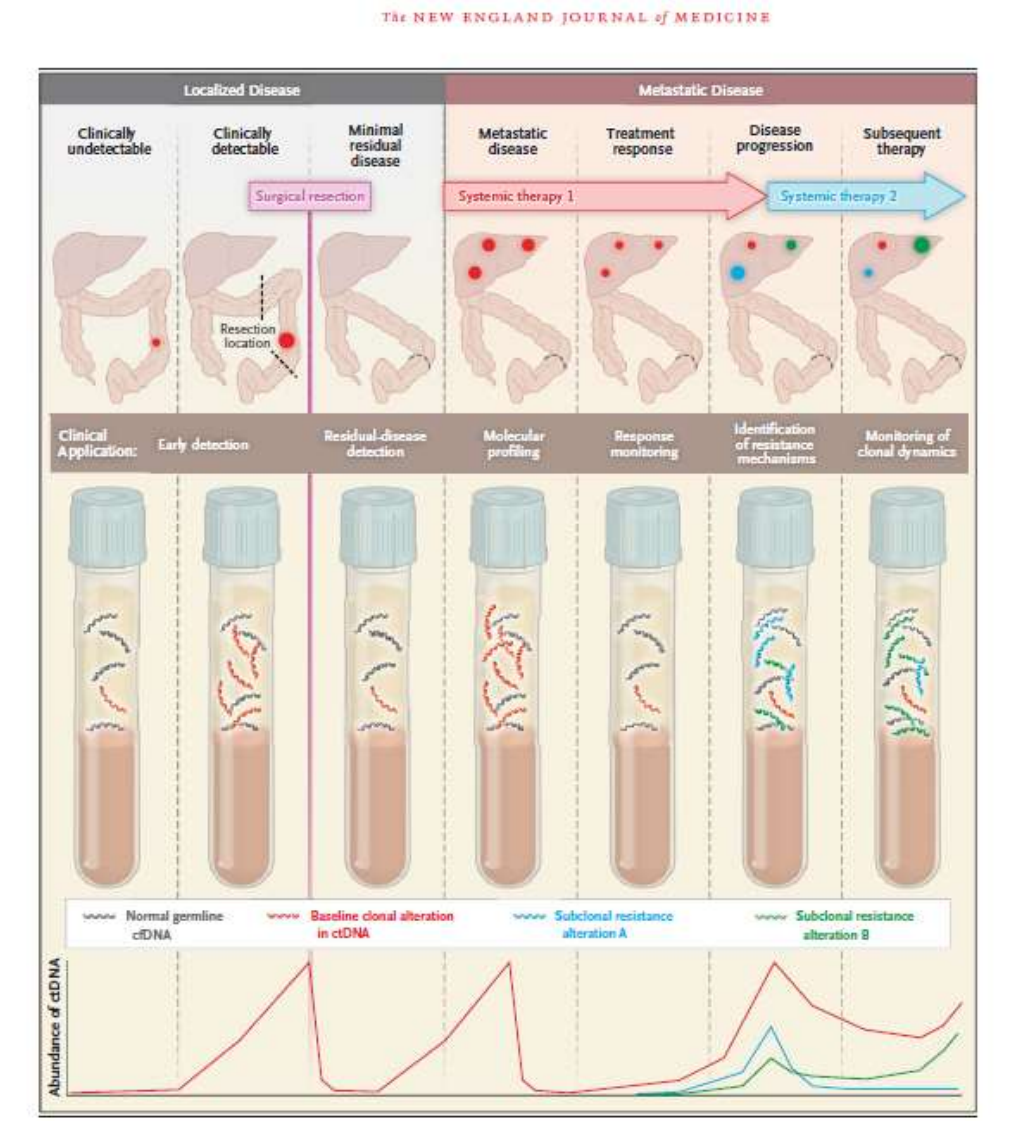
Siravegna G, et al. Nat Rev Clin Oncol 2017; ahead of print

FLUIDOS CORPORALES COMO FUENTE DE INFORMACIÓN MOLECULAR DEL CANCER



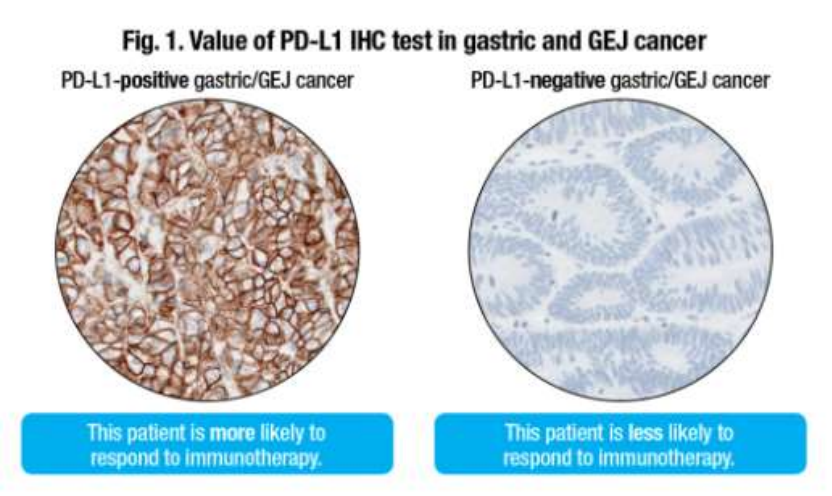
Siravegna G, et al. Nat Rev Clin Oncol 2017; ahead of print

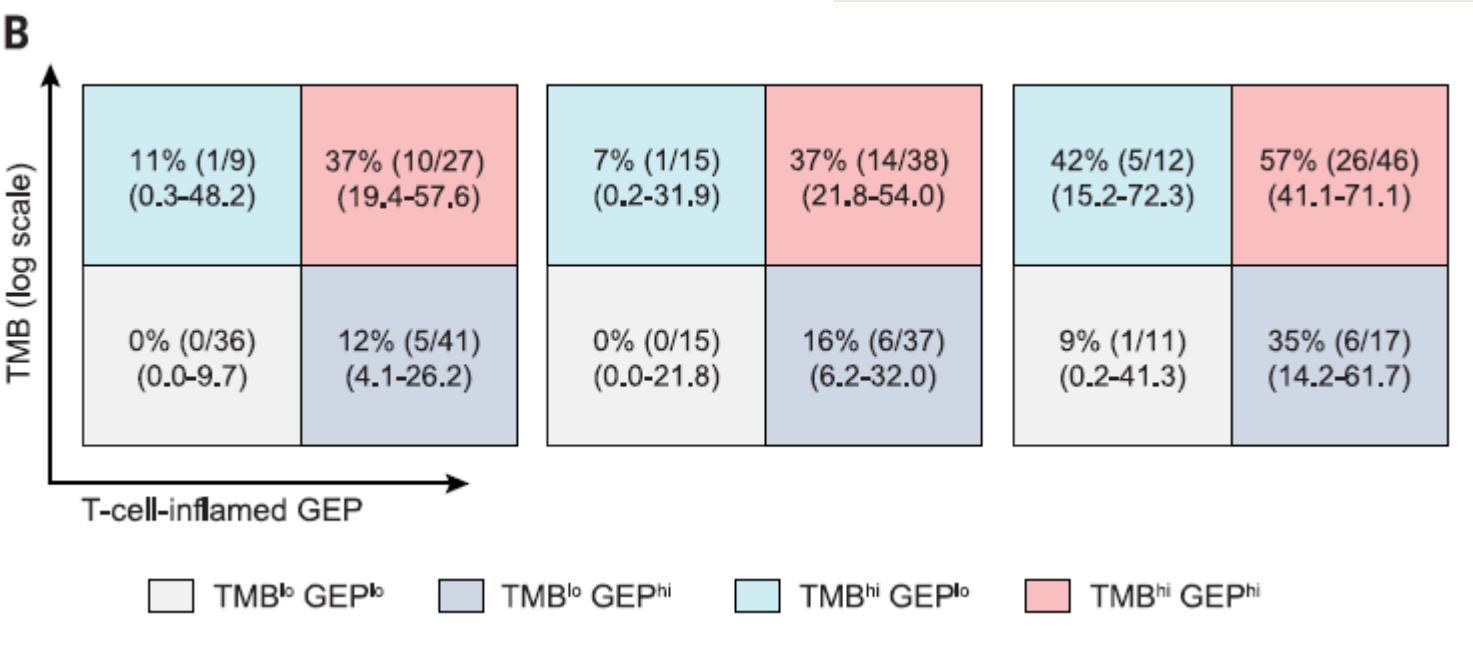
LAS BIOPSIAS LIQUIDAS PERMITEN MONITORIZAR LA EVOLUCIÓN CLONAL DEL CANCER



Corcoran,R.NEJM, 2018

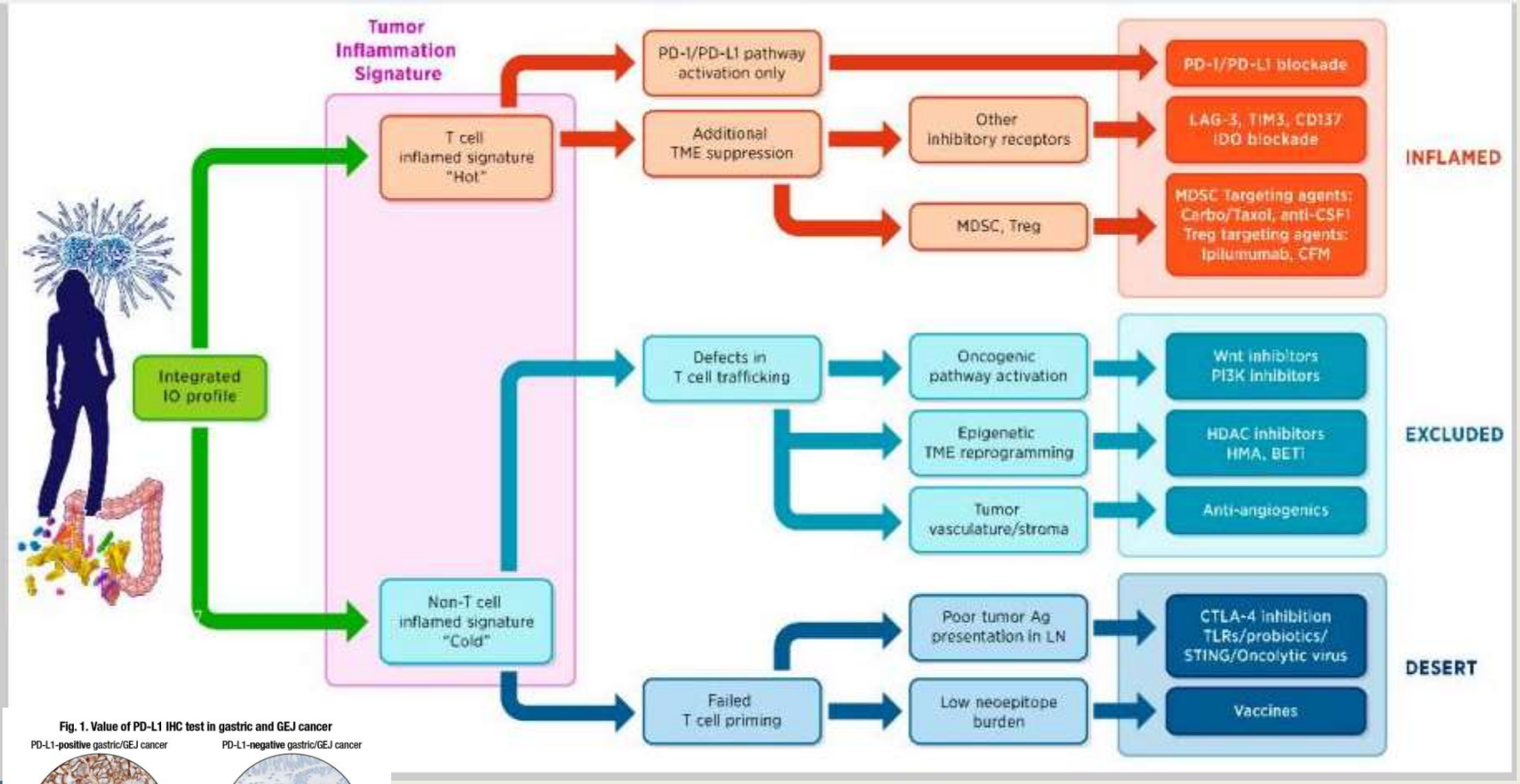
EVOLUCIÓN DE LOS BIOMARCADORES EN INMUNOTERAPIA

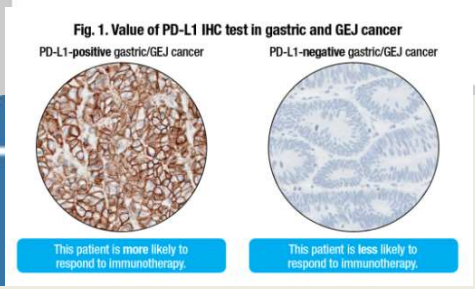




Cristescu 2018

EVOLUCIÓN DE LOS BIOMARCADORES EN INMUNOTERAPIA





PDL1 expression

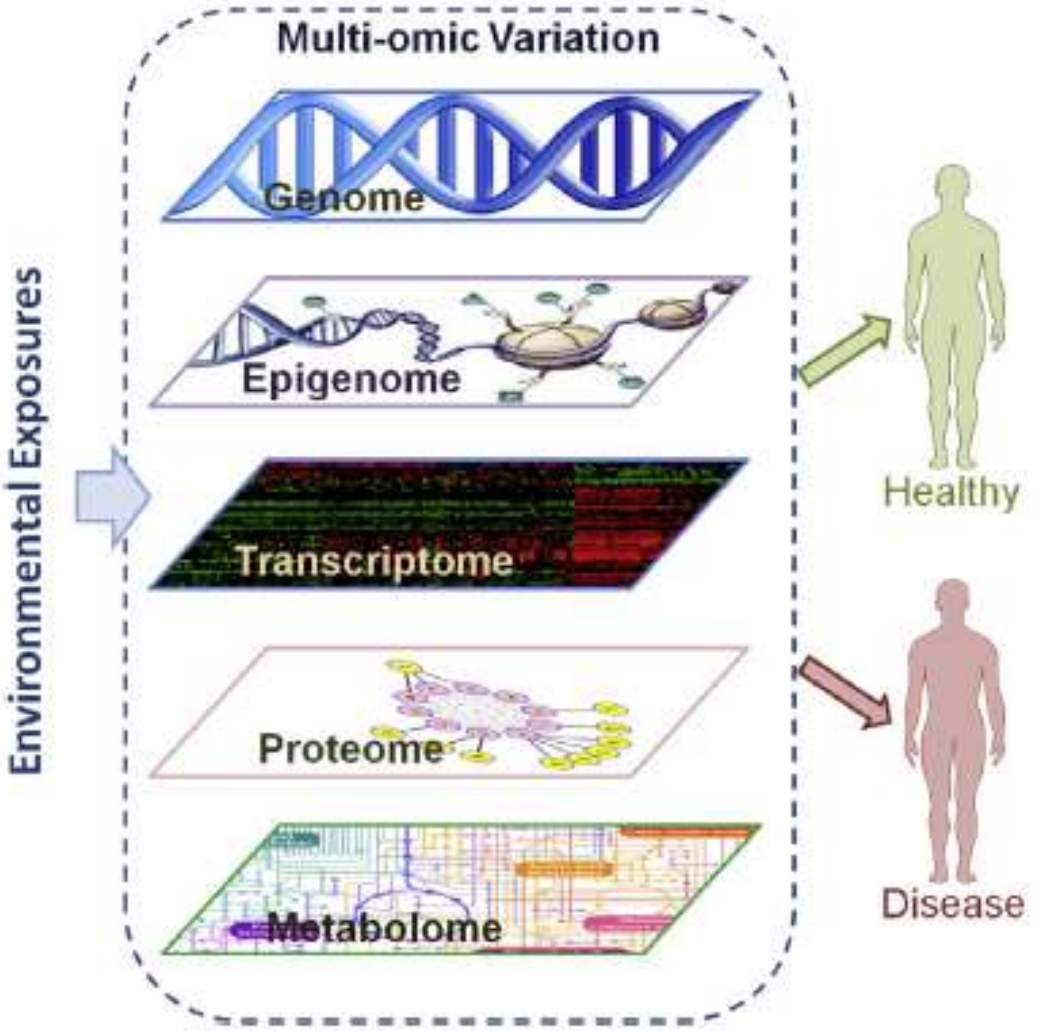
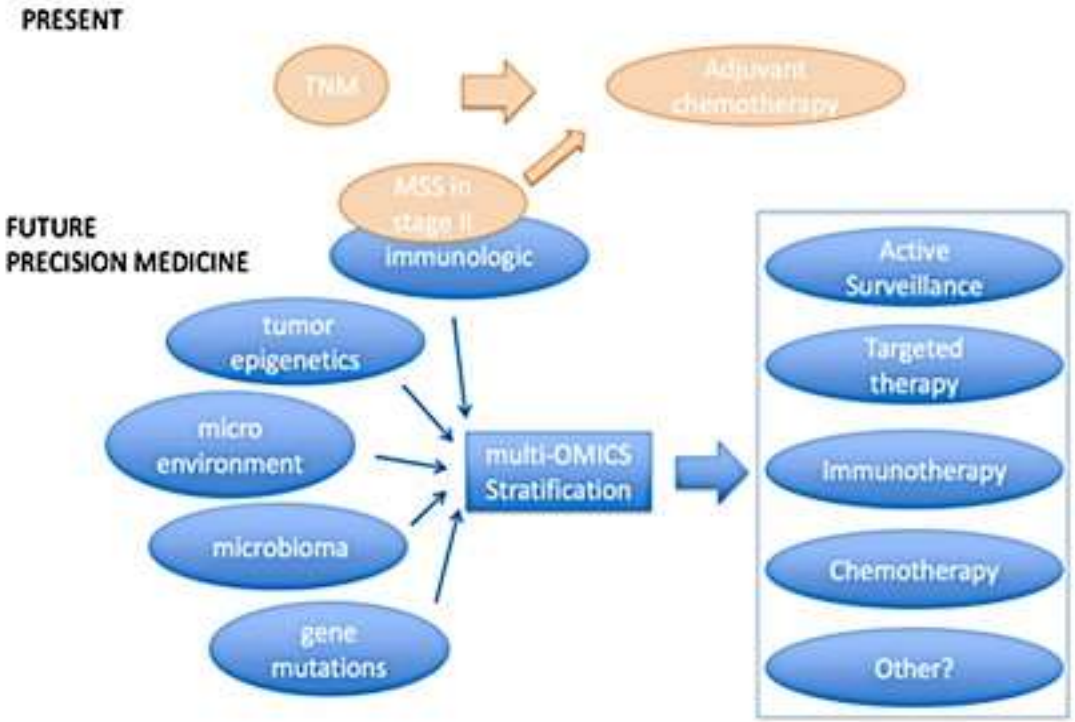


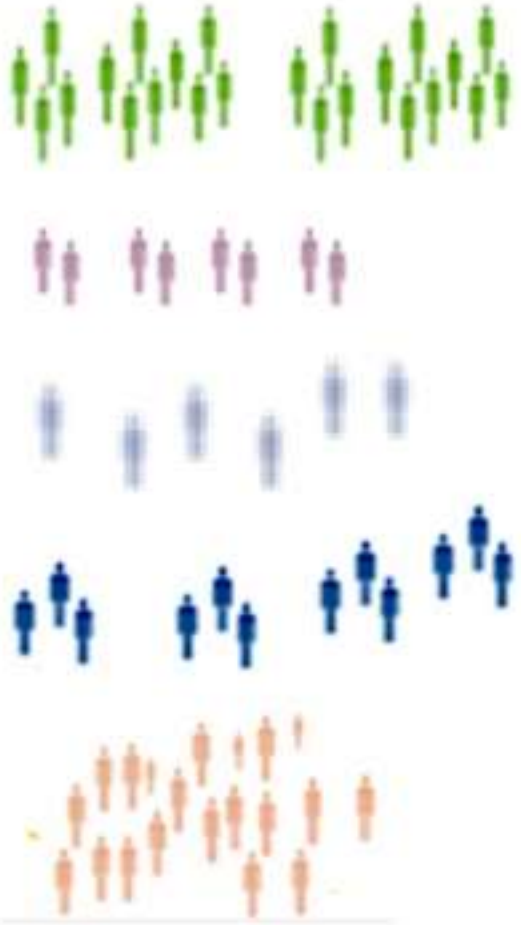
Figure 1 Conceptual model of multi-omics and human disease.

Advances in Genetics, Volume 93, 2016, Pages 147-190

How to select better patients for adjuvant treatment?

STAGE II and III





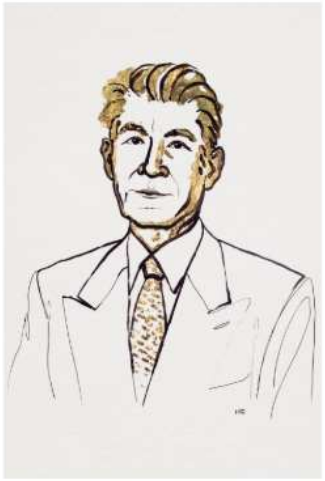
Presented by Clara Montagut. ESMO congress 2018

The Nobel Prize in Physiology or Medicine 2018

Ill. Niklas Elmehed. © Nobel Media

James P. Allison

Prize share: 1/2

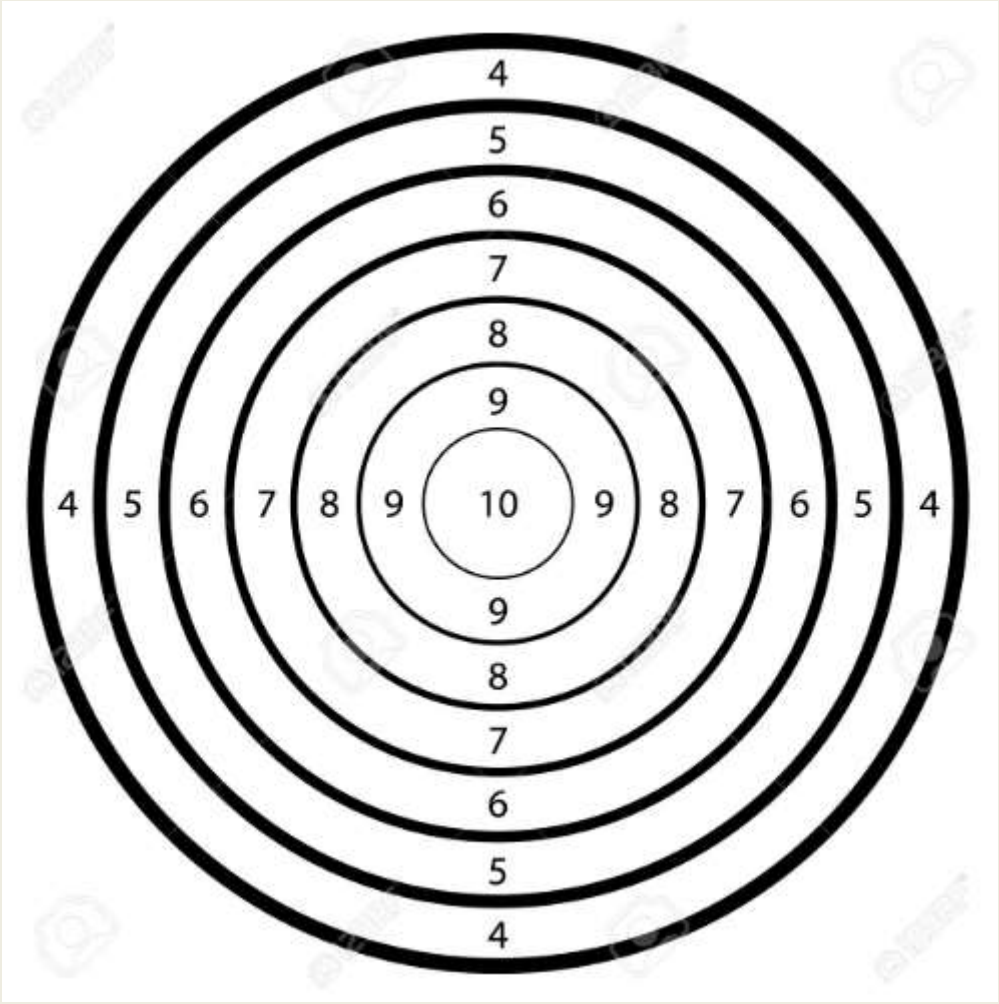


Ill. Niklas Elmehed. © Nobel Media

Tasuku Honjo

Prize share: 1/2

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation."



De la teoría a la práctica

EVOLUCIÓN DEL TRATAMIENTO DEL MELANOMA

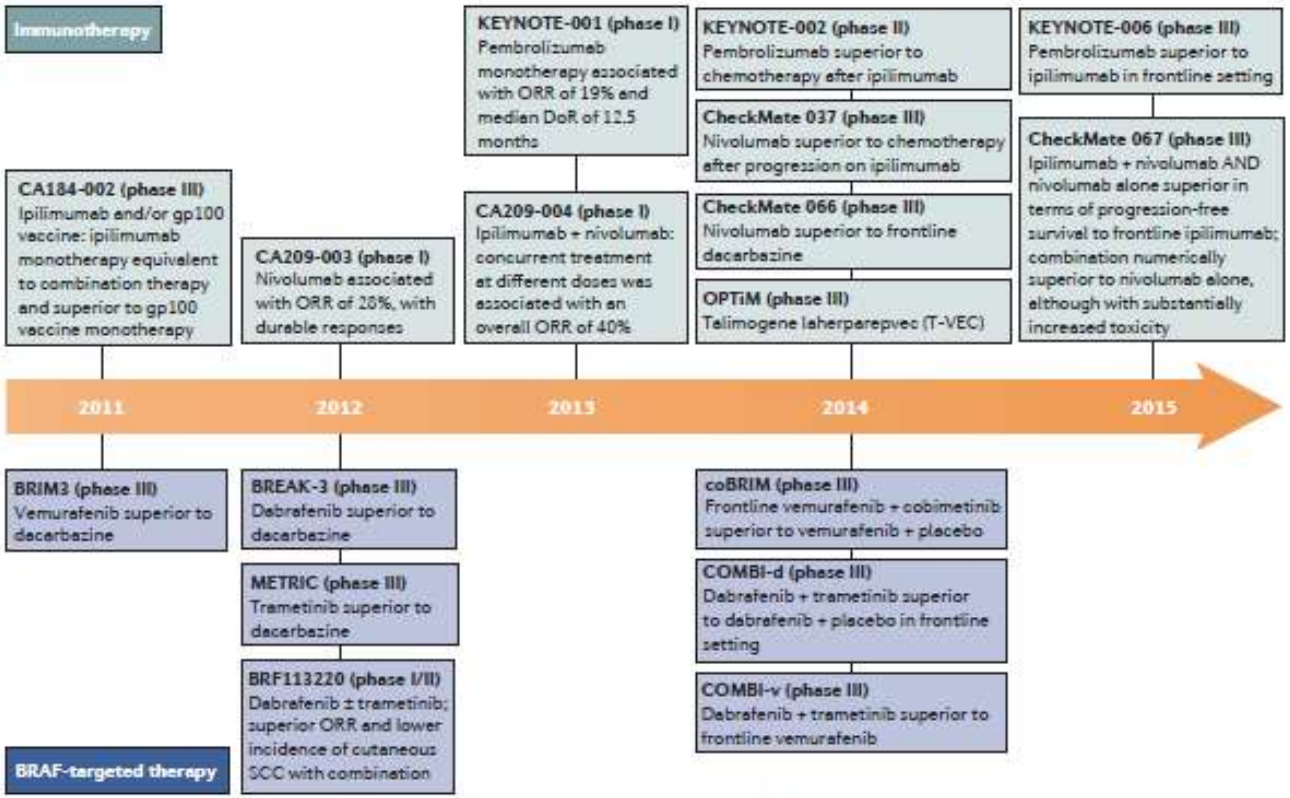


Figure 1 | **Timeline charting the seminal, practice-changing clinical trials in advanced-stage melanoma.** Over the past decade, rapid improvements in efficacy of melanoma therapeutics have been made. Since 2011, all reported large, randomized, phase III studies conducted in patients with advanced-stage disease have met their primary end points, ultimately providing a range of treatment options. Studies of immunotherapies have included ipilimumab, pembrolizumab, nivolumab, and the ipilimumab plus nivolumab combination. At the same time, monotherapy with BRAF (vemurafenib and dabrafenib) and MEK (trametinib) inhibitors, and subsequently combination therapy with BRAF and MEK inhibitors (dabrafenib plus trametinib, or vemurafenib plus cobimetinib) have been developed. In addition, Talimogene laherparepvec (T-VEC), a modified oncolytic herpes virus, has been clinically evaluated and approved. DoR, duration of response; GM-CSF, granulocyte macrophage colony-stimulating factor; ORR, objective response rate; SCC, squamous-cell carcinoma.

Luke, Nature reviews 2017

EVOLUCIÓN DEL TRATAMIENTO DEL MELANOMA

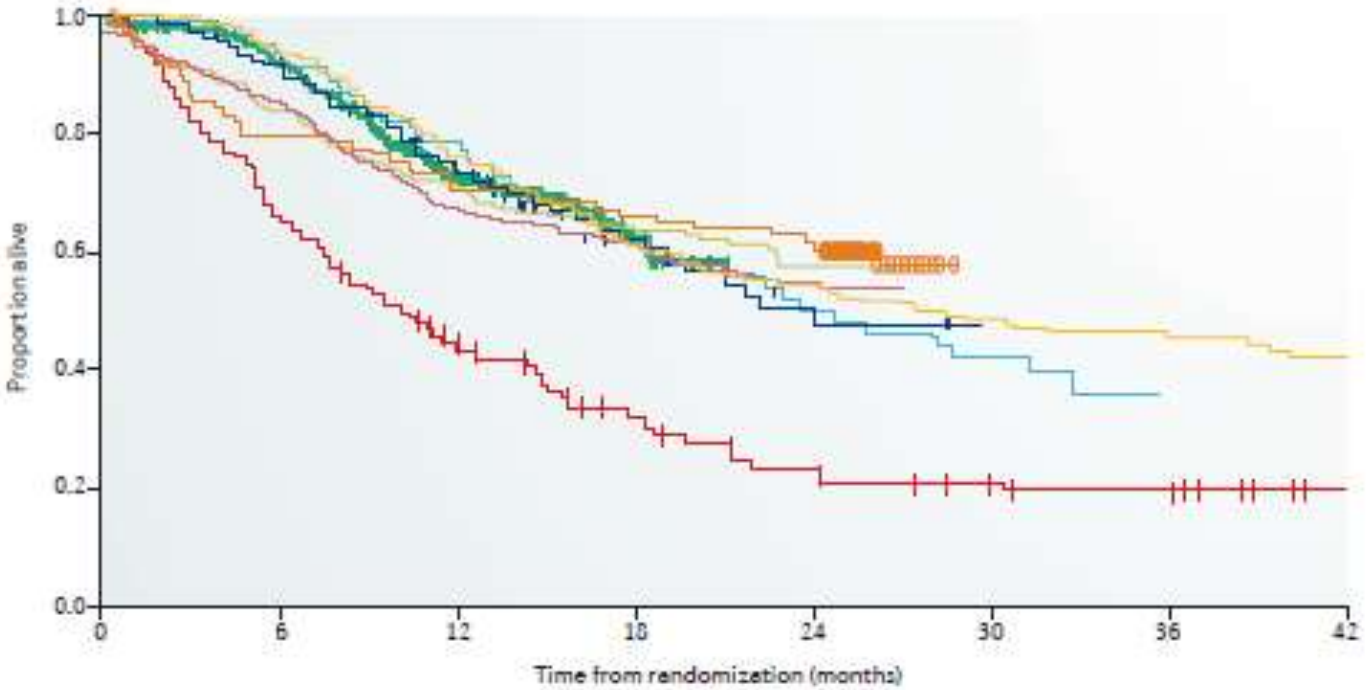
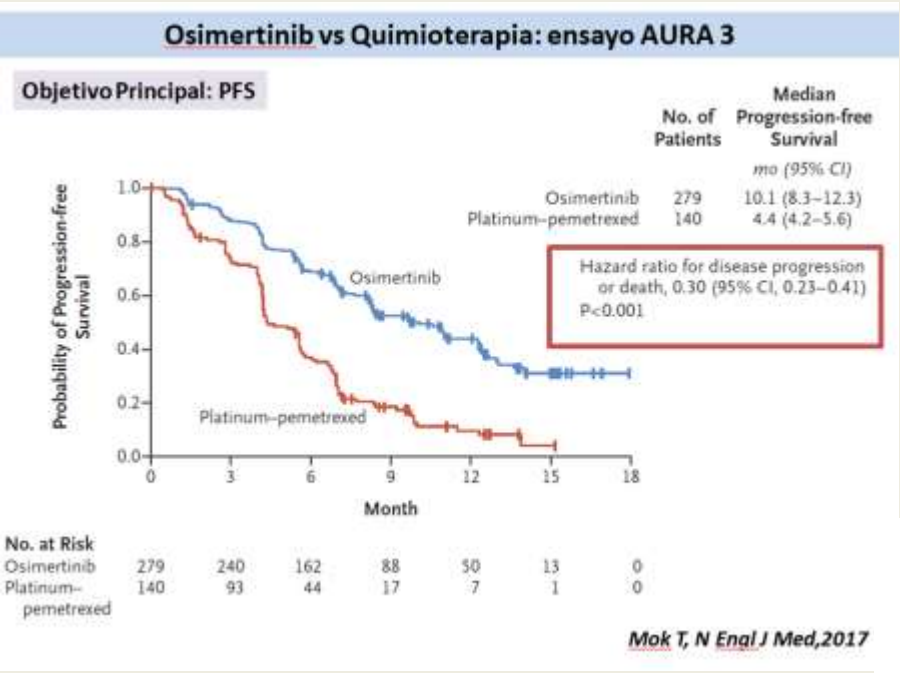


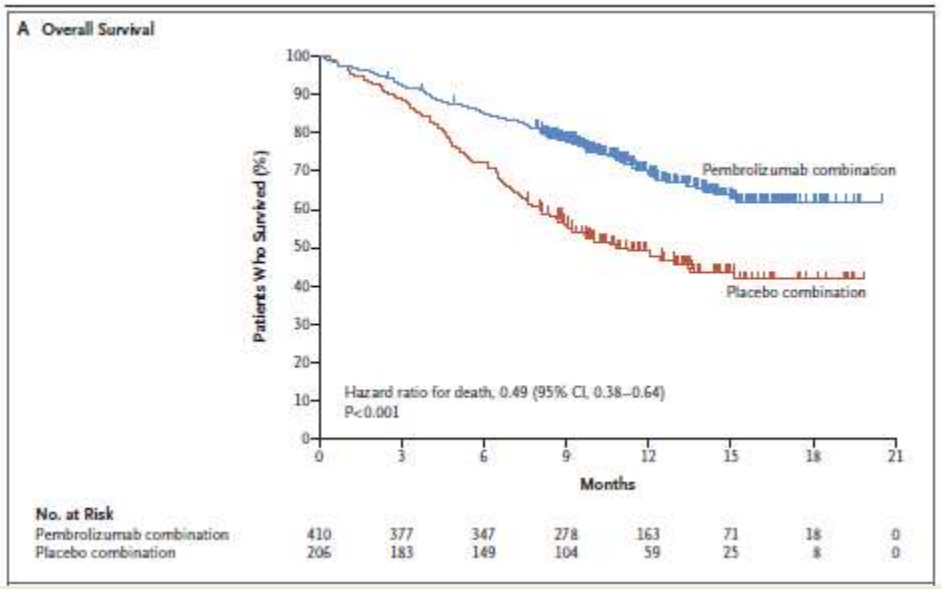
Figure 3 | **Summary of overall survival by Kaplan–Meier analysis across seminal clinical trials in patients with advanced-stage melanoma.** The clinical trials that have defined modern clinical care of patients with advanced-stage melanoma are shown with colour-coding to identify each study. The BRF113220, COMBI-d, COMBI-v and CoBRIM trials were performed only in patients with *BRAF*$^{V600E/K}$-mutant melanoma. Median and landmark overall survival outcomes have been improved with both BRAF-directed treatment and immunotherapy approaches. *n*, number of patients treated.

Luke, Nature Reviews 2017

EVOLUCIÓN DEL TRATAMIENTO DEL CÁNCER DE PULMÓN



Targeted therapy vs Chemo



Immunotherapy + Chemo

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander, A. Lisyanskaya, A. Floquet, A. Leary, G.S. Sonke, C. Gourley, S. Banerjee, A. Oza, A. González-Martín, C. Aghajanian, W. Bradley, C. Mathews, J. Liu, E.S. Lowe, R. Bloomfield, and P. DiSilvestro

ABSTRACT

RESULTS

Of the 391 patients who underwent randomization, 260 were assigned to receive olaparib and 131 to receive placebo. A total of 388 patients had a centrally confirmed germline *BRCA1/2* mutation, and 2 patients had a centrally confirmed somatic *BRCA1/2* mutation. After a median follow-up of 41 months, the risk of disease progression or death was 70% lower with olaparib than with placebo (Kaplan–Meier estimate of the rate of freedom from disease progression and from death at 3 years, 60% vs. 27%; hazard ratio for disease progression or death, 0.30; 95% confidence interval, 0.23 to 0.41; P<0.001). Adverse events were consistent with the known toxic effects of olaparib.

CONCLUSIONS

The use of maintenance therapy with olaparib provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a *BRCA1/2* mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo. (Funded by AstraZeneca and Merck; SOLO1 ClinicalTrials.gov number, NCT01844986.)

70% LOWER RISK!!!

The NEW ENGLAND JOURNAL of MEDICINE

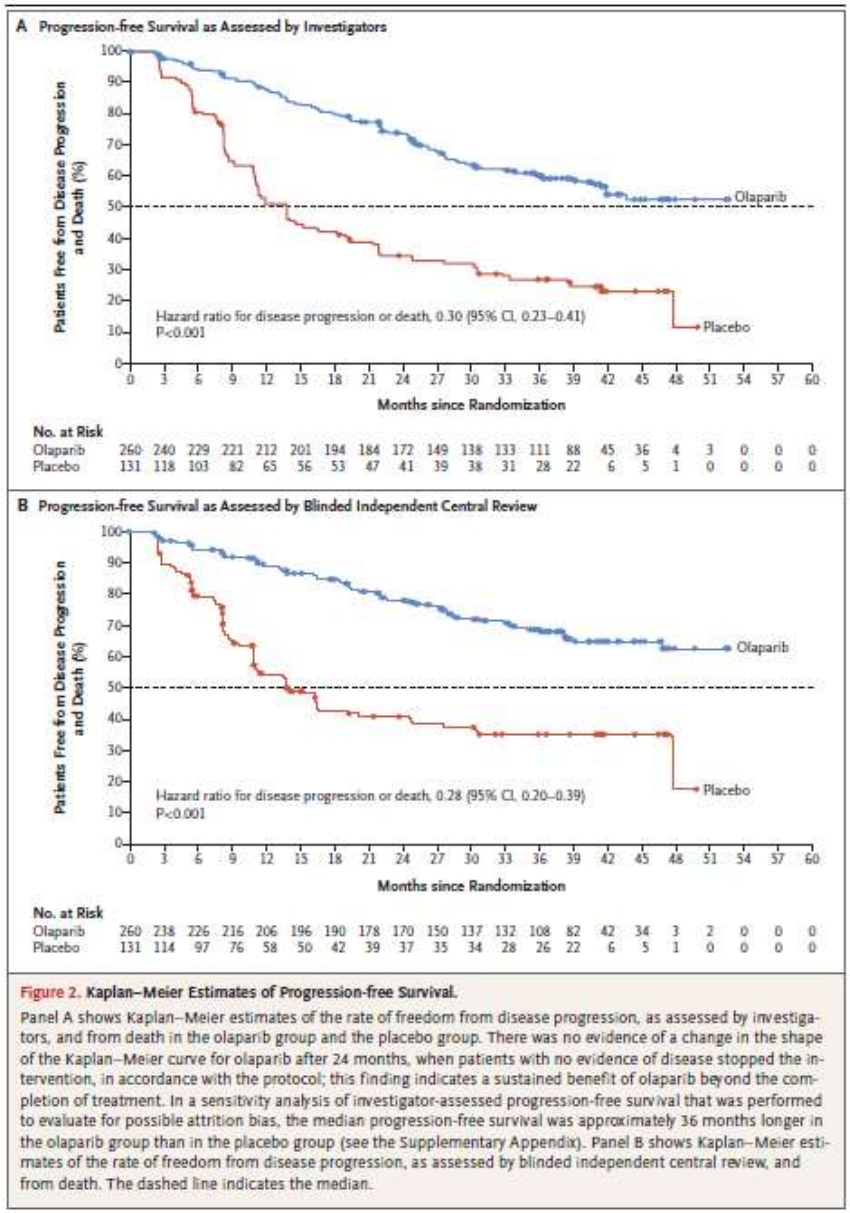
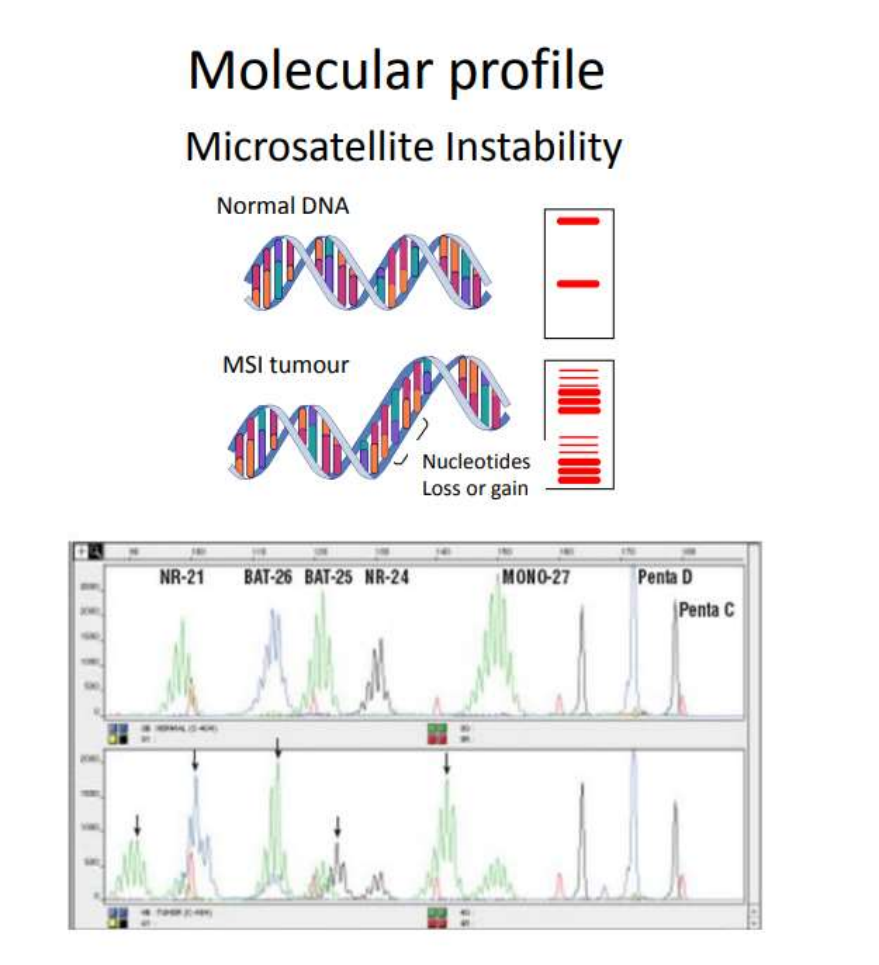


Figure 2. Kaplan–Meier Estimates of Progression-free Survival.

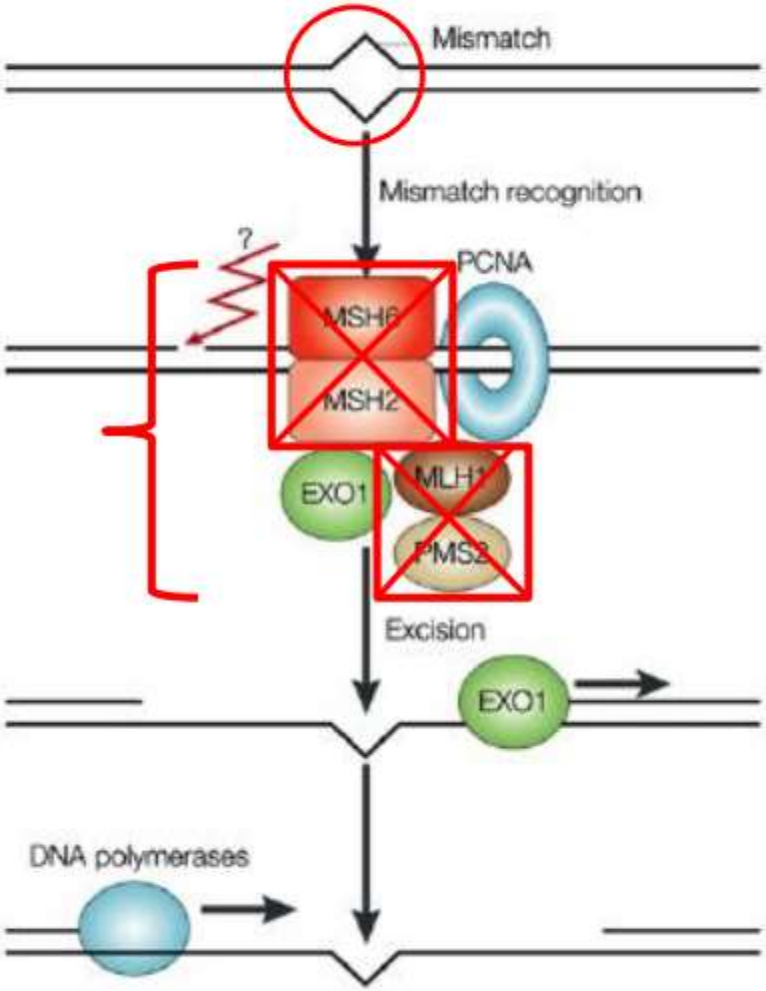
Panel A shows Kaplan–Meier estimates of the rate of freedom from disease progression, as assessed by investigators, and from death in the olaparib group and the placebo group. There was no evidence of a change in the shape of the Kaplan–Meier curve for olaparib after 24 months, when patients with no evidence of disease stopped the intervention, in accordance with the protocol; this finding indicates a sustained benefit of olaparib beyond the completion of treatment. In a sensitivity analysis of investigator-assessed progression-free survival that was performed to evaluate for possible attrition bias, the median progression-free survival was approximately 36 months longer in the olaparib group than in the placebo group (see the Supplementary Appendix). Panel B shows Kaplan–Meier estimates of the rate of freedom from disease progression, as assessed by blinded independent central review, and from death. The dashed line indicates the median.



- **<u>Microsatélites :</u>** secuencias repetitivas en el ADN y constituidos por unidades de repetición en tándem.
- Las regiones del genoma donde se encuentran los microsatélites son difíciles de replicar y las enzimas encargadas de la síntesis del ADN pueden resbalar y originar pequeños bucles, a causa de inserciones o deleciones de algunos nucleótidos, en la nueva cadena sintetizada.

Deficient MMR system

4 proteins for DNA reparation



→ MSI CRC carcinogenesis

DISPONEMOS DE BIOMARCADORES PREDICTORES EFICACES DE RESPUESTA?

CANCER BIOMARKERS

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

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The genomes of cancers deficient in mismatch repair contain exceptionally high numbers of somatic mutations. In a proof-of-concept study, we previously showed that colorectal cancers with mismatch repair deficiency were sensitive to immune checkpoint blockade with antibodies to programmed death receptor–1 (PD-1). We have now expanded this study to evaluate the efficacy of PD-1 blockade in patients with advanced mismatch repair–deficient cancers across 12 different tumor types. Objective radiographic responses were observed in 53% of patients, and complete responses were achieved in 21% of patients. Responses were durable, with median progression-free survival and overall survival still not reached. Functional analysis in a responding patient demonstrated rapid in vivo expansion of neoantigen-specific T cell clones that were reactive to mutant neopeptides found in the tumor. These data support the hypothesis that the large proportion of mutant neoantigens in mismatch repair–deficient cancers make them sensitive to immune checkpoint blockade, regardless of the cancers' tissue of origin.

Le et al., Science 357, 409–413 (2017) 28 July 2017

MMR deficient tumors

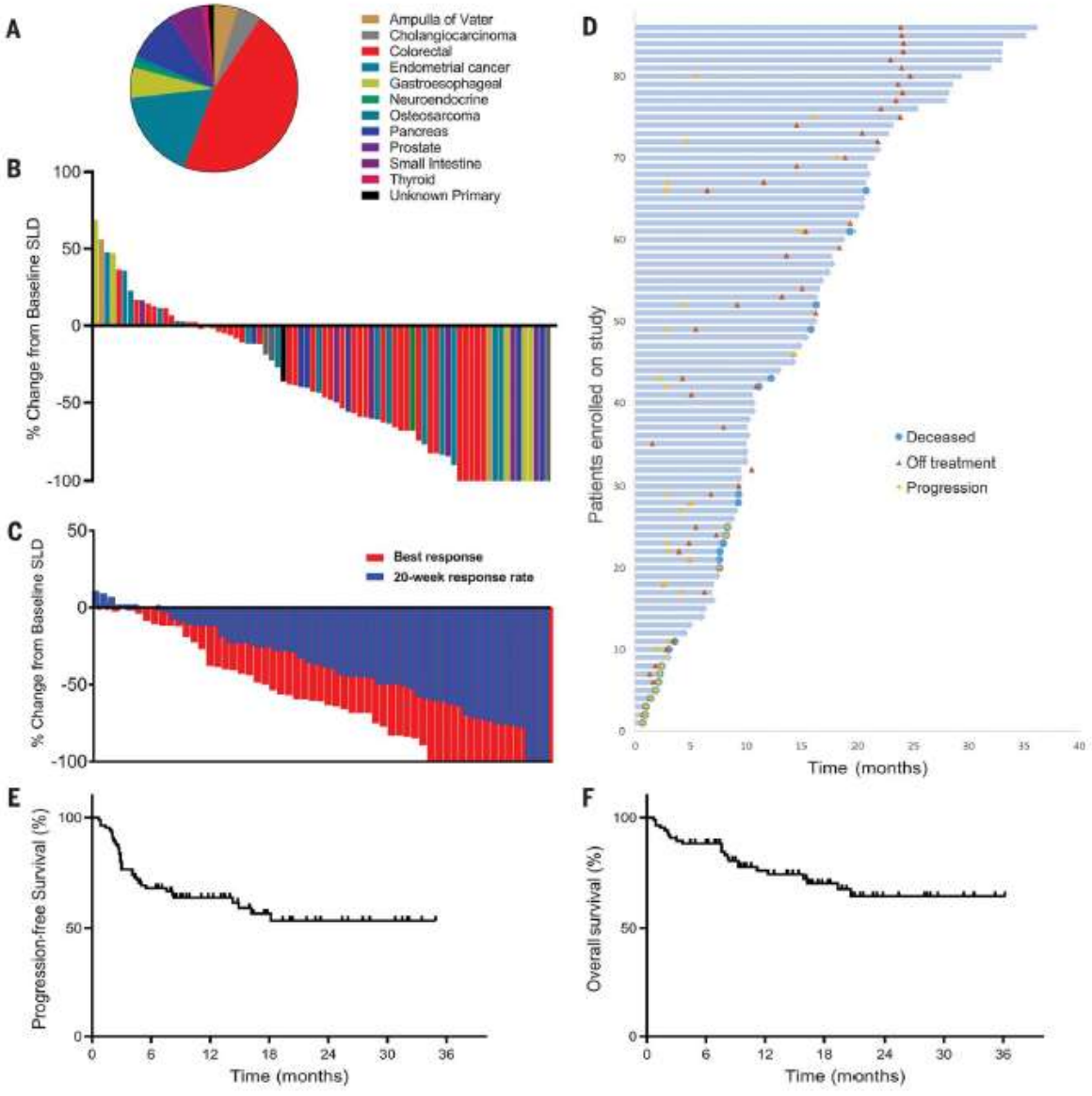

Fig. 1. Patient survival and clinical response to pembrolizumab across 12 different tumor types with mismatch repair deficiency. (**A**) Tumor types across 86 patients. (**B**) Waterfall plot of all radiographic responses across 12 different tumor types at 20 weeks. Tumor responses were measured at regular intervals; values show the best fractional change of the sum of longest diameters (SLD) from the baseline measurements of each measurable tumor. (**C**) Confirmed radiographic objective responses at 20 weeks (blue) compared to the best radiographic responses in the same patients (red). The mean time to the best radiographic response was 28 weeks. (**D**) Swimmer plot showing survival for each patient with mismatch repair–deficient tumors, indicating death, progression, and time off therapy. (**E** and **F**) Kaplan-Meier estimates of progression-free survival (E) and overall patient survival (F).

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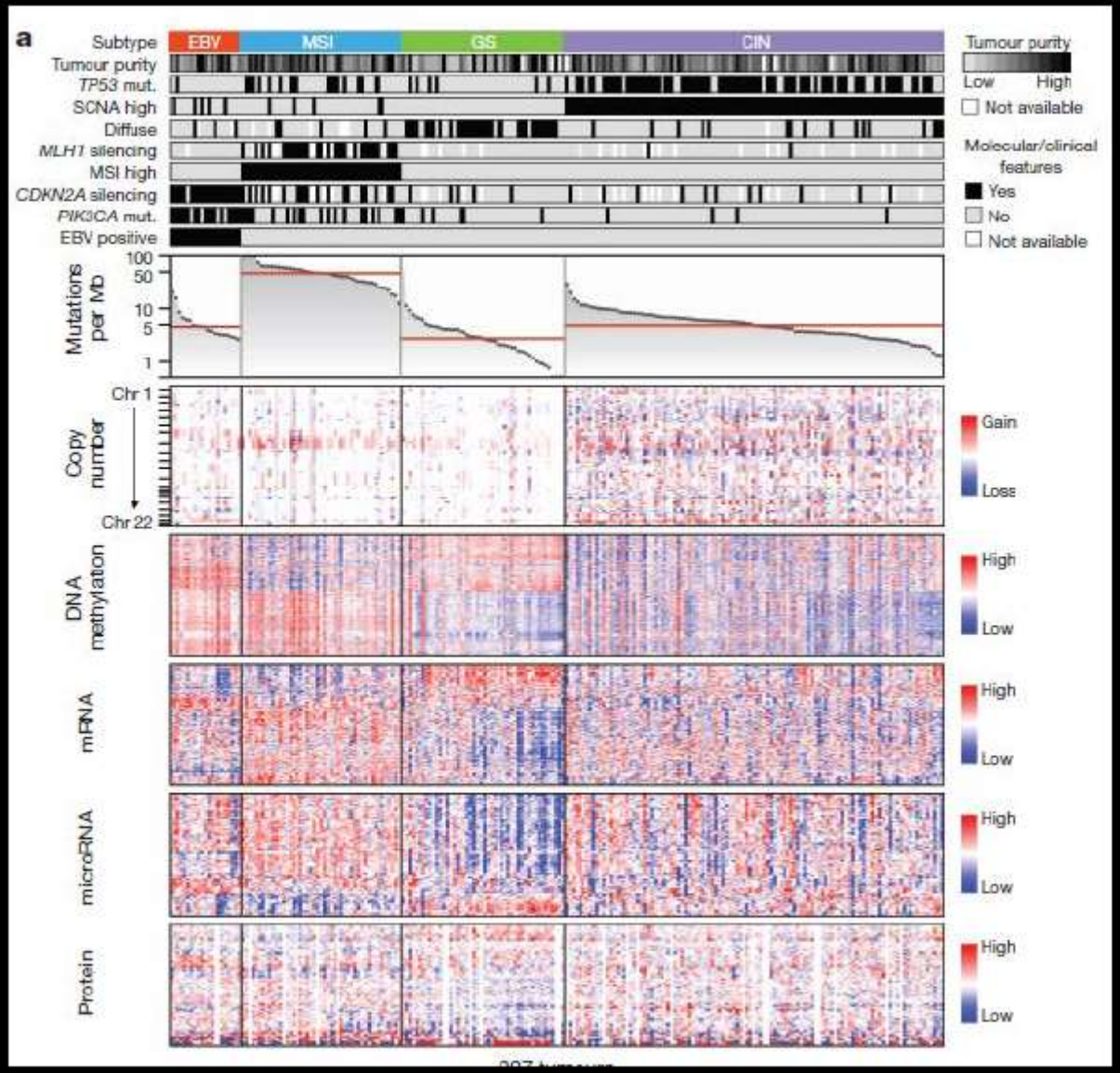
	Lei et al.			
Subtipo	**Mesenquimal**		**Proliferativo**	**Metabólico**
Histologia	Fenotipo difuso		intestinal	Intestinal
Vías activadas	EMT, TGF-B, VEGF. mTOR		E2F, MYC, RAS	SPEM
Procesos biológicos Con genes regulados al alza	Adhesion focal; interaccion ECM receptor		Ciclo celular, replicación del DNA	Procesos metabólicos
Sensibilidad a tratamientos	Respuesta a inhibidores PI3K , mTOR, terapia antiangiogénica?		Terapias dirigidas	Respuesta a 5-FU
	Cristescu et al.			
Subtipo	**MSS/EMT**	**MSI**	**MSS/TP53+**	**MSS/TP53-**
Histologia	difuso	intestinal	intestinal	intestinal
Vías activadas/ alteradas	PI3KCA MT CDH1 ↓	Vías mitóticas	PI3KCA MT ARID1A MT RHOA MT APC, KRAS MT	TP53 MT RHOA MT Her2, FGFR, CCNE1 Ampl
Procesos biológicos Con genes regulados al alza		hipermutado	EBV+	
Sensibilidad a tratamientos	Inhibidores PI3K; mTOR	Inmunoterapia	Inhibidores PI3K	Quimiosensible, terapias dirigidas
	Bass et al.			
Subtipo	GS	MSI	EBV	CIN
Histologia	difuso			intestinal
Vías activadas/ alteradas	Adhesion celular	Vías mitóticas hipermutado	Señal inmune	RAS
Procesos biológicos Con genes regulados al alza	CDH1 MT RHOA MT Fusión CLDN18-ARHGAP	Silenciamiento MLH1;	Mutaciones PI3KCA; sobreexpresión PD-L1/ PD-L2; EBV-CIMP;	Mutaciones TP53
Sensibilidad a tratamientos		Inmunoterapia	Inmunoterapia	Terapias dirigidas

TCGA Study (~3-4 Major GC Genomic Subtypes)



A) Chromosomal Instability (CIN)

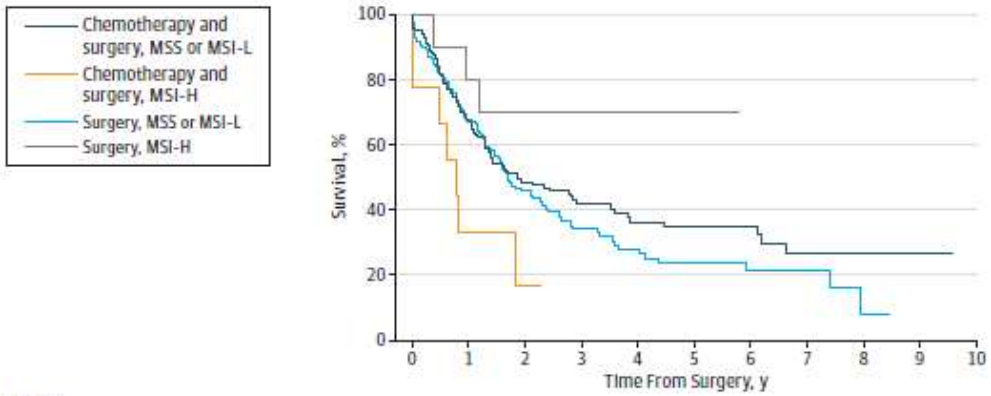
B) Microsatellite Instability (MSI)

C) Genome Stable (GS)

D) Epstein-Barr Virus (EBV)

USA TCGA (2014) *Nature*

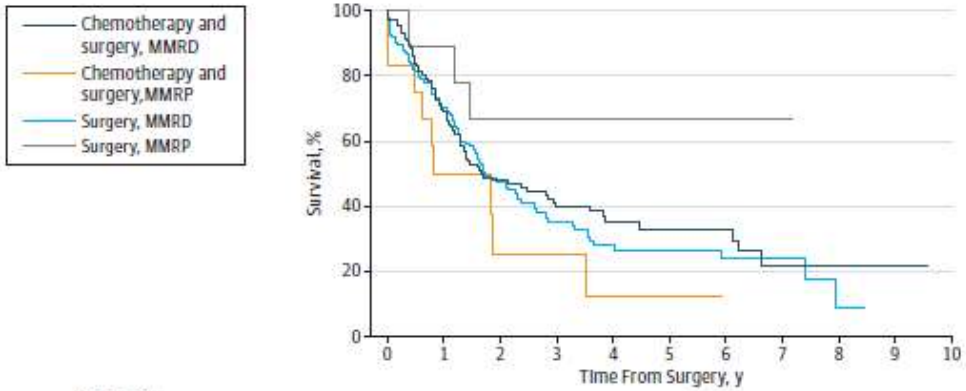
Figure 1. Overall Survival by Microsatellite Instability (MSI) Status and Treatment Arm in the Study Patients



No. at risk										
Chemotherapy and surgery, MSI-negative patients	129	85	58	42	27	22	15	6	3	1
Chemotherapy and surgery, MSI-positive patients	9	3	1							
Surgery, MSI-negative patients	151	100	58	37	21	13	9	7	1	
Surgery, MSI-positive patients	10	8	6	3	1	1				

Patients were dichotomized into 2 groups: high MSI (MSI-H) and microsatellite stable (MSS) or low MSI (MSI-L), which are analyzed separately in each treatment arm. Differences in overall survival were assessed using the Kaplan-Meier method and compared using the log-rank test. The hazard ratios for MSI-H vs MSS or MSI-L were 0.35 (95% CI, 0.11-1.11) for surgery alone ($P = .08$) and 2.22 (95% CI, 1.02-4.85) for chemotherapy and surgery ($P = .04$) (interaction $P = .01$). $P < .05$ was considered to be statistically significant.

Figure 2. Overall Survival by Mismatch Repair (MMR) Protein Status in the Study Patients

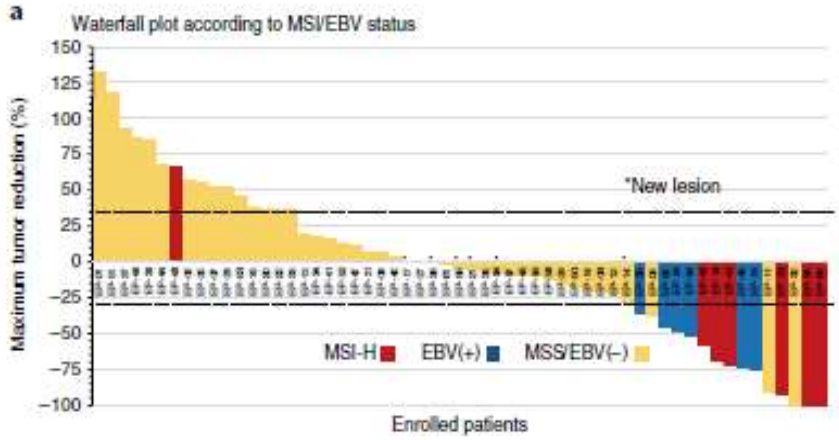


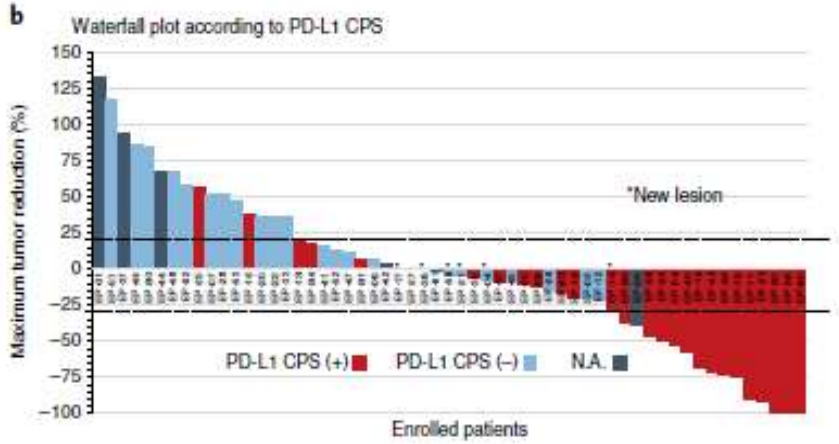
No. at risk										
Chemotherapy and surgery, MMRD	107	73	47	32	19	13	10	3	1	1
Chemotherapy and surgery, MMRP	12	6	2	2	1	1				
Surgery, MMRD	136	92	52	34	18	13	8	6	1	
Surgery, MMRP	9	8	5	2	1	1	1	1		

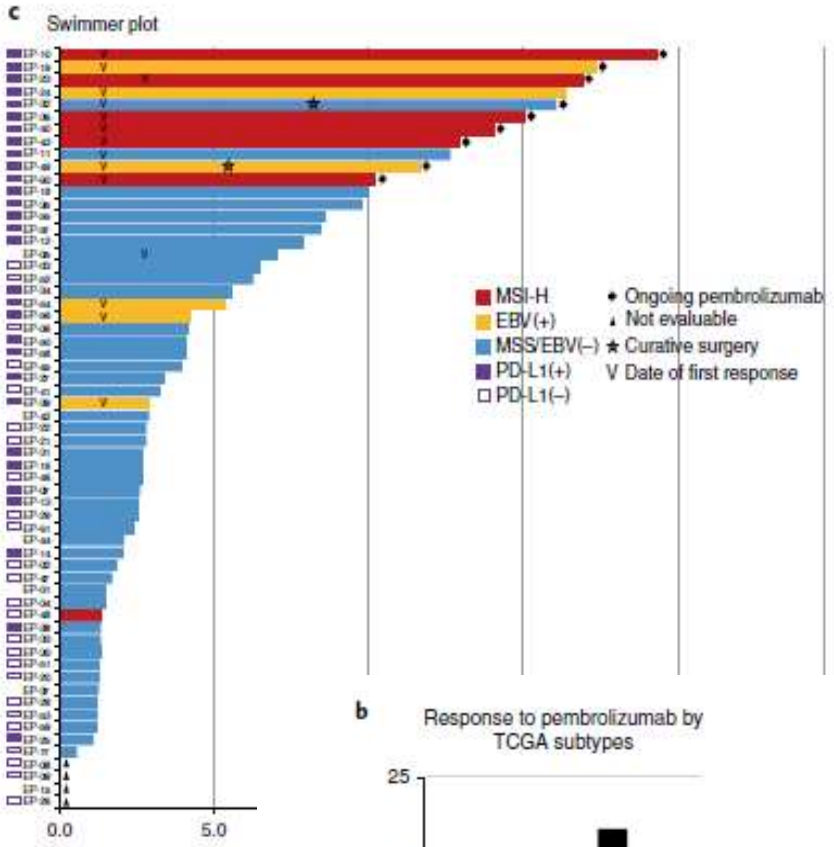
Patients were dichotomized into 2 groups: MMR deficiency (MMRD) and MMR proficiency (MMRP). The groups are analyzed separately in each treatment arm. Differences in overall survival were assessed using the Kaplan-Meier method and compared using the log-rank test. $P < .05$ was considered to be statistically significant.

No benefit from Chemo!

Smyth E. JAMA Oncol. **2017** Sep 1;3(9):1197-1203







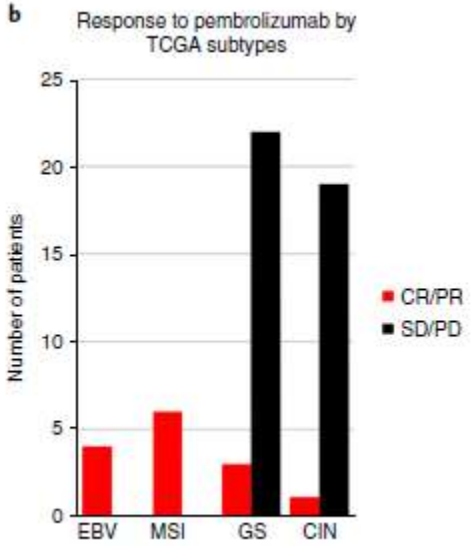


Fig. 1 | Response to pembrolizumab in patients with gastric cancer. a, Waterfall plot of response to p
EP represents each patient's identification number. *Y* axis represents percentage of maximum tumor r
Lower dotted line represents tumor reduction of 30% per RECIST, which defines partial response (PR)
represents percentage of maximum tumor reduction assessed according to RECIST 1.1 criteria. **c**, Swim
data. *X* axis represents the duration of pembrolizumab therapy for each patient. Patient identity numb

Kim,S. et al. Nature Medicine 2018

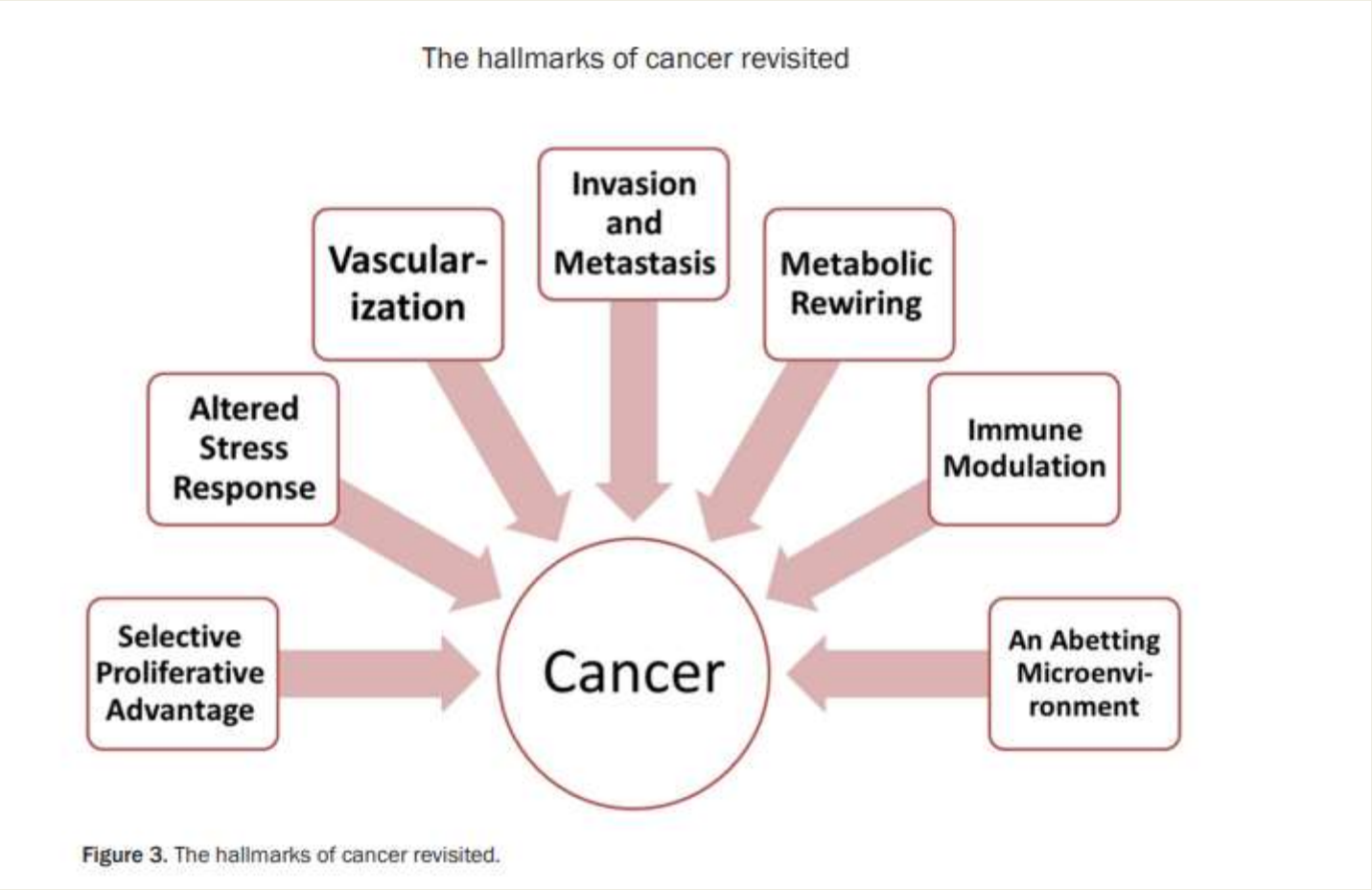


Figure 3. The hallmarks of cancer revisited.

Am J Cancer Res 2017;7(5):1016-1036

special article

Perspectives on Strengthening Cancer Research and Control in Latin America Through Partnerships and Diplomacy: Experience of the National Cancer Institute's Center for Global Health

executive summary

According to the Pan American Health Organization, noncommunicable diseases, including cancer, are the leading causes of preventable and premature death in the Americas. Governments and health care systems in Latin America face numerous challenges as a result of increasing morbidity and mortality from cancer. Multiple international organizations have recognized the need for collaborative action on and technical support for cancer research and control in Latin America. The Center for Global Health at the US National Cancer Institute (NCI-CGH) is one entity among many that are working in the region and has sought to develop a strategy for working in Latin America that draws on and expands the collaborative potential of engaged, skilled, and diverse partners. NCI-CGH has worked toward developing and implementing initiatives in collaboration with global partners that share the common objectives of building a global cancer research community and translating research results into evidence-informed policy and practice. Both objectives are complementary and synergistic and are additionally supported by an overarching strategic framework that is focused on partnerships and science diplomacy. This work highlights the overall strategy for NCI-CGH engagement in Latin America through partnerships and diplomacy, and highlights selected collaborative efforts that are aimed at improving cancer outcomes in the region.

Frech et al 2018

C/Can 2025

City Cancer Challenge

uicc
global cancer control
A MEMBERSHIP ORGANISATION
FIGHTING CANCER TOGETHER

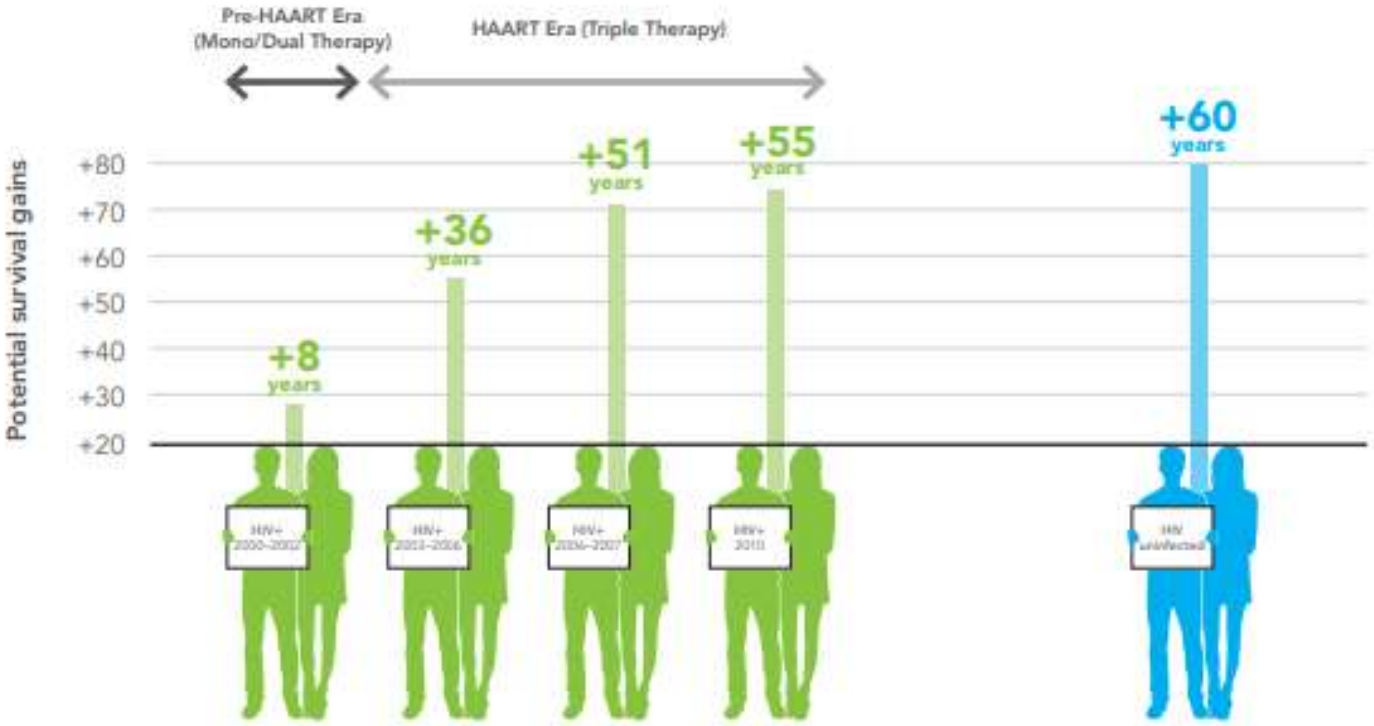
Ciudades Clave de Aprendizaje (Key Learning Cities)

Cali, Colombia	Asunción, Paraguay	Yangon, Myanmar	Kumasi, Ghana
			

UN BUEN EJEMPLO:

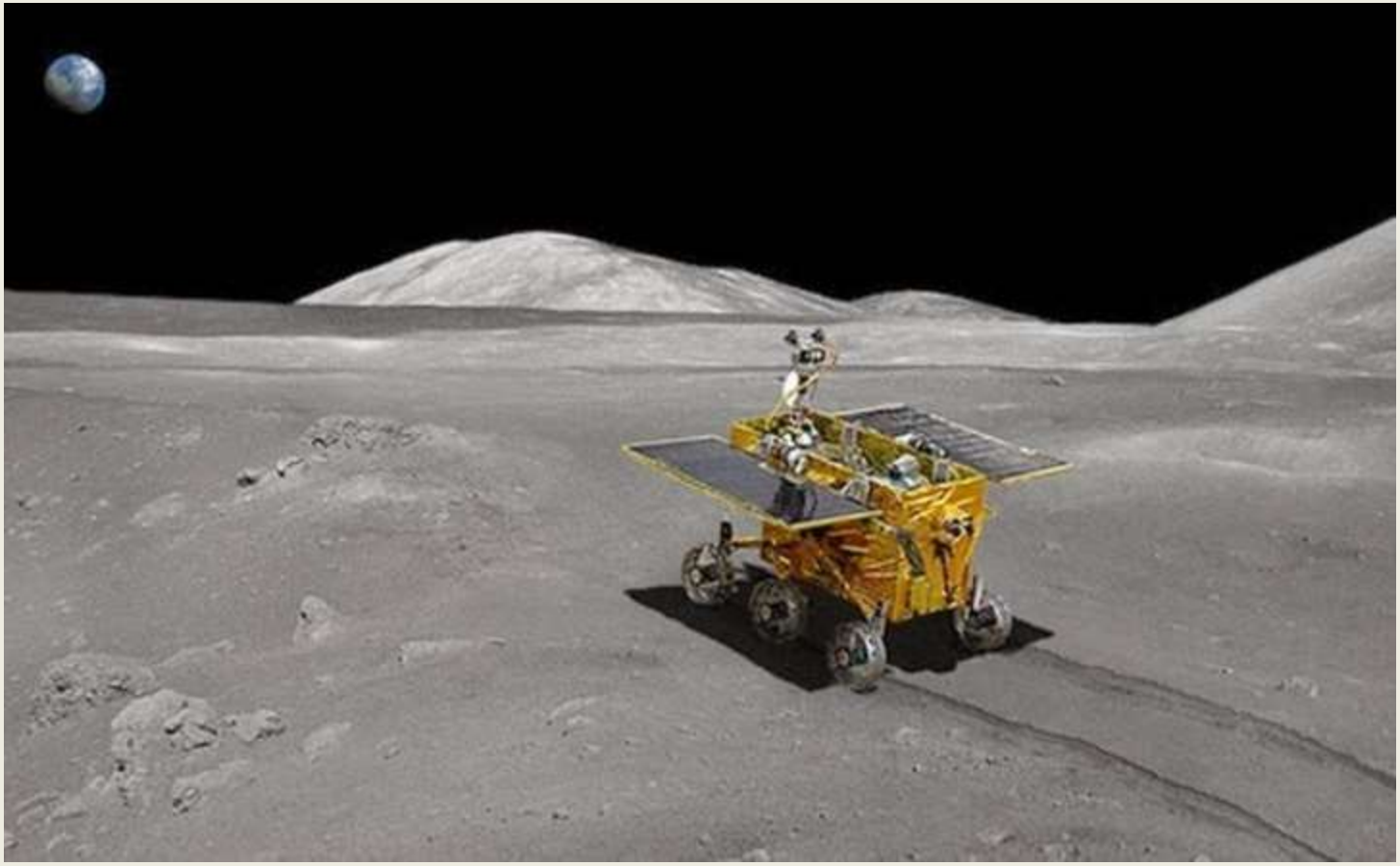
Fig. 1

HIV TREATMENT CAN NORMALIZE SURVIVAL

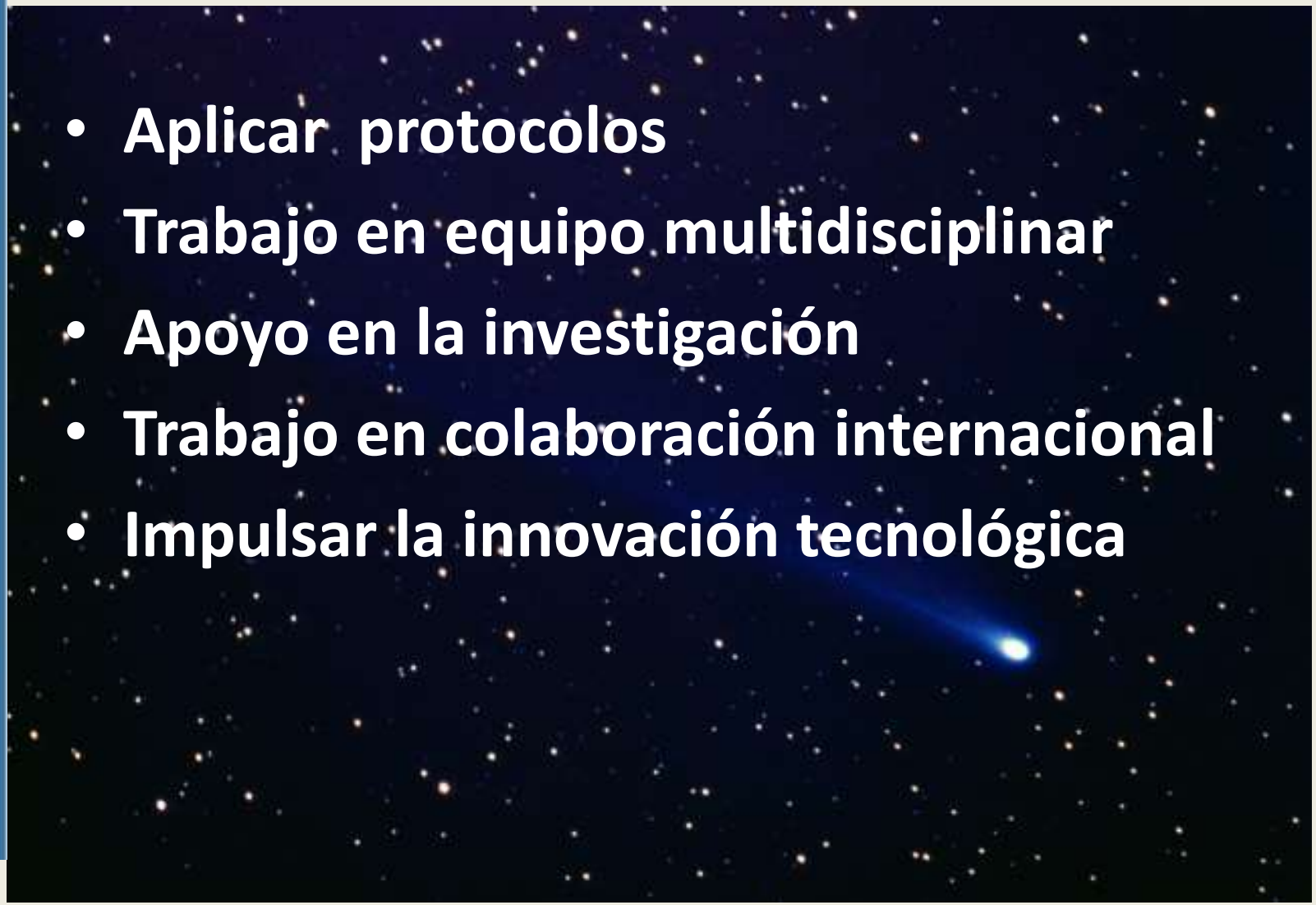


Expected impact of HIV treatment in survival of a 20 years old person living with HIV in a high income setting (different periods)

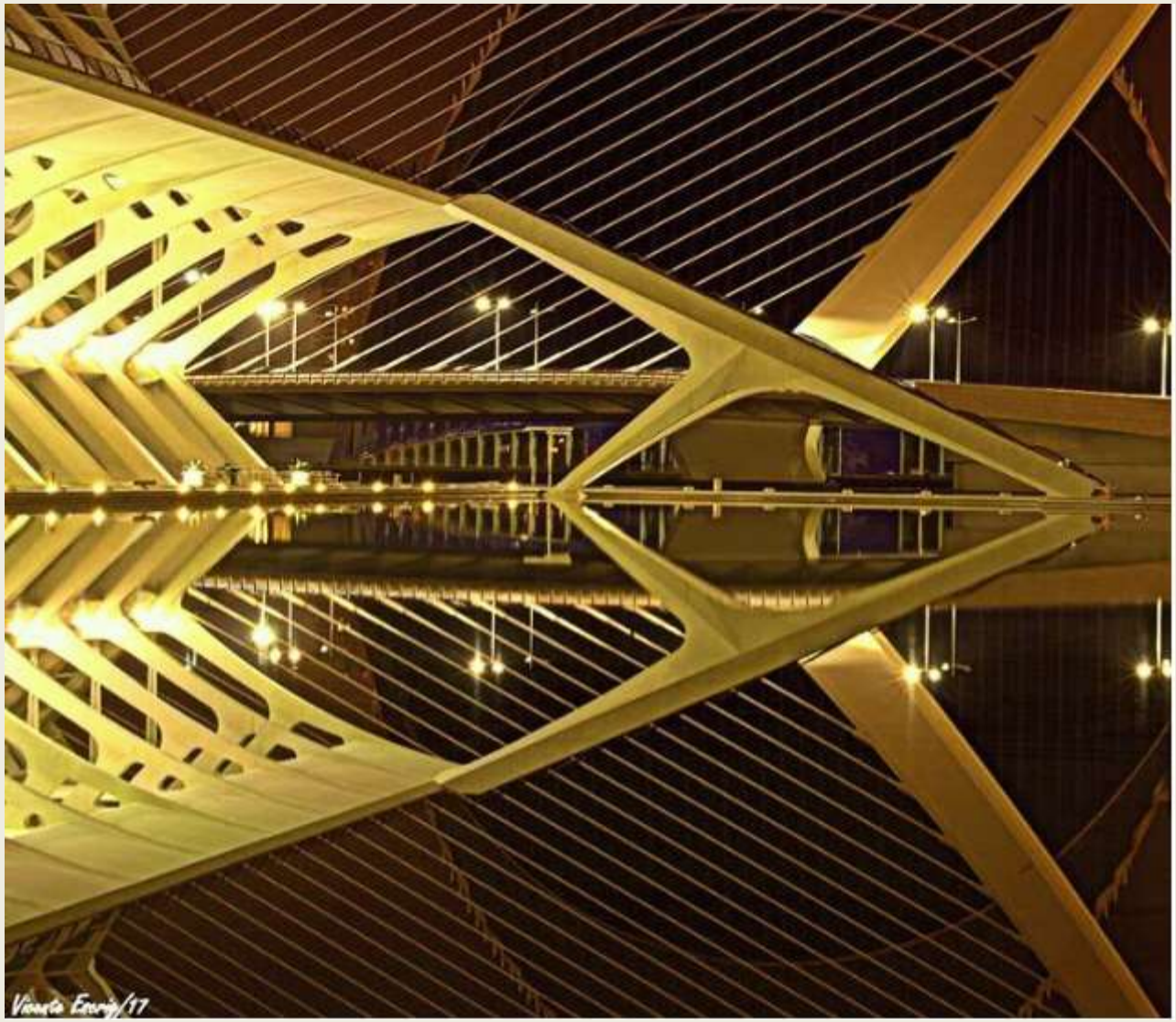
Source: Samji H et al., PLoS ONE, 2013.



Conclusiones



- **Aplicar protocolos**
- **Trabajo en equipo multidisciplinar**
- **Apoyo en la investigación**
- **Trabajo en colaboración internacional**
- **Impulsar la innovación tecnológica**



MUCHAS GRACIAS