Inmunología tumoral
Principios de inmunoterapia contemporánea

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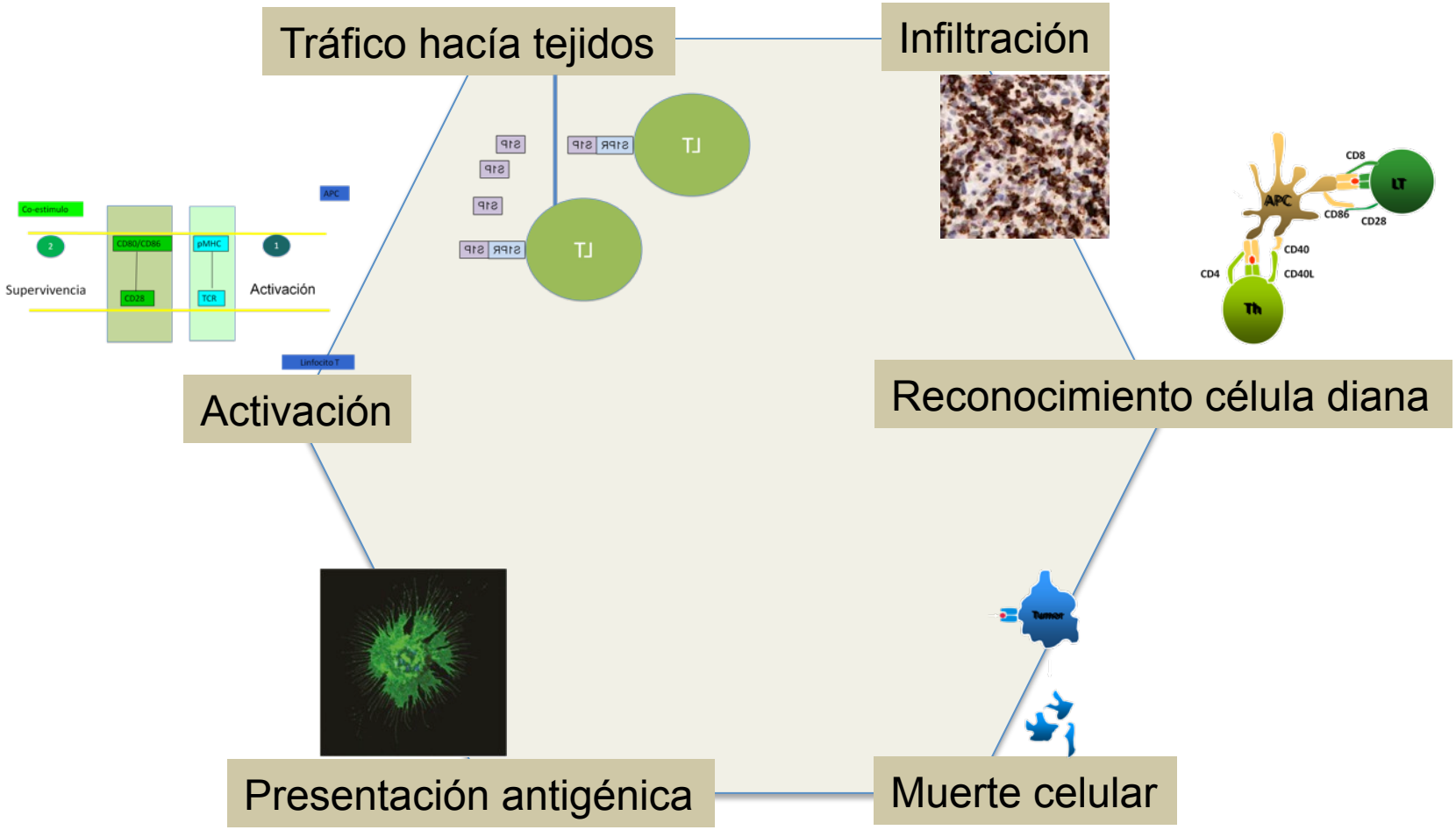
Contenido

- Respuesta inmune
- Evasión tumoral
- Melanoma metastásico
- Anti-CTLA4
- Anti-PD1
- Combinaciones

BREAKTHROUGH OF THE YEAR

Cancer
Immunotherapy

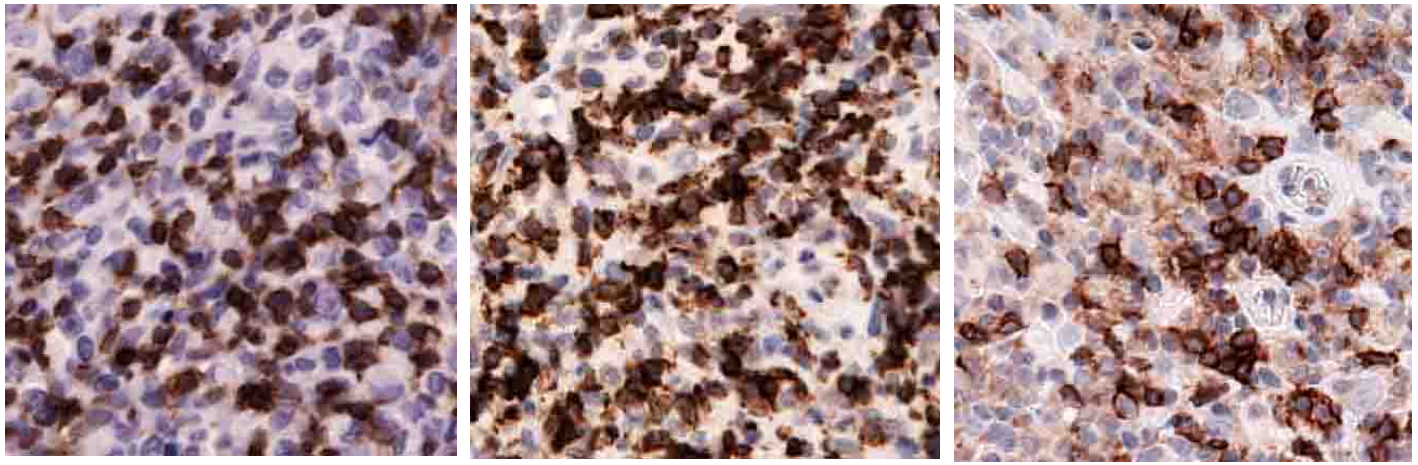
J Couzin-Frankel Science 2013;342:1432-1433
Wolchok Scientific American May 2014



Mellman I Immunity 2013

Respuesta inmune

CD3 **CD8** **CD4**



Galon J Nature Reviews Cancer 2012

Tumor associated antigens (TAA)

Producto de genes ***normales***

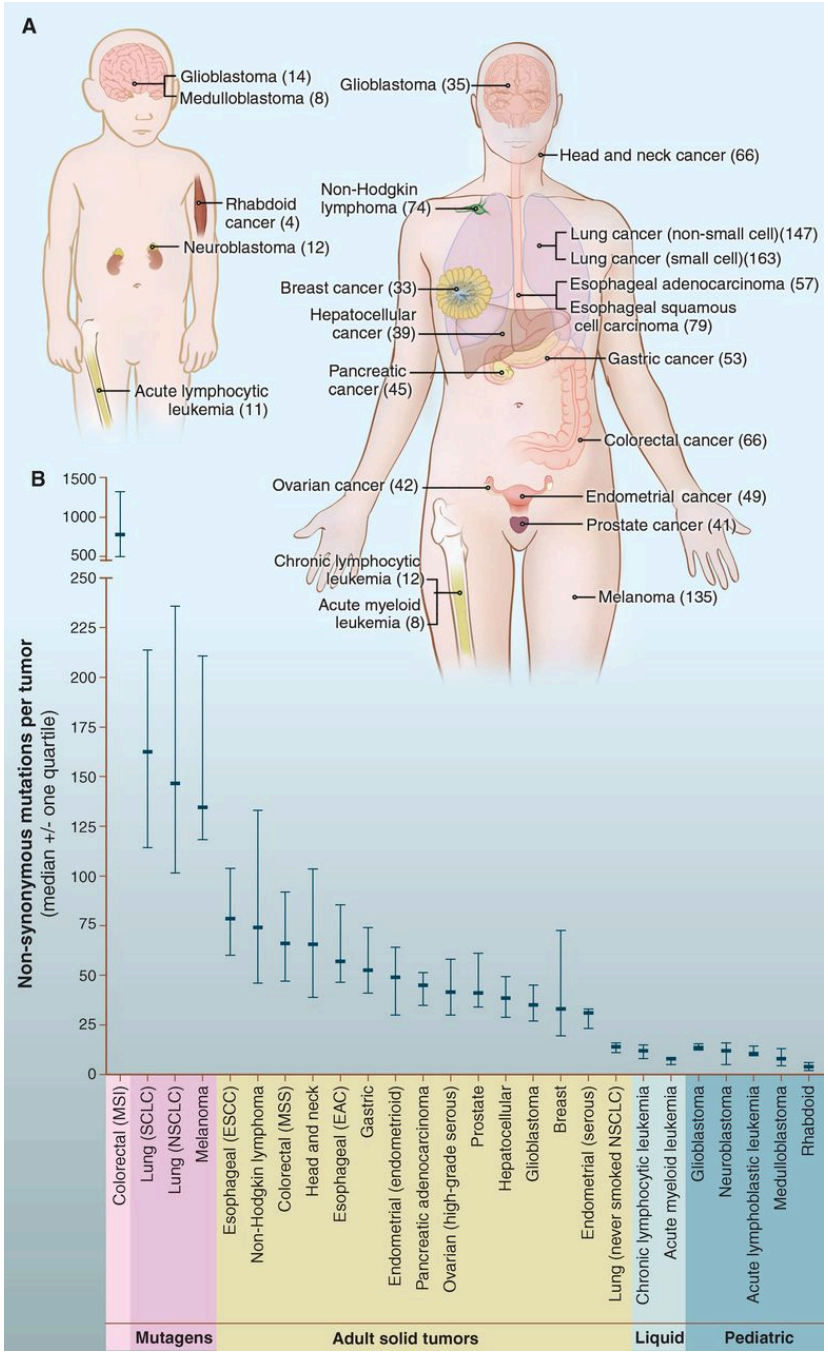
1. Sobreexpresión – HER2
2. Localización errónea – gp100
3. Tejido erróneo – NY-ESO-1
4. Antígenos fetales – CEA/AFP

Tumor specific antigens (TAA)

Producto de genes ***mutados***

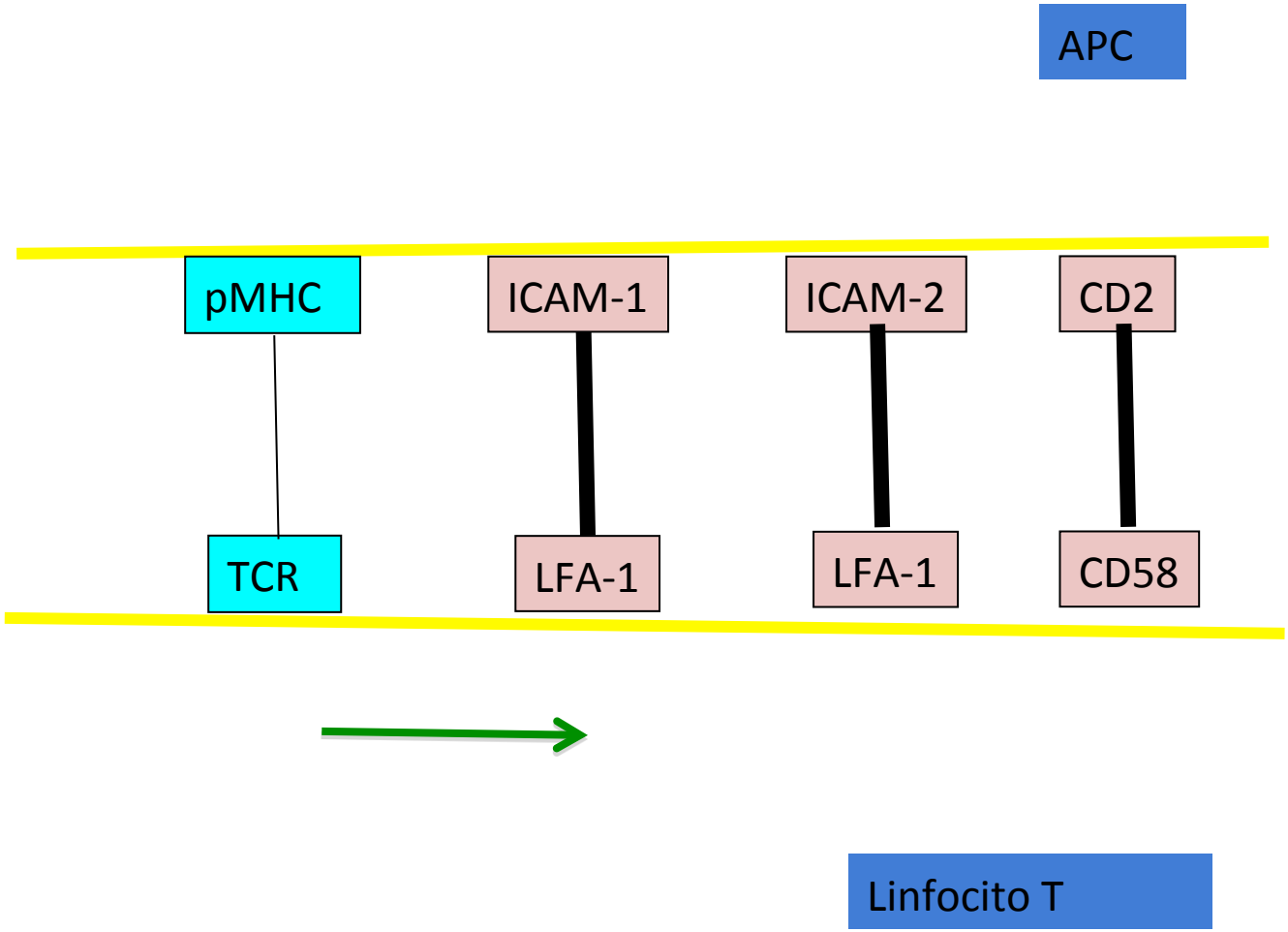
1. MUC-1
2. Cdk4
3. EGFR
4. p53

Diseñado por: Ivan Martínez Forero

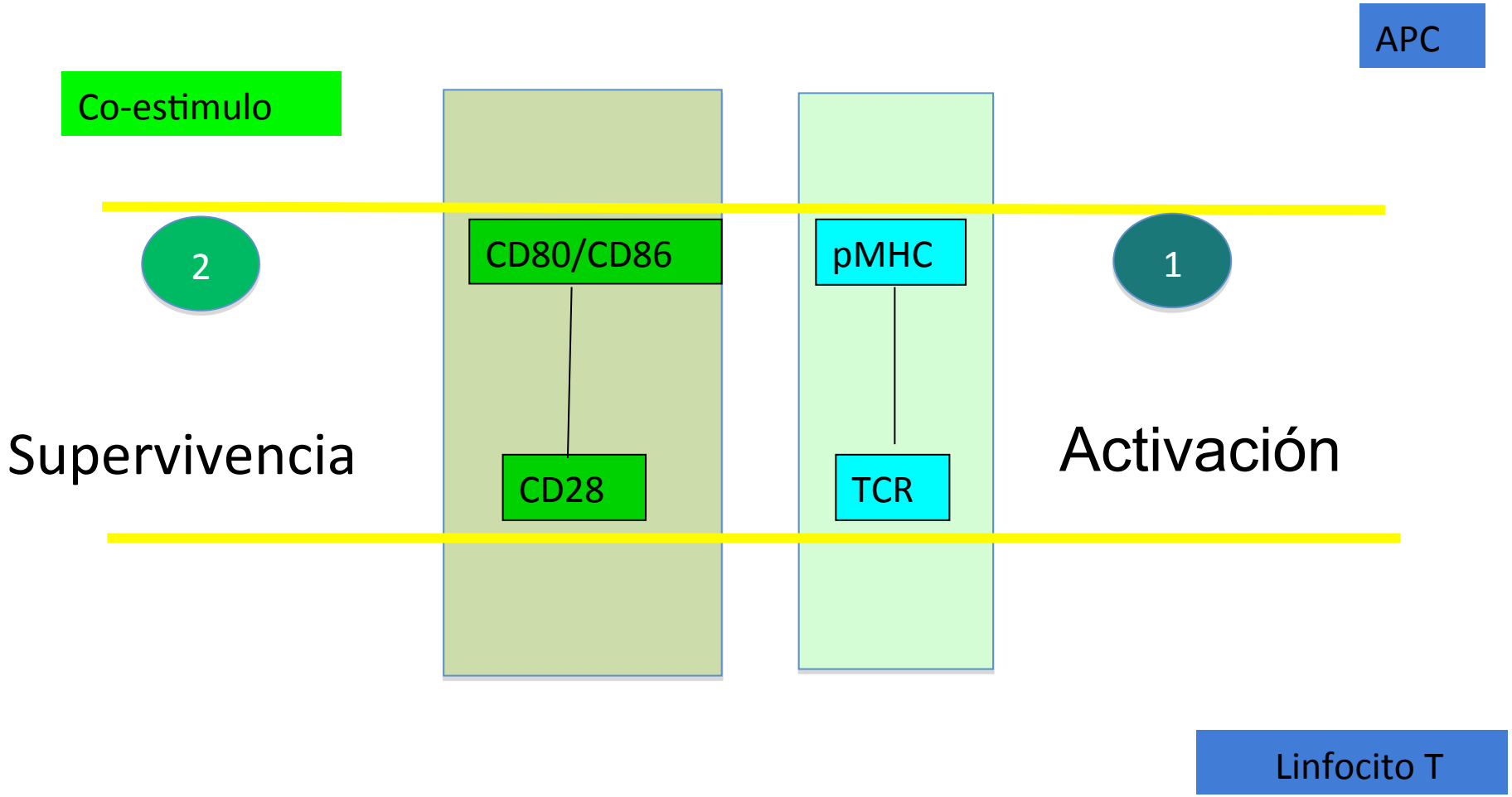


B Vogelstein et al. Science 2013;339:1546-1558

Interacción con células dendríticas



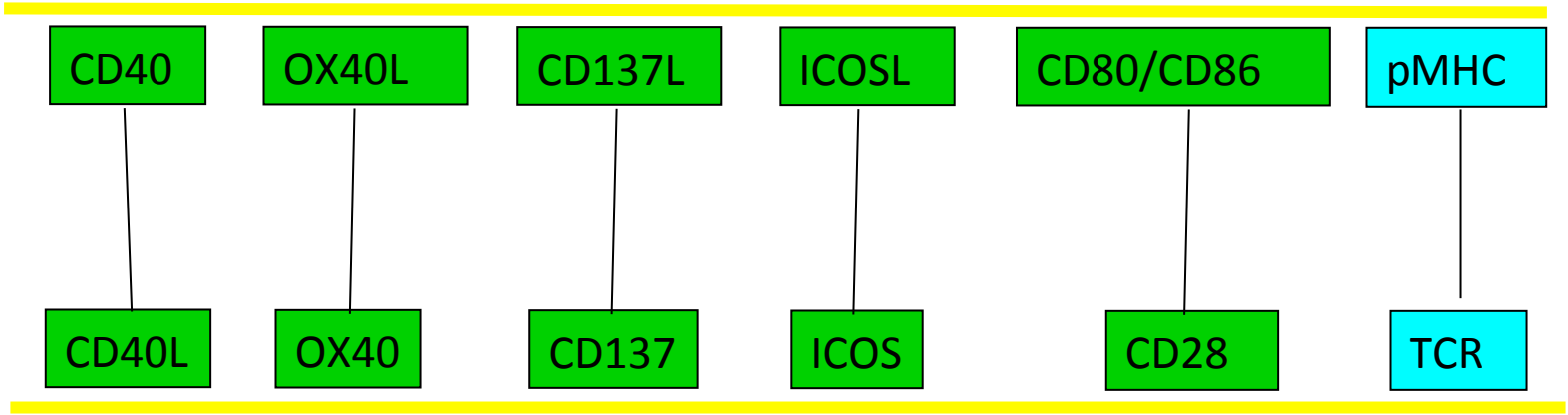
Abbas Immunology



Abbas Immunology

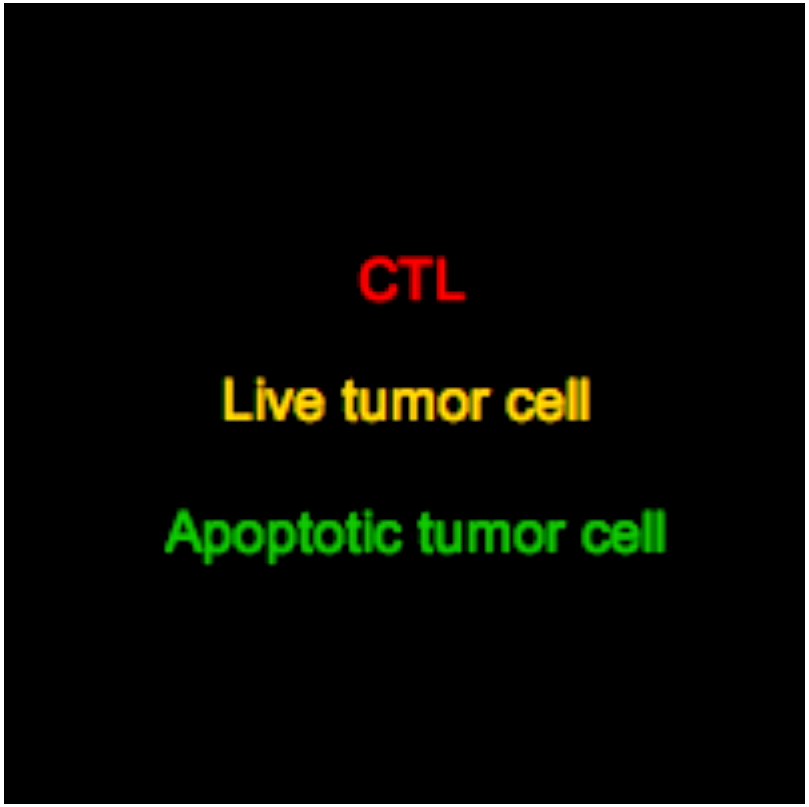
APC

Co-estimulo

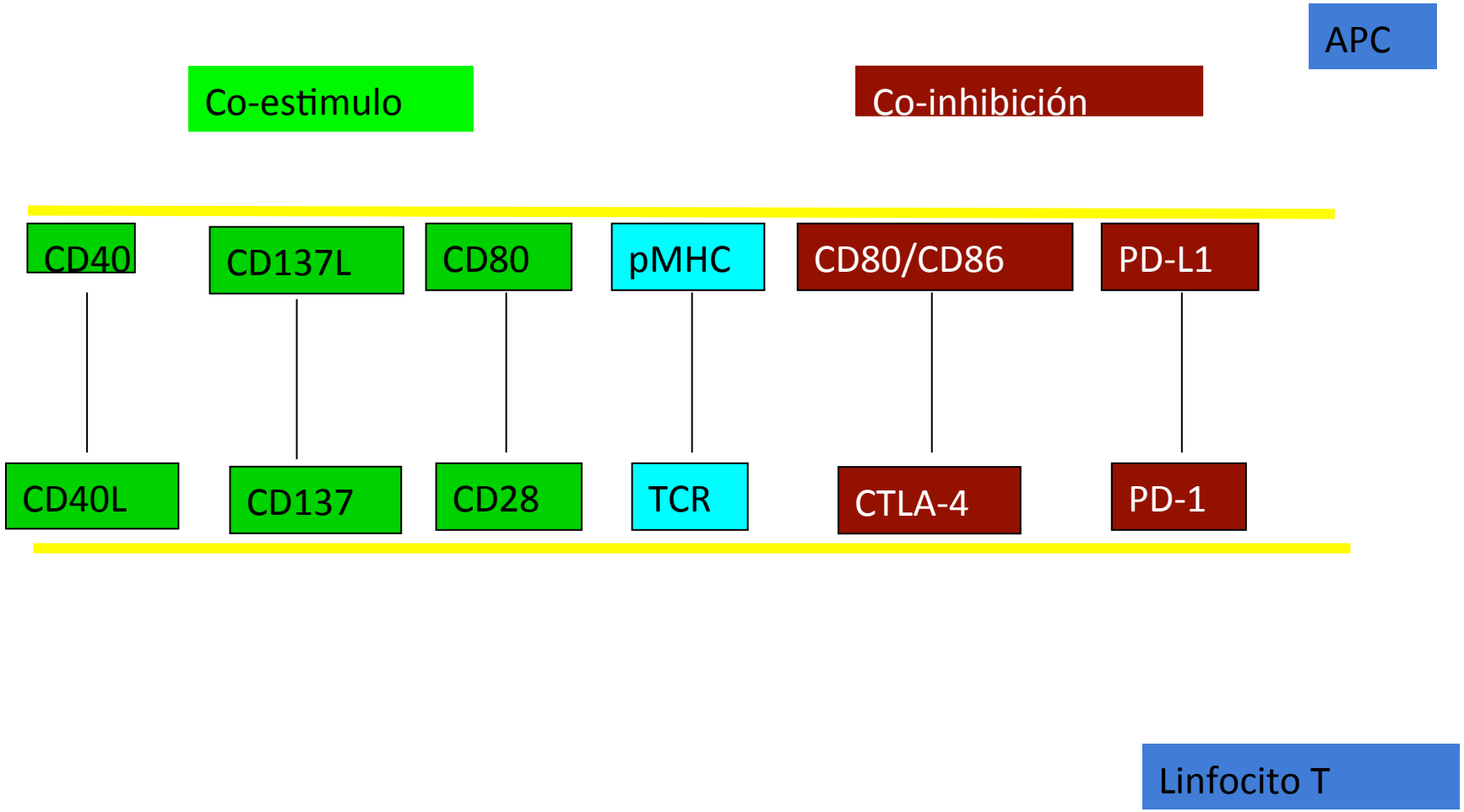


Linfocito T

Abbas Immunology

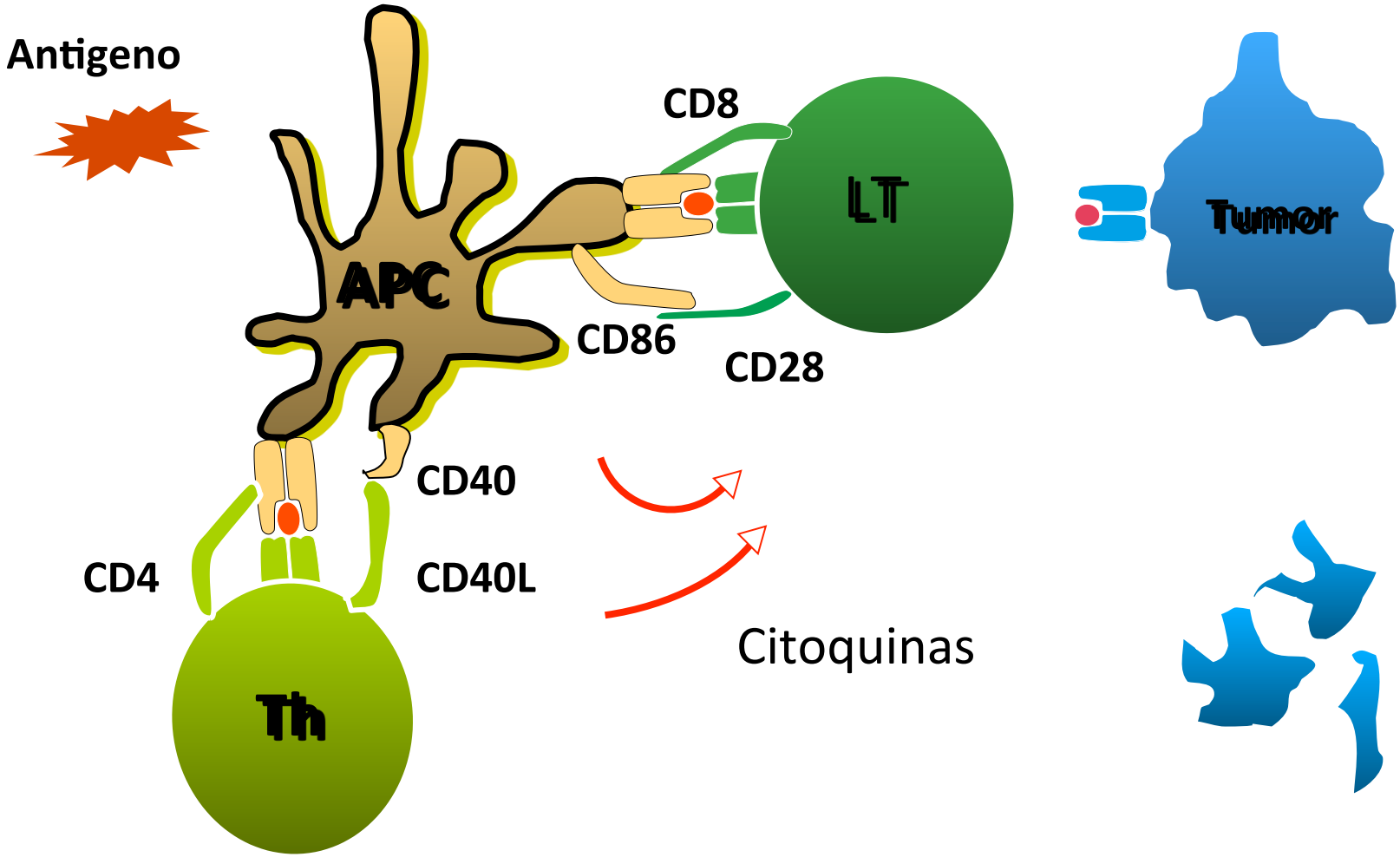


Bousso P Journal of Clinical Investigation 2006



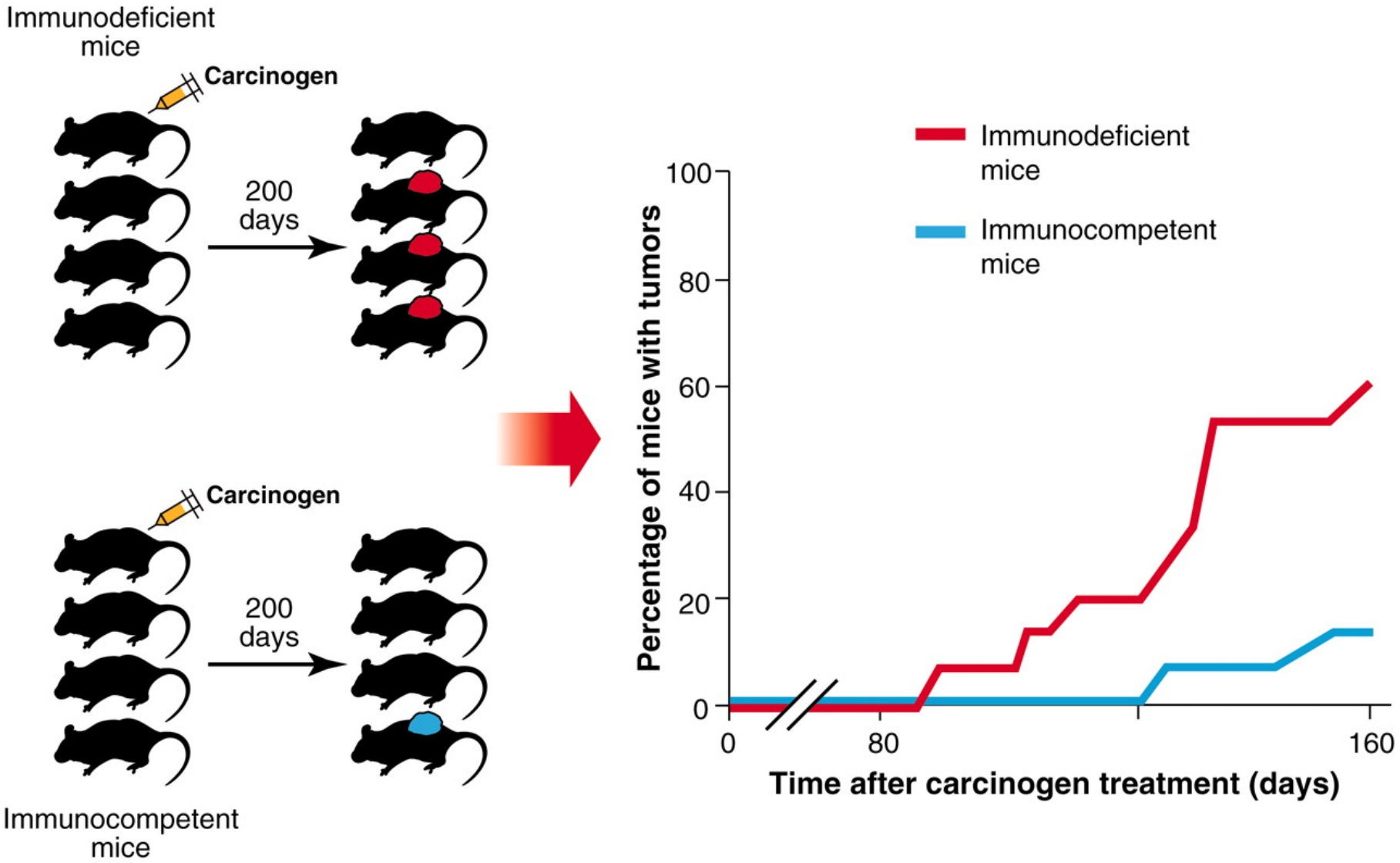
Mellman I Immunity 2013

Resumen



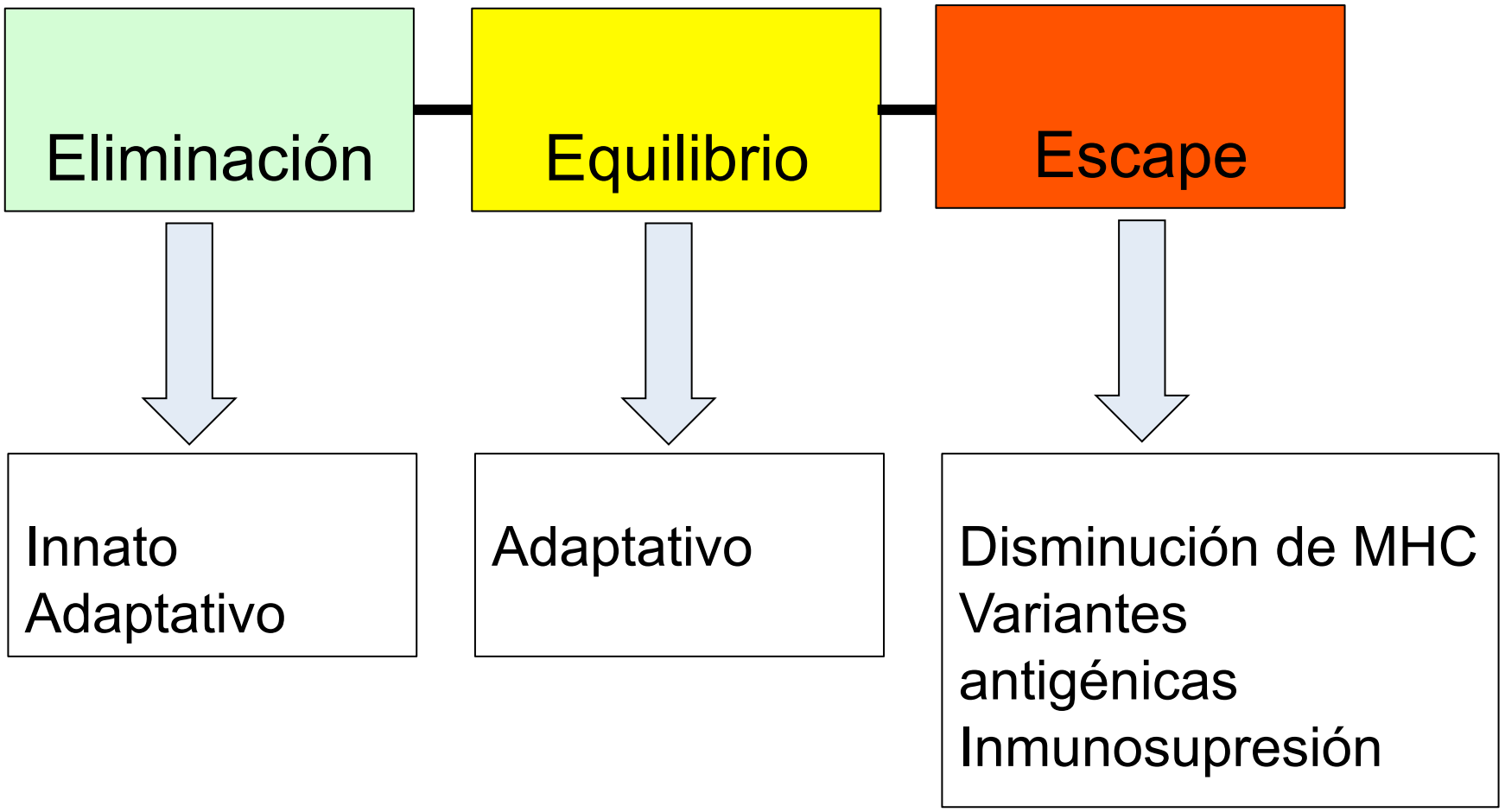
Abbas Immunology

Mecanismos de evasión tumoral

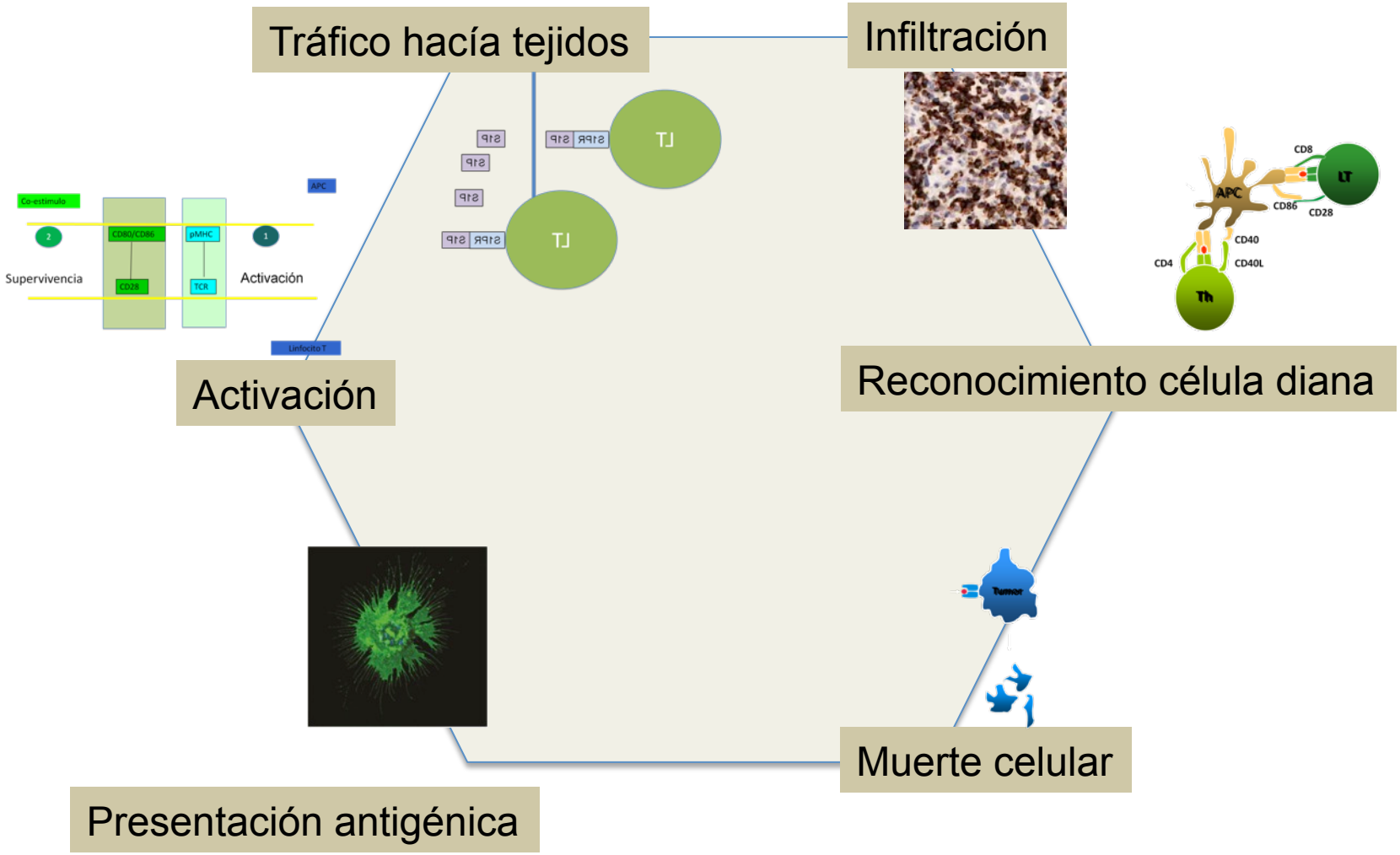


R D Schreiber et al. Science 2011;331:1565-1570

Inmuno-edición



Diseñado por: Ivan Martínez Forero



Mellman I Immunity 2013

Células del sistema inmune

1.T reguladoras

2.Mieloides supresoras

3.Macrófagos

Productos solubles

1. ***IL-10***
2. ***TGF-beta***

Células tumorales

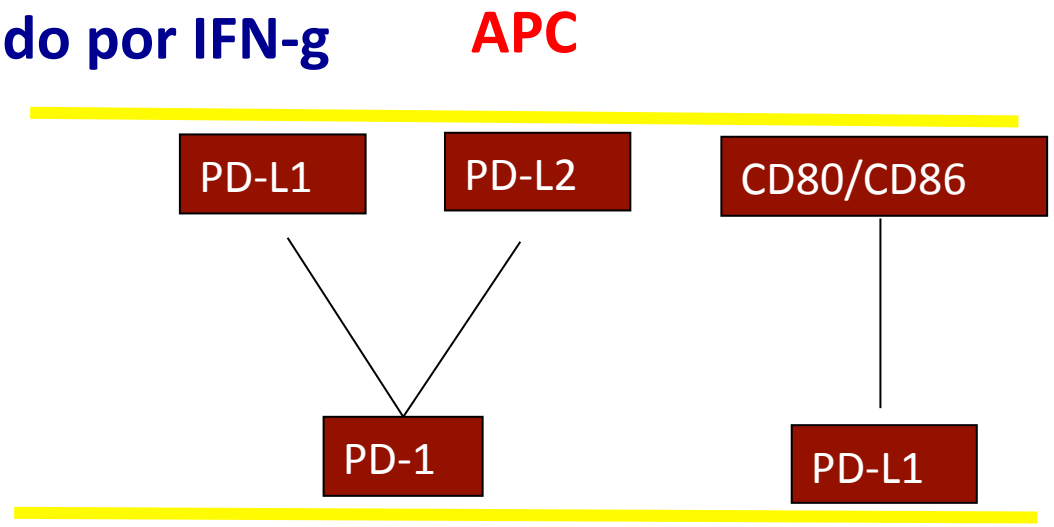
1.Disminución de MHC

2.Expresión de HLA-G

3.Expresión de PD-L1

Diseñado por: Ivan Martínez Forero

APC
Epitelio
Células tumorales
Inducido por IFN-g

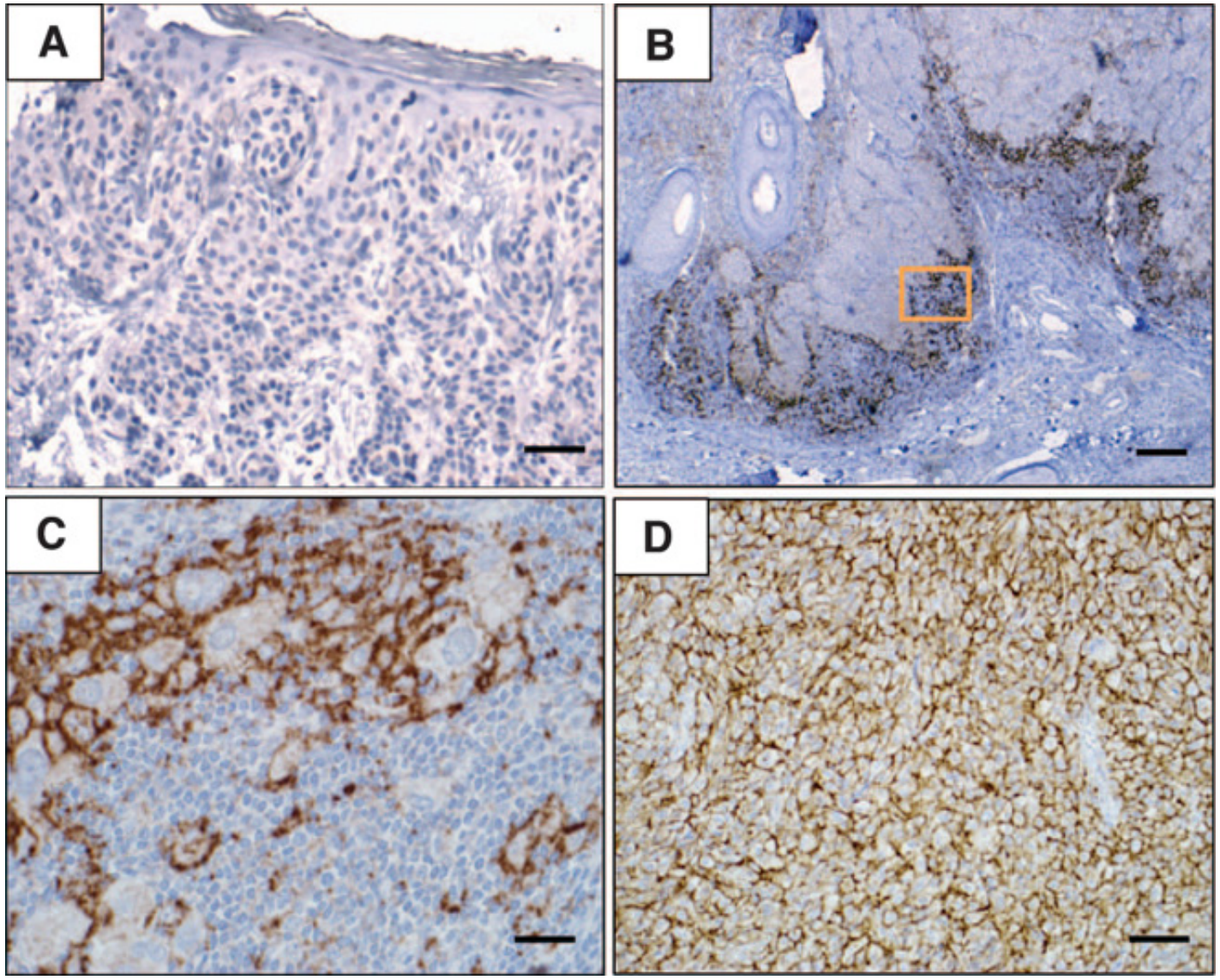


Linfocito T

Diseñado por: Ivan Martínez Forero

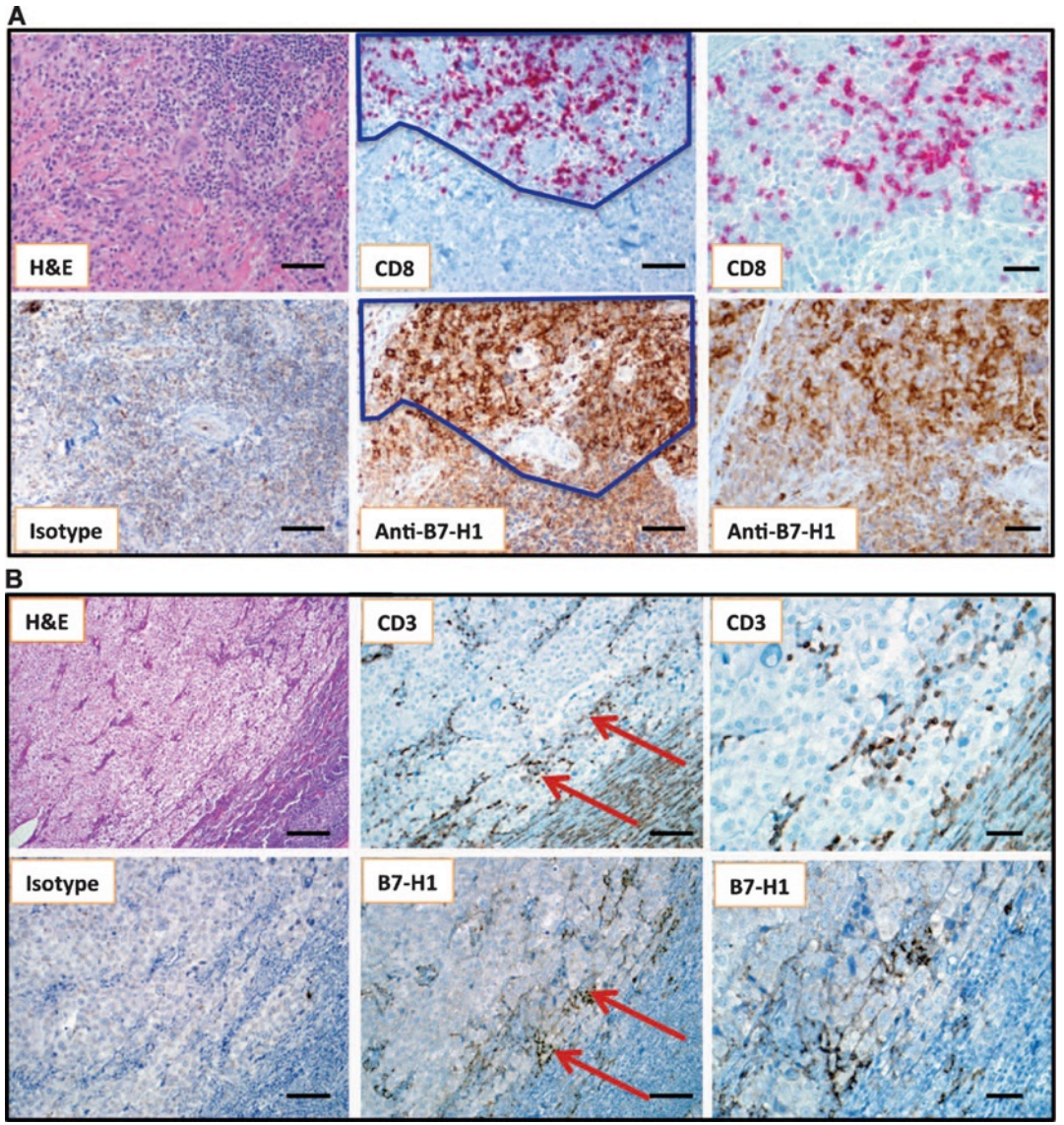
Nevus

Melanoma -Primario



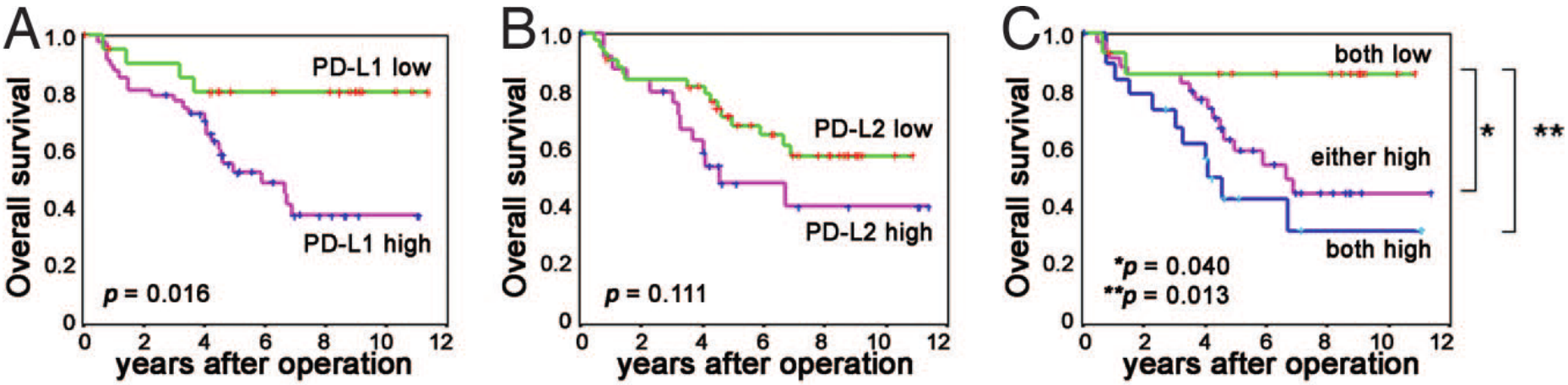
Met
Melanoma

J. M. Taube *et al., Sci Transl Med* 2012;4:127ra37

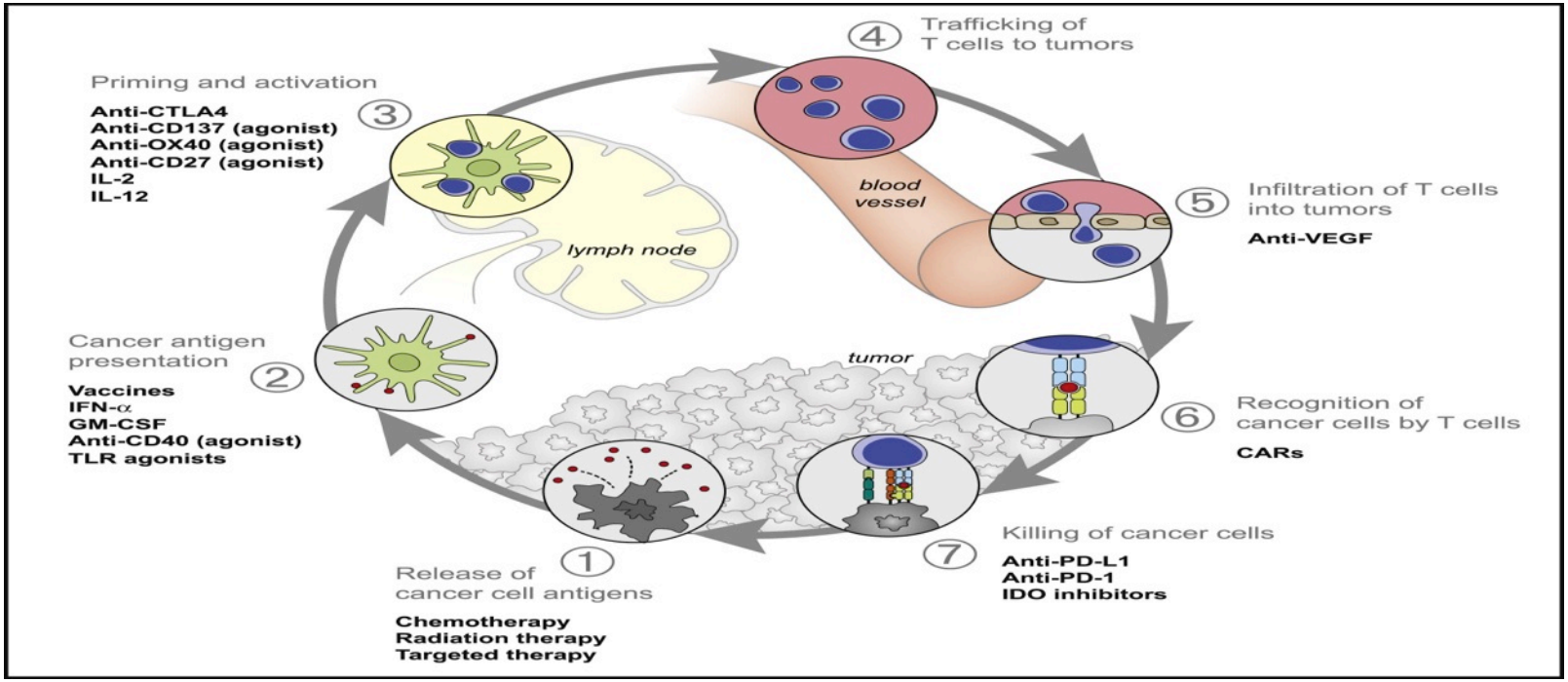


J. M. Taube *et al., Sci Transl Med* 2012;4:127ra37

PD-L1



H Nishimura et al. Science 2001;291:319-322

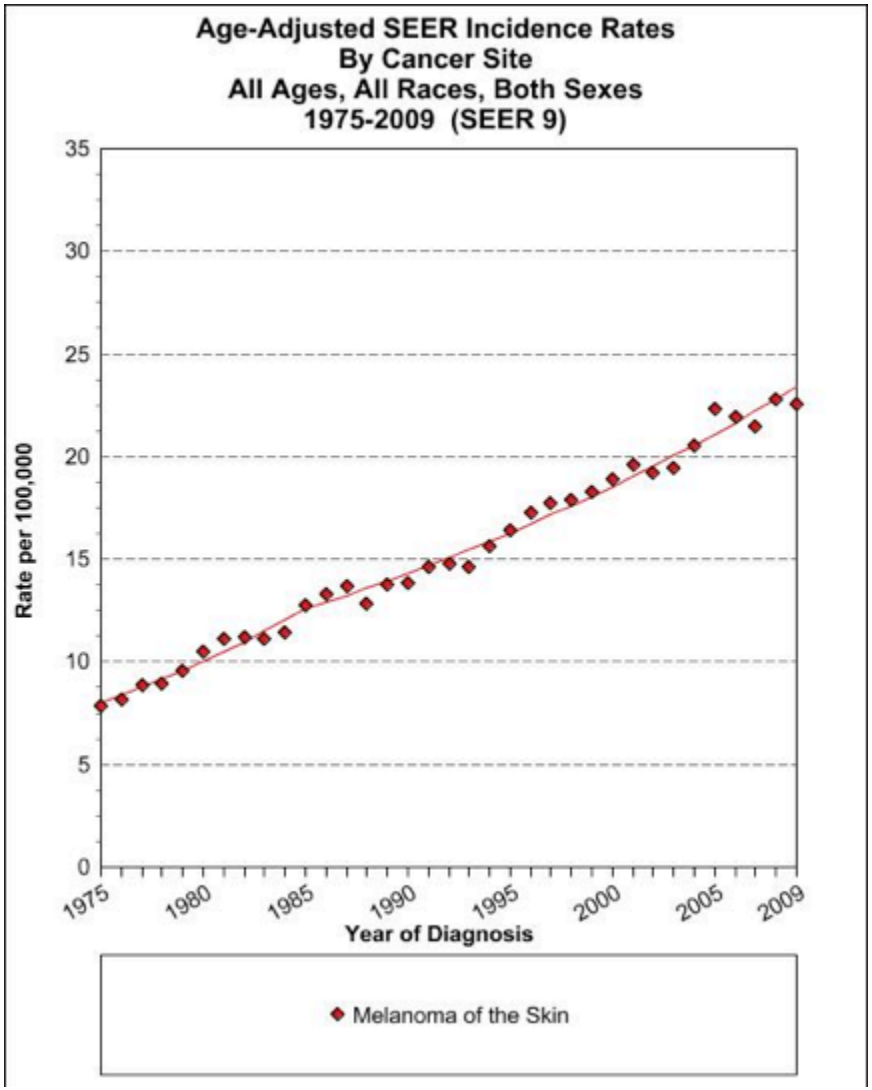


Mellman I Immunity 2013

Epidemiología (Incidencia)

5-10 % Cáncer Piel

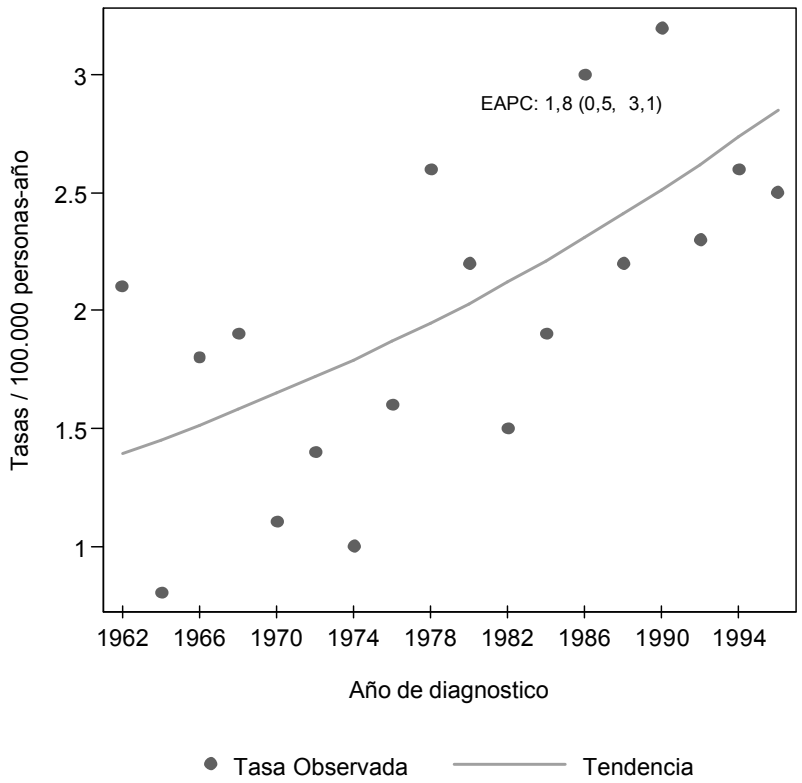
80% Mortalidad



SEER Acceso Agosto 15 de 2012

Epidemiología (Incidencia)

Colombia, Cali. Cambio medio anual de la tasa de incidencia de melanoma de piel estandarizada por edad con la población mundial estándar en mujeres durante el periodo 1962 - 1996



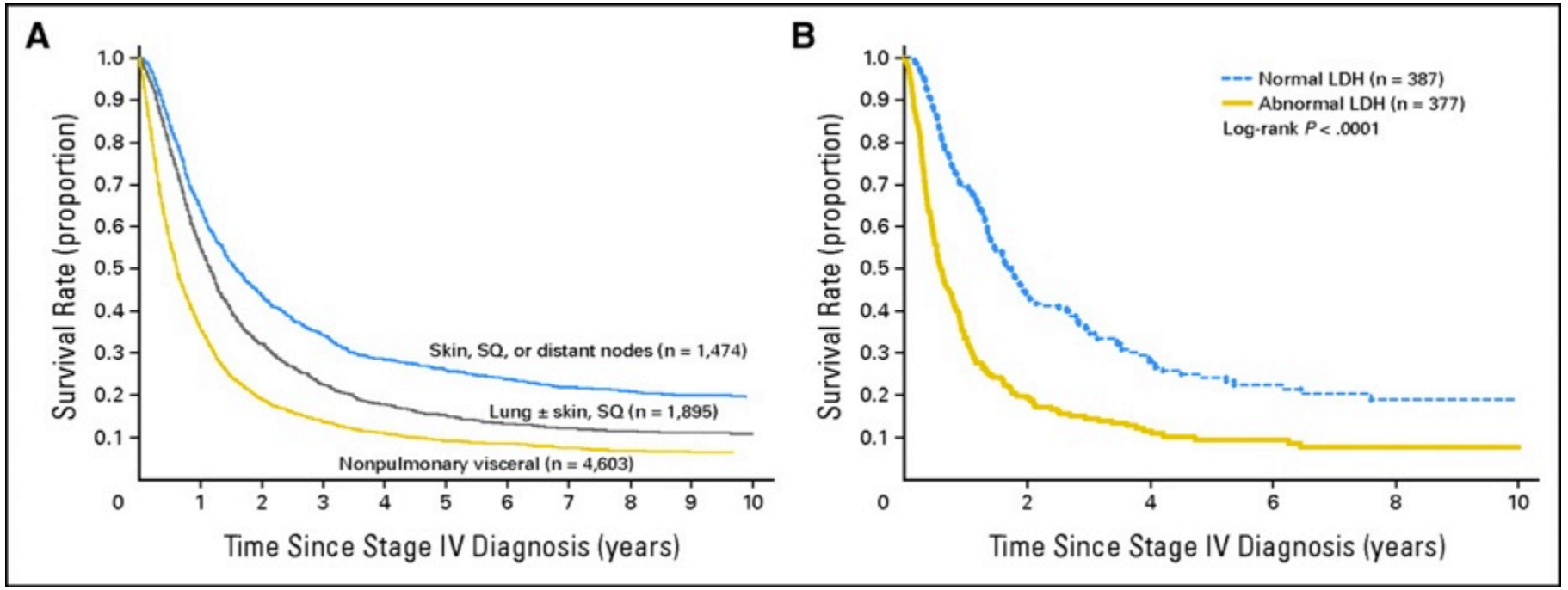
Fuente: Registro Poblacional de Cáncer de Cali
Departamento de Patología, Facultad de Salud
Universidad del Valle
Santiago de Cali, Valle, Colombia

Epidemiología (Diagnóstico)

Estado	Distribución (%)	Supervivencia 5 años (%)
Localizado	84	98.2
Regional	9	62.4
Extendido	4	15.1
Sin identificar	3	75.8

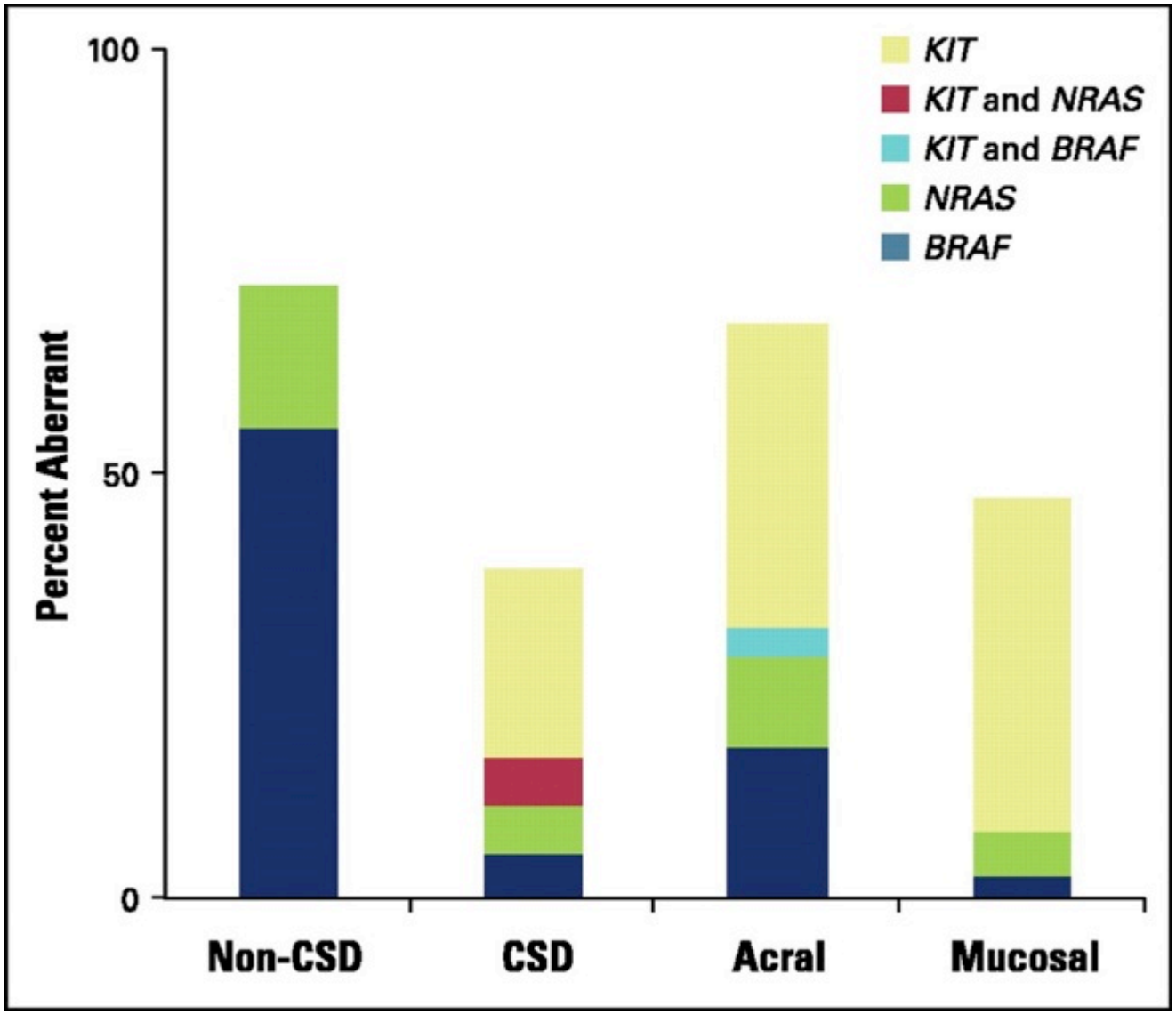
SEER Acceso Agosto 15 de 2012

Epidemiología (Metástasis)



Balch C M et al. JCO 2009;27:6199-6206

Marcadores genéticos - Tipos



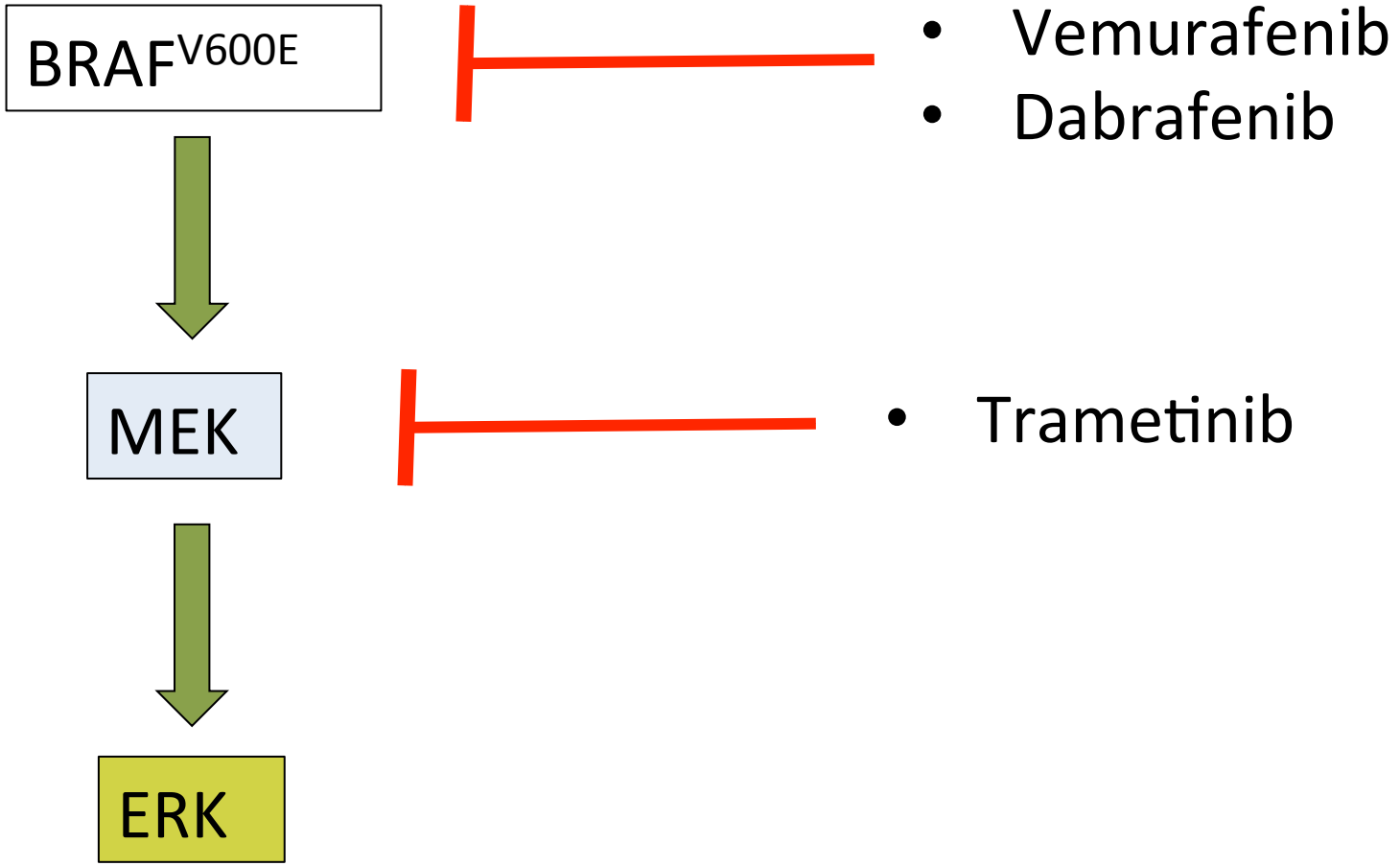
Curtin J A et al. JCO 2006;24:4340-4346

Opciones terapéuticas

- Dacarbazina
- IL-2
- Ipilimumab
- Terapia dirigida (BRAFi, MEKi)
- Combinaciones

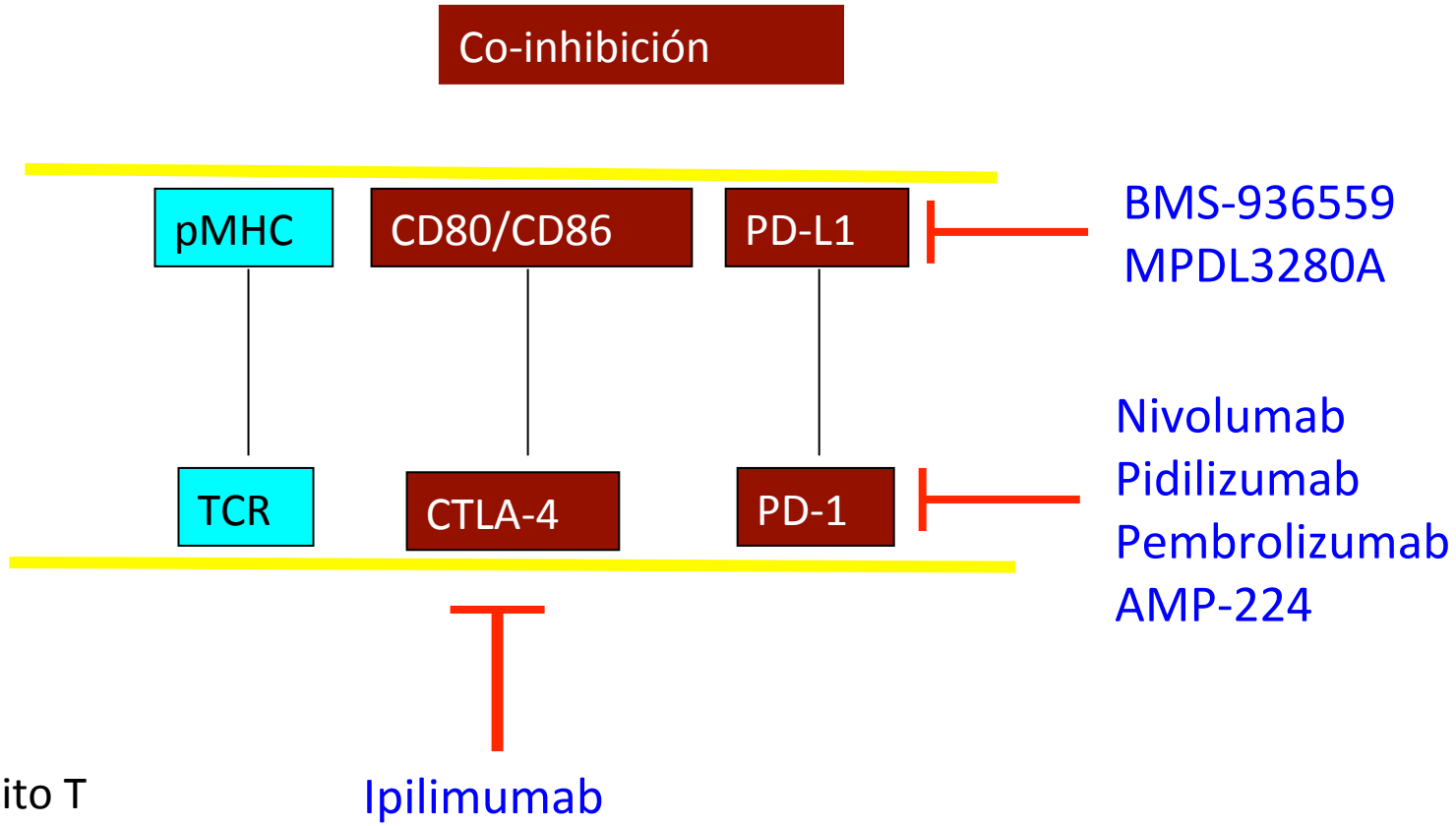
Targeting metastatic melanoma Annu Rev Med. 2012;63:171-83

Opciones terapéuticas



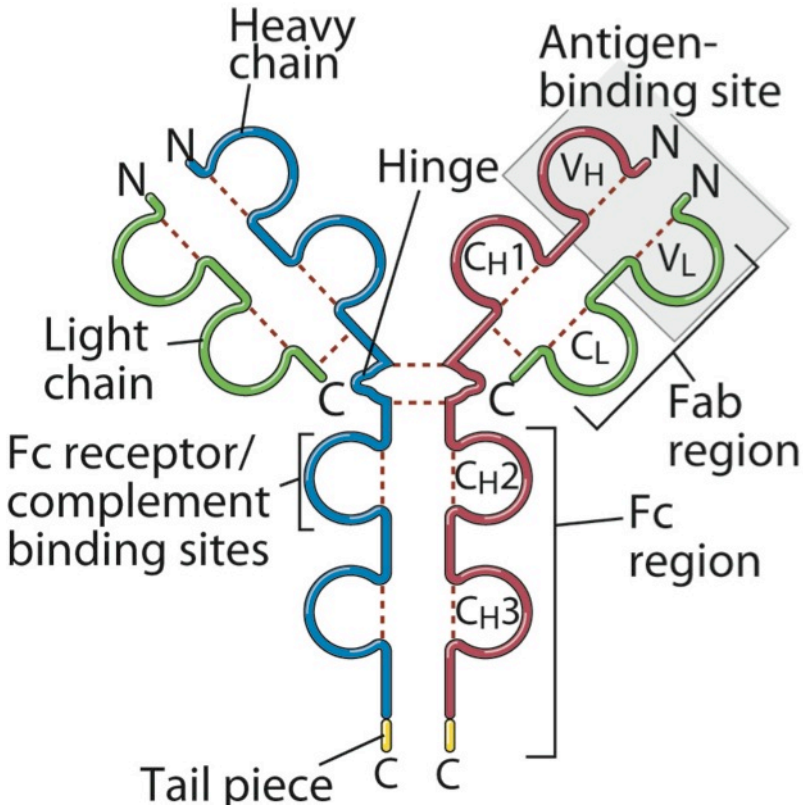
Diseñado por Iván Martinez Forero

Célula presentadora de antígeno



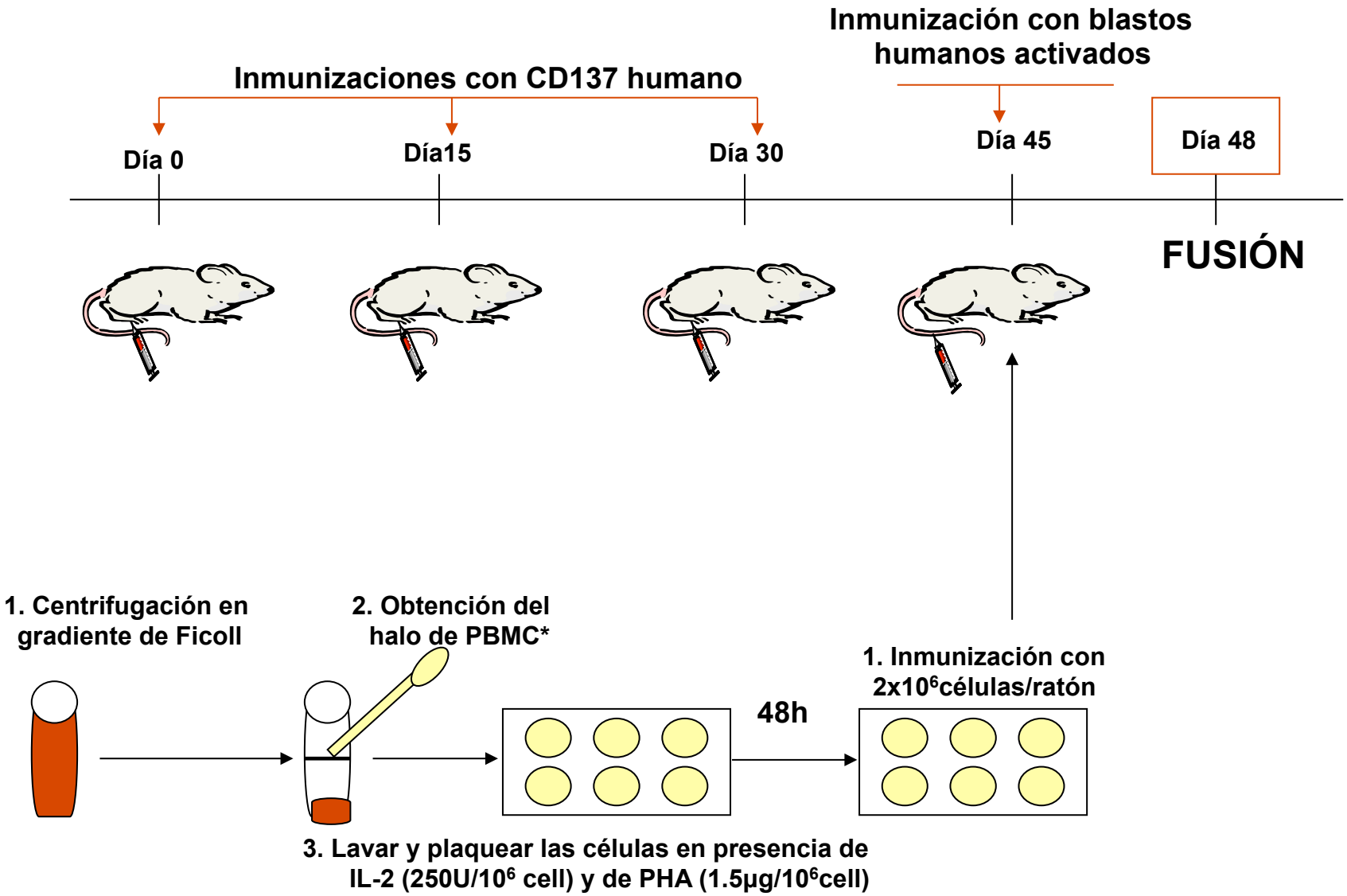
Diseñado por: Ivan Martínez Forero

Variable
Hipervariable – CDR
Región constante

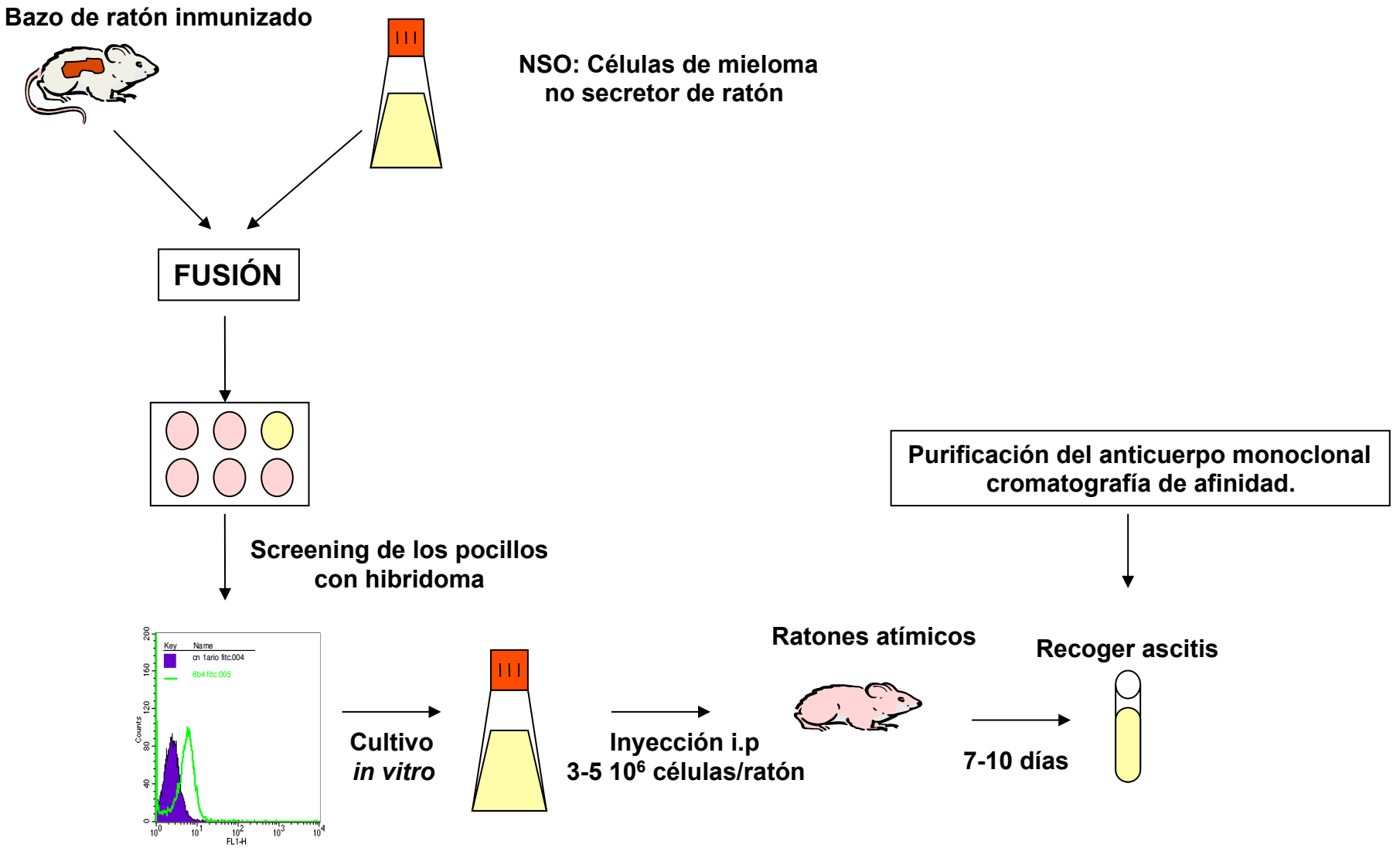


Humanos – Ipili**mu**mab
Humanizados – Región CDR (Ratón) Ej: Trastu**zu**mab
Quiméricos – Región Variable (Ratón) Ej: Ritu**xi**mab
Ratón – Muro**mo**nab

Abbas Immunology 2012

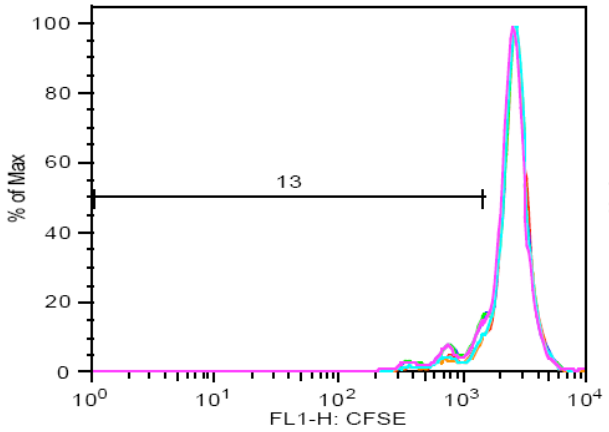


Martinez Forero I, JI 2013

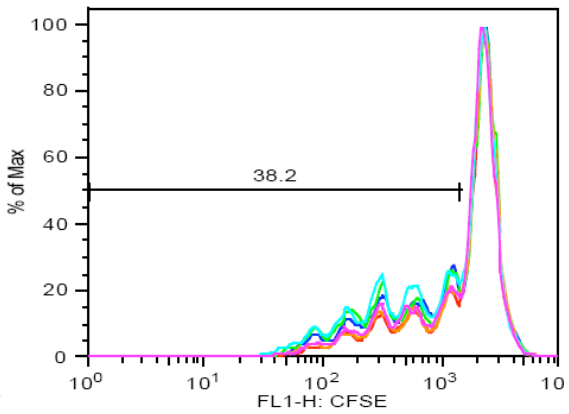


Martinez Forero I, JI 2013

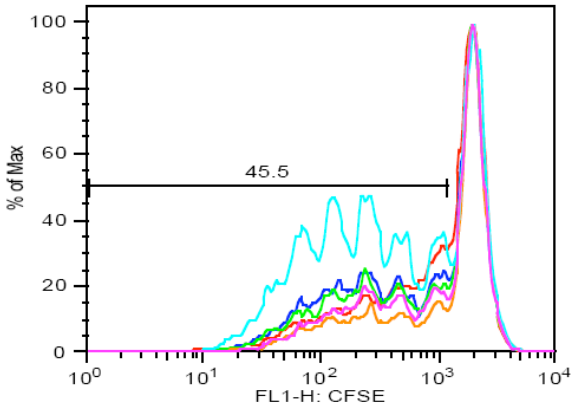
Dia 3



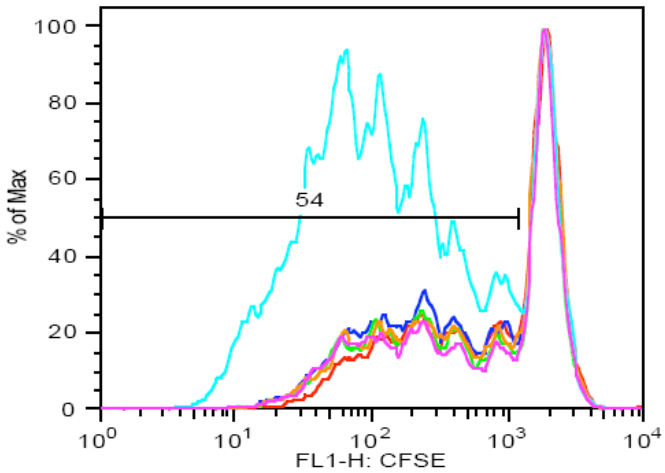
Dia 4



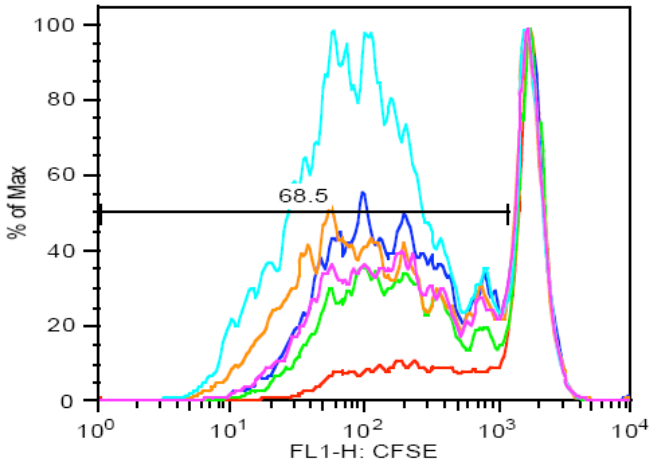
Dia 5



Dia 6



Dia 7

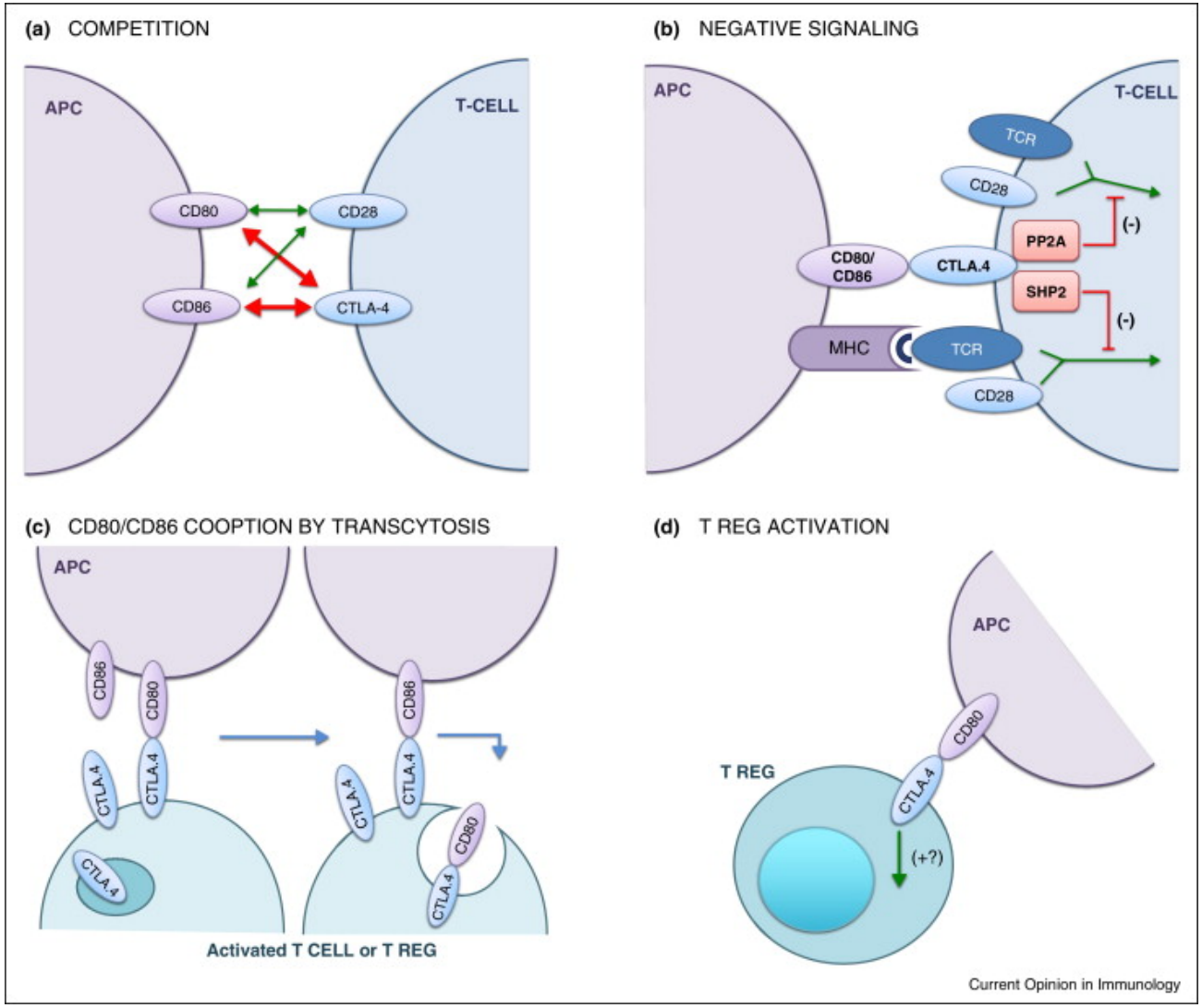


Martinez Forero I, JI 2013

Anti-CTLA4

- Cytotoxic lymphocyte associated antigen 4
- Aparece en LT activados y en Tregs
- Pertenece a la superfamilia de inmunoglobulinas
- Ligandos: CD80/CD86
- Compite con CD28

The blockade of immune checkpoints in cancer immunotherapy.Pardoll DM.Nat Rev Cancer. 2012 Mar 22;12(4):252-64

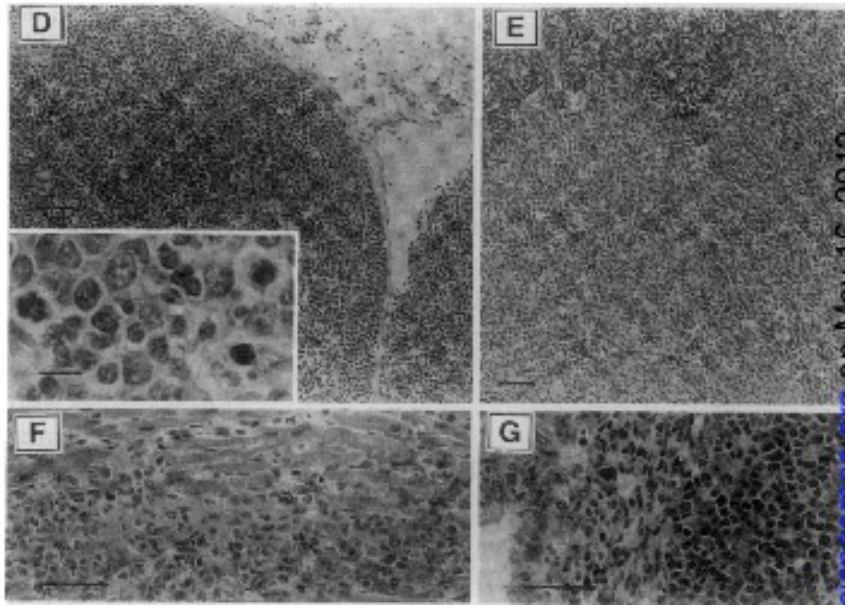


Melero I et al. Current Opinion in Immunology, Volume 27, 2014, 89 - 97

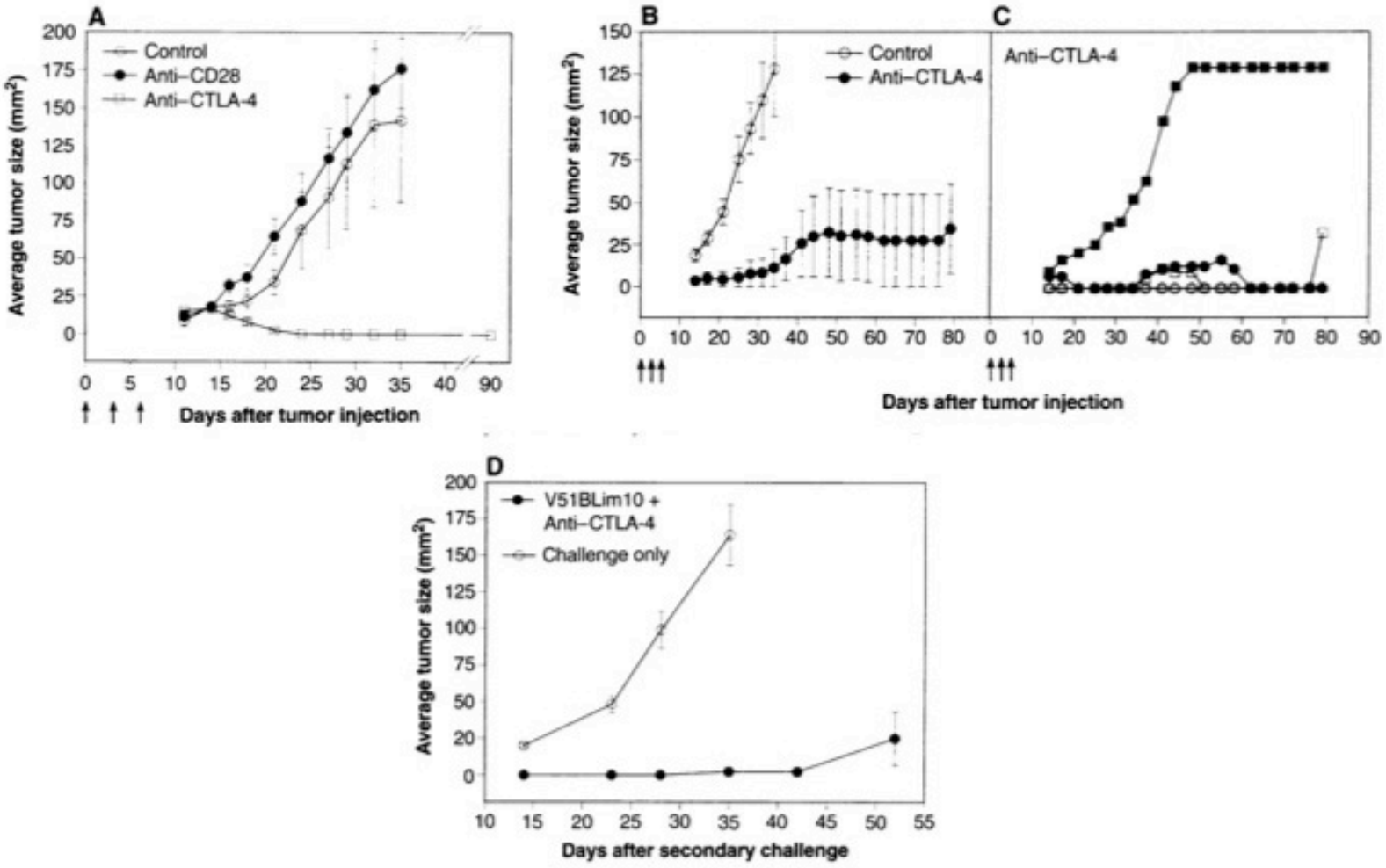
Anti-CTLA4

Mortalidad a 3 semanas
100%
Miocarditis

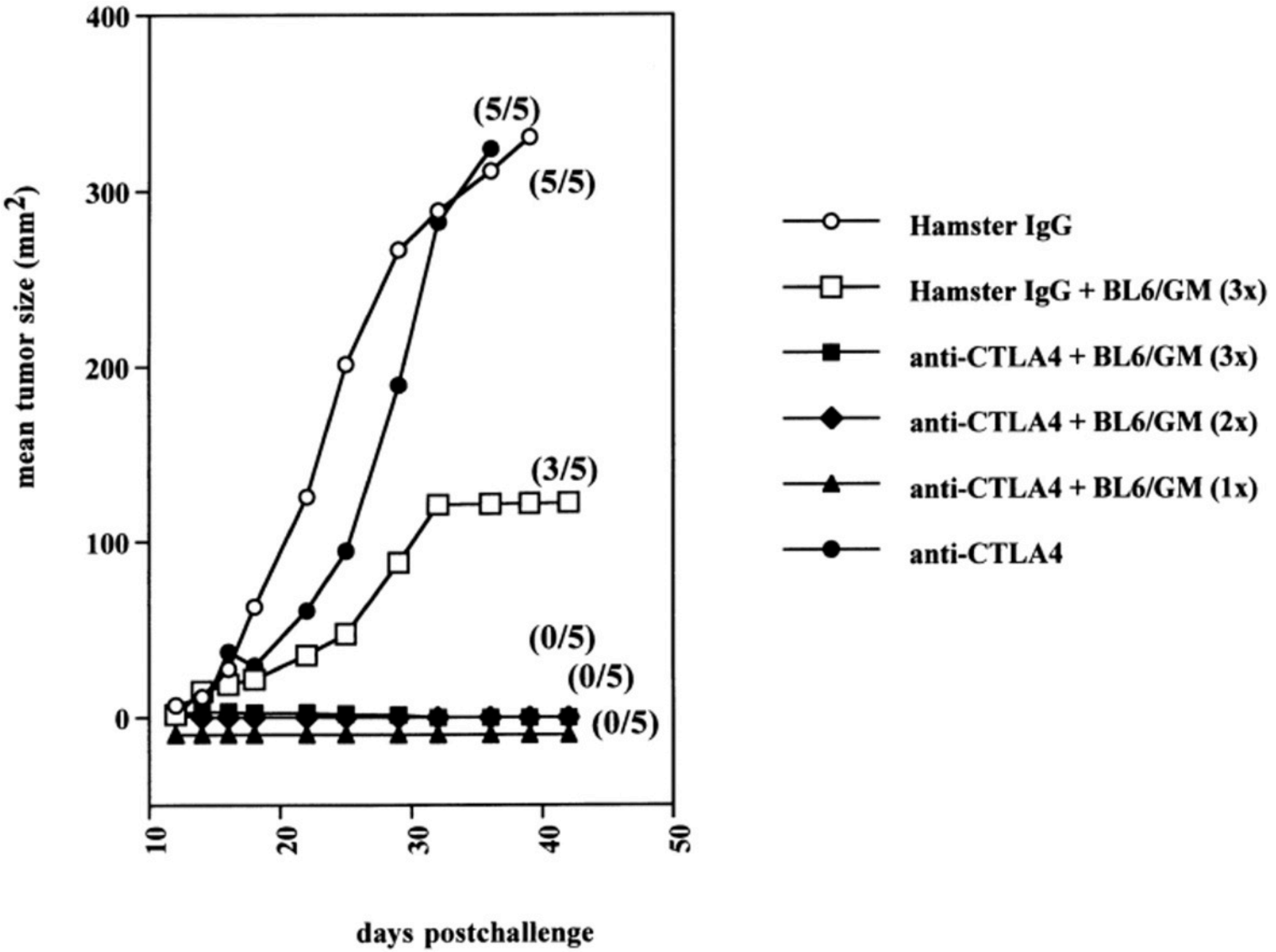
Geno-type	Wet weight (mg)		Lymphocytes (10^7)	
	Lymph nodes	Spleen	Lymph nodes	Spleen
Ctla-4$^{+/+}$	71	69	1.3	3.1
Ctla-4$^{+/-}$	97	77	1.7	3.1
Ctla-4$^{-/-}$	540	145	28.0	7.7
Ctla-4$^{-/-}$	380	501	12.0	16.5



Mak T Science 1995



Allison Science 1996



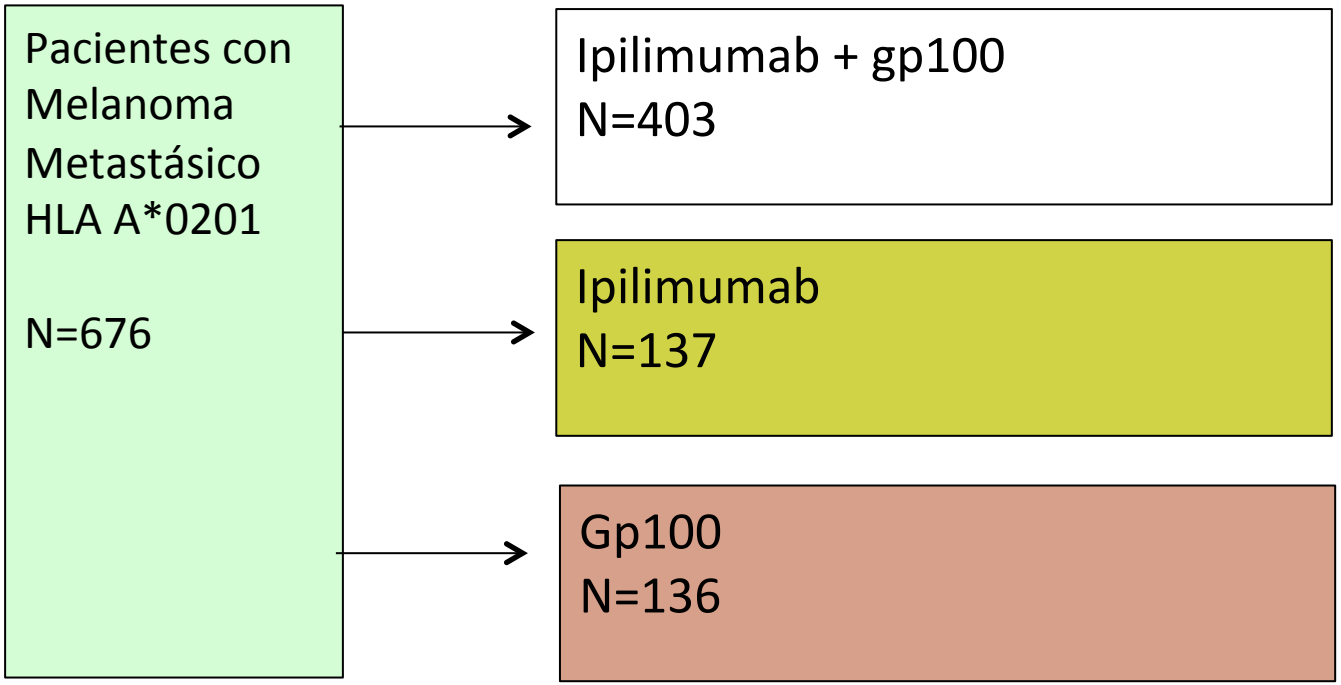
van Elsas A et al. J Exp Med 1999;190:355-366

Desarrollo - Ipilimumab

- Modelo pre-clínico **1996-2000**
- Fase 1/2 – **2000-2004**
- Fase 3 MDX-020 **2005-2009**
- Fase 3 CA184-024 **2006-2010**

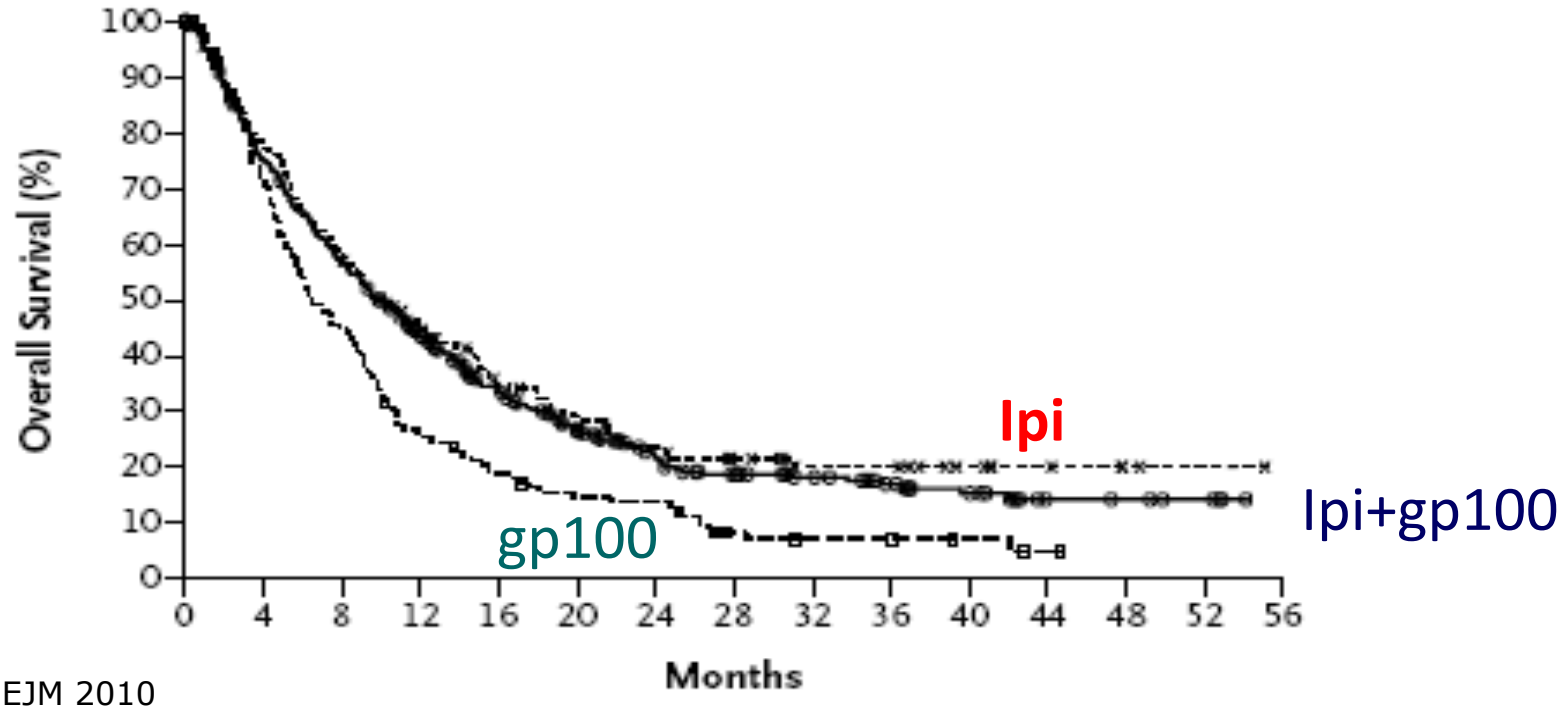
Ipilimumab: an anti-CTLA-4 antibody for metastatic melanoma.Lipson EJ, Drake CG.
Clin Cancer Res. 2011 Nov 15;17(22):6958-62.

Utilidad clínica



Hodi FS NEJM 2010

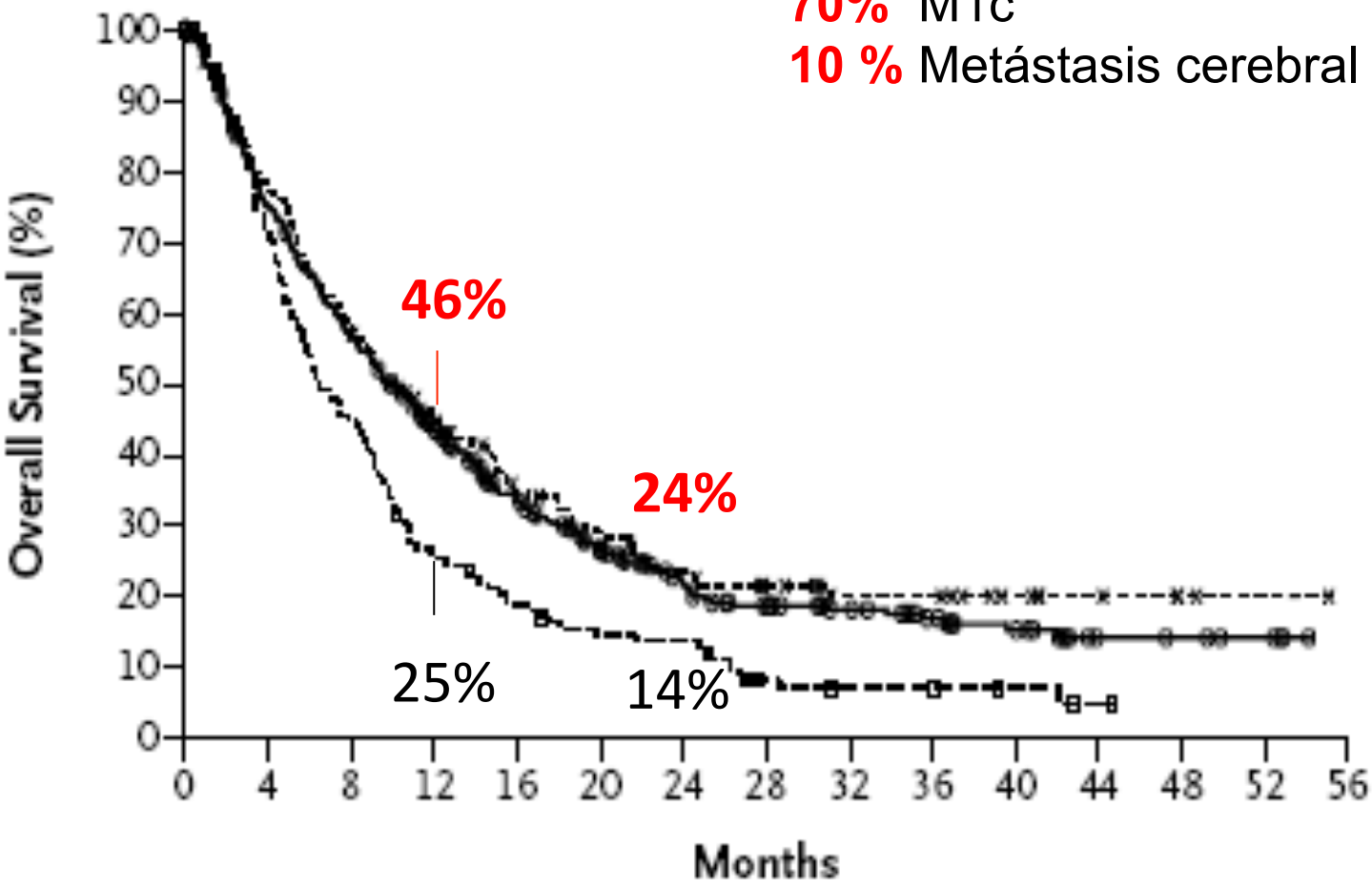
	HR	Median OS (m)
Ipi vs gp100	0.66	10 vs 6
Ipi+gp100 vs gp100	0.68	10 vs 6



Hodi FS NEJM 2010

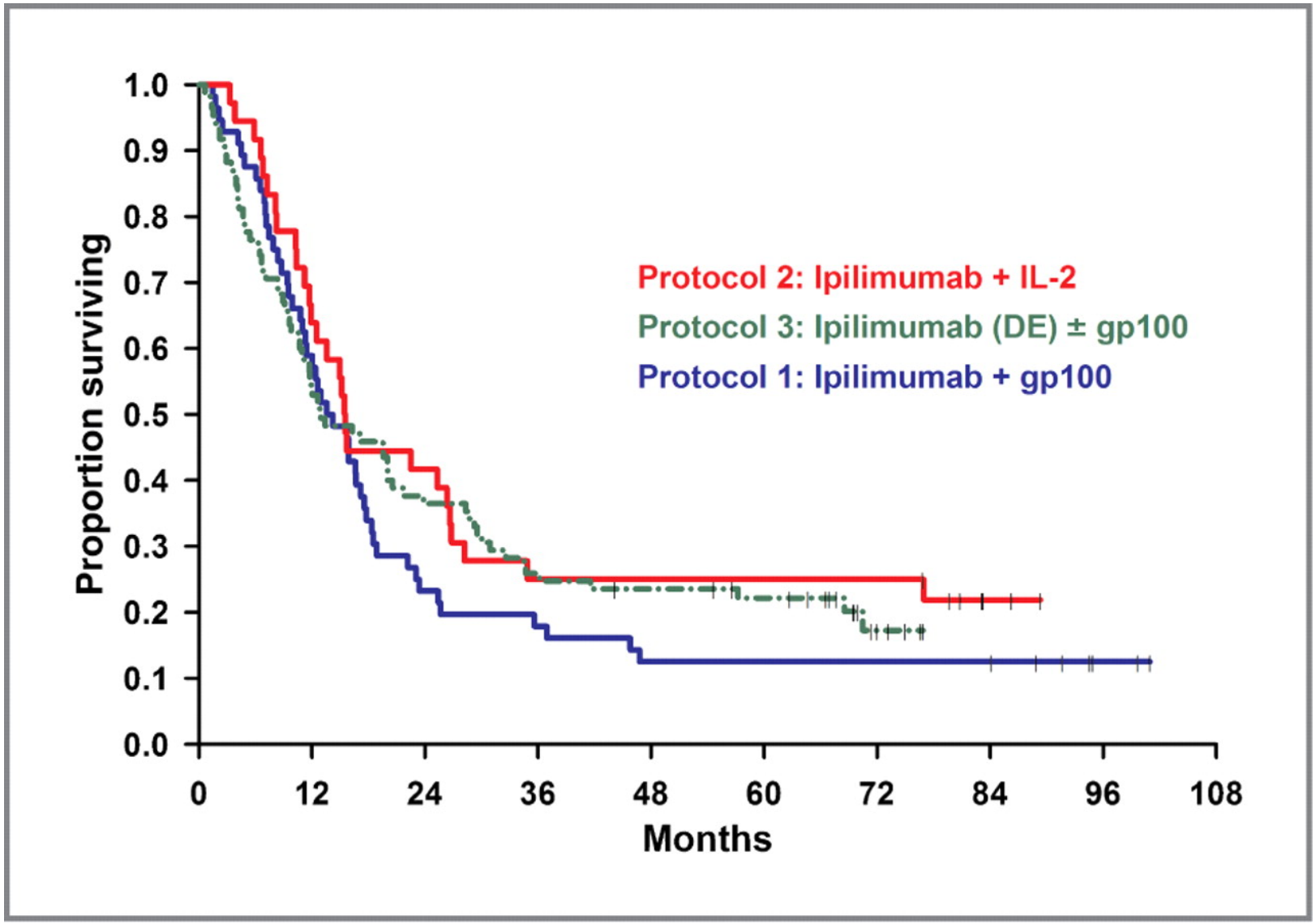
Utilidad clínica

70% M1c
10 % Metástasis cerebral



Hodi FS NEJM 2010

Utilidad clínica – largo plazo



Prieto P A et al. Clin Cancer Res 2012;18:2039-2047

Estudio	Ipi + gp100	Ipi+IL-2	Ipi
Pacientes	56	36	85
Seguimiento (meses)	92	84	71
Supervivencia (meses)	14	16	13
Reporte inicial			
PR	5	5	5
CR	2	3	0
OR número (%)	7 (13)	8 (22)	5 (11)
Reporte actual			
PR	**3**	**3**	**12**
CR	**4**	**6**	**5**
OR	**7 (13)**	**9 (25)**	**17 (20)**
PR (duración meses)	42,5,4		71,66,56, 68,25, 15, 11, 10, 9, 7, 6, 5
CR (duración meses)	99,94,94,88	89,86,83,83,79,76	76,74,62,54,42

Prieto P A et al. Clin Cancer Res 2012;18:2039-2047

POOLED ANALYSIS OF LONG-TERM SURVIVAL DATA FROM PHASE II AND PHASE III TRIALS OF IPILIMUMAB IN METASTATIC OR LOCALLY ADVANCED, UNRESECTABLE MELANOMA

Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, Chen TT, Berman DM, Wolchok JD

Abstract Number 24LBA

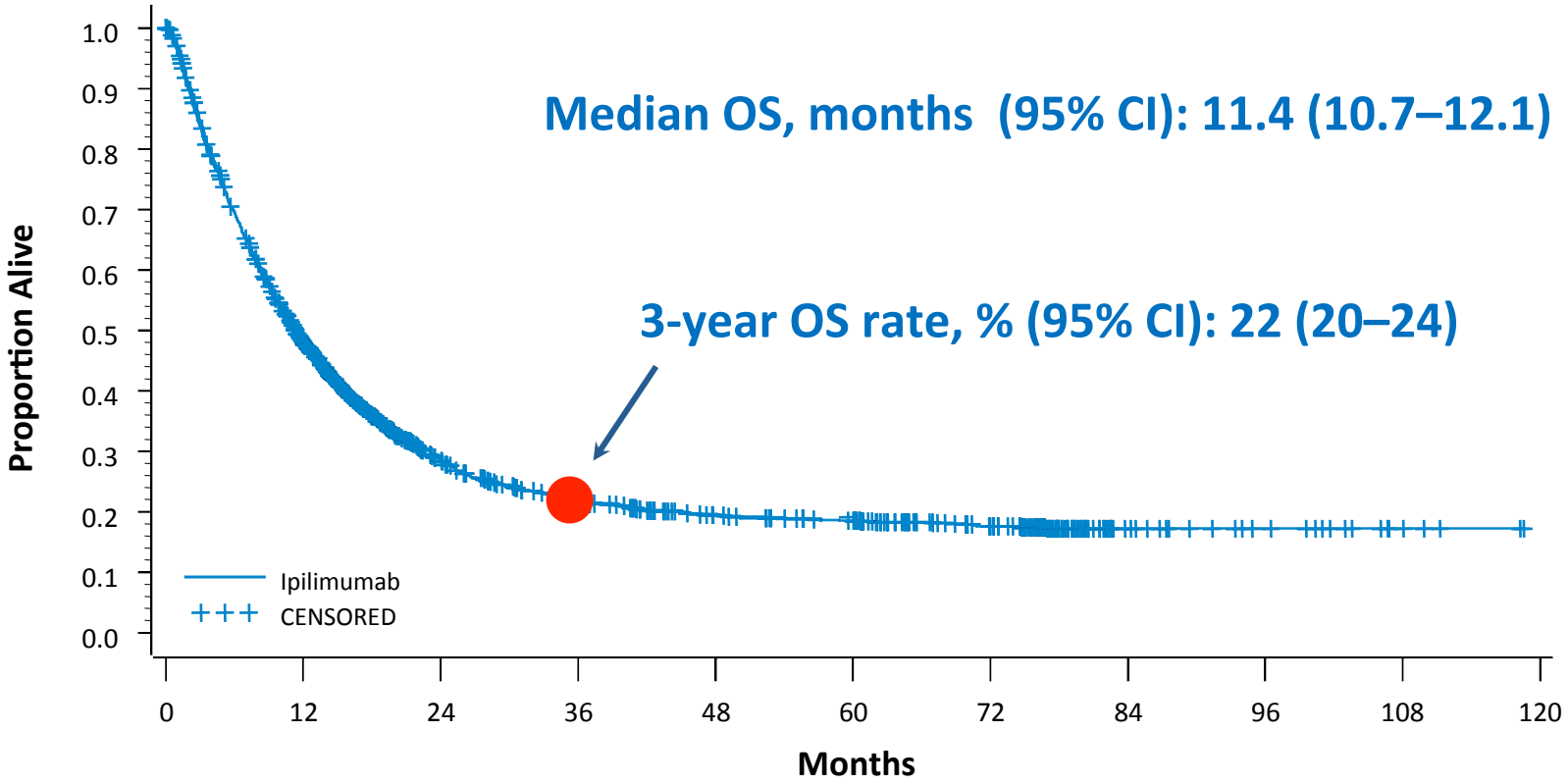
Studies Included in OS Analyses*

Study ID	Phase	N	Population	Dose	Retreatment or Maintenance
MDX010-20	3	540	Previously treated	3 mg/kg ± gp100	Retreatment
CA184-024	3	250	Treatment-naive	10 mg/kg + DTIC	Maintenance
CA184-022	2	217	Previously treated	0.3, 3, 10 mg/kg	Maintenance
CA184-008	2	155	Previously treated	10 mg/kg	Maintenance
CA184-007	2	115	Treatment-naive or previously treated	10 mg/kg ± budesonide	Maintenance
CA184-004	2	82	Treatment-naive or previously treated	3, 10 mg/kg	Maintenance
CA184-042	2	72	Melanoma with brain metastases	10 mg/kg	Maintenance
NCI04C0083	1/2	88	Previously treated	3, 5, 9 mg/kg ± gp100	Not included
NCI02C0106	1/2	56	Previously treated	3 mg/kg + gp100 3 → 1 mg/kg + gp100	Not included
NCI03C0109	1/2	36	Previously treated	0.1, 0.3, 1, 2, 3 mg/kg + IL-2	Not included
CA184-338	Observational	160	Treatment-naive	3 mg/kg	No (induction only)
CA184-332	Observational	90	Treatment-naive	3 mg/kg	No (induction only)
CA184-045**	Expanded Access Program (EAP)	2985	Previously treated	3, 10 mg/kg	Maintenance for 10 mg/kg

*Total of 1861 patients for primary analysis; N=4846 patients including EAP. **US EAP treatment protocol.

Hodi FS ESMO 2013Abstract Number 24LBA

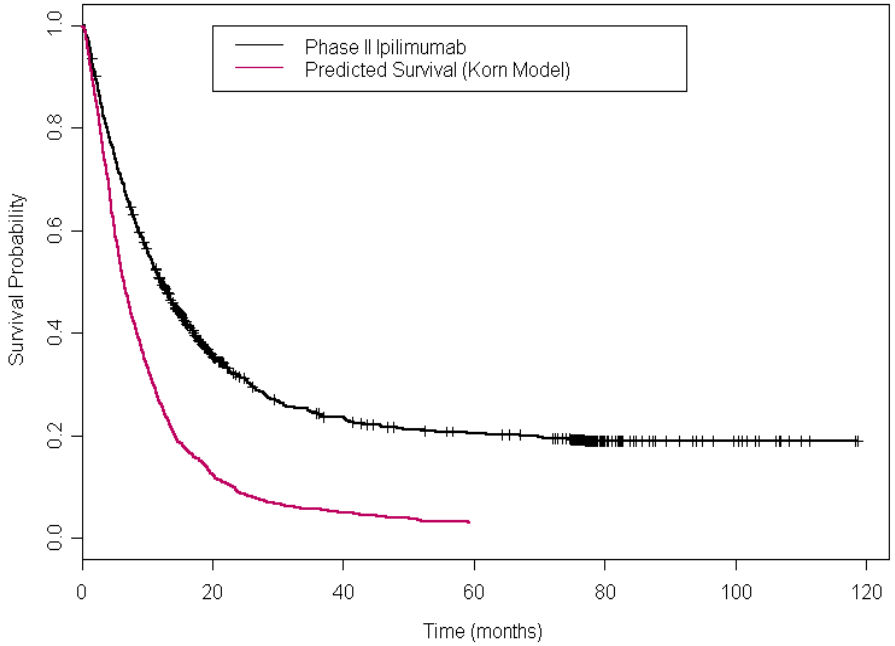
Primary Analysis of Pooled OS Data: 1861 Patients

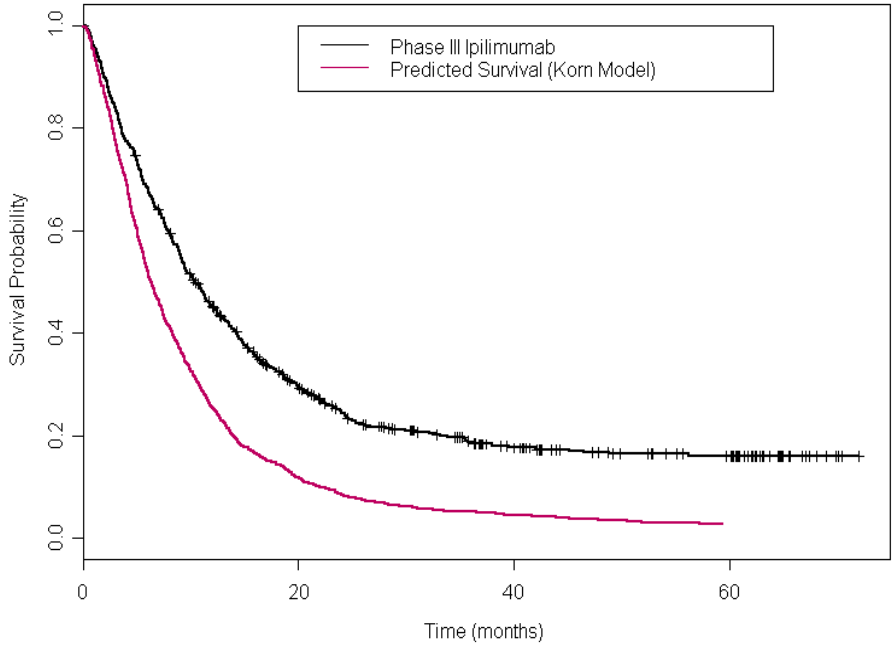


Patients at Risk

Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

OS Relative to Historical Data

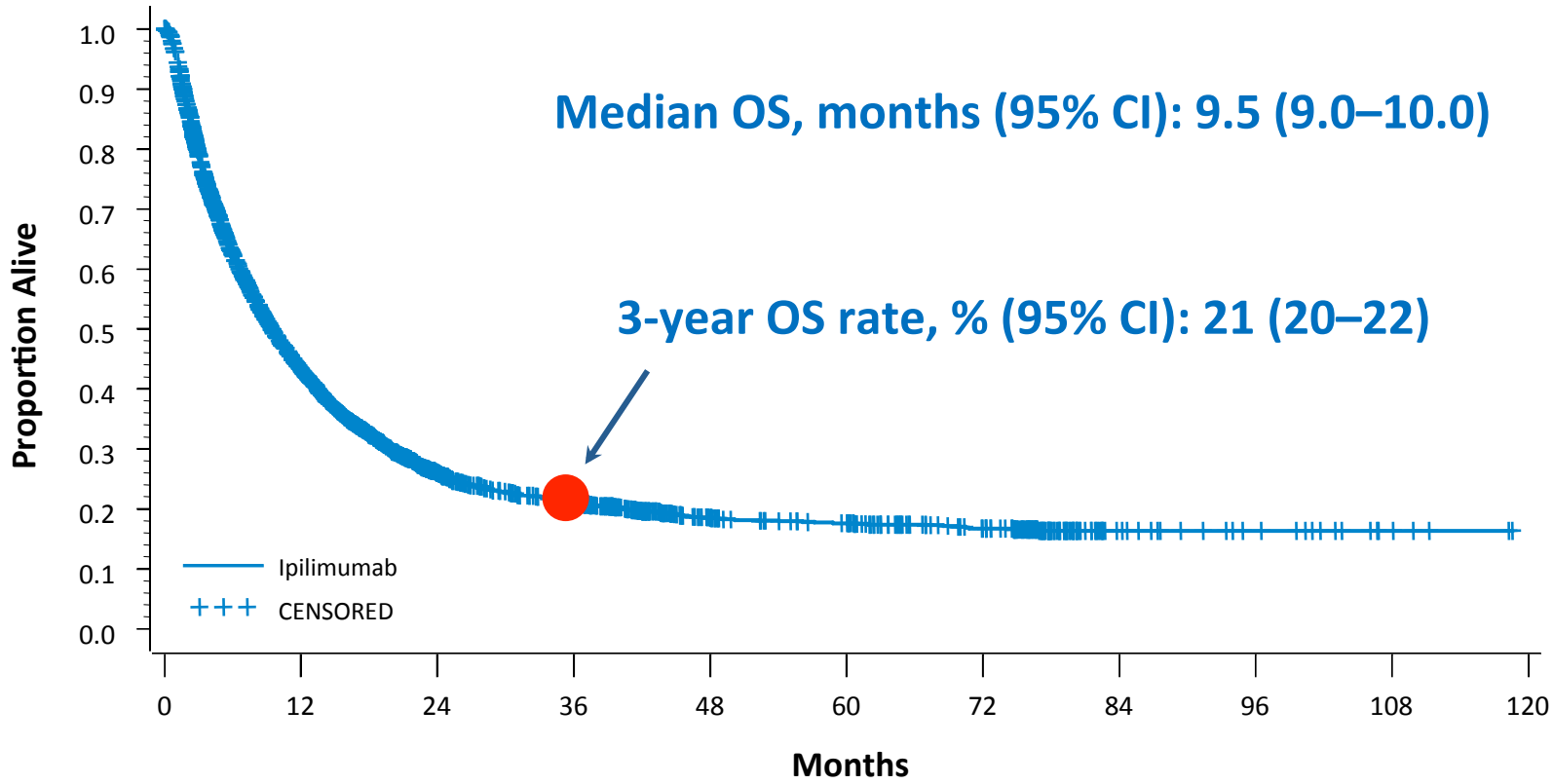




- Historical controls (pre-Braf inhibitor era)
  - Phase II: 1278 patients in 42 cooperative group trials from 1975 to 2005
  - Phase III: 3739 patients in 10 trials from 1999 to 2011
  - Data were adjusted by key prognostic factors

Hodi FS ESMO 2013Abstract Number 24LBA

Pooled OS Analysis Including EAP Data: 4846 Patients



Patients at Risk

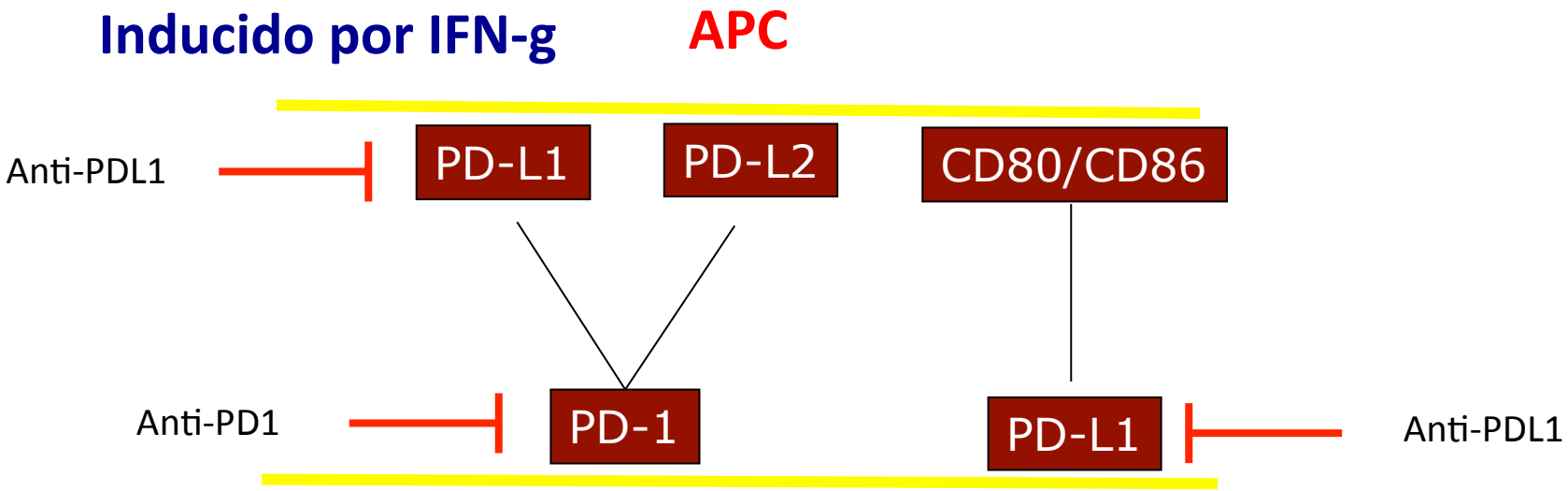
Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0

The addition of the EAP data confirms the LTS benefit in a less selected patient population

Hodi FS ESMO 2013Abstract Number 24LBA

Anti-PD1

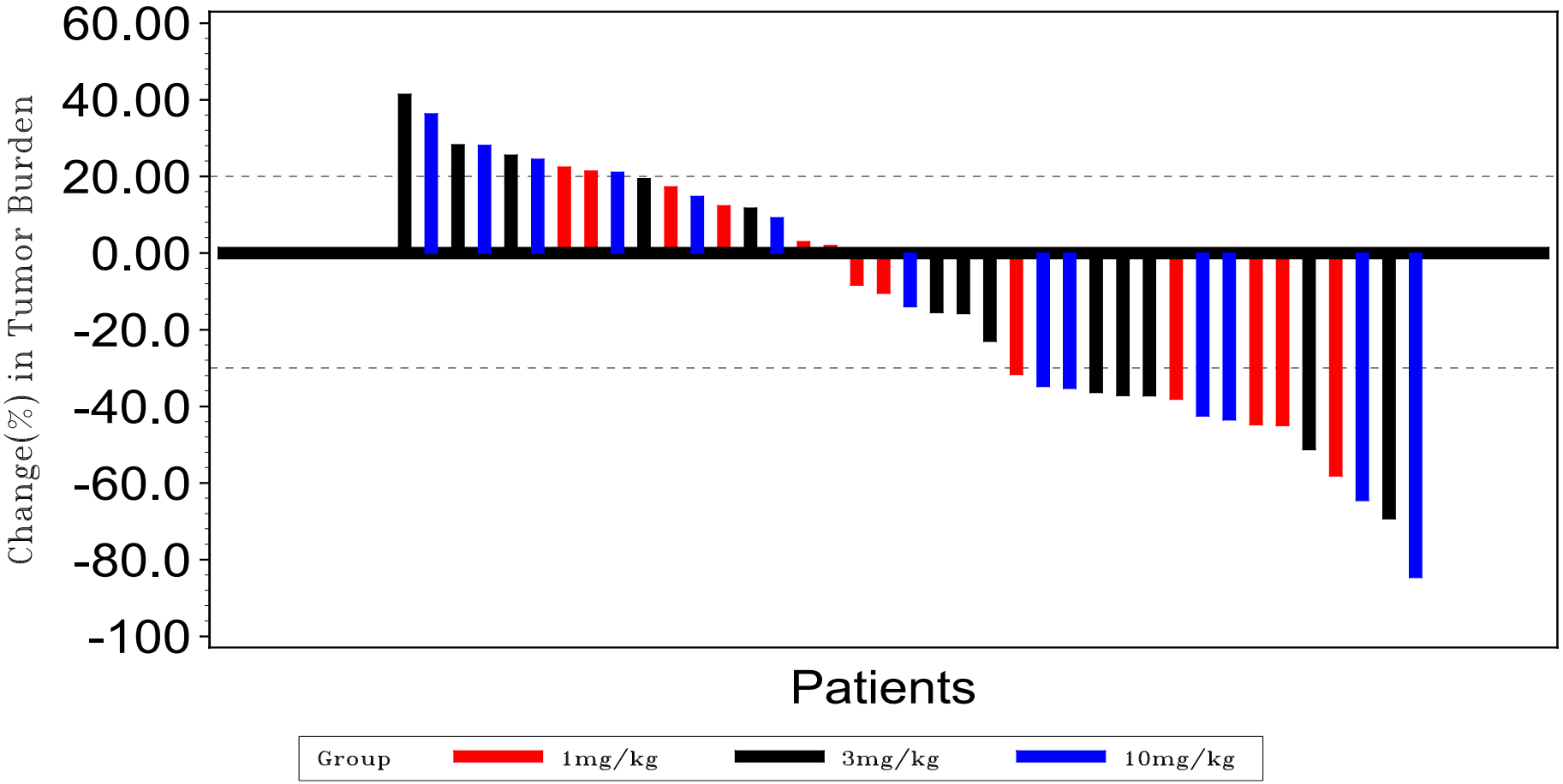
APC
Epitelio
Inducido por IFN-g



Linfocito T

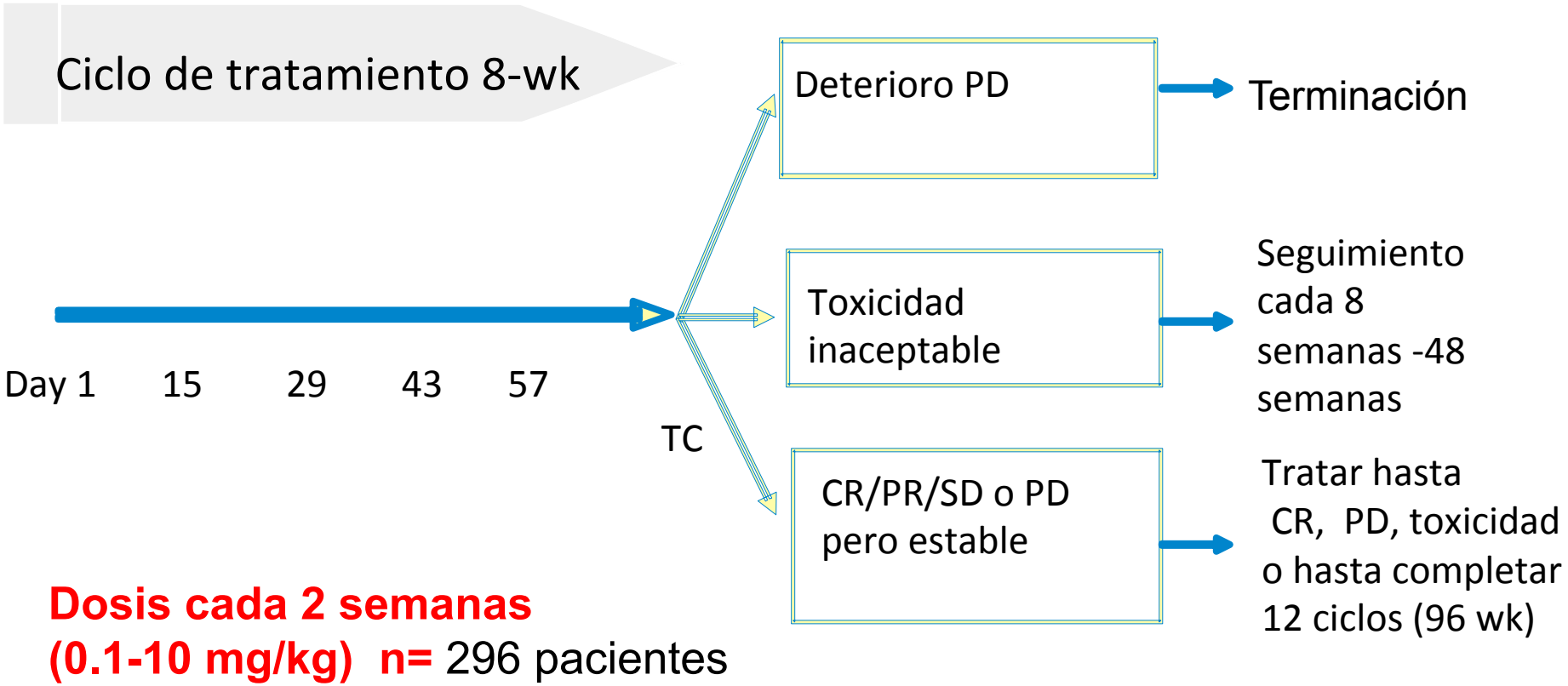
Diseñado por: Ivan Martínez Forero

Inmunoterapia. PD-1



Topalian S JCO 2010

Anti-PD-1 Fase 1



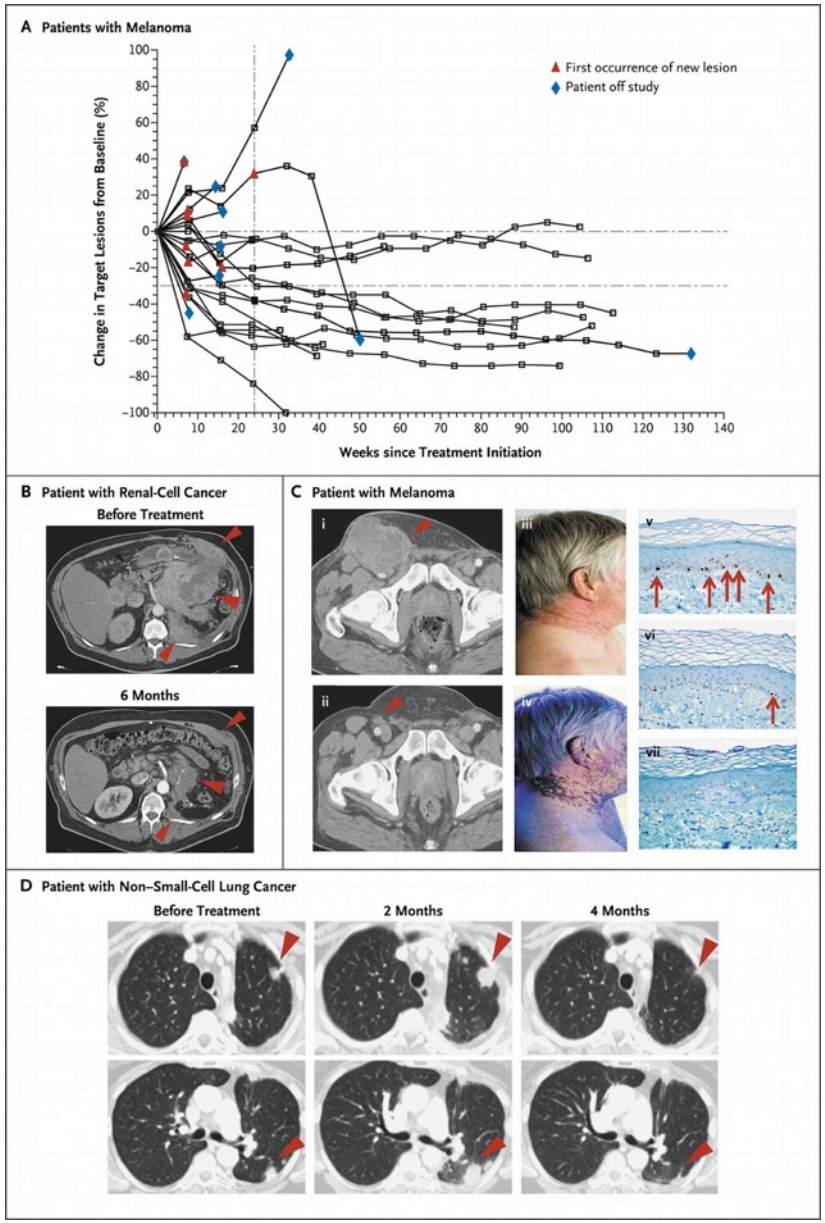
Dosis cada 2 semanas
(0.1-10 mg/kg) n= 296 pacientes

Eligibilidad: MEL, RCC, NSCLC, CRC, o CRPC con PD después de 1-5 terapia sistémica

Topalian S NEJM 2012

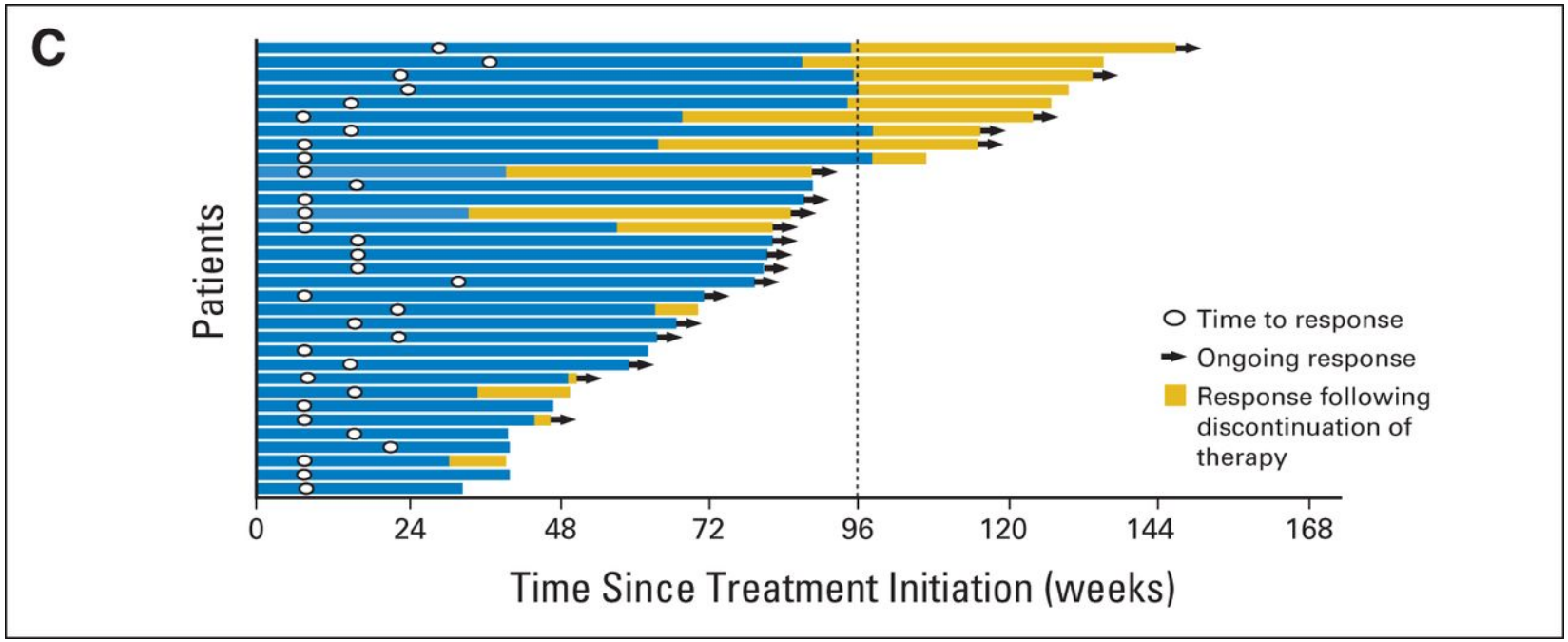
Inmunoterapia. PD-1

28% Melanoma
27 % Cancer Renal
18 % NSCLC
G3-4 AE 13%



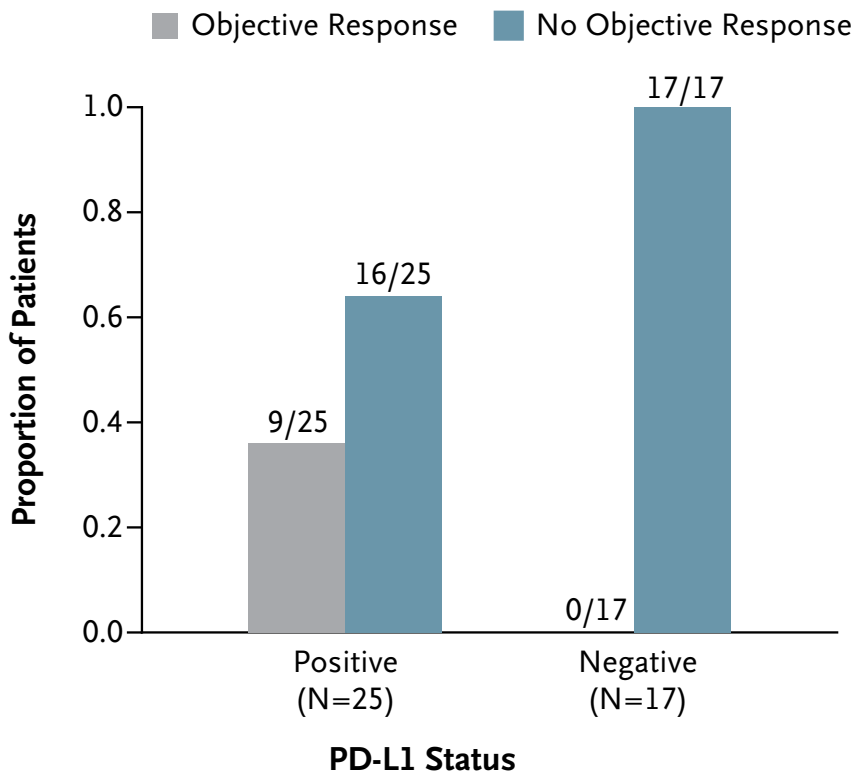
Topalian S NEJM 2012

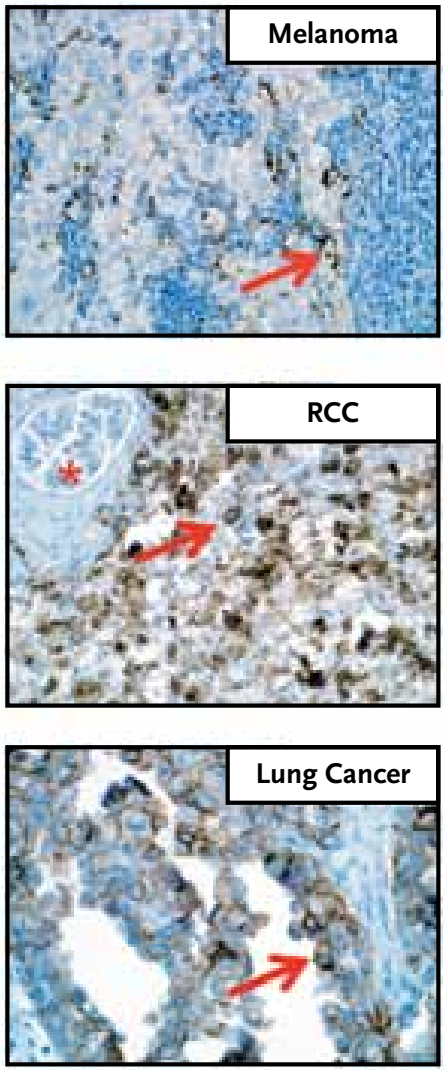
Characteristics of tumor regression in patients with melanoma receiving PD-1 therapy.



Topalian S L et al. JCO 2014;32:1020-1030

Anti-PD-1 Fase 1





28% Melanoma

27 % Cancer Renal

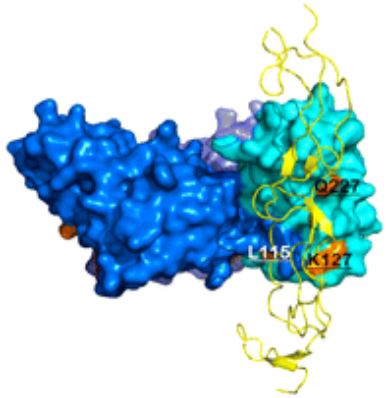
18 % NSCLC

G3-4 AE 13%

Topalian S NEJM 2012

Anti-CD137
Combinaciones

CD137 (4-1BB, TNFRSF9)



CD137, also known as 4-1BB, is a surface glycoprotein involved in T-cell costimulation. Member of the TNF receptor superfamily (TNFRSF9).

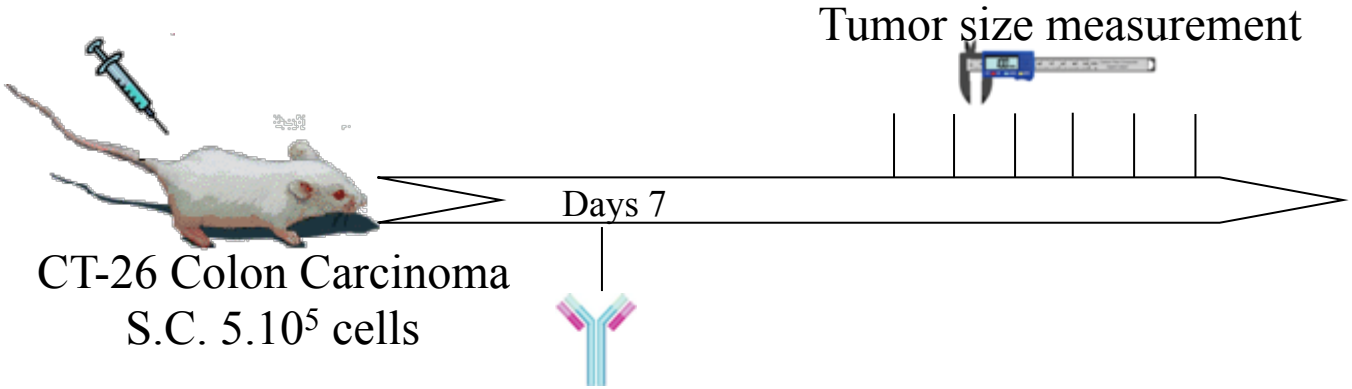
Its cognate ligand is CD137L, which is expressed on APCs.

Functions:T cell proliferation, inhibition of apoptosis, enhances cytotoxic activity and cytokine production.

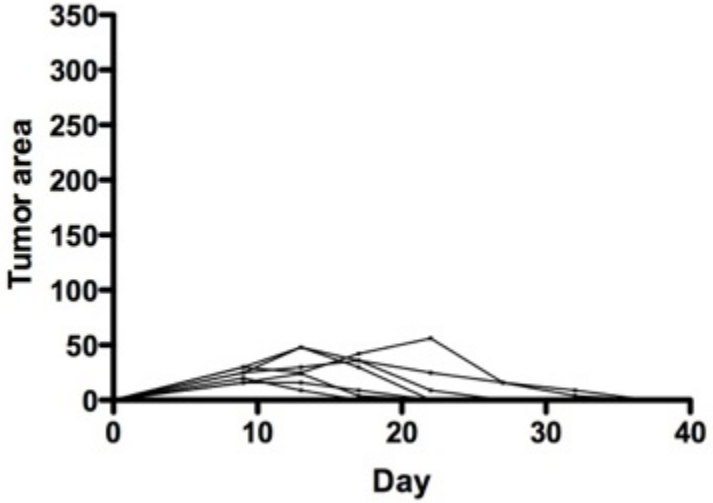
Therapeutic target, treatment with agonist anti-CD137 mAb can overcome tumor antigen tolerance.

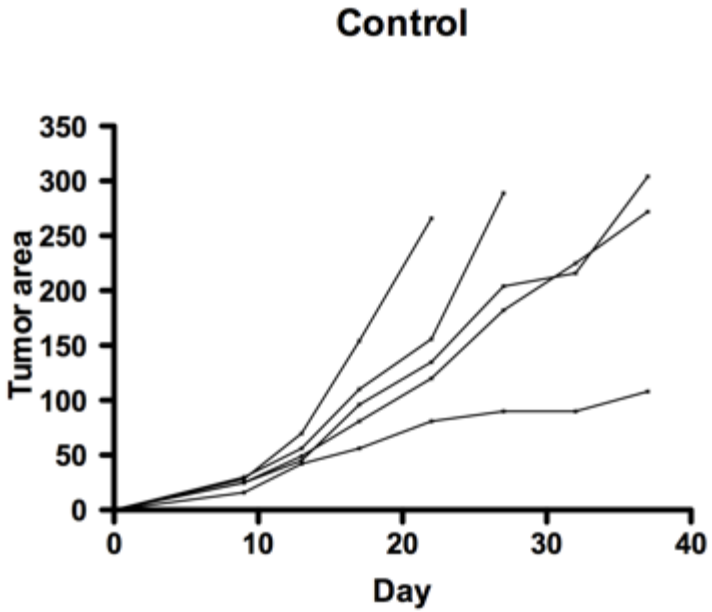
Anti-human CD137 agonist mAb are undergoing phase I/phase II clinical trials

CT26 subcutaneous model

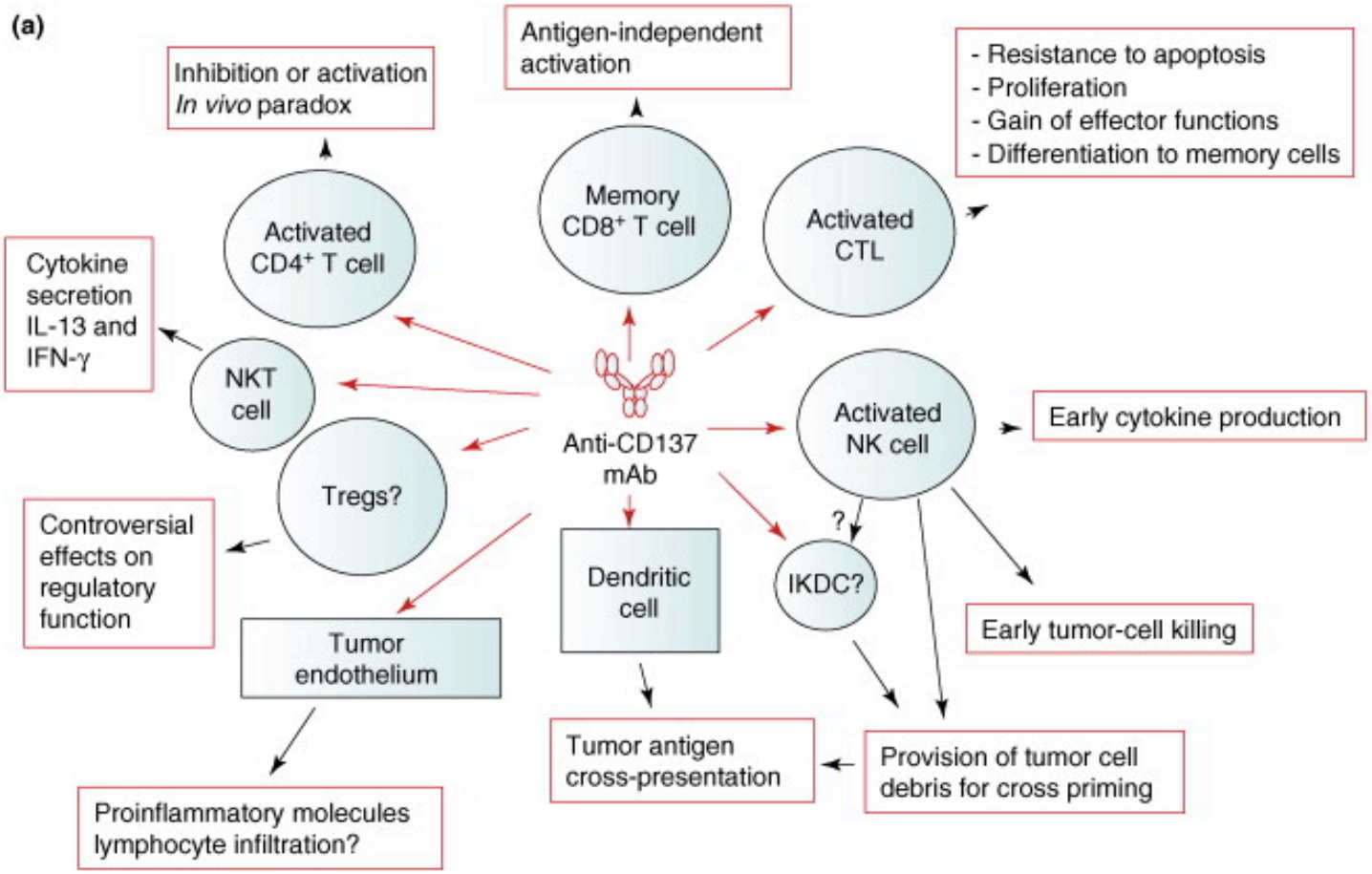


100 µg i..p. dose of control rat IgG or anti-CD137 mAb





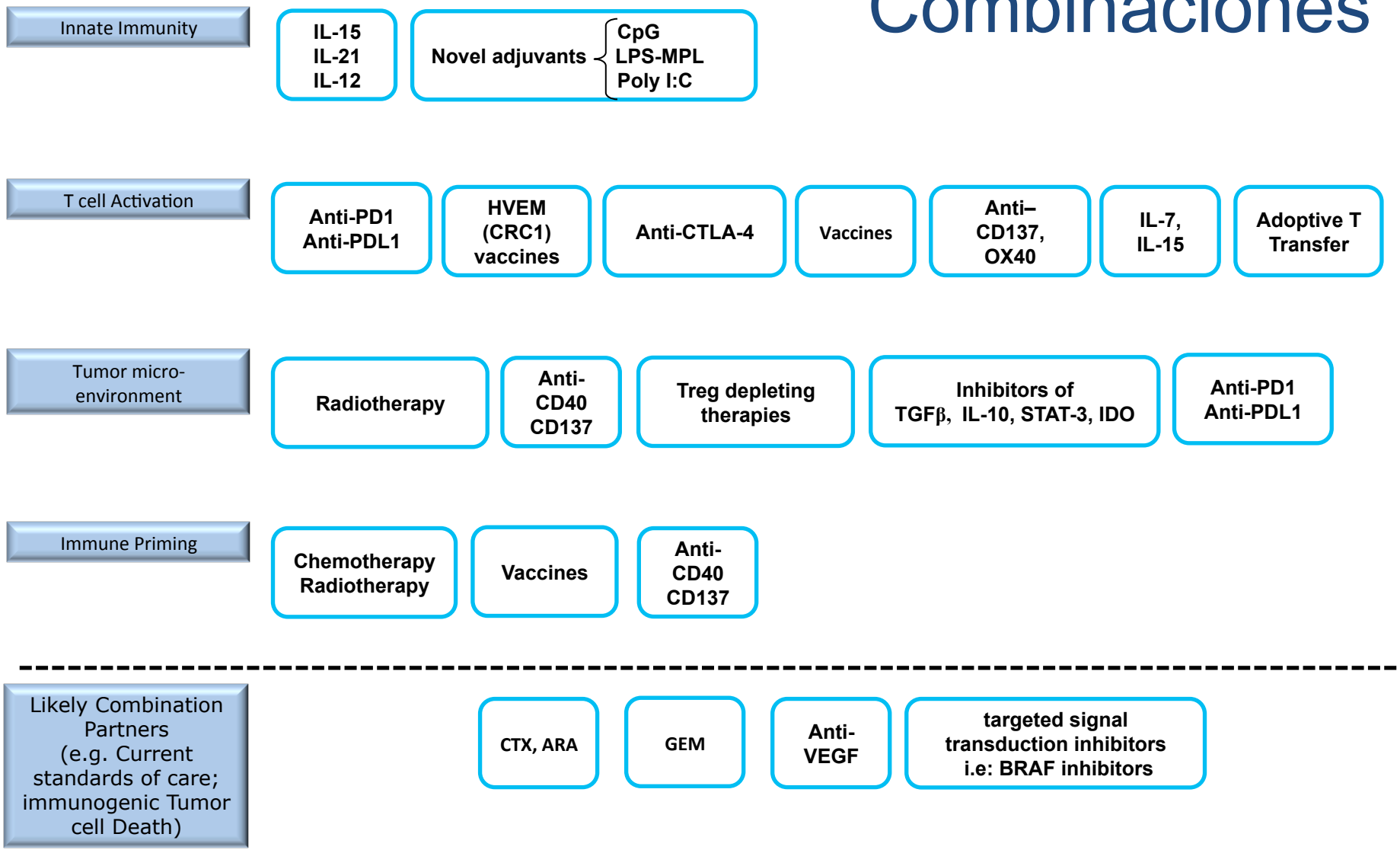
Potential mechanisms underlying the strong anti-tumoral preclinical potency of anti-CD137 treatment



Anti-CD137 act on many target cells, thereby providing a multi-task concerted set of actions that ultimately give rise to the antitumor immune response. It is assumed that ligation on activated CTLs is the major site of action but the contribution of ligation on antigen-presenting cells, NK lymphocytes and tumor endothelium remain to be thoroughly explored.

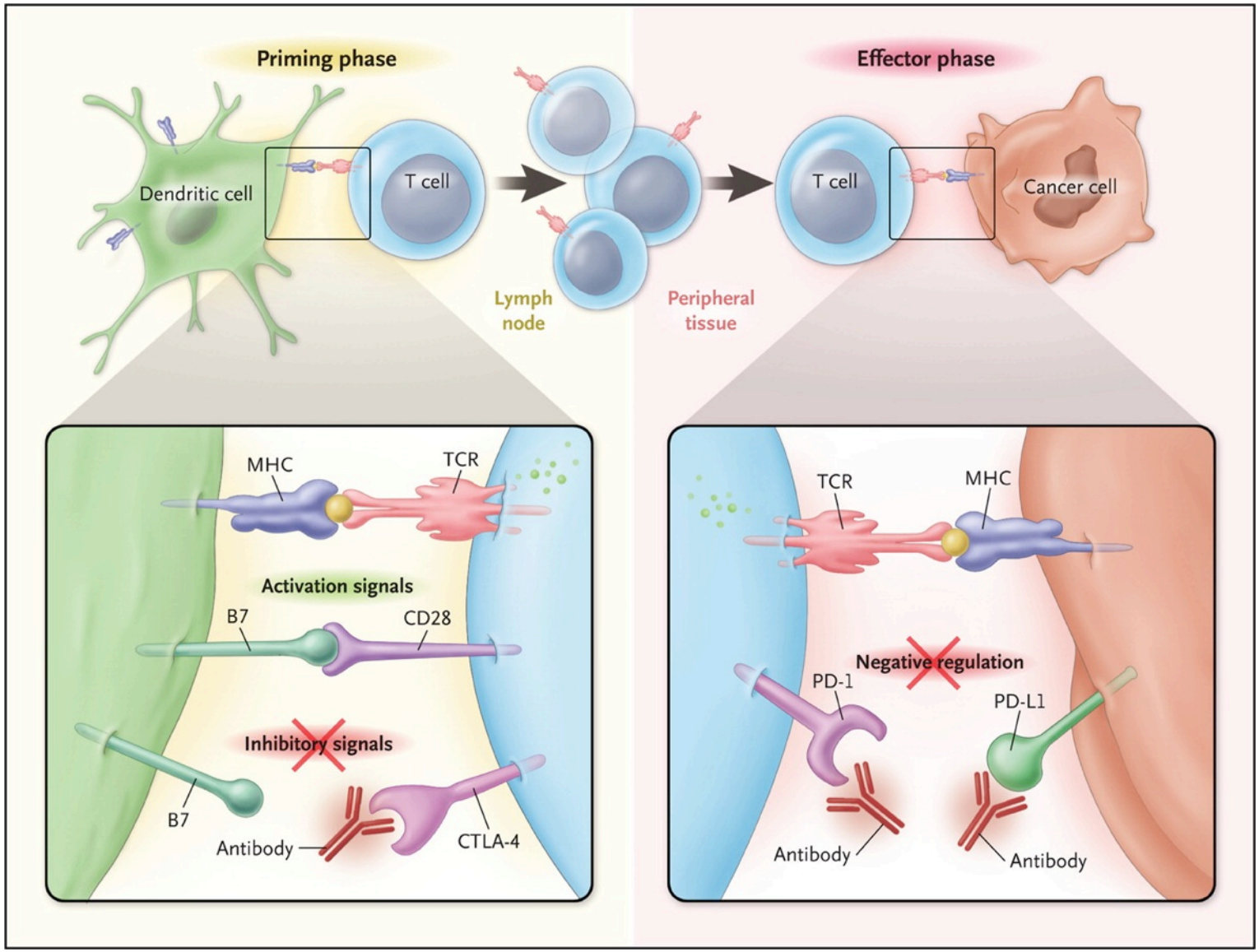
Melero et al, Trends in Pharmacological Sciences, August 2008

Combinaciones



Martinez Forero I. JTM 2012

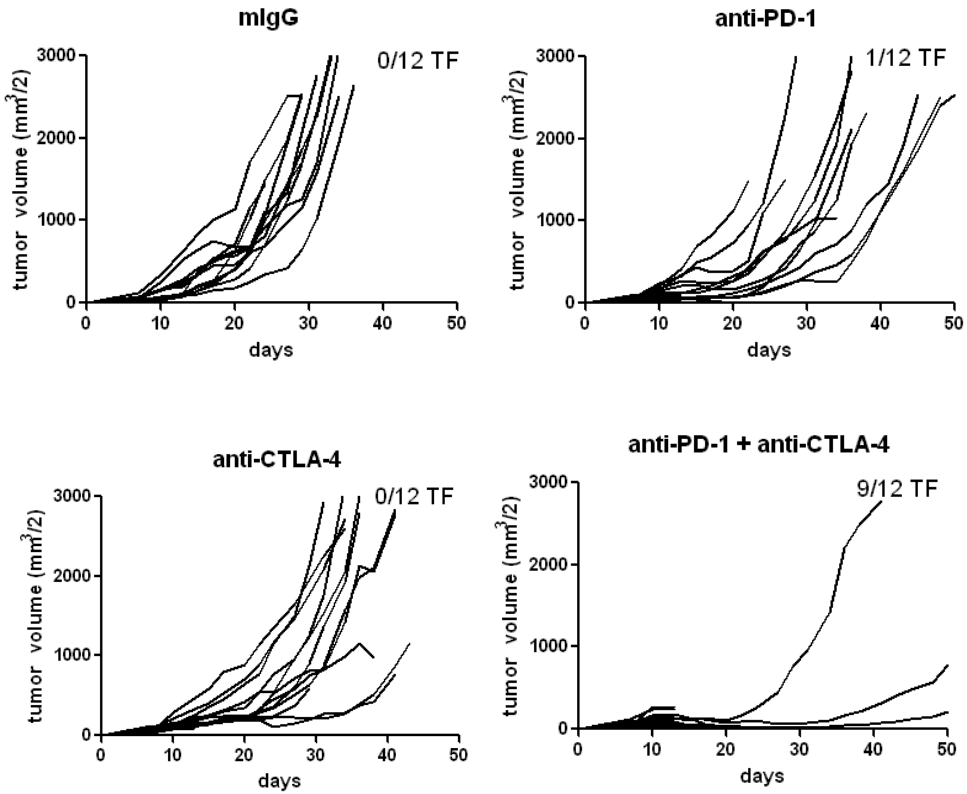
Anti CTLA4 + Anti PD-1



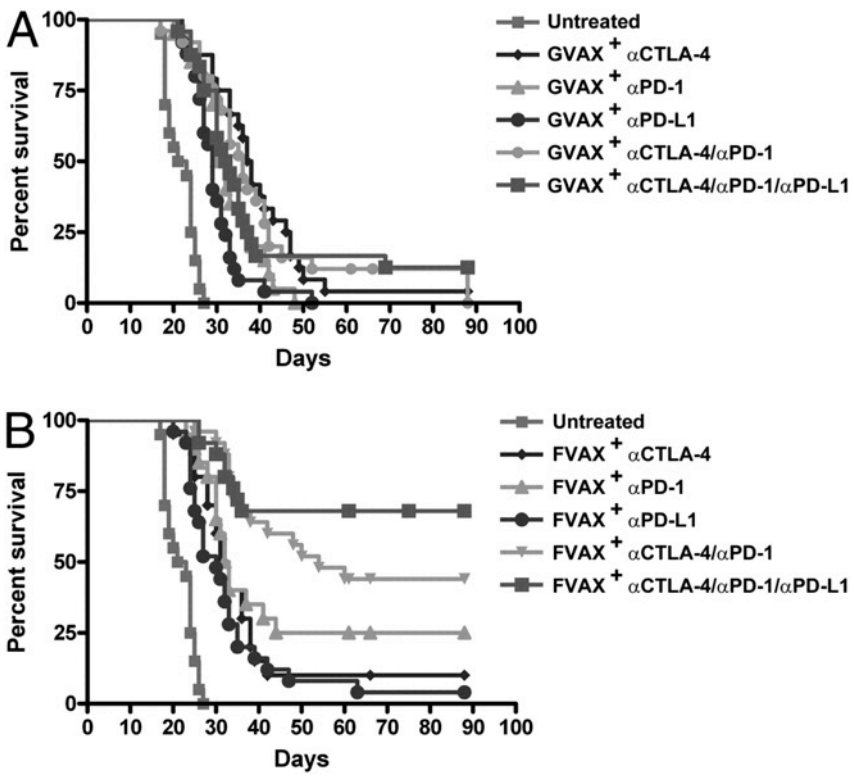
Ribas A NEJM 2012

Anti CTLA4 + Anti PD-1

MC38



B16



Curran M A et al. PNAS 2010;107:4275-4280
Korman A J Immunol 2007

Combinaciones Anti CTLA4 + Anti PD-1

- **Ipilimumab:** 3 mg/kg cada 3 wk, 4 dosis (Fase 3)
  - ORR: 11%; 2 pacientes CR[1]
  - Mediana OS: 10.1 mo;[1] Sobrevida a 2 años (Fase 2): 18%[2]
  - EA Grado 3-4 : 23%; diarrea (5%) y colitis (5%)[1]

- **Nivolumab**: 0.1 mg/kg -10 mg/kg cada 2 wk, ≤48 dosis (Fase 1b)
  - ORR: 30 %; 1 paciente CR (3 mg/kg)[3]
  - Mediana OS: 16.8 mo;[4] Sobrevida a 2y: 43%[4]
  - EA Grado 3-4 : 14%; diarrea (1%), pneumonitis (1%), hipofosfatemia (1%)[3]

[1]Hodi et al. NEngl J Med. 2010;363:711-23. [2]Wolchok et al. Ann Oncol 2013 May10 [Epub ahead of print]. [3]Topalian et al. N Engl J Med 2012;2443-54. [4]Sznol et al. ASCO 2013, oral presentation, abs CRA9006.

Combinaciones Anti CTLA4 + Anti PD-1

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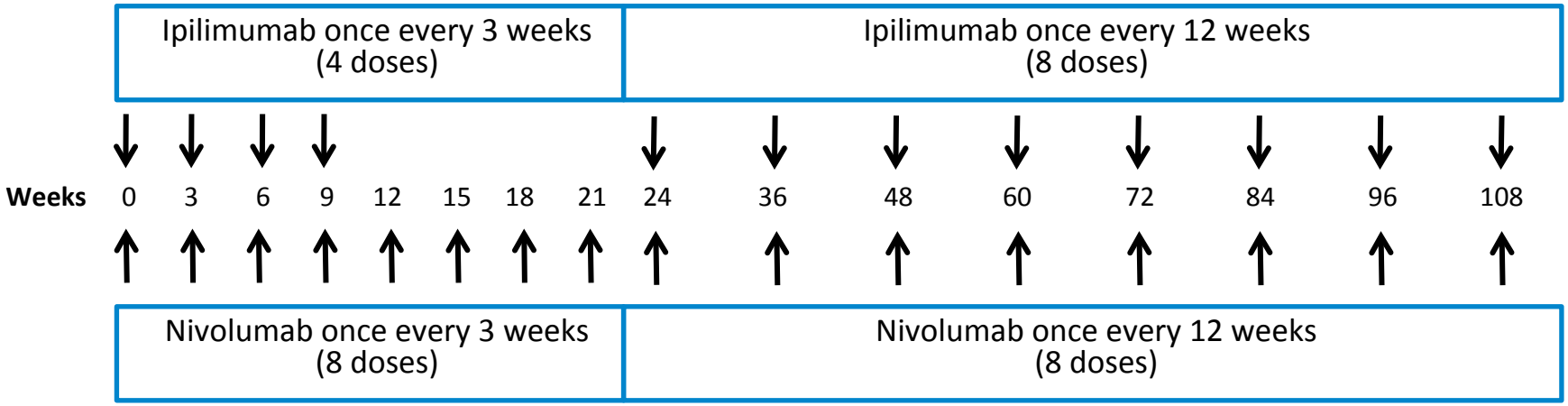
Ipilimumab + Nivolumab Fase 1

Cohort	PD-1 Dose (mg/kg)	Ipilimumab Dose (mg/kg)
Concurrent regimen		
	0.3	3
	1	3
	3	1
	3	3
Sequenced regimen		
	1	Prior
	3	Prior

Wolchok NEJM 2013

Ipilimumab + PD-1 Fase 1

Concurrent Cohorts



- First tumor assessment at 12 weeks

Sequenced Cohorts

- Following prior ipilimumab, patients received nivolumab every 2 weeks for a maximum of 48 doses
- First tumor assessment at 8 weeks

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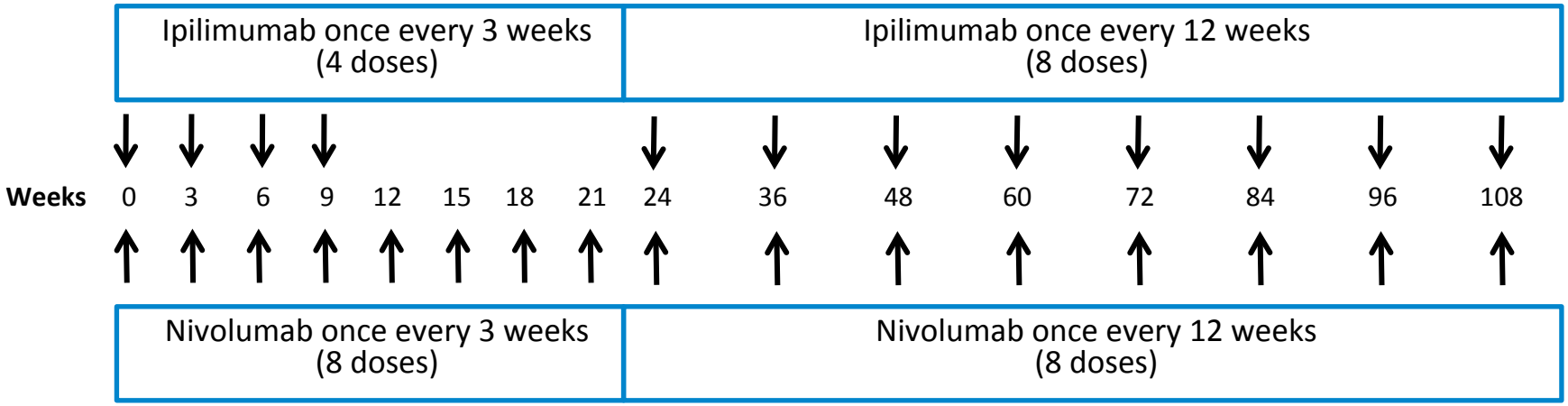
Ipilimumab + PD-1 Fase 1

Concurrent Cohorts



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Sequenced Cohorts

- Following prior ipilimumab, patients received nivolumab every 2 weeks for a maximum of 48 doses
- First tumor assessment at 8 weeks

Wolchok NEJM 2013

Ipilimumab + PD-1 Fase 1

Clinical Activity: Sequenced Regimen

Nivolumab (mg/kg)	Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	≥80% Tumor Reduction at 8 wk n (%)
1	16	1	5	38 [15-65]	4 (25)
3	14	0	0	0	0
Sequenced	30	1	5	20 [8-39]	4 (13)

- With sequenced nivolumab after prior ipilimumab, 20% of patients had confirmed objective responses
- 13% of patients had ≥80% tumor reduction at their first scheduled 8-week tumor assessment (rapid and deep responses)

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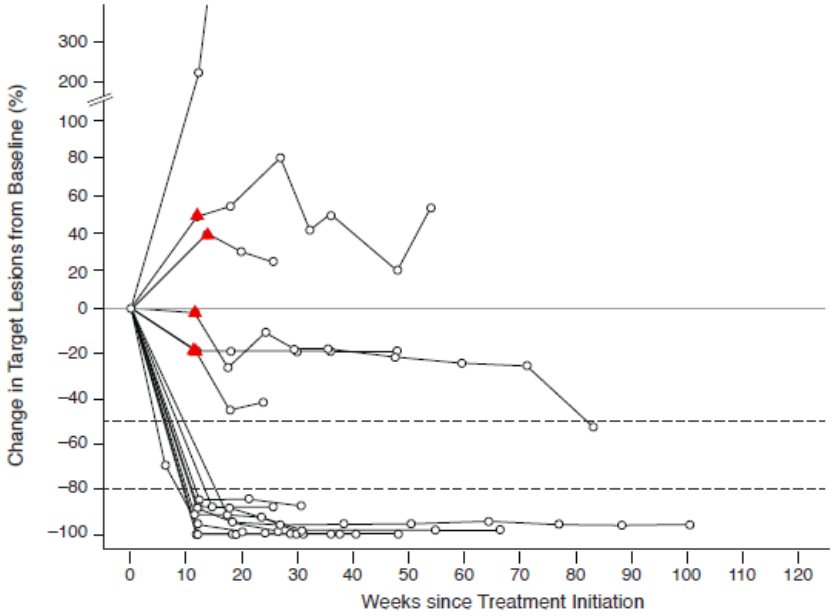
Ipilimumab + PD-1 Fase 1

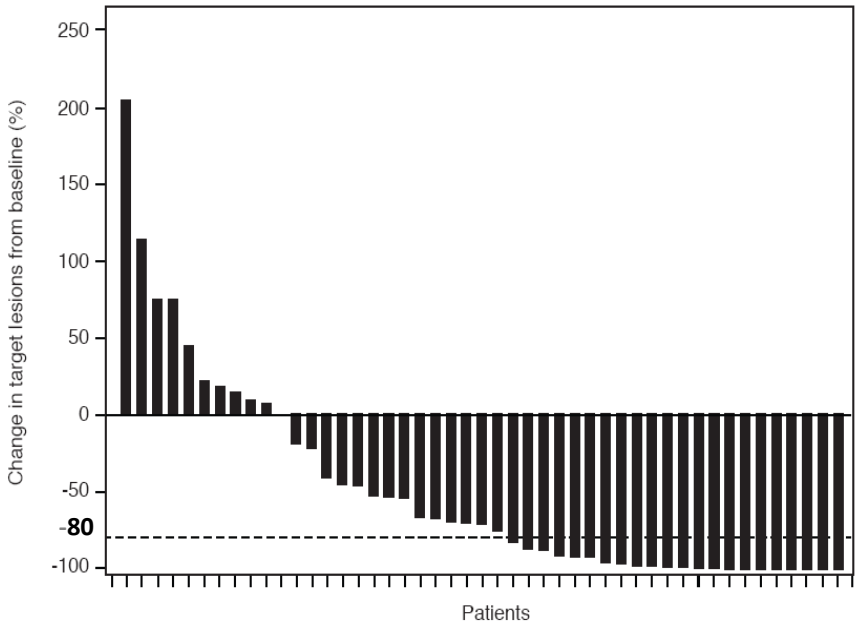
Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab					
0.3	3	14	1	2	21 [5-51]	4 (29)
1	3	17	3	6	53 [28-77]	7 (41)
3	1	15	1	5	40 [16-68]	5 (33)
3	3	6	0	3	50 [12-88]	0
Concurrent		52	5	16	40 [27-55]	16 (31)

- With concurrent treatment of nivolumab + ipilimumab, 40% (range 21-53%) of patients had confirmed objective responses
- About one third of patients (31%) had rapid and deep tumor regressions

Wolchok NEJM 2013

Ipilimumab + PD-1 Fase 1

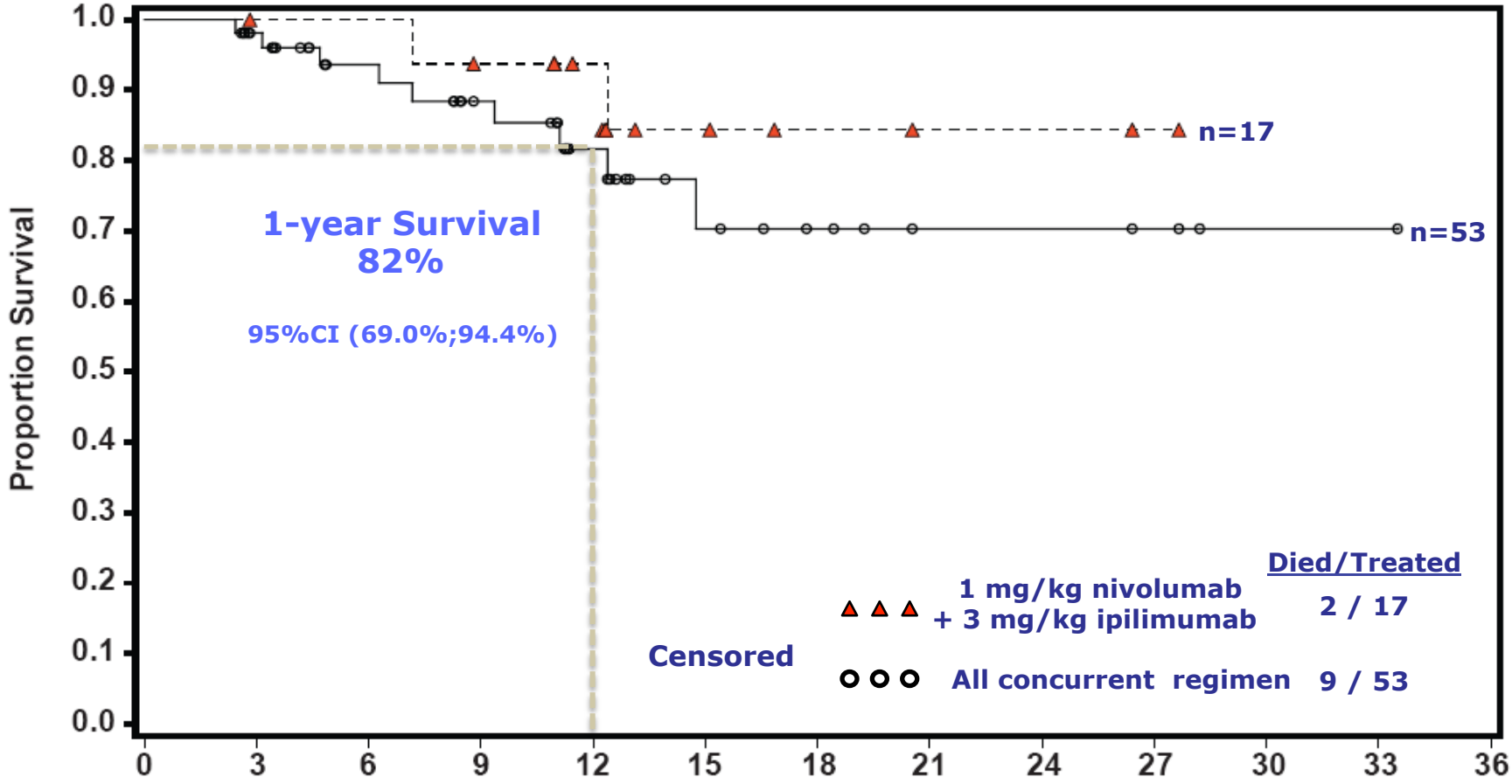




	ORR	>80% Tumor Reduction
Ipilimumab	**7%**	**<3%**
Nivolumab	**28%**	**<2%**
Combination (cohort 2)	**53%**	**41%**

Wolchok JD et al. N Engl J Med 2013. DOI: 10.1056/ NEJMoa1302369

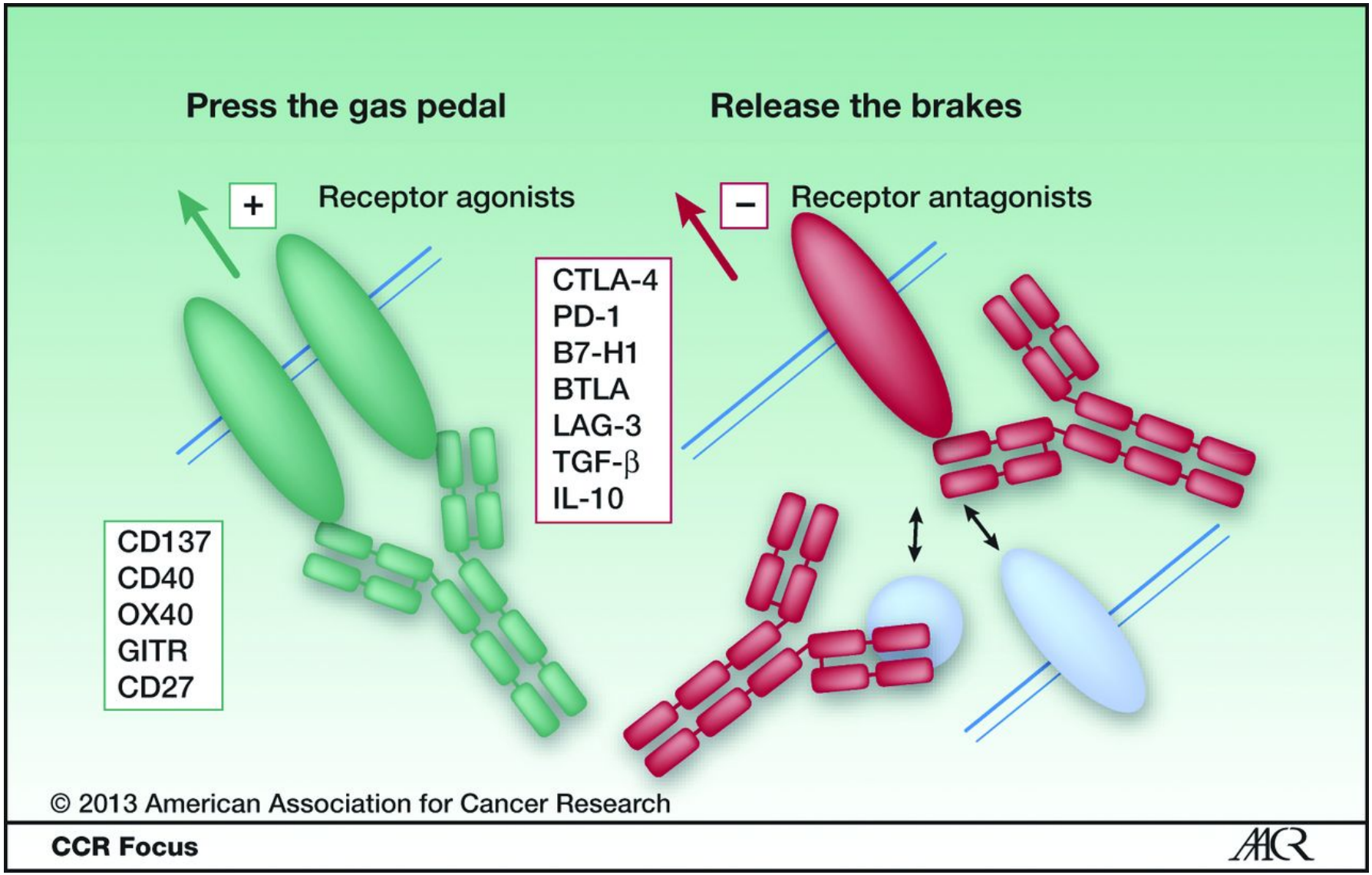
Preliminary Survival of Patients Treated with the Concurrent Regimen



Patients at Risk

1 mg + 3 mg	17	16	16	14	10	5	3	2	2	1	0	0	0
All concurrent	53	47	36	29	19	10	7	4	4	3	1	1	0

Wolchok JD et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1302369



Melero I et al. Clin Cancer Res 2013;19:997-1008