

B-cells: How do they Work and How Can We Use Them to Combat Cancer?

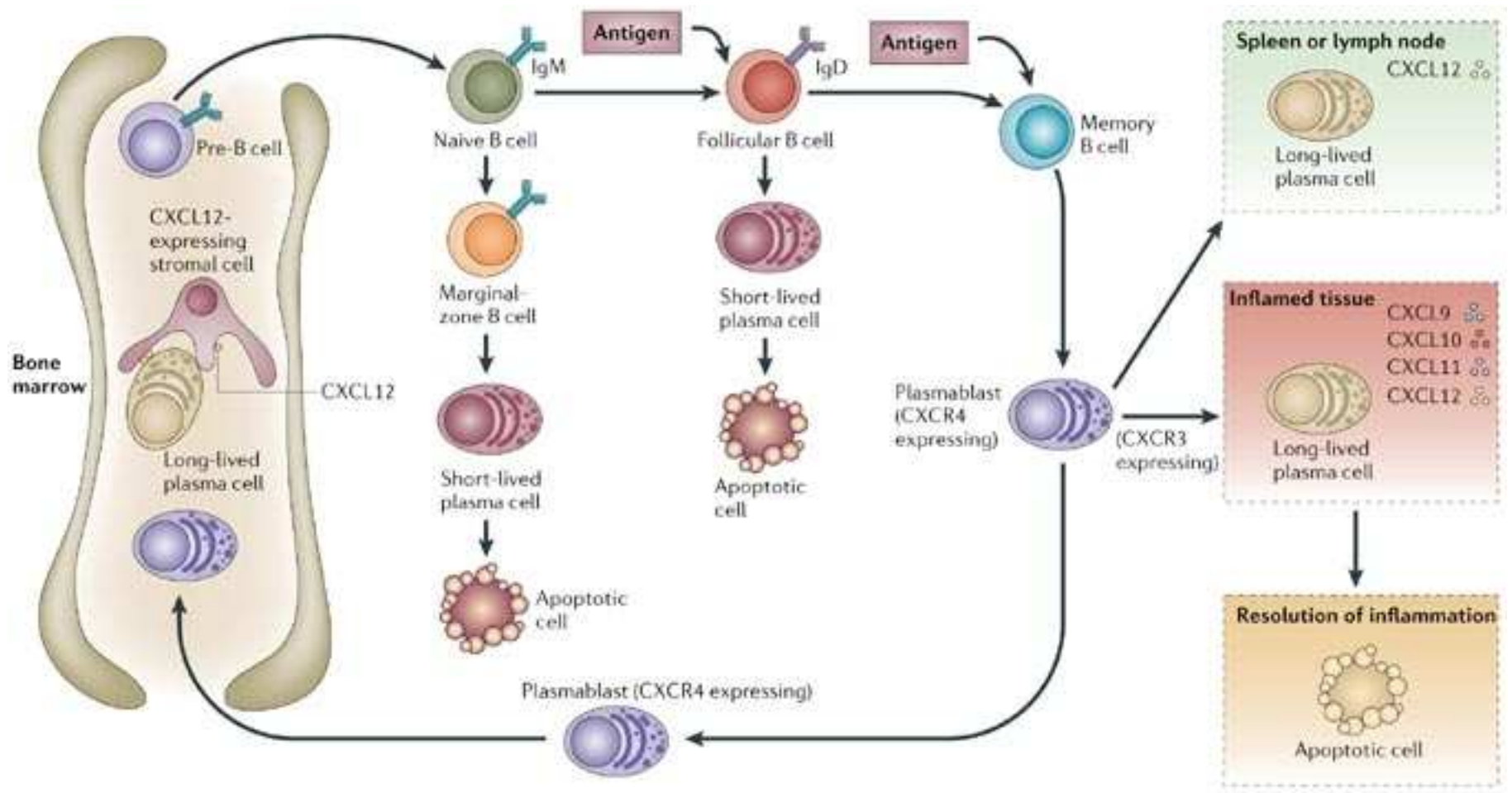
Edmund K. Waller, MD, PhD, FACP
Emory University

Disclosures for Edmund Waller

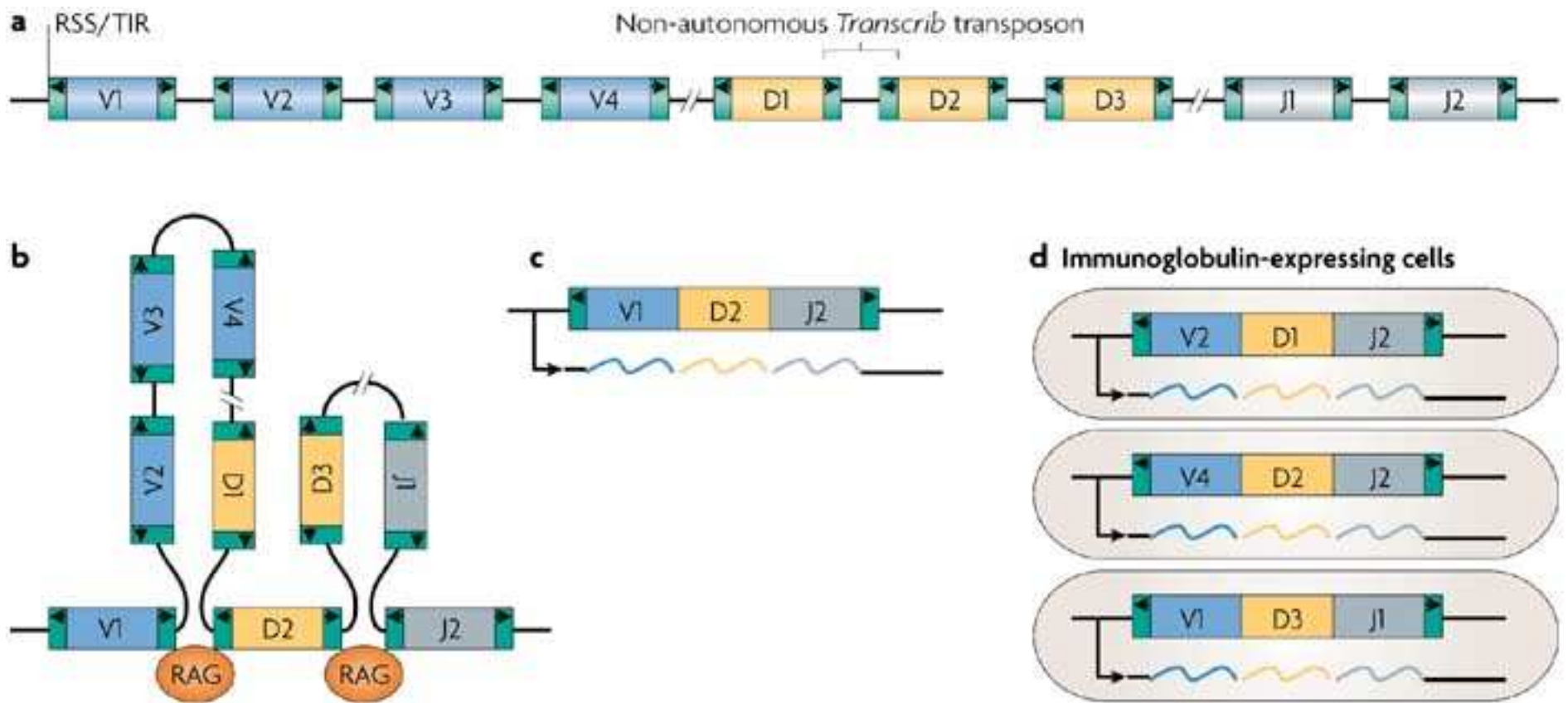
(none relevant to current subject matter except *)

- Consulting to industry
 - Outsuka
 - Haplomics
- Biotech Start-up Co-founder
 - Cambium Medical Technologies (manufactured platelet lysate)
- Clinical Research Investigator
 - Sanofi
 - Outsuka
 - *CureTech

B cell Ontogeny



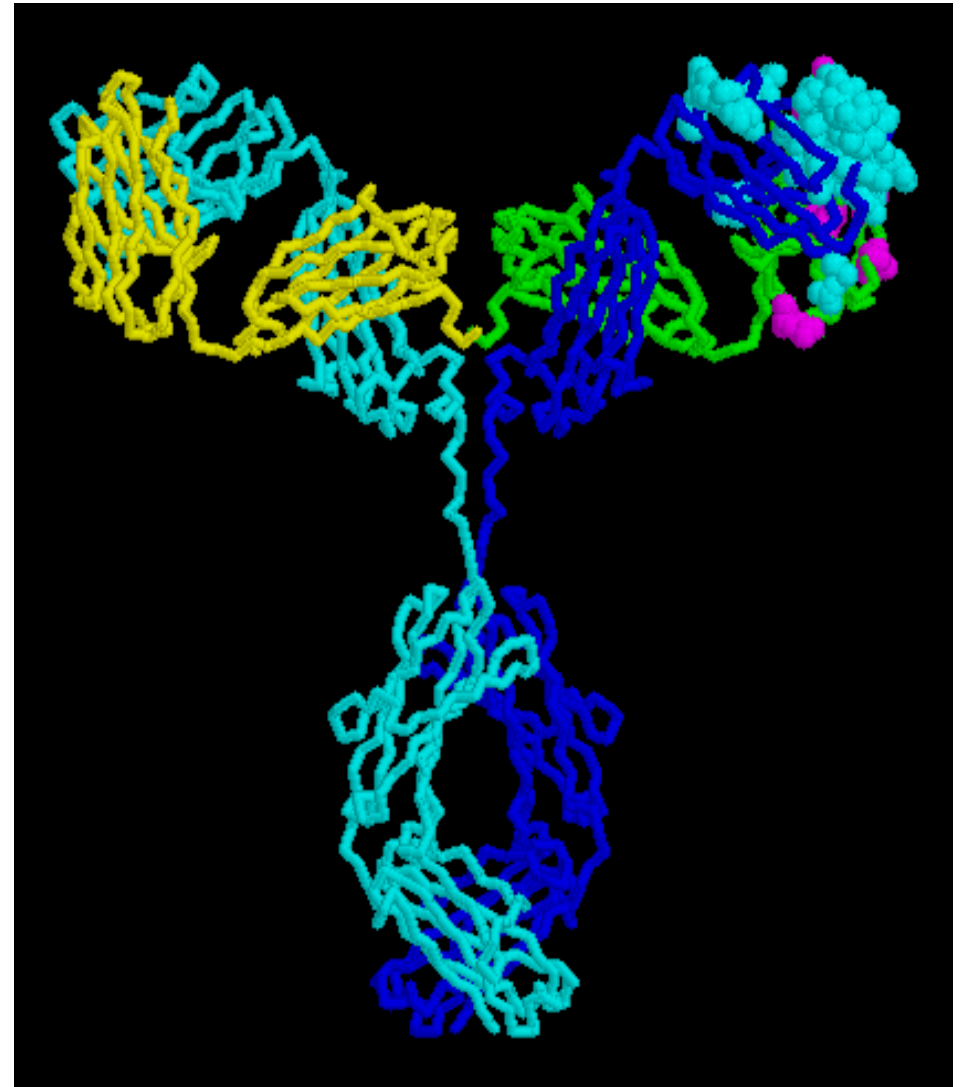
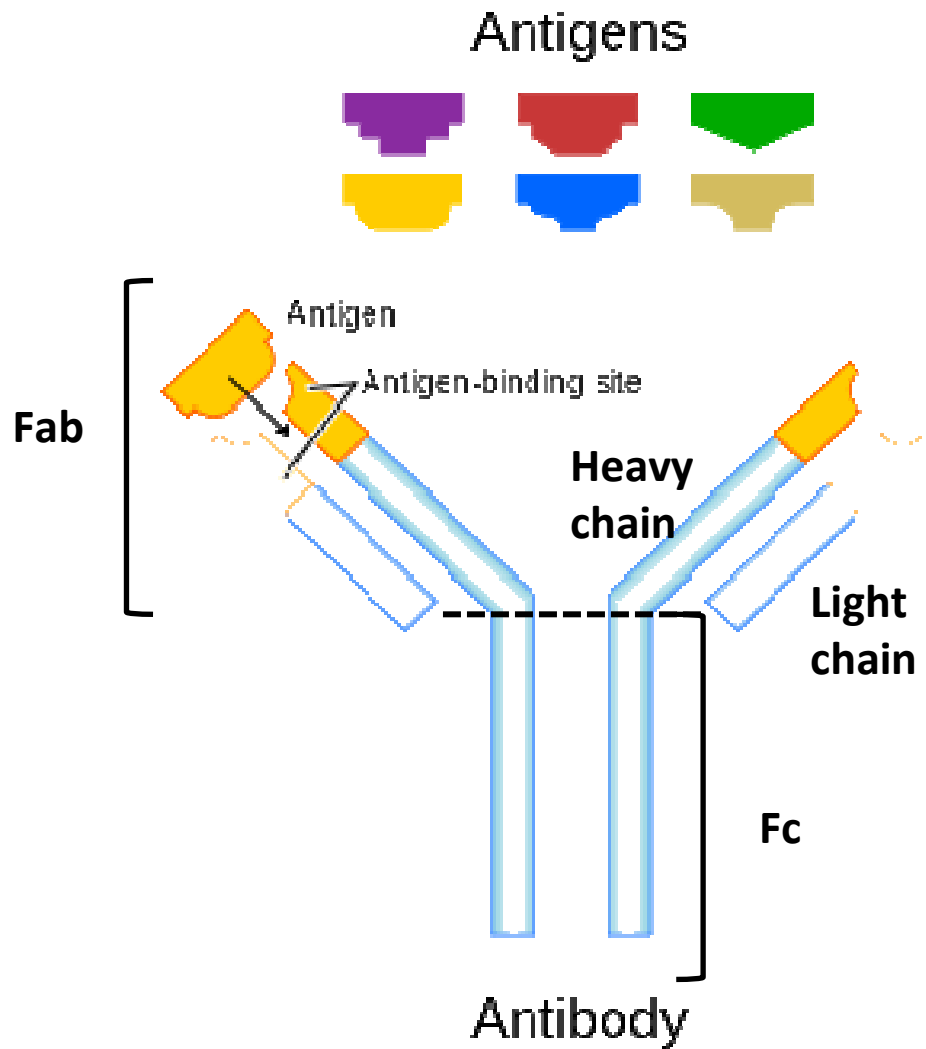
Immunoglobulin gene rearrangements and somatic mutations create up to 10^{12} different Immunoglobulin genes



Nature Reviews | Genetics

Slotkin and Martienssen *Nature Reviews Genetics* **8**, 272-285 (April 2007)

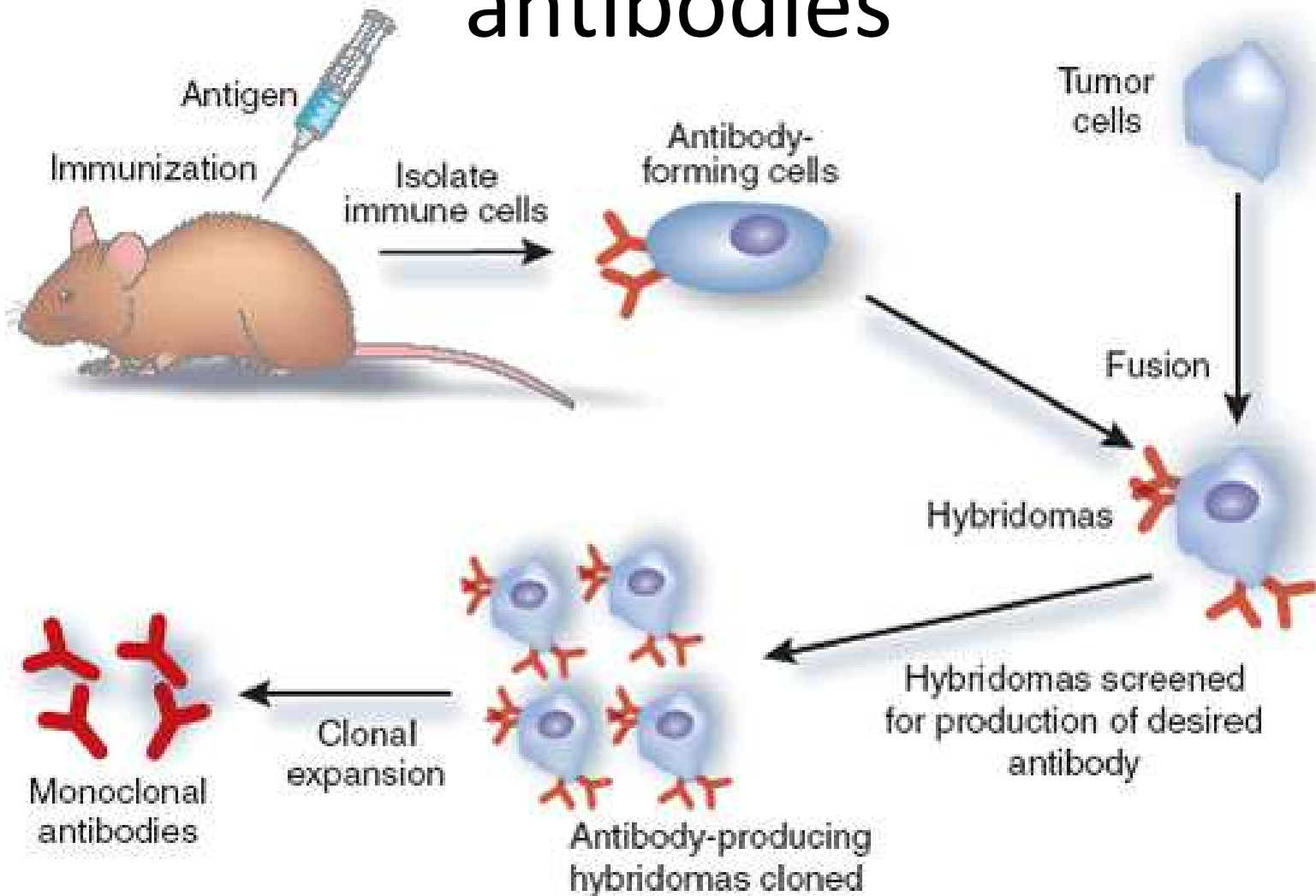
Antibody structure and function



<http://en.wikipedia.org/wiki/Antibody>

http://www2.ac-lyon.fr/enseignement/biologie/ress/logiciel/ana_ras/rasmol.html

Classical generation of monoclonal antibodies



B-cell lymphoma expressing idiotypic determinants was an original clinical target for monoclonal Ab

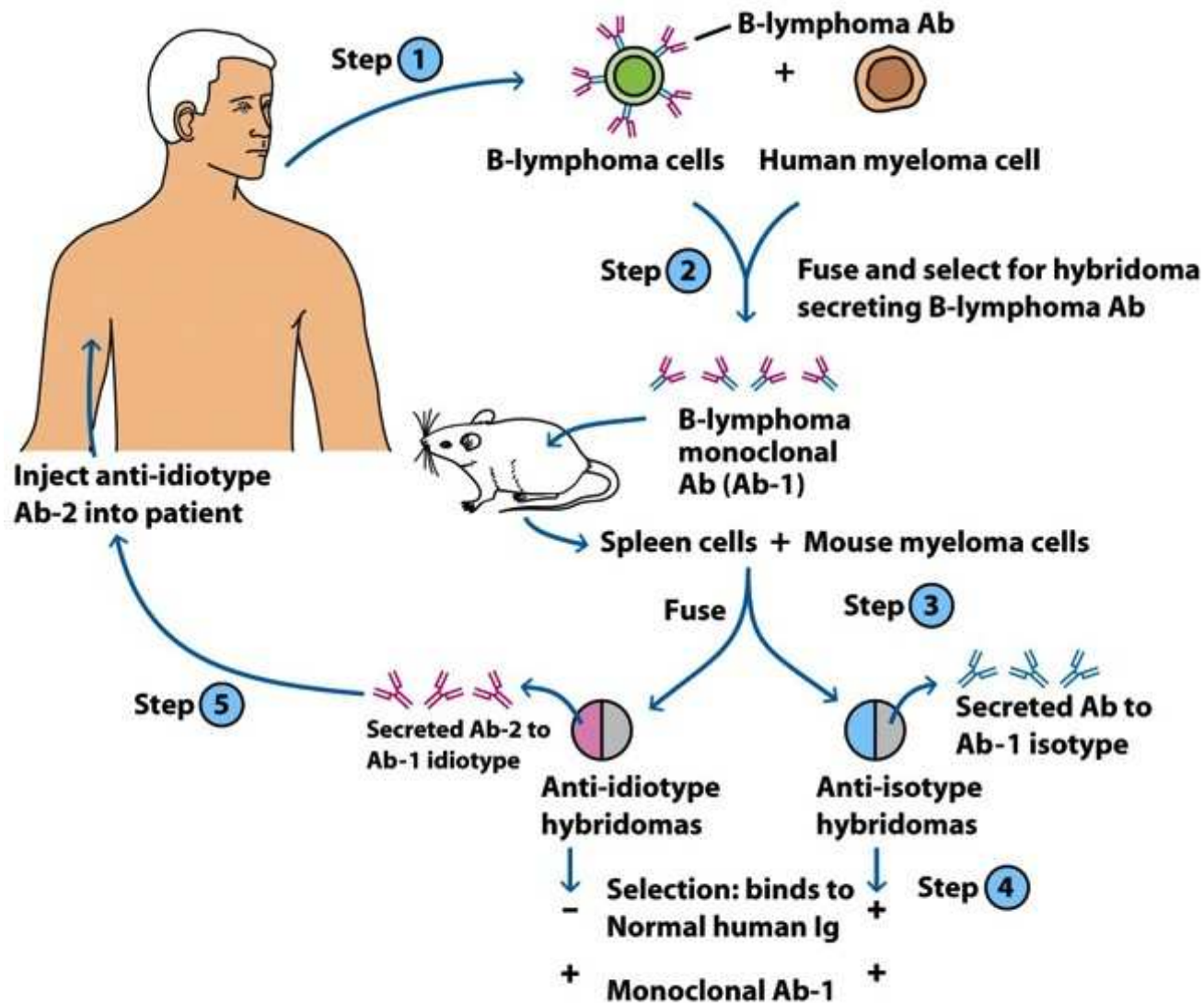
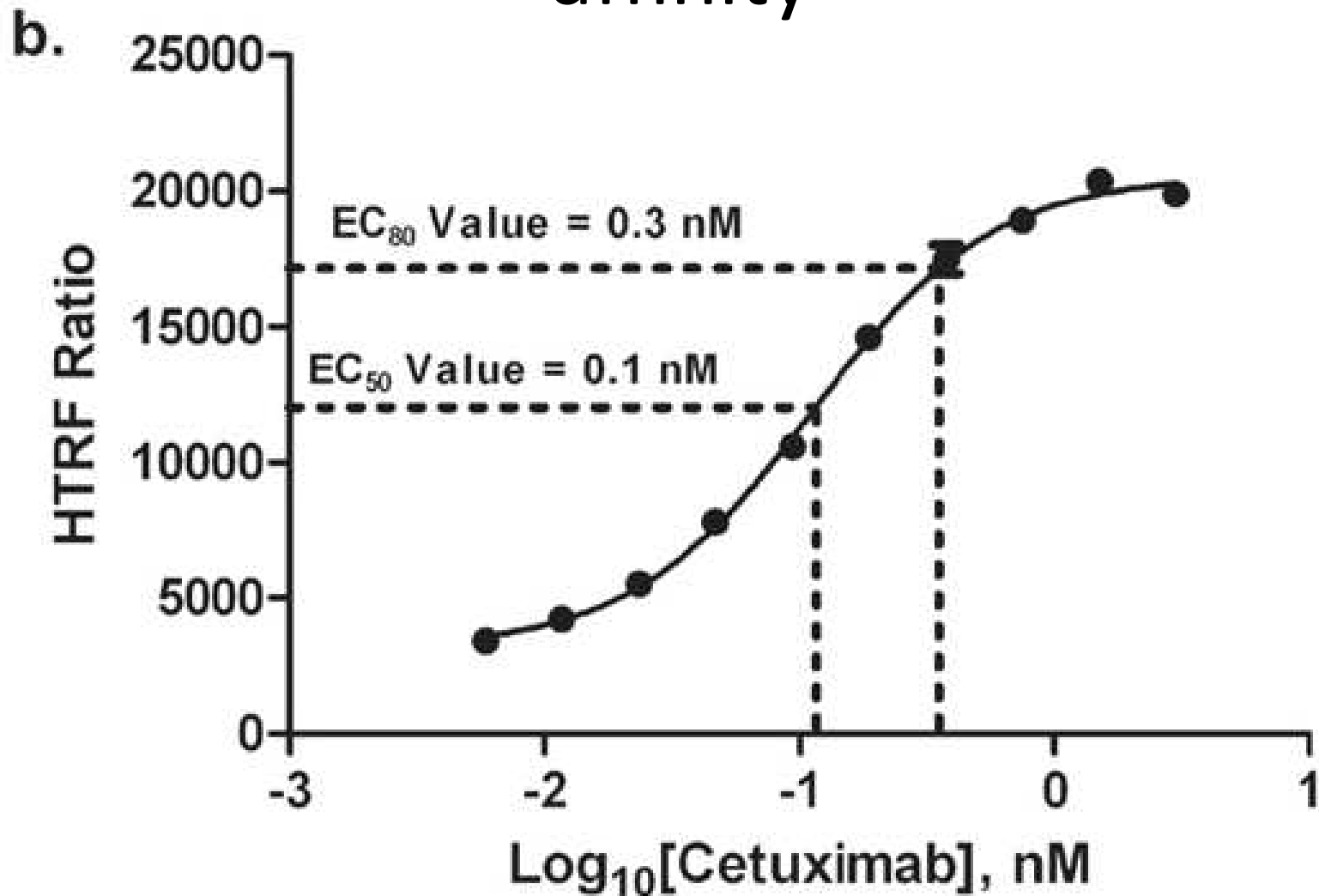
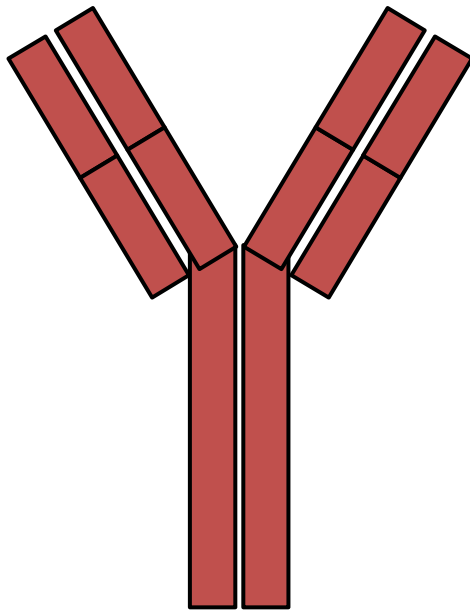


Figure 21-13
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W. H. Freeman and Company

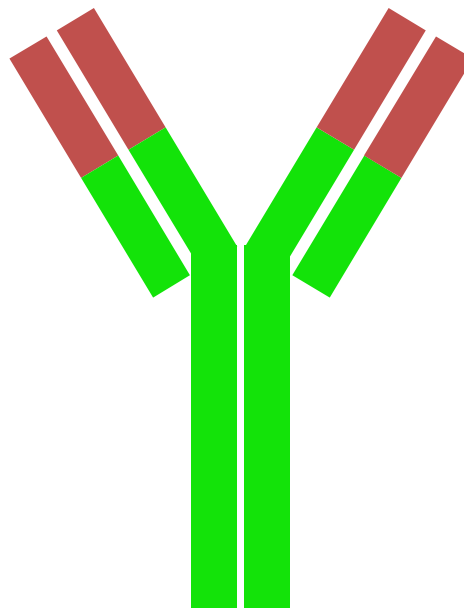
Monoclonal antibodies have high affinity



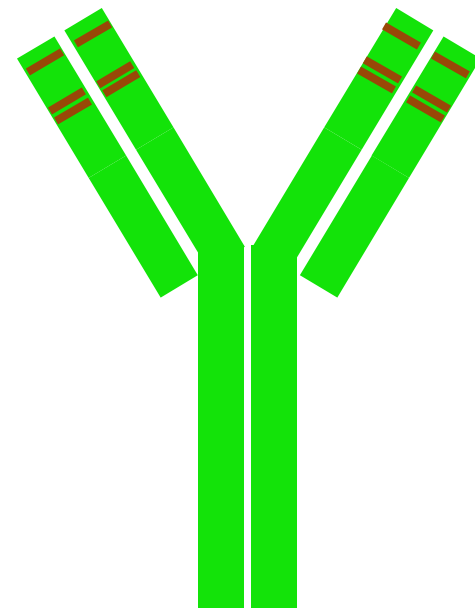
Genetically Engineered Antibodies for Humoral Cancer Immuno-therapy



Murine native
(e.g. ibritumomab)



Chimeric
(e.g. rituximab)



Humanized
(e.g. trastuzumab)

Composition



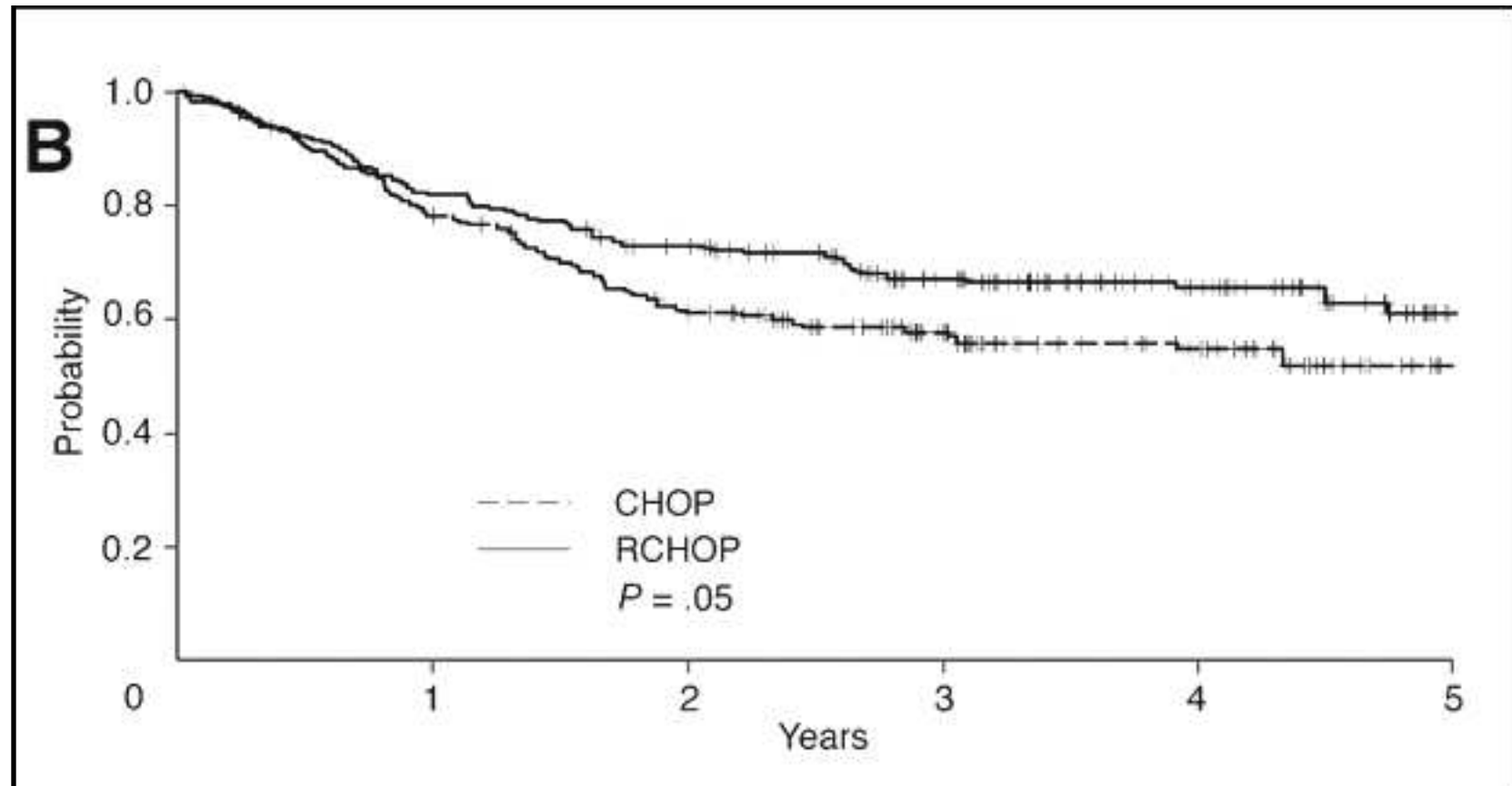
Human

Murine

Commercial monoclonal antibodies used to treat cancer

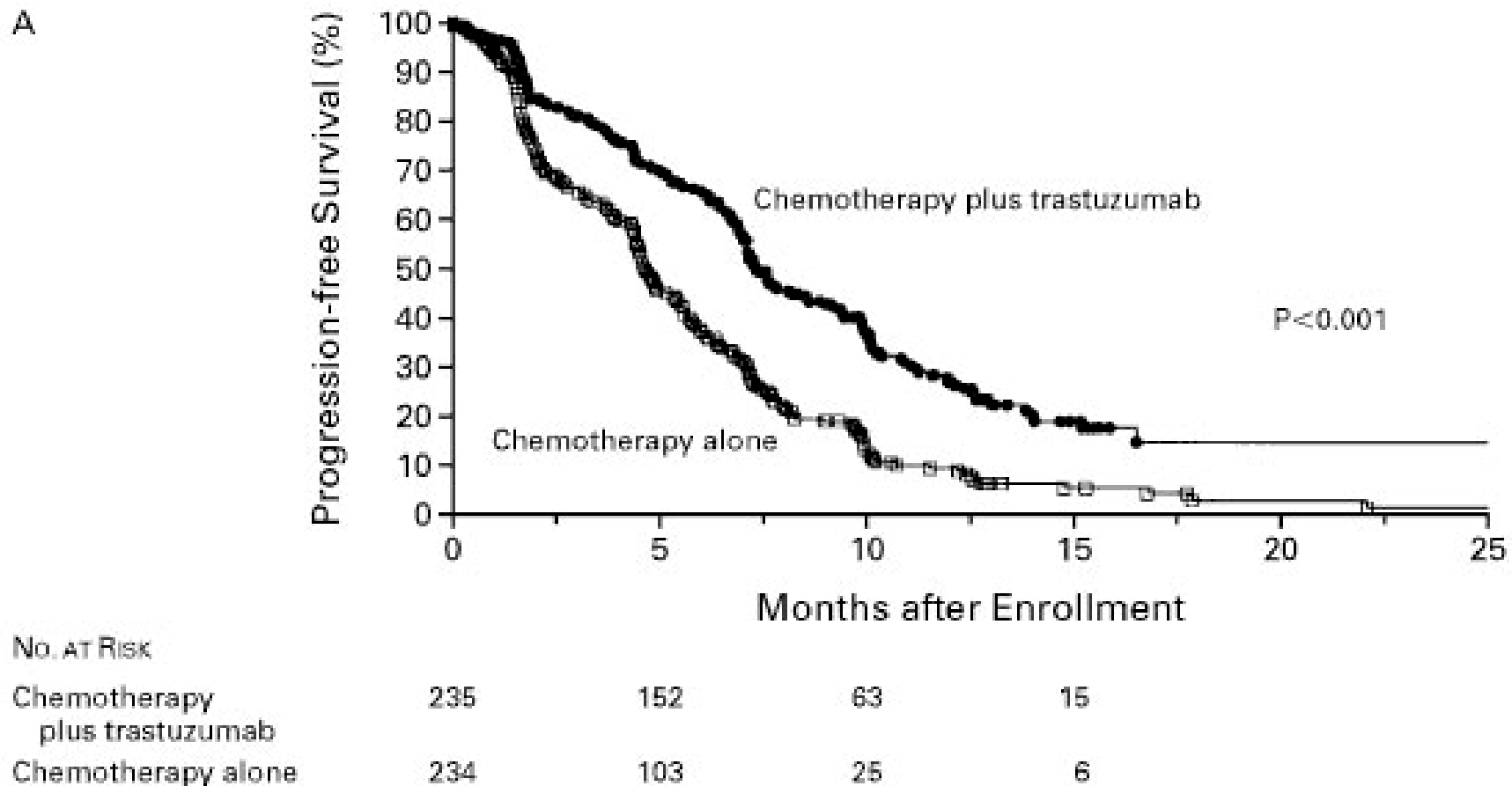
Rituximab	Anti-CD20	Non-Hodgkin's lymphoma 1998 (1997)
Trastuzumab	Anti-HER2	Breast cancer 2000 (1998)
Gemtuzumab ozogamicin	Anti-CD33	Acute myeloid leukemia NA (2000#)
Alemtuzumab	Anti-CD52	Chronic lymphoid leukemia 2001 (2001)
Tositumomab-I131	Anti-CD20	Non-Hodgkin lymphoma NA (2003)
Cetuximab	Anti-EGFR	Colorectal cancer 2004 (2004)
Ibritumomab tiuxetan	Anti-CD20	Non-Hodgkin's lymphoma 2004 (2002)
Bevacizumab	Anti-VEGF	Colorectal cancer 2005 (2004)
Panitumumab	Anti-EGFR	Colorectal cancer 2007 (2006)
Catumaxomab	Anti-EPCAM	Malignant ascites 2009 (NA)
Ofatumumab	Anti-CD20	Chronic lymphocytic leukemia 2010 (2009)
Ipilimumab	Anti-CTLA-4	Metastatic melanoma 2011 (2011)
Brentuximab vedotin	Anti-CD30	immunoconjugate Hodgkin 2012 (2011)
Pertuzumab	Anti-HER2	Breast Cancer 2013 (2012)
Ado-Trastuzumab emtansine	Anti-HER2	immunoconjugate Breast cancer 2013 (2013)

Rituximab-CHOP is superior to CHOP alone in older patients with diffuse large B-cell lymphoma.



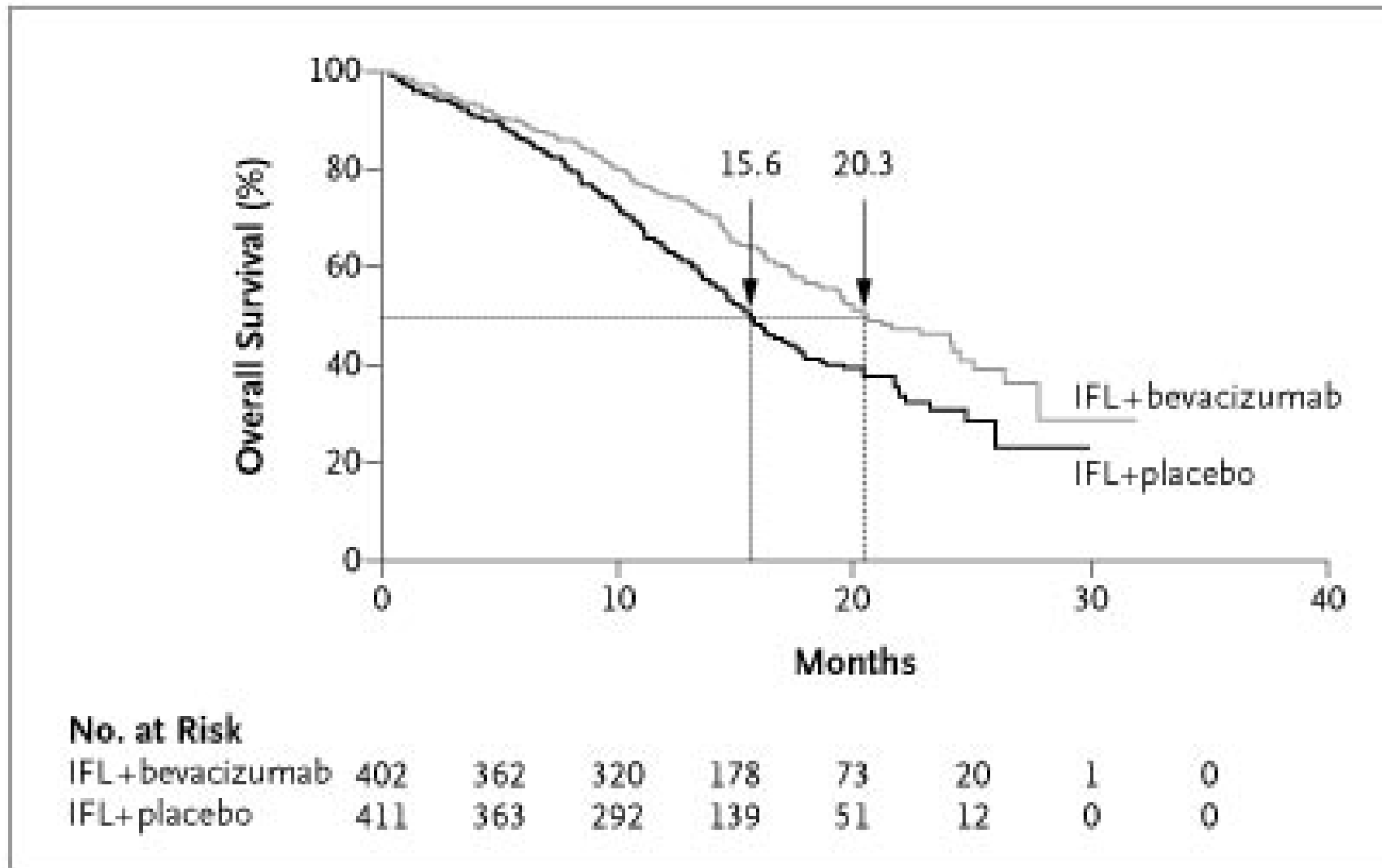
Habermann TM, JCO 2006

Trastuzumab antibody to HER2 improves survival in patients with metastatic breast cancer



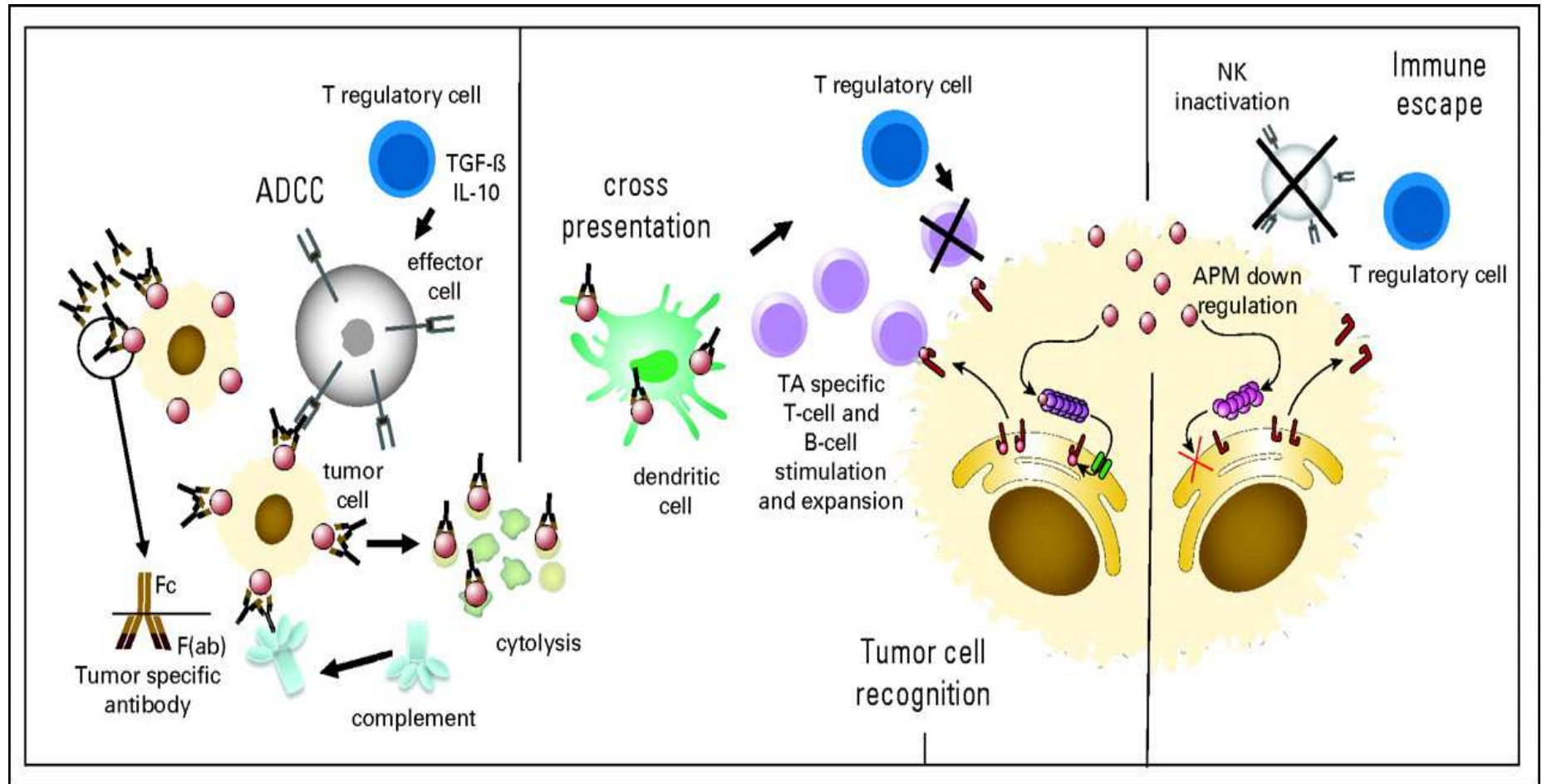
Dennis J. Slamon, , NEJM 2001

Bevacizumab added to Irinotecan, fluorouracil, and leucovorin improves survival in patients with metastatic colorectal cancer



Herbert Hurwitz, NEJM 2004

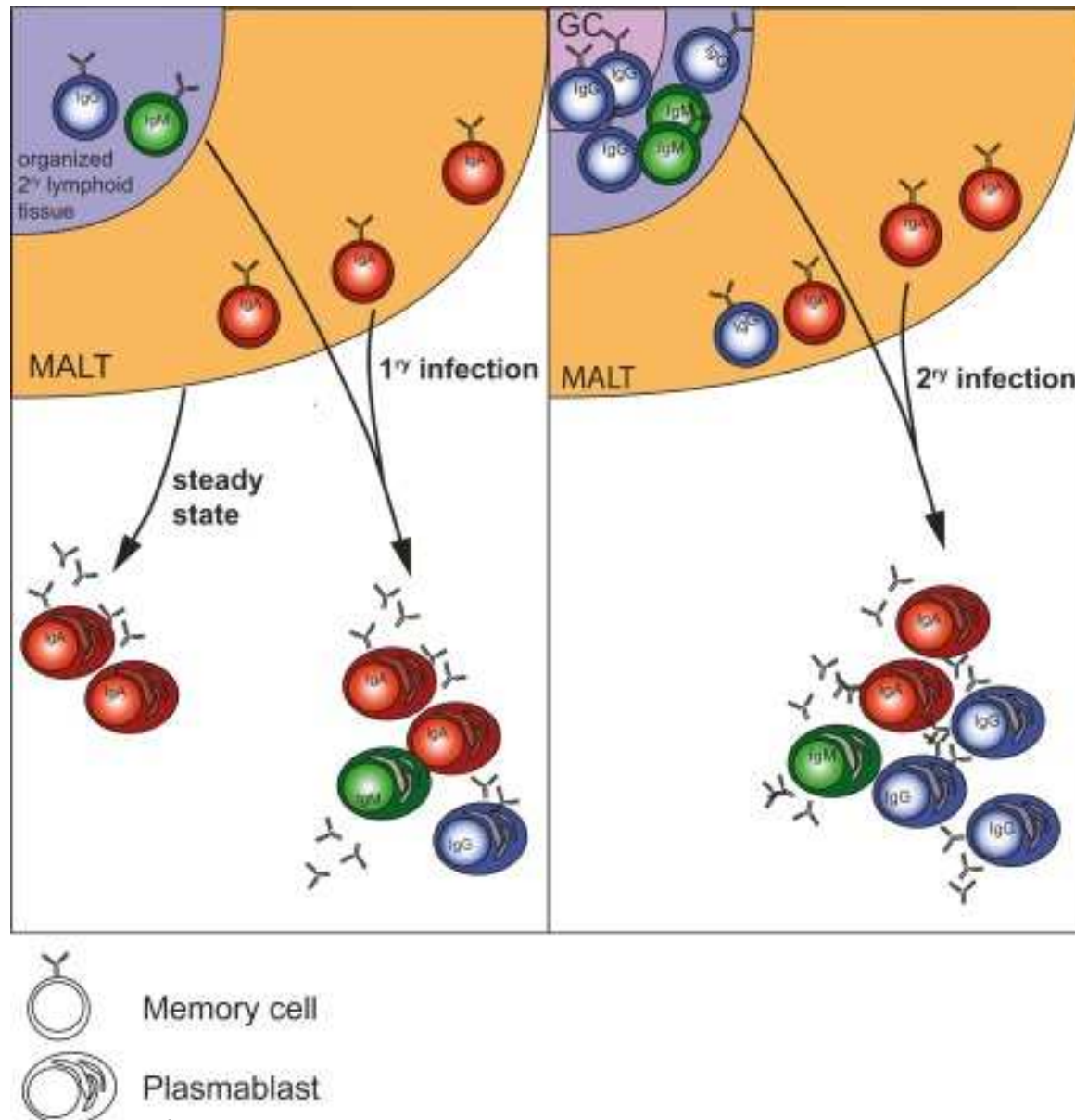
Immune cellular network mediated by tumor antigen (TA)–targeted monoclonal antibodies (mAbs) in the tumor microenvironment to induce antitumor activity.



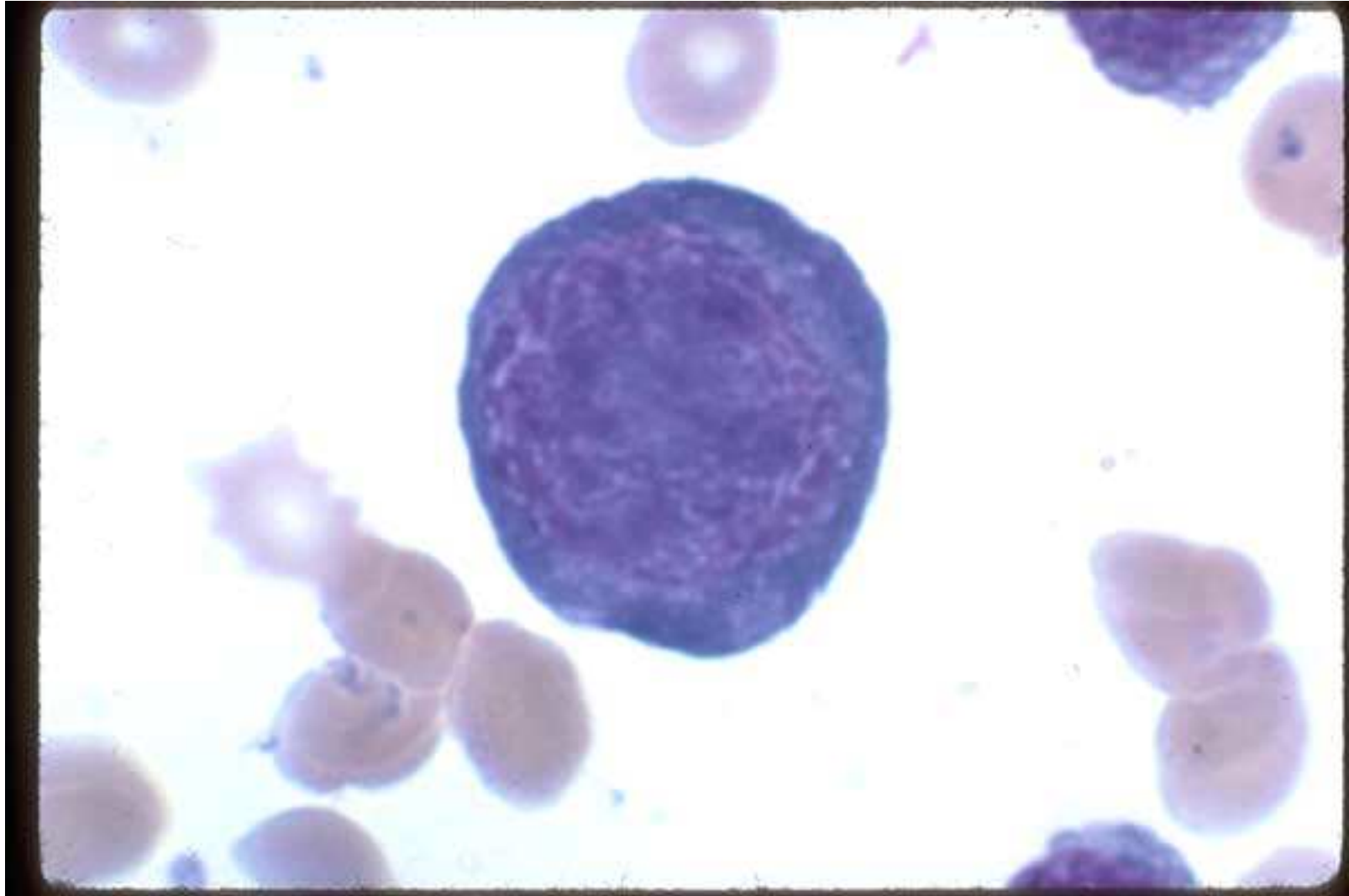
Ferris R L et al. JCO 2010;28:4390-4399

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Primary and secondary plasma cell responses

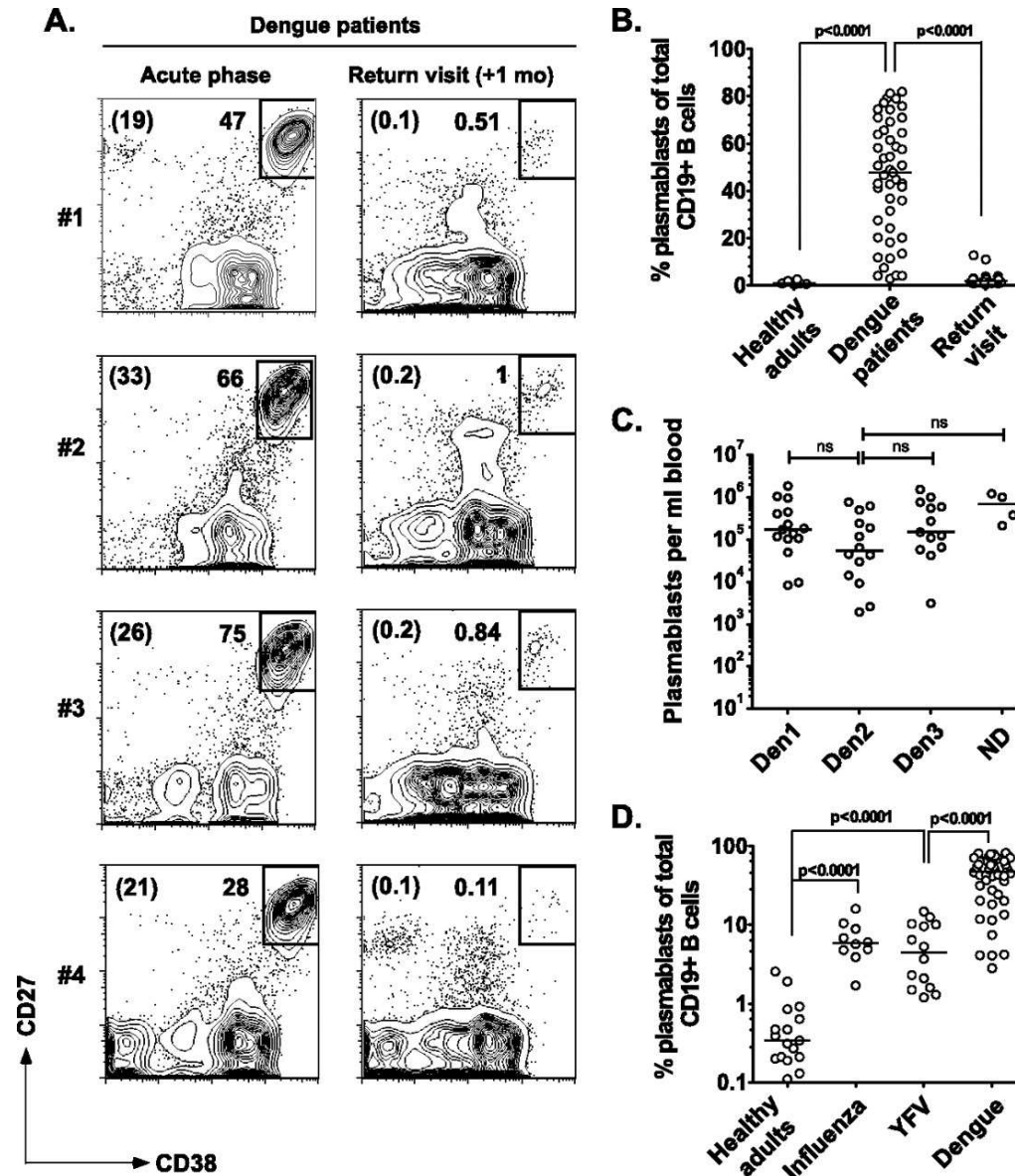


Plasmablast

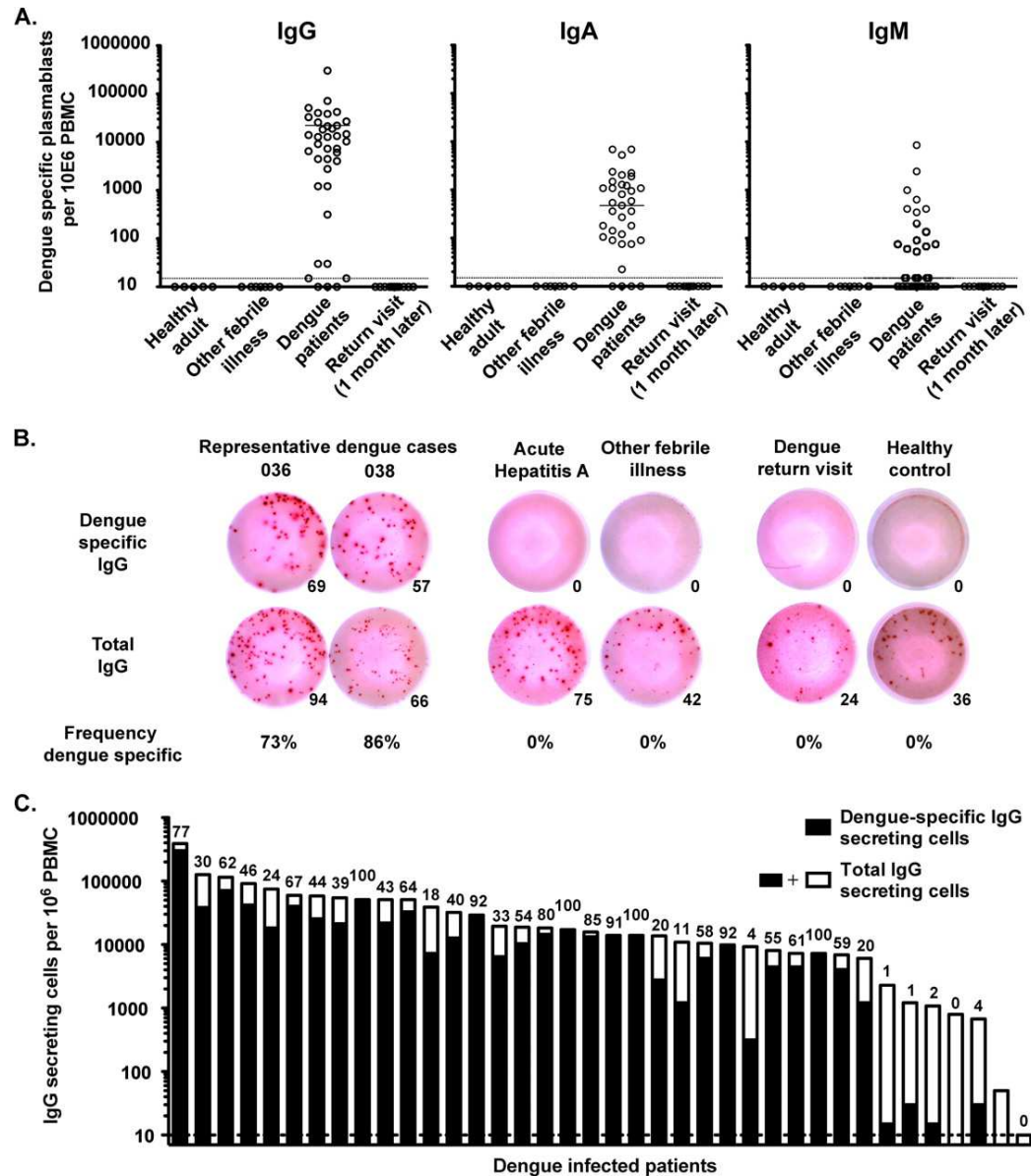


[http://image.bloodline.net/stories/storyReader\\$739.html](http://image.bloodline.net/stories/storyReader$739.html)

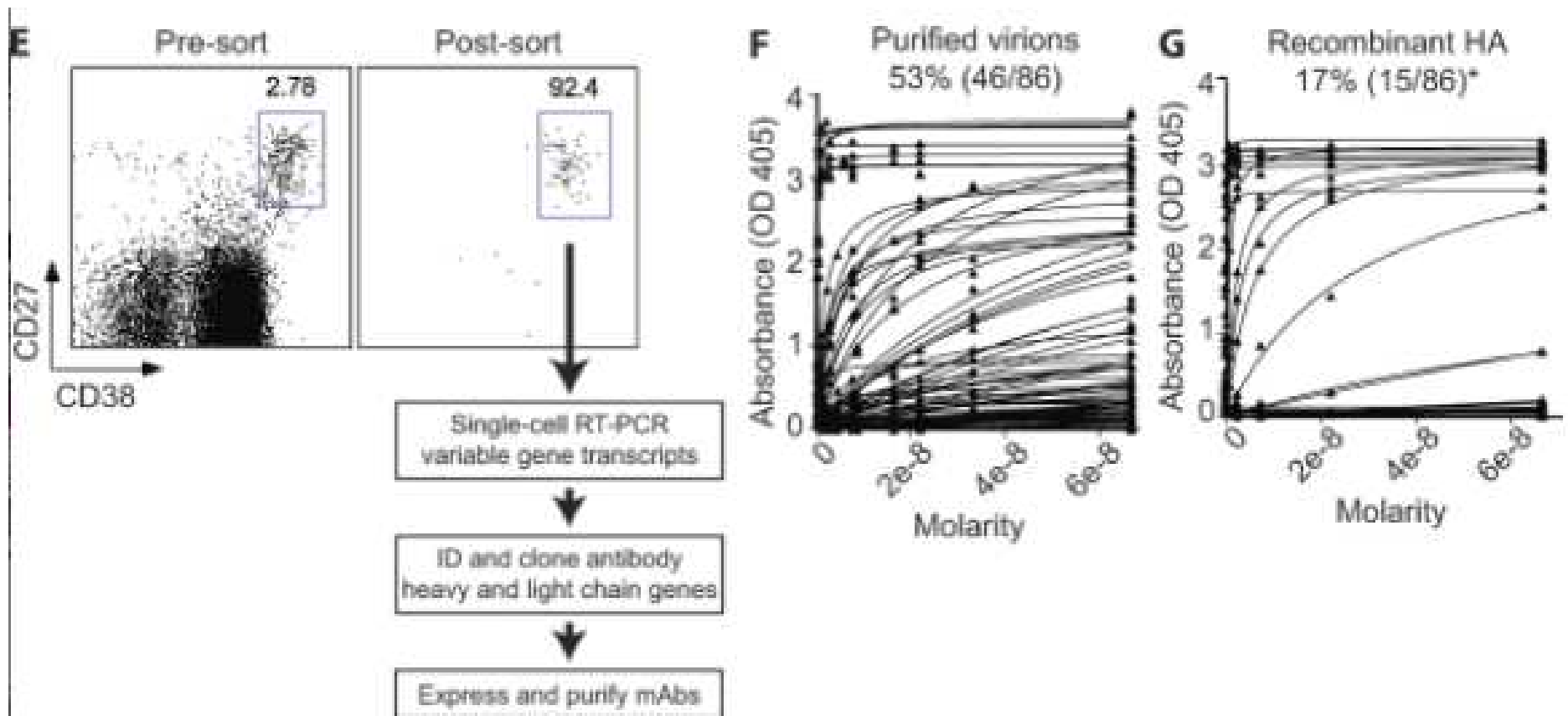
Potent plasmablast responses induced during acute dengue virus infection.



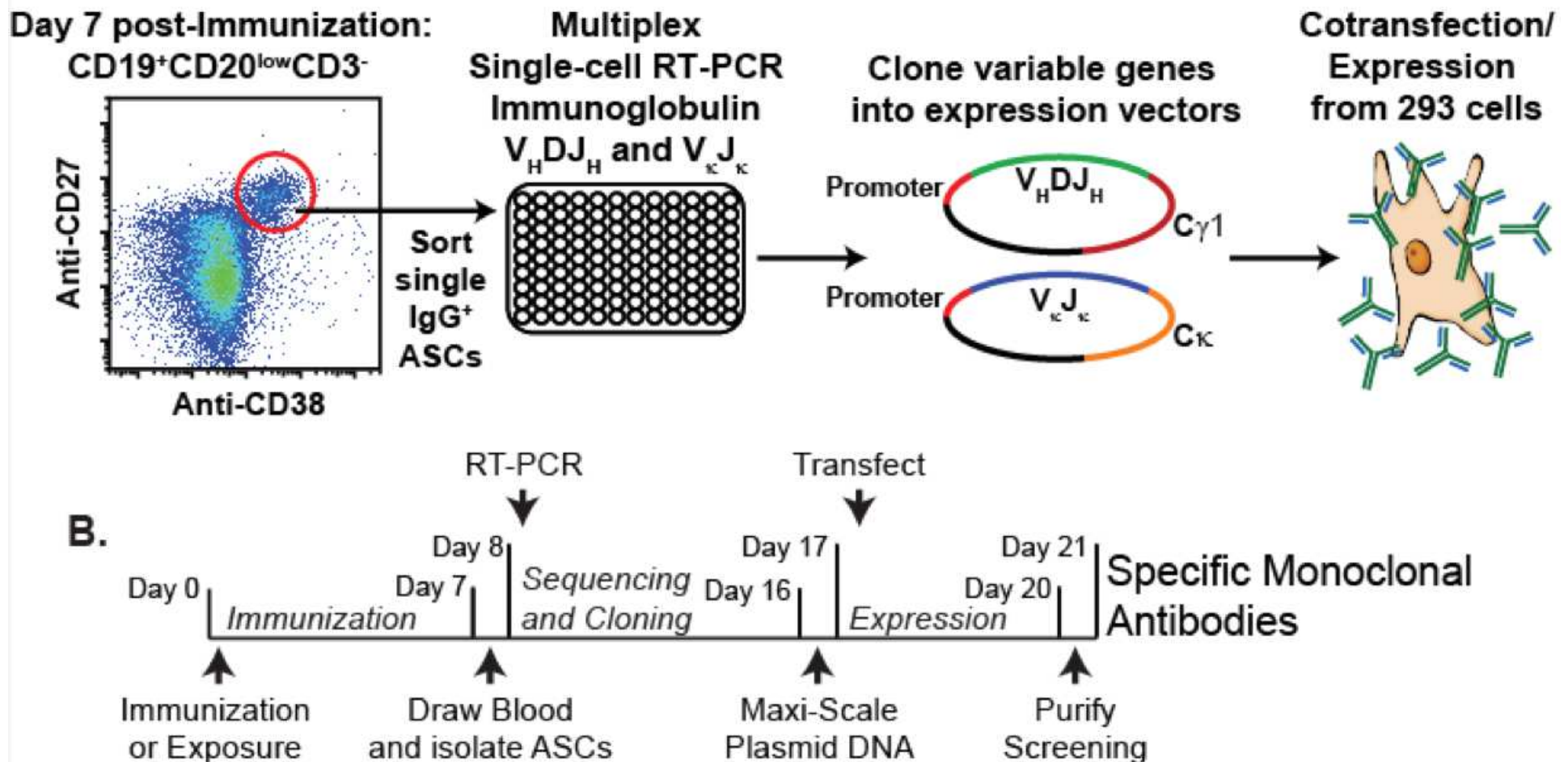
The majority of the plasmablasts induced by dengue virus infection are virus specific.



High-affinity monoclonal antibodies can be generated from FACS-isolated plasmablasts



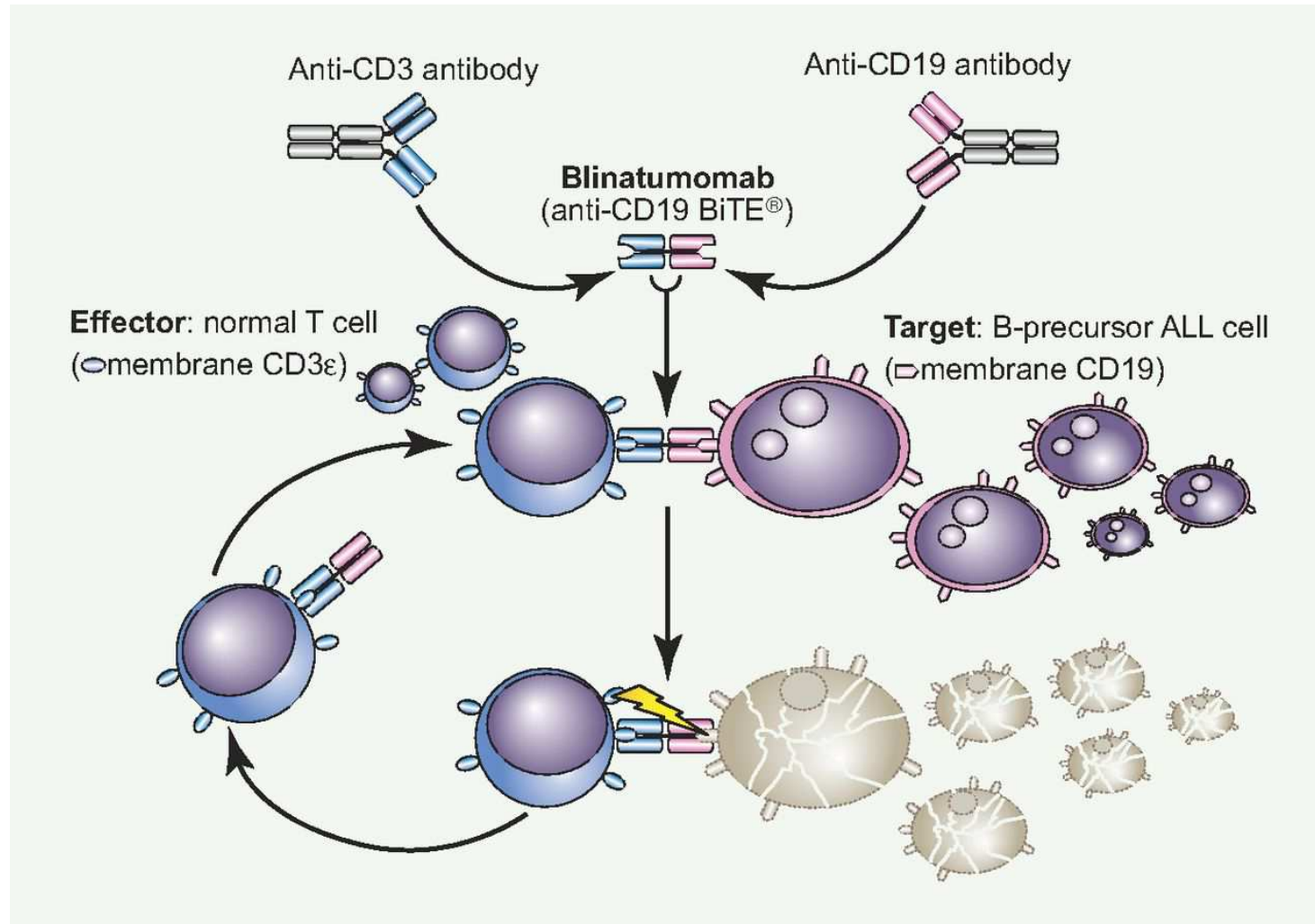
Strategy to generate tumor-specific human monoclonal antibodies following cancer vaccines



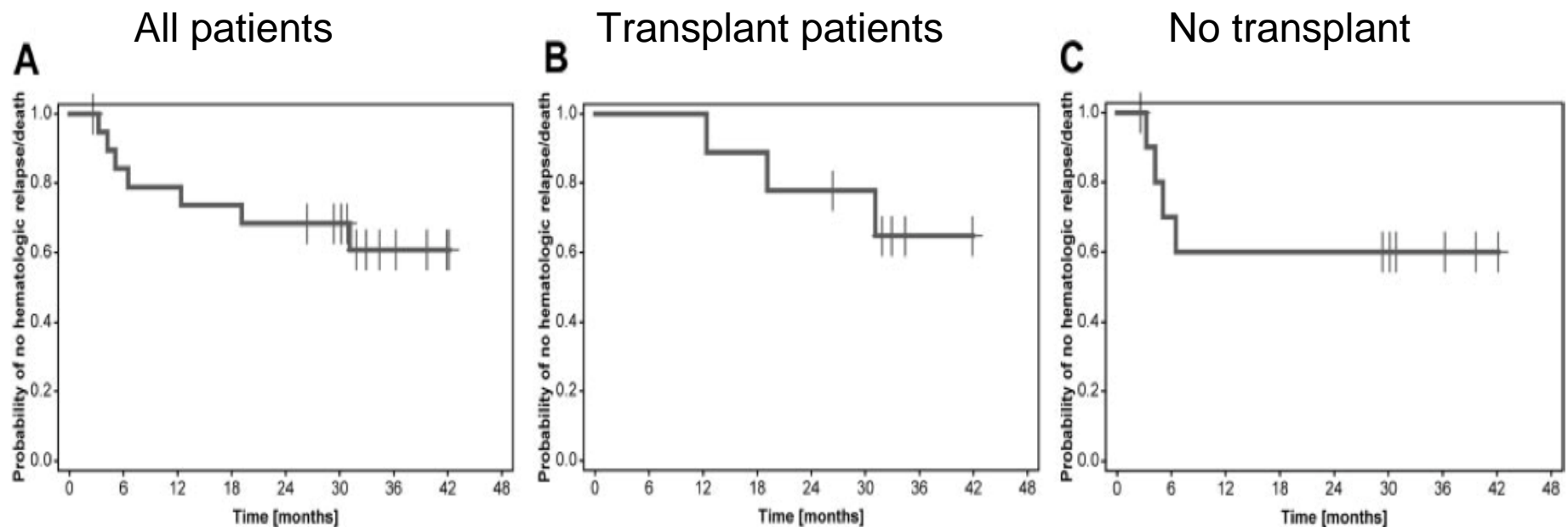
New developments in antibody therapy

- Antibodies to check-point blockade
 - Anti-PD1
 - Anti-PD-L1
- Bi-specific antibodies
 - BiTES (bridge T cells to target)
- Expressing antibodies directly on effector cells
 - CAR T-cells (MoAb expression on T cells)
 - CAR NK cells (MoAb expression on NK cells)

Blinatumomab is a novel bispecific construct that reacts simultaneously to normal CD3+ T cells and CD19+ ALL cells (BiTE mechanism)



Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL



What can be done to enhance the latent anti-tumor immune responses in patients?

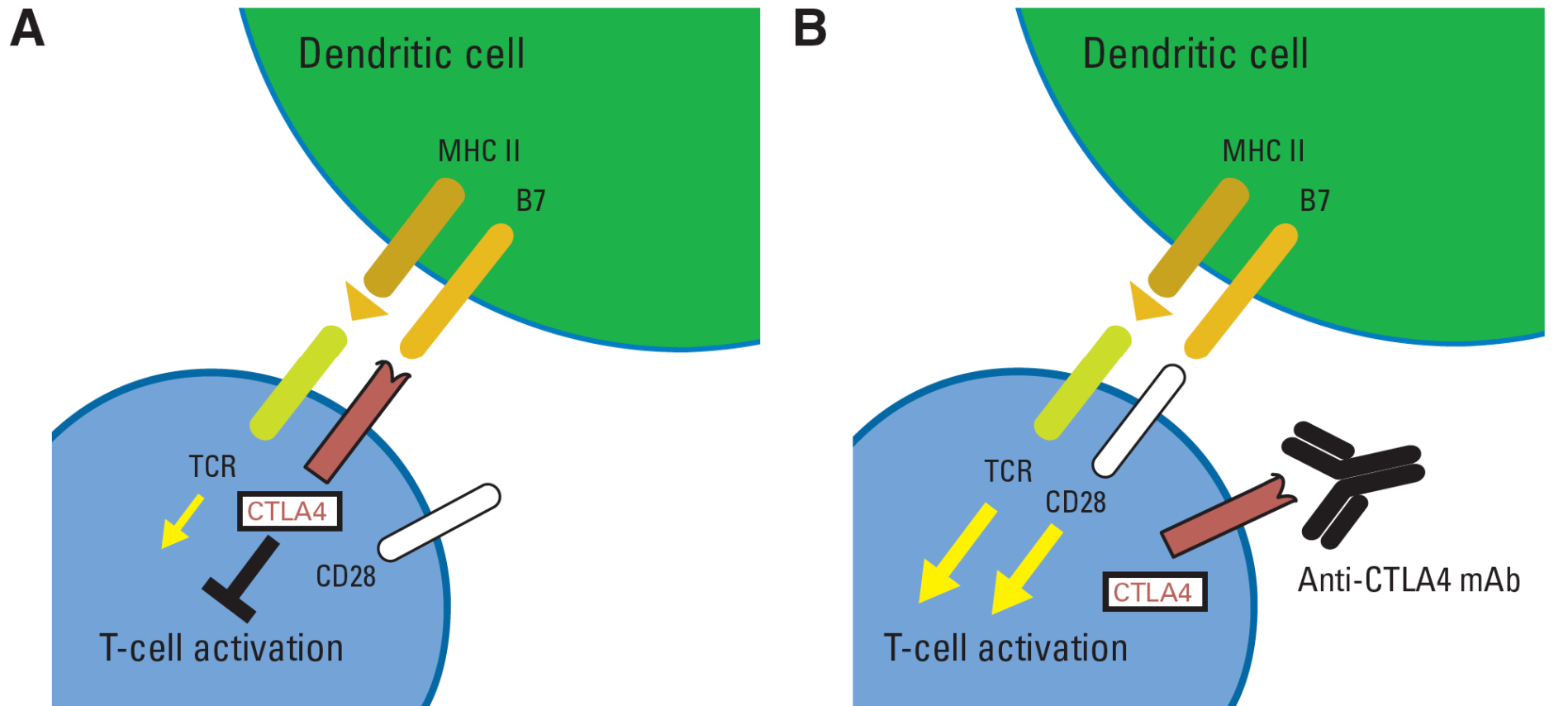
Blocking inhibitory signaling to enhance latent autologous anti-tumor immunity:

Anti-CTLA-4

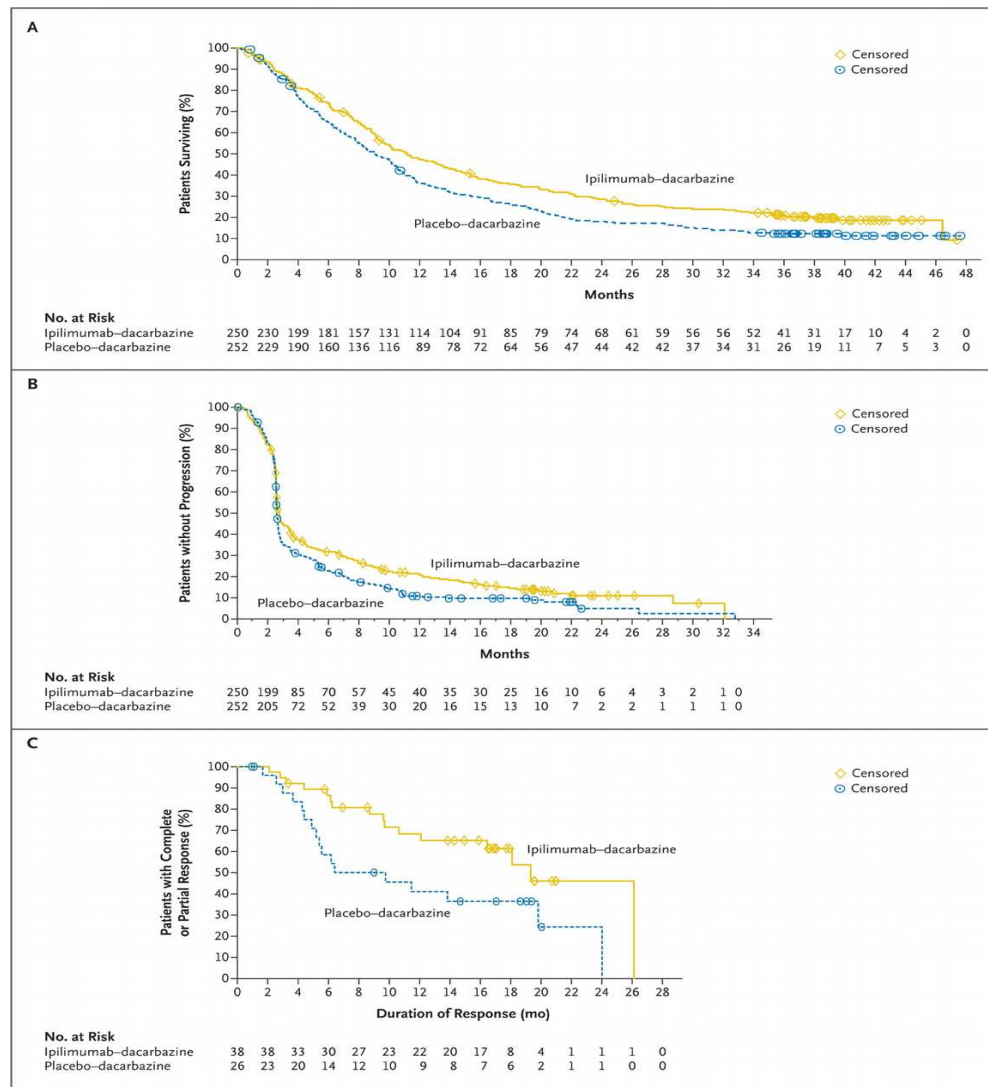
Anti-PDL/PDL1

Depleting T-reg

Role of blocking antibodies to CTLA4 signaling in T-cell activation and cellular immunotherapy

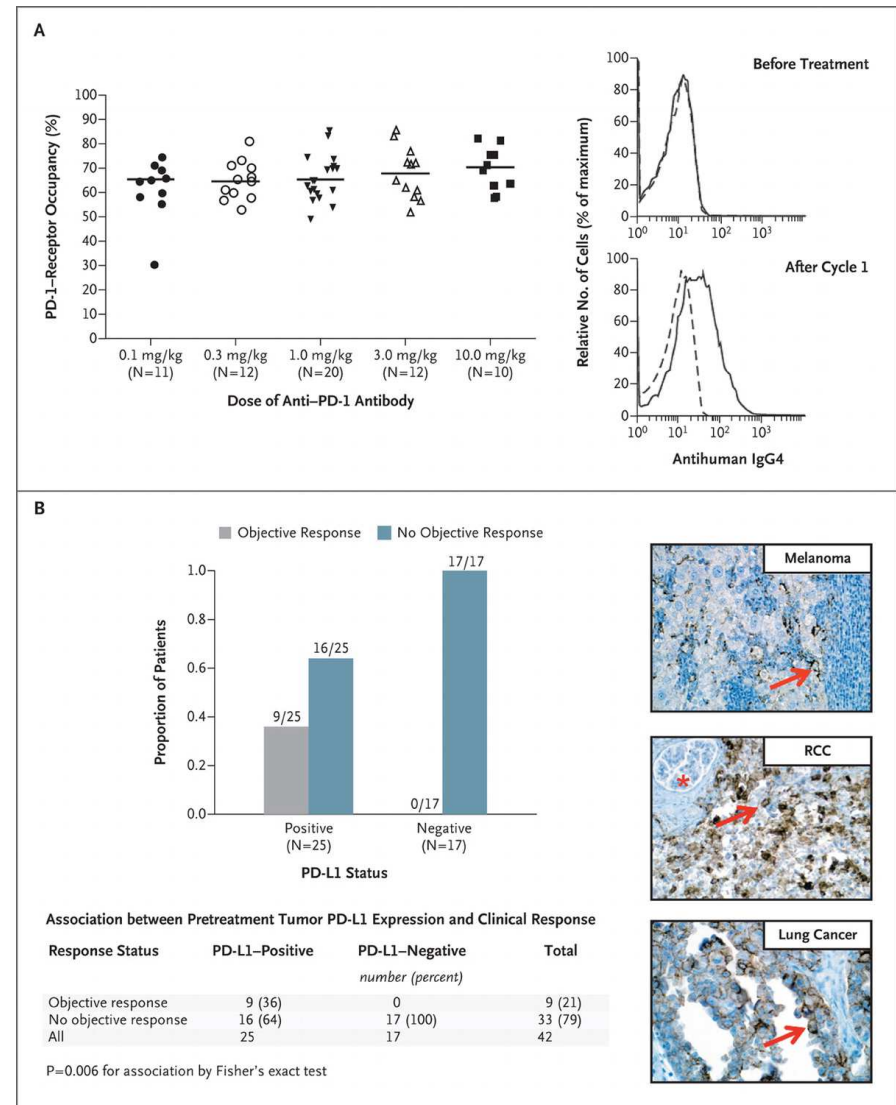
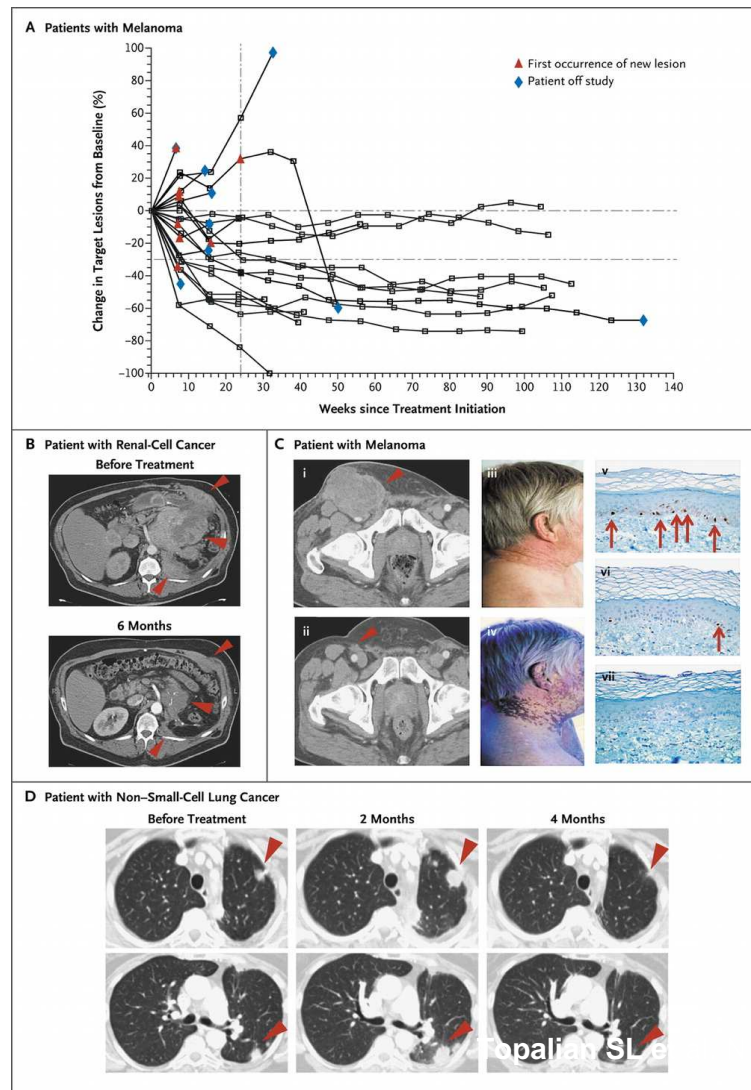


Ipilimumab (anti-CTLA-4) increased survival of patients with previously treated metastatic melanoma



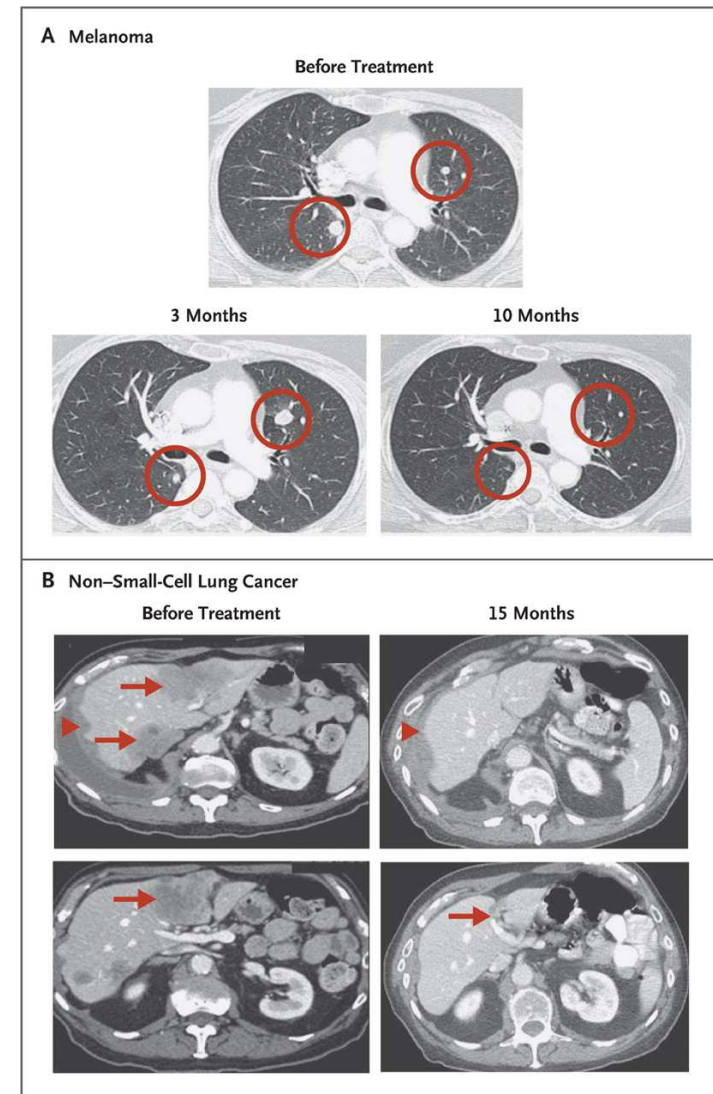
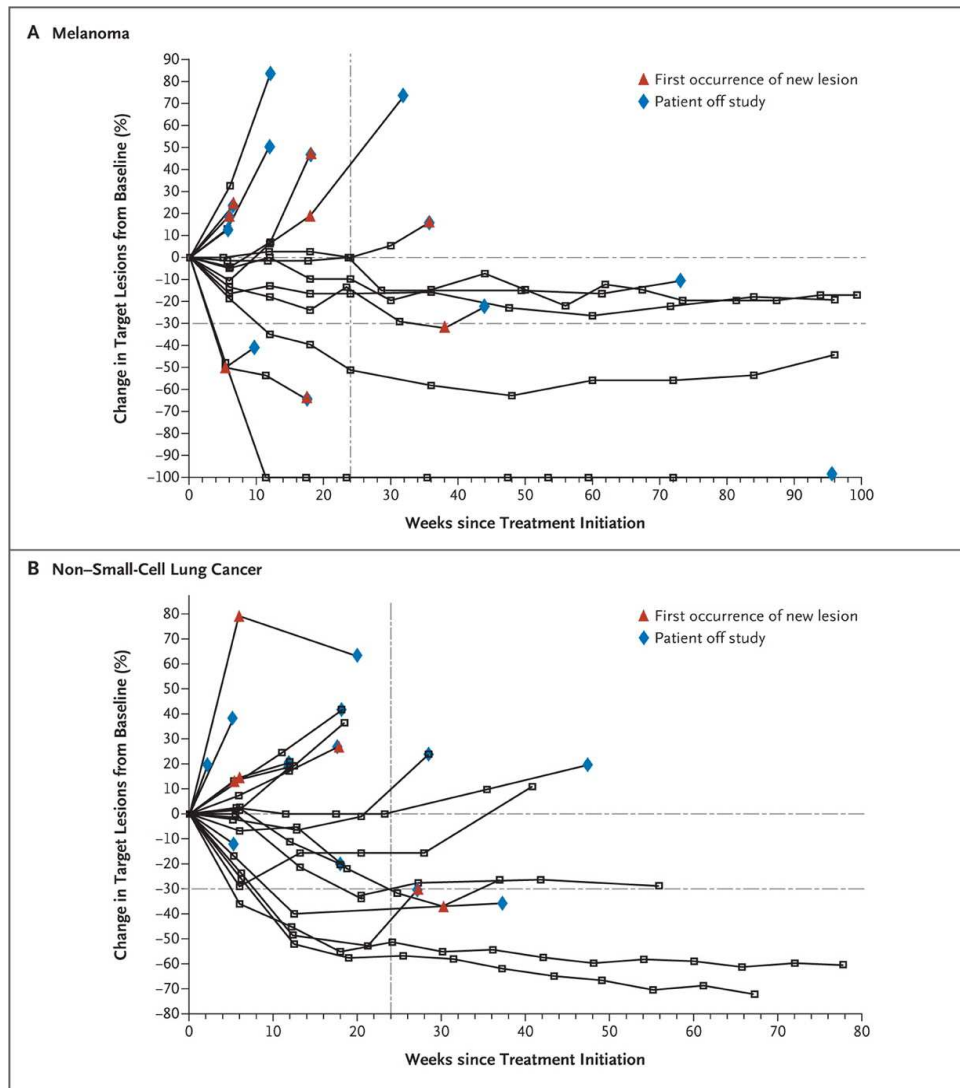
Robert C et al. 2011. N Engl J Med 364:2517-2526.

Activity of Anti-Programmed Death 1 (PD-1) Antibody in Patients with Treatment-Refractory Melanoma, Non-Small-Cell Lung Cancer, or Renal-Cell Cancer.



Topalian et al. NEJM 2012

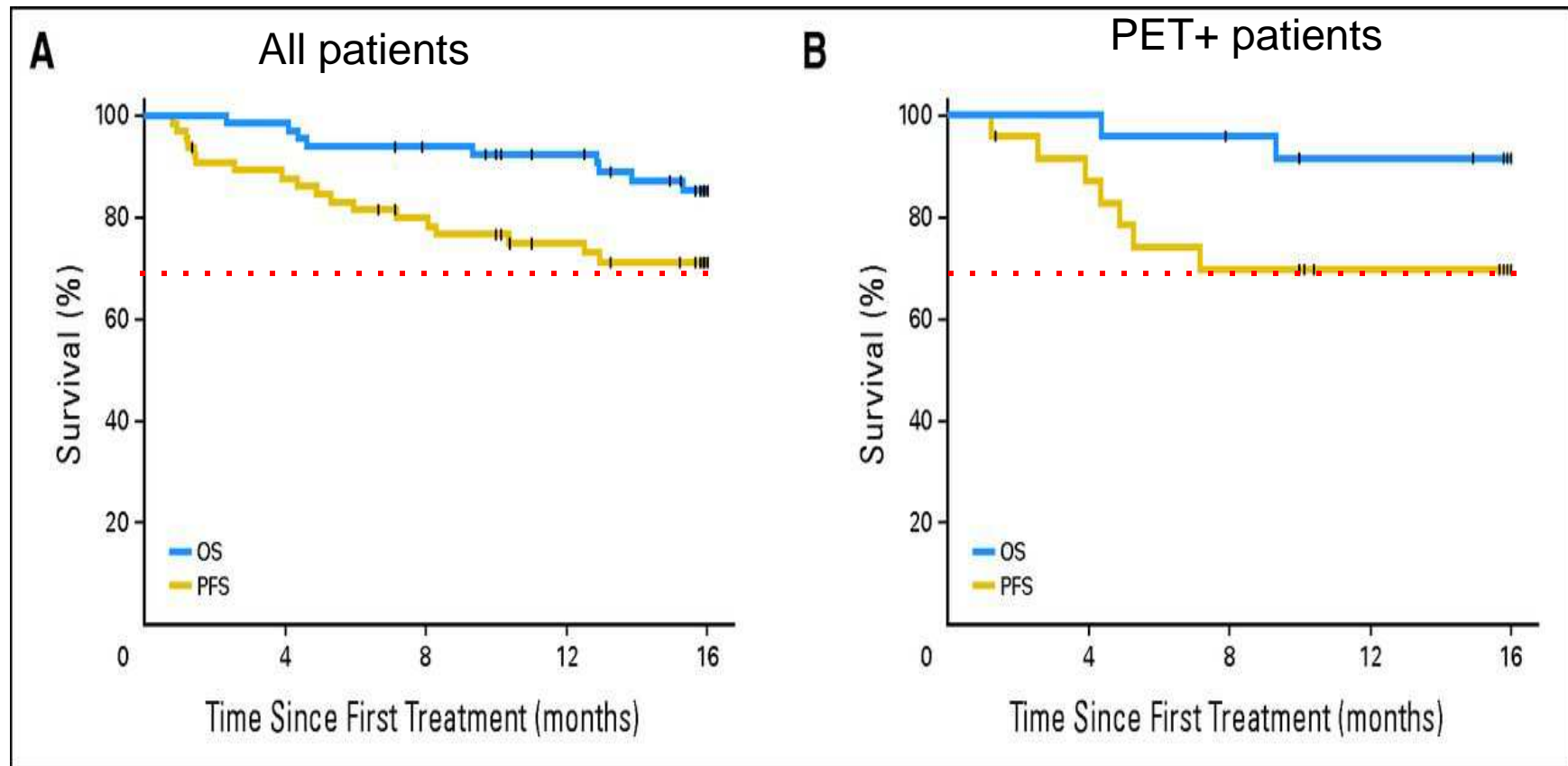
Activity of Anti-PD-L1 Antibody in Patients with Advanced Melanoma and Non-Small-Cell Lung Cancer.



Brahmer et al. NEJM 2012

Phase 2 study: Promising clinical outcomes after pidilizumab treatment following auto-transplant in NHL patients .

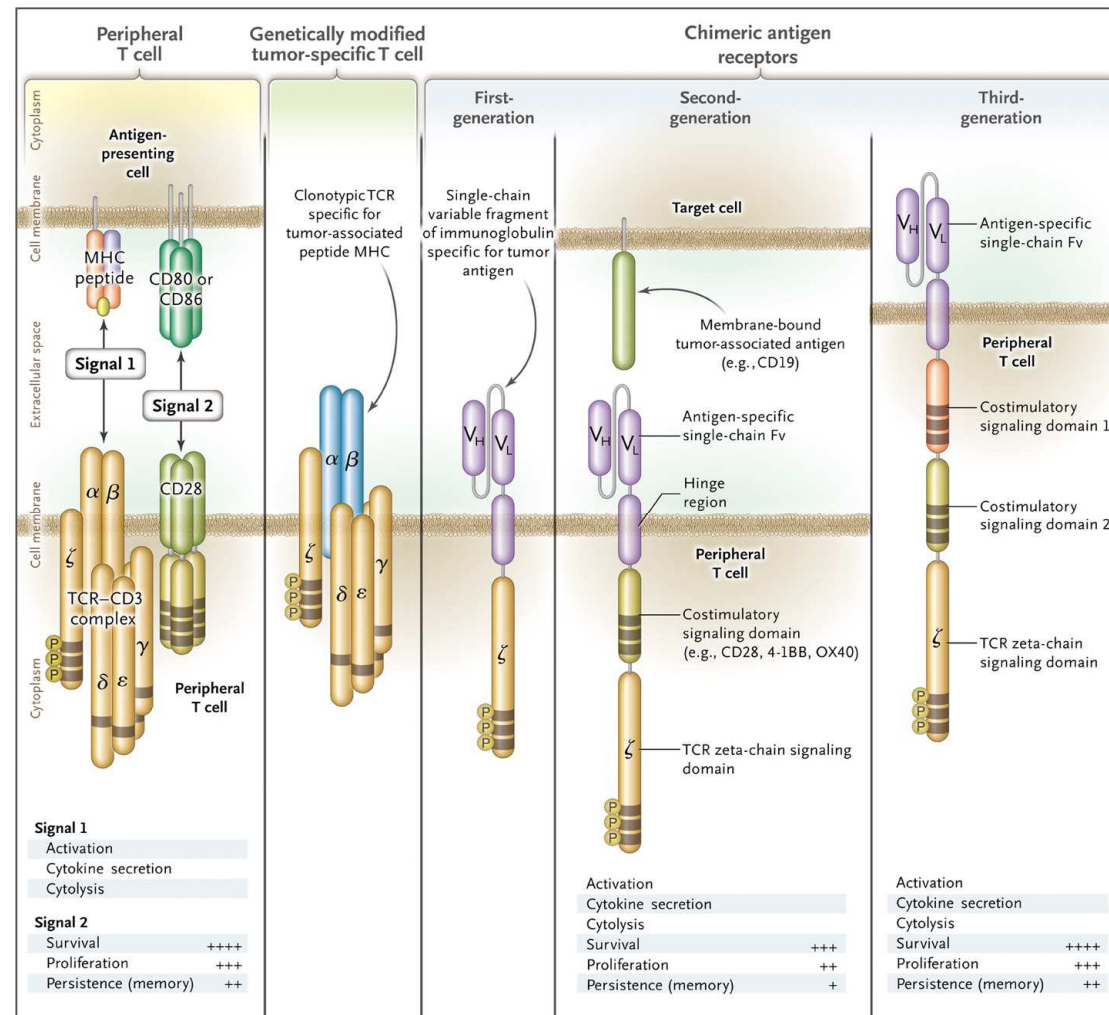
Pidilizumab was administered intravenously at a dose of 1.5 mg/kg every 42 days for three cycles, beginning 30 to 90 days from AHSCT.



Armand P et al. JCO 2013;31:4199-4206

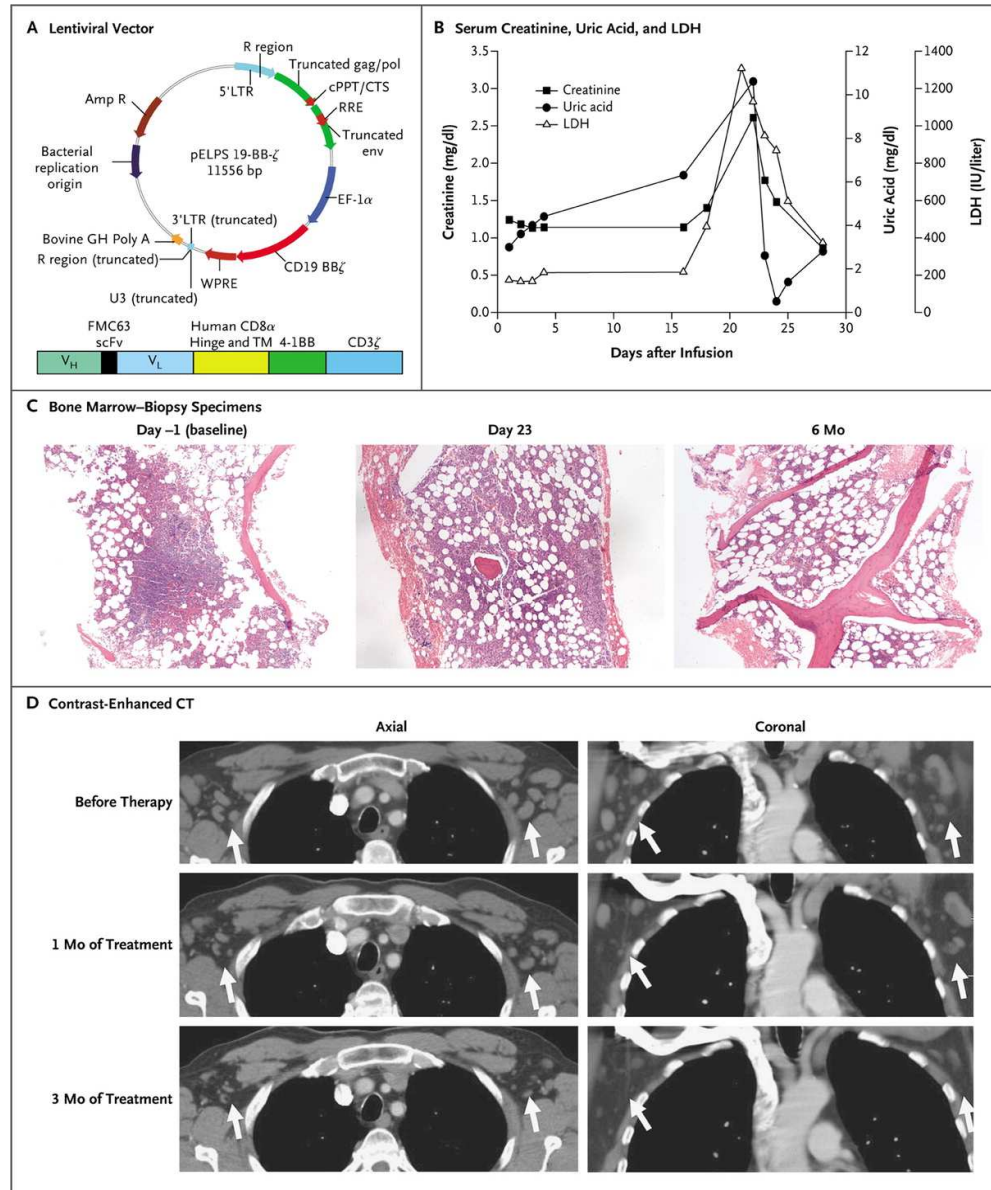
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Strategy of genetically-modified T-cells expressing antibodies with anti-tumor specificity



Urba WJ, Longo DL. 2011. N Engl J Med. 365:754-757.

CAR autologous T-cell immunotherapy in CLL



Porter DL et al. 2011 N Engl J Med. 365:725-733.

Conclusions

- Monoclonal antibodies to tumor-associated antigens have had a major clinical impact on improving survival in cancer patients
- New strategies to generate human MoAb to TAA may yield new targets for MoAb therapy
- Bi-specific MoAb to TAA and effector cells can be used to enhance cell-mediated immunity to cancer
- MoAb to TAA expressed directly on effector cells can augment cell-mediated immunity