V SIMPOSIO GETHI | 18/19 noviembre de 2019

Ilustre Colegio Oficial de Médicos de Madrid. Aula Jiménez Díaz. Madrid

Patrones inmunológicos a través de diferentes histologías

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Ignorancia o tolerancia

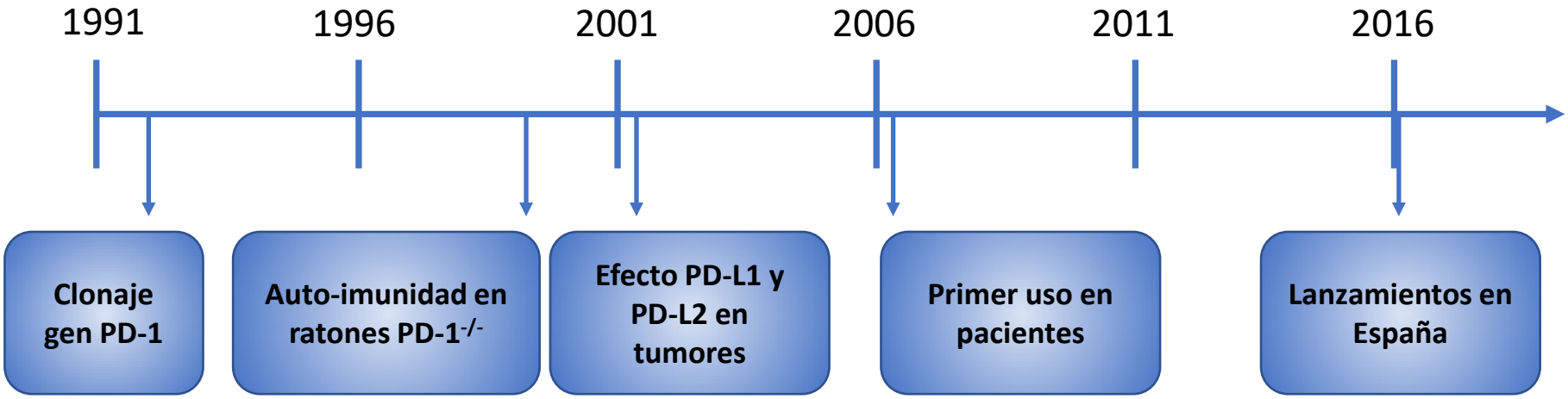
The Danger Model: A Renewed Sense of Self

Polly Matzinger

SCIENCE VOL 296 12 APRIL 2002

Tumors are entities for which both the INS and the Danger models have the same prediction, namely, that tumors should not stimulate immunity, either (INS) because they are not

Desarrollo de PD-1 como diana terapéuticas



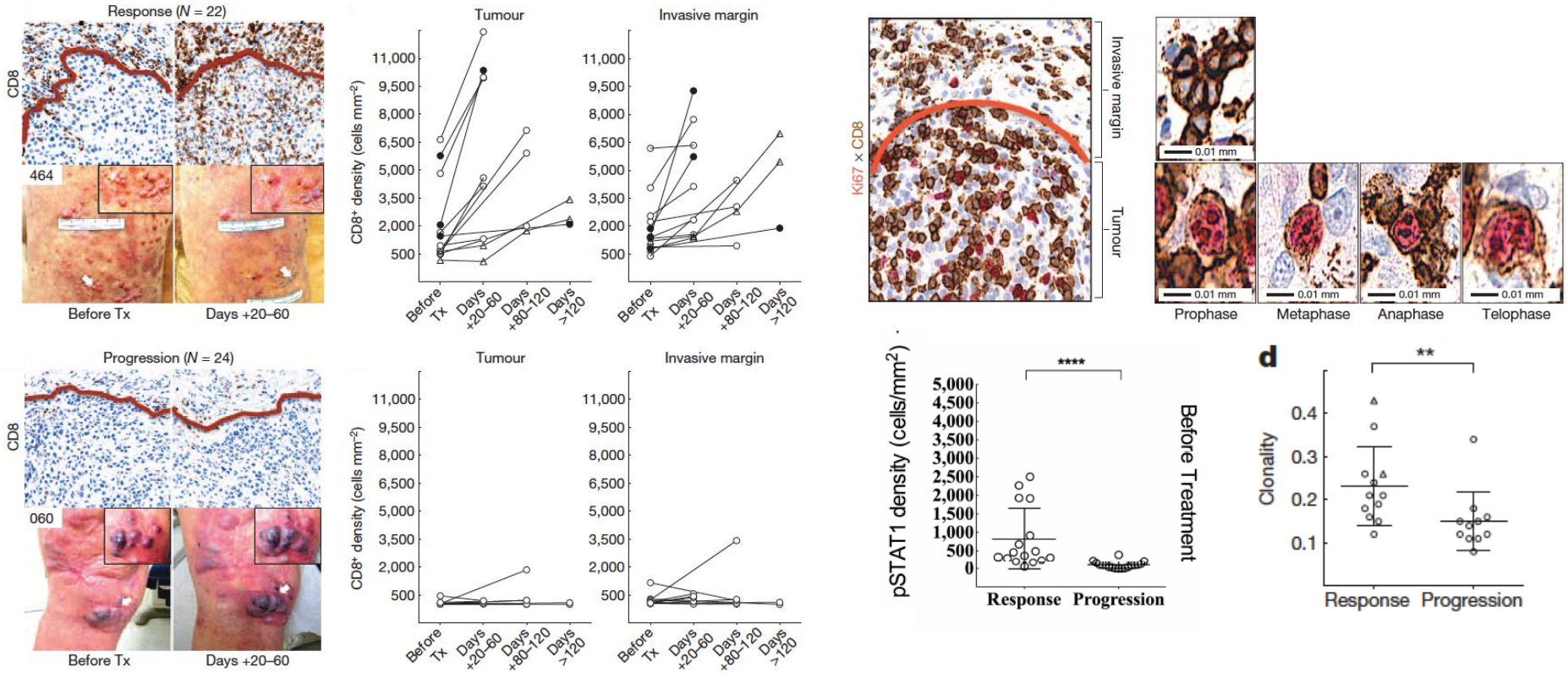
Tasuku Honjo

Arlene Sharpe

Gordon Freeman

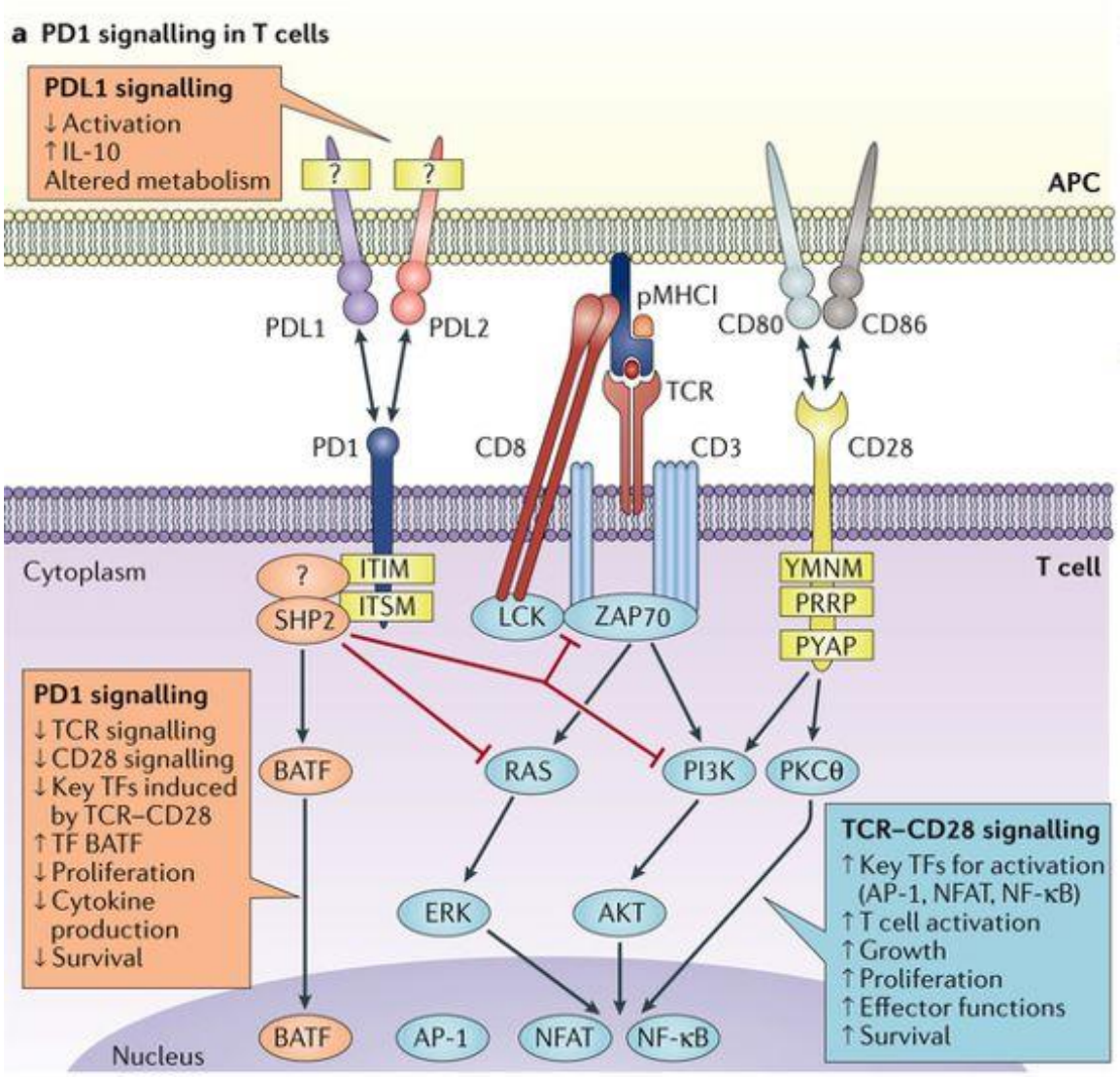
Lieping Chen

PD-1 reactiva respuestas endógenas



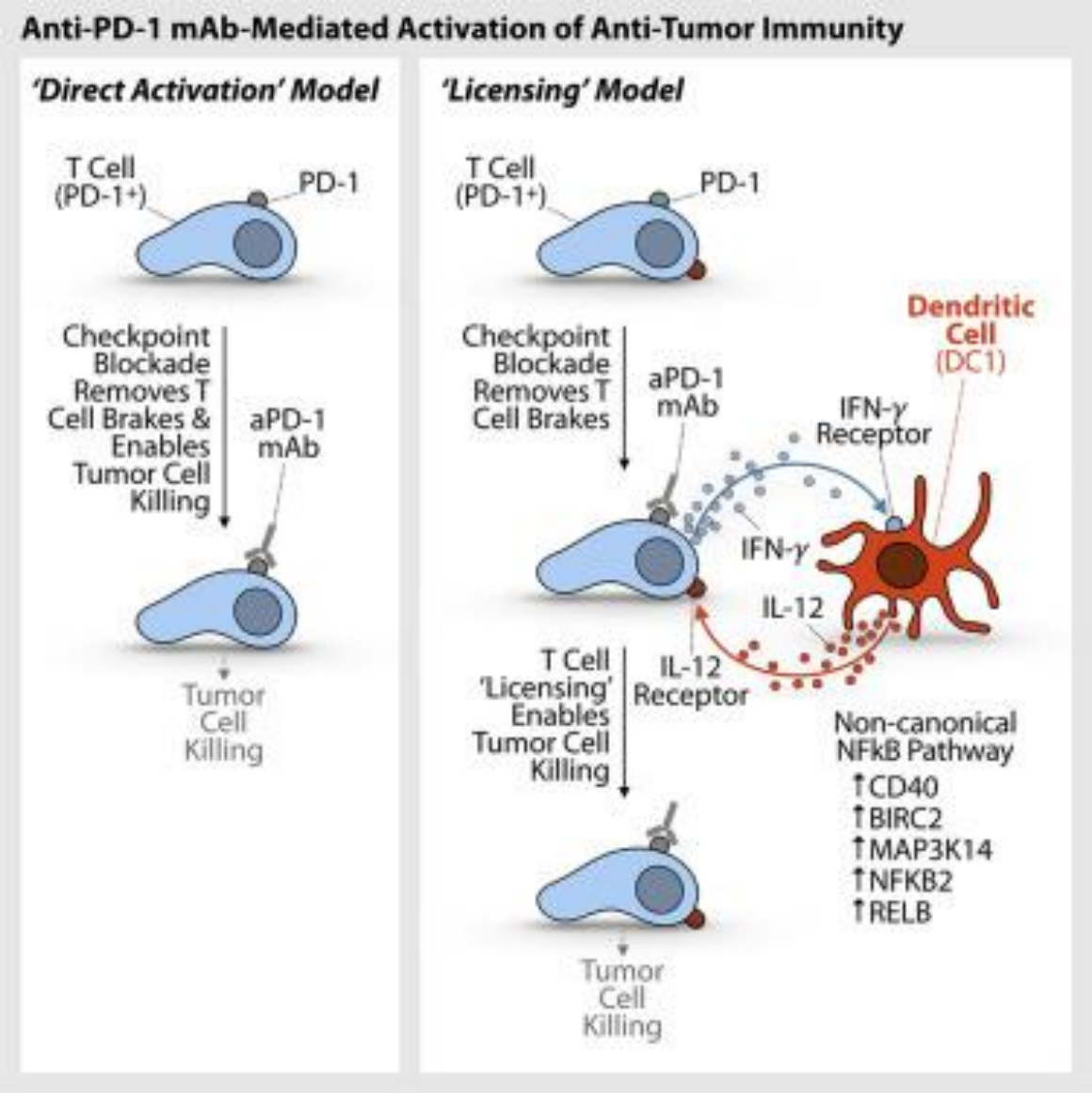
PC Tumeh *et al. Nature* **515**, 568-571 (2014)

Señalización de PD-1 en células T



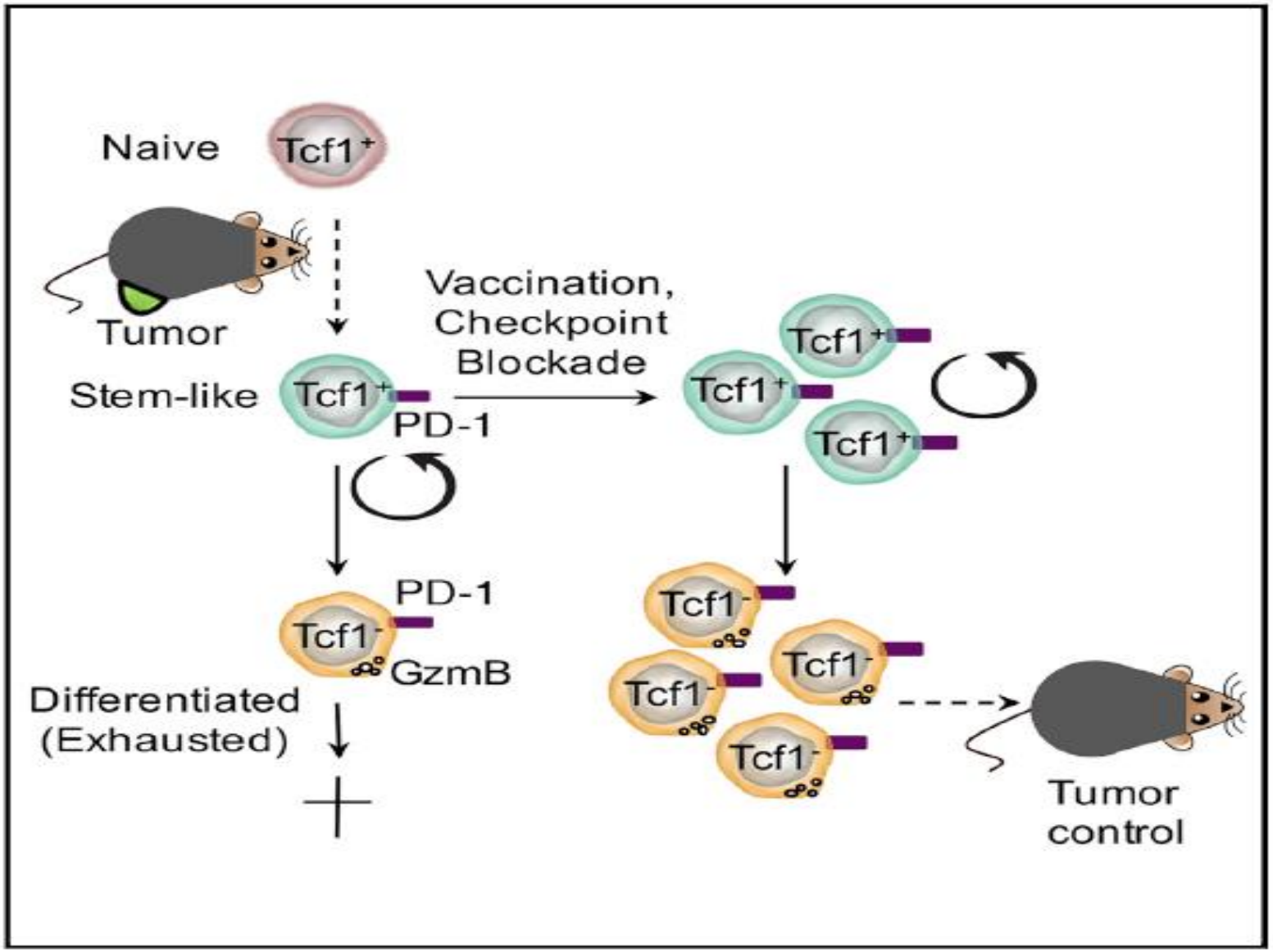
Sharpe AH et al. Nat Rev Immunol. 2018

Modelo de licencia de la actividad de anti-PD-1



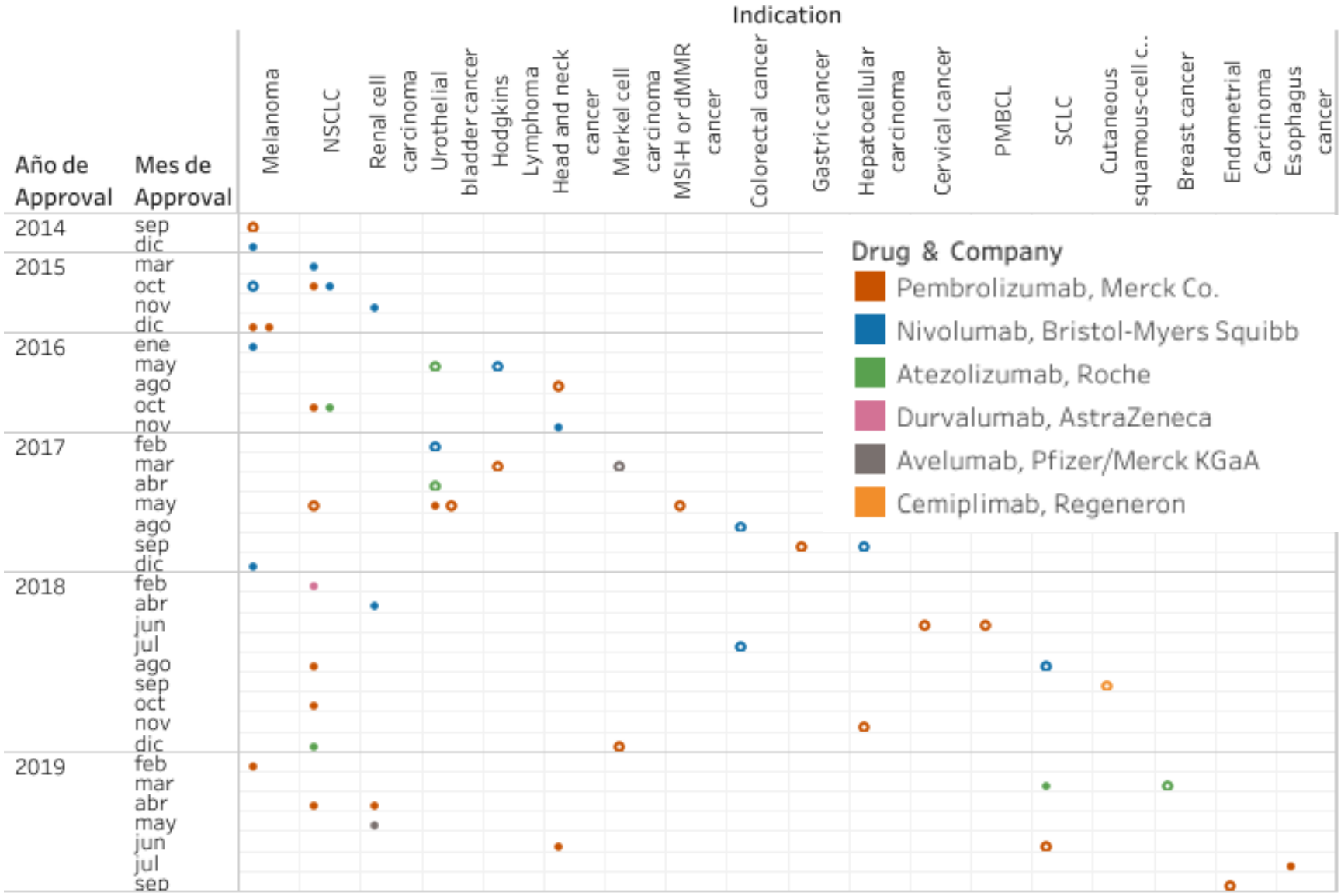
Garris CS A et al. Immunity. 2018

Expansión de CD8+PD-1low por anti-PD-1



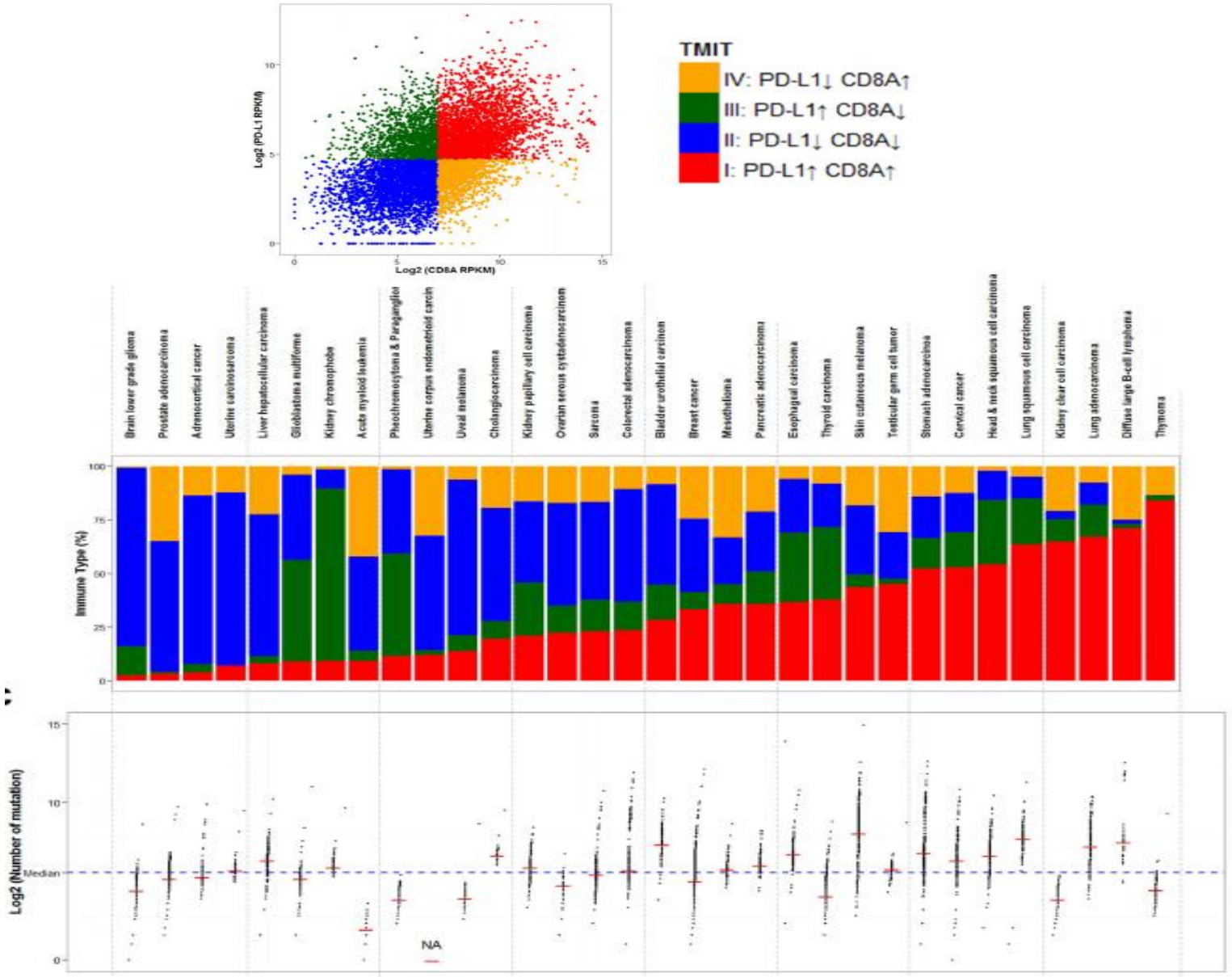
Siddiqui I et al. Immunity. 2019

Aprobaciones de anticuerpos anti-PD1/PD-L1 por FDA



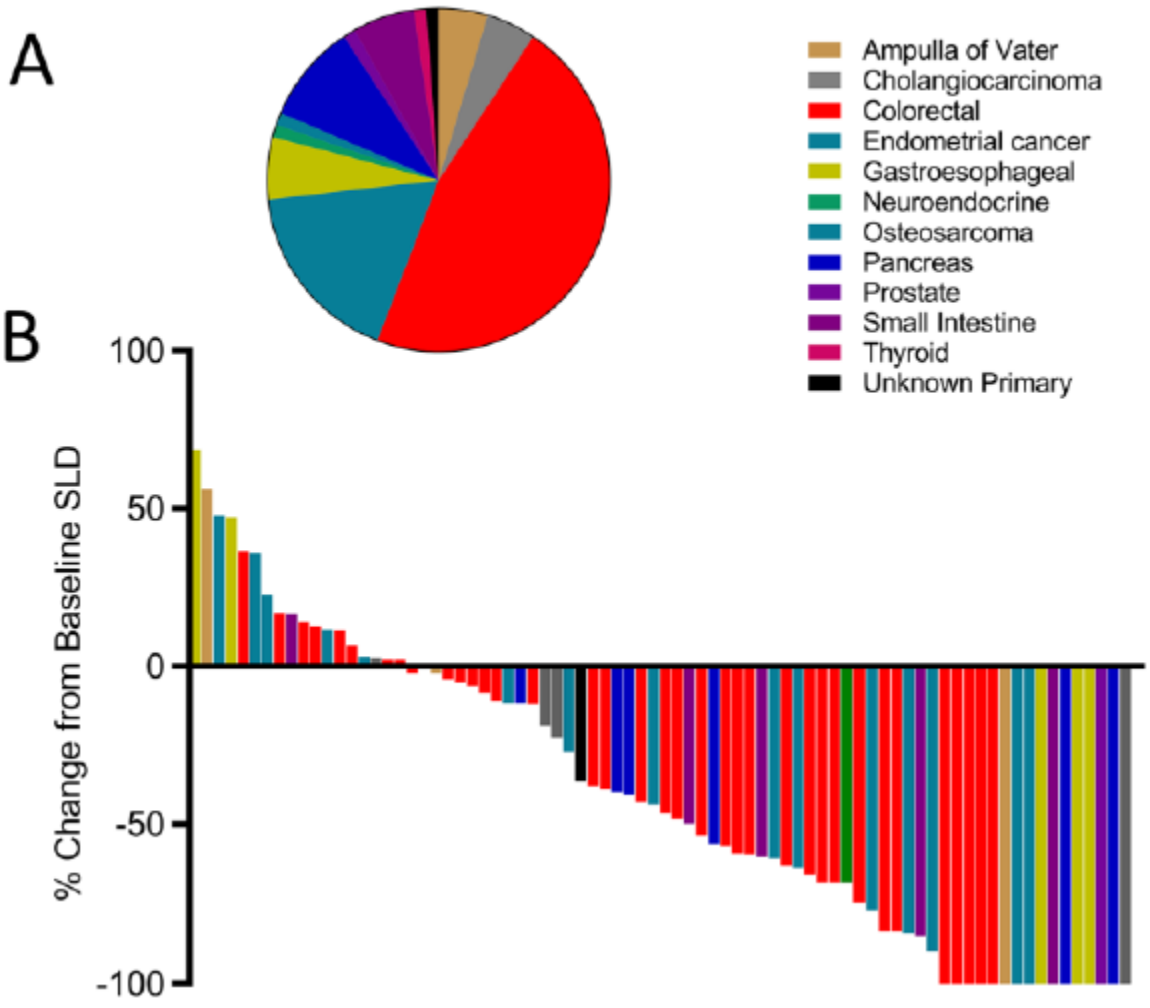
http://www.cancerresearch.org/scientists/clinical-accelerator/landscape-of-immuno-oncology-drug-development/pd-1-pd-l1-landscape

Infiltración de CD8 v PD-L1 en diferentes tumores



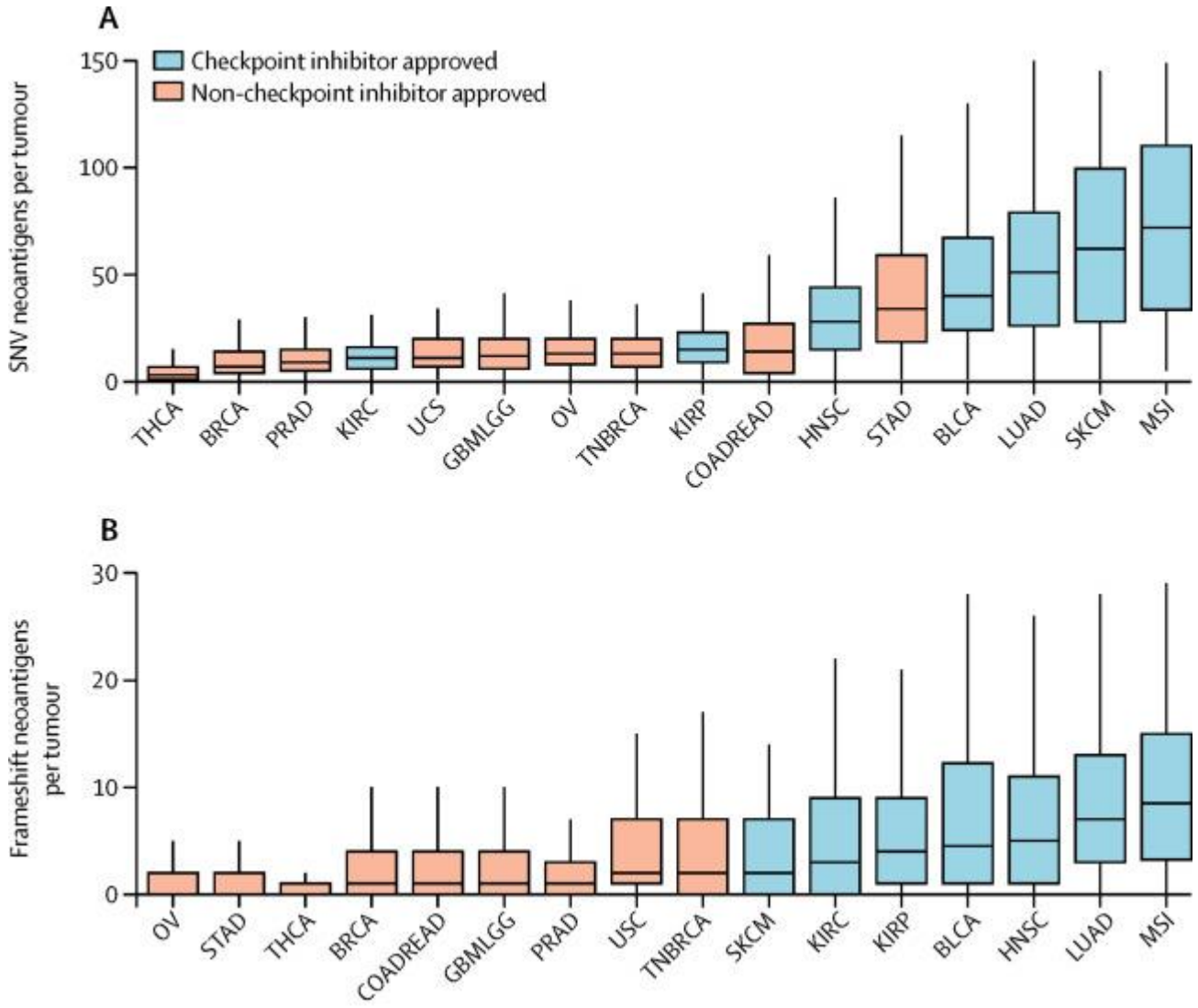
Ock CY et al. Clin Cancer Res. 2016 10.1158/1078-0432.CCR-15-2834.

Inestabilidad de microsatélites



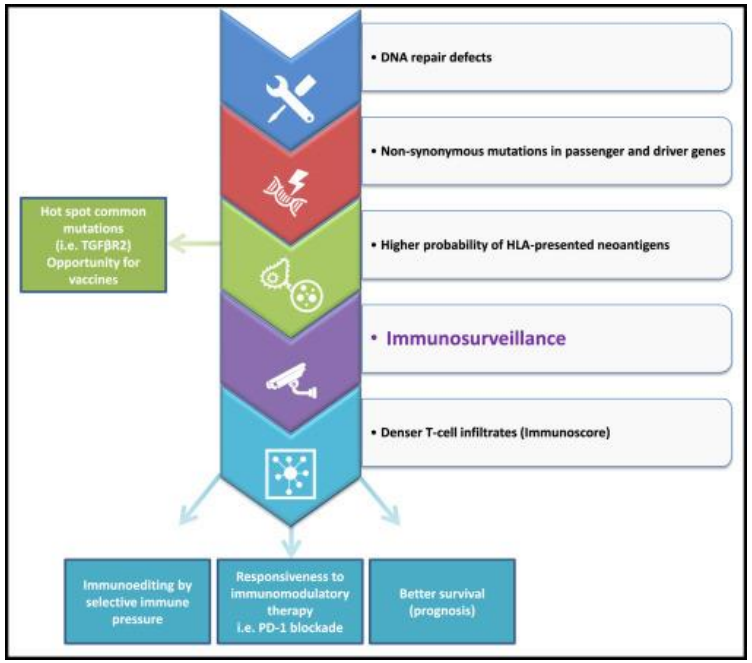
Dung TL et al. Science. 2017. 357: 409-413.

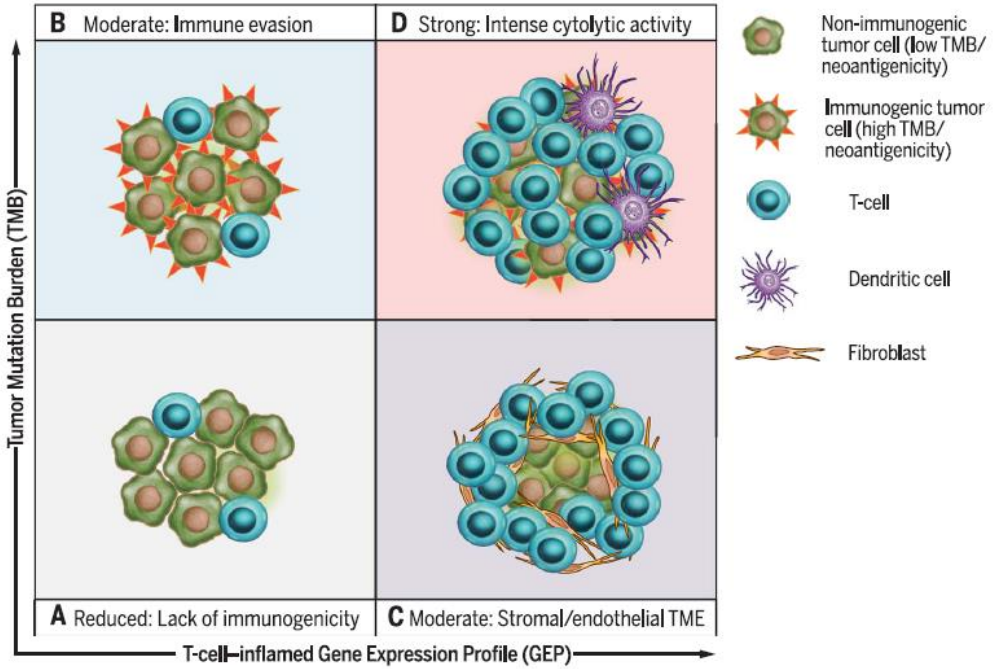
Neoantígenos

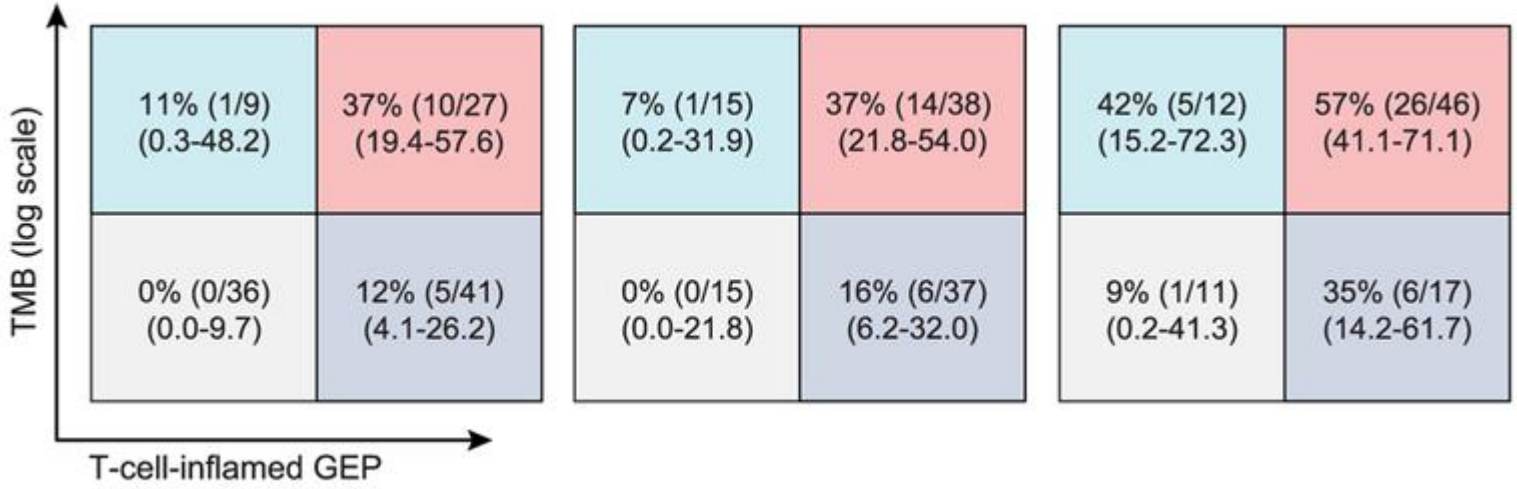


Turajilic S et al. Lancet Oncology. 2017.

Combinación de biomarcadores



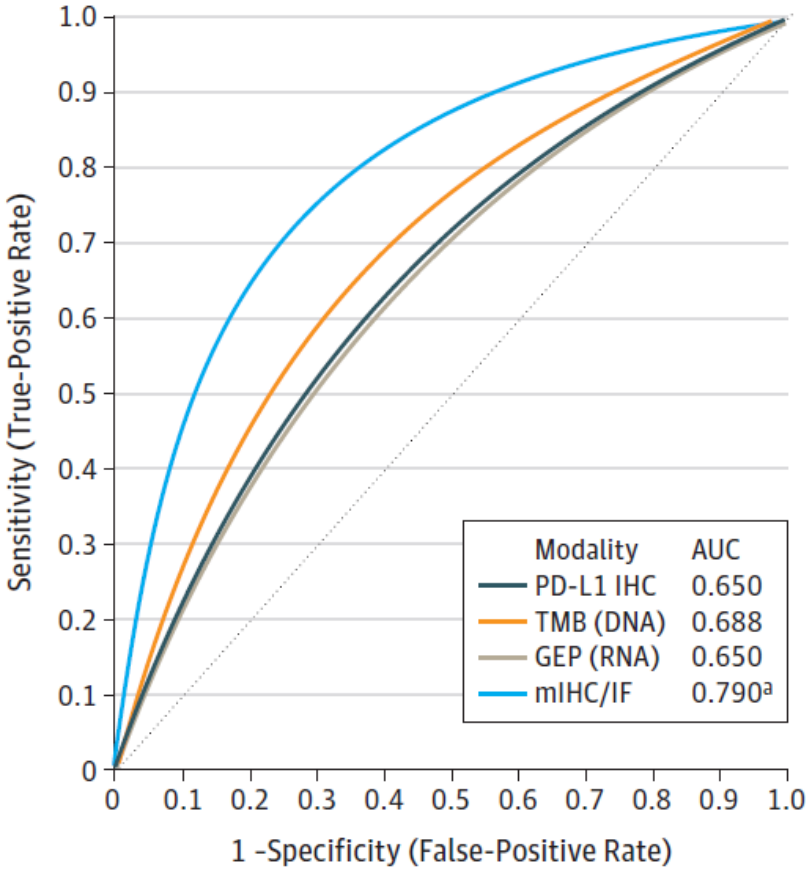


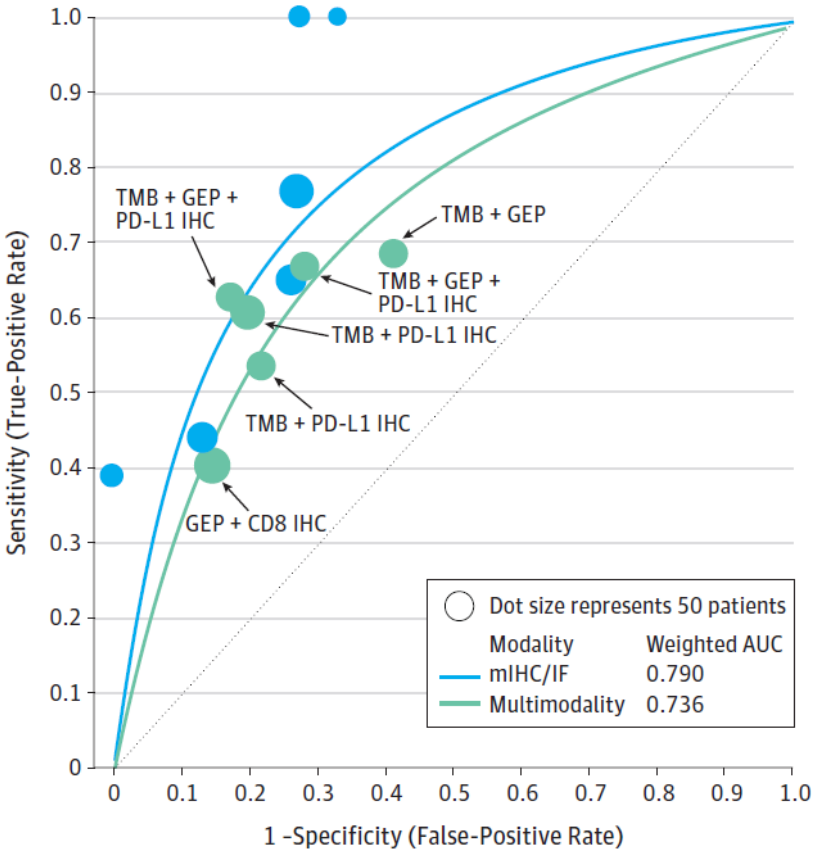


Berraondo P et al. Immunity. 2016-

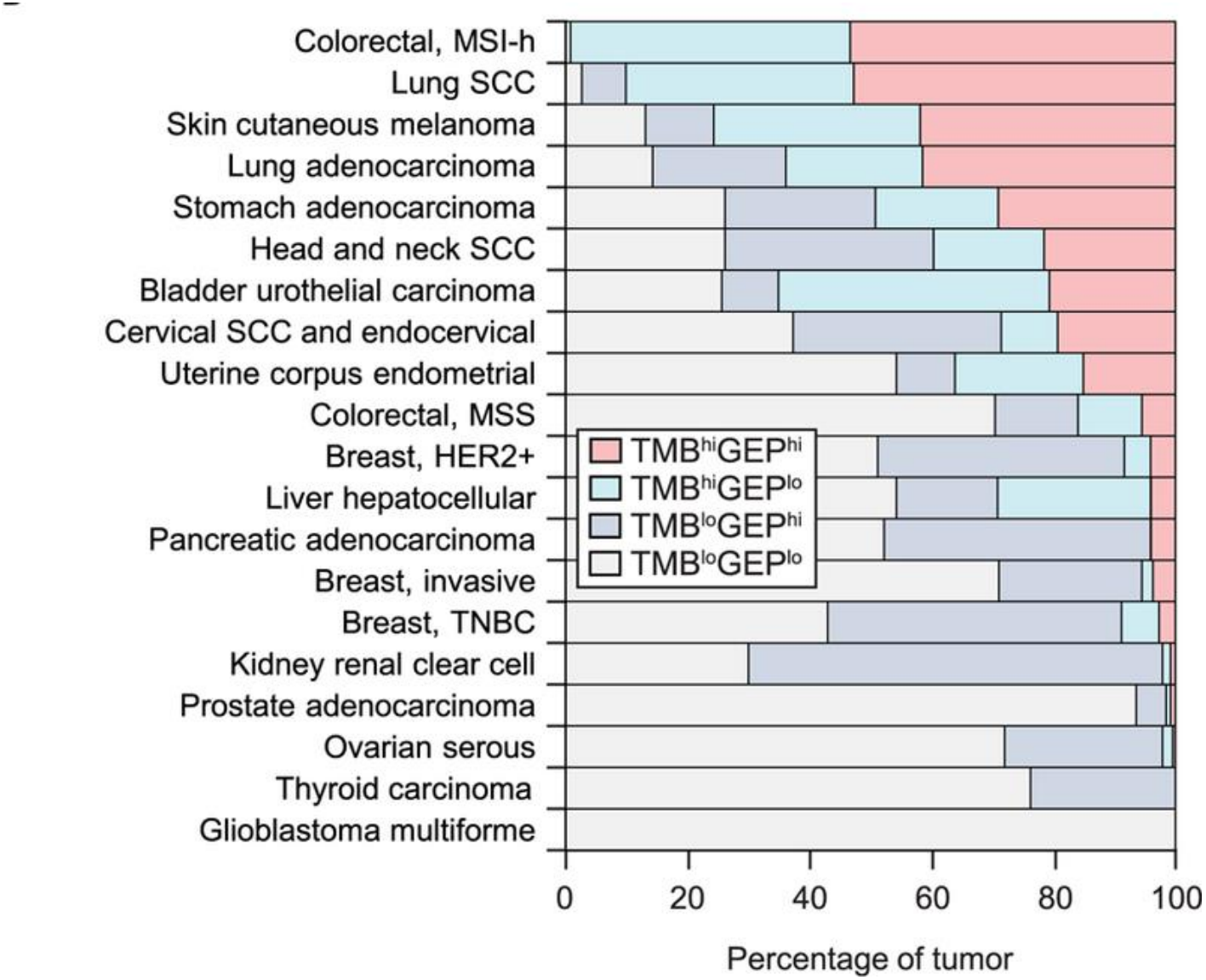
Cristescu R et al. Science. 2018.

Combinación de biomarcadores





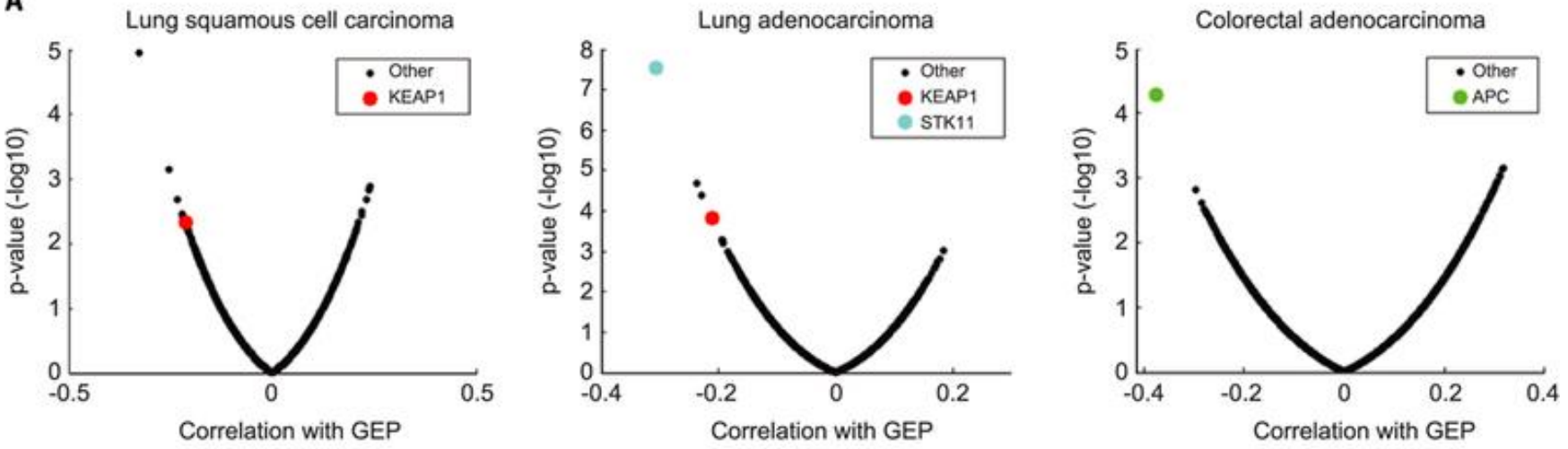
Combinación de biomarcadores



Cristescu R et al. Science. 2018.

Efecto de mutaciones conductoras

A

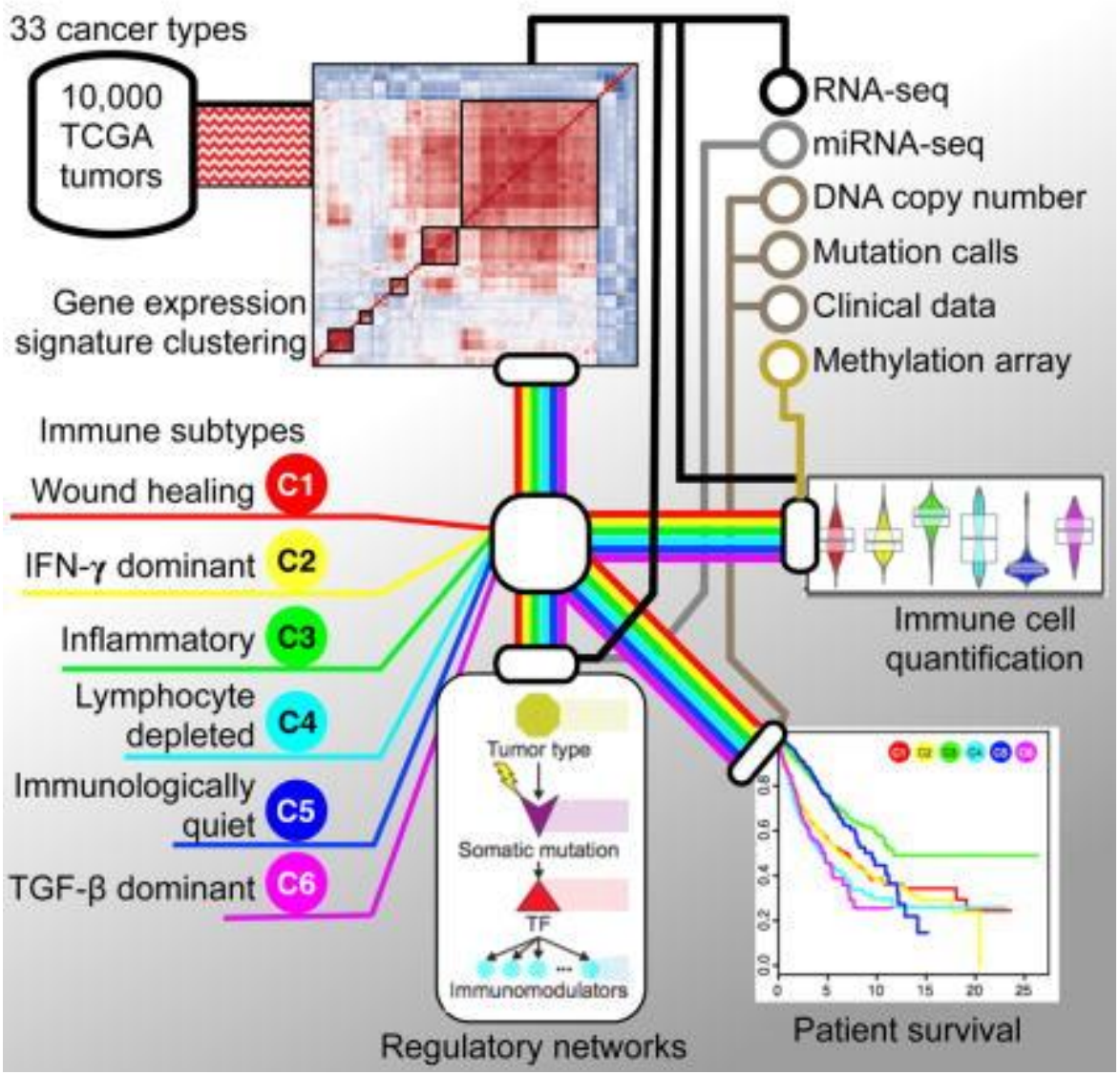


B

Indication	***STK11***	***APC***	*MYBPC2*	*ALMS1*	*DYNC2H1*	*OR4N3P*	*PTPRB*	*L1TD1*	*BANK1*	*ZNF423*	***KEAP1***	*COL11A1*	*GLTPD2*	*CSMD1*	*TJP3*	*CARD11*
Lung adenocarcinoma	-5.28	0.54	-0.54	0.14	0.25	0.48	0.01	0.21	-0.98	-2.13	-2.1	-0.06	0	-2.01	0	-1.18
Lung SCC	0.04	-0.02	0	-2.51	0.07	0	-1.71	0.97	0.08	0.17	-1.87	0.23	-0.14	0.33	0.13	-0.03
Colorectal adenocarcinoma	1.09	-4.9	0.46	0.17	0.24	0	0.44	-2.18	-0.26	0.62	0.76	0.02	-2.02	0.67	-2.01	0.57
Skin cutaneous melanoma	-0.69	0.11	-3.07	1.23	0.06	-2.22	-2.18	0.15	-2.16	-0.4	0.81	0.17	0.48	-0.16	-0.22	0.41
Liver hepatocellular carcinoma	0	-1.42	0.3	-0.85	-2.35	0	-0.11	0.69	-0.62	-1.44	0.25	-0.87	0	-0.18	0	-2.01
Head and neck SCC	0.03	-0.03	1.07	0.18	0.37	-0.07	0.65	0	0.52	0.1	-0.25	-2.04	0	0.09	0.43	-0.03
Uterine corpus endometrial carcinoma	0.45	0.4	0.13	1.41	0.52	0	1.08	0.78	-0.07	0.36	1.5	0.64	0.11	0.33	1	0.45
Stomach adenocarcinoma	-0.1	0.14	-0.18	0.62	0.66	0	0.13	0.62	-0.22	0.42	0.23	0.19	0	0.79	1.61	-0.03
Cervical squamous cell carcinoma	-0.4	0.14	0.51	-0.09	0.59	-0.32	-0.4	0.43	-0.01	-0.48	0	-1.02	0.39	-0.17	-0.32	-0.62
Bladder urothelial carcinoma	0	0.54	0.33	0.39	0.09	0	-0.3	0	0.92	0.38	0.44	-0.2	0	-0.42	0.68	0.12
Pan-cancer	-0.48	-0.9	-0.91	1.21	0.56	0.03	-0.27	0.54	-1.05	0.07	0.14	0.41	-1.64	1.13	0.17	0.02

Cristescu R et al. Science. 2018.

Panorama inmune del cáncer

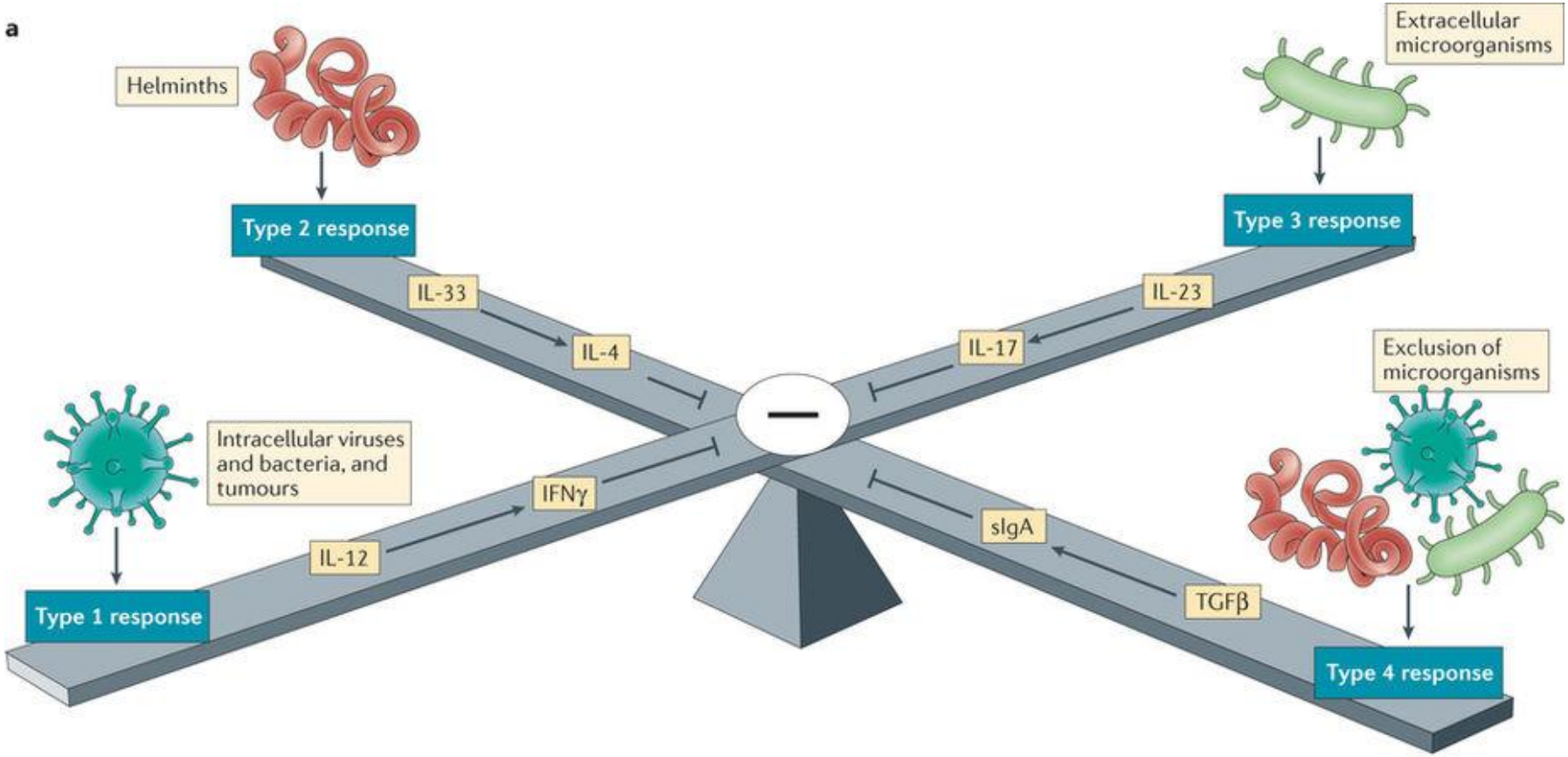


Panorama inmune del cáncer

	Macrophage: lymphocyte	Th1:Th2	Proliferation	Intratumoral heterogeneity	Other
Wound healing	Balanced	Low	High	High	
IFN-γ dominant	Lowest	Lowest	High	Highest	Highest M1 and highest CD8 T cells
Inflammatory	Balanced	High	Low	Lowest	Highest Th17
Lymphocyte depleted	High	Minimal Th	Moderate	Moderate	
Immunologically quiet	Highest	Minimal Th	Low	Low	Highest M2
TGF-β dominant	High	Balanced	Moderate	Moderate	Highest TGF-β signature

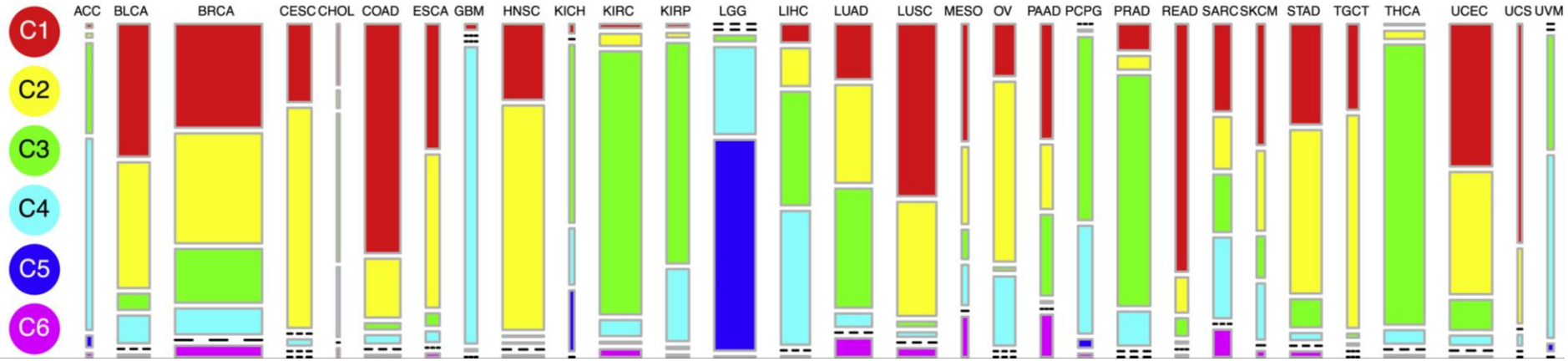
Thorsson V et al. Immunity 2018.

Panorama inmune del cáncer



Eberl G. Nat Rev Immunol. 2016 Aug;16(8):524-32.

Panorama inmune del cáncer



Wound healing
IFN-γ dominant
Inflammatory
Lymphocyte depleted
Immunologically quiet
TGF-β dominant

C1 (Wound Healing) Colorectal cancer (COAD, READ) and lung squamous cell carcinoma (LUSC),breast carcinoma (BRCA) luminal A head and neck squamous cell carcinoma (HNSC) classical, and the chromosomally unstable (CIN) gastrointestinal subtype.

C2 (IFN-γ Dominant) highly mutated BRCA, gastric, ovarian (OV), HNSC, and cervical tumors (CESC).

C3 (Inflammatory) kidney, prostate (PRAD), pancreatic cancers (PAAD), and papillary thyroid carcinomas (THCA).

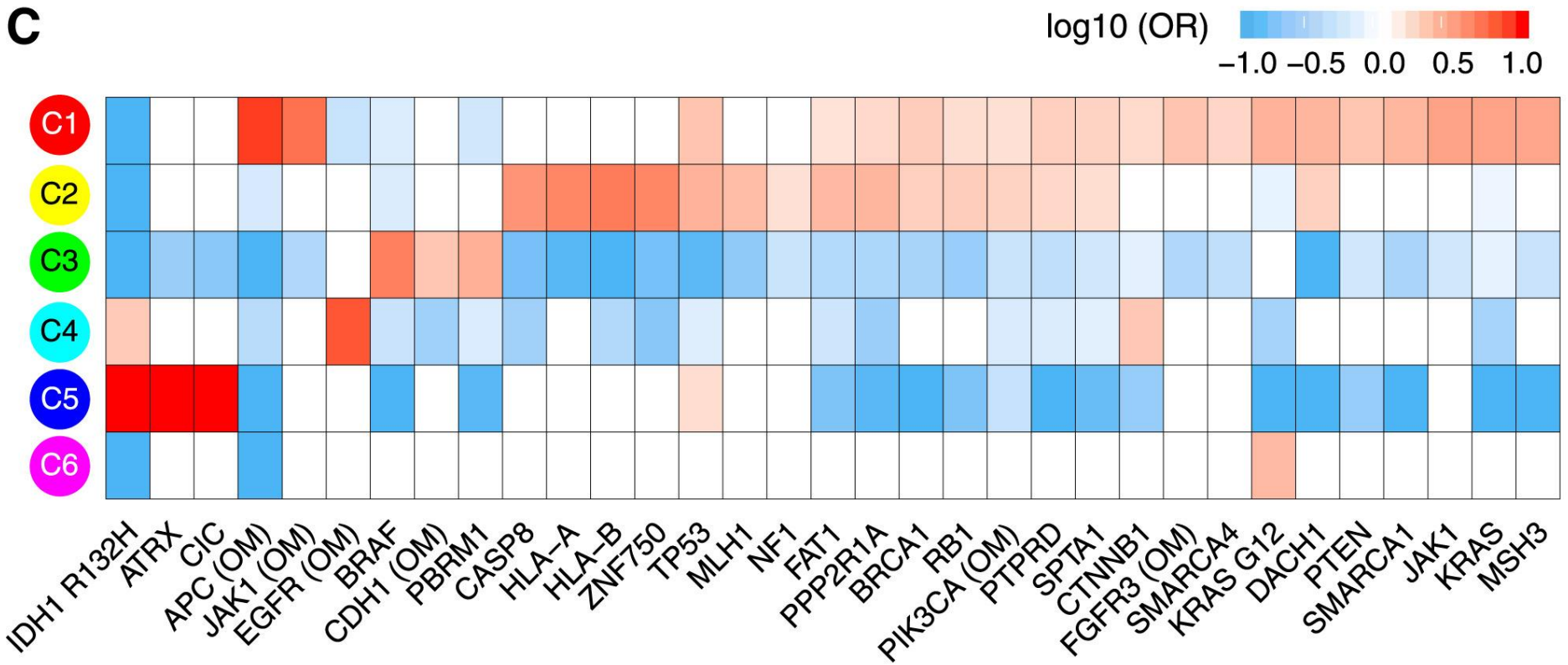
C4 (Lymphocyte Depleted) adrenocortical carcinoma (ACC), pheochromocytoma and paraganglioma (PCPG), hepatocellular carcinoma (LIHC), and gliomas.

C5 (Immunologically Quiet), gliomas (LGG)

C6 (TGF-β Dominant), small group of mixed tumors not dominant in any one TCGA subtype,

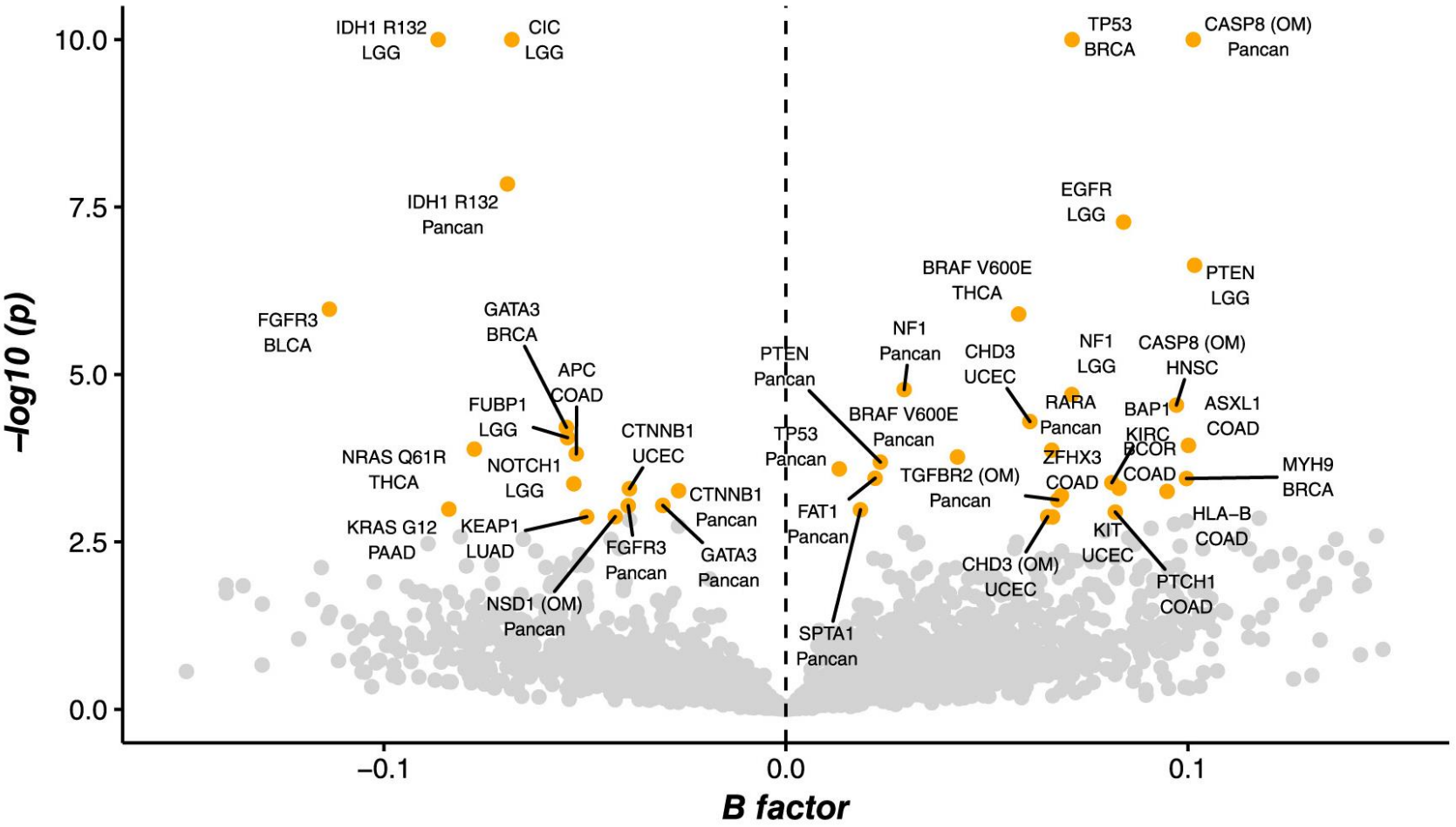
Thorsson V et al. Immunity 2018.

Panorama inmune del cáncer



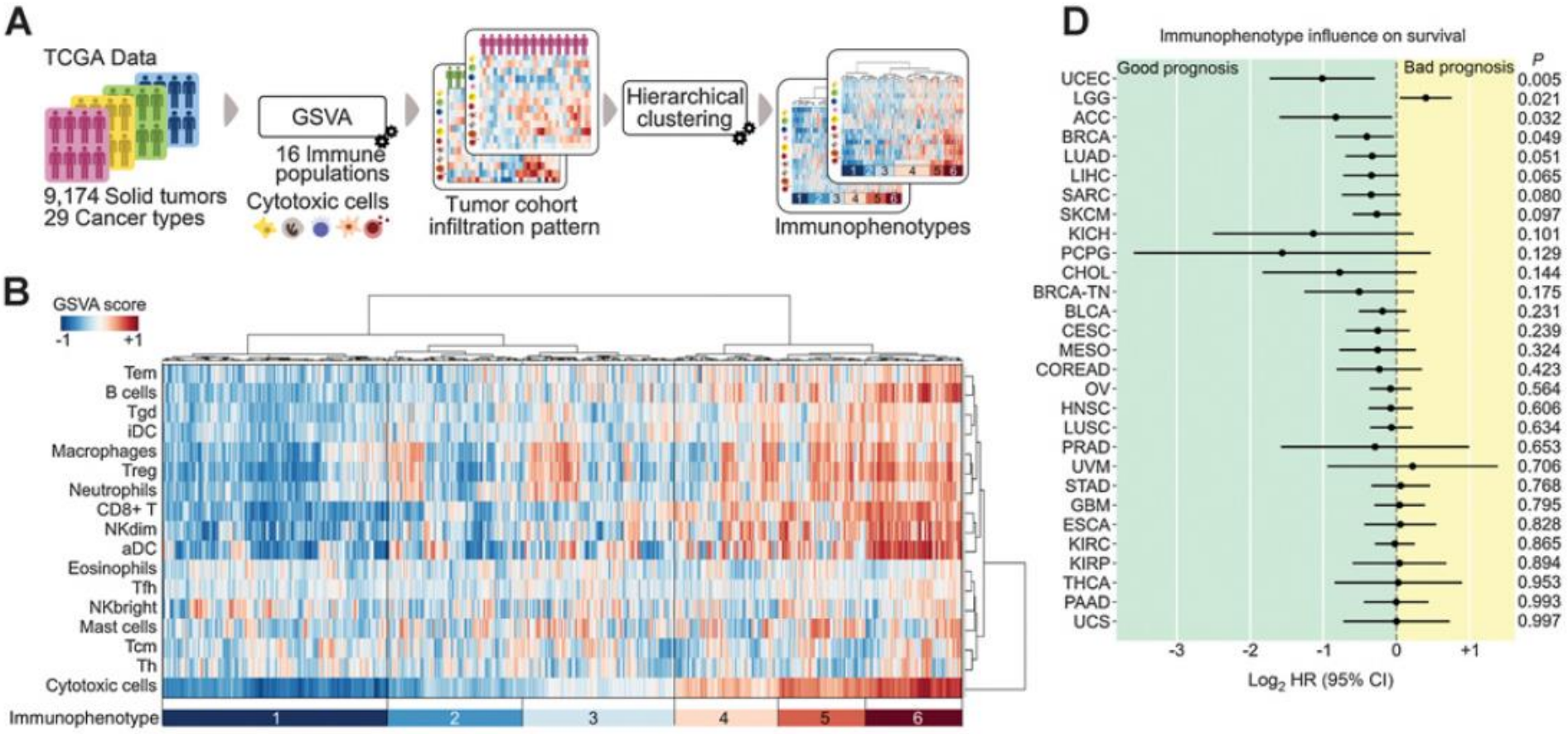
Thorsson V et al. Immunity 2018.

Panorama inmune del cáncer

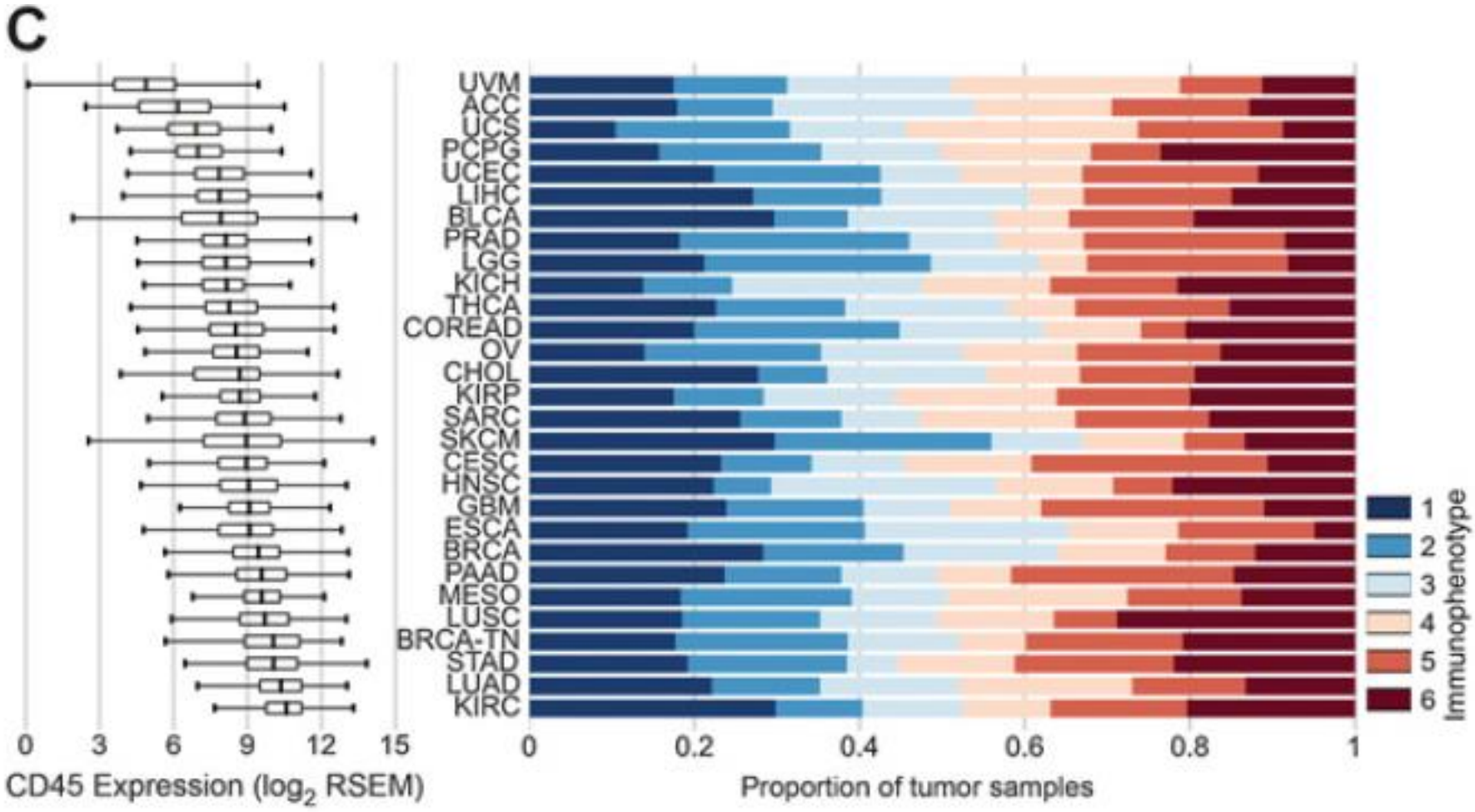


Specific driver mutations correlated with lower (*CTNNB1*, *NRAS*, or *IDH1*) or higher (*BRAF*, *TP53*, or *CASP8*) leukocyte levels across all cancers

Panorama inmune del cáncer

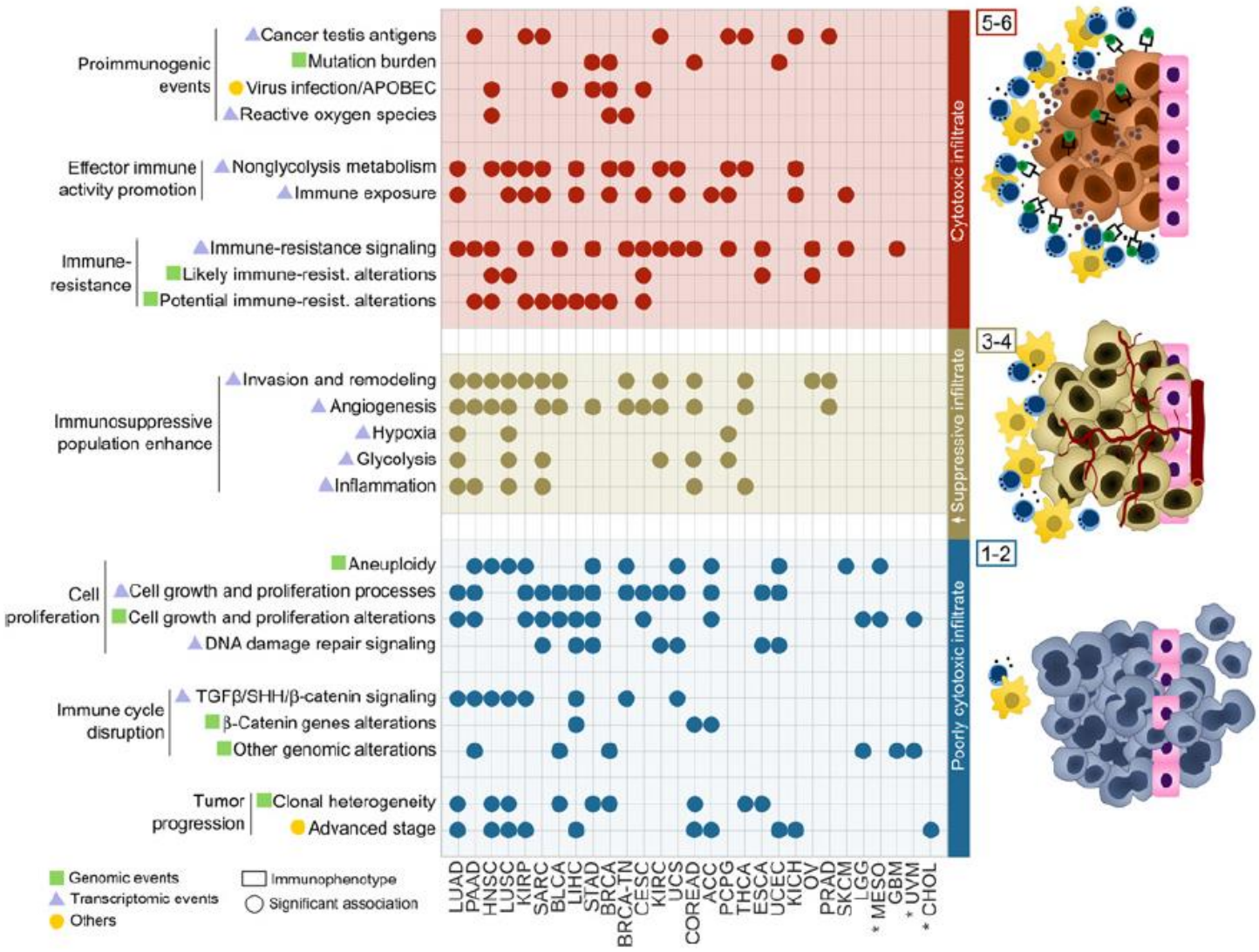


Panorama inmune del cáncer



Tamborero D et al. Clin Can Res 2019.

Panorama inmune del cáncer



Tamborero D et al. Clin Can Res 2019.

Conclusions

- La generación de respuestas inmune endógenas es frecuente.

- Se han propuesto diversos biomarcadores y combinaciones de biomarcadores.

- Se pueden establecer seis inmunofenotipos:

1) reparación de heridas
2) dominados por IFNγ
3) Inflamatorios
4) deplecionado de linfocitos
5) inmunológicamente silente
6) dominado por TGF-β.

- Mutaciones conductoras influyen en la infiltración inmune.