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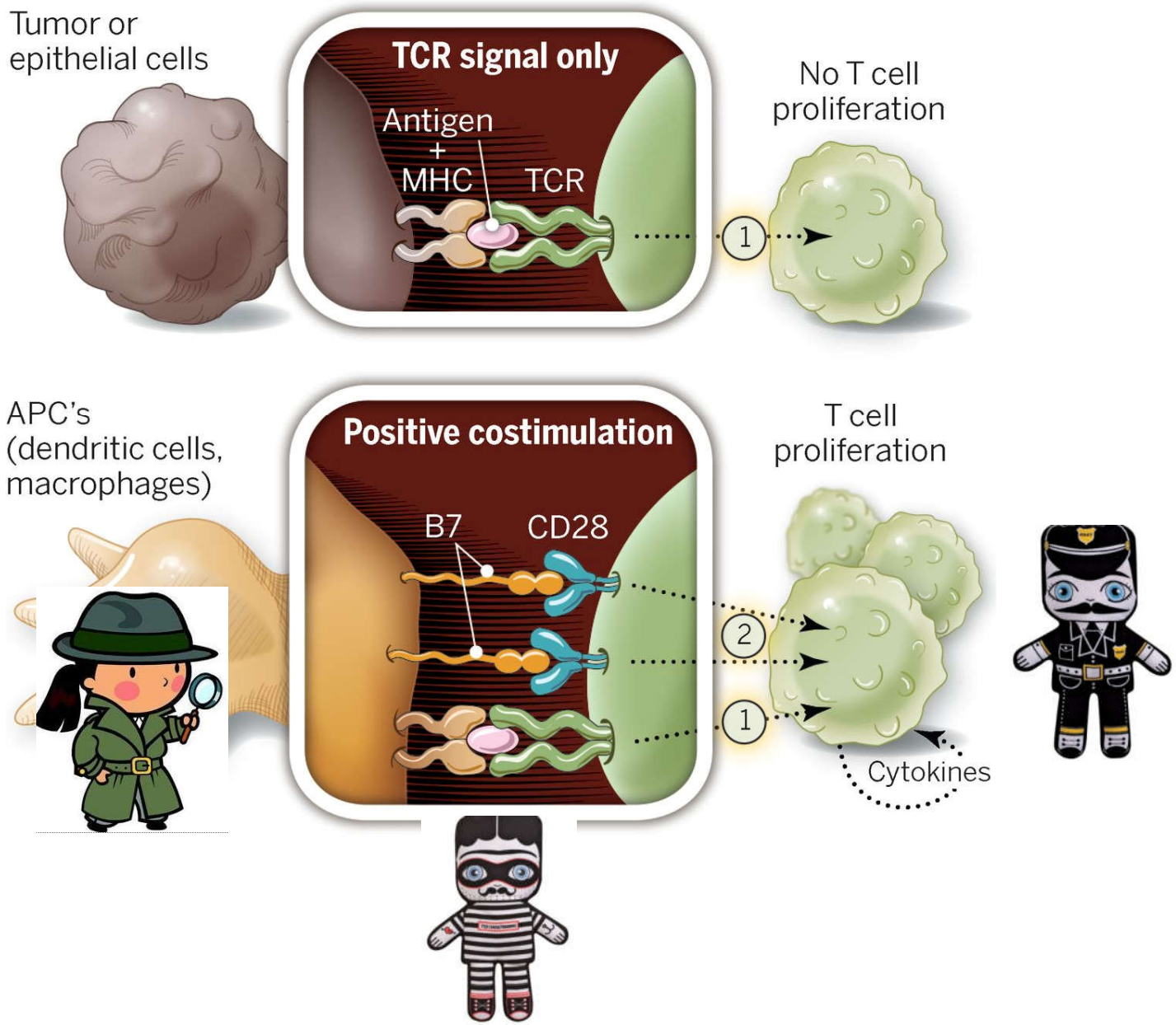
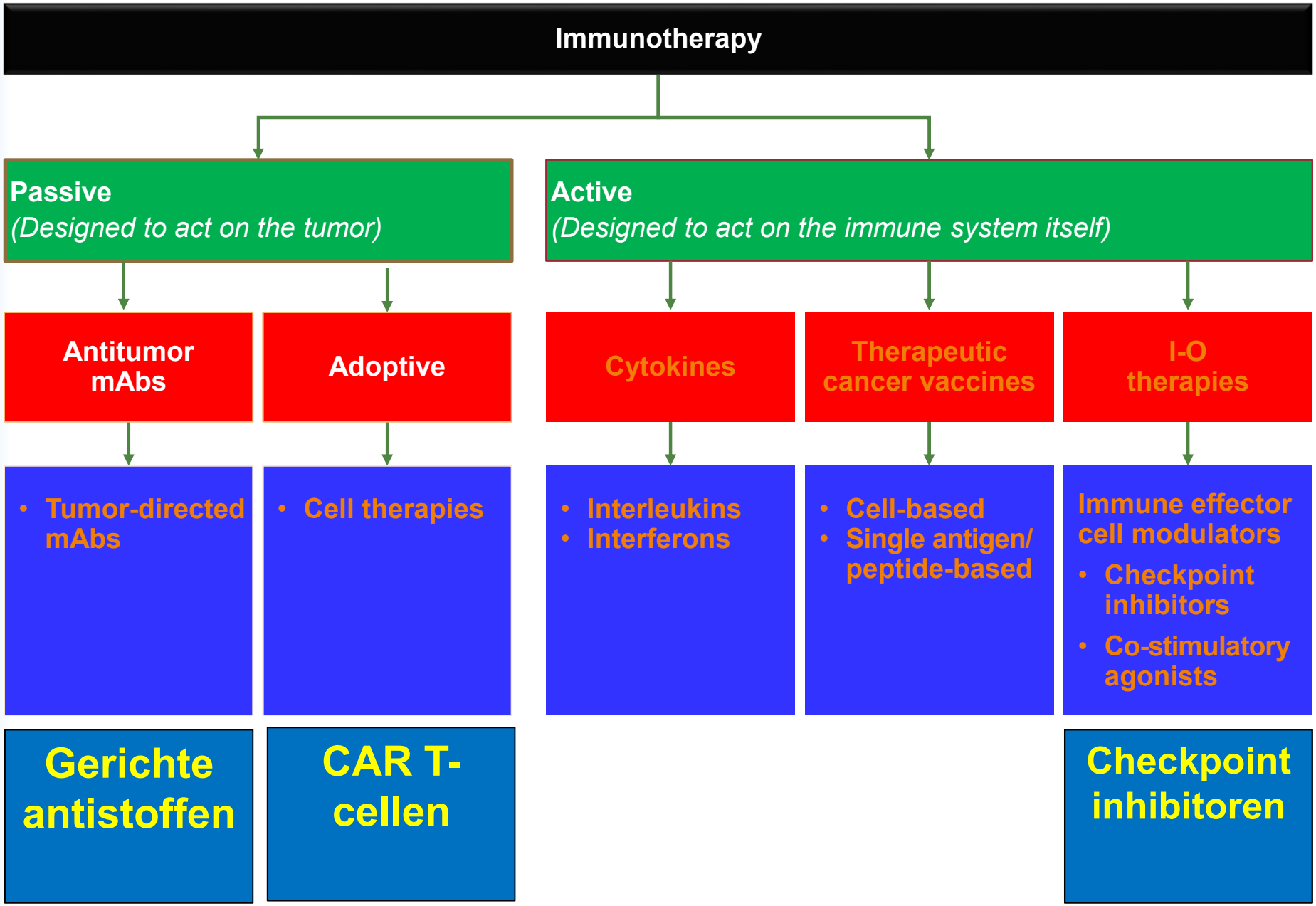


Sharma P, Allison JP. Science 2015;348:56-61

Onco-immunotherapie



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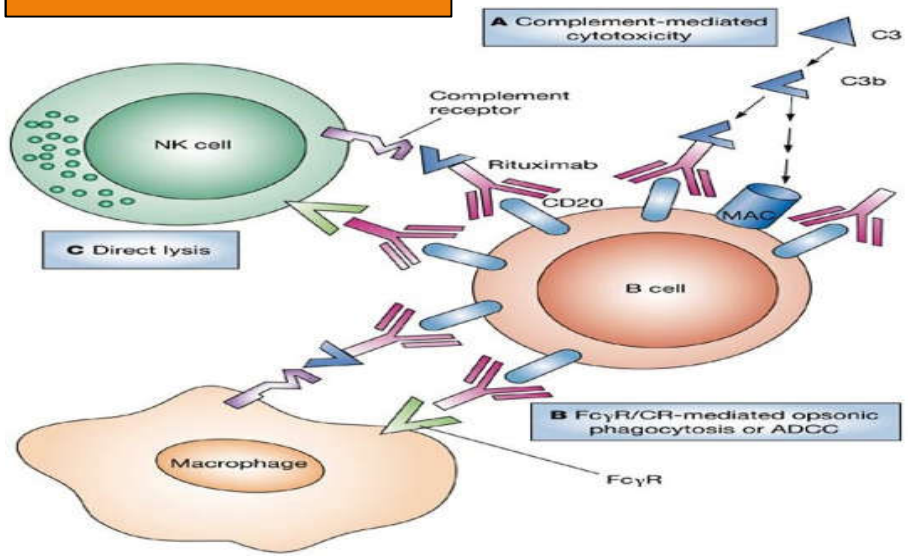

Taylor RP, Lindorfer MA. Nat Clin Practice Rheumatol 2007;3:86-95
Pouget JP, et al. Nat Rev Clin Oncol 2011;8:720-34
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Brown P. Blood 2018;131:1497-8

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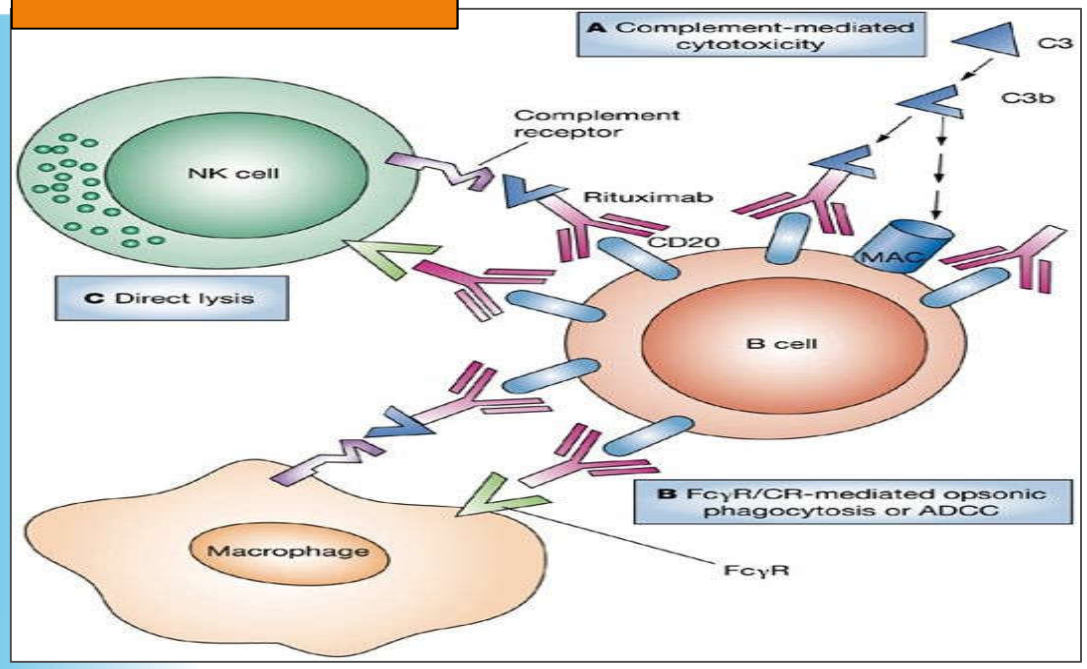

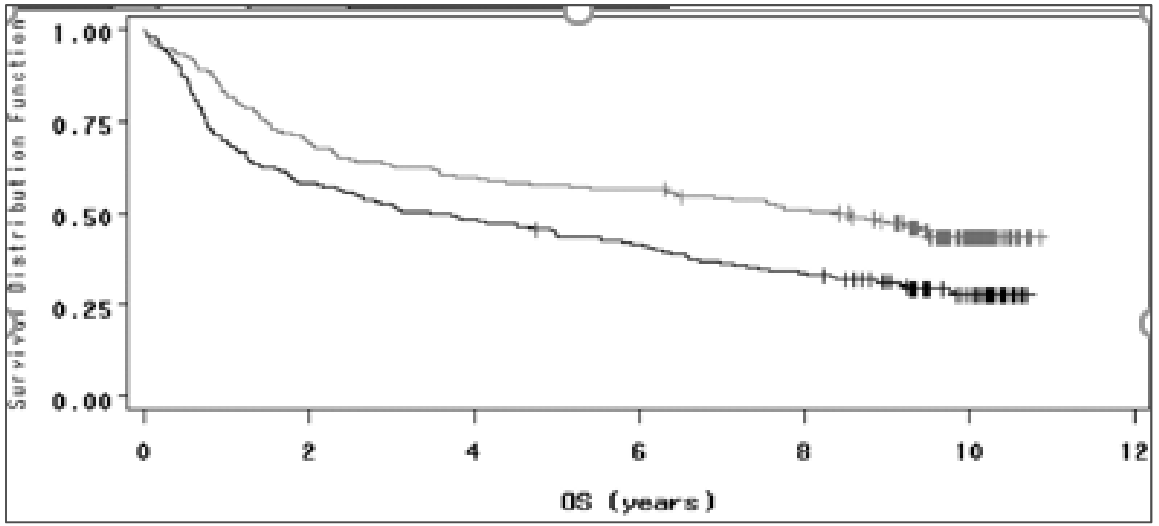

Taylor RP, Lindorfer MA. Nat Clin Practice Rheumatol 2007;3:86-95
Coiffier B, et al. Blood 2010;116:2040-5

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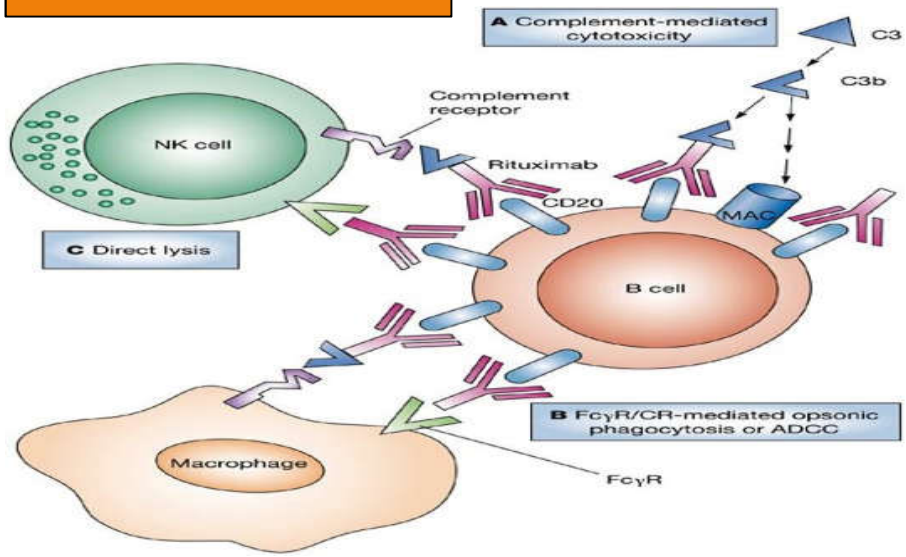

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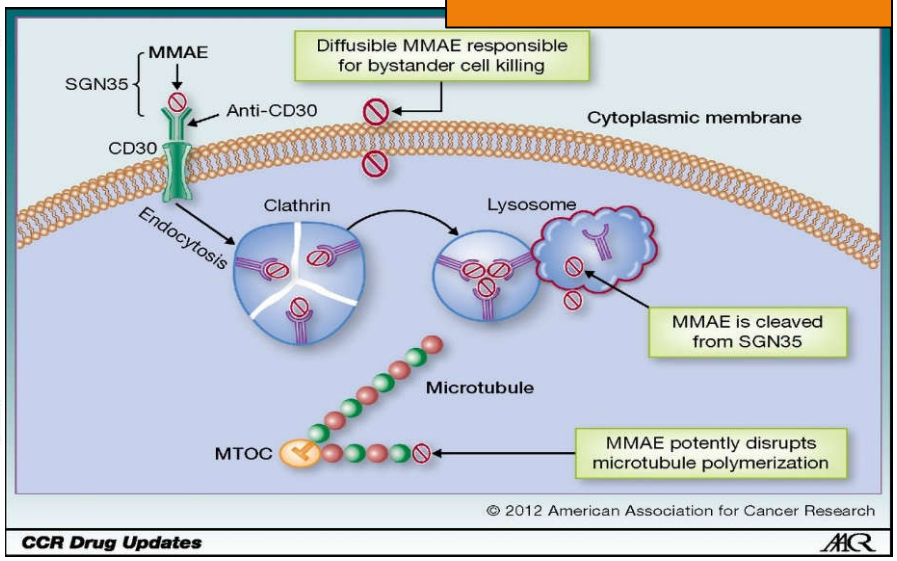

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Brown P. Blood 2018;131:1497-8

Gerichte antistoffen

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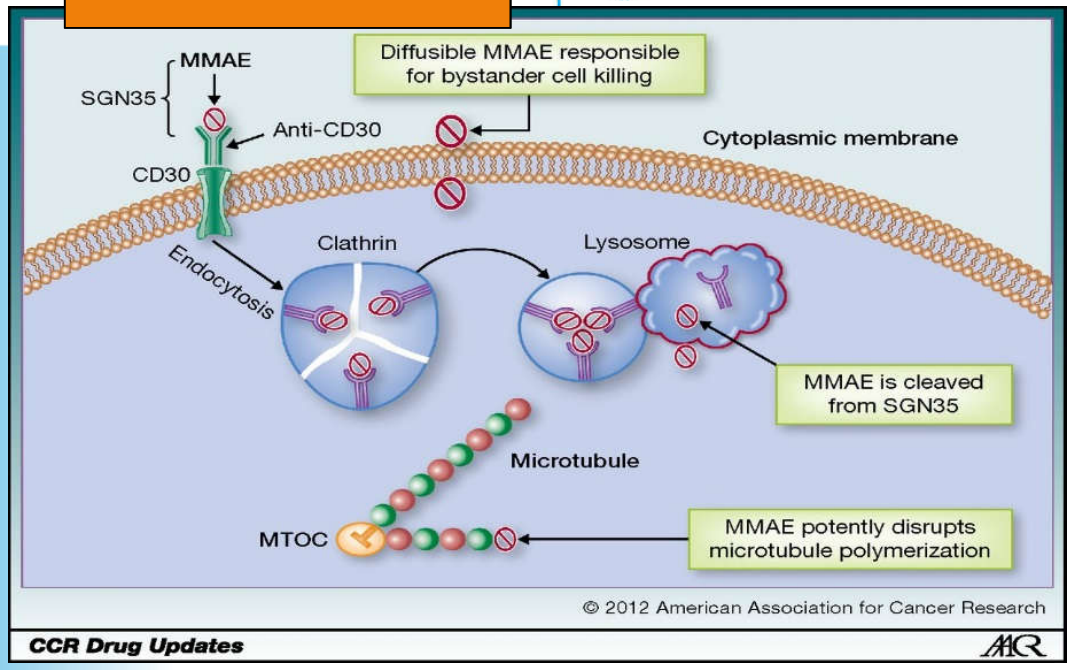

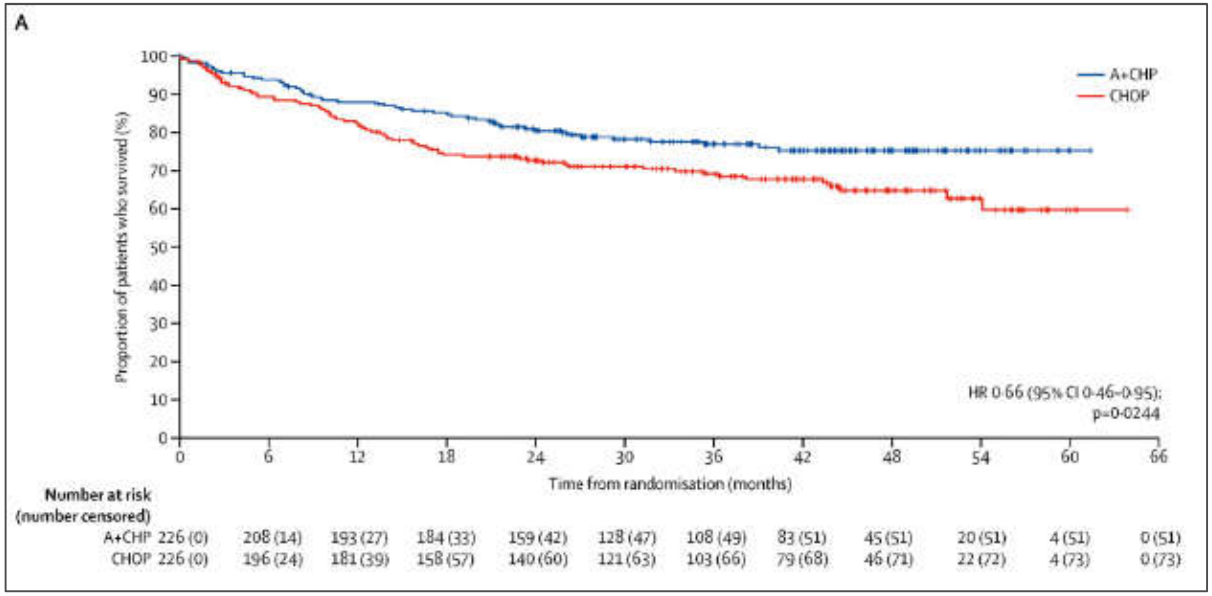

Deng C, et al. Clin Cancer Res 2012;19:22-7
Horwitz S, et al. Lancet 2019;393:229-40

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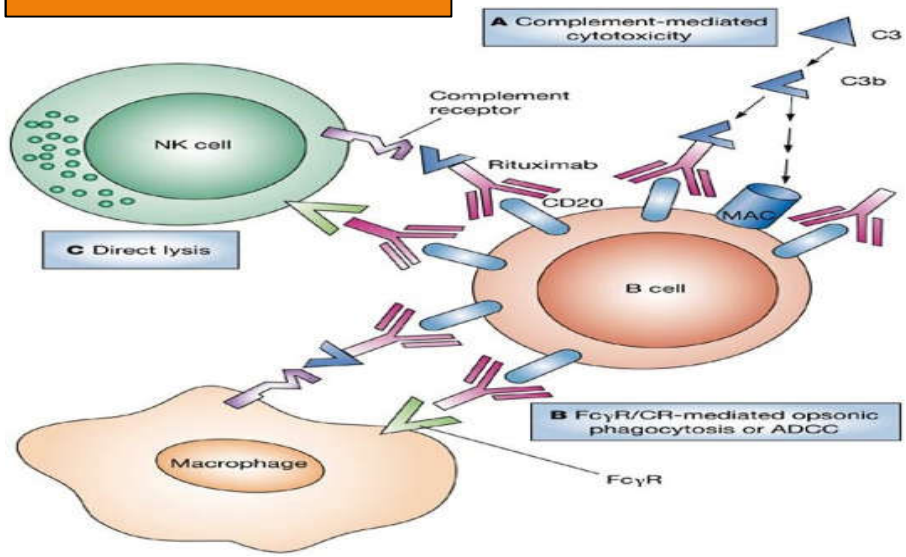

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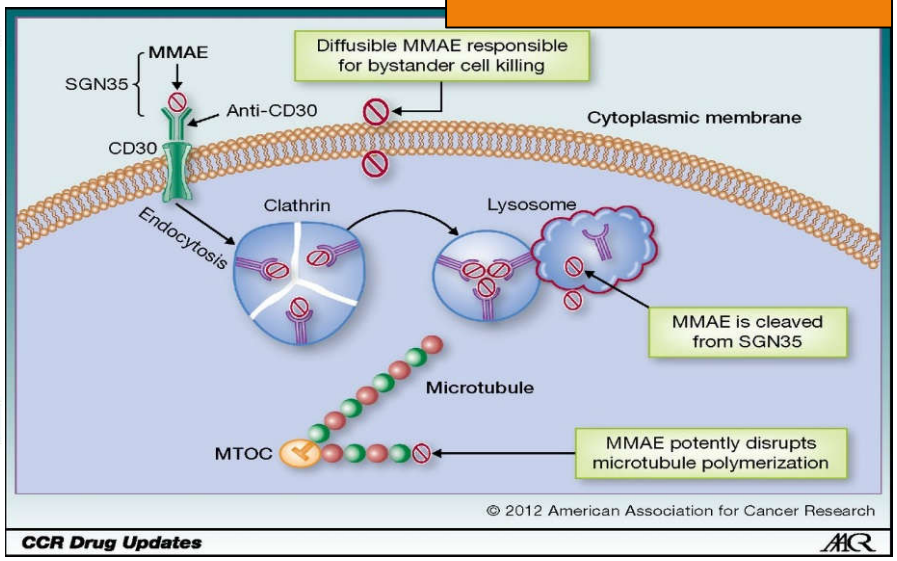

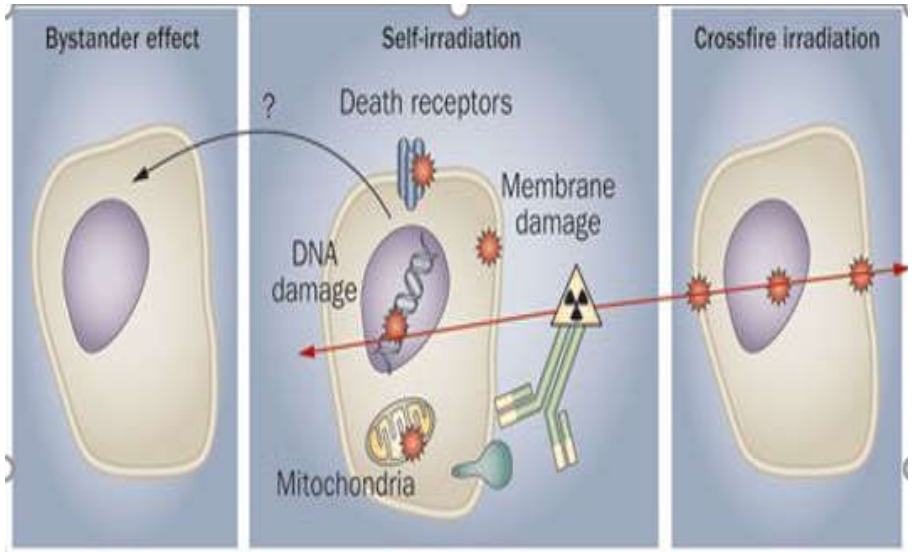

Radio-immuno

Taylor RP, Lindorfer MA. Nat Clin Practice Rheumatol 2007;3:86-95
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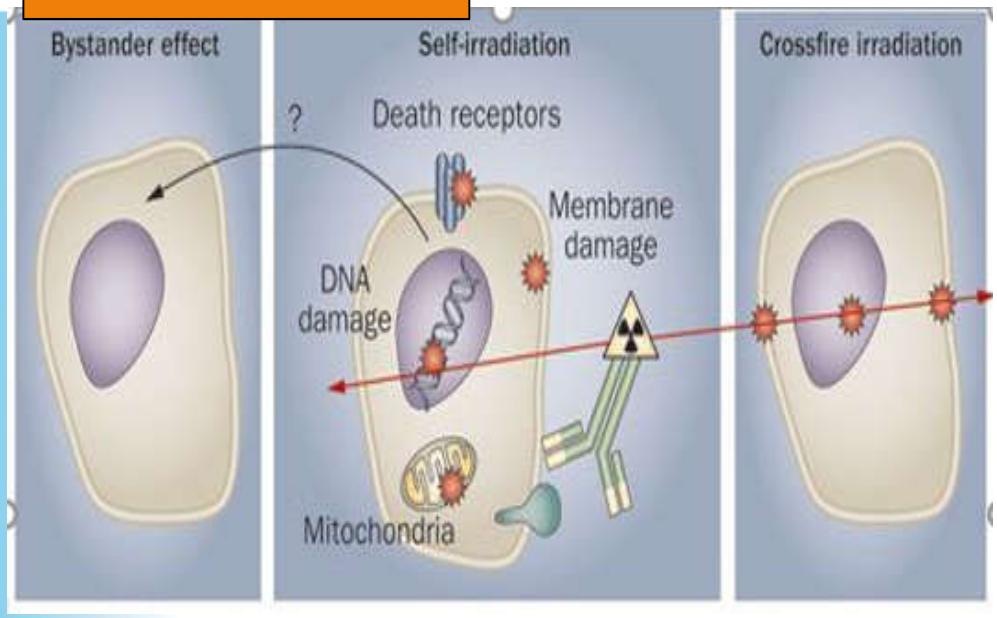
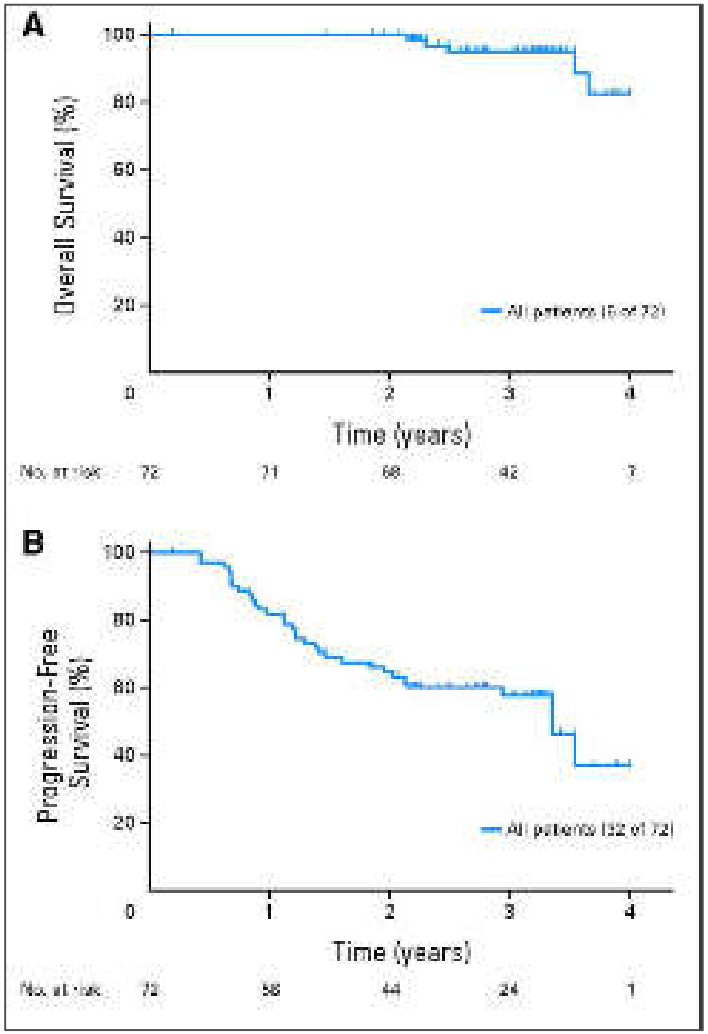
Gerichte antistoffen

Radio-immuno





Pouget JP, et al. Nat Rev Clin Oncol 2011;8:720-34
Illidge TM. J Clin Oncol 2014;32:212-8

Gerichte antistoffen

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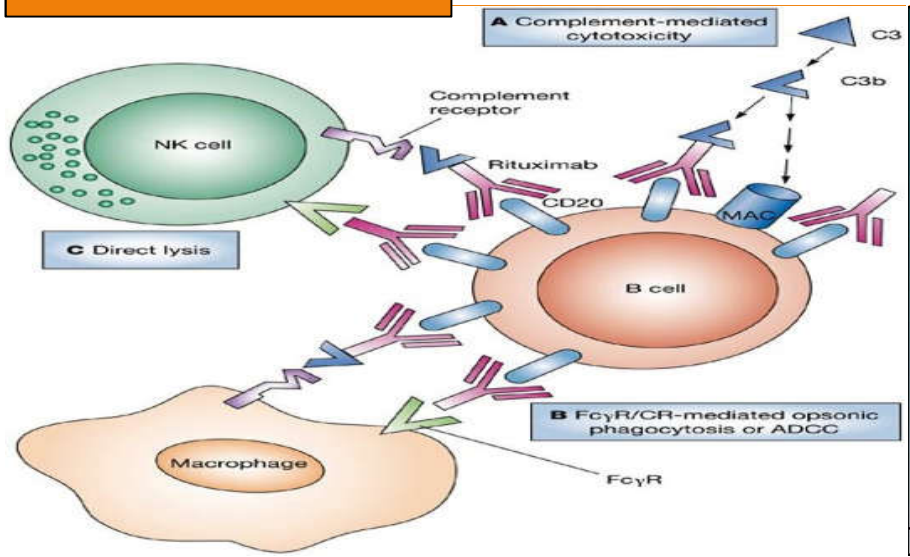
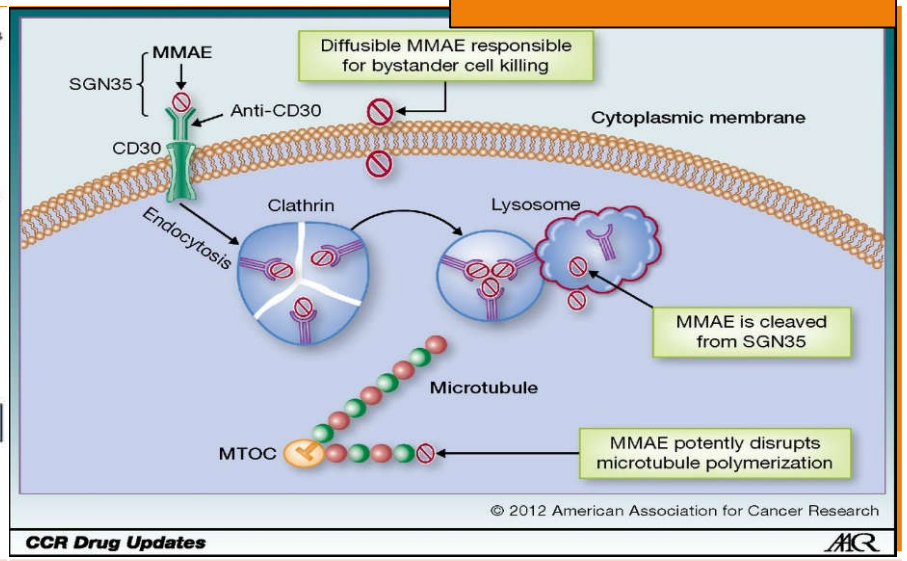
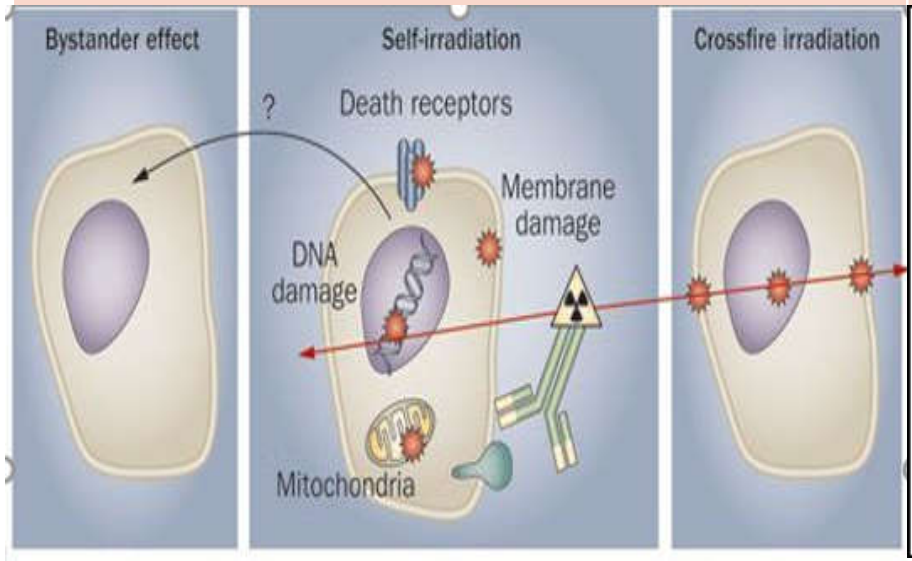
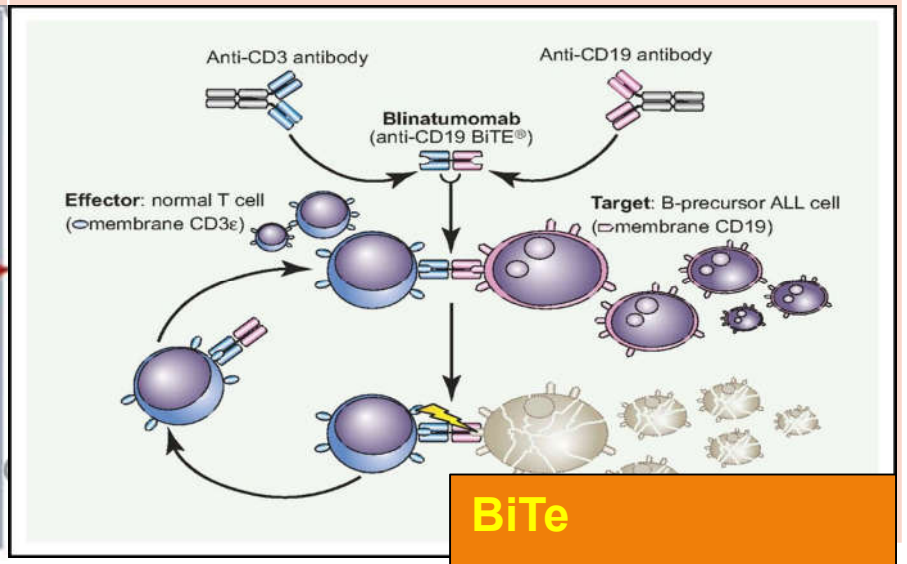


Antibody-drug





Radio-immuno



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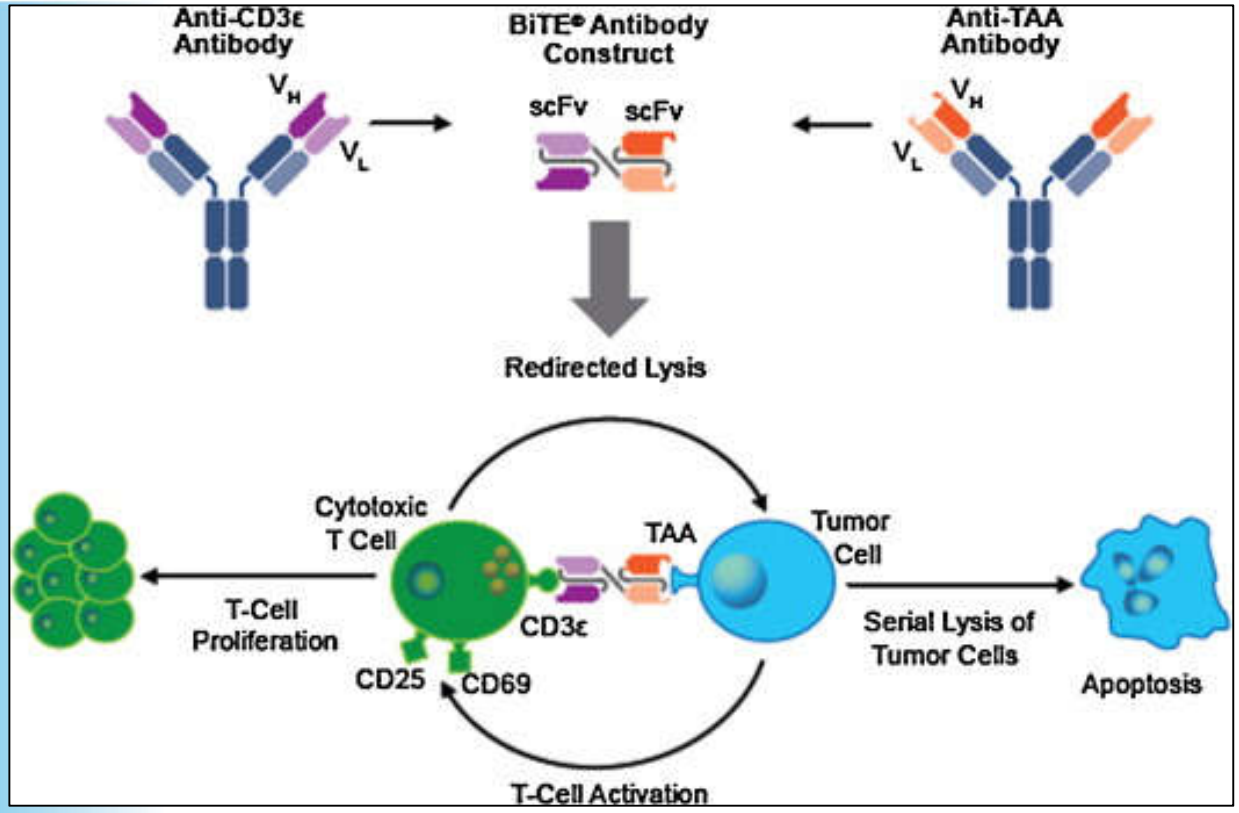

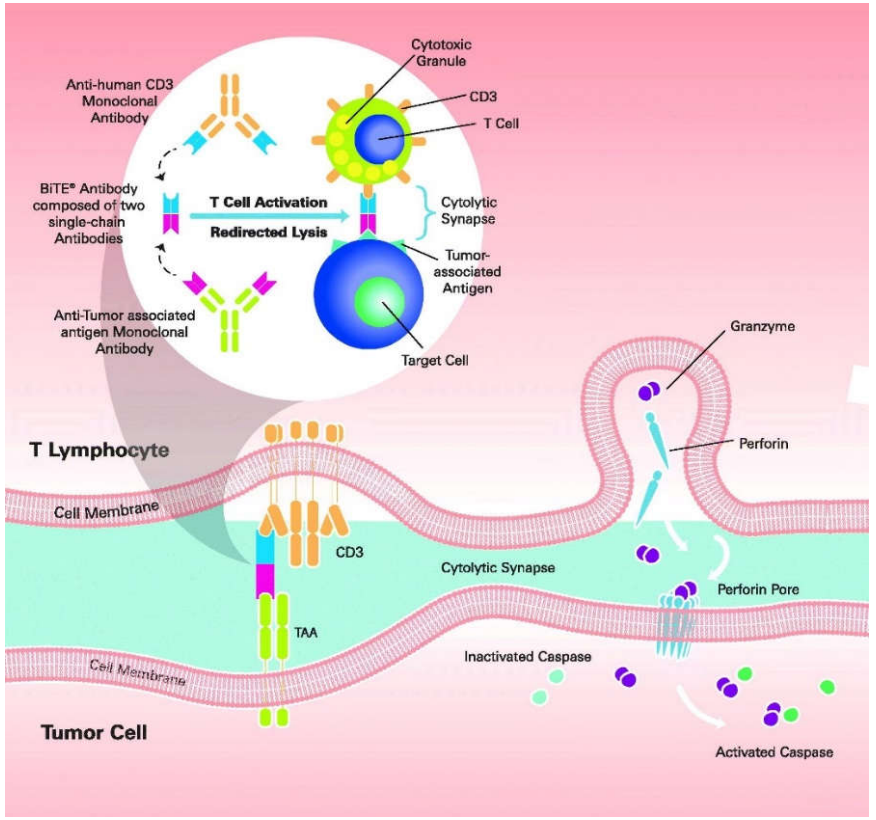

BiTe = Bispecfieke T-cel Engager

Zugmaier G, et al. Mol Immunol 2015;67:58-66
Goebeler ME, Bargou R. Leuk Lymphoma 2016;57:1021-32

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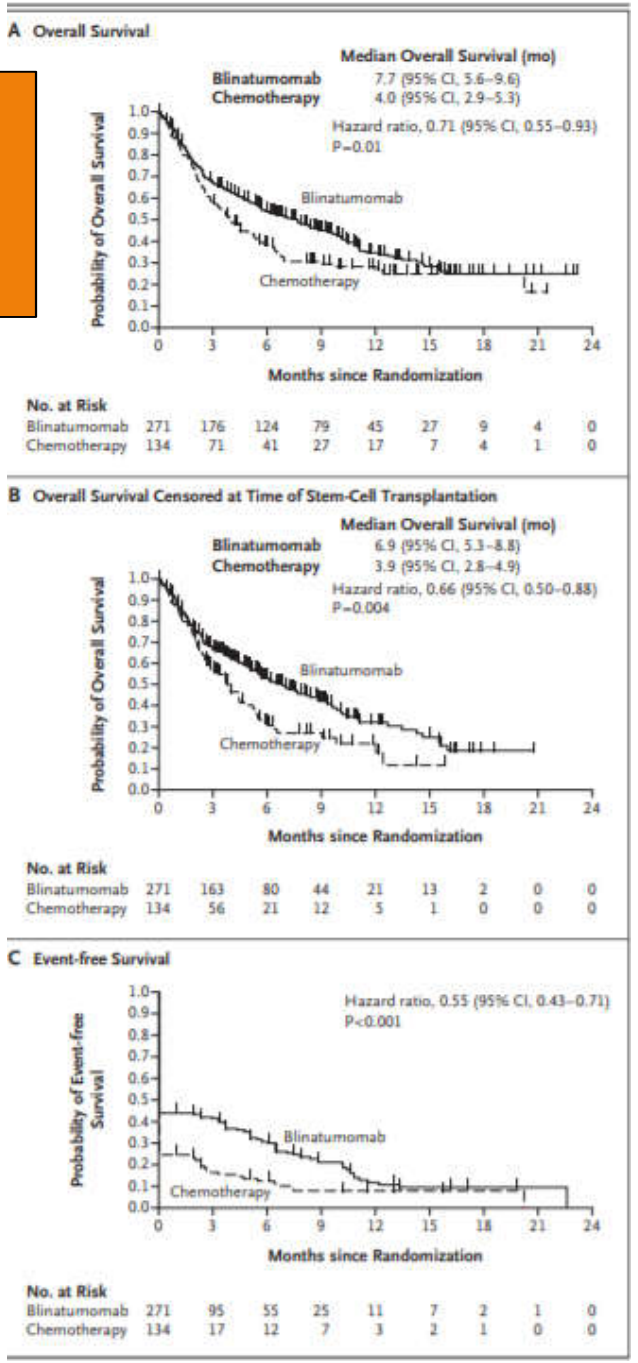
Tower trial [Blinatumomab]

Blinatumomab clinical trials.

Patient population, phase	Number of patients	Remission rate (CR/CRh)	MRD-negative rate among responders	Survival (median follow up)	Salvaged to transplant	Reference, ClinicalTrials.gov identifier
Adult MRD of B-precursor ALL, phase II	21	N/A	80%	RFS 65% (33 months)	50%	Topp *et al.* [2011, 2012], NCT00560794
Adult MRD of B-precursor ALL, phase II	116	N/A	80%	N/A	N/A	Goekbuget *et al.* [2014], NCT01207388
Adult R/R B-precursor ALL, phase I/II	36	69%	88%	OS 9.8 months (12.1 months); RFS 7.6 months (9.7 months)	52%	Topp *et al.* [2014], NCT01209286
Adult Ph- R/R B-precursor ALL, phase II	189	43%	82%	OS 6.1 months (9.8 months); RFS 5.9 months (8.9 months)	40%	Topp *et al.* [2015a], NCT01466179
Pediatric and adolescent R/R B-precursor ALL, phase I	41	32%	77%	OS 5.7 months; RFS 8.3 months (12.4 months)	69%	Von Stackelberg *et al.* [2014], NCT01471782
Pediatric and adolescent R/R B-precursor ALL, phase II	39	31%	42%	OS 4.3 months (6 months); RFS 5.6 months	50%	Gore *et al.* [2014], NCT01471782

ALL, acute lymphoblastic leukemia; CR, complete remission; CRh, complete remission with partial hematologic recovery; MRD, minimal residual disease; OS, overall survival; Ph, Philadelphia chromosome; RFS, relapse-free survival; R/R, relapsed/refractory.



Zugmaier G, et al. Mol Immunol 2015;67:58-66
Kantarjian H, et al. N Engl J Med 2017;376:836-47

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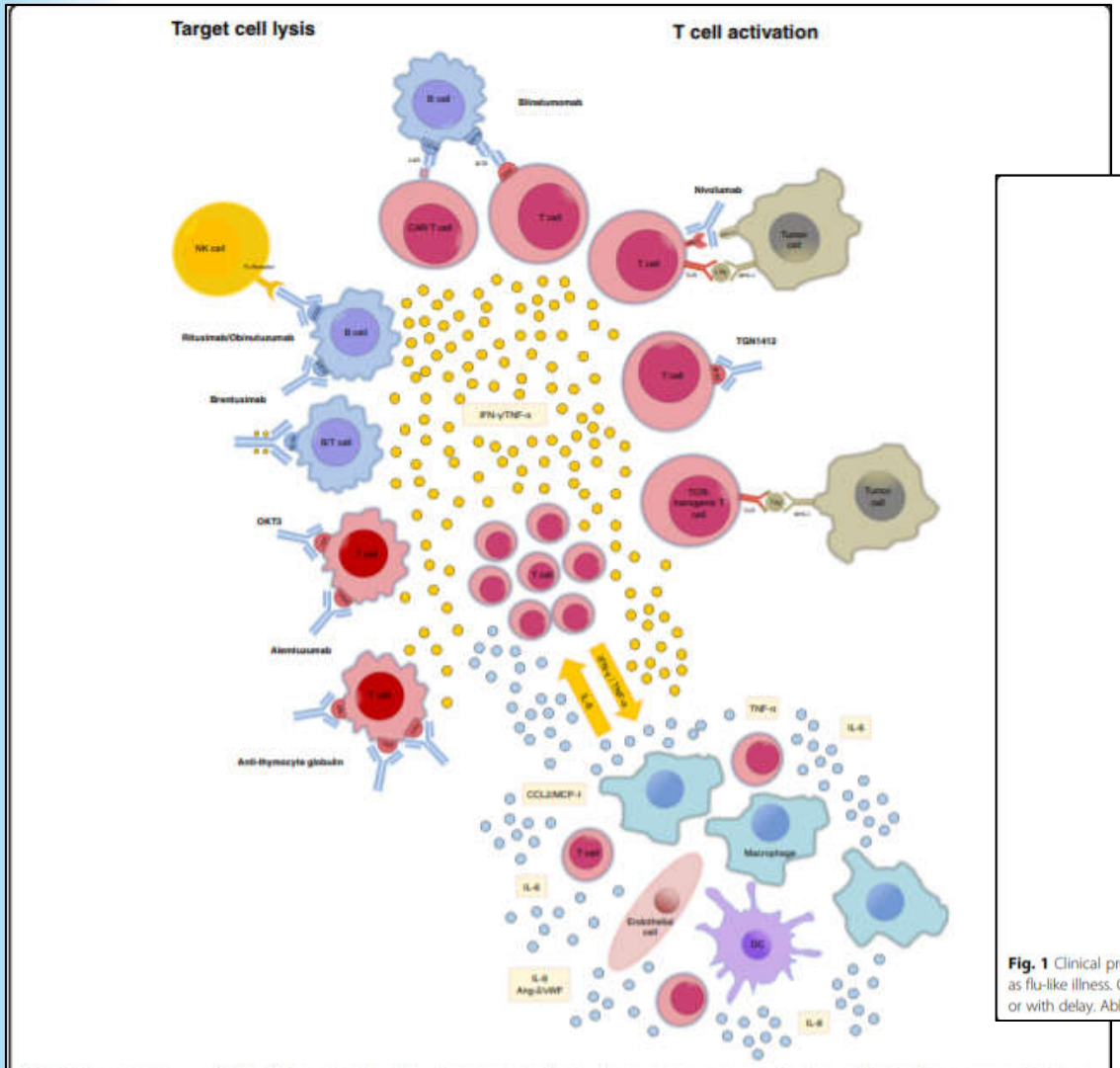

Fig. 2 Reported inducers of CRS. CRS can be induced by direct target cell lysis with consecutive release of cytokines like interferon gamma (IFN-γ) or tumor necrosis factor alpha (TNF-α) or by activation of T cells due to therapeutic stimuli with subsequent cytokine release. These cytokines trigger a chain reaction due to the activation of innate immune cells like macrophages and endothelial cells with further cytokine release. Abbreviations: Ang-2: Angiopoetin 2; CAR: chimeric antigen receptor; DC: dendritic cell; IFN-γ: interferon gamma; MHC-I: major histocompatibility complex I;NK cell: natural killer cell; PD-(L)1: programmed cell death protein (ligand) 1; TCR: T cell receptor.; TNF-α: tumor necrosis factor alpha; vWF: von Willebrand factor

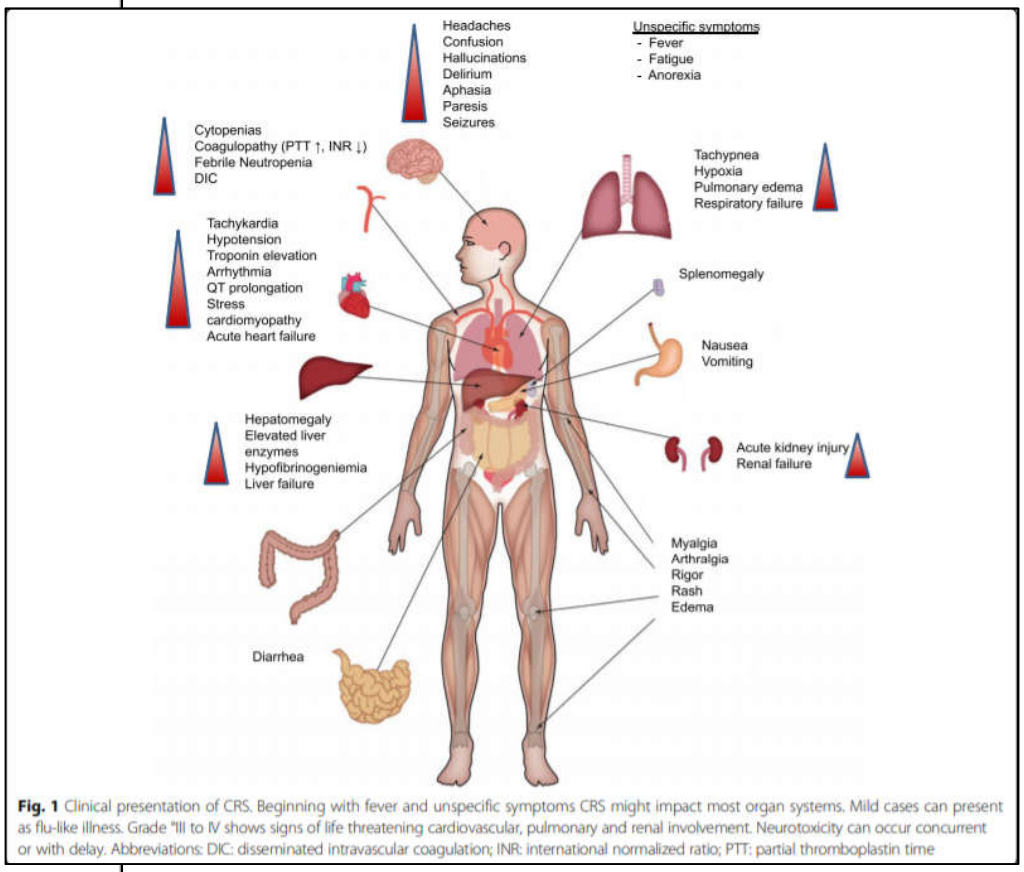

Fig. 1 Clinical presentation of CRS. Beginning with fever and unspecific symptoms CRS might impact most organ systems. Mild cases can present as flu-like illness. Grade °III to IV shows signs of life threatening cardiovascular, pulmonary and renal involvement. Neurotoxicity can occur concurrent or with delay. Abbreviations: DIC: disseminated intravascular coagulation; INR: international normalized ratio; PTT: partial thromboplastin time

Shimabukuro-Vornhagen A, et al. J Imunother Cancer 2018;6:56

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Toxicity	Grade	Action	Co-medication
Cytokine release syndrome	Grade 3*	Withhold blinatumomab until resolved, then re-start blinatumomab at 9 μg/day. Escalate to 28 μg/day after 7 days if the toxicity does not recur. If the interruption of blinatumomab is no longer than 7 days continue blinatumomab application to a total of 28 days. If the AE lasts longer than 7 days, start a new treatment cycle after the AE resolved.	20 mg dexamethasone i.v. 1 hr before start of treatment and at any dose step
	Grade 4*	Discontinue blinatumomab permanently	
Neurological toxicity	Seizure	Discontinue blinatumomab permanently if more than 1 seizure occurs	
	Grade 3*	Withhold blinatumomab until no more than grade 1 (mild) and for at least 3 days, then re-start blinatumomab at 9 μg/day. Escalate to 28 μg/day after 7 days if the toxicity does not recur. If the interruption of blinatumomab is no longer than 7 days continue blinatumomab application to a total of 28 days. If the AE lasts longer than 7 days, start a new treatment cycle after the AE resolved. If the toxicity occurred at 9 μg/day or if the toxicity takes more than 7 days discontinue blinatumomab permanently	
	Grade 4*	discontinue blinatumomab permanently	
Other clinically relevant adverse events	Grade 3*	Withhold blinatumomab until no more than grade 1 (mild) and for at least 3 days, then re-start blinatumomab at 9 μg/day. Escalate to 28 μg/day after 7 days if the toxicity does not recur, If the interruption of blinatumomab is no longer than 7 days continue blinatumomab application to a total of 28 days. If the AE lasts longer than 7 days, start a new treatment cycle after the AE resolved. If the toxicity occured at 9 μg/day or if the toxicity takes more than 14 days to resolve discontinue blinatumomab permanently	
	Grade 4*	discontinue blinatumomab permanently	

Table 1. Clinical signs and symptoms associated with CRS

Organ system	Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, seizures

Lee DW, et al. Blood 2014;124:188-95
Goebeler ME, Bargou R. Leuk Lymphoma 2016;57:1021-32

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Table 5
Neurotoxicity caused by agents commonly used in patients with hematologic malignancies.

Acute encephalopathy (delirium)	Chronic encephalopathy (dementia)	Seizures	Cerebellar dysfunction (ataxia)	Aseptic meningitis	Peripheral neuropathy
5-Azacytidine	Carmustine	Asparaginase	Blinatumomab	Cytarabine (IT)	5-Azacitidine
Asparaginase	Cisplatin	Busulfan (HD)	Cyclosporin A	Liposomal	Bortezomib
Blinatumomab	Corticosteroids	Carmustine	Cytarabine	cytarabine (IT)	Brentuximab
Capecitabine	Cytarabine	Chlorambucil	Nelarabine	Methotrexate (IT)	Cabazitaxel
Carmustine	Dacarbazine	Cisplatin	Procarbazine	Rituximab (IT)	Capecitabine
Chlorambucil	Fludarabine	Corticosteroids		IVIg	Carboplatin
Cisplatin	Ifosfamide	Cyclophospha-		Monoclonal	Carfilzomib
Cladribine	Methotrexate	mide (HD)		antibodies	Cisplatin
Corticosteroids	Rituximab (IT)	Cyclosporin A		NSAIDs	Cladribine
Cyclophosphamide		Cytarabine		Trimethoprim-sulfamethoxazole	Cytarabine
Cyclosporin A		Dacarbazine			Etoposide
Cytarabine		Dimethyl sulfoxide			Fludarabine
Dacarbazine		Erythropoietin			Gemcitabine
Dimethyl sulfoxide		Etoposide (HD)			Ifosfamide
Etoposide (HD)		Fludarabine (HD)			Ipilimumab
Fludarabine		Gemcitabine			Ixabepilone
Gemcitabine		Hydroxyurea			Lenalidomide
Hydroxyurea		Ifosfamide			Nab-paclitaxel
Ifosfamide		Methotrexate			Nelarabine
Imatinib		Nelarabine			Oxaliplatin
Methotrexate (HD, IV, IT)		Teniposide			Procarbazine
Mitomycin C		Thalidomide			Sorafenib
Nelarabine		Vincristine			Sunitinib
Nitrosoureas (HD)					Taxotere
Procarbazine					Teniposide
Tacrolimus					Thalidomide
Thalidomide					Vinka alkaloids
Thiotepa (HD)					
Vincristine					

HD, high-dose; IT, intrathecal; IV, intravenous; IVIg, intravenous γ-globulin; NSAIDs, nonsteroidal anti-inflammatory drugs.

Magge RS, DeAngelis LM. Blood Rev 2015;29:93-100

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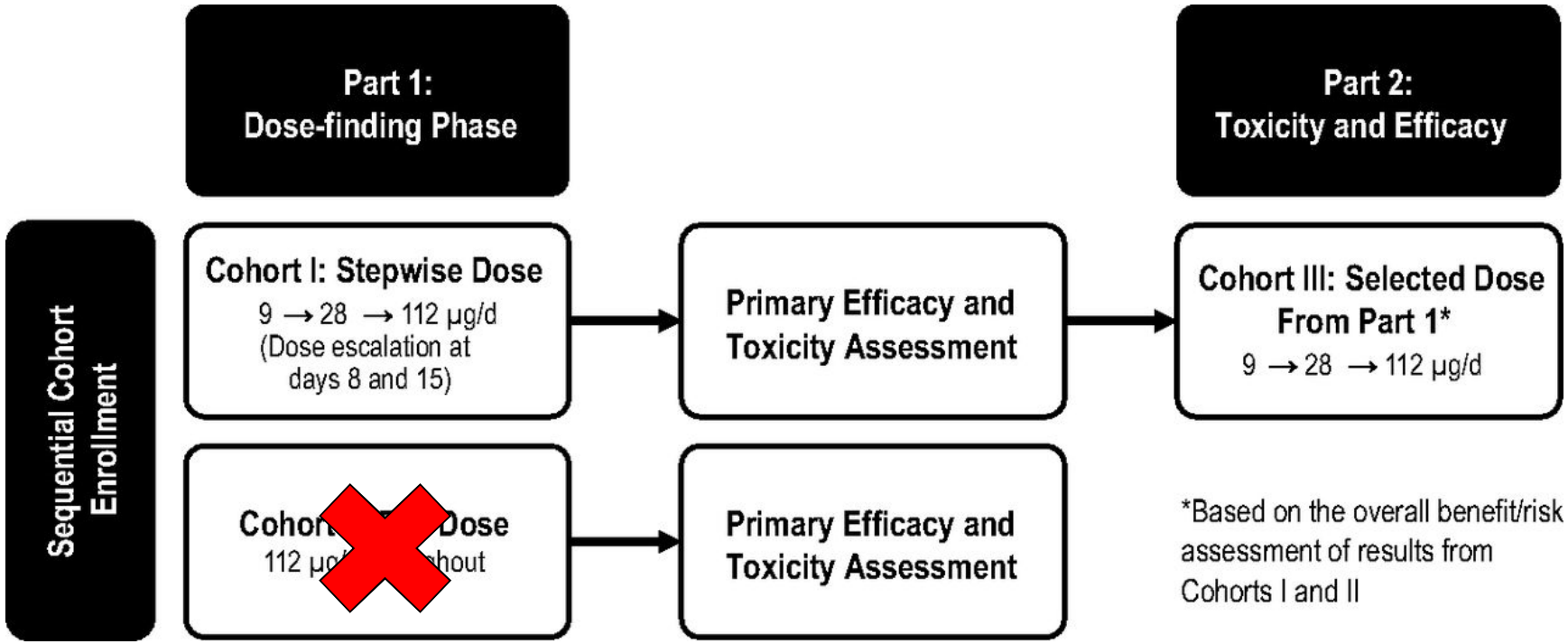

Viardot A, et al. Blood 2016;127:1410-16

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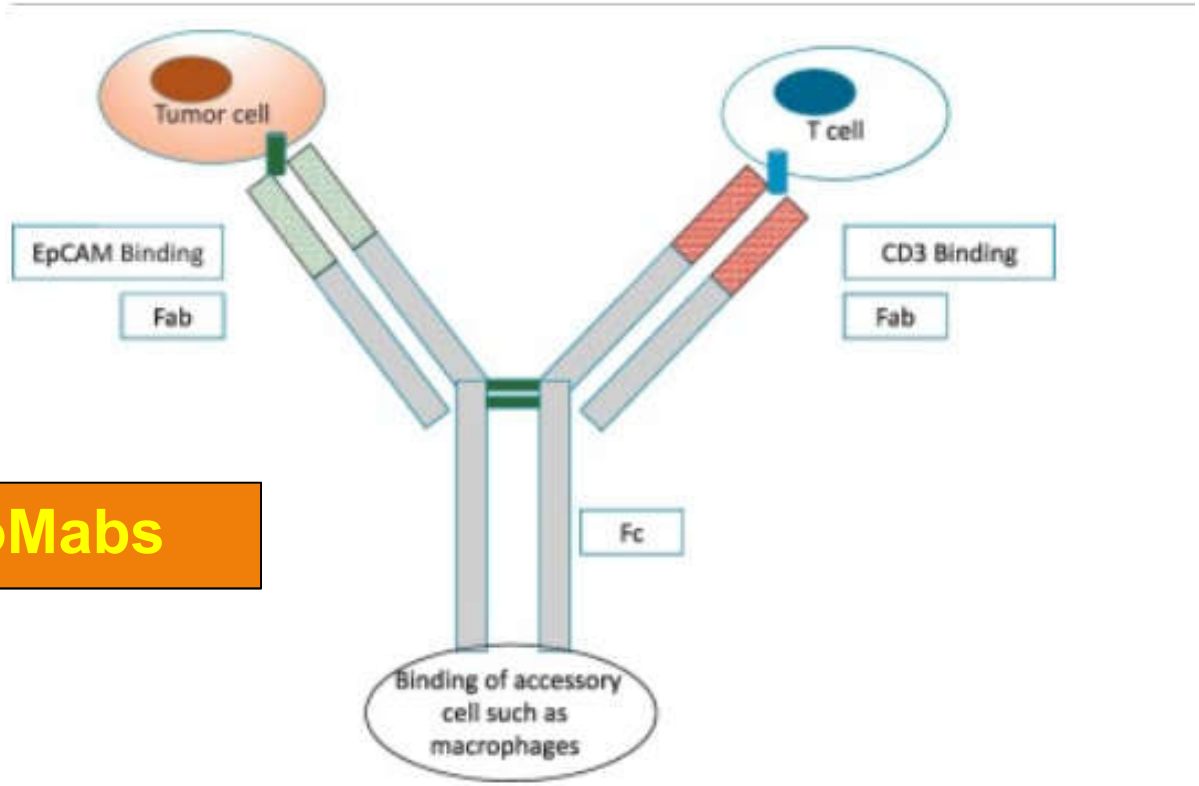

TrAbs/TrioMabs

Krishnamurthy A, Jimeno A. Parmacol Ther 2018;185:122-34

Generation of a Half-Life Extended Anti-CD19 BiTE® Antibody Construct Compatible with Once-Weekly Dosing for Treatment of CD19-Positive Malignancies

Grit Lorenczewski, Matthias Friedrich, Roman Kischel, Christoph Dahlhoff, Jonas Anlahr, Mercedesz Balazs, Dan Rock, Michael C Boyle, Rebecca Goldstein, Angela Coxon, and Tara Chapman-Arvedson

Blood 2017 130:2815;

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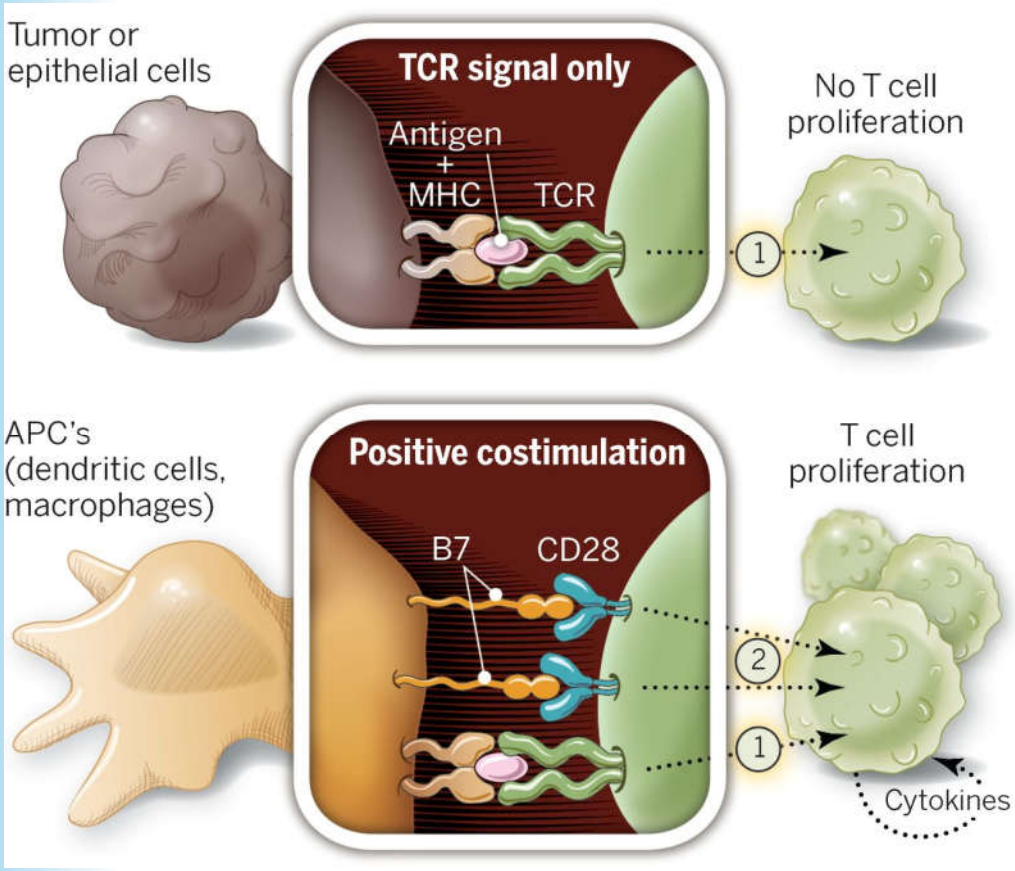

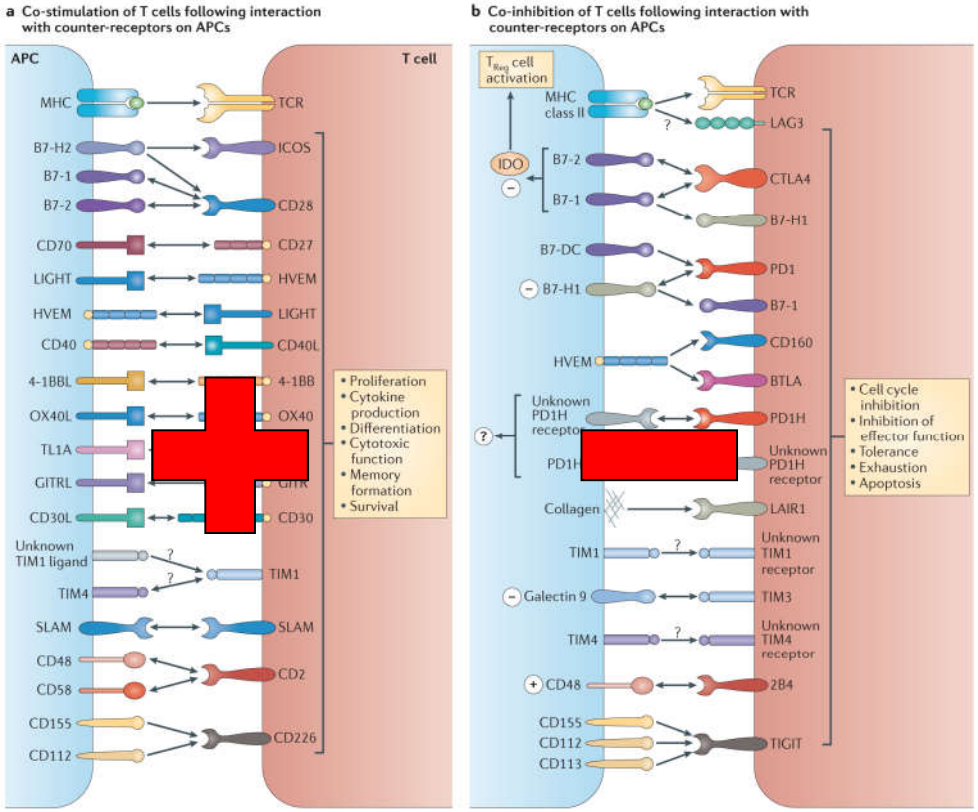

Cheng L, Flies DB. Nat Rev Immunol 2013;13:227-42
Sharma P, Allison JP. Science 2015;348:56-61

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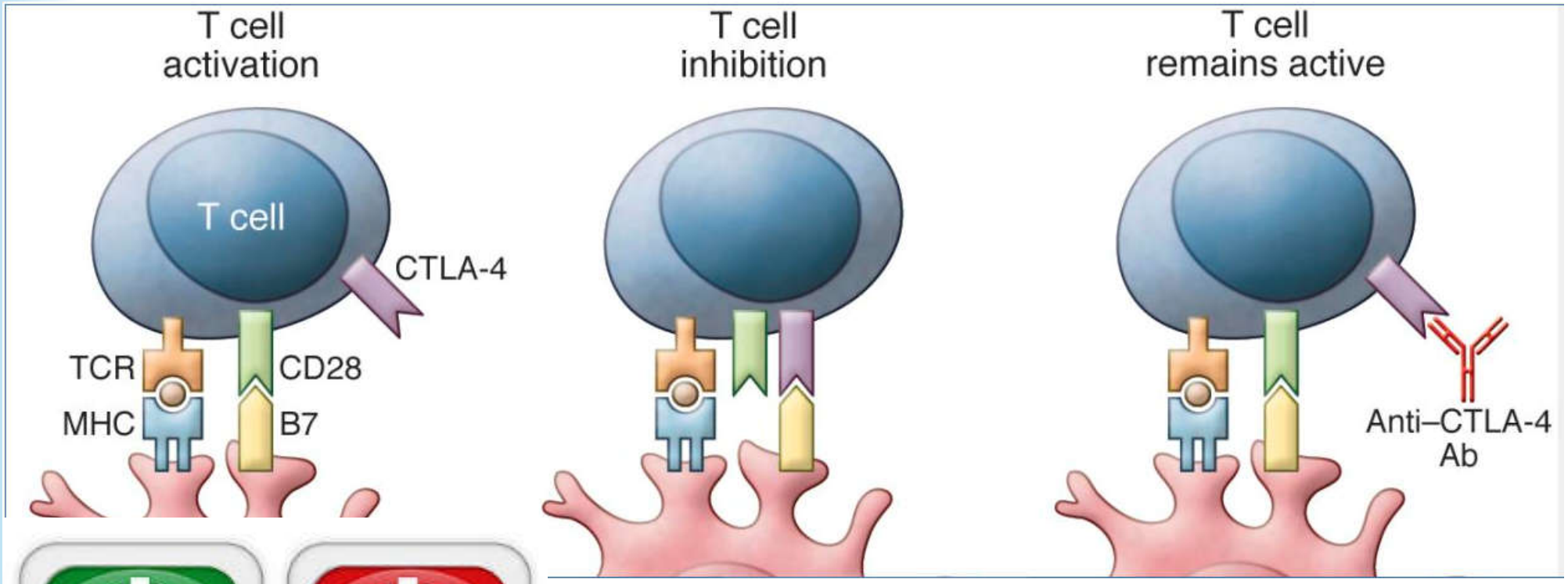

Buchbinder E, Hodi FS. J Clin Invest 2015;125:3377-83

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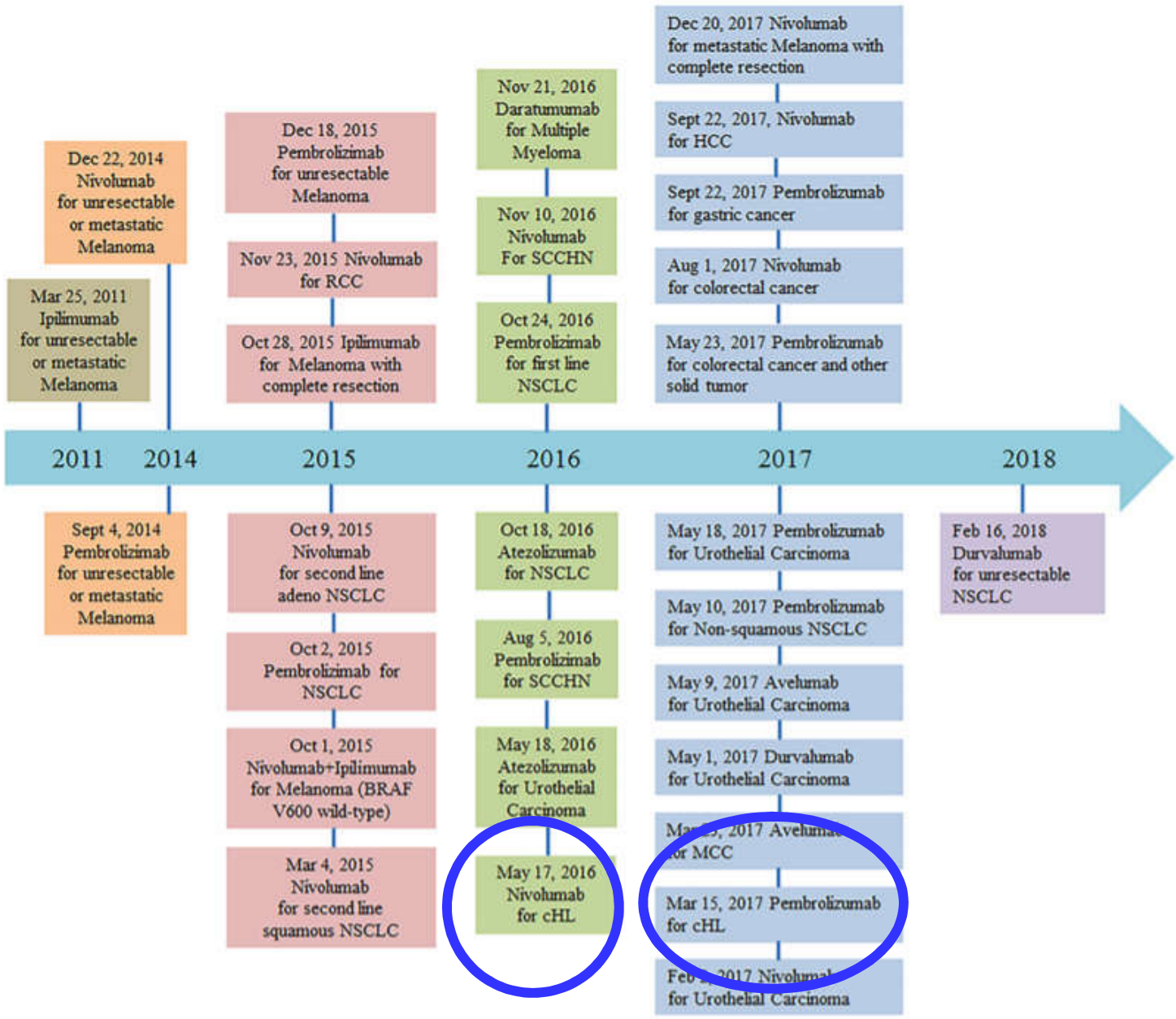

Ford ML, et al. Nat Rev Nephrol 2014;10:14-24

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Uniek toxiciteitsprofiel (irAEs)

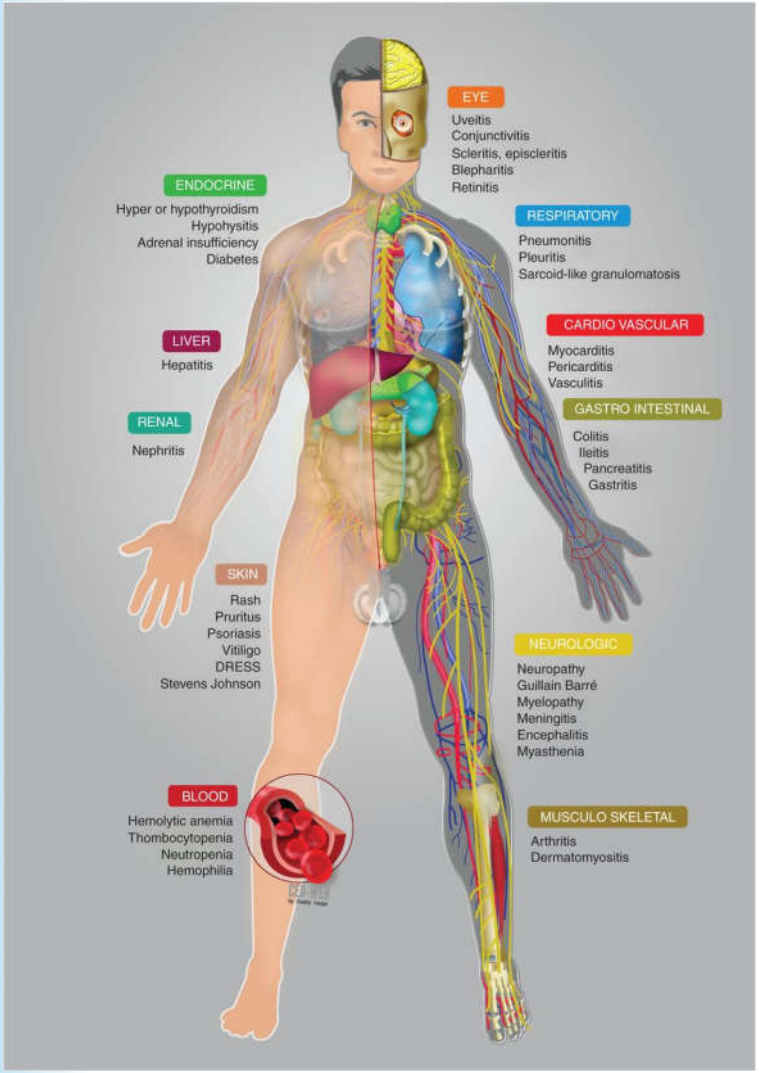

Table 1 | **Adverse events associated with immune-checkpoint blockade**

Immune-mediated adverse event	Manifestations	Management
Enterocolitis	Diarrhoea, abdominal pain, mucus or blood in stool	Antidiarrhoeals followed by systemic corticosteroids if persistent; infliximab if refractory
Pneumonitis	Dyspnoea, cough	Systemic corticosteroids
Hepatitis	ALT/AST, bilirubin elevation	Systemic corticosteroids; mycophenolate mofetil if refractory
Dermatitis	Pruritic/macular/papular rash, Stevens–Johnson syndrome (rare), toxic epidermal necrolysis (rare)	Topical betamethasone or oral antihistamines; systemic corticosteroids if refractory
Neuropathy	Sensory/motor neuropathy, Guillain–Barre syndrome (rare), myasthenia gravis (rare)	Systemic corticosteroids
Endocrinopathy	Hypothyroidism, hyperthyroidism, hypopituitarism, adrenal insufficiency, hypogonadism, Cushing's syndrome (rare)	Systemic corticosteroids, appropriate hormone replacement (potentially long-term)
Other irAEs	Arthritis, nephritis, meningitis, pericarditis, uveitis, iritis, anaemia, neutropenia	Organ-system specific

Severe immune-mediated adverse events require permanent discontinuation of therapy and initiation of high-dose systemic corticosteroids. Therapy should be withheld for moderate immune-mediated adverse events or symptomatic endocrinopathy. Non-immune aetiology should be ruled out when possible, and manufacturer recommendations should be reviewed for the latest guidance and dosing information. ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAEs, immune-related adverse events.

Champiat S et al. Ann Oncol 2016;27:559-74

Khalil DN, et al. Nat Rev Clin Oncol 2016;13:273-90