Immunoterapia del glioblastoma

finocchiaro.gaetano@hsr.it

Glioblastoma: the standard

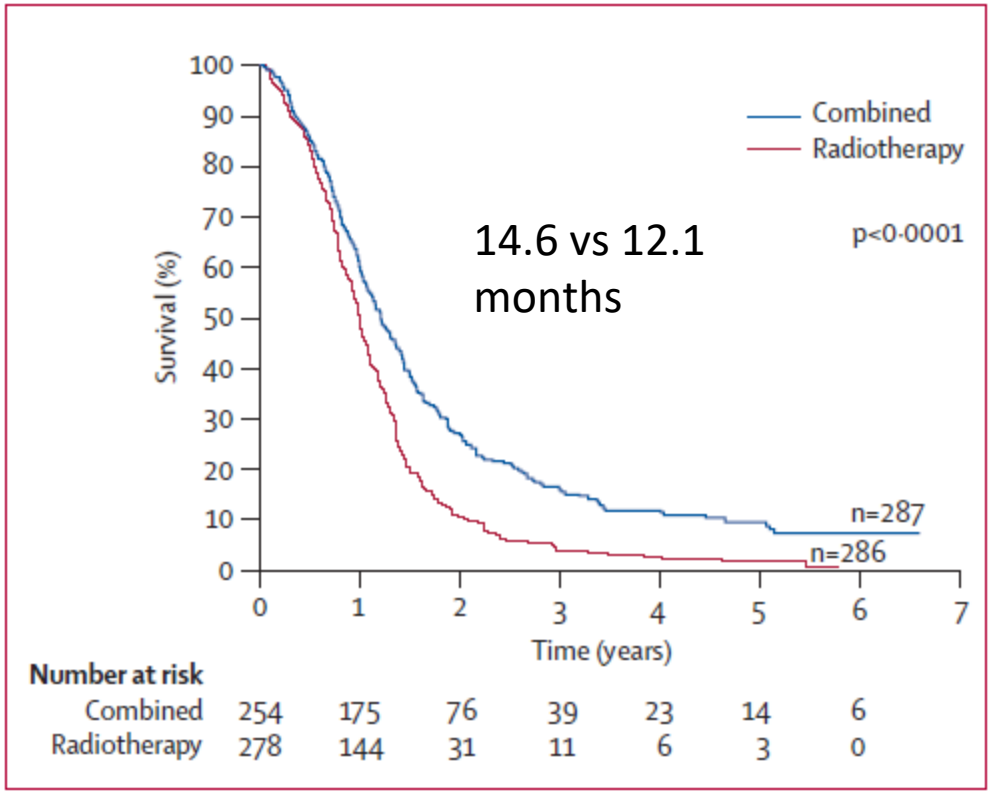


Figure 2: **Kaplan-Meier estimates of overall survival by treatment group**

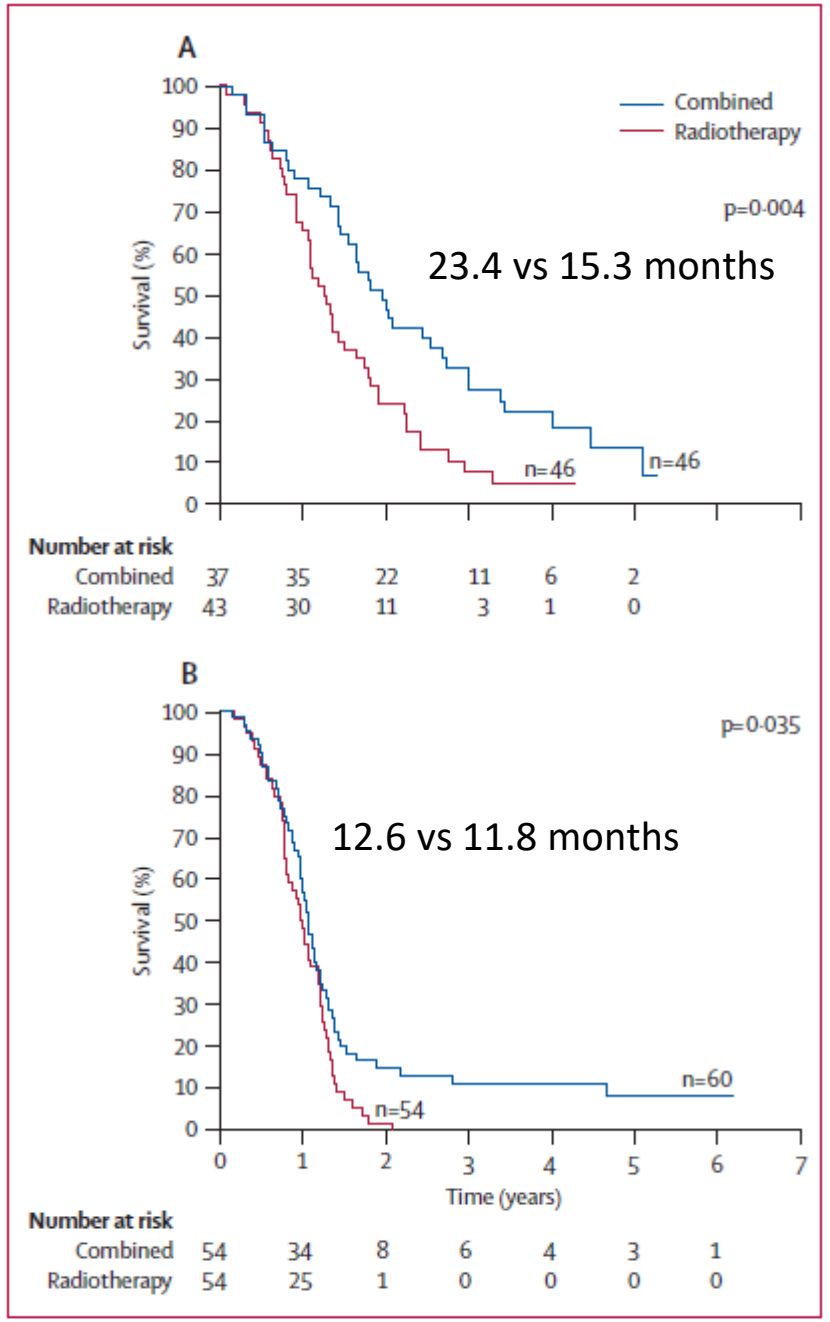
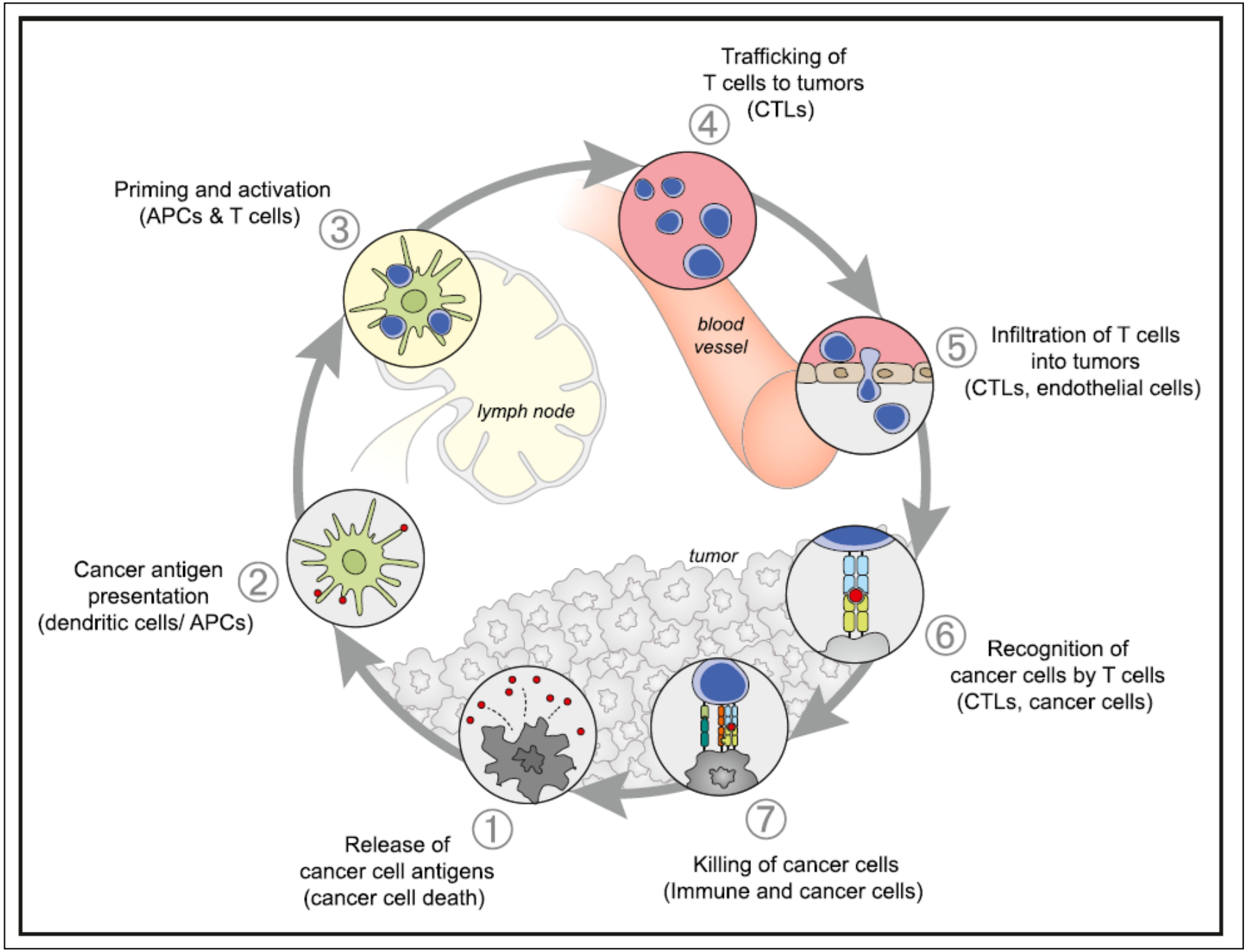


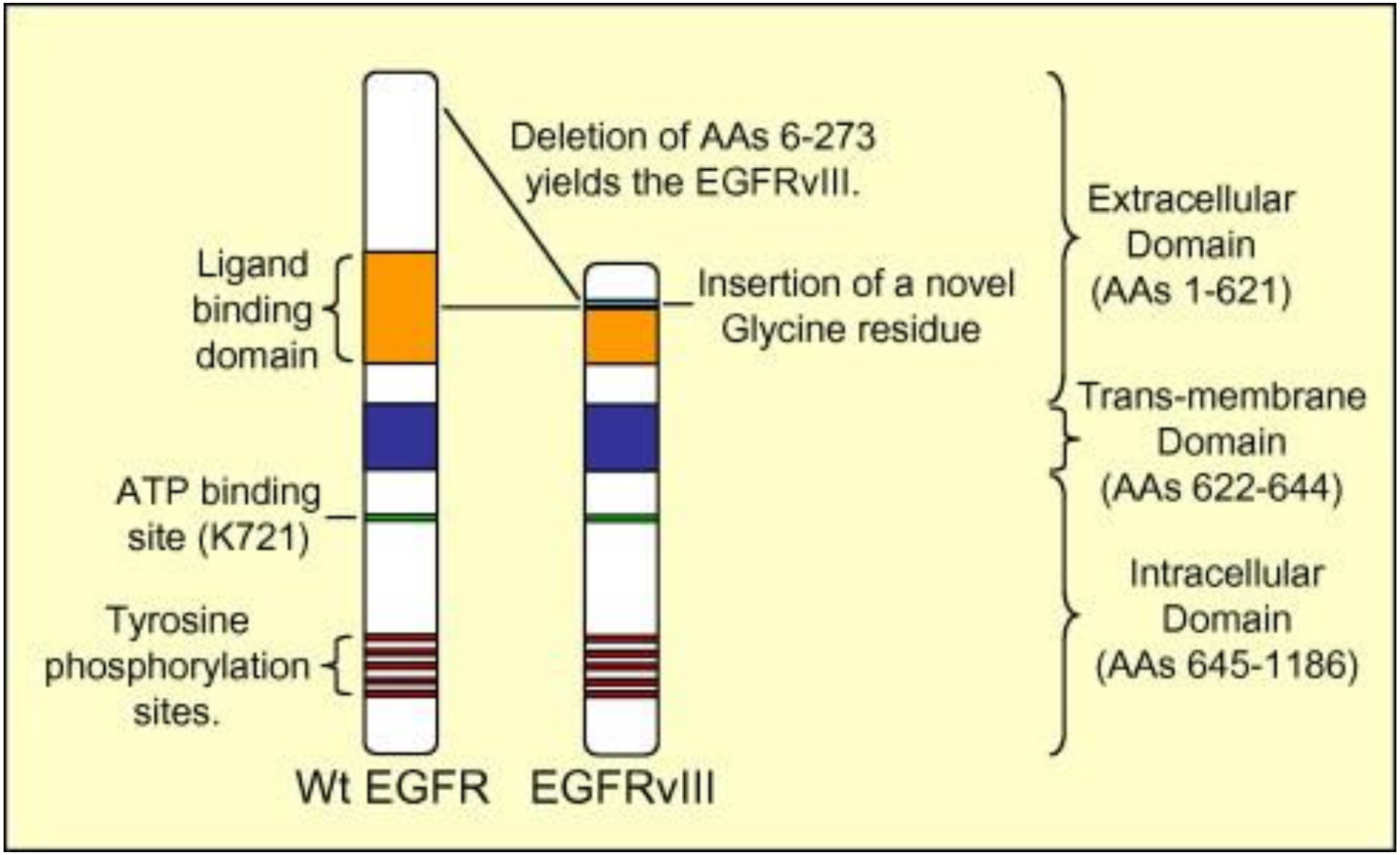
Figure 4: **Kaplan-Meier estimates of overall survival by *MGMT* status**
Patients with methylated *MGMT* (A). Patients with unmethylated *MGMT* (B).

The cancer-immunity cycle



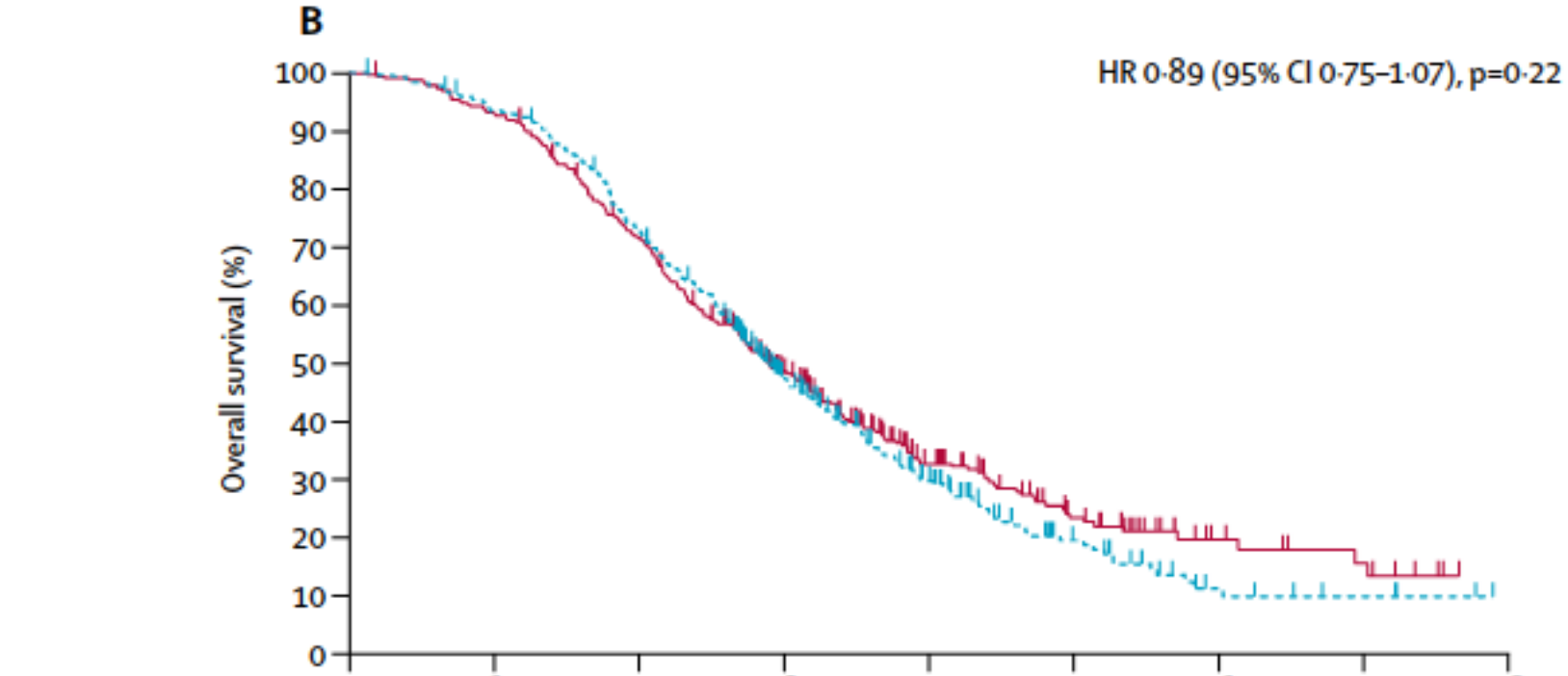
Chen and Mellman, Immunity 2013

Epidermal Growth Factor Receptor variant III (EGFRvIII)

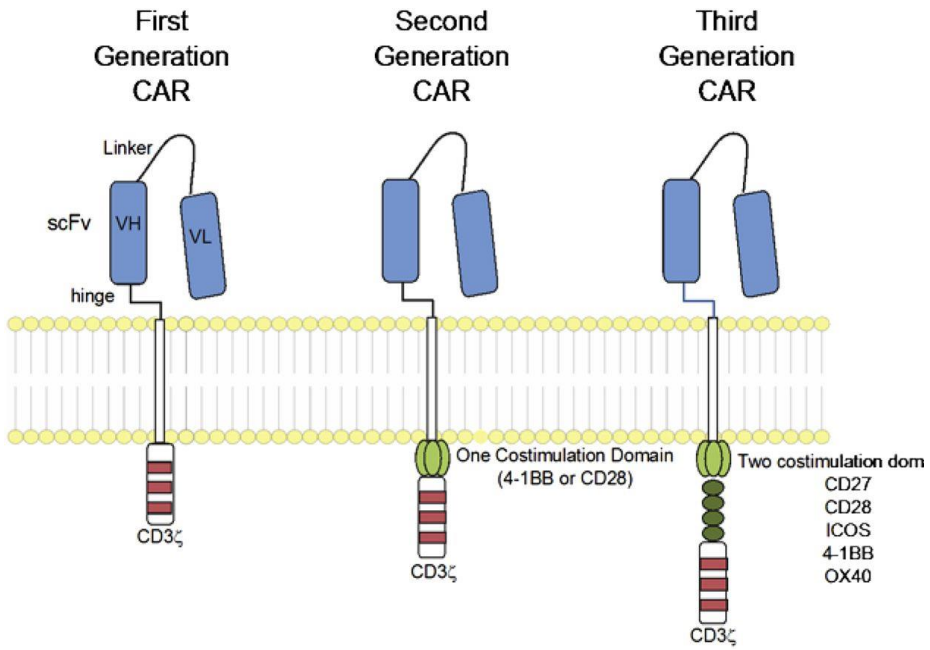


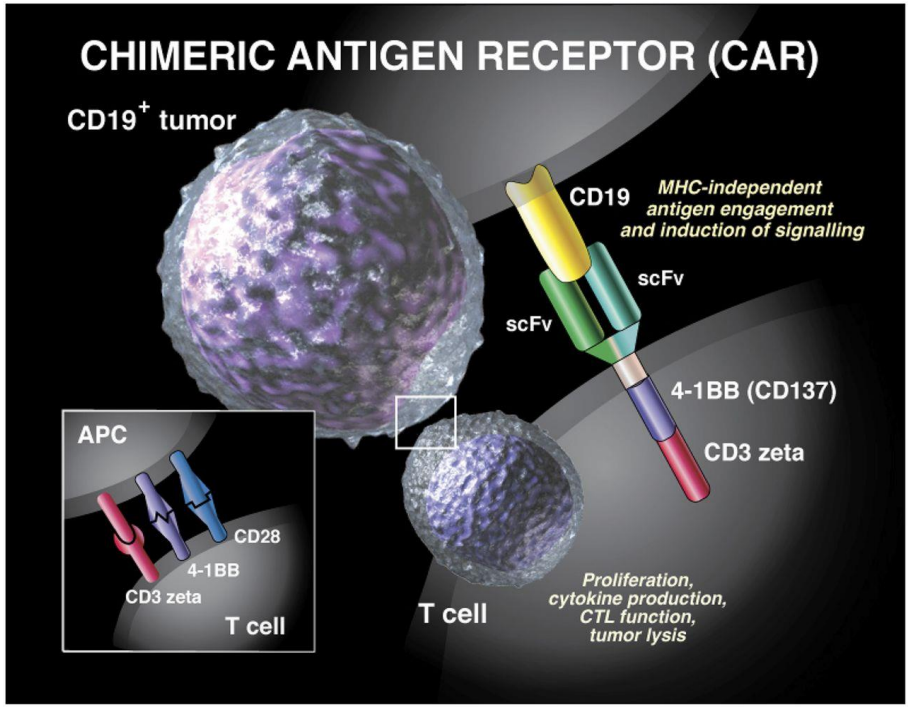
Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial

*Michael Weller, Nicholas Butowski, David D Tran, Lawrence D Recht, Michael Lim, Hal Hirte, Lynn Ashby, Laszlo Mechtler, Samuel A Goldlust, Fabio Iwamoto, Jan Drappatz, Donald M O'Rourke, Mark Wong, Mark G Hamilton, Gaetano Finocchiaro, James Perry, Wolfgang Wick, Jennifer Green, Yi He, Christopher D Turner, Michael J Yellin, Tibor Keler, Thomas A Davis, Roger Stupp, and John H Sampson, for the ACT IV trial investigators**

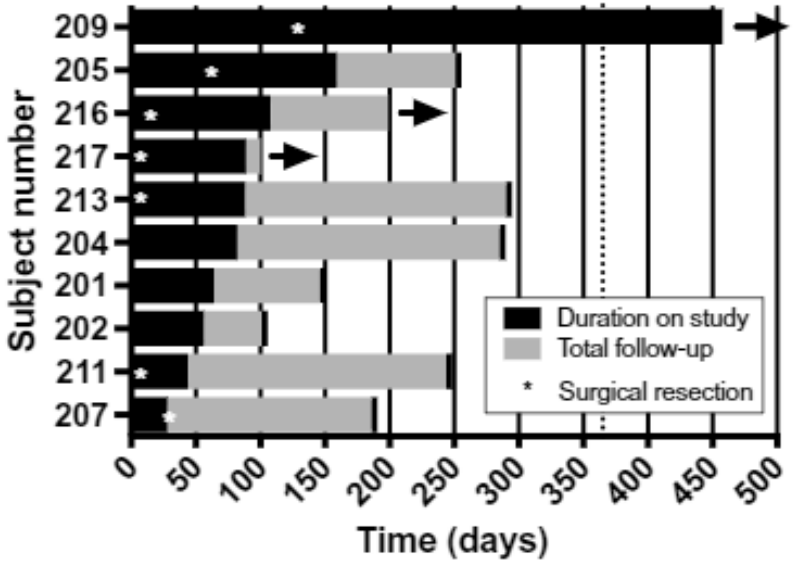


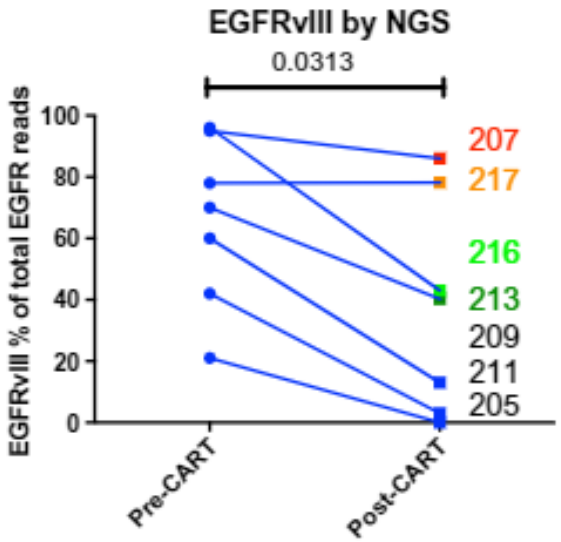
Number at risk (number censored)									
Rindopepimut + temozolomide	371 (0)	345 (1)	261 (5)	159 (25)	72 (68)	32 (92)	12 (108)	7 (111)	0 (117)
Control + temozolomide	374 (0)	347 (3)	268 (7)	149 (35)	73 (61)	25 (90)	8 (98)	4 (101)	0 (105)

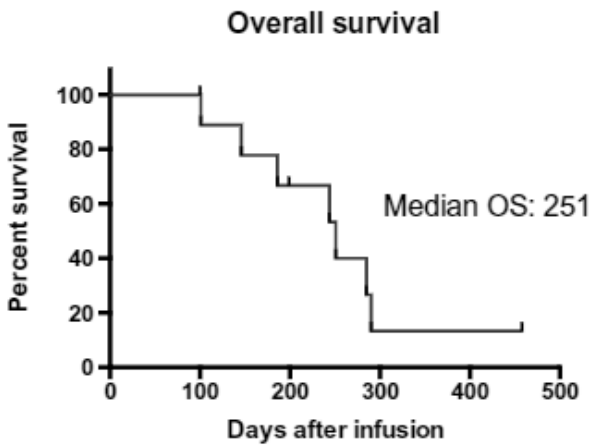




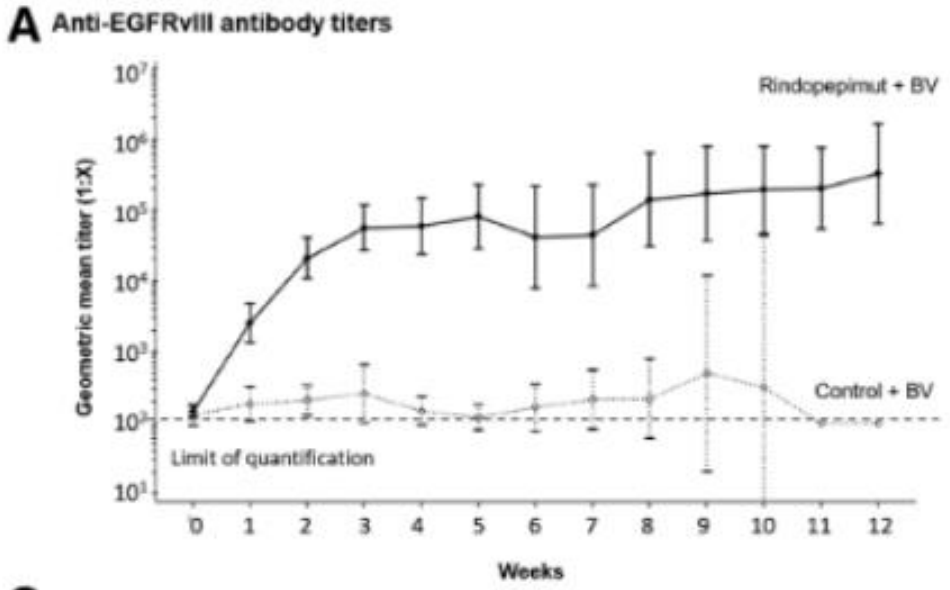
A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma
(O' Rourke et al, Science Transl Med 2017)

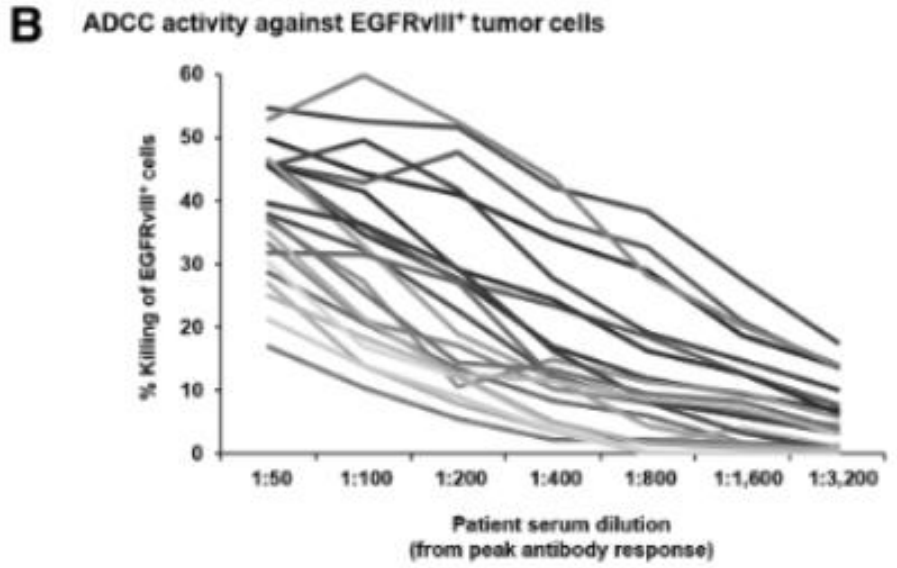


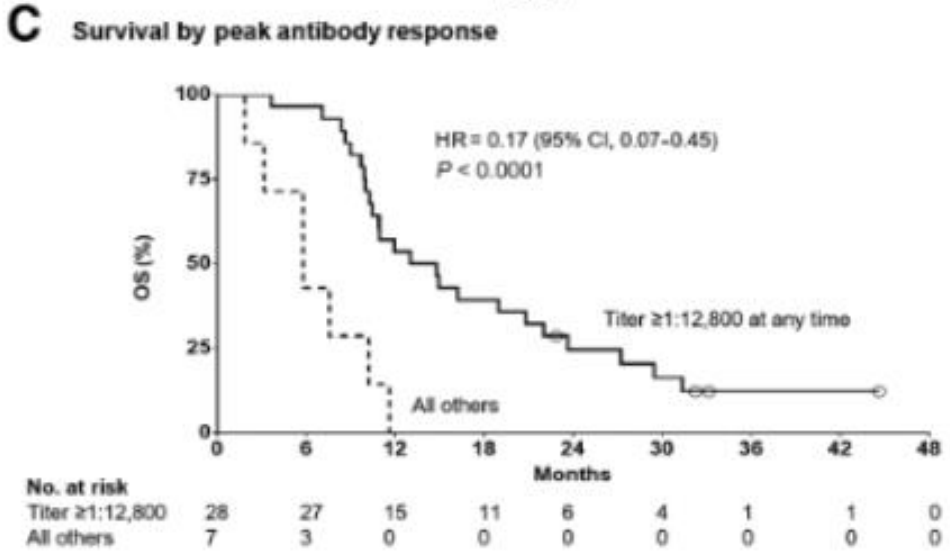


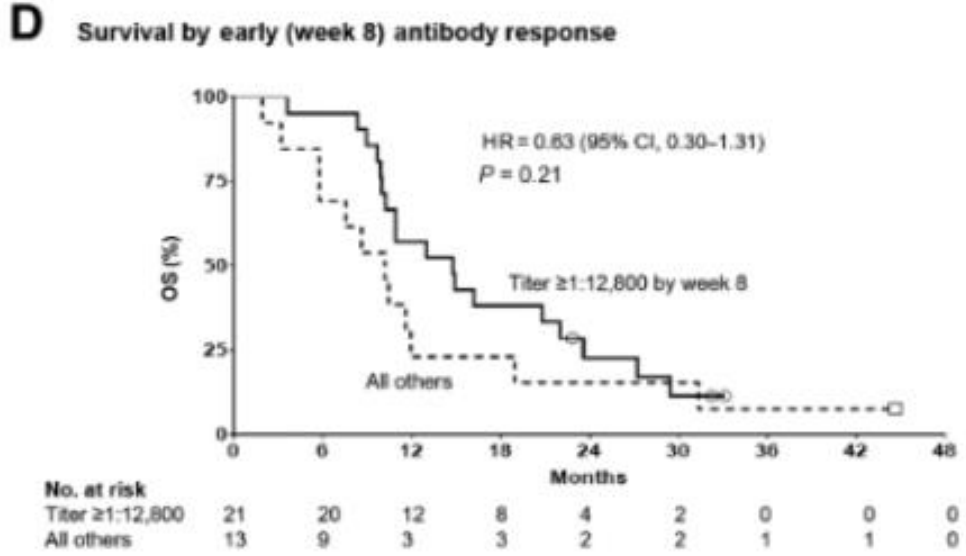


Rindopepimut with Bevacizumab for Patients with Relapsed EGFRvIII-Expressing Glioblastoma (ReACT): Results of a Double-Blind Randomized Phase II Trial (Reardon et al, Clin Cancer Res 2020)



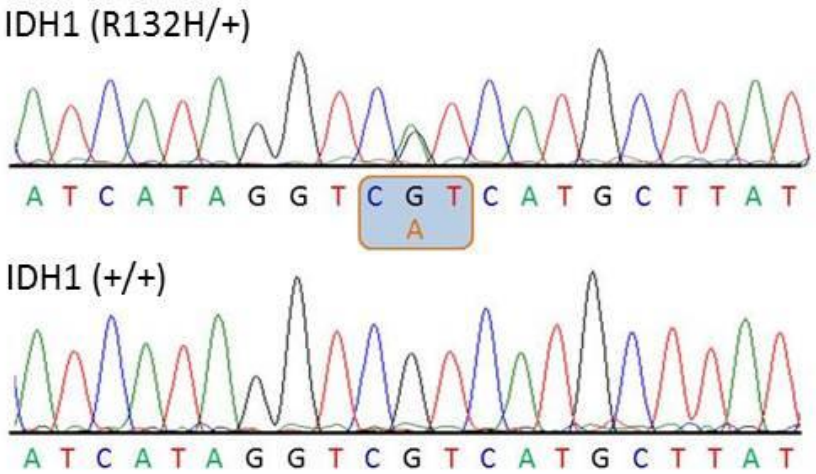


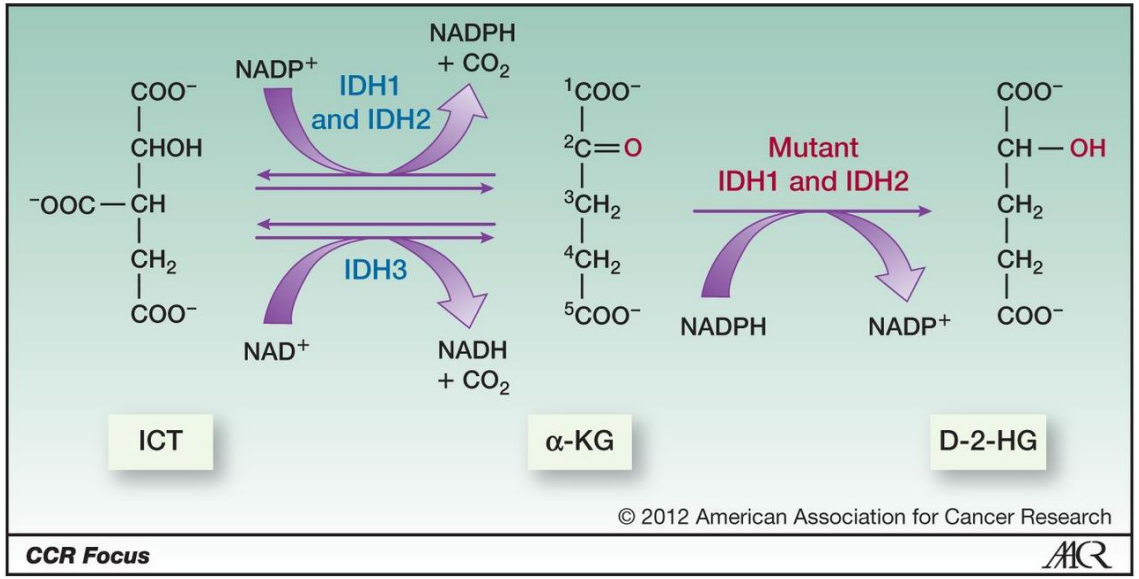


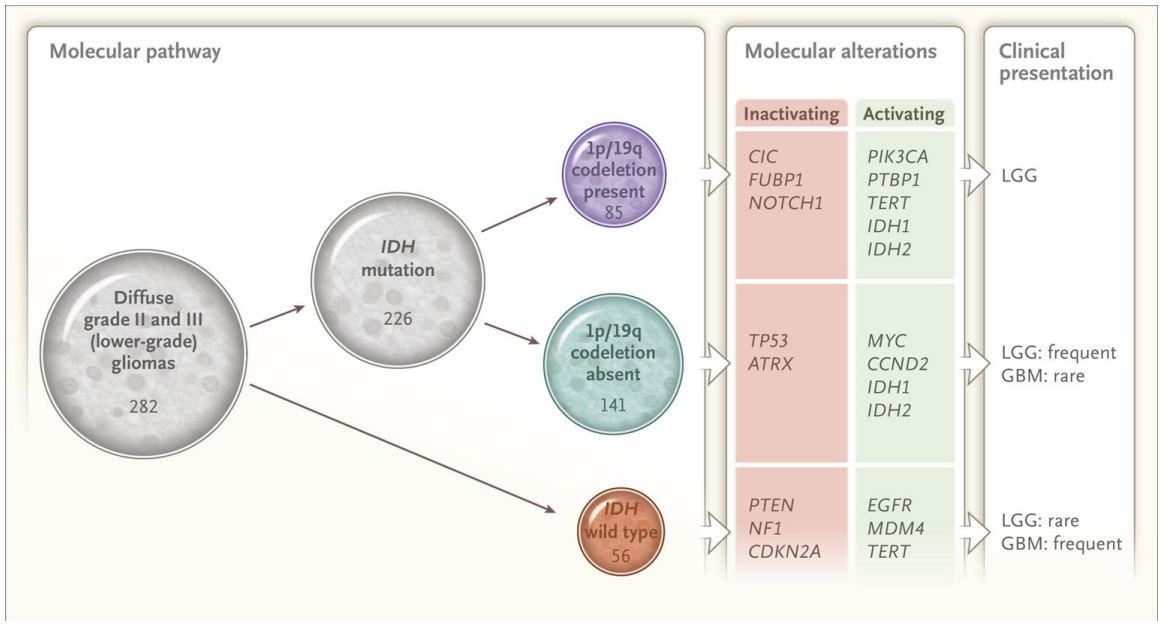


IDH1 Mutations Are Early Events in the Development of Astrocytomas and Oligodendrogliomas

Watanabe et al, Am J Pathol, 2009

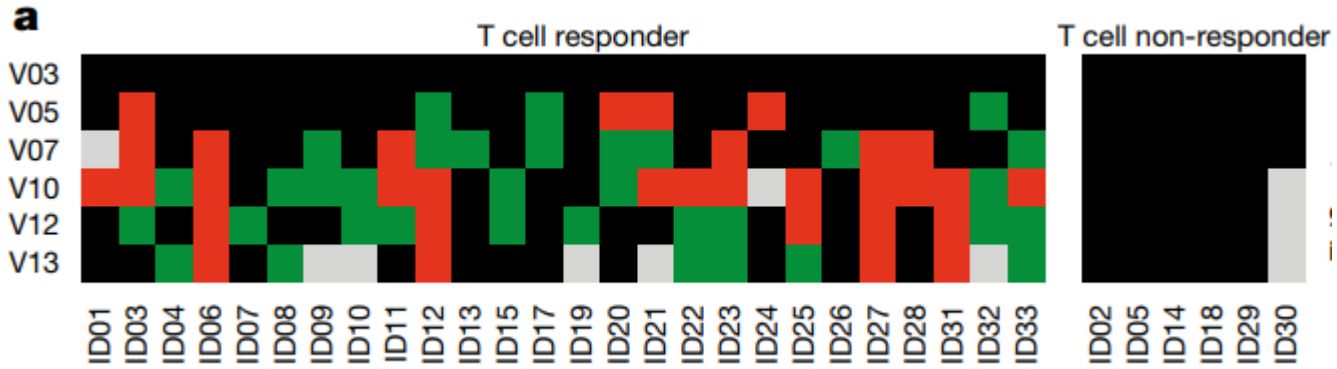


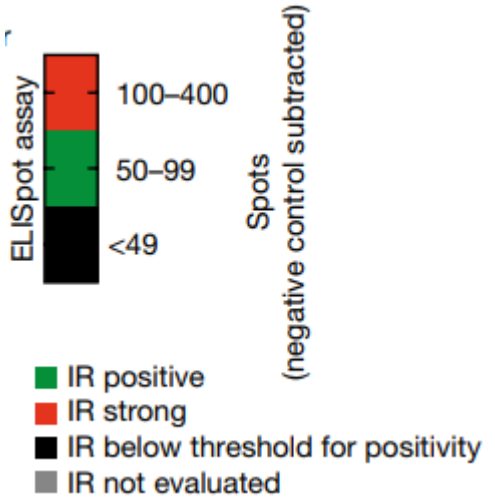


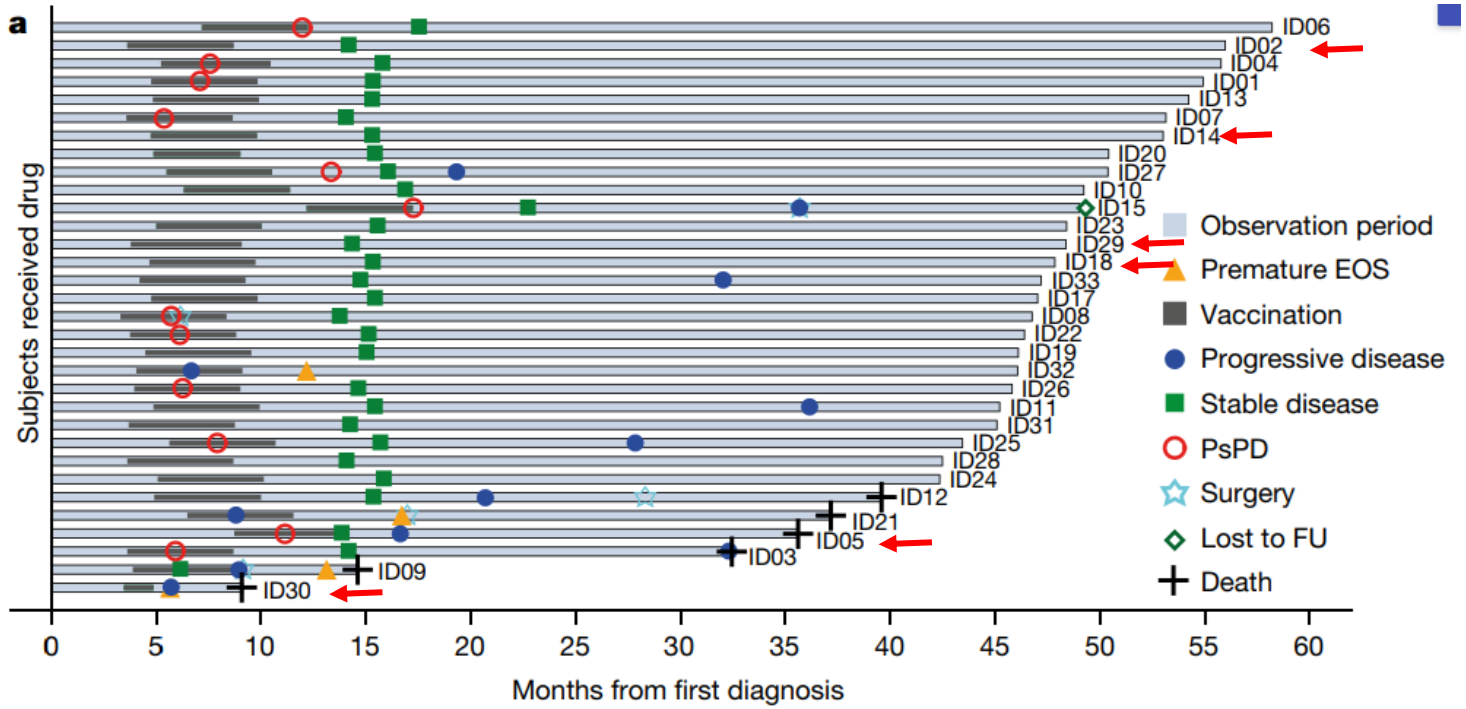


- R-2-hydroxyglutarate (R-2-HG) promotes histone methylation (Lu, Ward et al, Nature 2012).
- Tumor-derived R-2-HG induces a perturbation of nuclear factor of activated T cells transcriptional activity and polyamine biosynthesis, resulting in suppression of T cell activity (Bunse et al, Nat Med 2018)

A vaccine targeting mutant IDH1 in newly diagnosed glioma

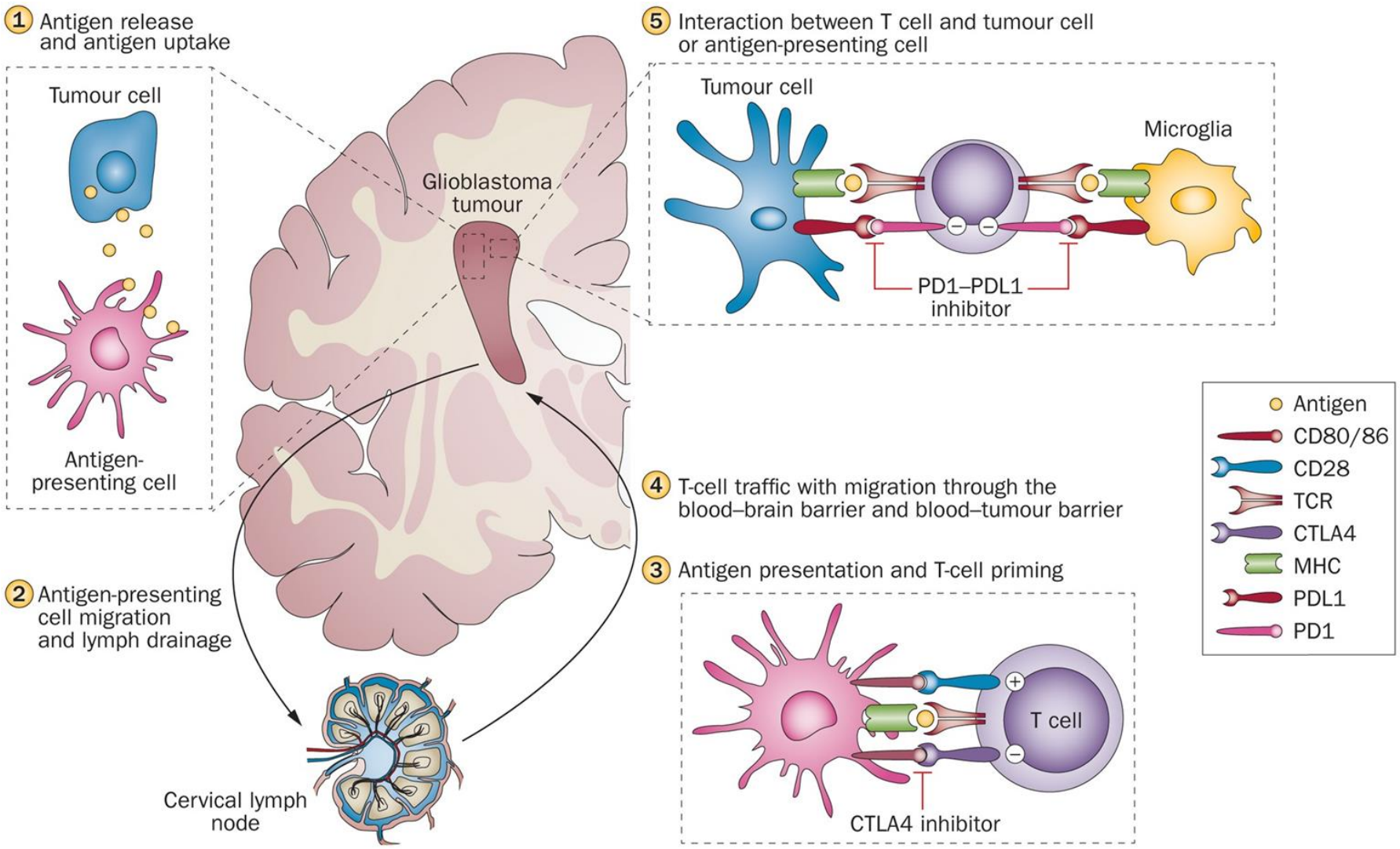






Platten et al, Nature 2021

Immune Checkpoint Inhibitors



Preusser et al, 2015

Nature Reviews | Neurology

JAMA Oncology | Original Investigation

Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma

The CheckMate 143 Phase 3 Randomized Clinical Trial

David A. Reardon, MD; Alba A. Brandes, MD; Antonio Omuro, MD; Paul Mulholland, PhD; Michael Lim, MD; Antje Wick, MD; Joachim Baehring, MD; Manmeet S. Ahluwalia, MD; Patrick Roth, MD; Oliver Bähr, MD; Surasak Phuphanich, MD; Juan Manuel Sepulveda, MD, PhD; Paul De Souza, MD; Solmaz Sahebjam, MD; Michael Carleton, PhD; Kay Tatsuoka, PhD; Corina Taitt, MD; Ricardo Zwirtes, MD; John Sampson, MD; Michael Weller, MD

Key Points

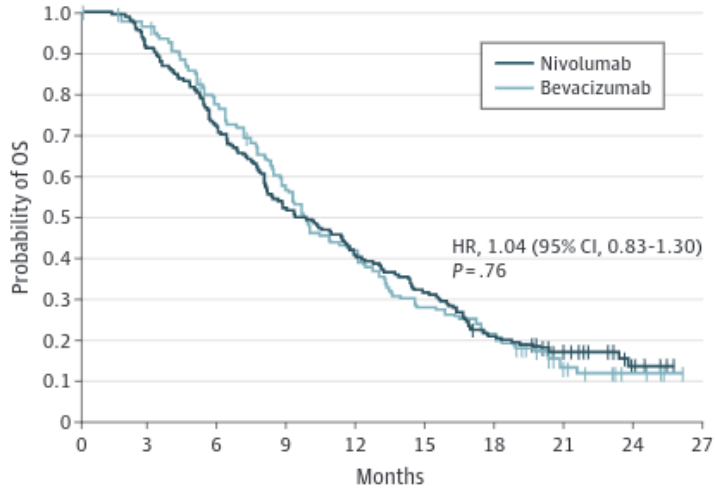
Question Does programmed cell death 1 immune checkpoint inhibition with nivolumab improve overall survival compared with bevacizumab treatment for patients with recurrent glioblastoma?

Findings In this randomized phase 3 clinical trial of 369 patients diagnosed with recurrent glioblastoma treated with nivolumab, an improved survival benefit was not observed in patients who received nivolumab compared with bevacizumab-treated control patients.

Meaning Additional research is needed; nivolumab monotherapy did not improve overall survival compared with bevacizumab in the treatment of recurrent glioblastoma. A study of nivolumab in combination with radiotherapy and temozolomide in patients with newly diagnosed glioblastoma with methylated *MGMT* promoter is ongoing.

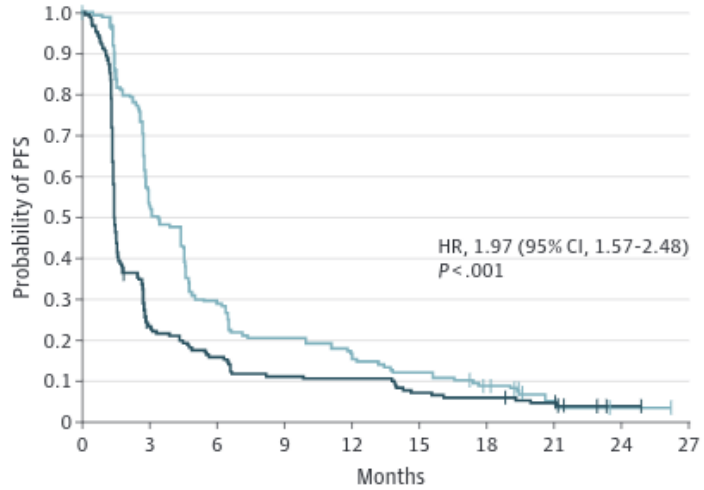
A Probability of OS by intervention

Intervention	Events, No.	Median OS (95% CI), months	OS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	154	9.8 (8.2-11.8)	72.3 (65.2-78.2)	41.8 (34.7-48.8)	21.7 (16.1-27.9)
Bevacizumab	147	10.0 (9.0-11.8)	78.2 (71.2-83.6)	42.0 (34.6-49.3)	21.6 (15.8-28.0)



B Probability of progression-free survival

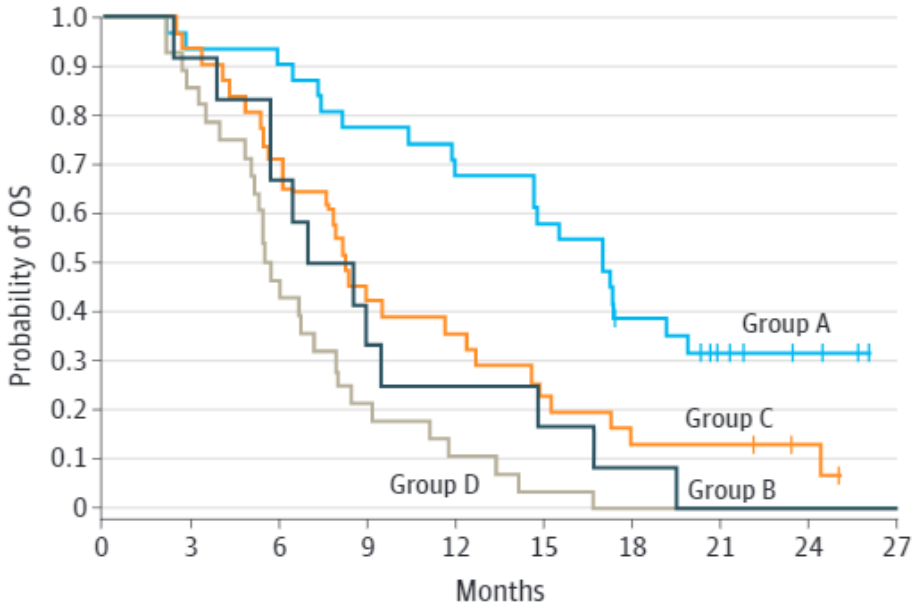
Intervention	Events, No.	Median PFS (95% CI), months	PFS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	171	1.5 (1.5-1.6)	15.7 (10.8-21.5)	10.5 (6.5-15.5)	5.8 (3.0-10.0)
Bevacizumab	146	3.5 (2.9-4.6)	29.6 (22.7-36.9)	17.4 (11.9-23.7)	8.9 (5.1-14.1)



JAMA Oncol. doi:10.1001/jamaoncol.2020.1024
Published online May 21, 2020.

B Nivolumab

Group	No. of events/ No. of patients	Median OS (95% CI), months
Group A: *MGMT* methylated; no baseline corticosteroid use	21/31	17.0 (11.9-19.8)
Group B: *MGMT* methylated; baseline corticosteroid use	12/12	7.7 (3.9-14.8)
Group C: *MGMT* unmethylated; no baseline corticosteroid use	27/30	8.3 (6.2-12.6)
Group D: *MGMT* unmethylated; baseline corticosteroid use	28/28	5.6 (5.0-7.2)

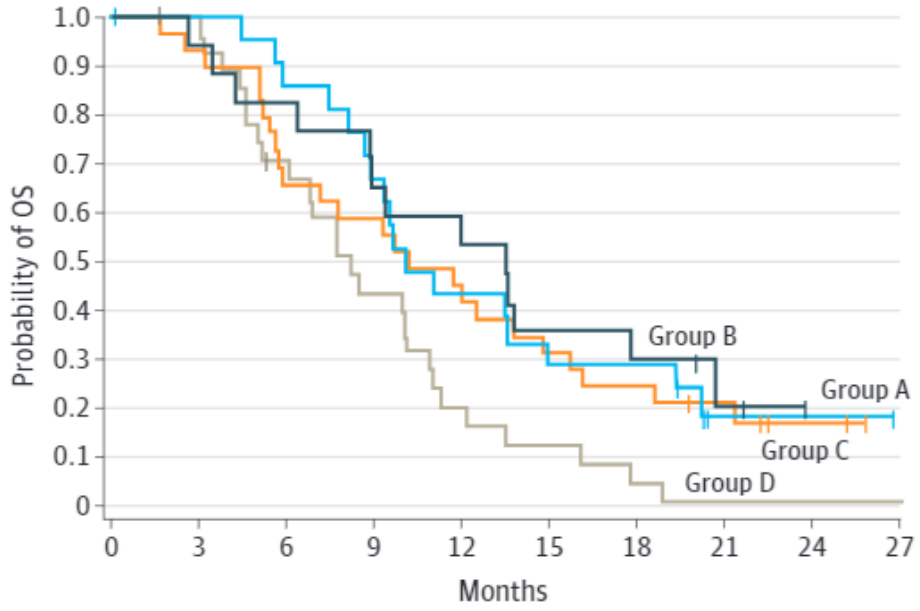


No. at risk

Group A	31	29	28	24	21	18	11	7	3	0
Group B	12	11	8	4	3	2	1	0	0	0
Group C	30	28	22	13	11	7	4	4	2	0
Group D	28	24	13	6	3	1	0	0	0	0

C Bevacizumab

Group	No. of events/ No. of patients	Median OS (95% CI), months
Group A: *MGMT* methylated; no baseline corticosteroid use	17/22	10.1 (8.7-14.9)
Group B: *MGMT* methylated; baseline corticosteroid use	13/17	13.5 (6.4-20.7)
Group C: *MGMT* unmethylated; no baseline corticosteroid use	24/29	10.3 (5.9-14.9)
Group D: *MGMT* unmethylated; baseline corticosteroid use	26/28	8.3 (5.2-10.2)



No. at risk

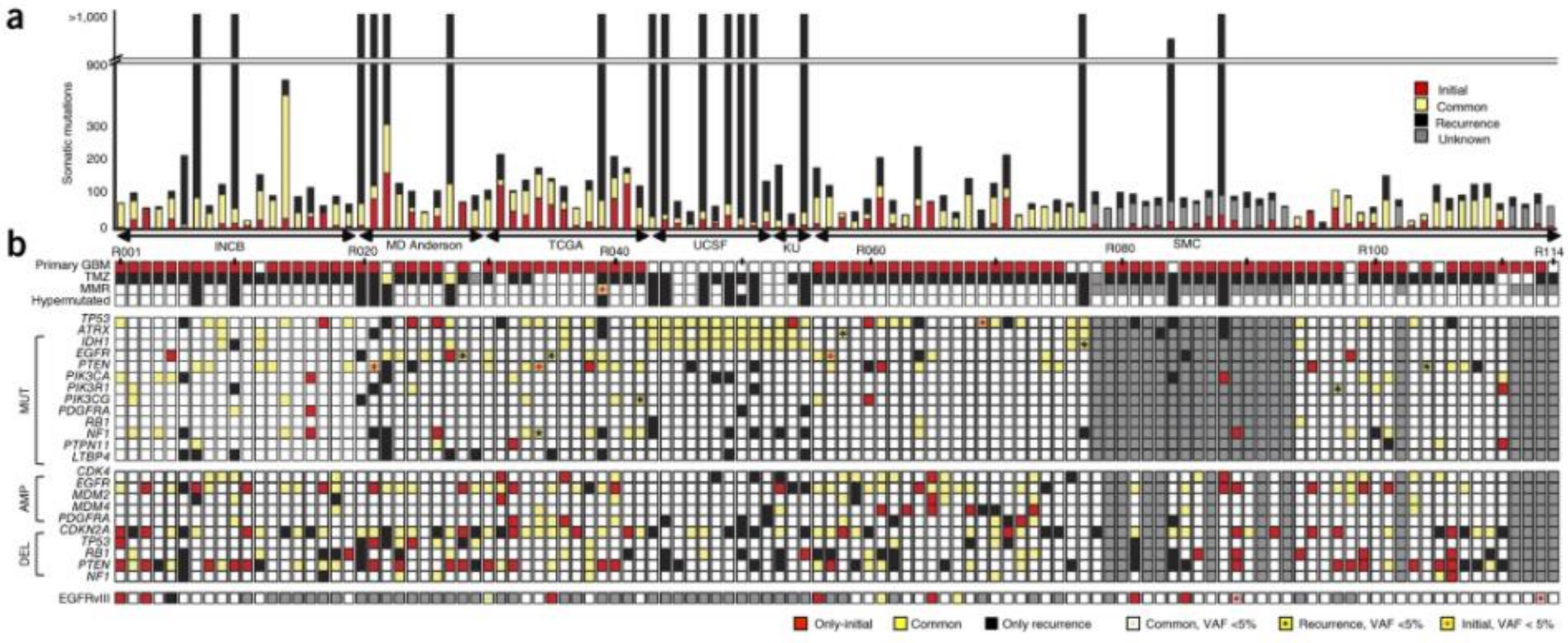
Group A	22	21	18	14	9	6	6	1	1	0
Group B	17	16	14	11	9	6	5	2	0	0
Group C	29	27	19	17	13	9	7	5	2	0
Group D	28	27	18	11	5	3	1	0	0	0

Reardon et al, JAMA Oncol 2020

Clonal evolution of glioblastoma under therapy

Jiguang Wang, Emanuela Cazzato, Erik Ladewig, Veronique Frattini, Daniel I S Rosenbloom, Sakellarios Zairis, Francesco Abate, Zhaoqi Liu, Oliver Elliott, Yong-Jae Shin, Jin-Ku Lee, In-Hee Lee, Woong-Yang Park, Marica Eoli, Andrew J Blumberg, Anna Lasorella, Do-Hyun Nam ✉, Gaetano Finocchiaro ✉, Antonio Iavarone ✉ & Raul Rabadan ✉

Nature Genetics **48**, 768–776(2016) | Cite this article



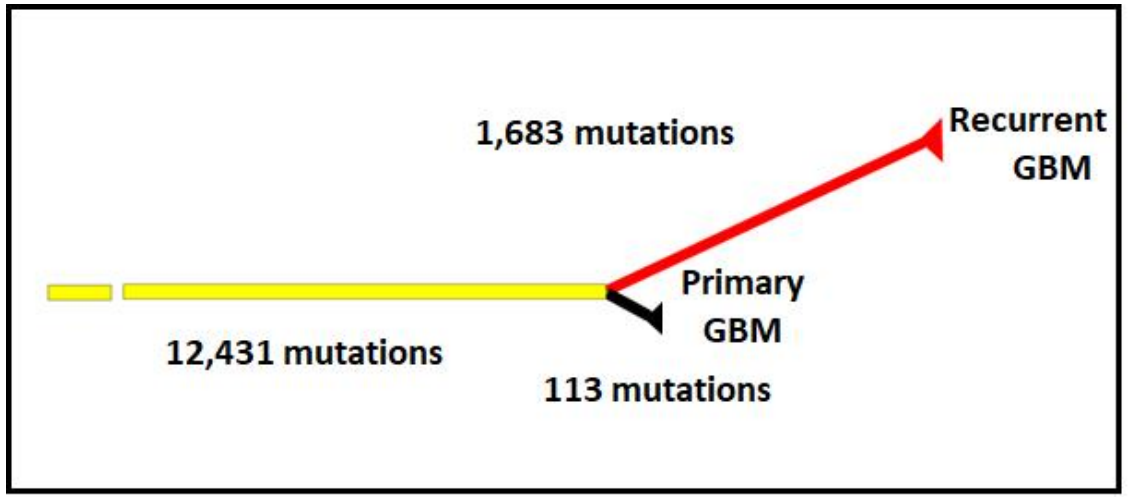
Cancer Immunology, Immunotherapy
https://doi.org/10.1007/s00262-020-02769-4

ORIGINAL ARTICLE

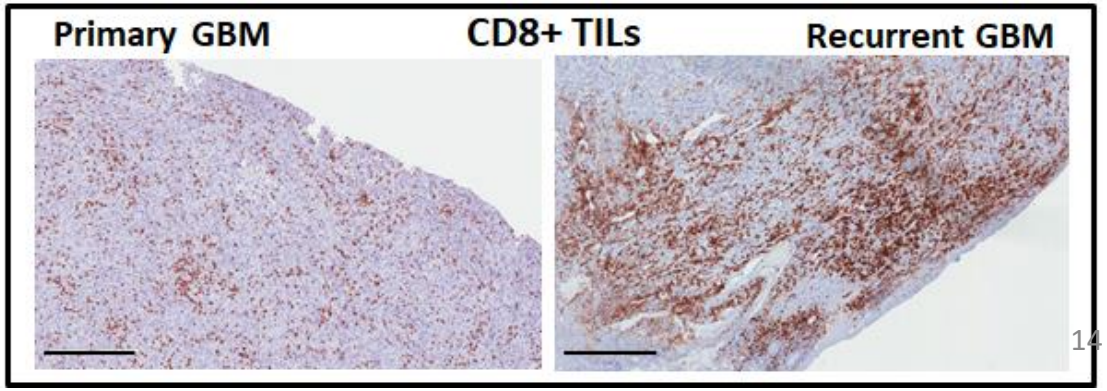
High tumor mutational burden and T-cell activation are associated with long-term response to anti-PD1 therapy in Lynch syndrome recurrent glioblastoma patient

Elena Anghileri[1] · Natalia Di Ianni[1,2] · Rosina Paterra[1] · Tiziana Langella[1] · Junfei Zhao[3] · Marica Eoli[1] · Monica Patanè[4] · Bianca Pollo[4] · Valeria Cuccarini[5] · Antonio Iavarone[6] · Raul Rabadan[3] · Gaetano Finocchiaro[1] · Serena Pellegatta[1,2]

Received: 24 March 2020 / Accepted: 15 October 2020

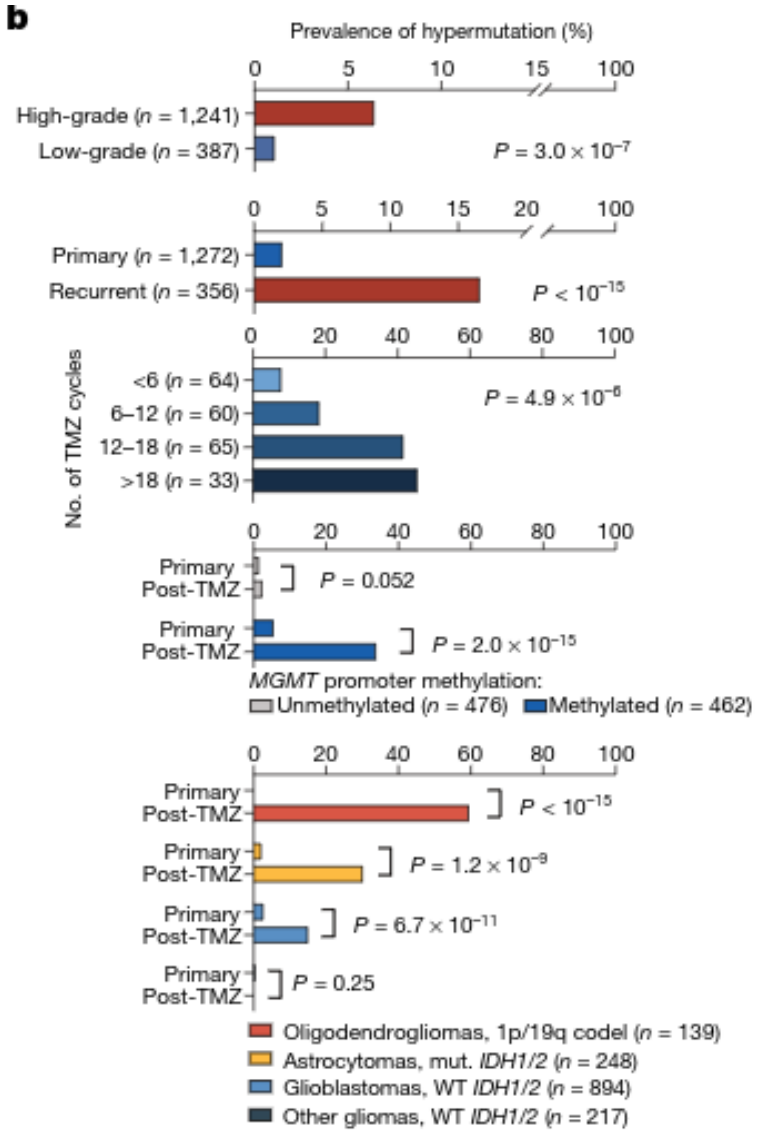


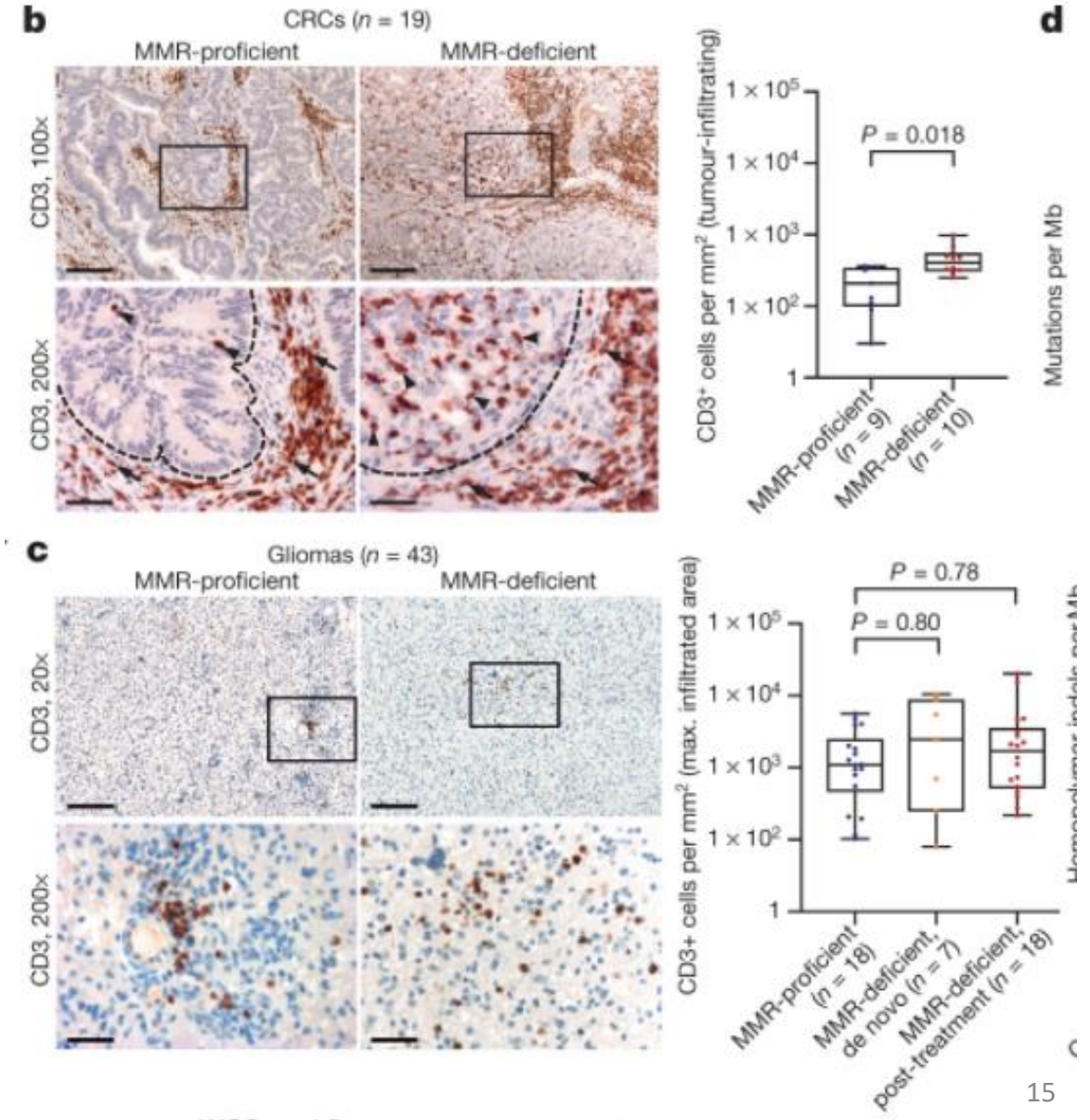
- First surgery>second surgery: 13 months.
- Second surgery on (NIVOLUMAB): 68 months
- Pathogenic mutation in the MSH2 (R359S) gene (germline).
- Immunologically: generation of CD8+ T memory cells and persistent activation of CD4+ Tcells



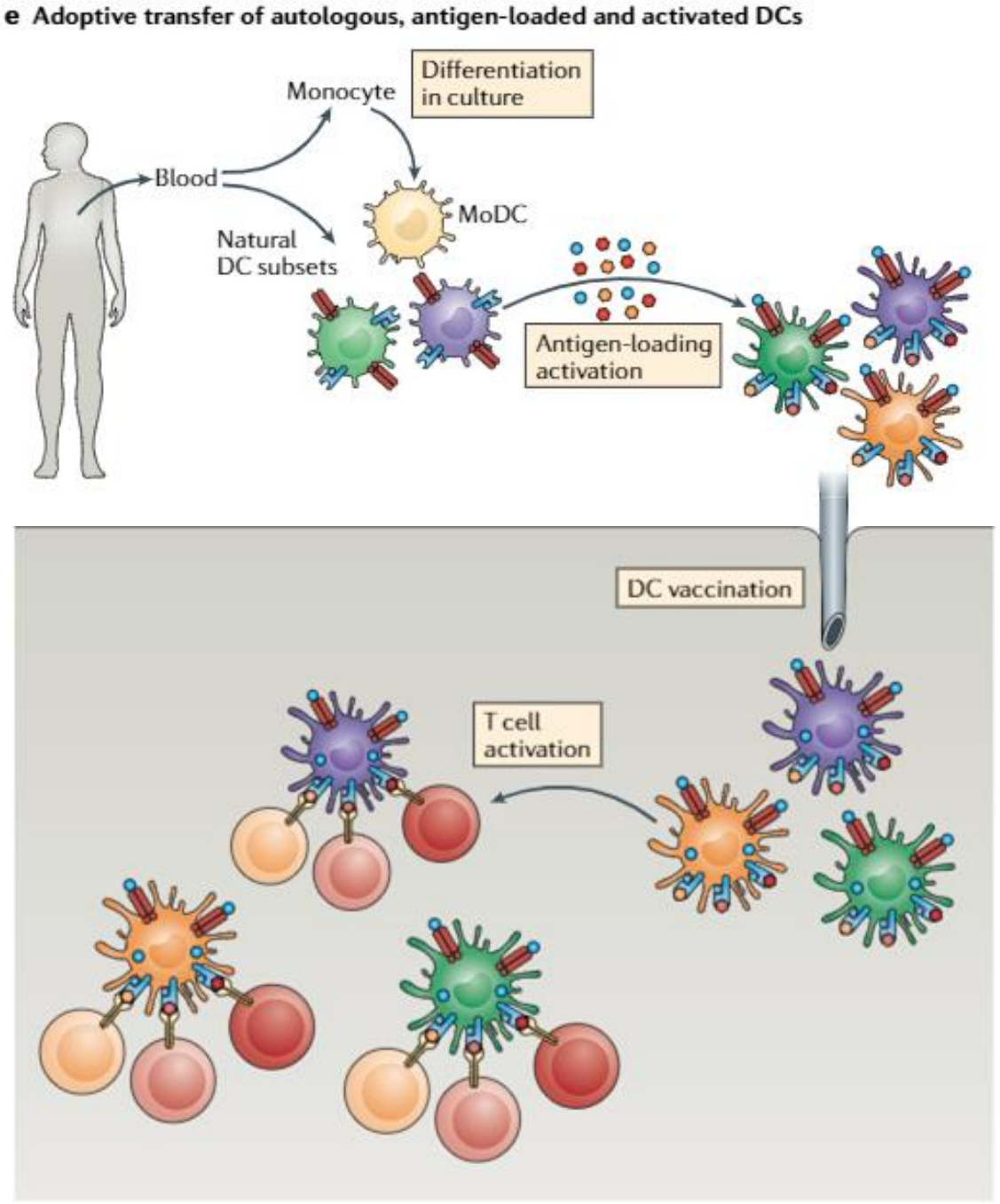
Mechanisms and therapeutic implications of hypermutation in gliomas

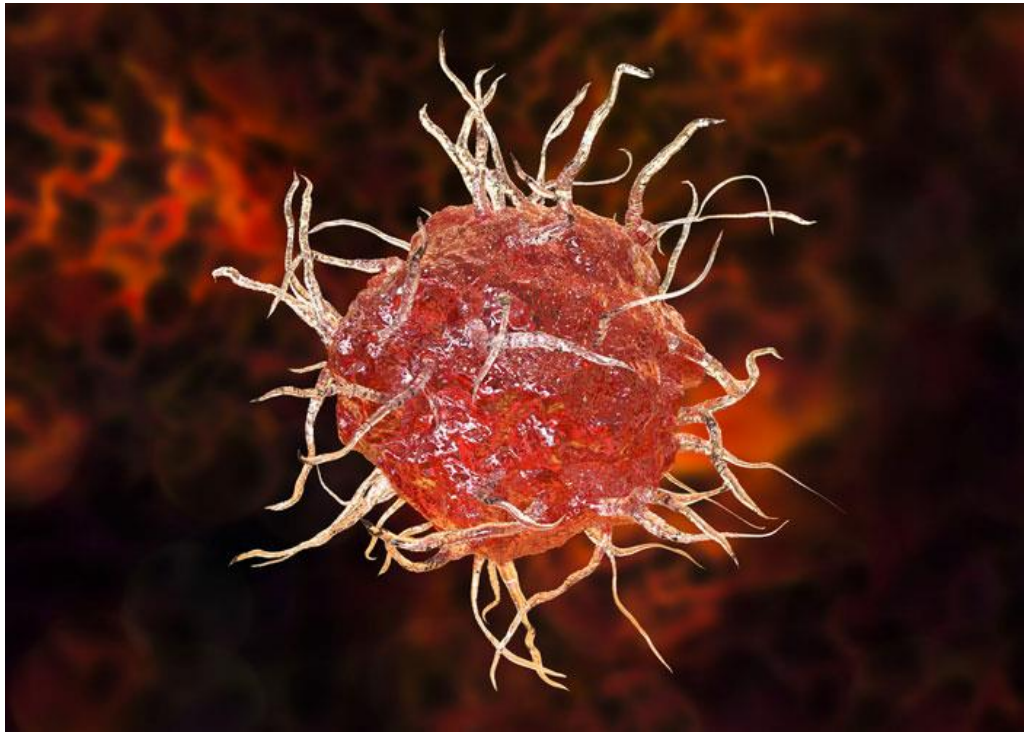
Touat et al, Nature 2020





Dendritic Cells





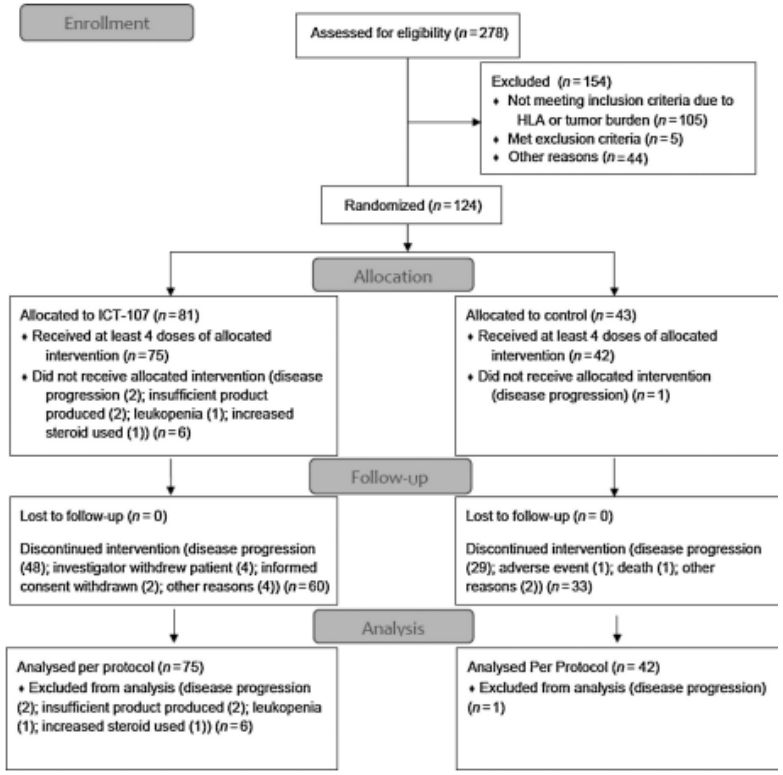
Wculek et al,
Nature Rev Immunol 2020

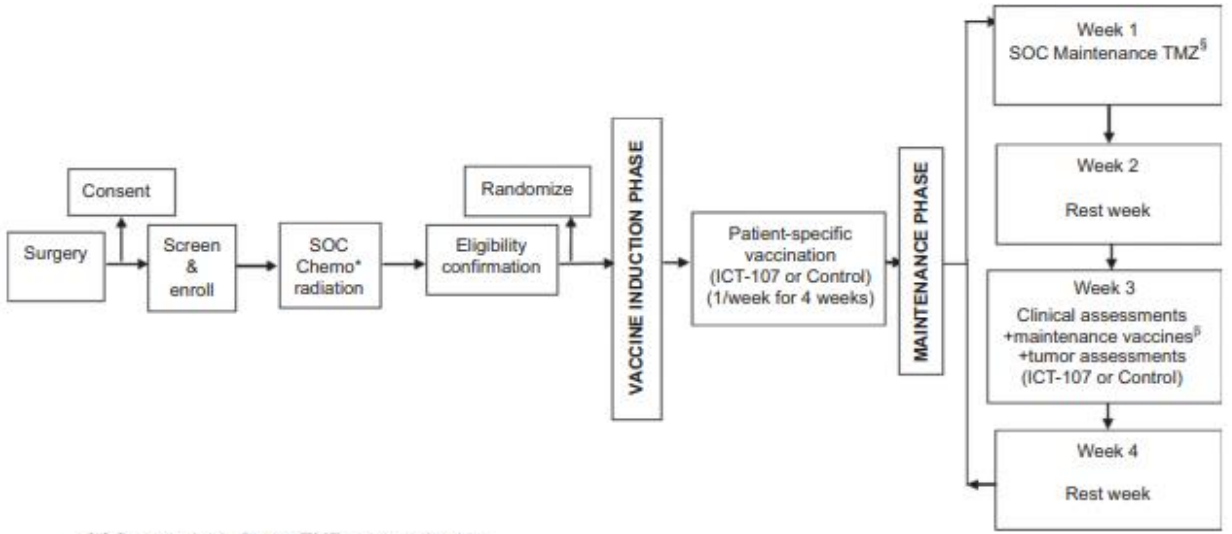
Clinical Trials: Immunotherapy

Clinical Cancer Research

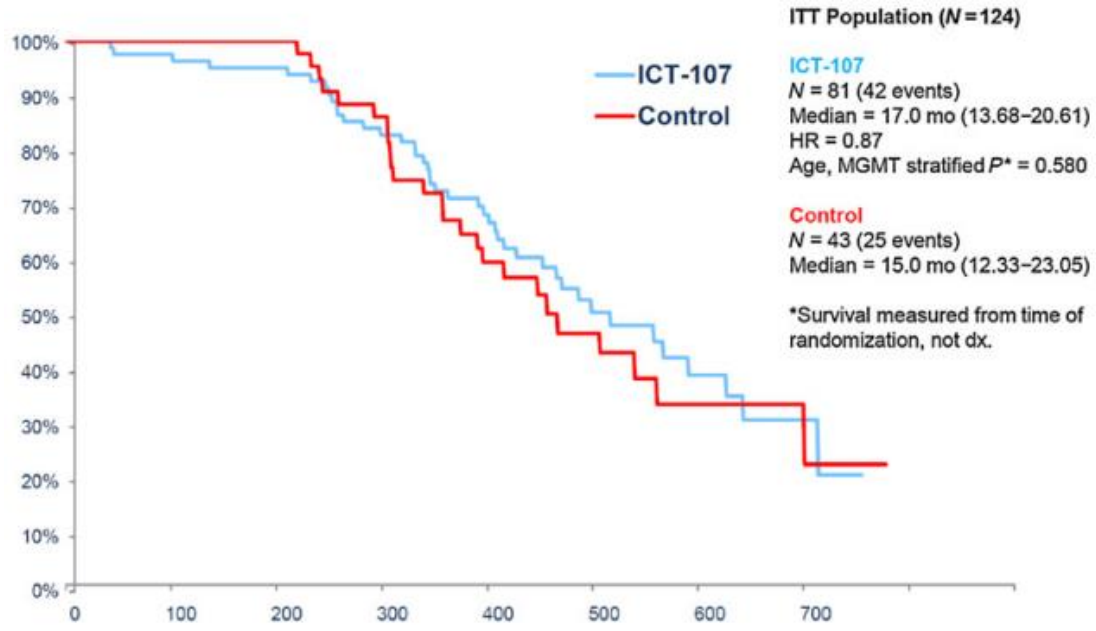
A Randomized Double-Blind Placebo-Controlled Phase II Trial of Dendritic Cell Vaccine ICT-107 in Newly Diagnosed Patients with Glioblastoma

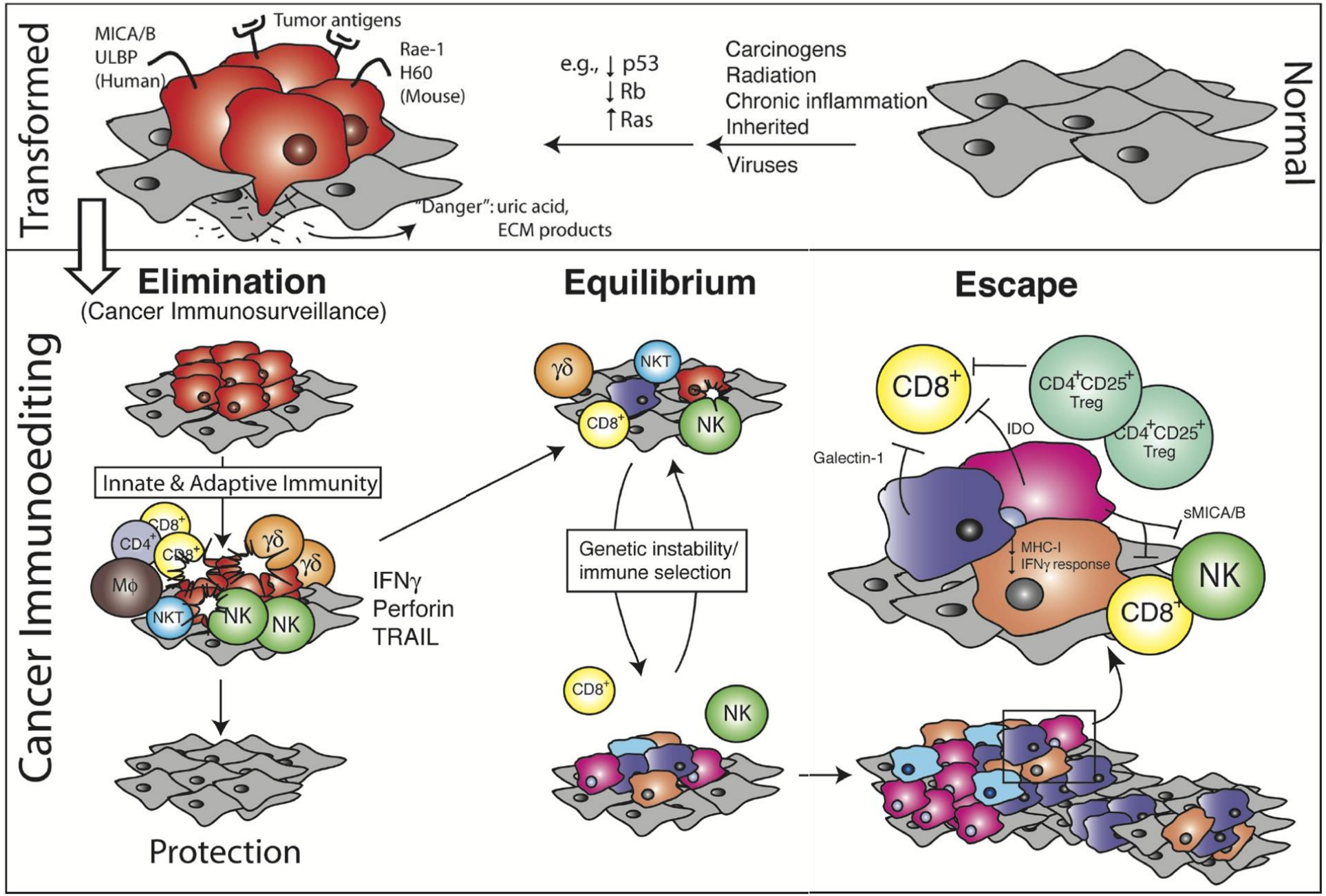
Patrick Y. Wen[1], David A. Reardon[1], Terri S. Armstrong[2], Surasak Phuphanich[3], Robert D. Aiken[4], Joseph C. Landolfi[5], William T. Curry[6], Jay-Jiguang Zhu[7], Michael Glantz[8], David M. Peereboom[9], James M. Markert[10], Renato LaRocca[11], Donald M. O'Rourke[12], Karen Fink[13], Lyndon Kim[14], Michael Gruber[15], Glenn J. Lesser[16], Edward Pan[17], Santosh Kesari[18], Alona Muzikansky[19], Clemencia Pinilla[20], Radleigh G. Santos[20], and John S. Yu[21,22,23]





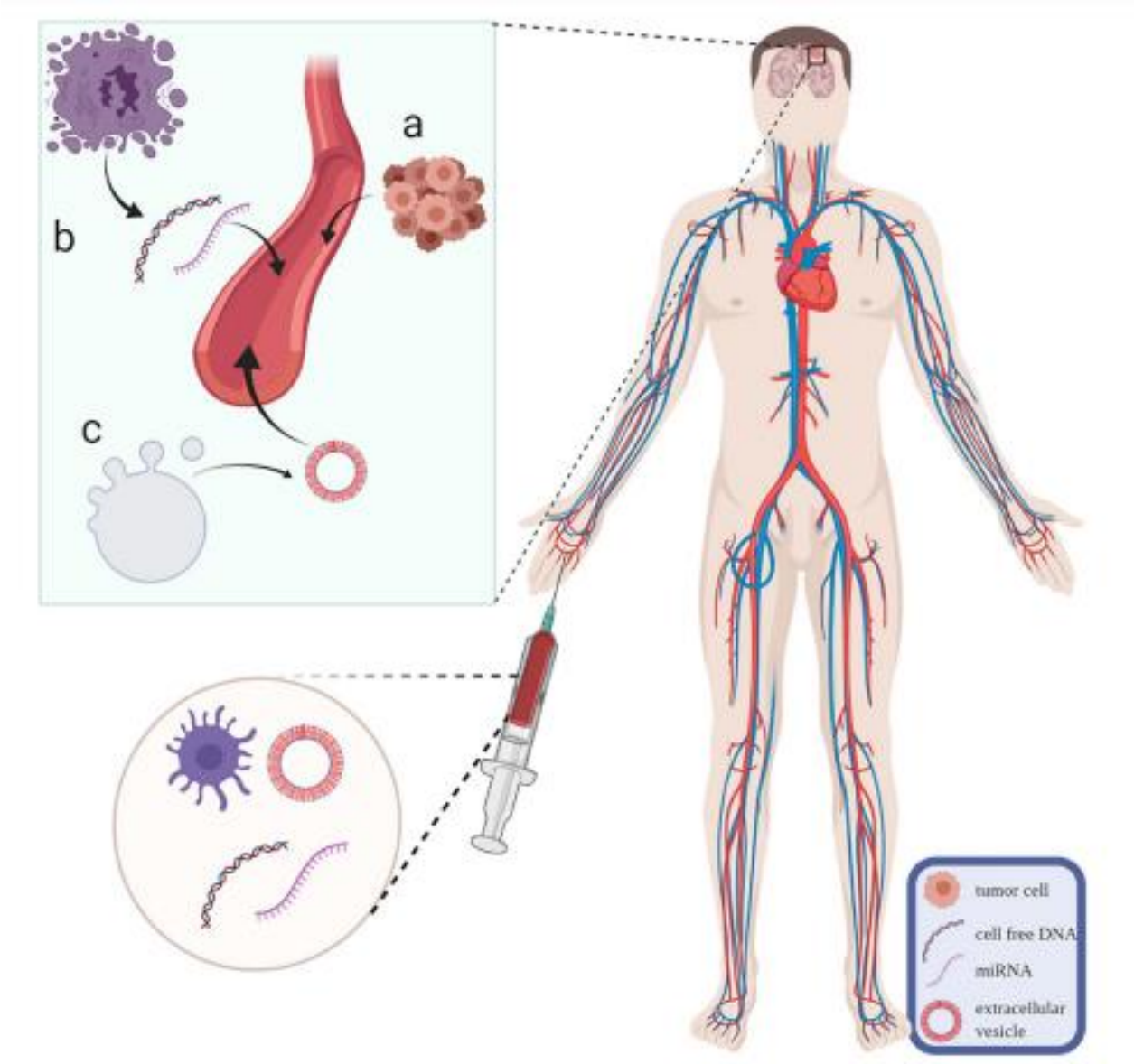
SOC = standard of care; TMZ = temozolomide



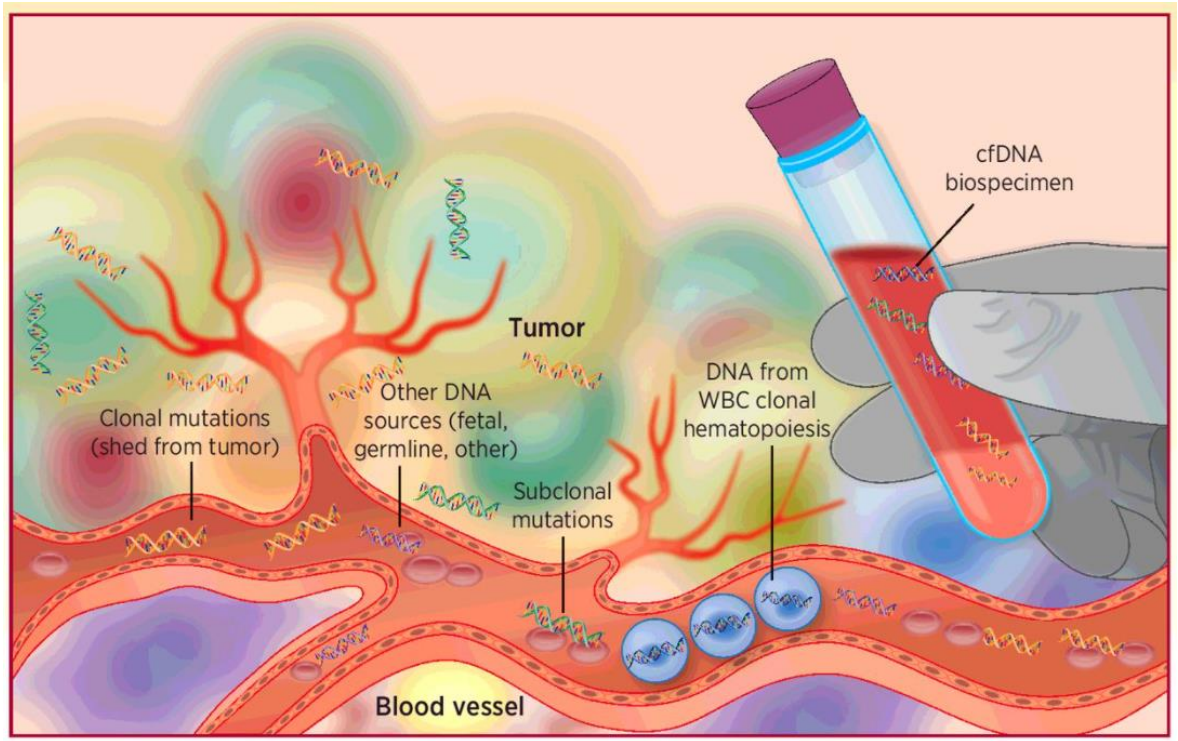


Dunn, Old and Schreiber, Immunity 2004

Liquid biopsies approaches for gliomas



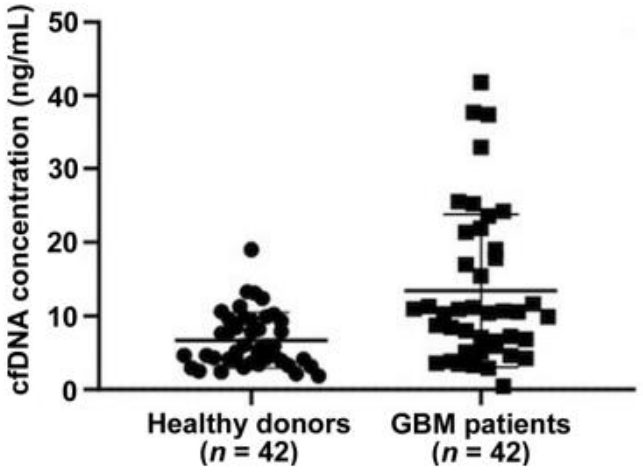
False-Positive Plasma Genotyping Due to Clonal Hematopoiesis
Hu, Ulrich et al, Clin Cancer Res 2018

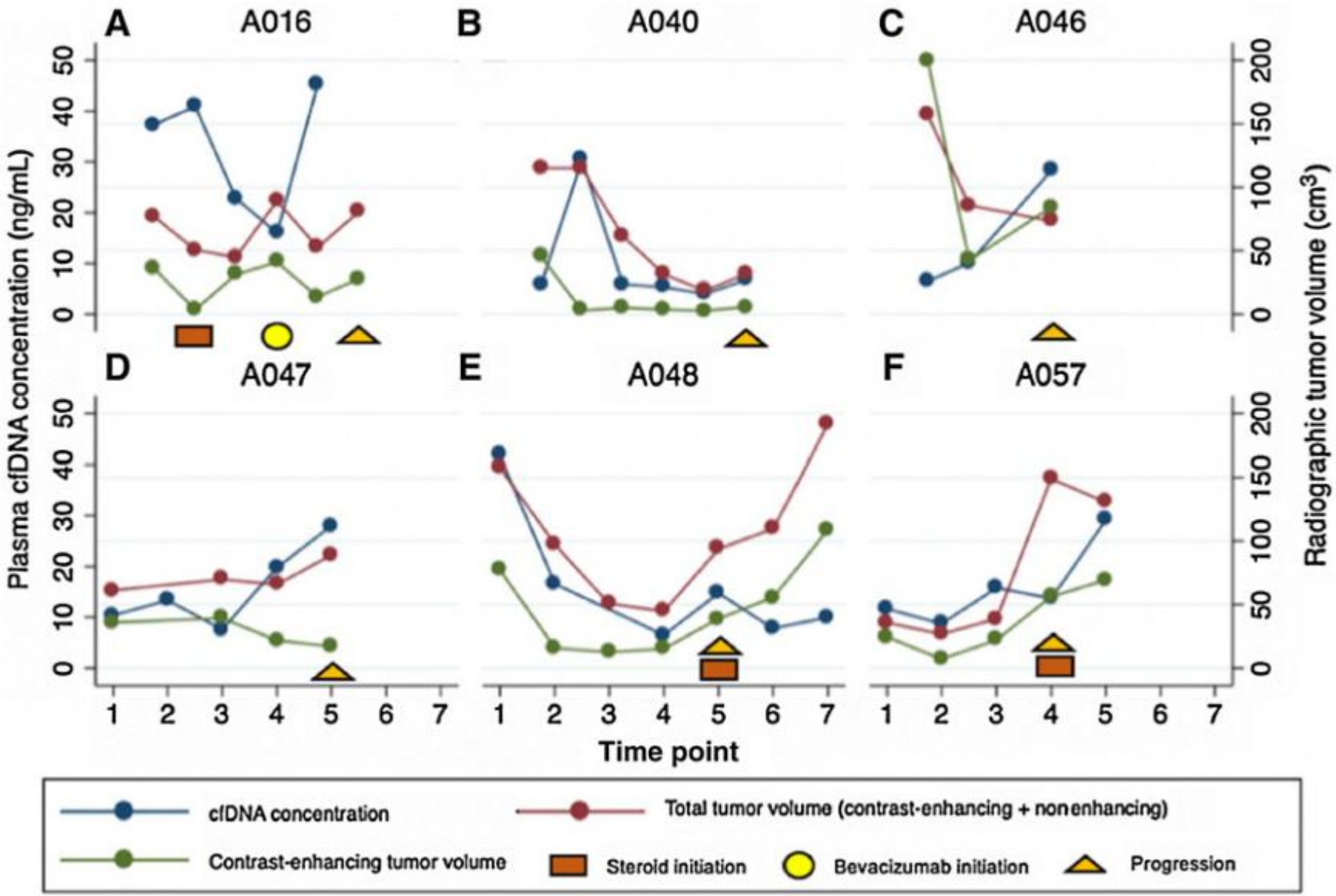


Mathios et al, NeuroMolecular Medicine 2021

Clinical Utility of Plasma Cell-Free DNA in Adult Patients with Newly Diagnosed Glioblastoma: A Pilot Prospective Study

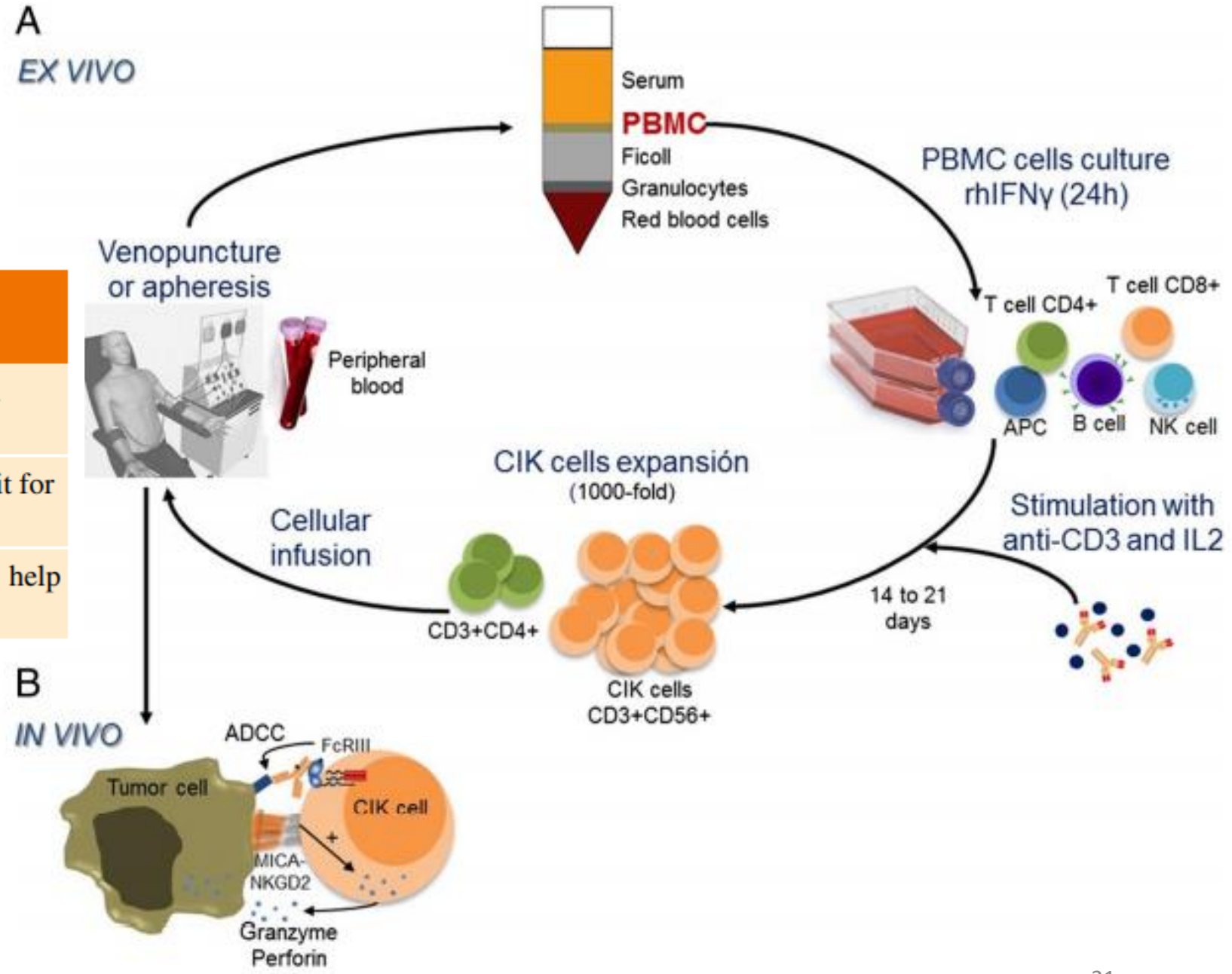
Bagley et al, Clin Cancer Res 2020





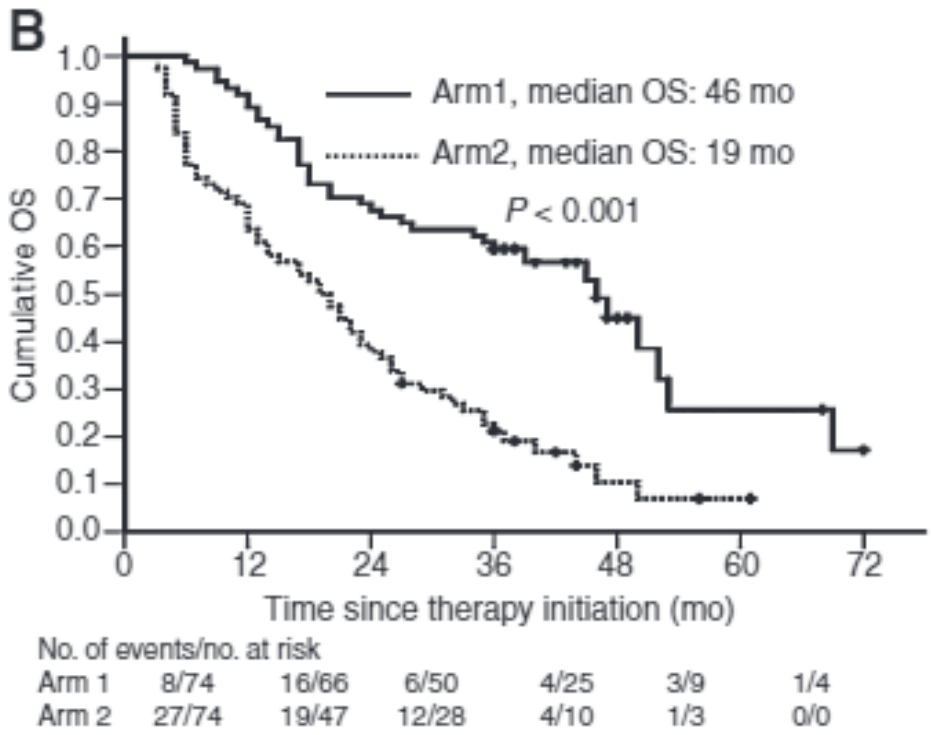
Cancer Immunotherapy with Cytokine-Induced Killer (CIK) cells

Key Points
CIK cells are a heterogeneous cell population with a mixed T-NK cell phenotype.
Immunotherapy with CIK cells exerts clinical benefit for some cancer patients.
Novel experimental strategies with CIK cells may help to improve anti-tumor immune responses.



Mata-Molanes et al, 2017

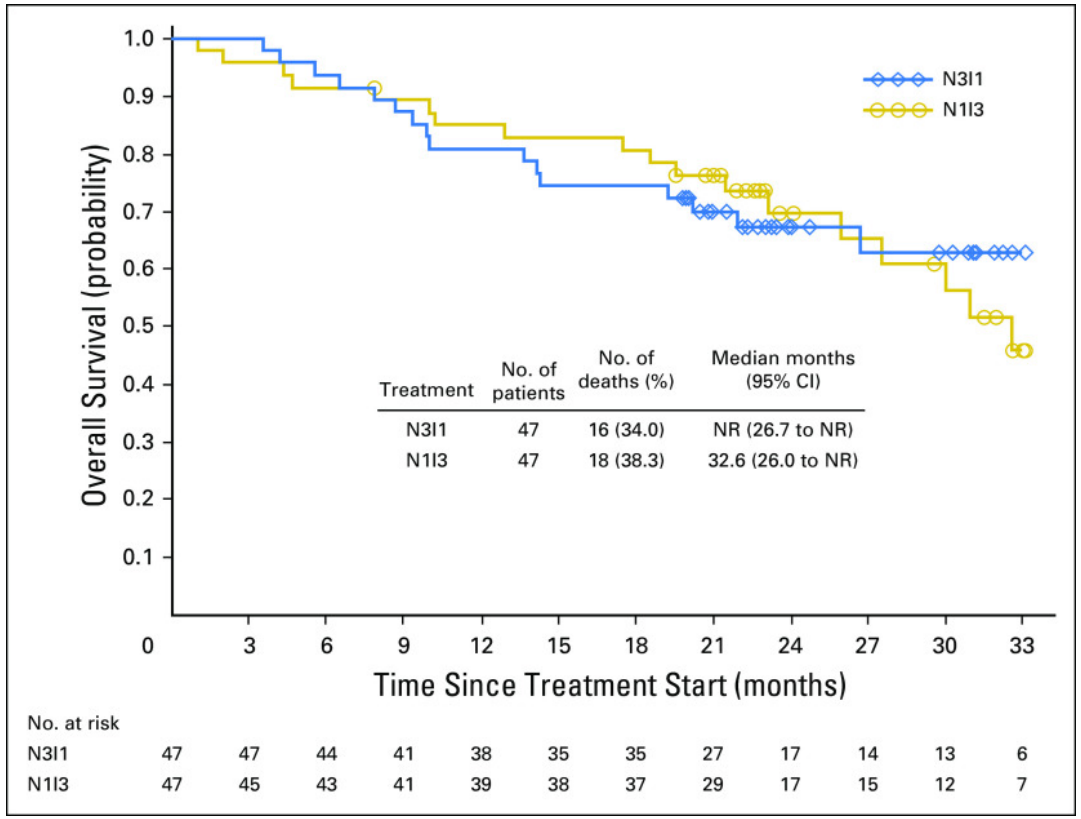
Randomized Study of Autologous Cytokine-Induced Killer Cell Immunotherapy in Metastatic Renal Carcinoma (Liu et al CCR 2012)



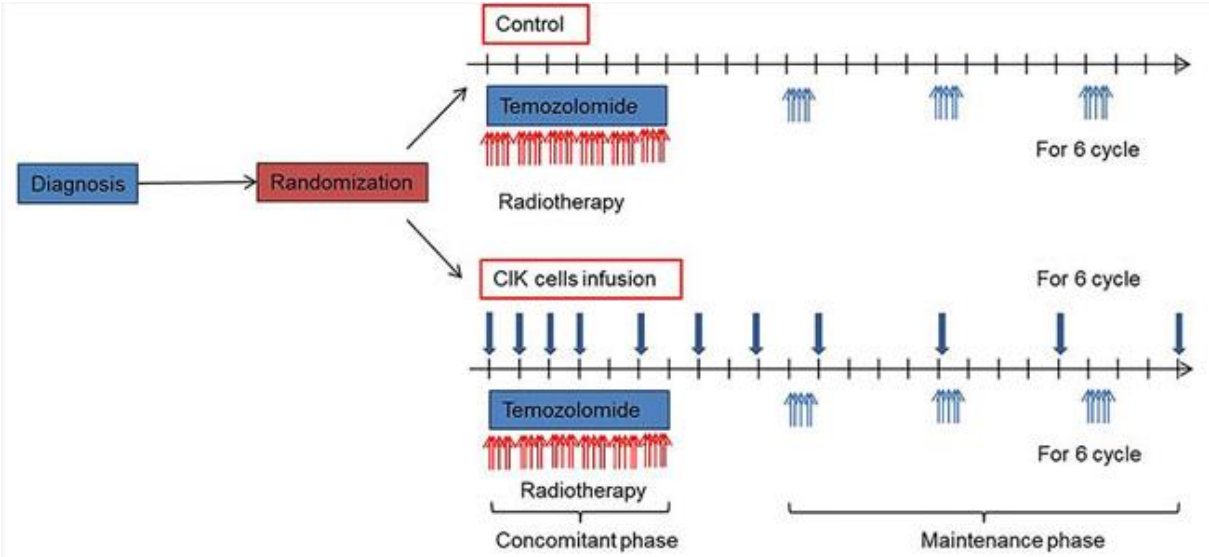
Arm 1: CIK

Arm 2: IL-2 and IFNalpha 2

Safety and Efficacy of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study (Hammers et al, JCO 2017)

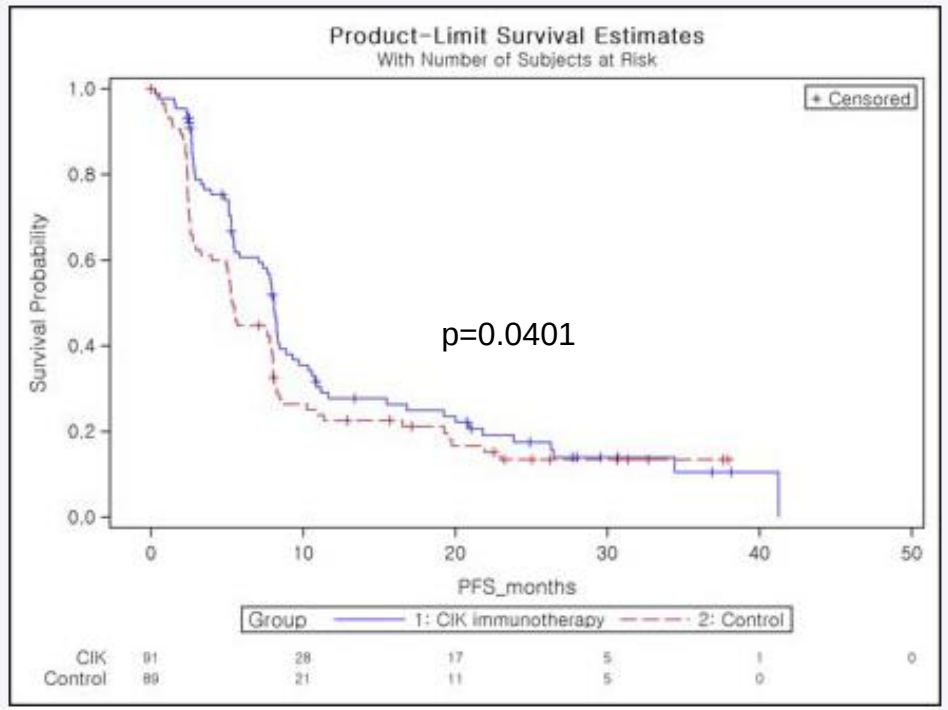


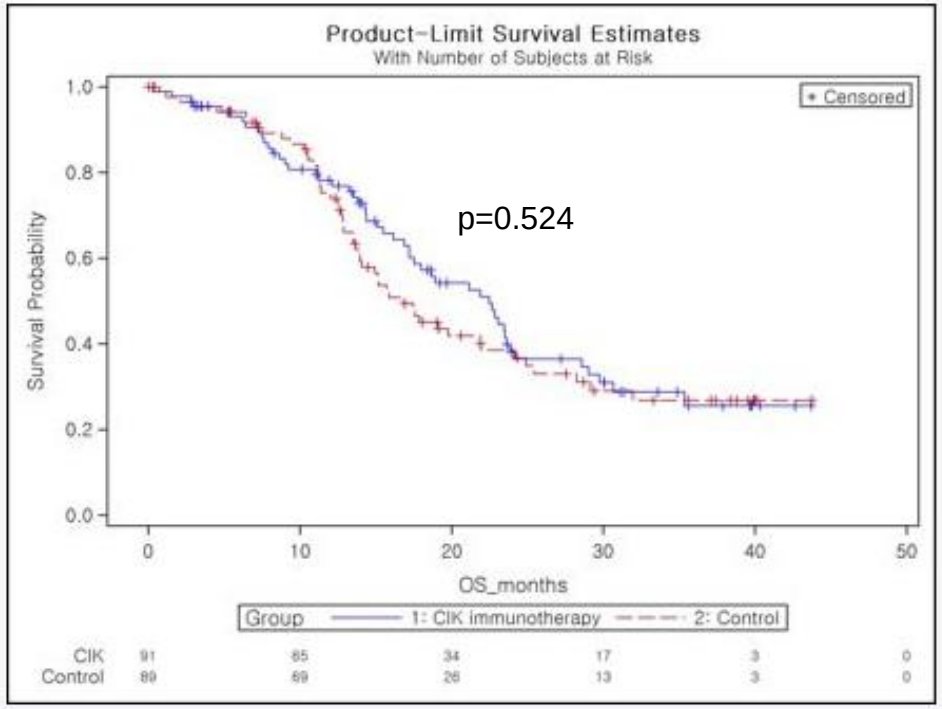
Phase III randomized trial of autologous cytokine-induced killer cell immunotherapy for newly diagnosed glioblastoma in Korea (Kong et al, Oncotarget 2017)



	CIK immunotherapy group (*N*= 91)	Control group (*N*= 89)
No. of events (Death or PD), n (%)	70 (76.9%)	71 (79.8%)
Median PFS [95% CI]	8.1 [5.8, 8.5]	5.4 [3.3, 7.9]

	CIK immunotherapy group (*N*= 91)	Control group (*N*= 89)
Incidence rate (Death), n (%)	51 (56.04)	52 (58.43)
Median OS [95% CI]	22.47 [17.20, 23.85]	16.88 [13.91, 21.94]





PLOS ONE

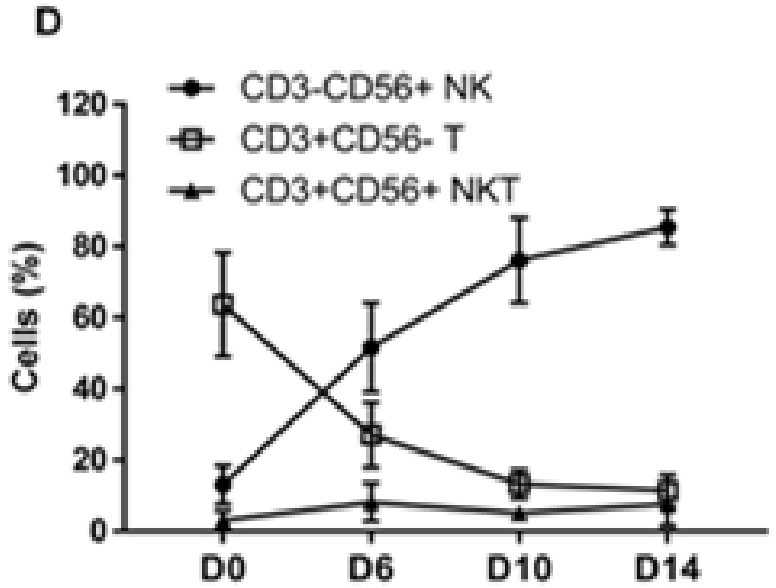
OPEN ACCESS PEER-REVIEWED

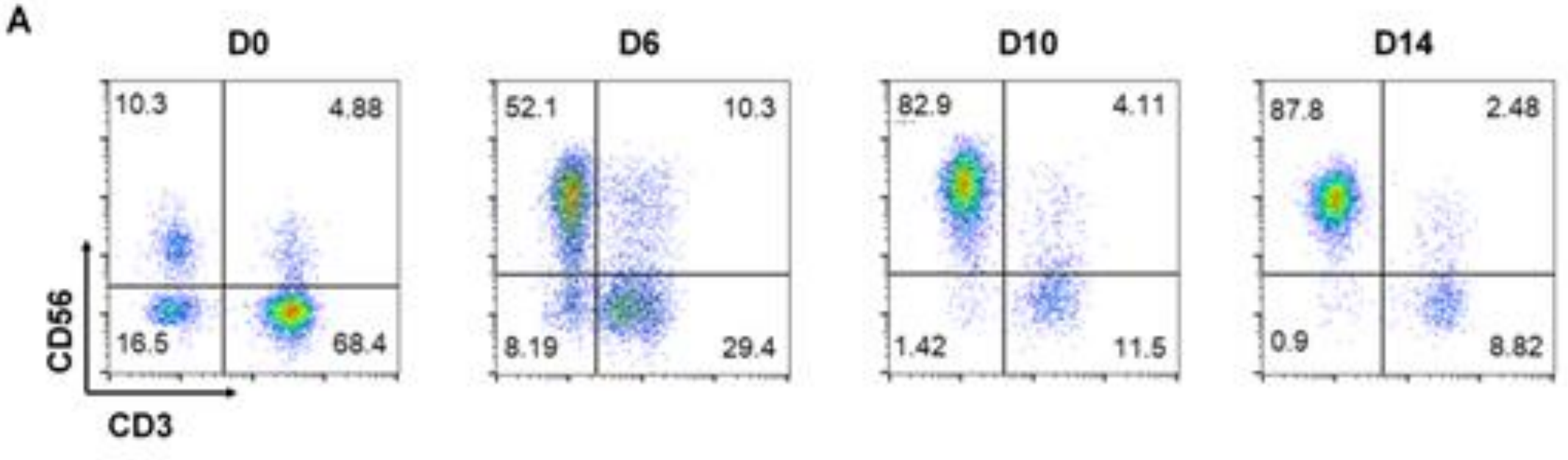
RESEARCH ARTICLE

Autologous adoptive immune-cell therapy elicited a durable response with enhanced immune reaction signatures in patients with recurrent glioblastoma: An open label, phase I/IIa trial

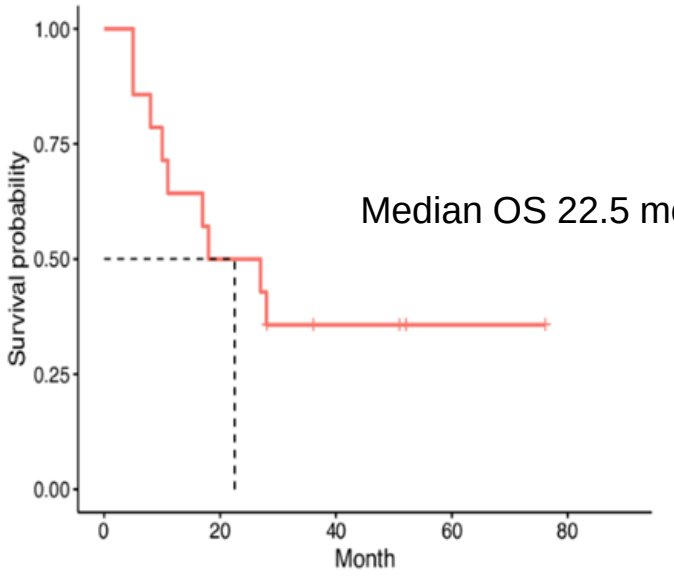
Jaejoon Lim, YoungJoon Park, Ju Won Ahn, JeongMin Sim, Su Jung Kang, Sojung Hwang, Jin Chun, Hyejeong Choi, Sang Heum Kim, Duk-Hee Chun, Kyoung Su Sung, KyuBum Kwack, Kyunggi Cho

Published: March 10, 2021 • https://doi.org/10.1371/journal.pone.0247293



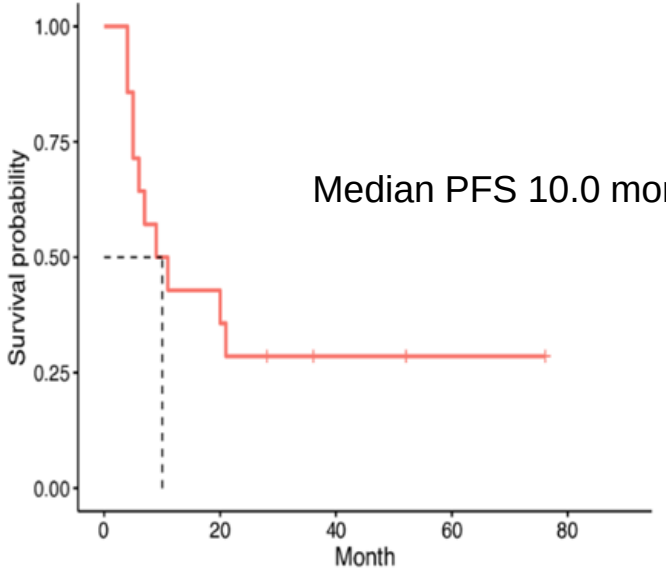


A



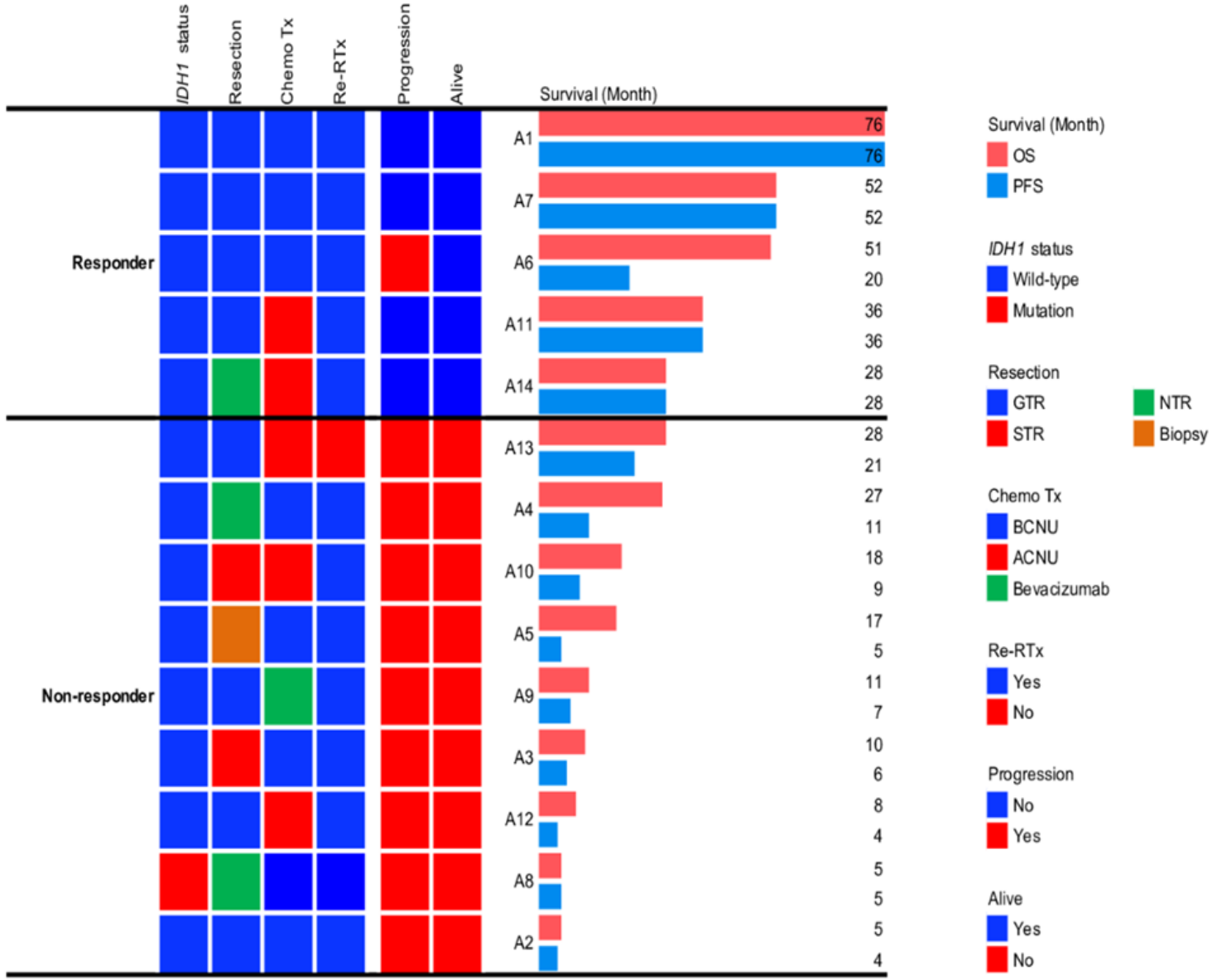
Median OS 22.5 months

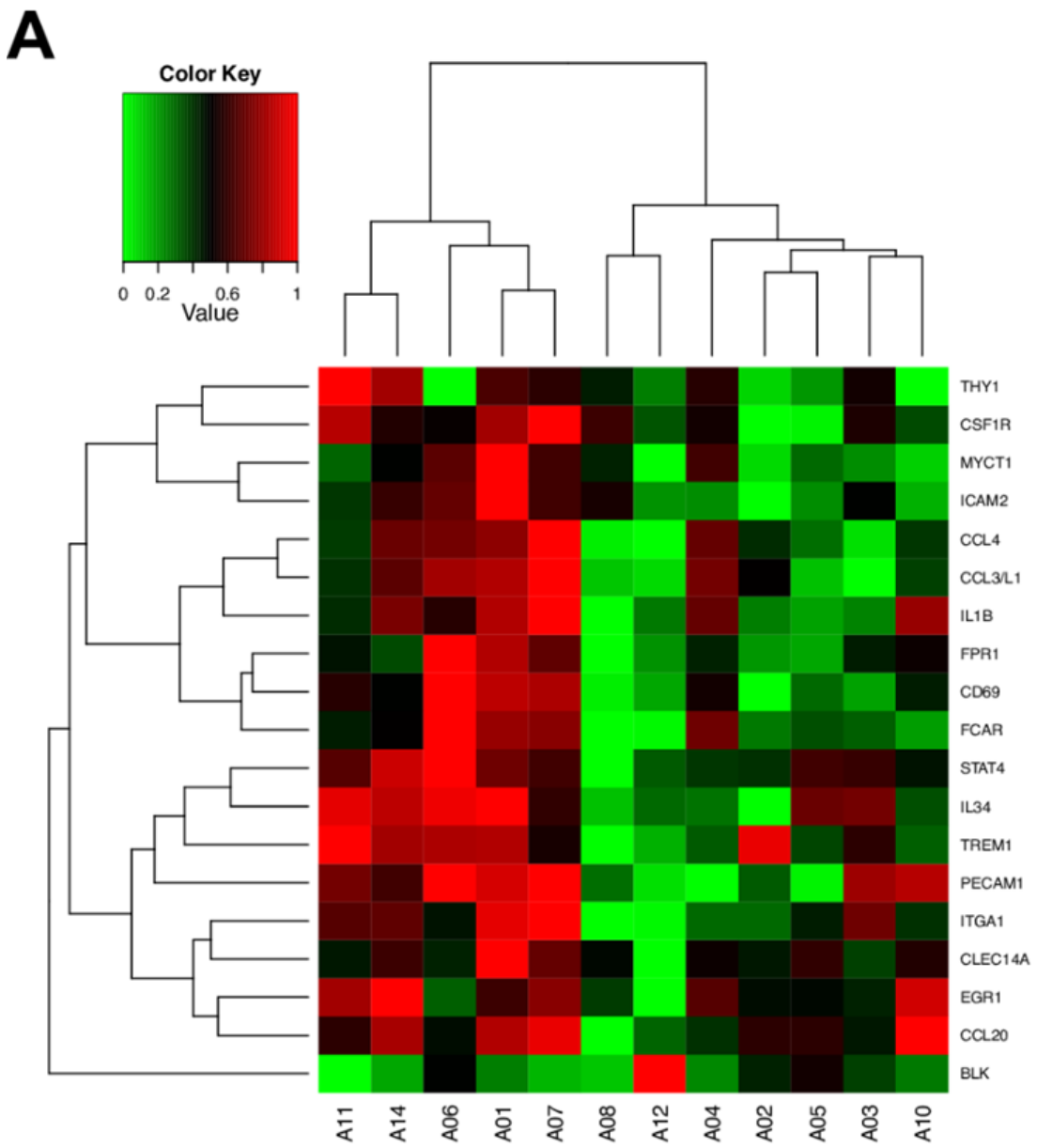
B



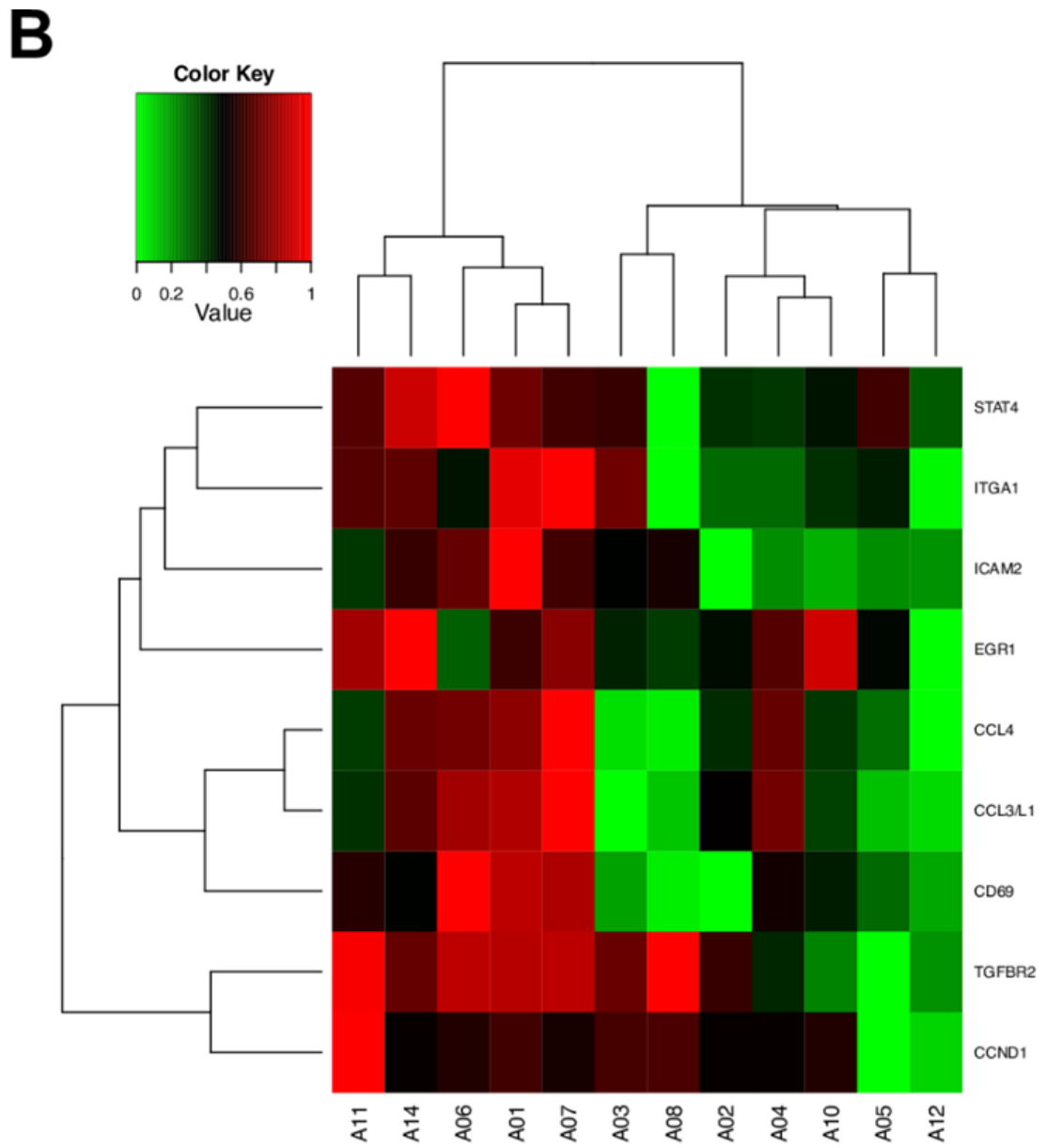
Median PFS 10.0 months

C



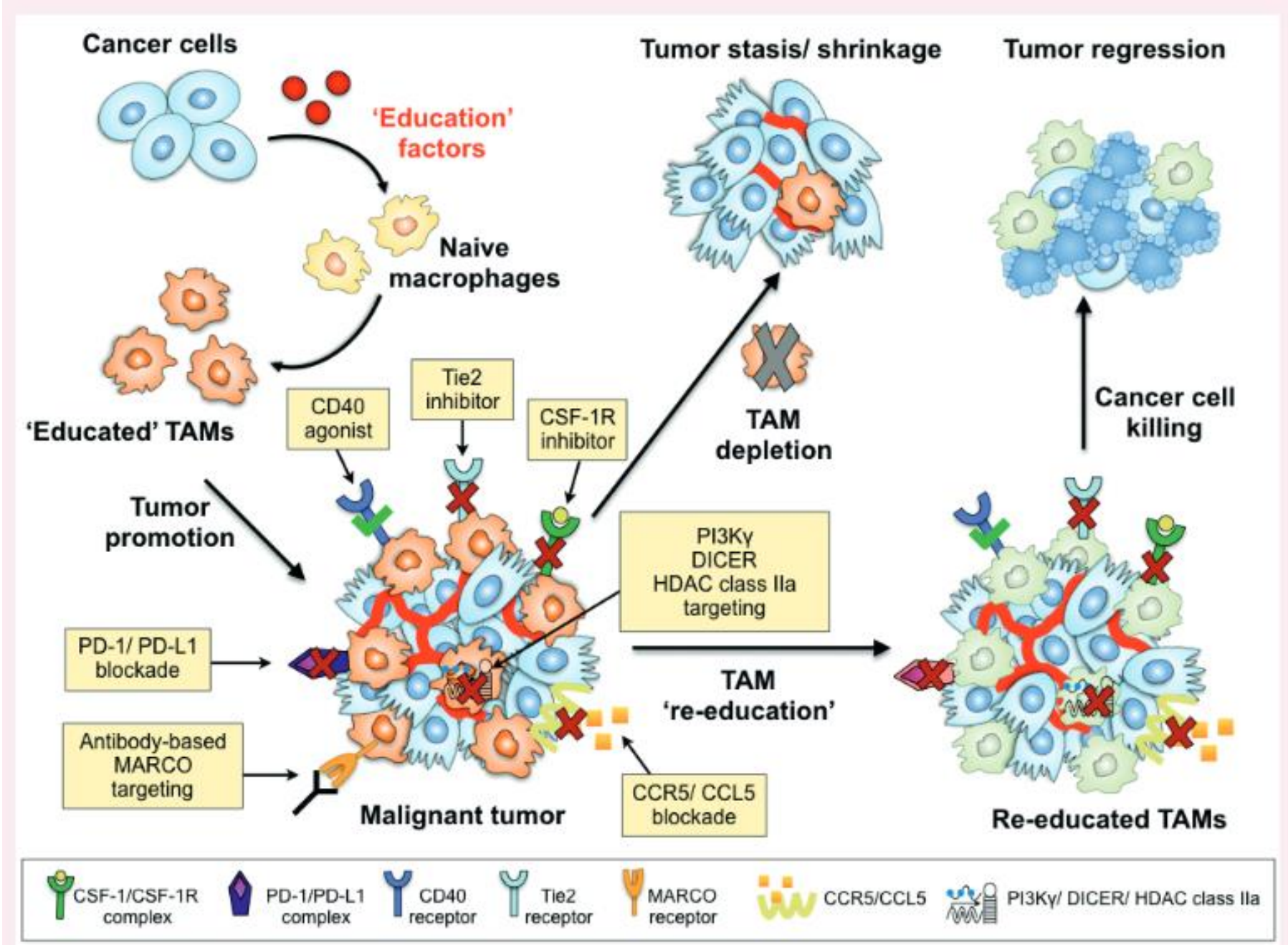


Immune Cell Localization to Tumors



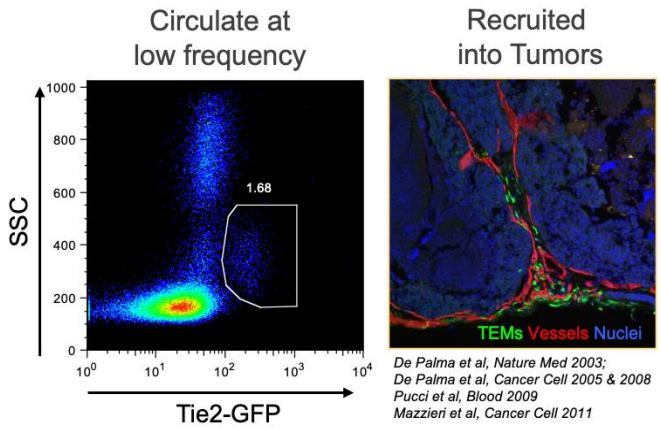
Recognition of Cancer Cells by T-cells

Macrophage targeting strategies in cancer

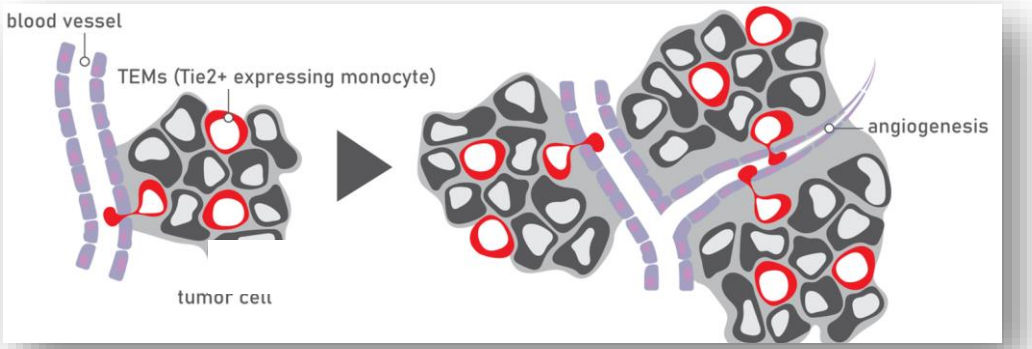


Kowal 2019, Immunotherapy

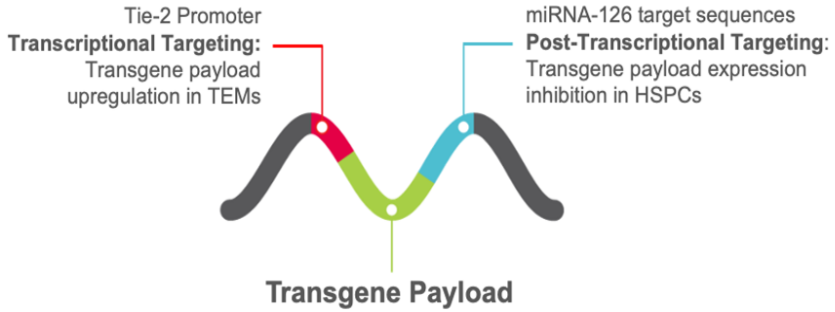
TEMs a Natural Trojan Horse to Deliver Therapy to Solid Tumors

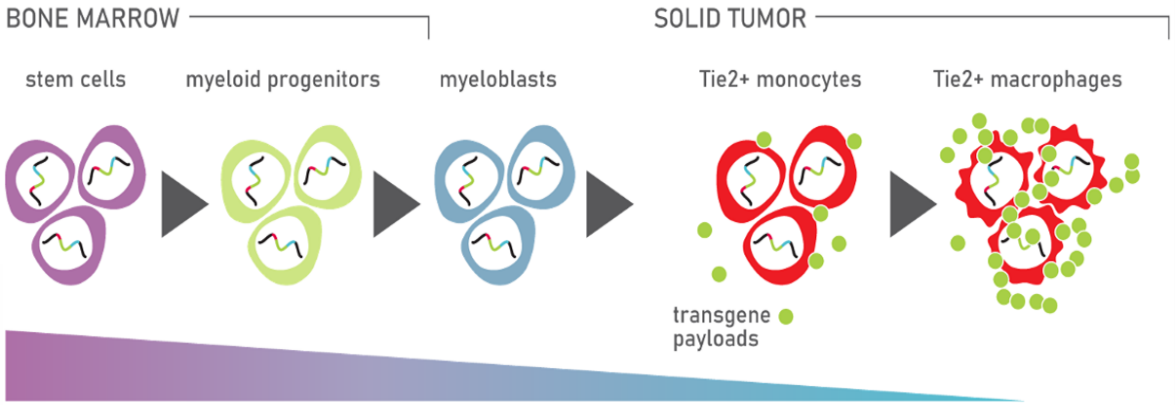


- Bone-marrow derived pro-tumoral tumor infiltrating monocytes
- Subset of TAMs
- Angiogenic & Immunosuppressive
- Peri-vascular localization
- Genetic ablation of TEMs curbs tumor growth



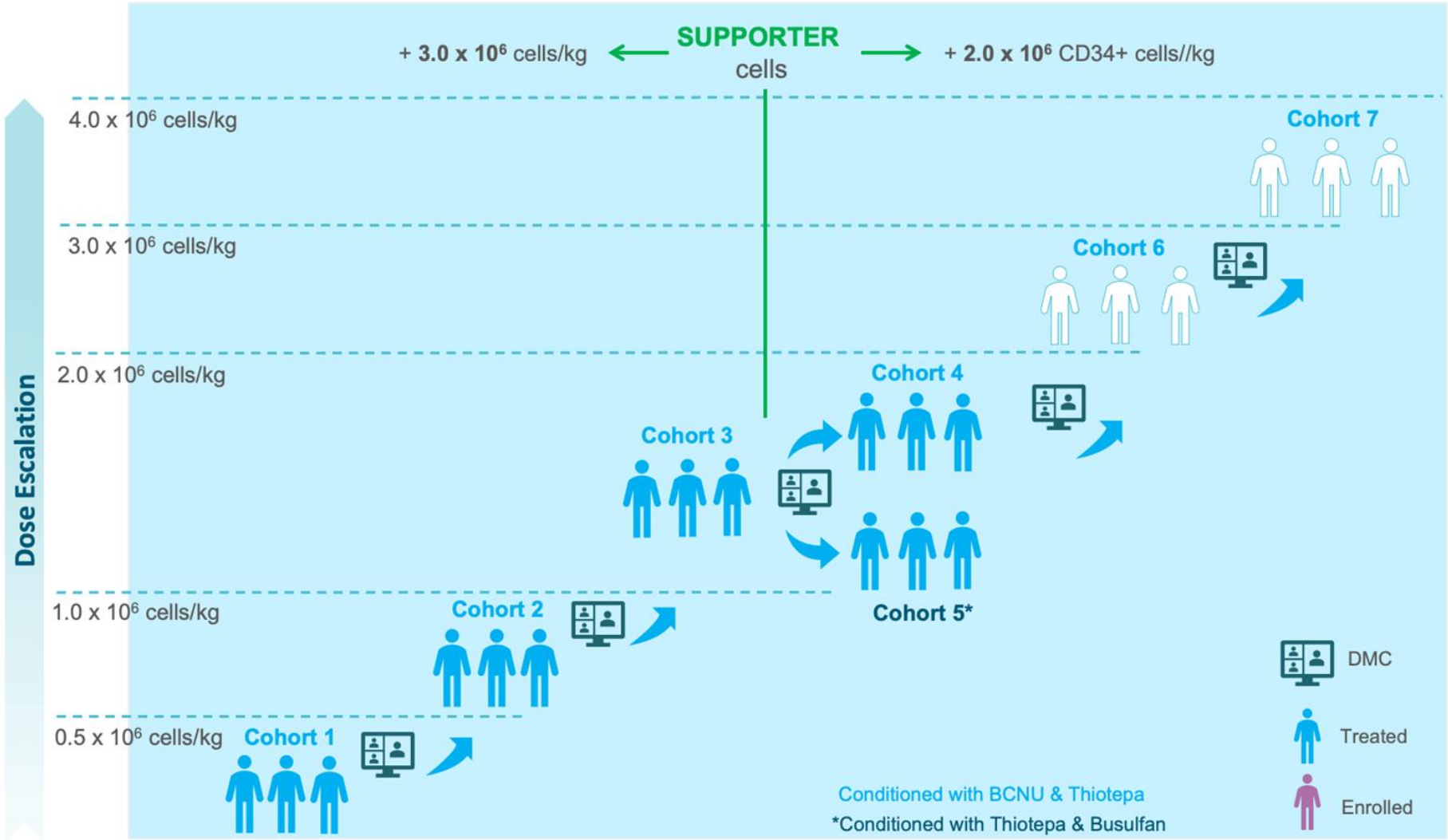
Transgene Expression Technology for Controlled and Targeted Payload Delivery inside Solid Tumors





Interaction of miRNAs with their **miRNA-Targets** regulates gene expression via mRNA degradation and translational repression

TEM-GBM:Temferon Phase 1/2a Design in Glioblastoma



A multi-center, open-label, dose escalation & long-term follow-up study in GBM patients with unmethylated MGMT promoter

Inclusion Criteria

- Histologically confirmed, **newly diagnosed supratentorial glioblastoma** with **unmethylated MGMT** gene promoter.
- Patients have undergone **complete** or **partial tumor resection** and are eligible for adjuvant radiotherapy
- **18-70** years old, in **good clinical condition** (ECOG 0-1, KPS>70%)
- life expectancy >6mts, **adequate organ function**


IMPOSSIBLE IS NOTHING