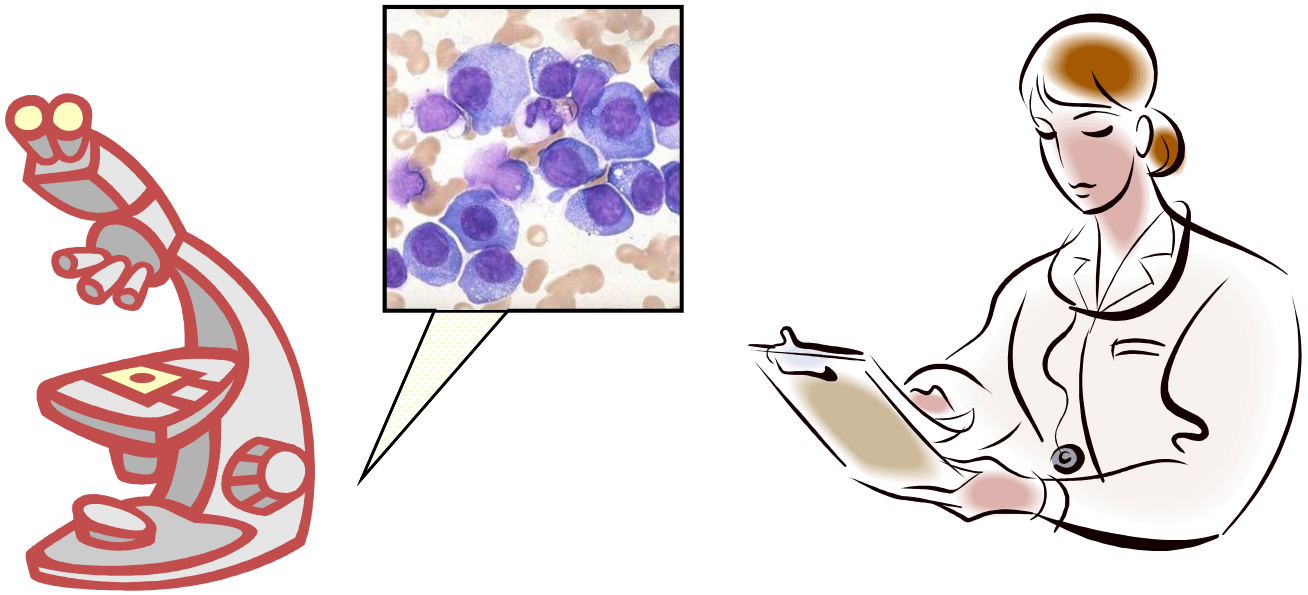
がんに対する抗体療法の技術革新と新展開

Technological innovation of antibody therapy for cancer and its perspectives

February 16, 2019

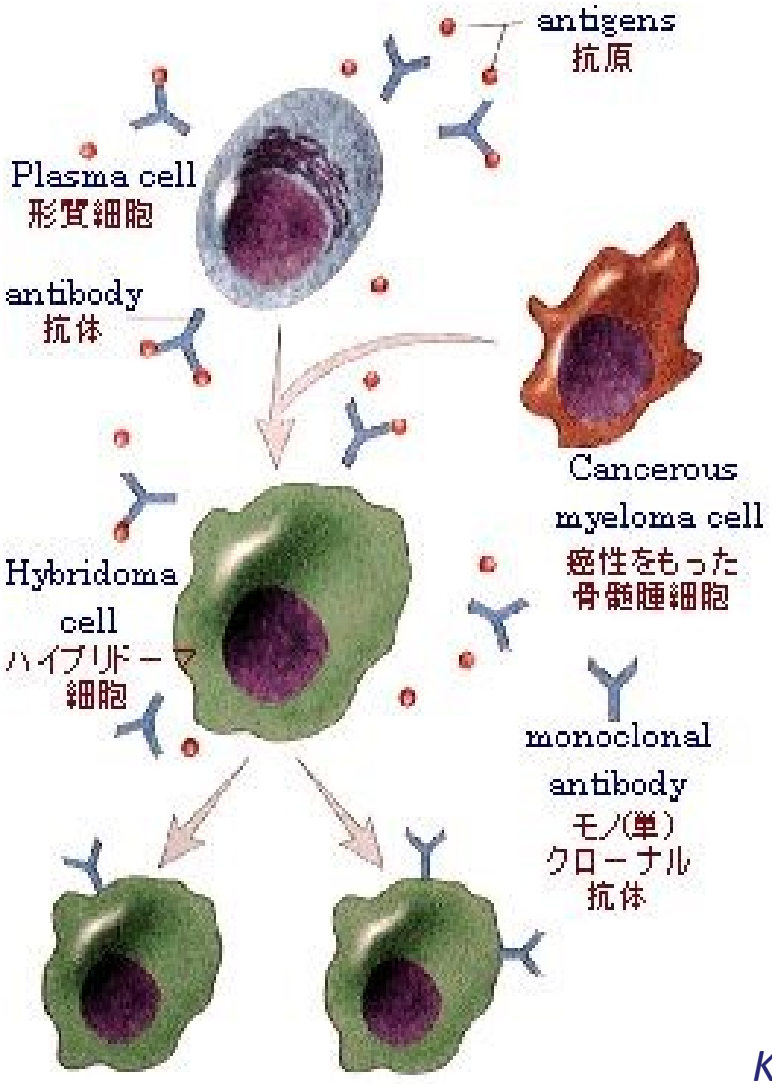


Shinsuke Iida, M.D.

Department of Hematology and Oncology

Nagoya City University Graduate School of Medical Sciences

Monoclonal antibodies (mAbs) for cancer therapy

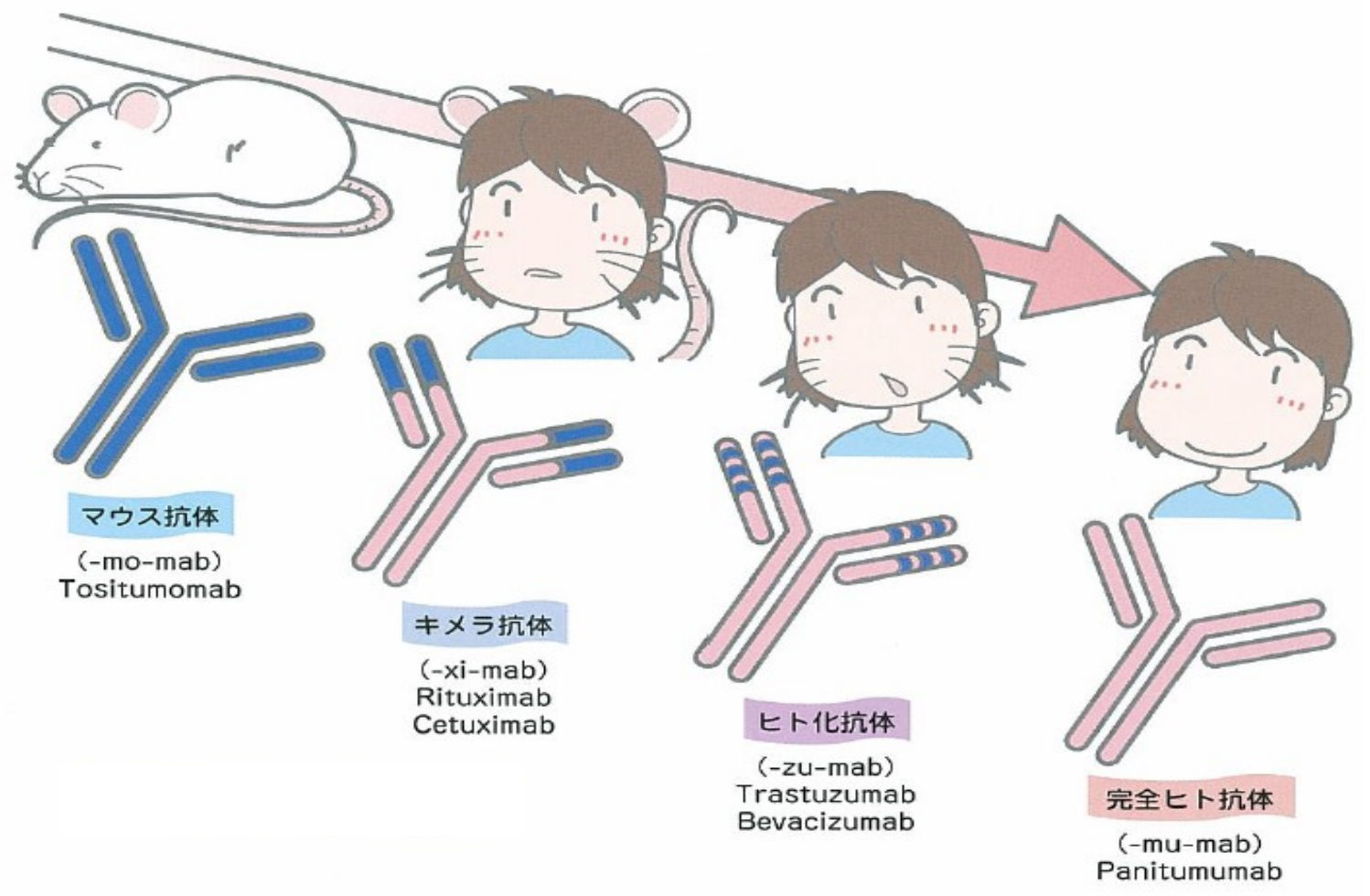


Monoclonal Antibody, mAb:

- Recognizes a single antigen
- Prepared from a single Ab producing plasma cell-derived hybridoma clone
- Massively produced by biotechnology
- Attacks just one antigen expressed on the cancer cells

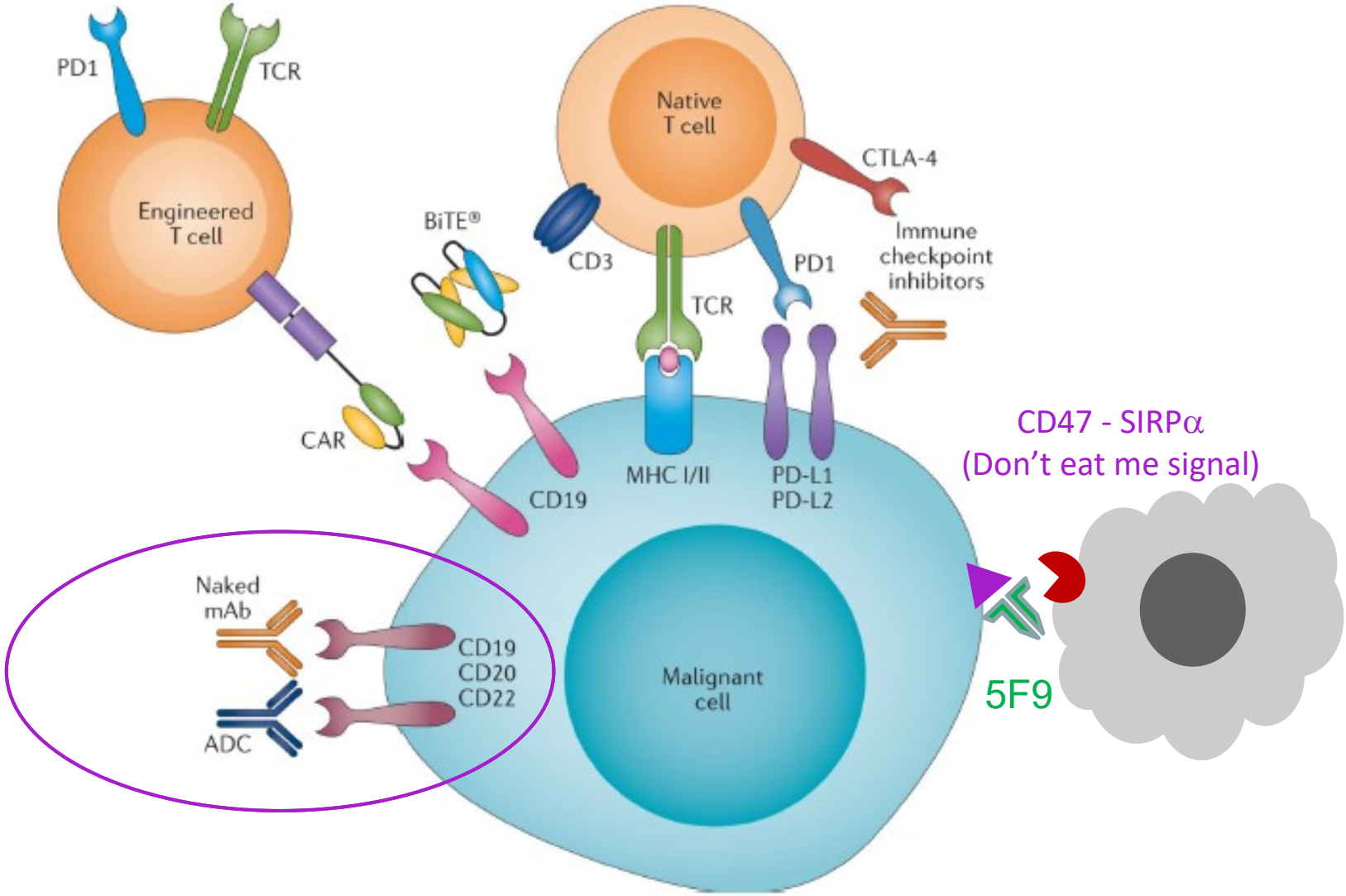
Köhler G & Milstein C, 1975

Advances in molecular biology have made it possible to generate chimeric and humanized mAbs applicable to cancer treatment



Provided by Chugai Pharmaceutial Inc.

Mechanisms of action of immunotherapy modalities in B-cell malignancies

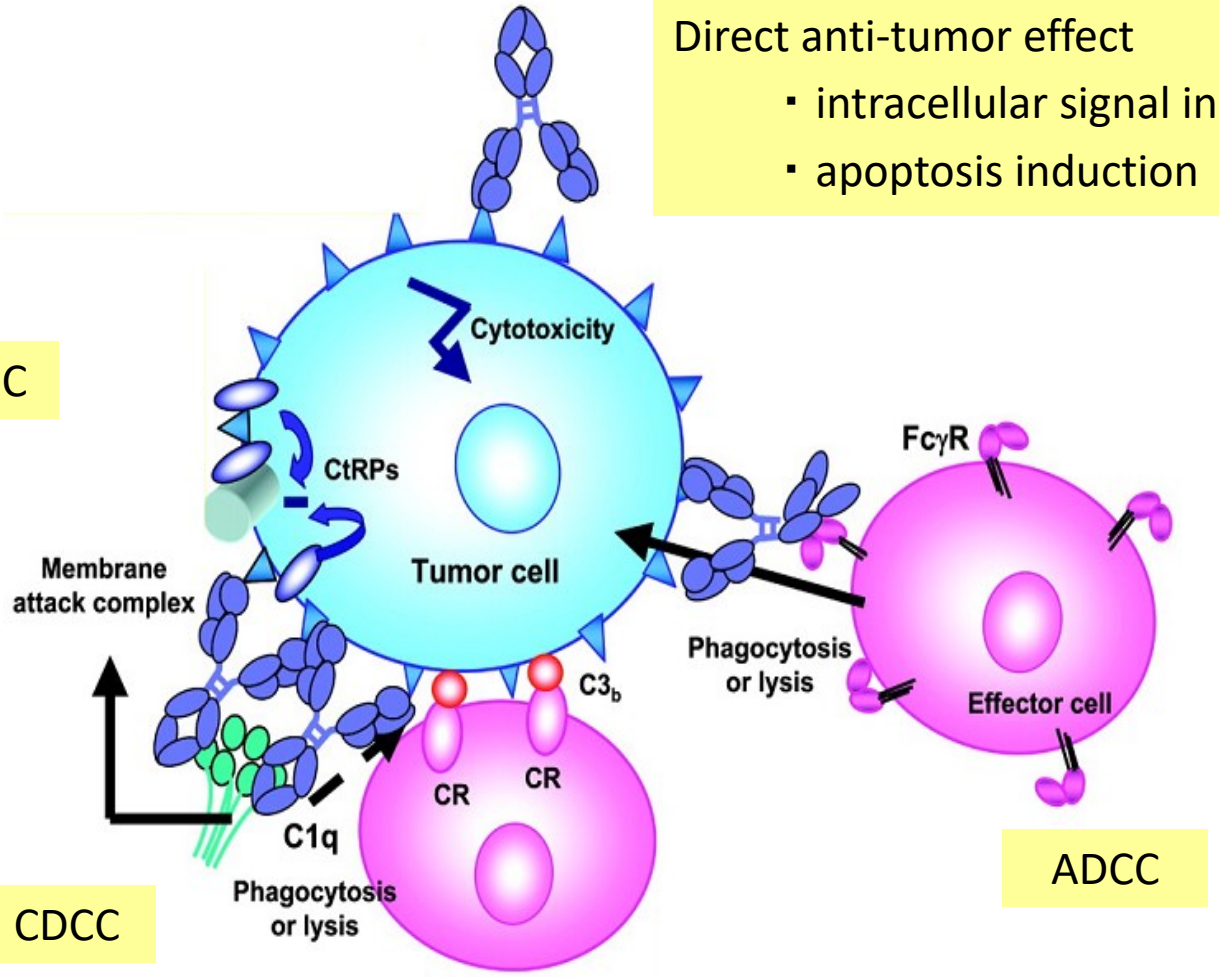


Batlevo CL et al. Nat Rev Clin Oncol 2016; 13: 25-40.

Anti-tumor effect attributed by mAb

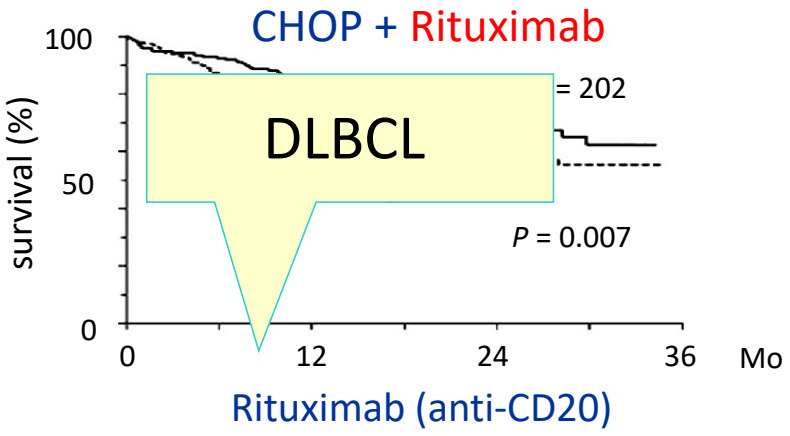
Direct anti-tumor effect

- intracellular signal inhibition
- apoptosis induction

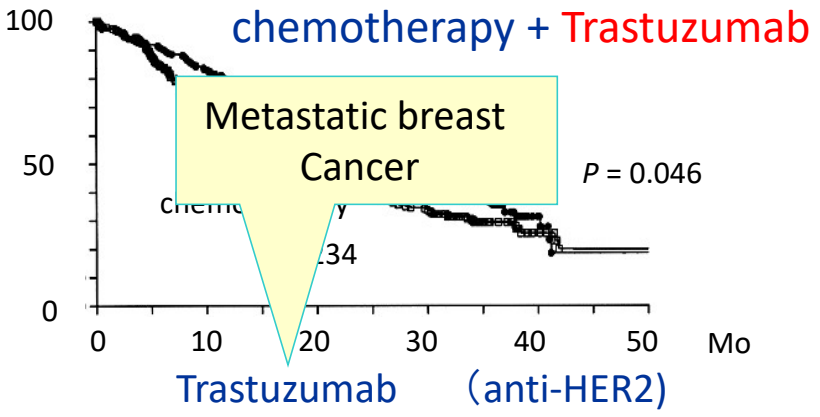


Antibody dependent cellular cytotoxicity (ADCC)
Complement dependent cellular toxicity (CDCC)
Complement dependent cytotoxicity (CDC)

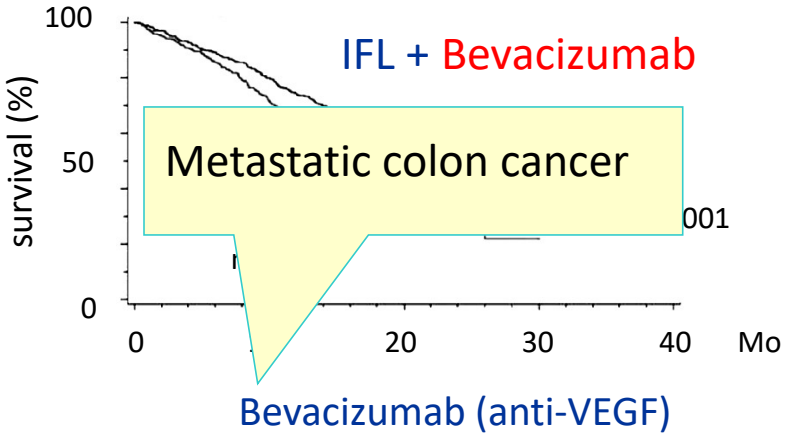
Monoclonal antibodies in Cancer treatment



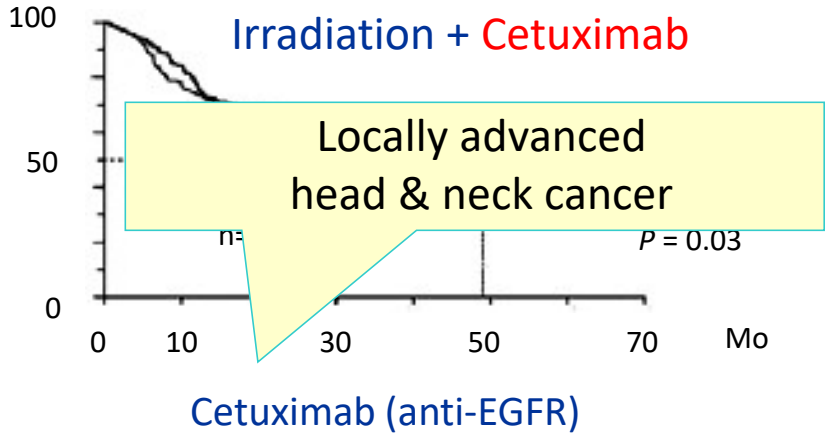
N Engl J Med 346, 235-242 (2002).



N Engl J Med 344, 783-792 (2001)



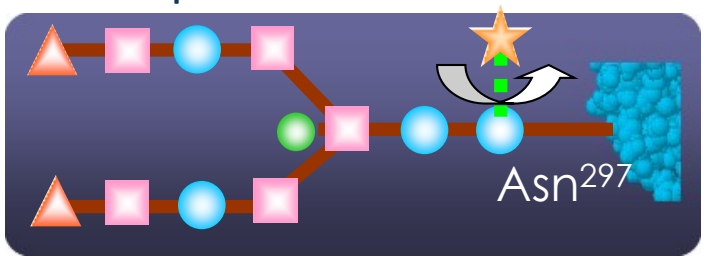
N Engl J Med 350, 2335-2342 (2004)



N Engl J Med 354, 567-578 (2006)

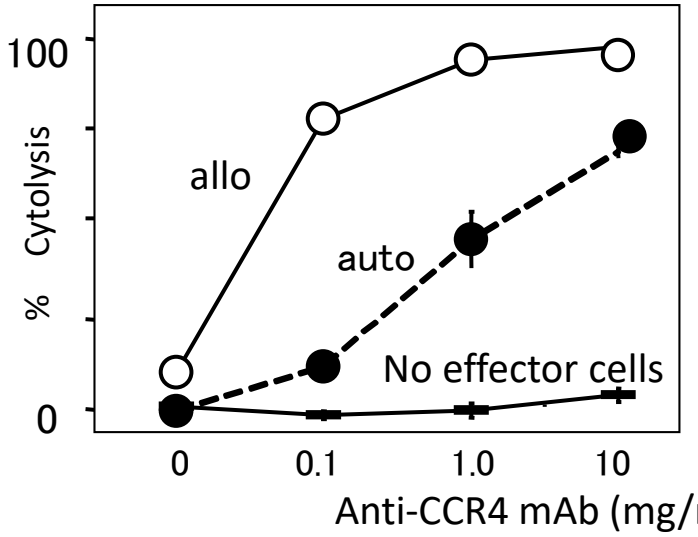
Engineered mAb by which enhances ADCC activity against cancer cells

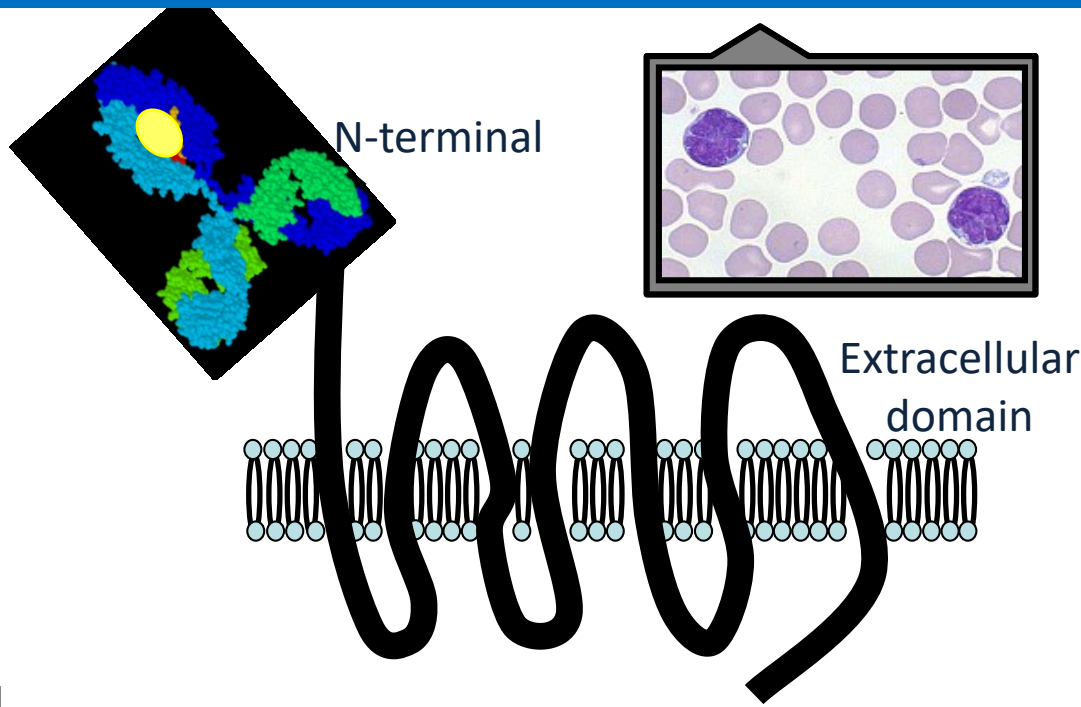
Mogamulizumab targeting CCR4 expressed on ATLL cells



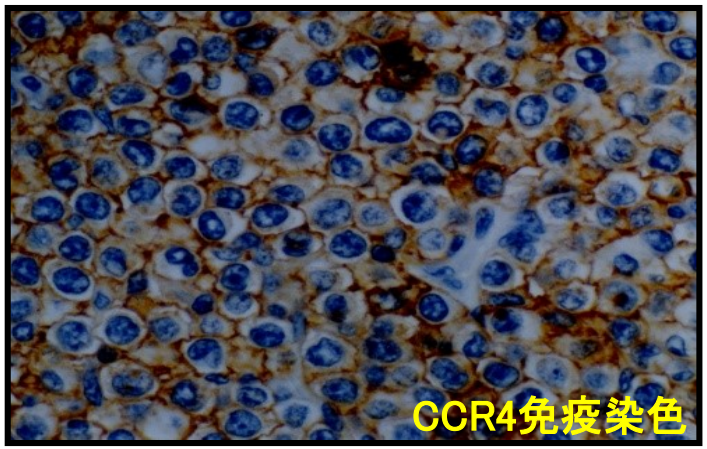
Enhanced ADCC effect by defucosylated Fc regions

Shinkawa et al, J Biol Chem 2003;278:3466





CCR4 (CC chemokine receptor 4)



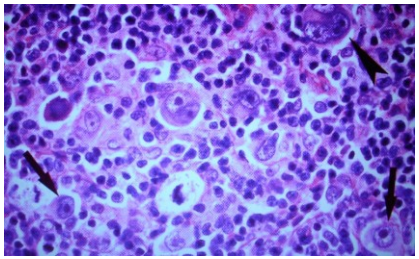
Ishida T, Ueda R, et al. Clin Cancer Res 2003; 9: 3625; 2004; 10: 7529.

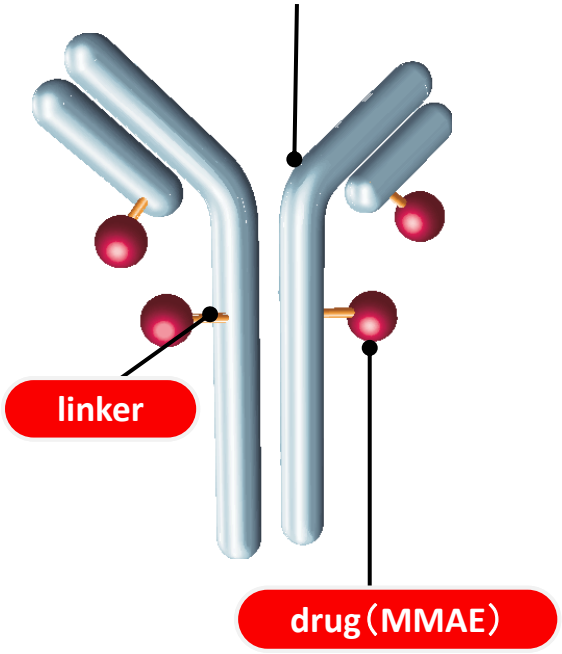
Antibody-drug conjugate in Cancer treatment

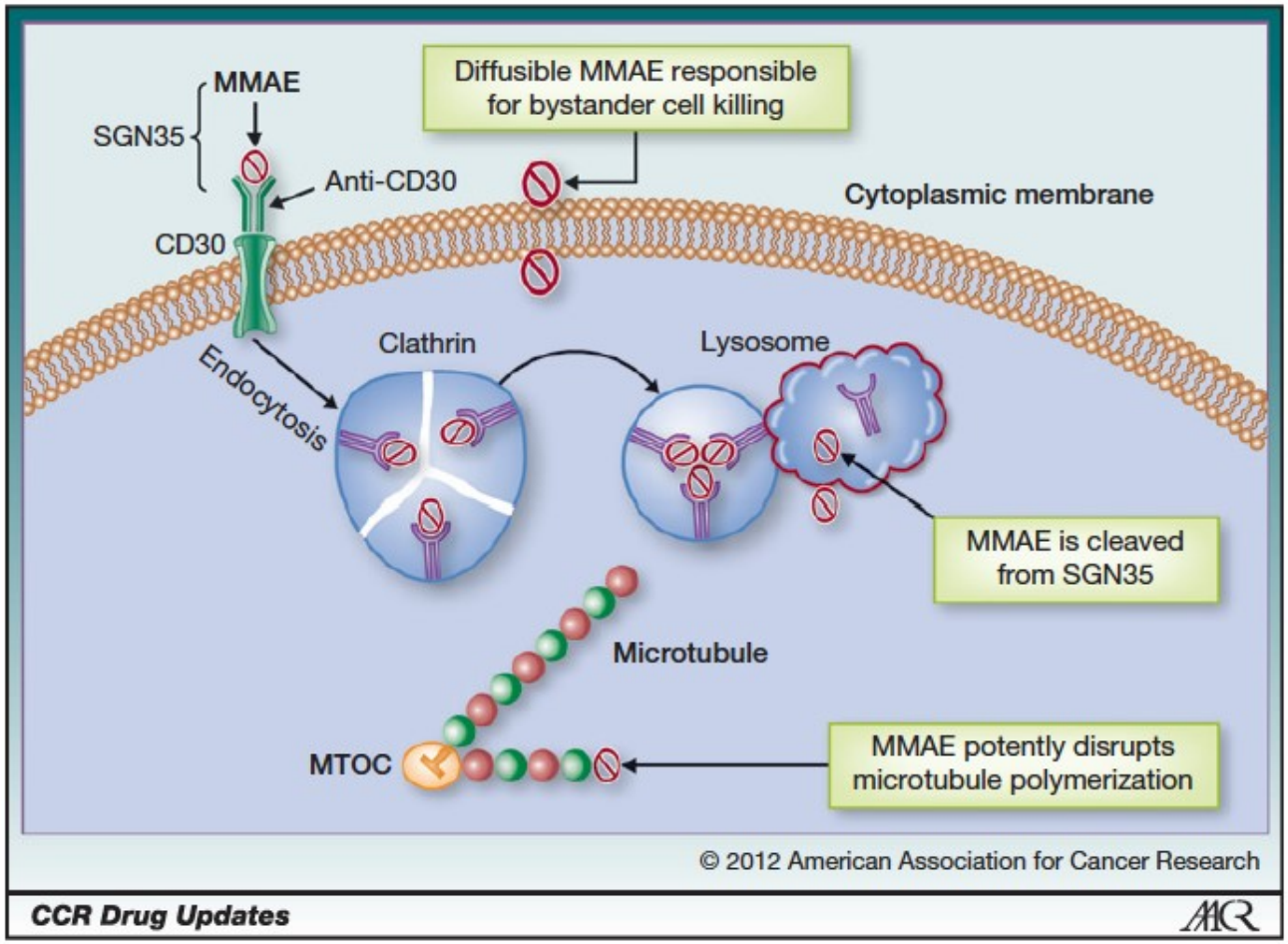
- Monomethyl aurinostatin (MMAC)

Brentuximab vedotin

- **Indication: CD30 positive Hodgkin's lymphoma and Anaplastic large cell lymphoma**



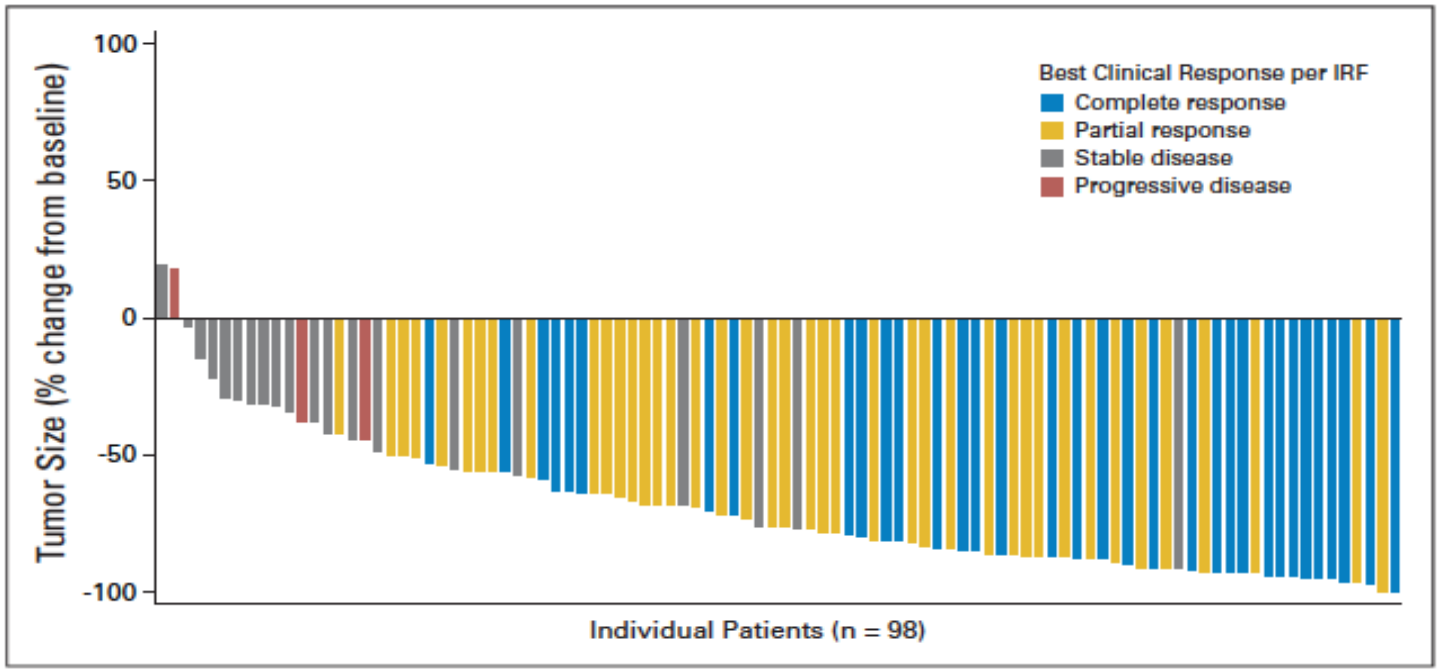




Deng C, et al. Clin Cancer Res 2012; 19: 22-27.

Brentuximab vedotin for Hodgkin's lymphoma relapsed after autologous stem cell transplantation

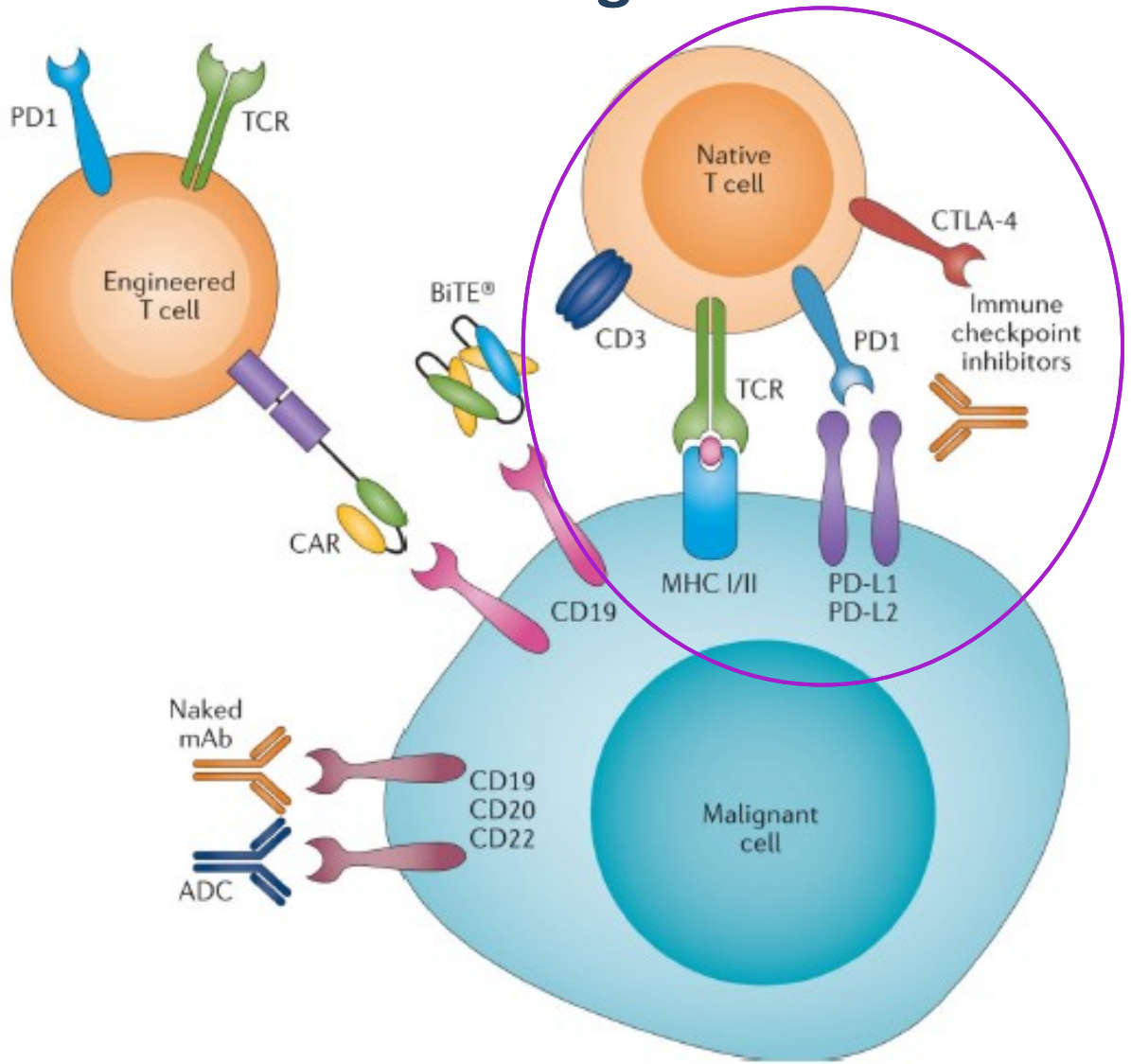
SGN035-0003 trial



CR 34%, Overall response rate 75%
Median duration of response: 6.7 mos（20.5 mos for the patients with CR）

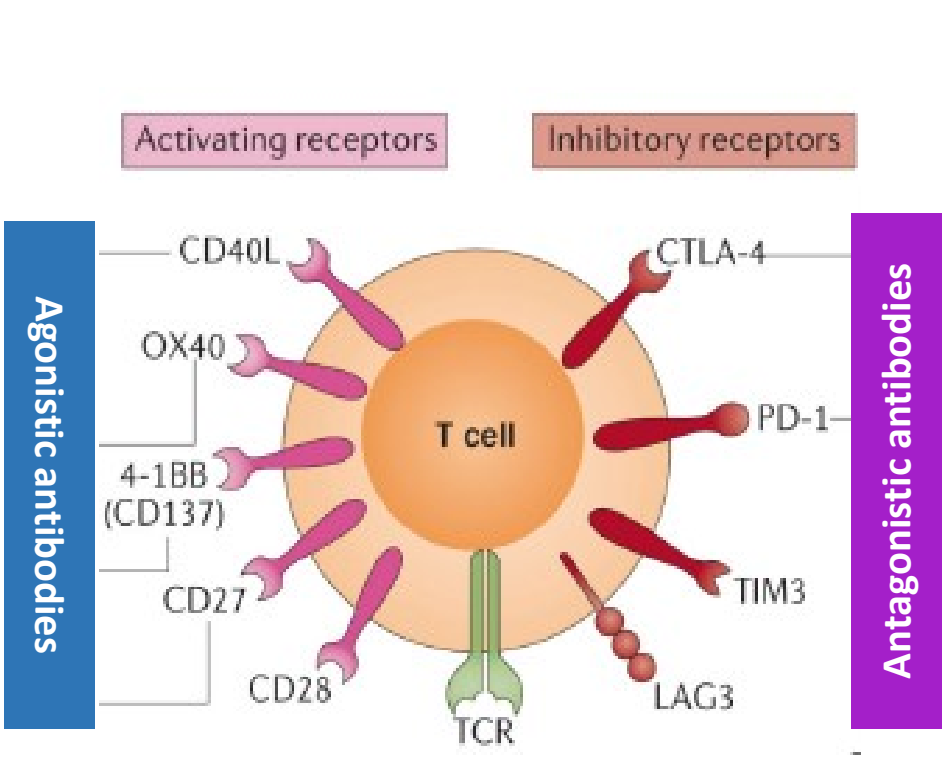
Younes A et al. J Clin Oncol 30: 2183-9, 2012.

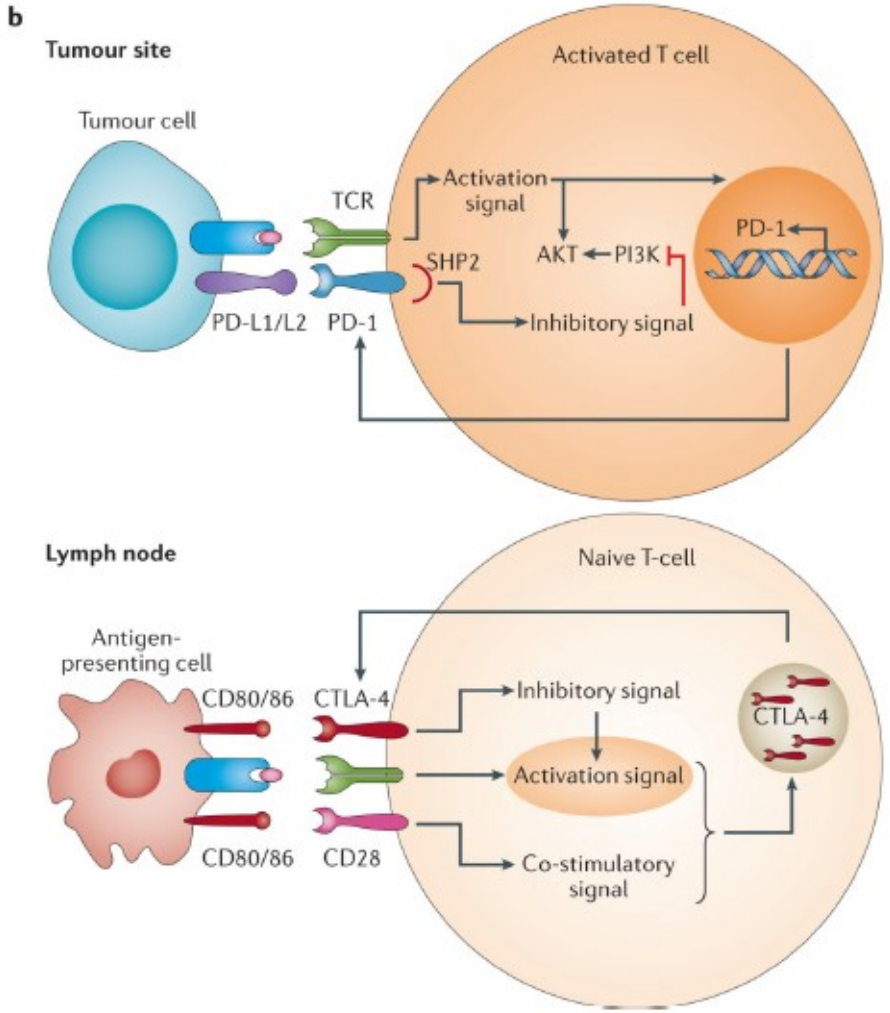
Mechanisms of action of immunotherapy modalities in B-cell malignancies



Batlevo CL et al. Nat Rev Clin Oncol 2016; 13: 25-40.

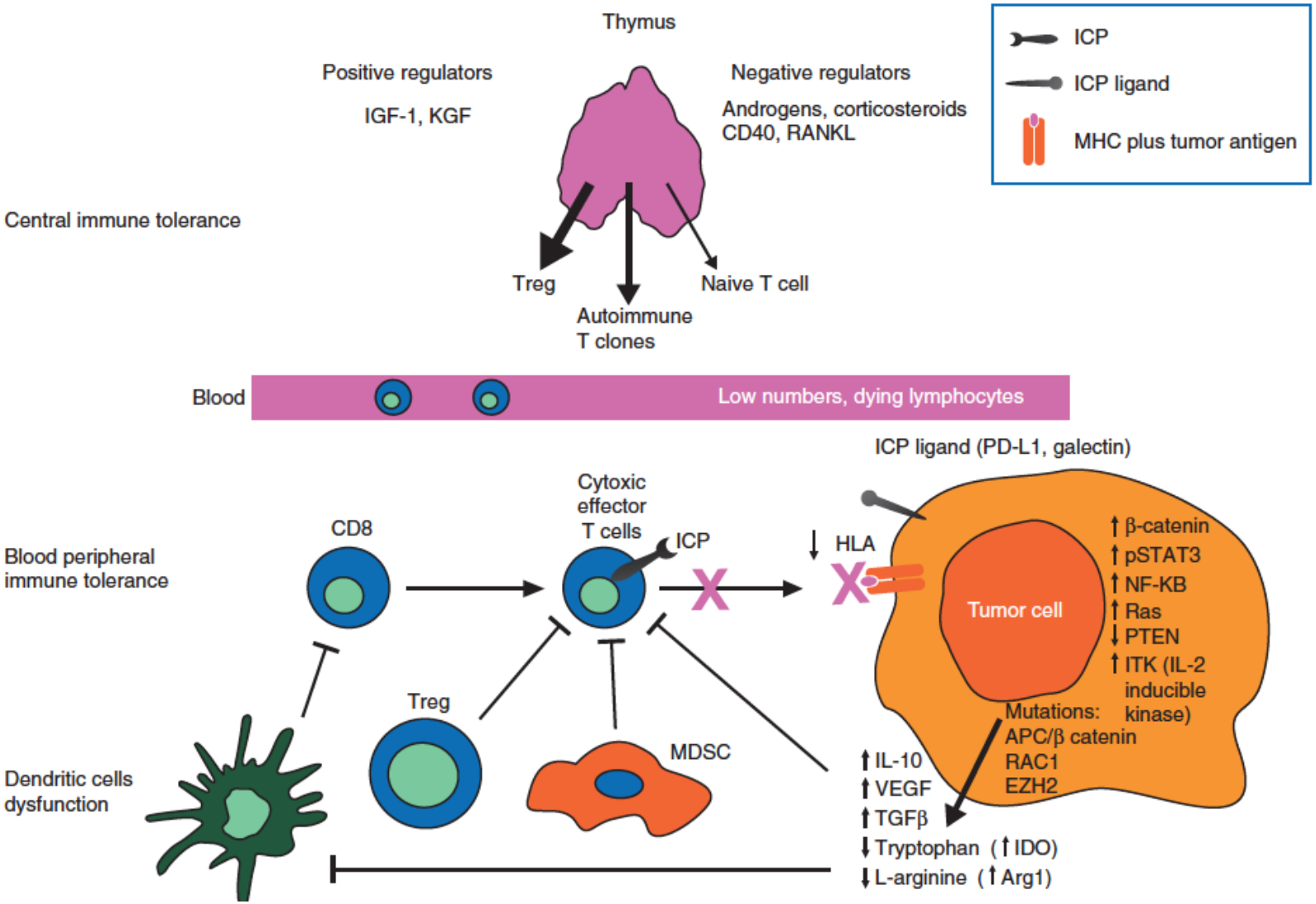
Immune-checkpoint blockade in Cancer treatment





Batlevo CL et al. Nat Rev Clin Oncol 2016; 13: 25-40.

Mechanisms of immune tolerance in lymphatic tissues and tumor microenvironment



ICP; Immune checkpoint protein

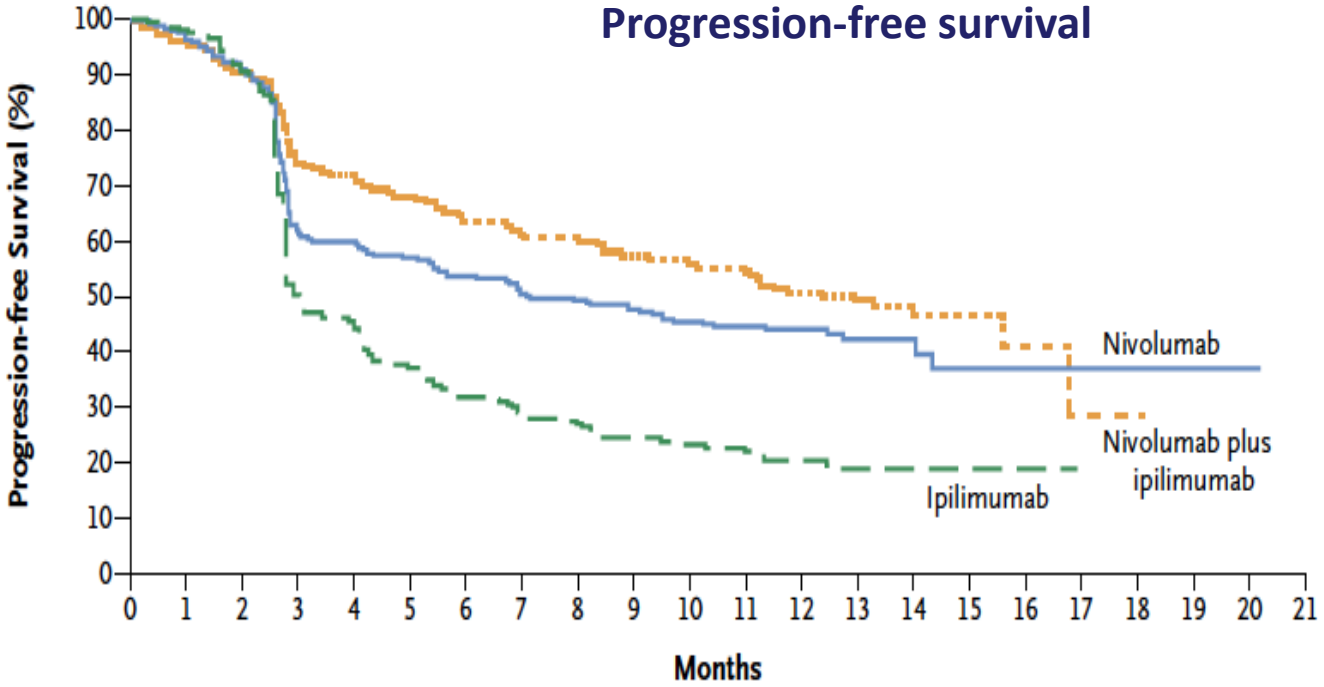
Salama AKS & Moschos SJ Ann Oncol 2017; 28: 57-74.

Combination strategy to overcome immune tolerance

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

A Intention-to-Treat Population

Progression-free survival



No. at Risk																						
Nivolumab	316	292	271	177	170	160	147	136	132	124	106	86	50	38	14	9	6	2	1	1	1	0
Nivolumab plus ipilimumab	314	293	275	219	208	191	173	164	163	151	137	116	65	54	18	11	7	2	1	0	0	0
Ipilimumab	315	285	265	137	118	95	77	68	63	54	47	42	24	17	7	4	3	0	0	0	0	0

Median PFS: 6.9mo vs 11.5mo vs 2.9mo in Nivo, Nivo plus Ipi and Ipi arm

Larkin JV, et al. N Engl J Med 2015; May 31

Rates of grade ¾ treatment-related AEs reported in trials of concurrent CTLA-4 and PD-1 pathway blockade

	Grade 3/4 AEs (%)
All treatment-related AEs	51–64
Colitis	4–17
Lipase increased	9–15
ALT increased	8–12
AST increased	6–11
Diarrhea	7–11
Rash	5–9
Amylase increased	≤6
Pyrexia	0–3
Fatigue	1–5
Dyspnea	≤3
Hypophysitis	≤2
Pneumonitis	≤2
Headache	≤2

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed death-1.

Immune-related AEs:

Spectrum of AEs with Ipi plus Nivo was similar to monotherapy,

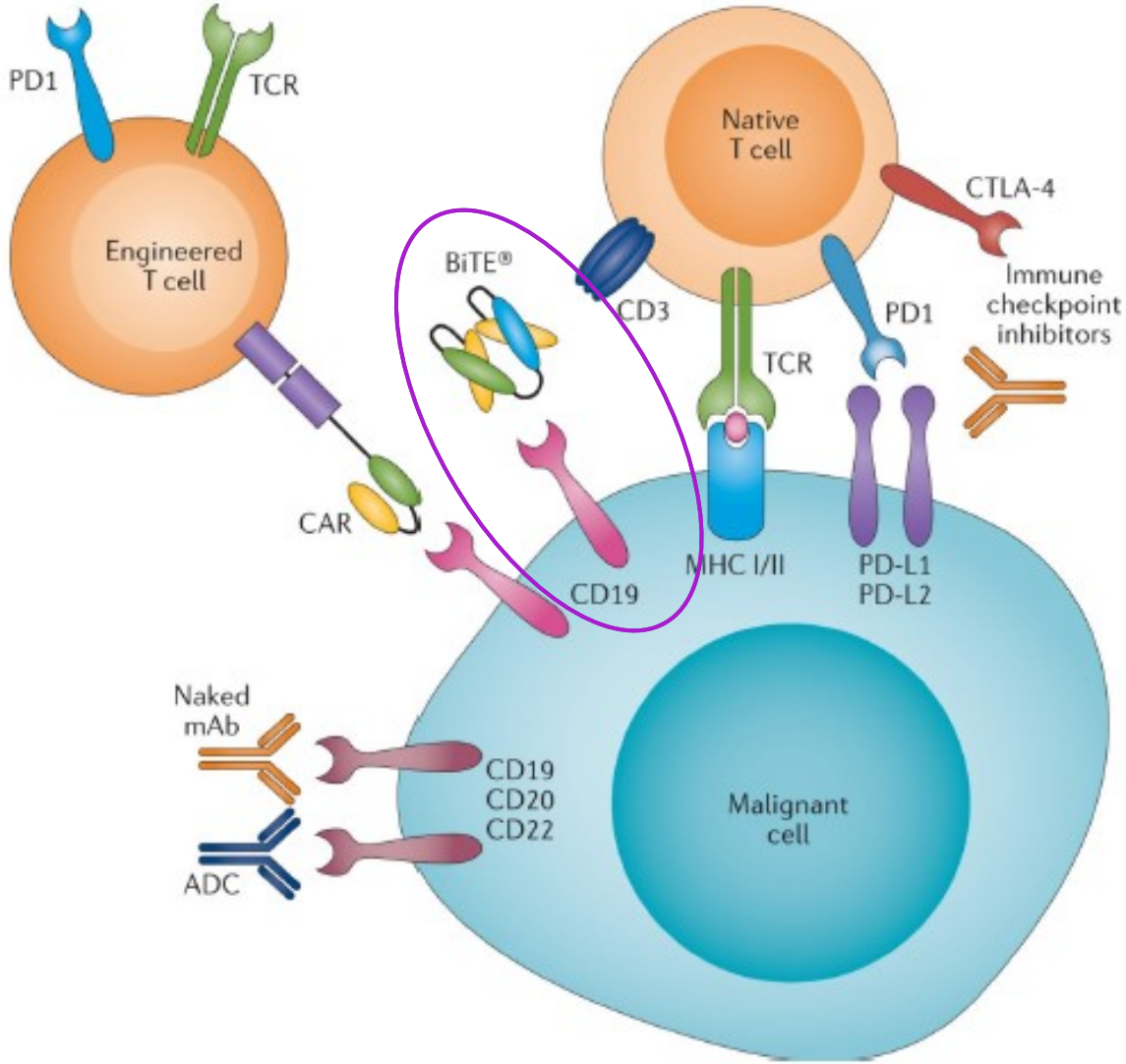
but

Incidence of serious AEs was higher in the Ipi plus Nivo arm compared with Monotherapy-treated patients.

irAE may occur early in the course of therapy with combination treatment.

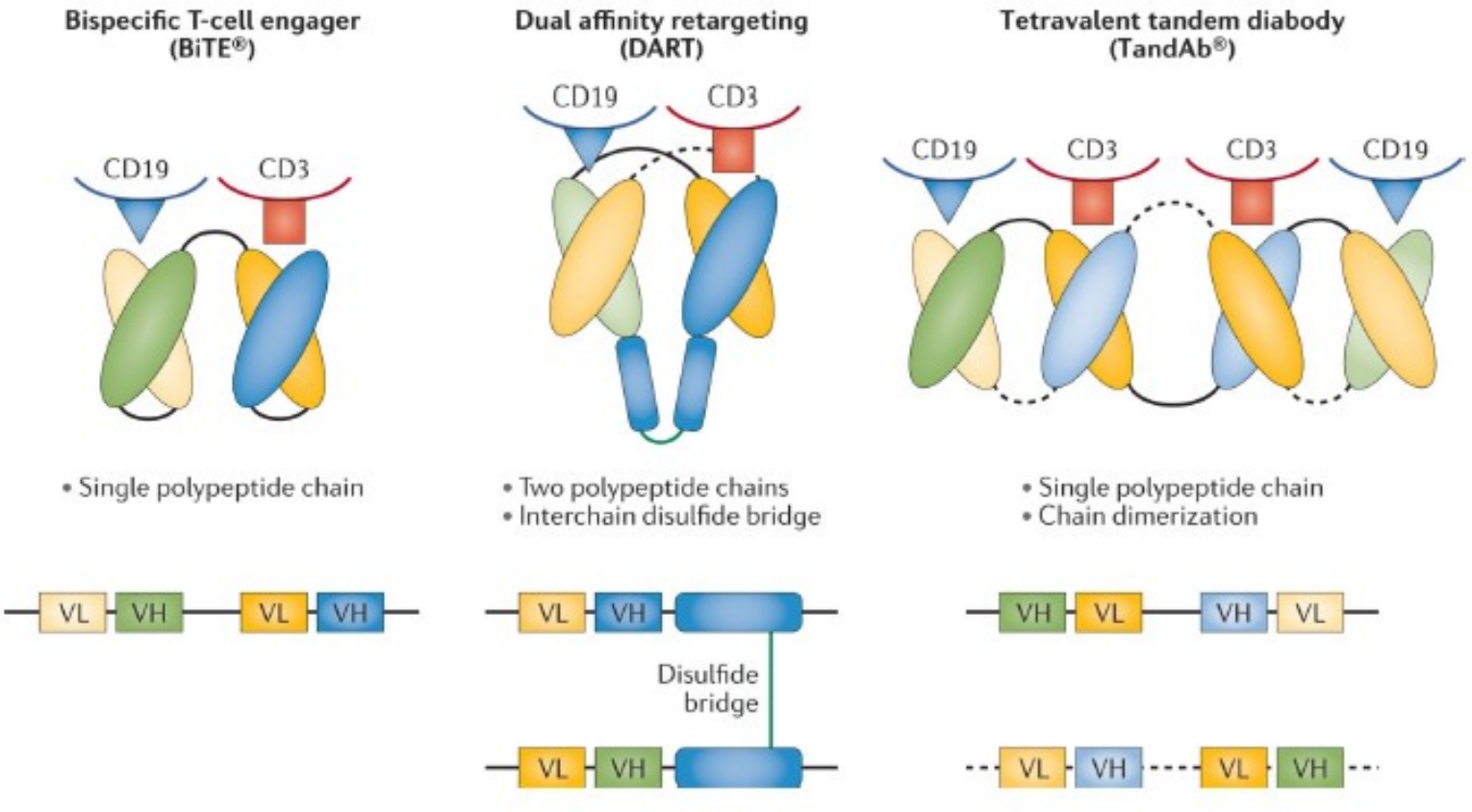
Salama AKS & Moschos SJ Ann Oncol 2017; 28: 57-74.

Mechanisms of action of immunotherapy modalities in B-cell malignancies



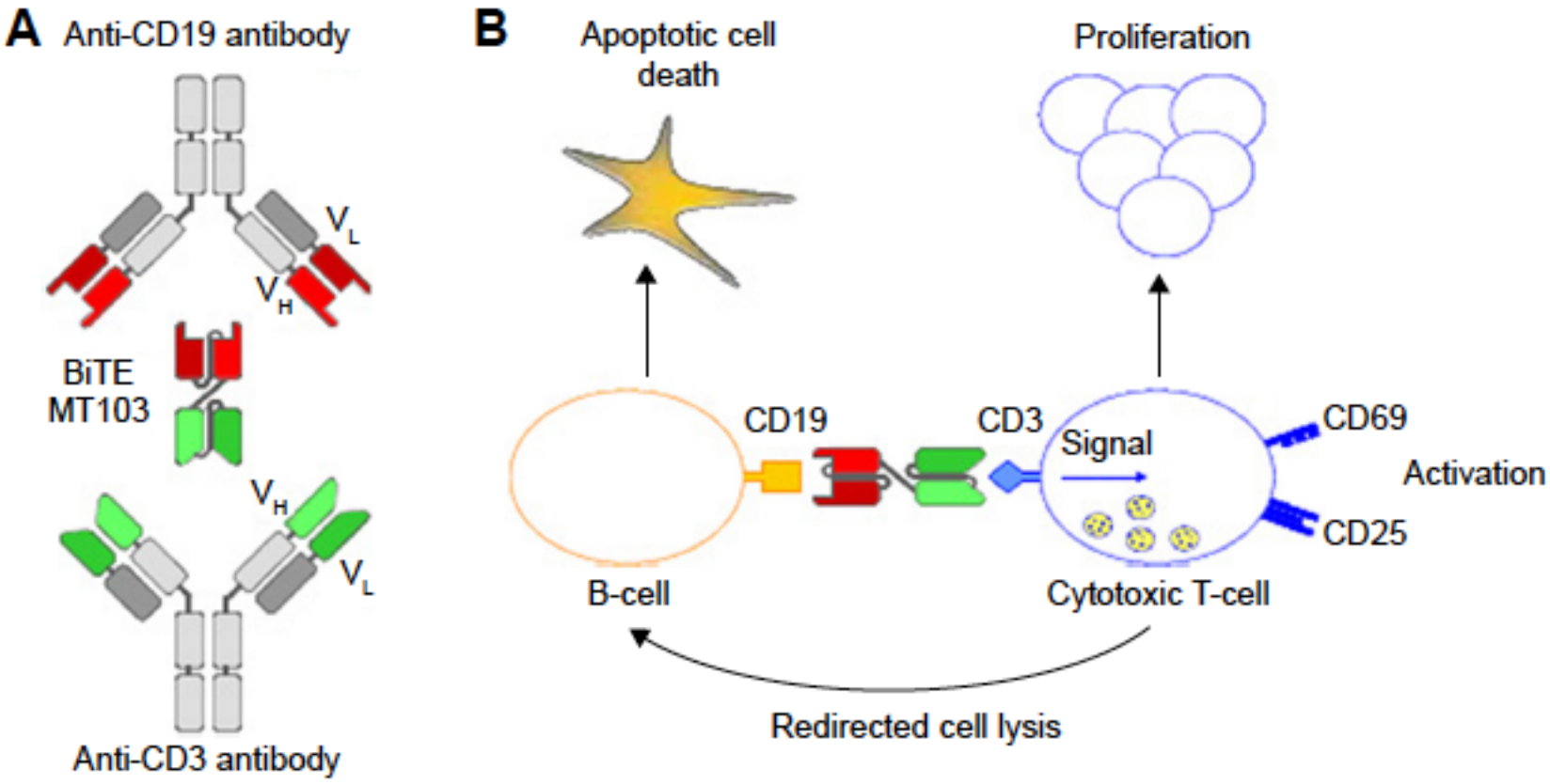
Batlevo CL et al. Nat Rev Clin Oncol 2016; 13: 25-40.

T-cell-engaging antibodies for cancer



Batlevo CL et al. Nat Rev Clin Oncol 2016; 13: 25-40.

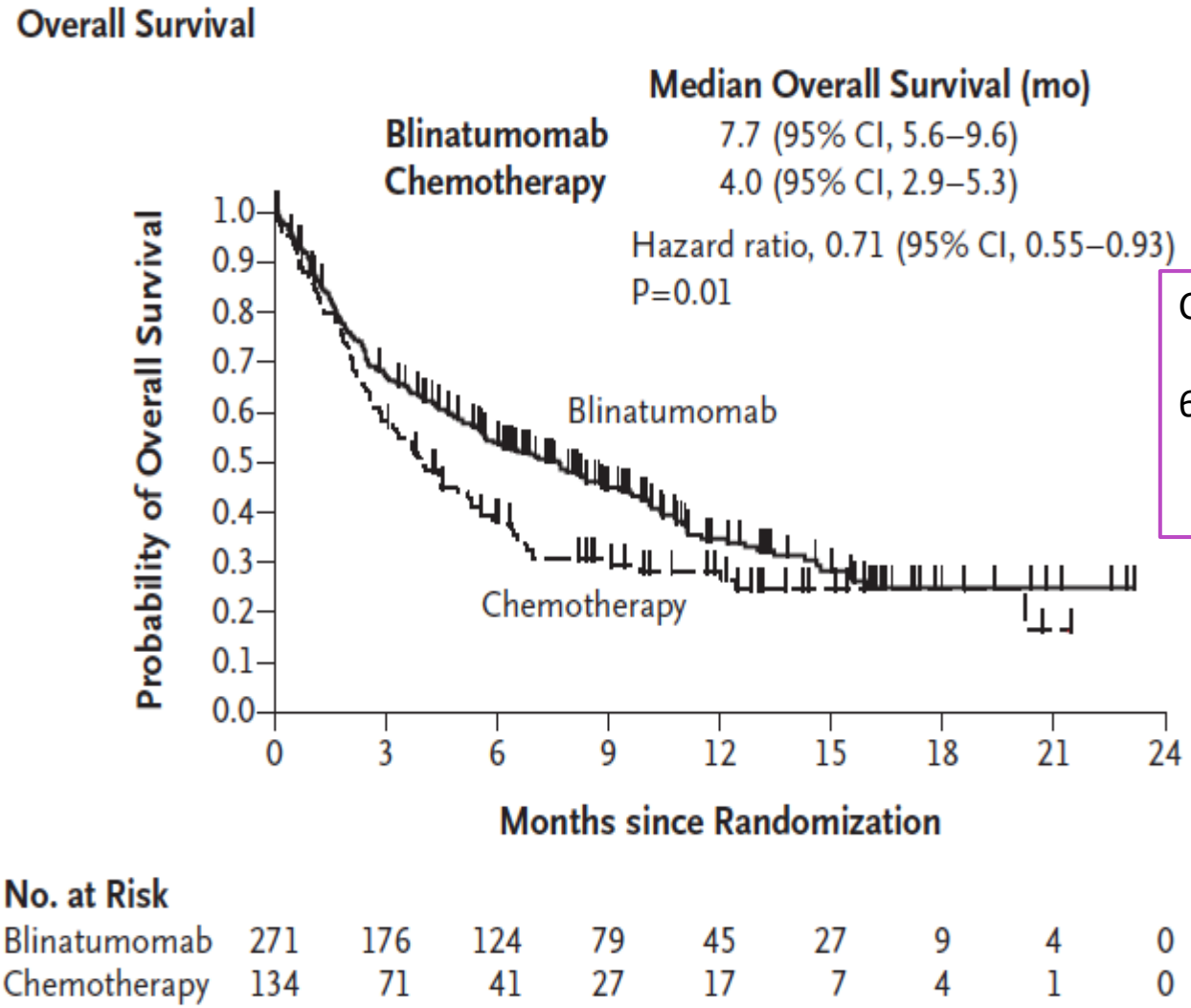
Bispecific T-cell engager (BiTE)



A. Generation, structure and B. mode of action of blinatumomab

Le Jeune C & Thomas X. Drug Design, Development and Therapy 2016;10:757-765.

Blinatumomab: Results of Randomized phase 3 study

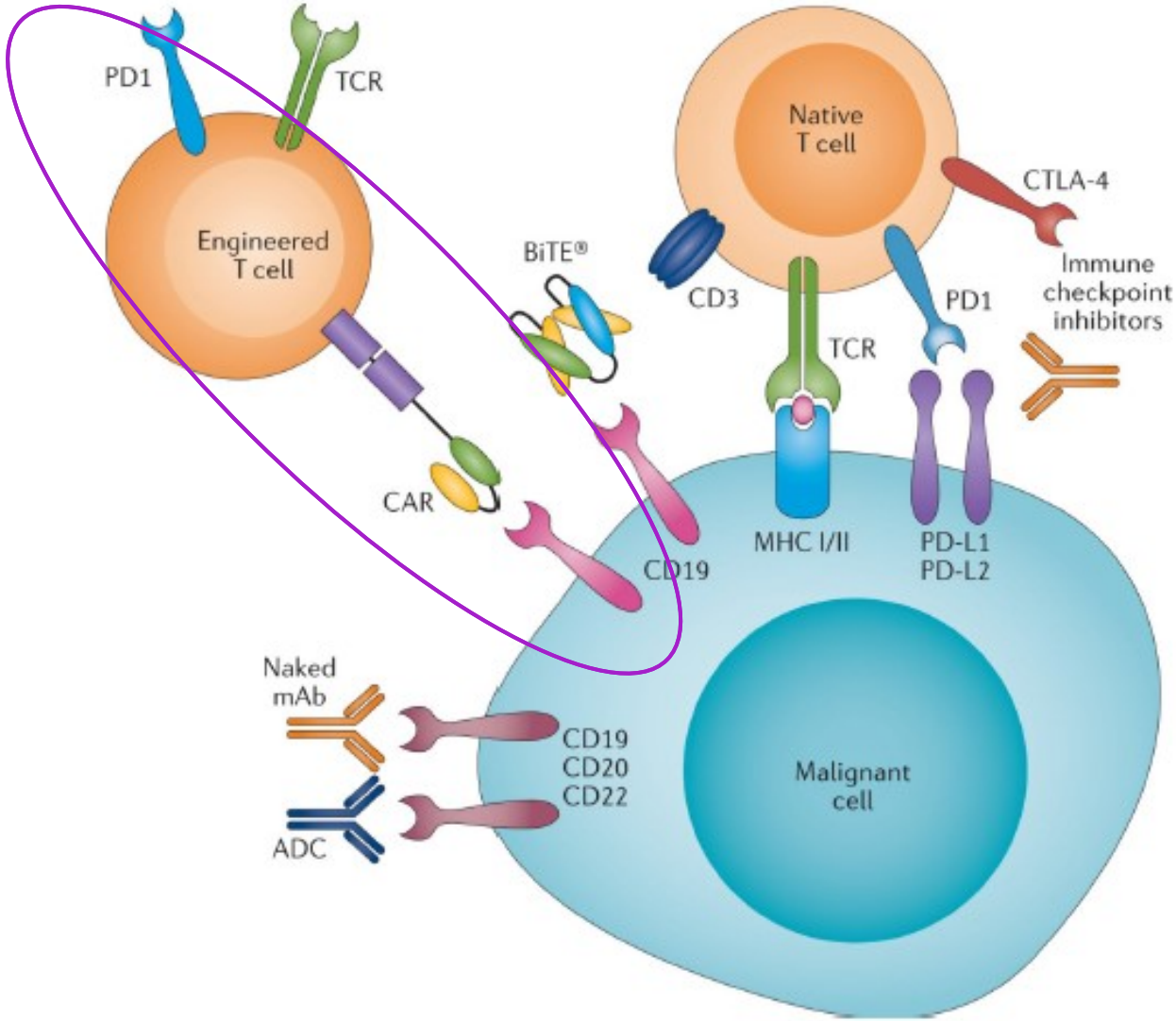


CR with full hematologic recovery:
34% vs 16%, P < 0.001

6-mo Event-free survival:
31% vs 12%, HR 0.55 (0.43-0.71)
P < 0.001

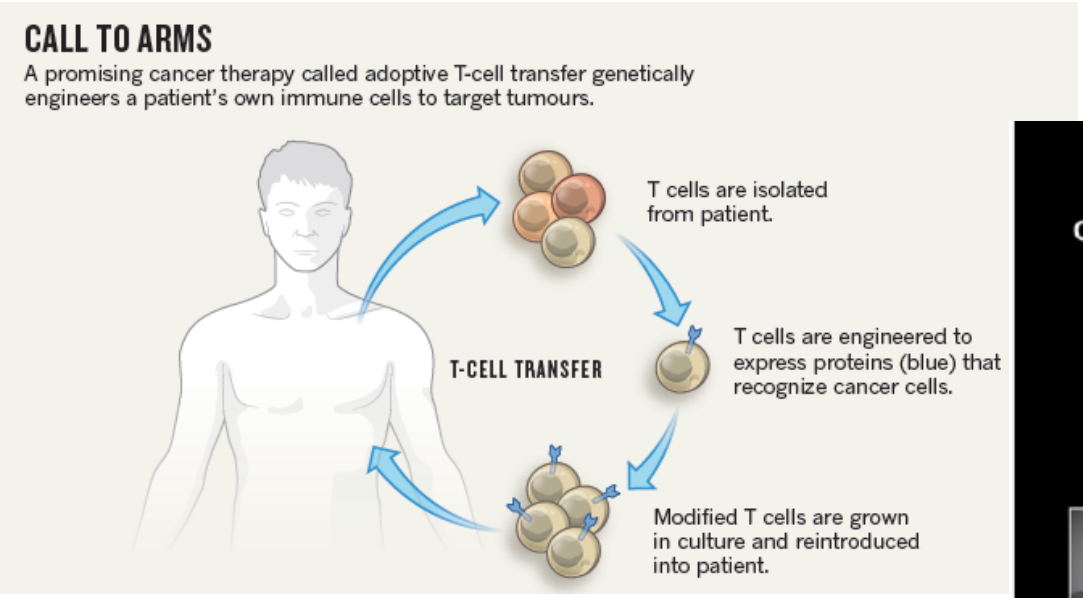
Kantarjian H et al. N Engl J Med 2017; 376: 836-847.

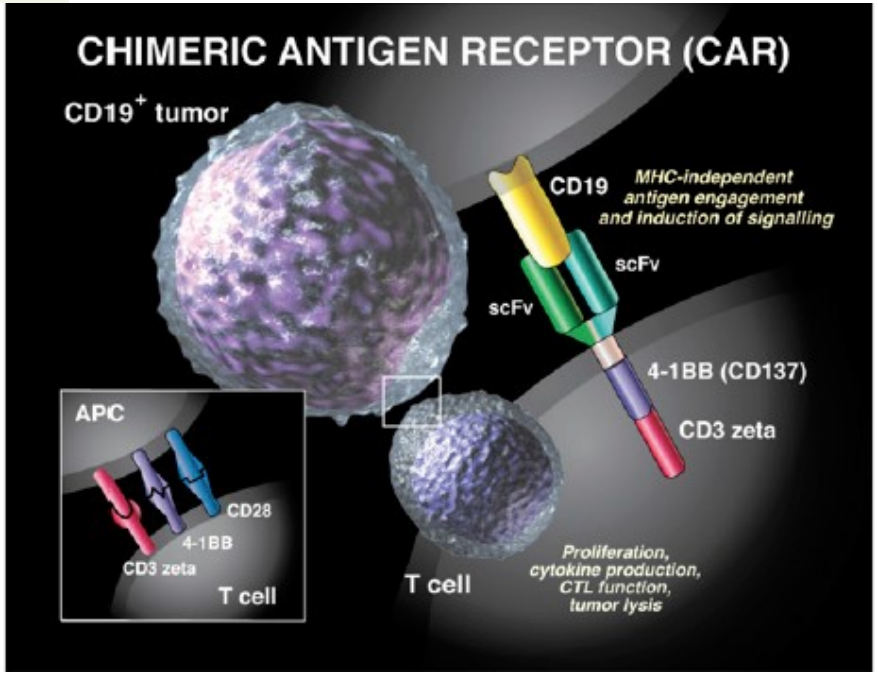
Mechanisms of action of immunotherapy modalities in B-cell malignancies

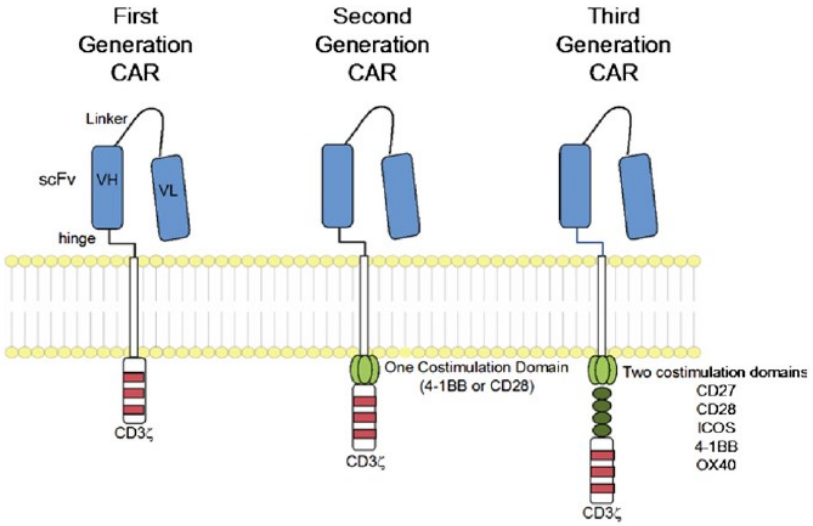


Batlevo CL et al. Nat Rev Clin Oncol 2016; 13: 25-40.

CAR-T therapy against CD19-positive lymphoid malignancies

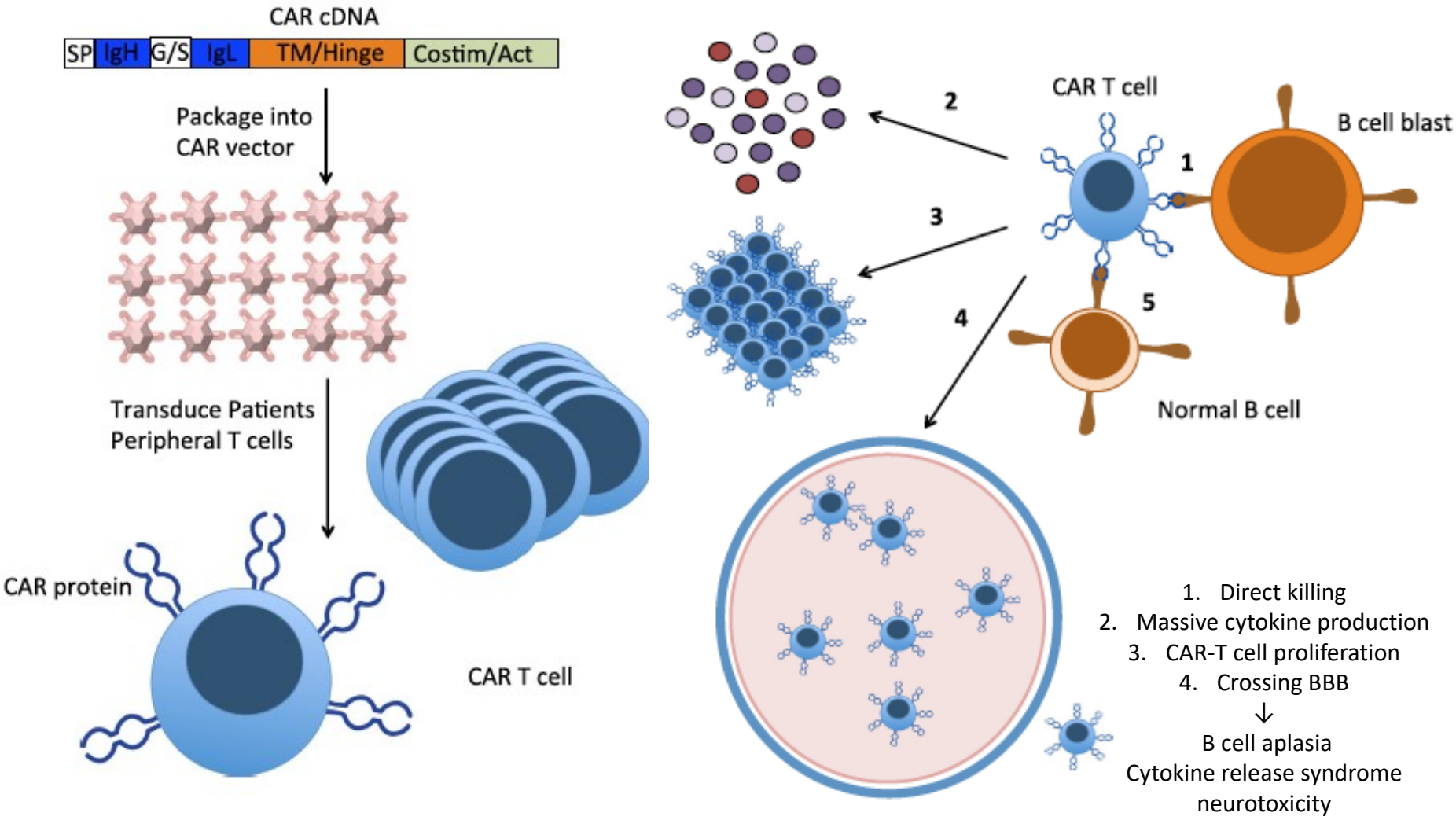






Ledford H Nature 2014; 516: 156.
Maude SL, et al. Blood 2015; 125: 4017-4023.

Biology and clinical application of CAR T cells for B-cell malignancies



Davila ML & Sadelain M Int J Hematol 2016; published online June 4

CD19-chimeric antigen receptor T-cell (CTL019) in DLBCL

N=15 (9 DLBCL, 2 indolent lymphoma, 4 CLL)

Conditioning regimen consisting of CPA of 120 or 60mg/kg and five day doses of Flu 25mg/m^2 *followed* by a single infusion of 1-5x10^6 CAR-T cells/kg

8/15: (53.3%) CR

4/7: DLBCL CR

4/15: PR

1/15: SD

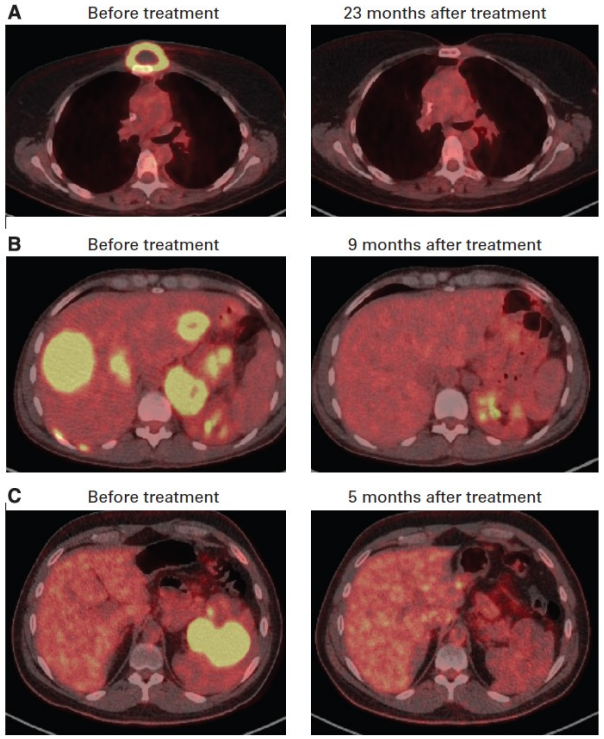
2/15: NA

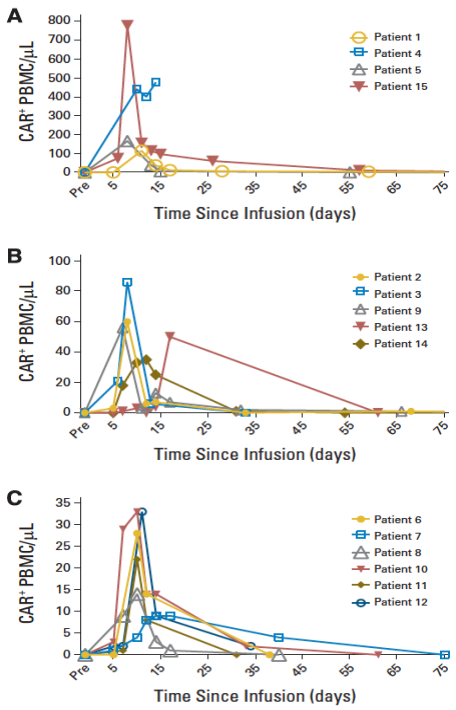
Toxicity:

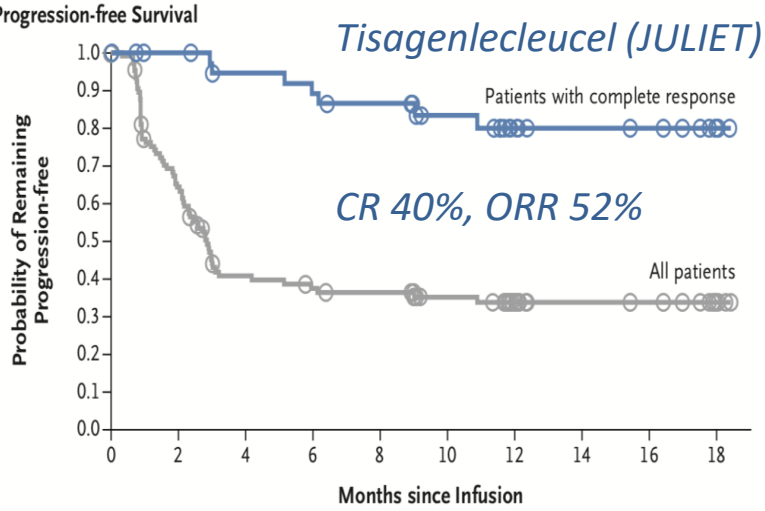
fevre, hypotension, delirium

Other neurological symptims

1 pt death 16 days after infusion







Kochenderfer JN et al. J Clin Oncol 2014; 33: 540-9.; Shuster SJ et al. NEJM 2019; 380: 45-56.

Today's topics

- Effective combination of immune checkpoint inhibitor and way to overcome its resistance without augmenting immune-related adverse events
  - Speakers: Drs. Wada H and Ohue Y
- ADC technology can be applied to various cancer types?
  - Speakers: Drs. Nagai H, Agatsuma T and Bhadauria H
- Activation of effector T-cells by BiTE technology or transduction of CAR. What are the idealistic targets in cancer therapy and this type of approach can be applied to various tumors? --- Infrastructure in Japan
  - Speakers: Drs. Klinger M, Gilbert MJ and Hosen N

Thank you for your attention!

Department of Hematology and Oncology,
Nagoya City University Graduate School of Medical Sciences