11th SPAEN Annual Conference
22-24 April 2021

COMPREHENSIVE CANCER CENTER Krebszentrum GRAZ
Medizinische Universität & LKH-Univ. Klinikum

Immunotherapy and Gene Cell Therapy: an overview

Joanna Szkandera
Division of Clinical Oncology
Department of Internal Medicine
Medical University of Graz

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History of Immunotherapy

1890 (Coley)
First cancer vaccine developed (Coley´s Toxin)

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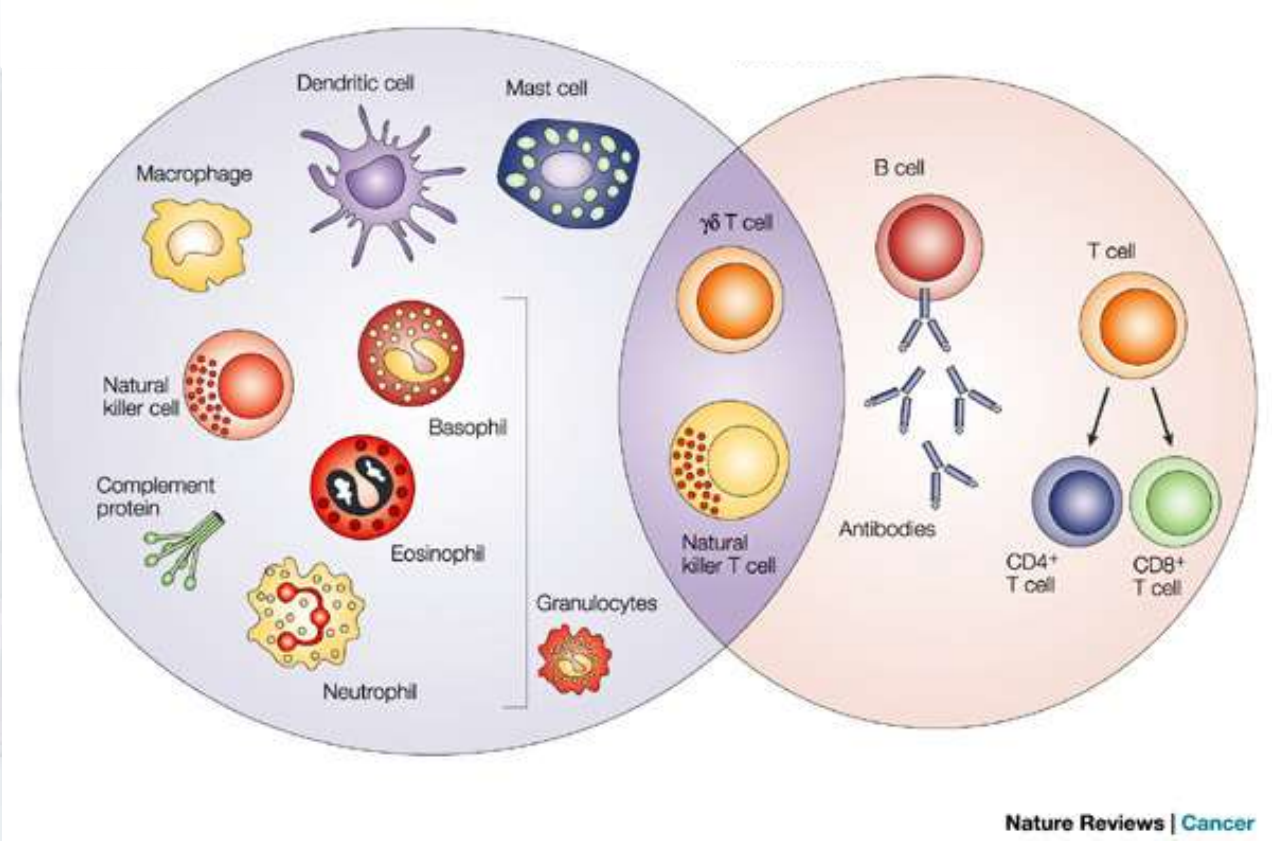
Innate and Adaptive Immunity

Innate immunity
Inborn
Inspecific
Quick

Adaptive immunity
After contact to pathogen
Specific and more potent
Needs some time but has memory



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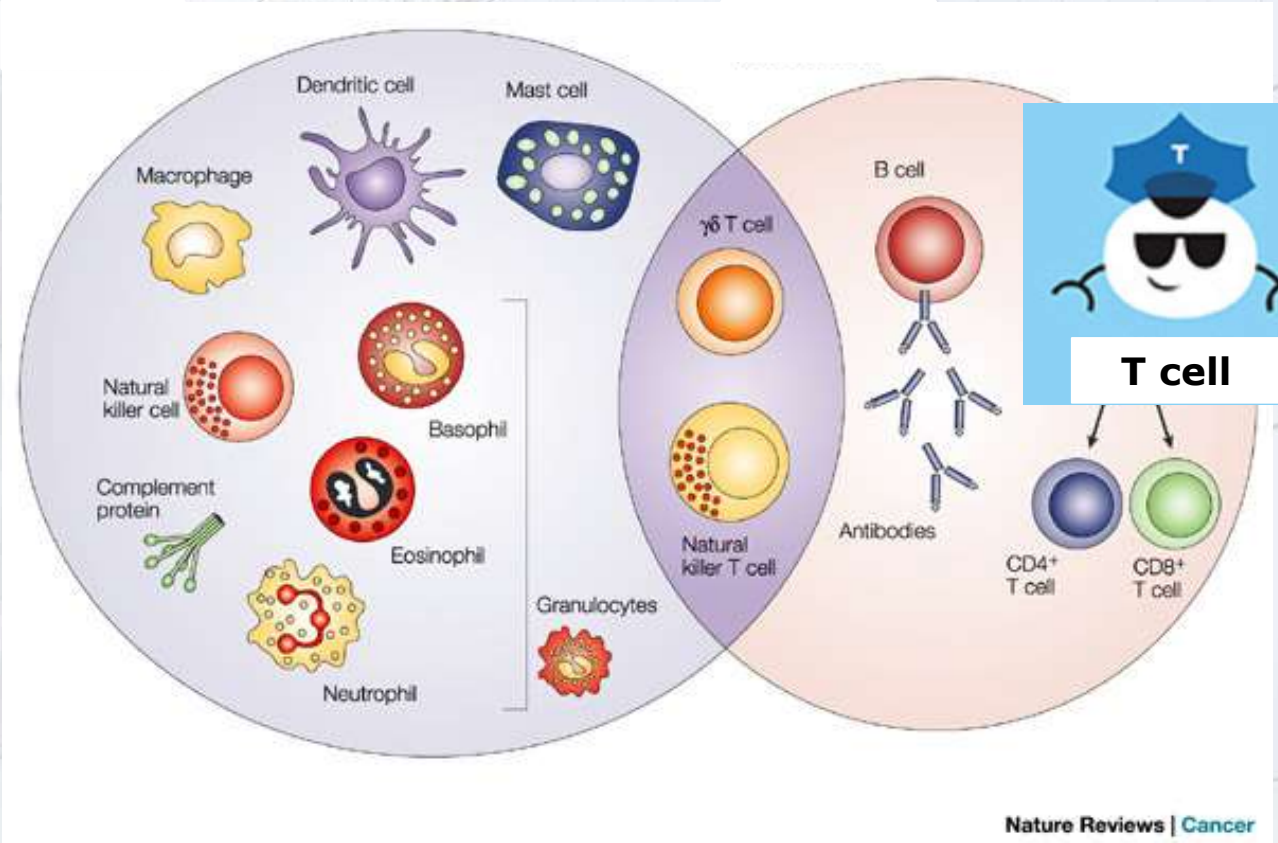
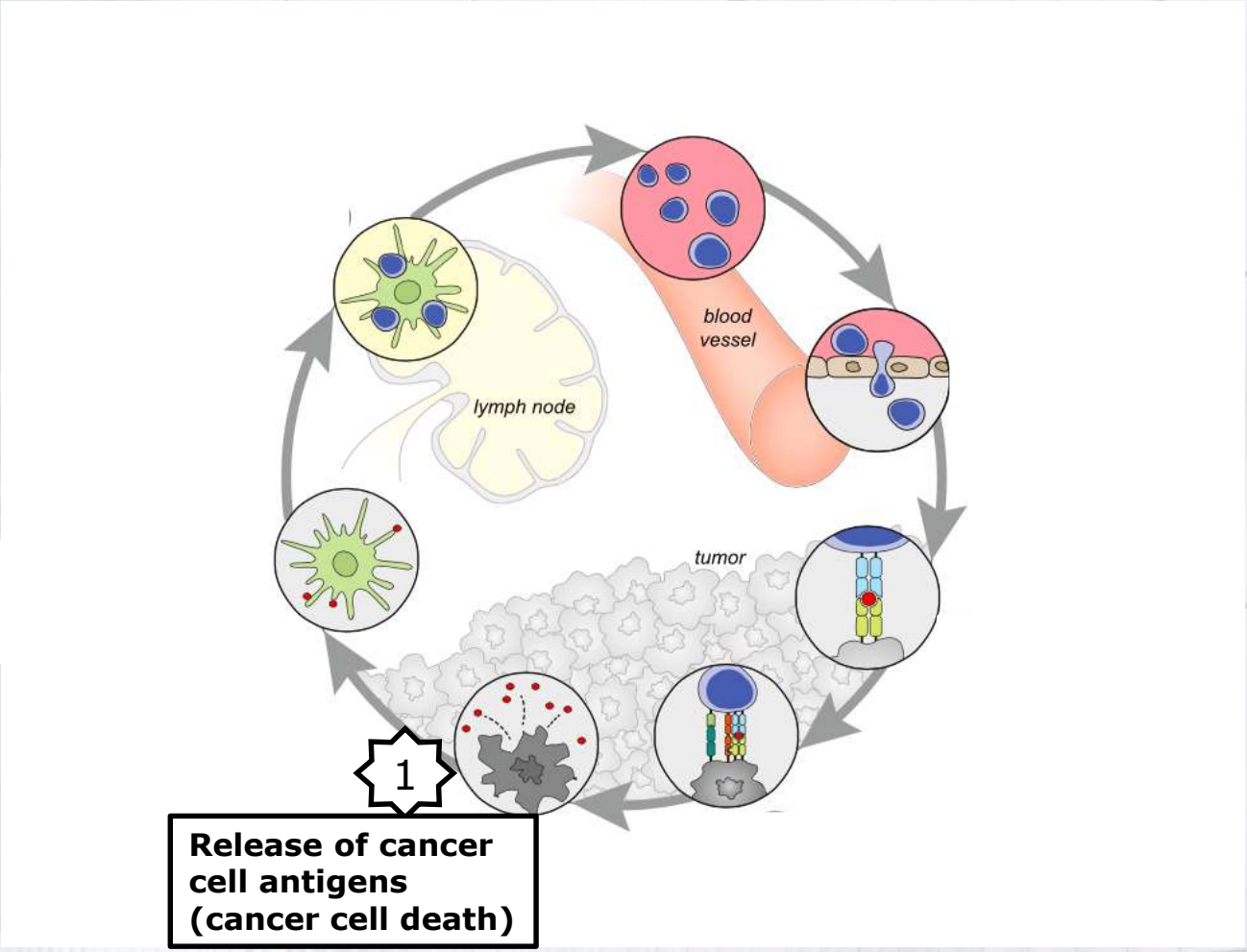


Nature Rev Cancer 2004;4:11-22

The Cancer Immunity Cycle



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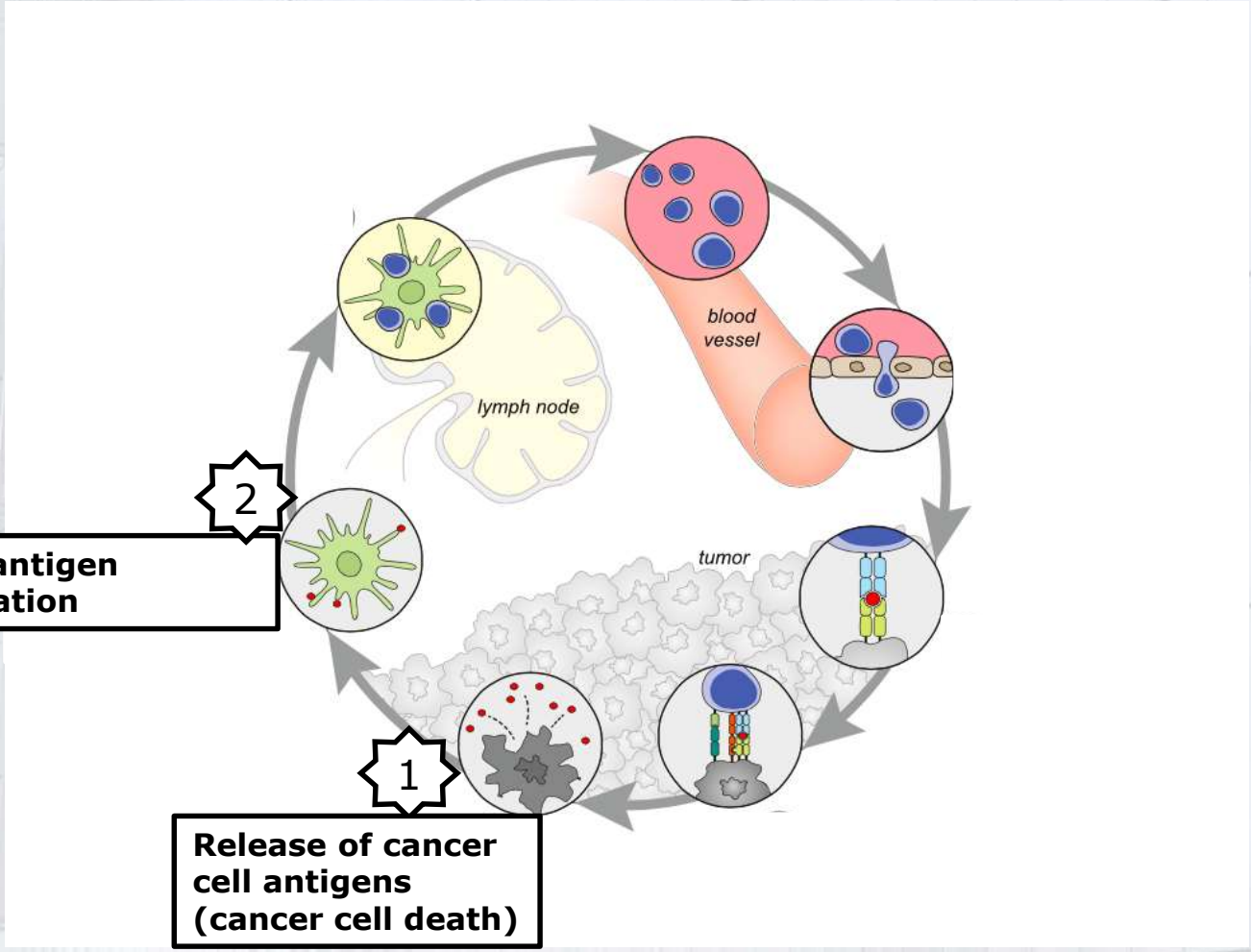

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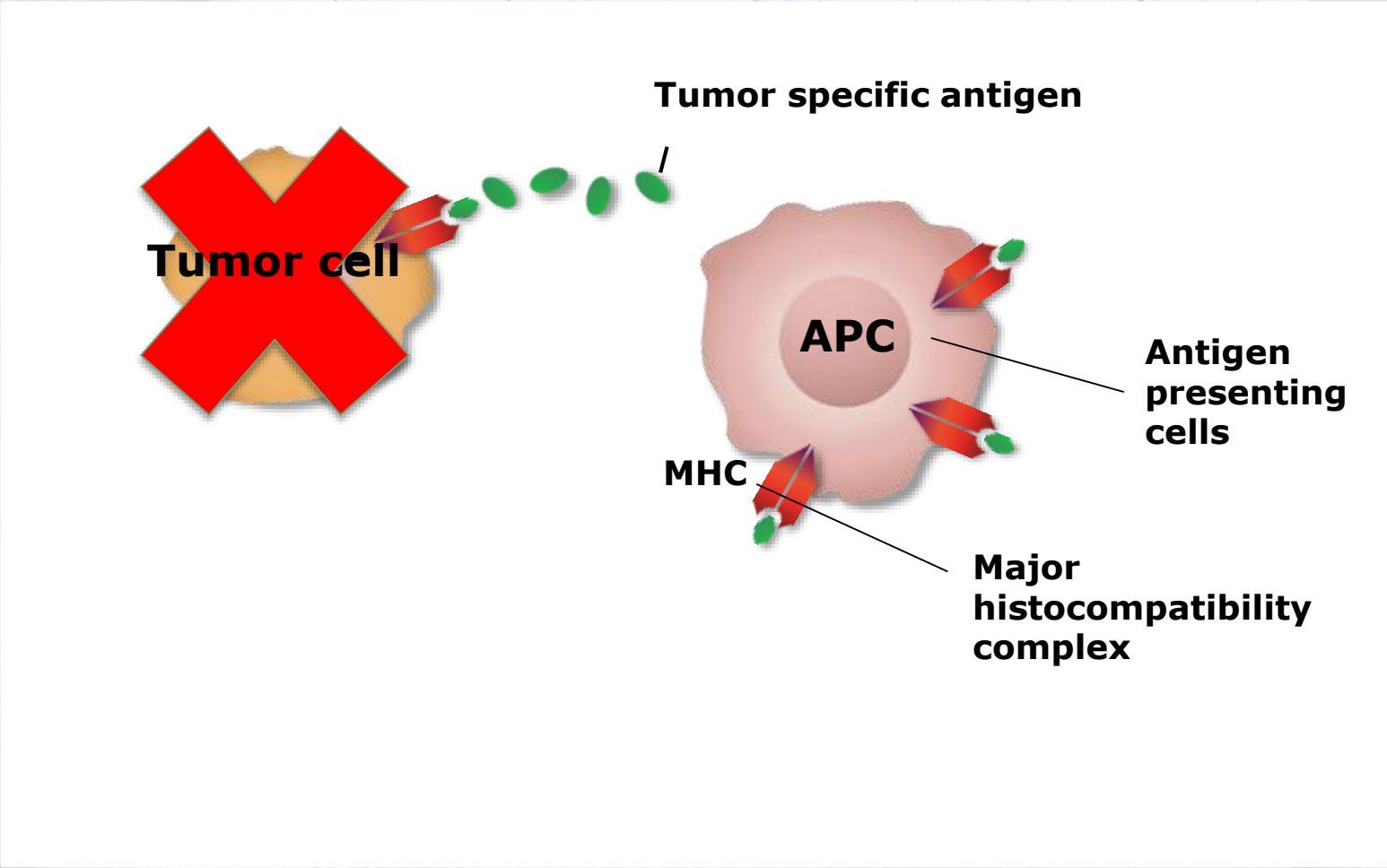
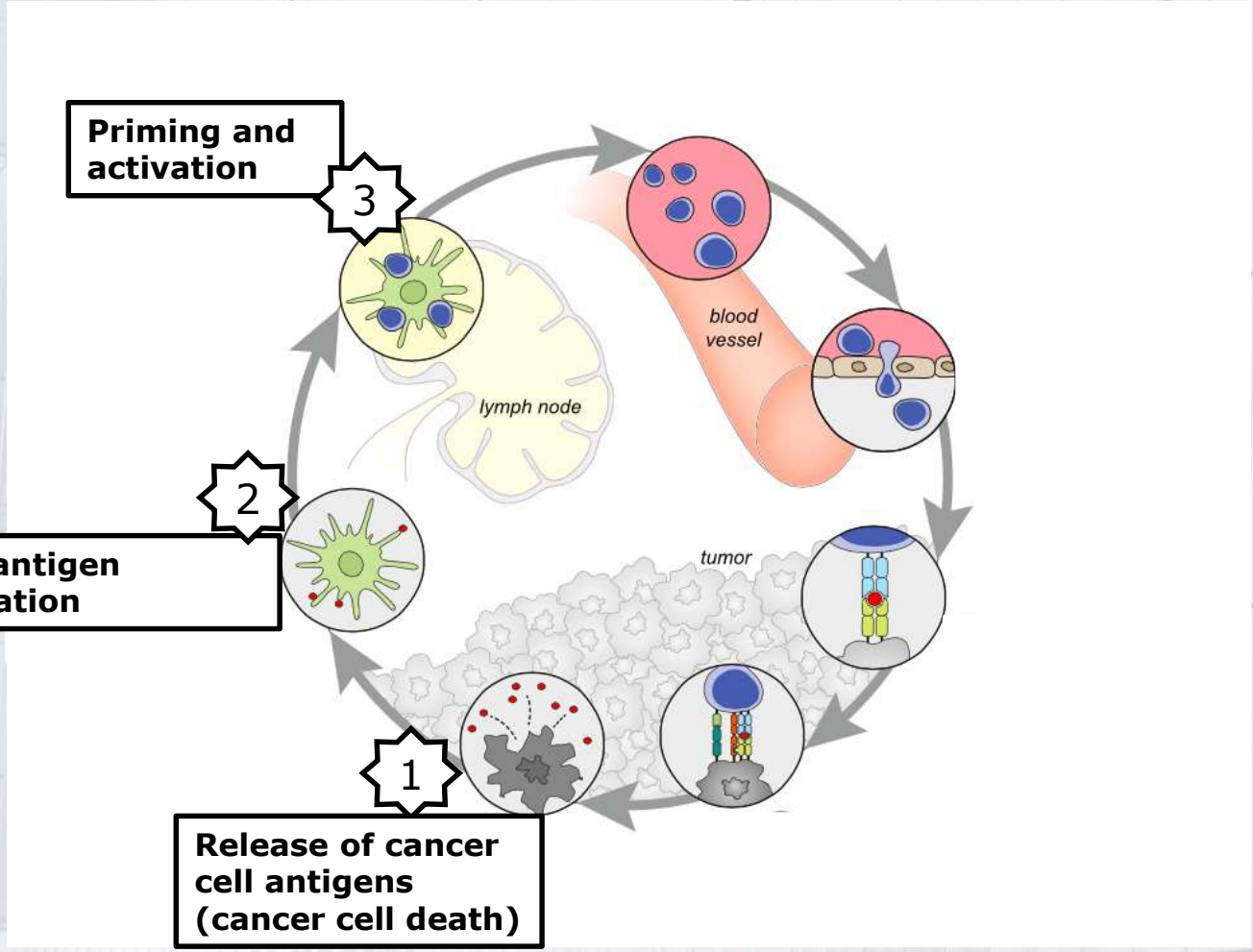
Innate and Adaptive Immunity



Mellman I et al. *Nature*. 2011;480(7378):480-489

The Cancer Immunity Cycle



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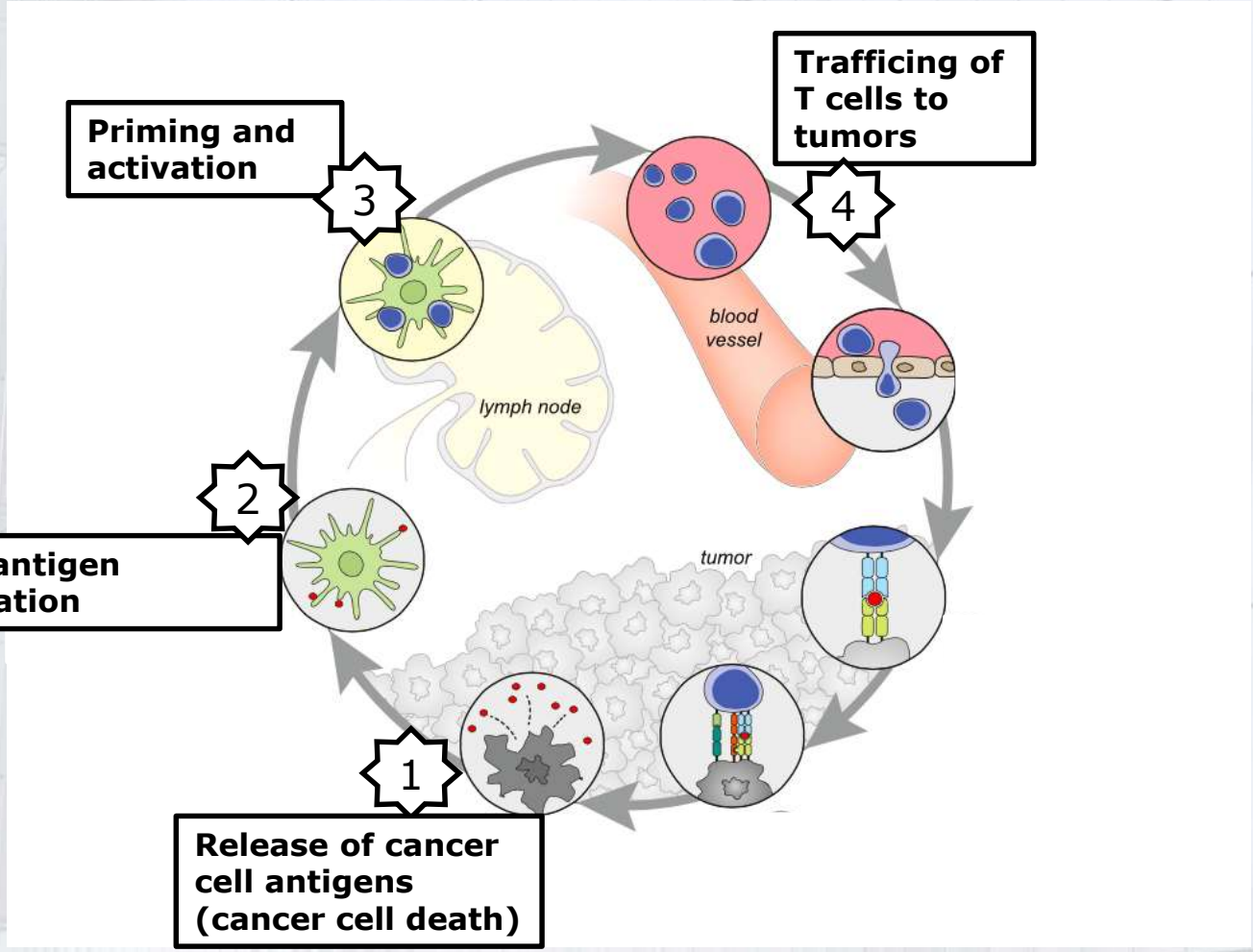

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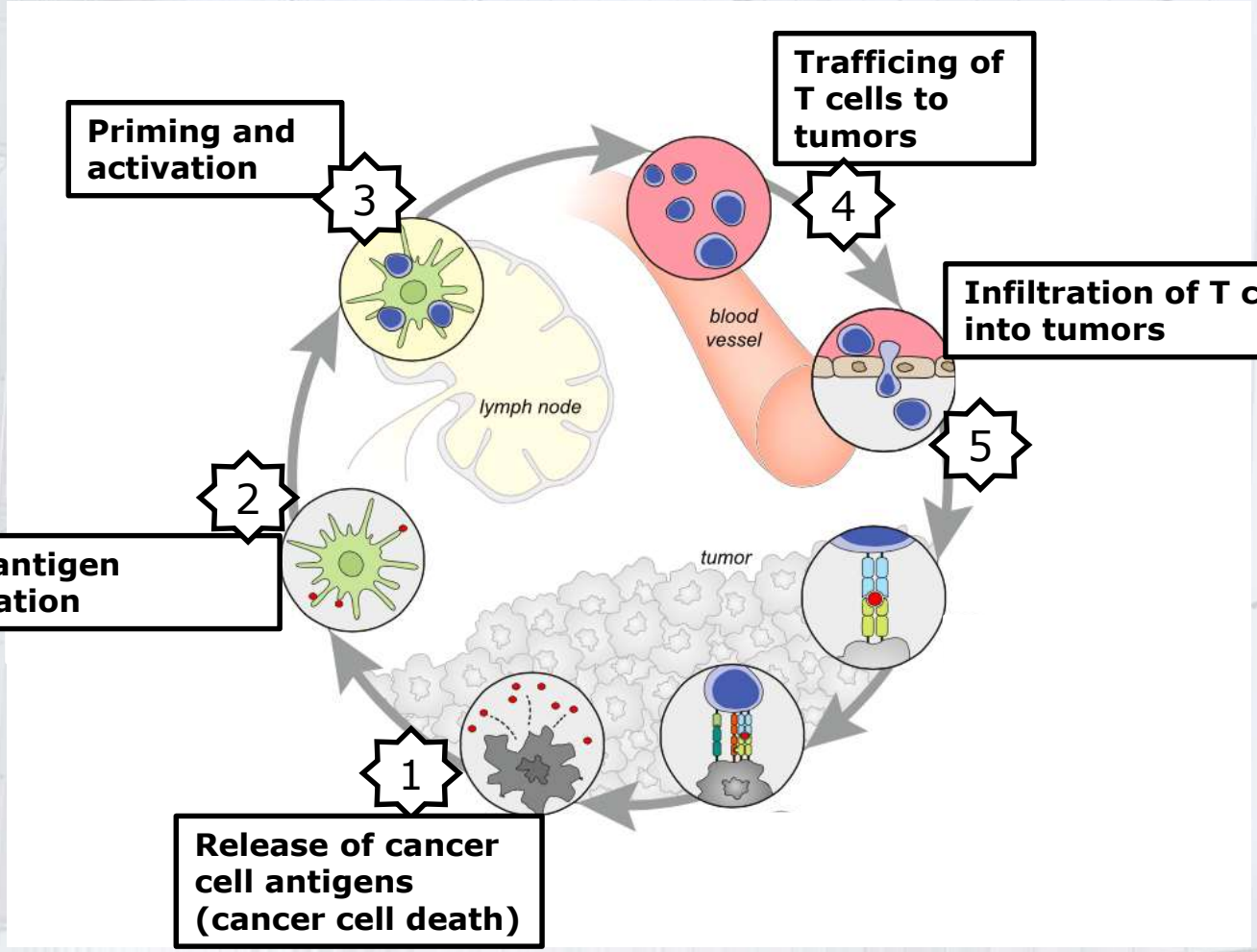

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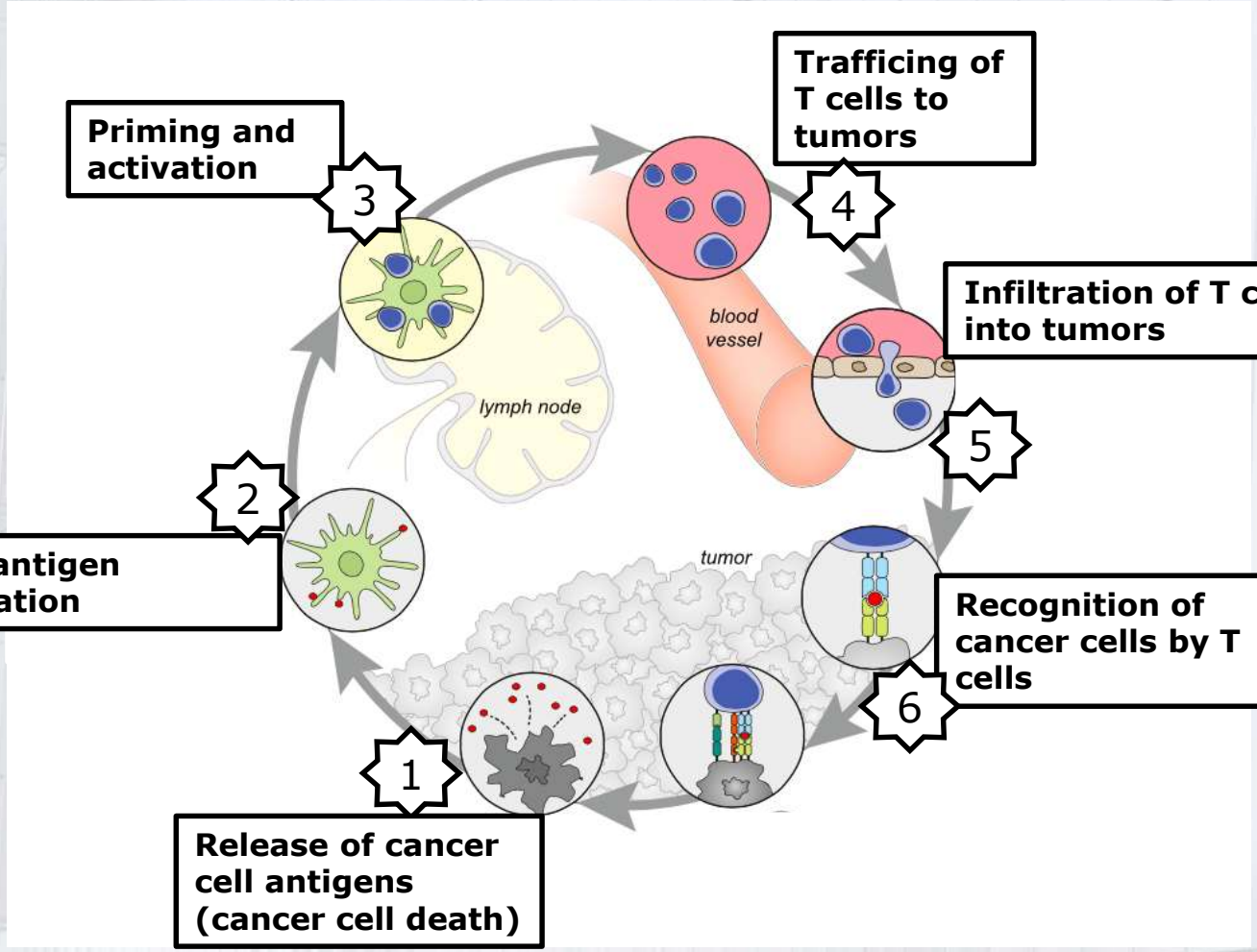

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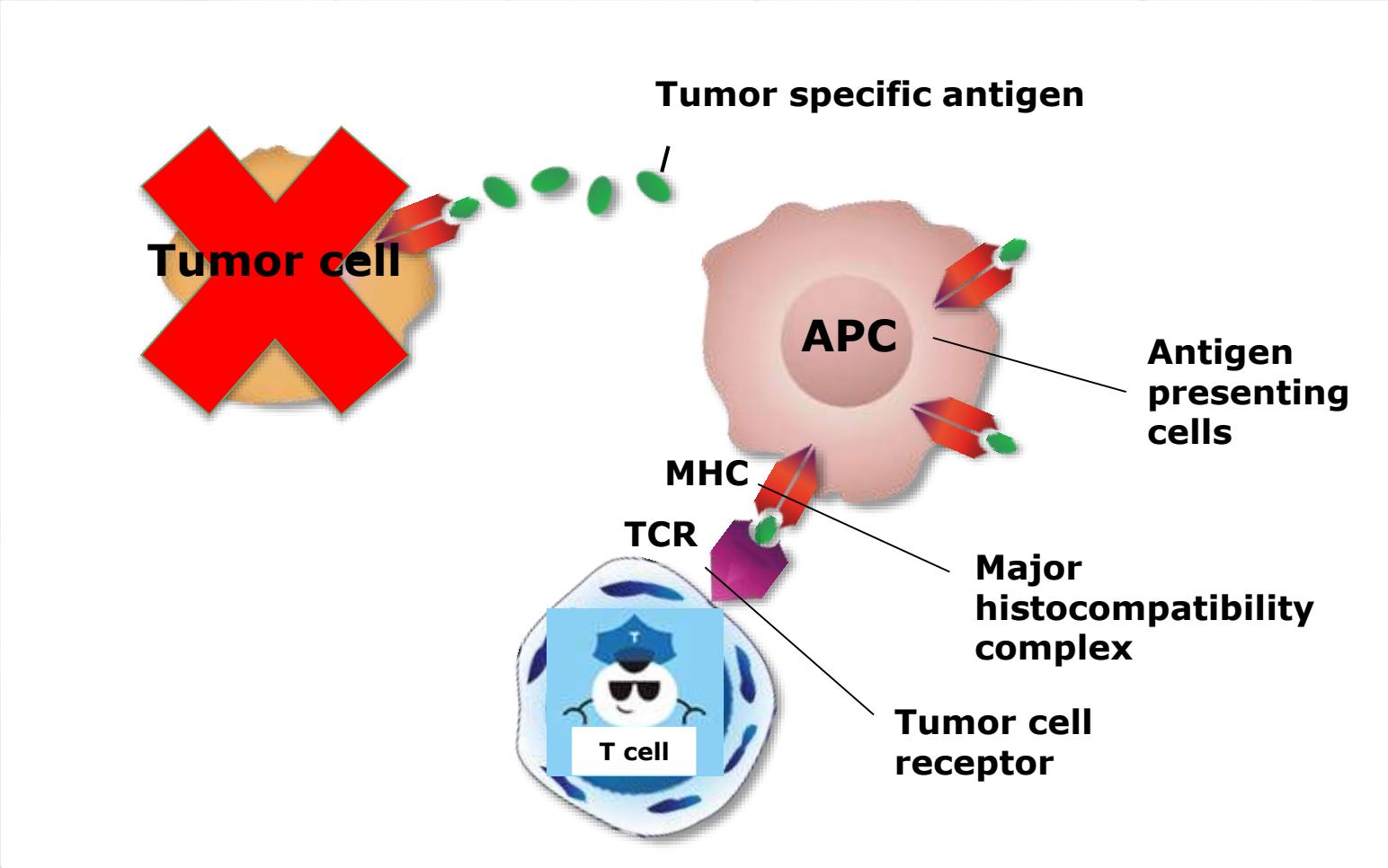

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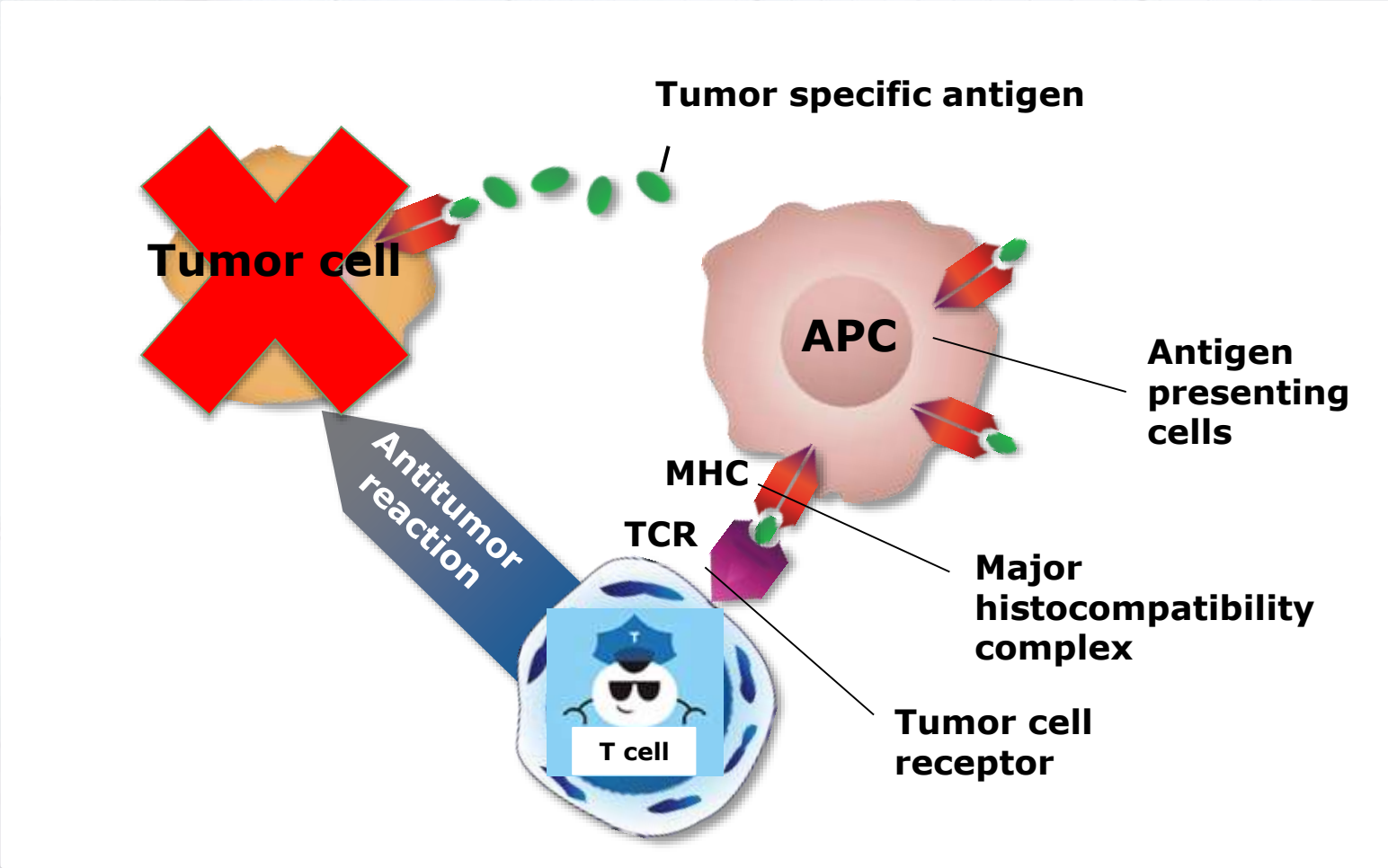

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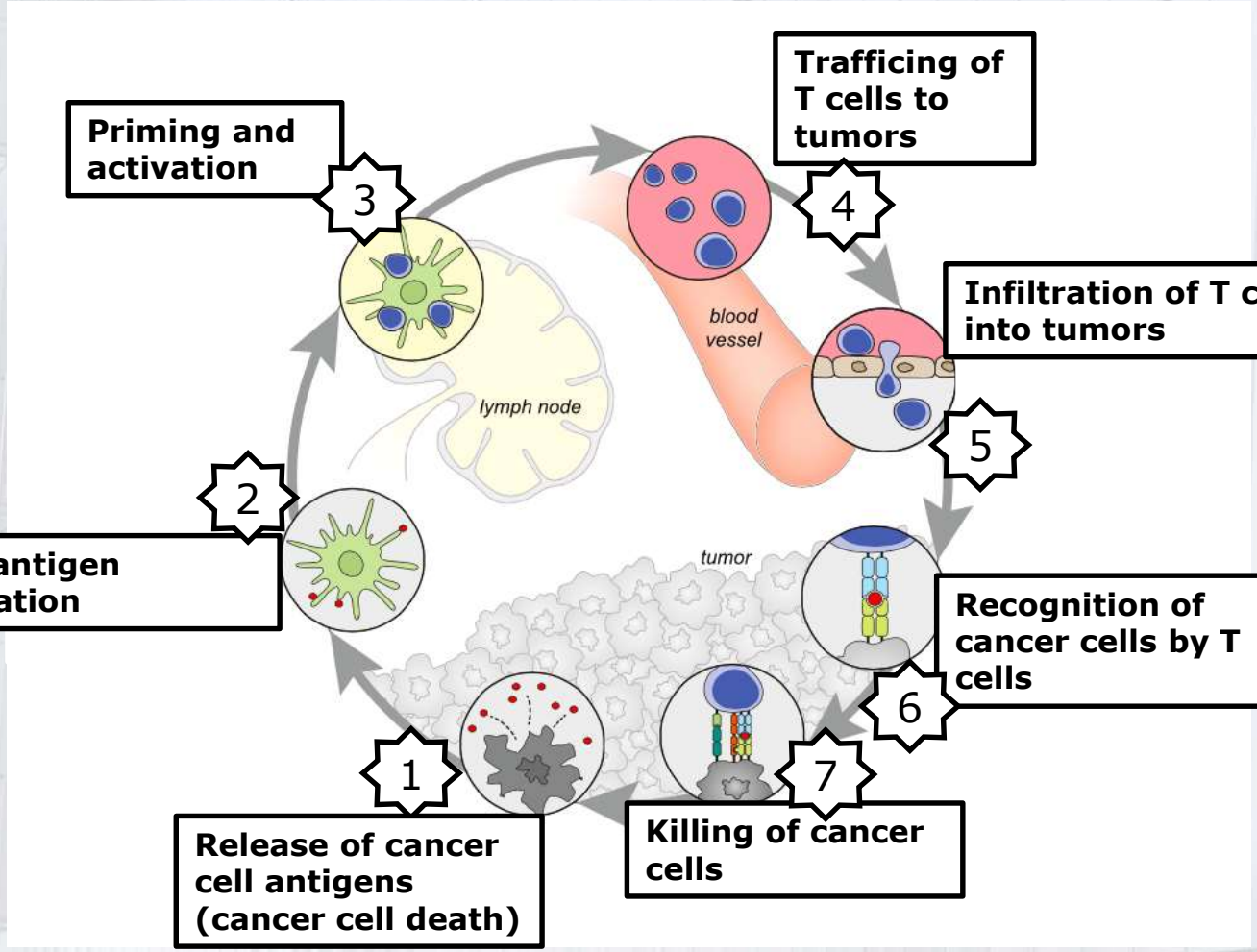

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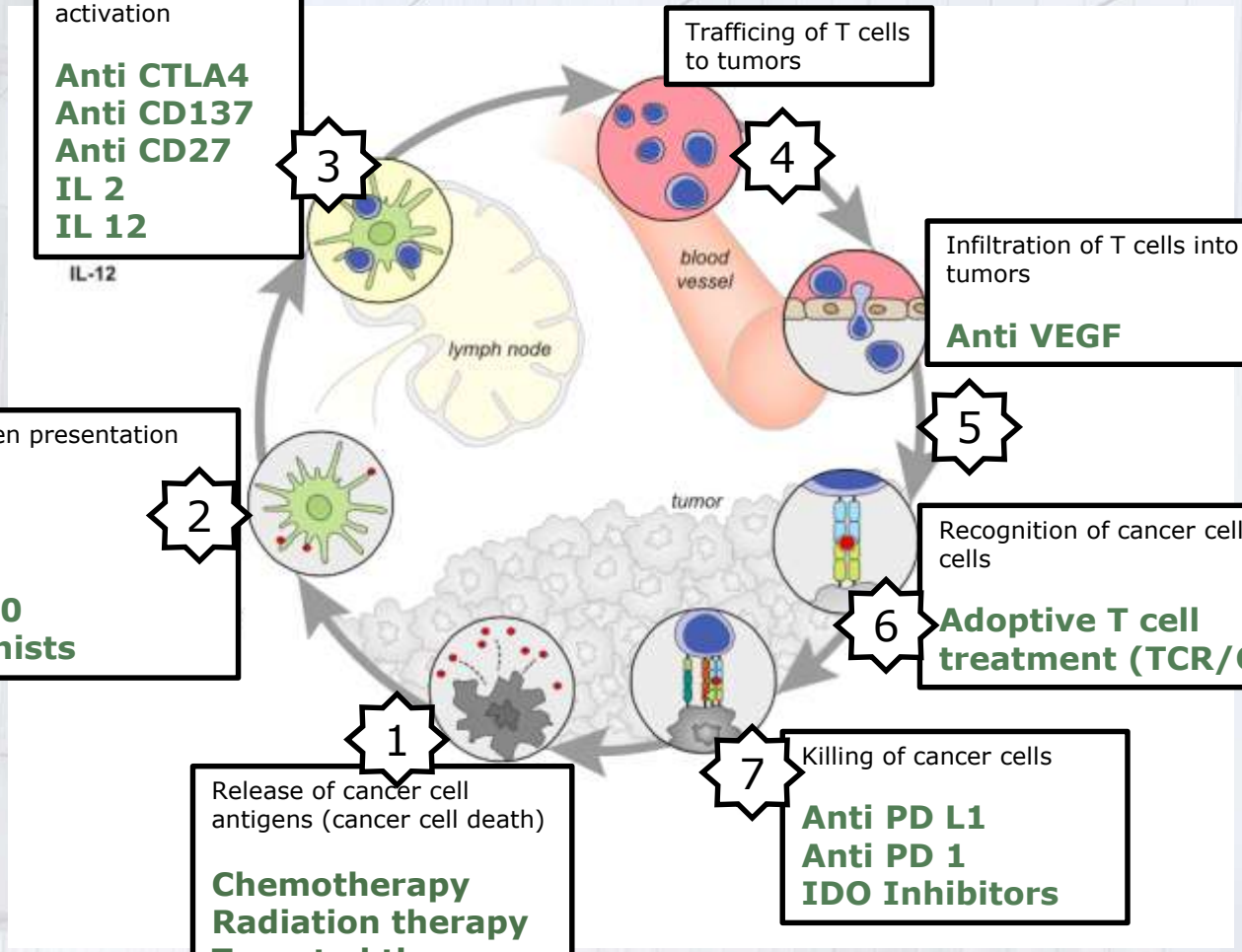

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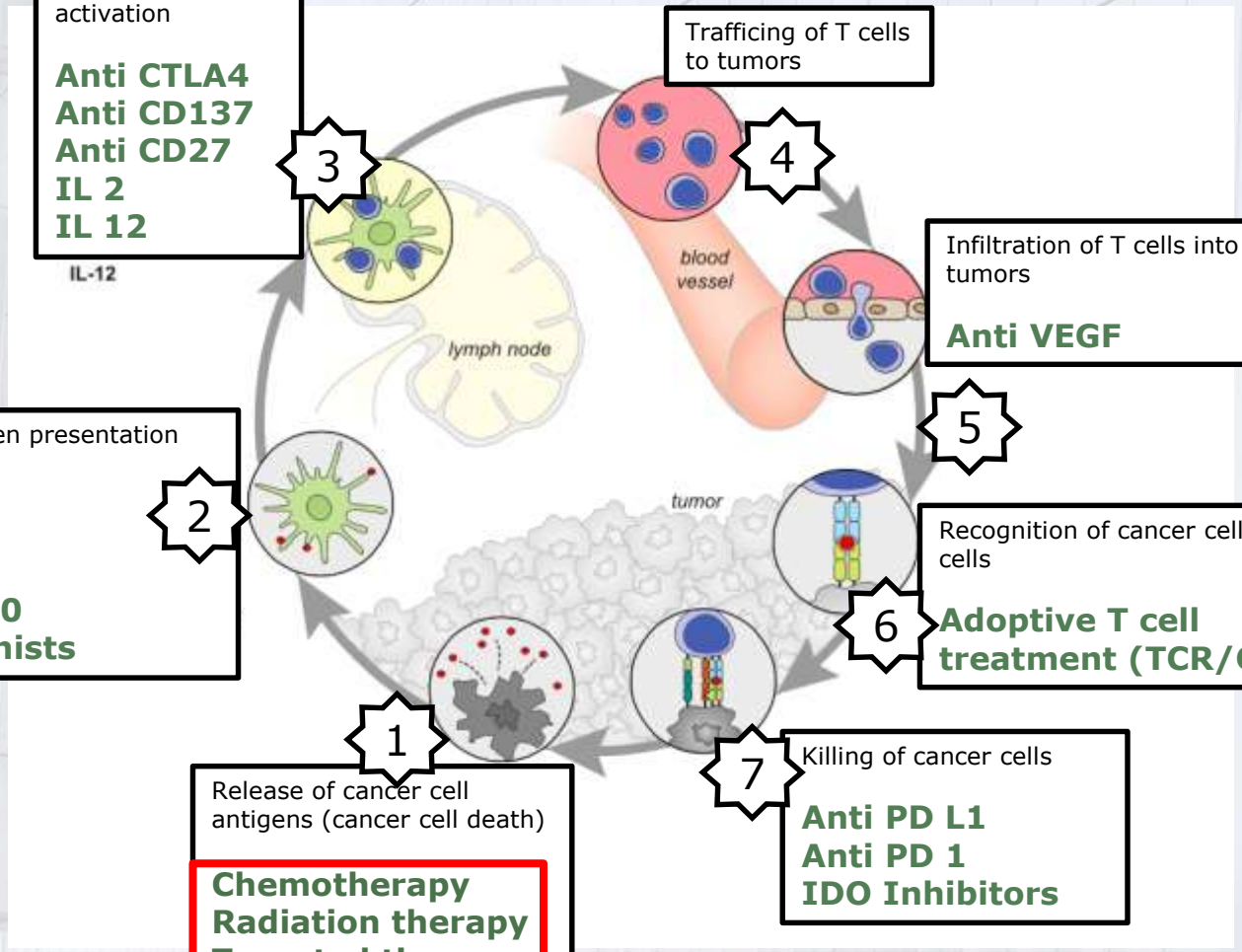

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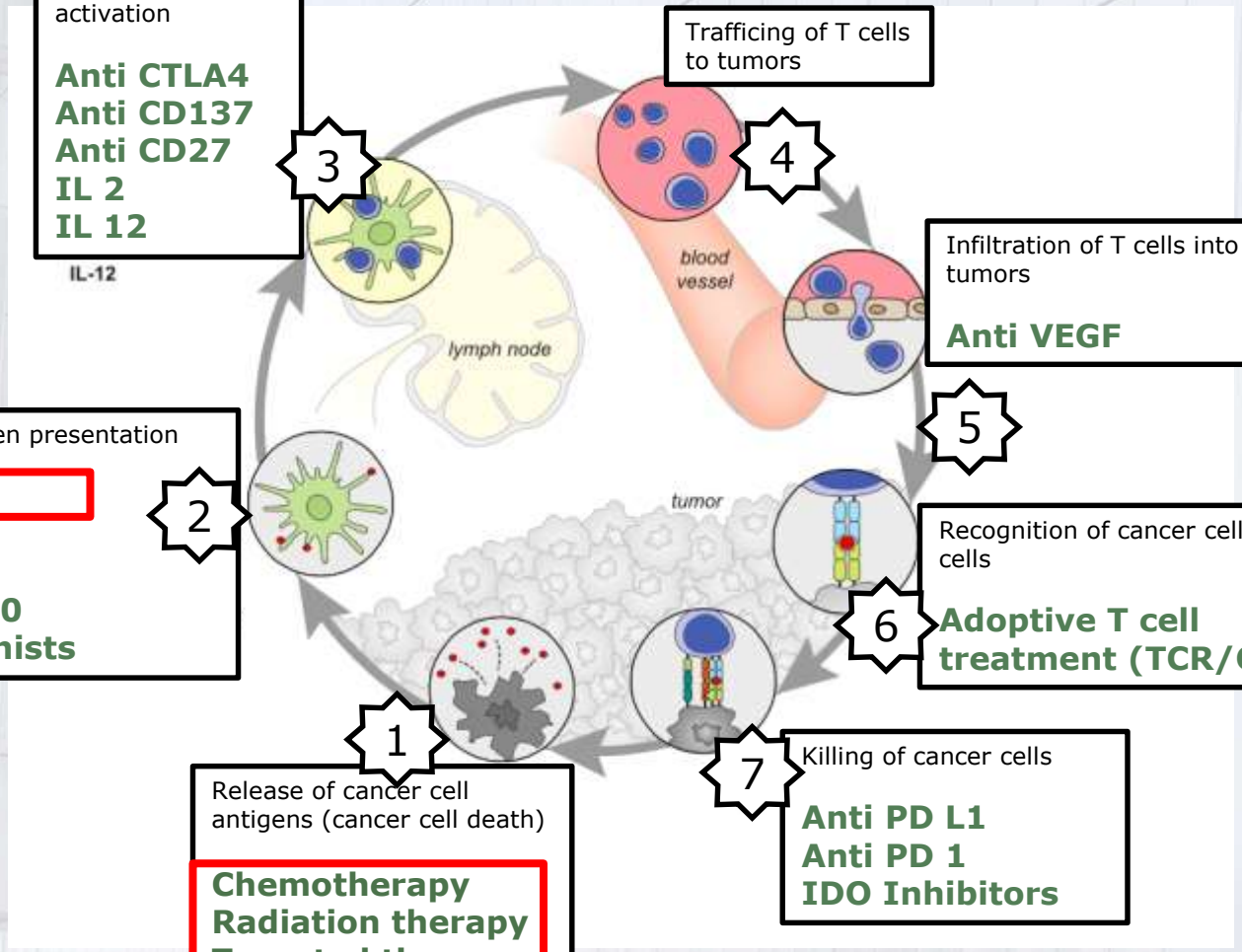

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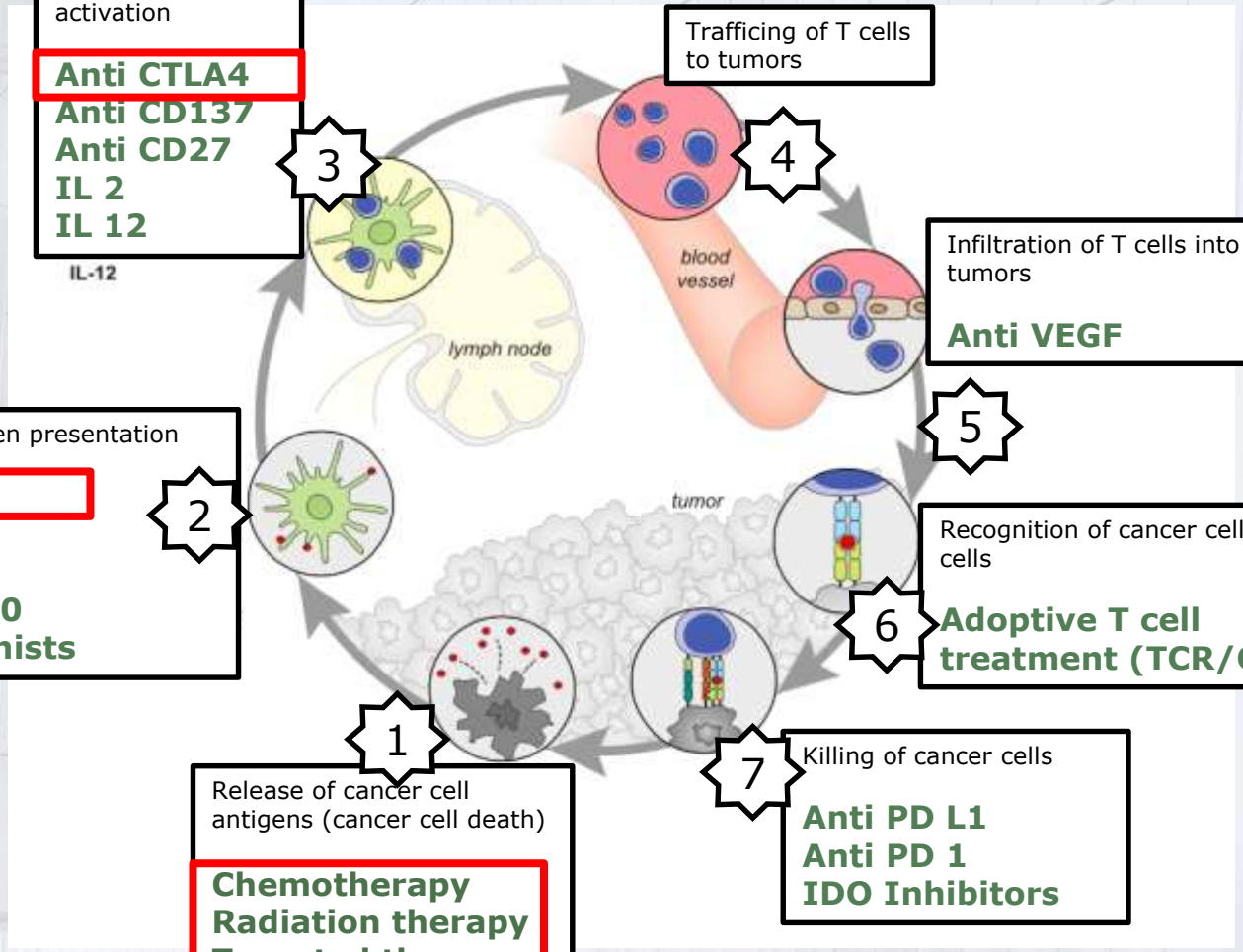

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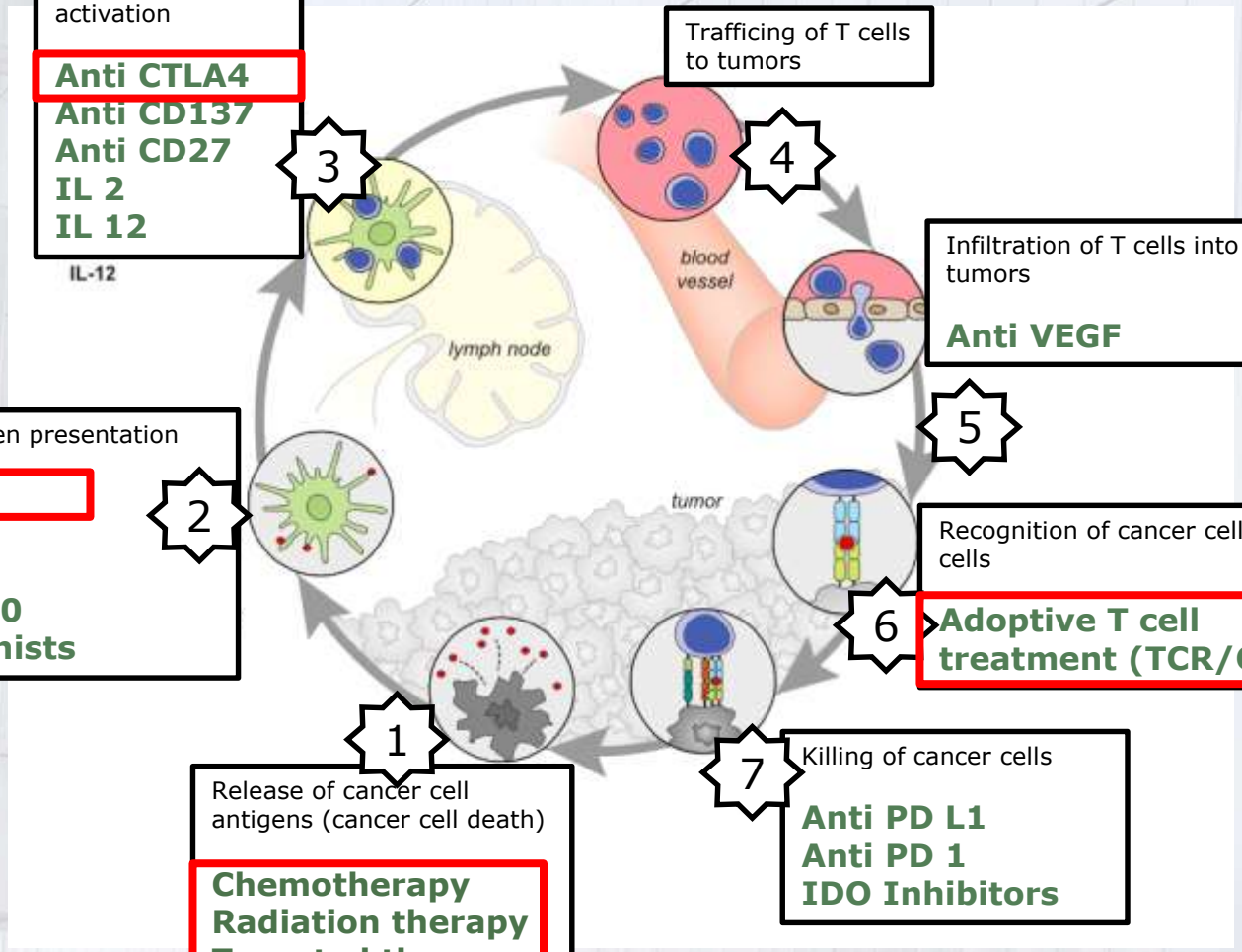

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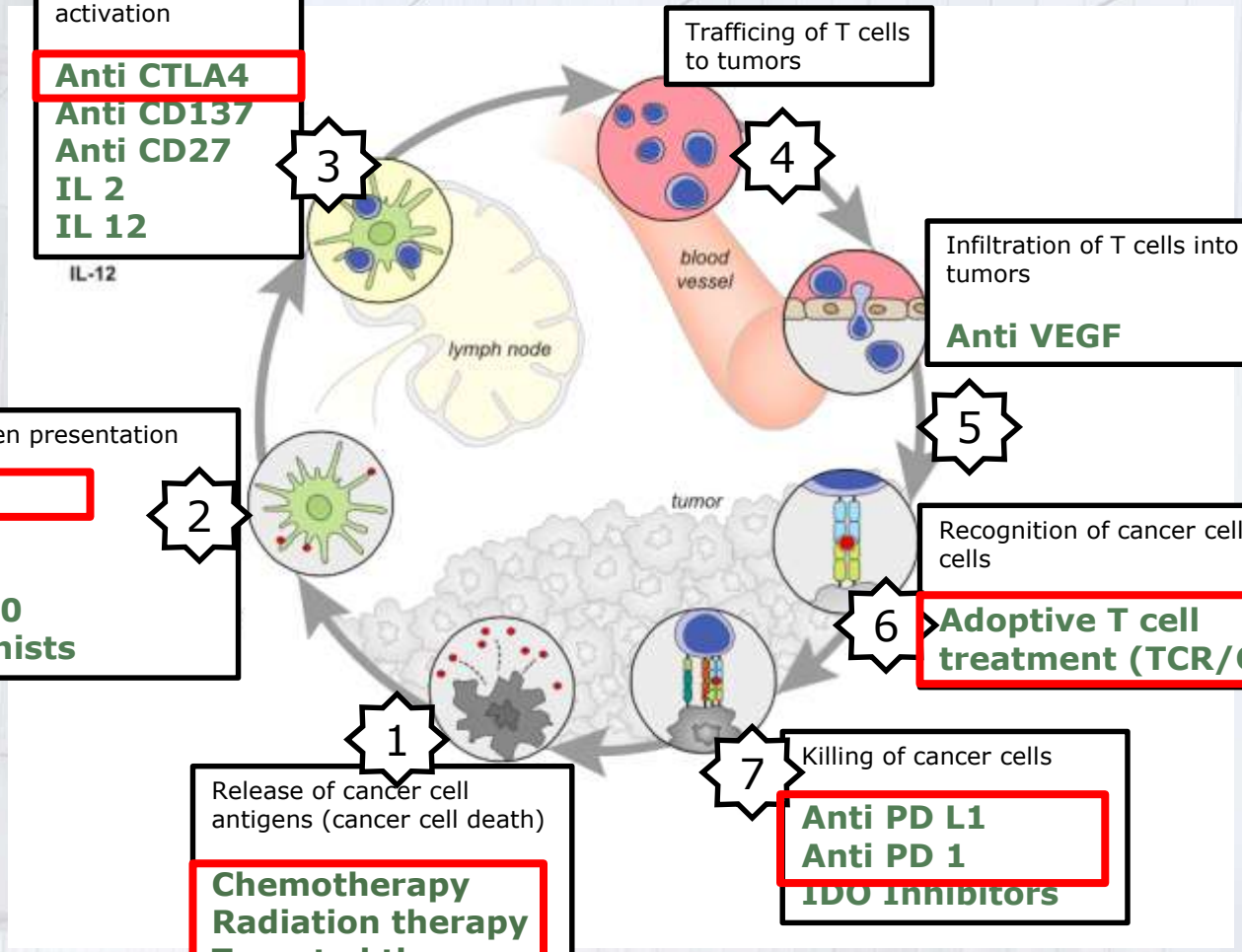

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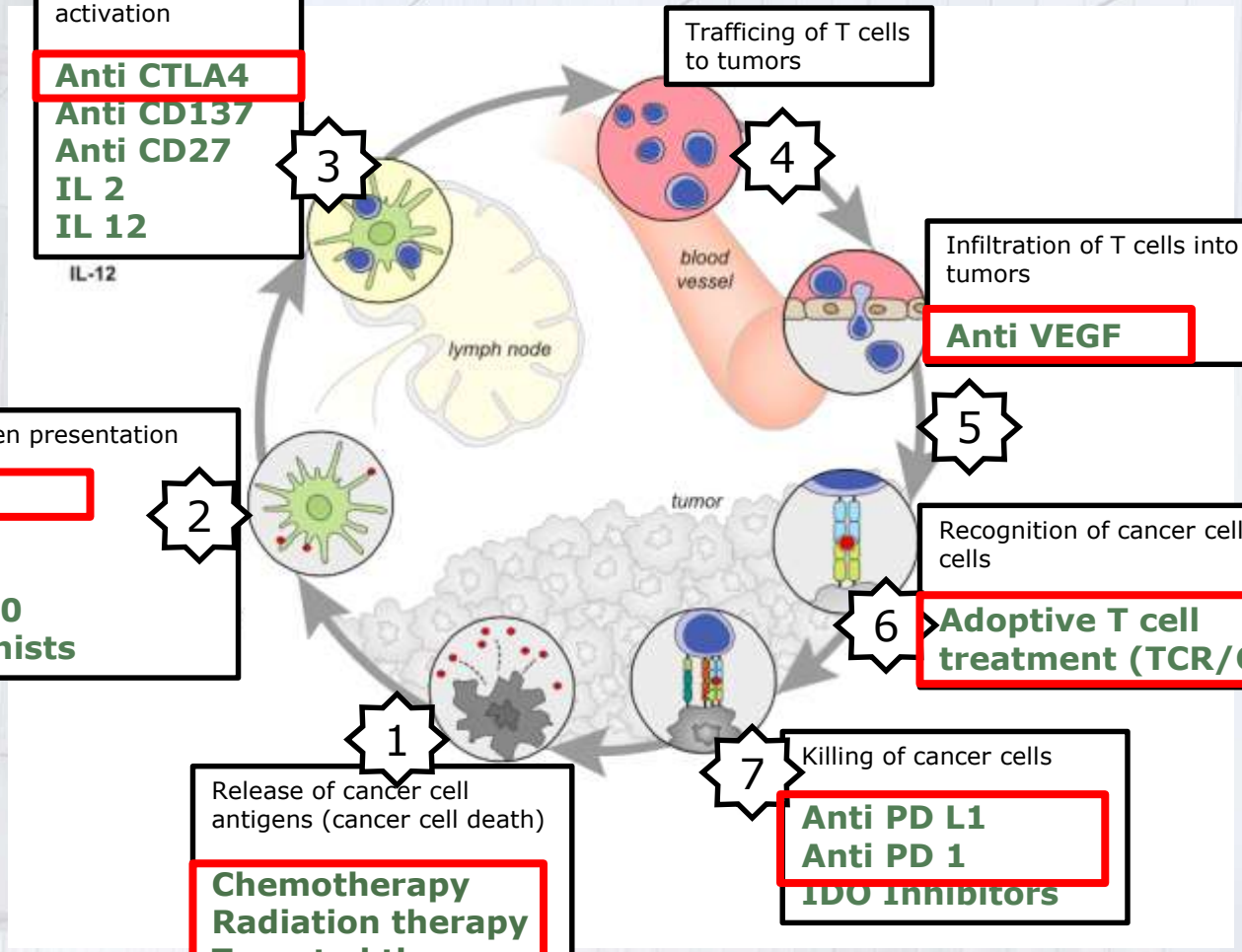

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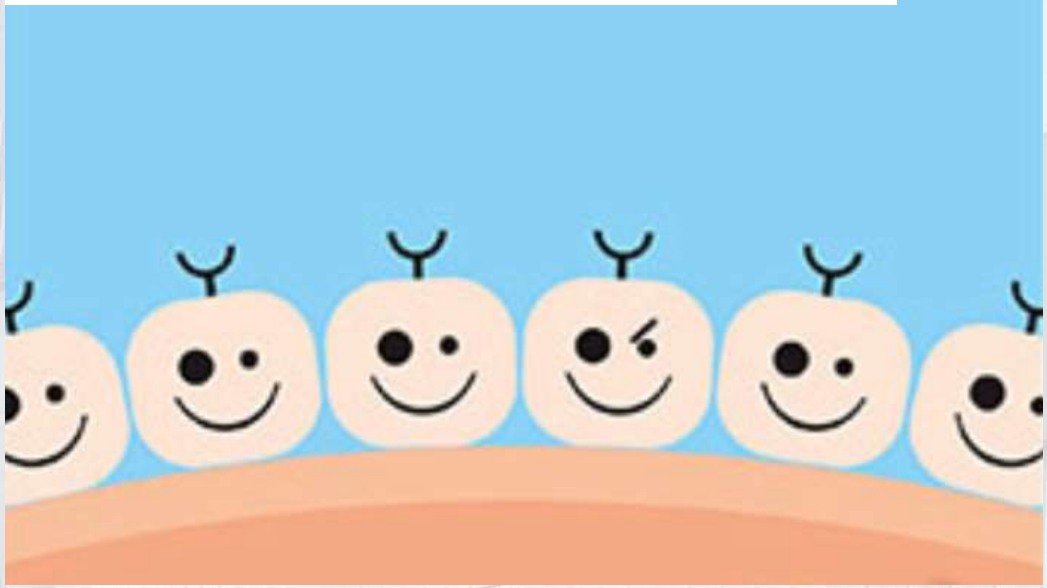
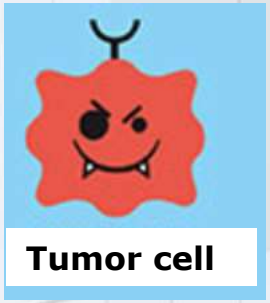
Innate and Adaptive Immunity

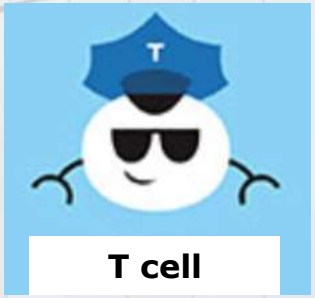
EVERYTHING SEEMS PEACEFUL



Healthy cell



Tumor cell



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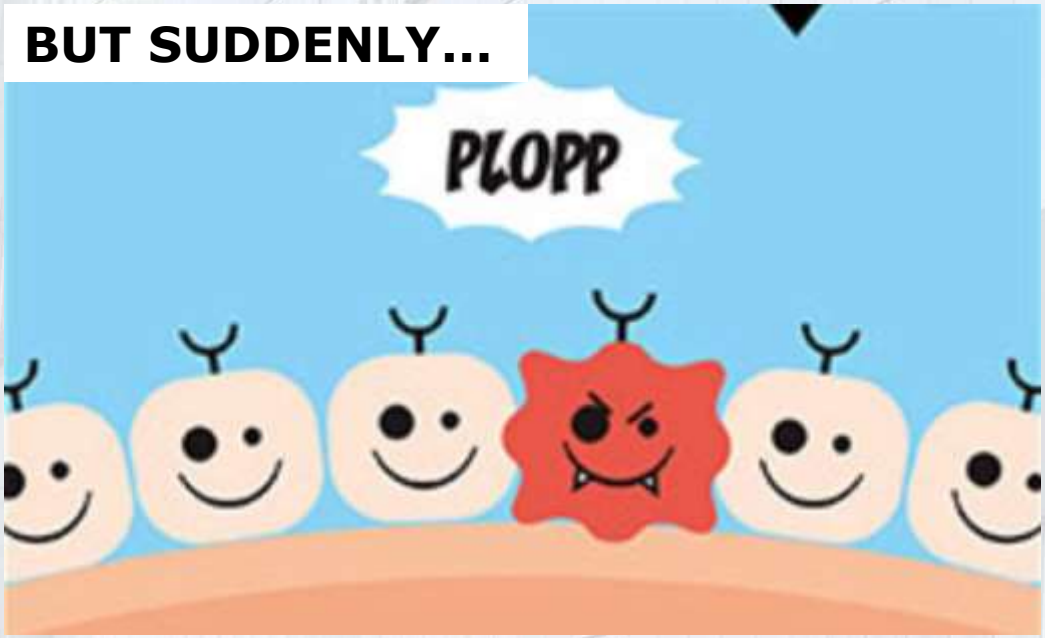


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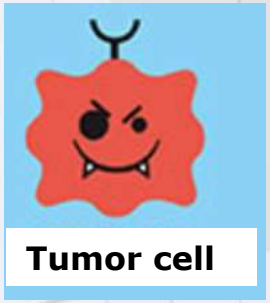
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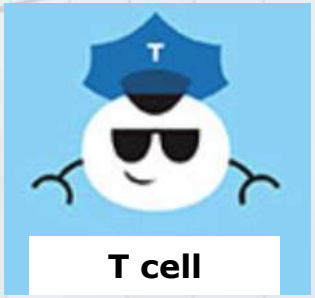

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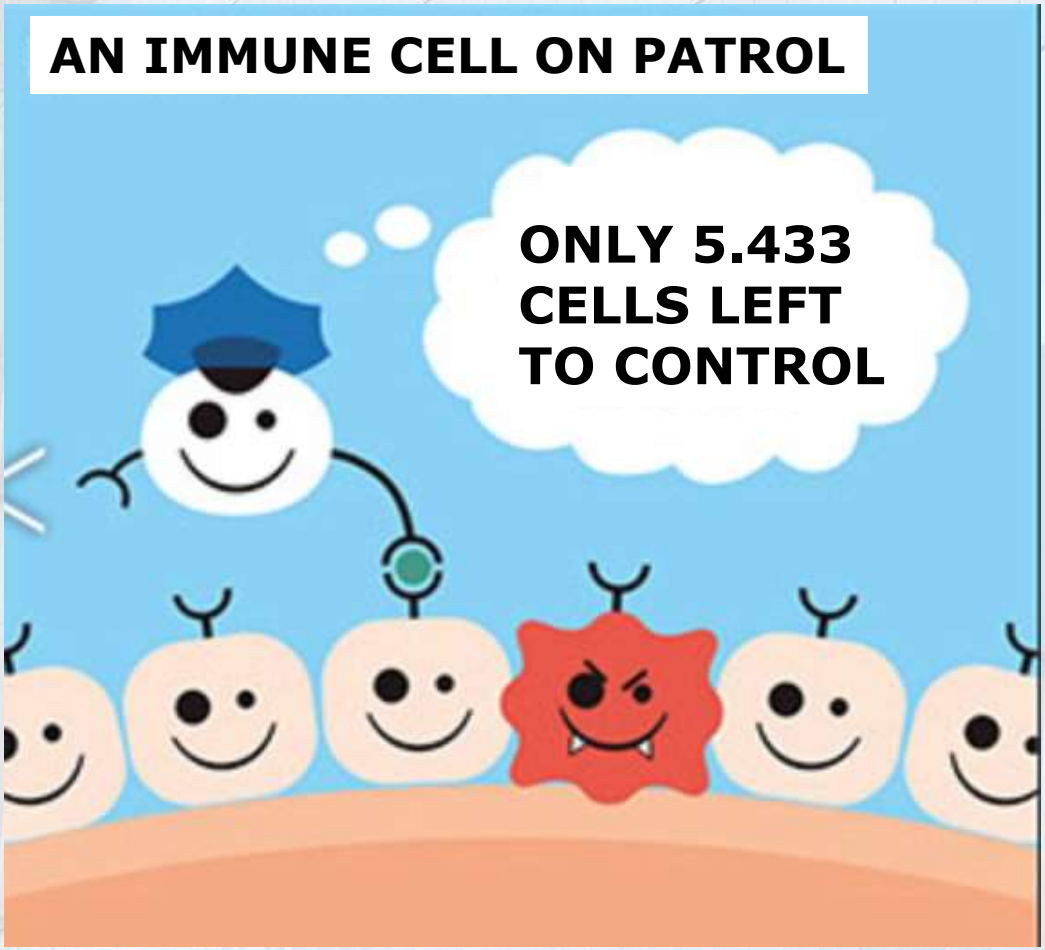

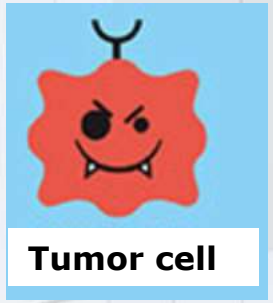

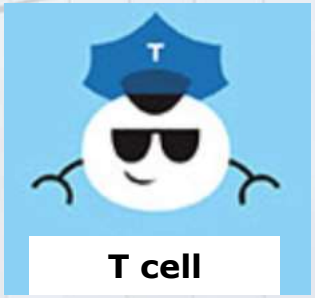

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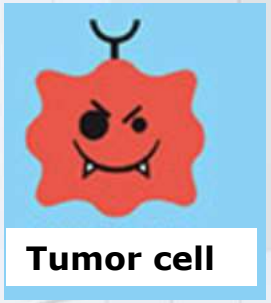
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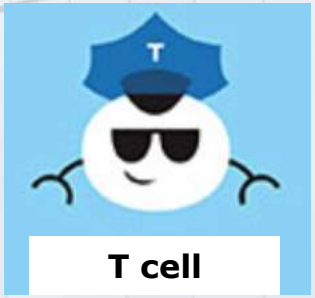

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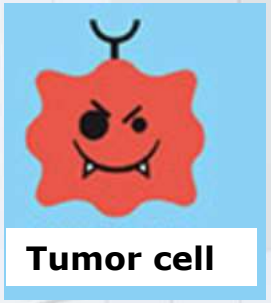

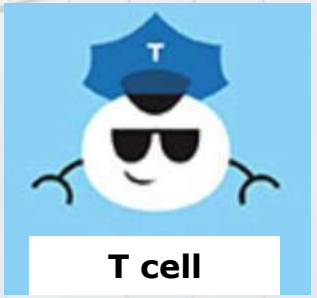

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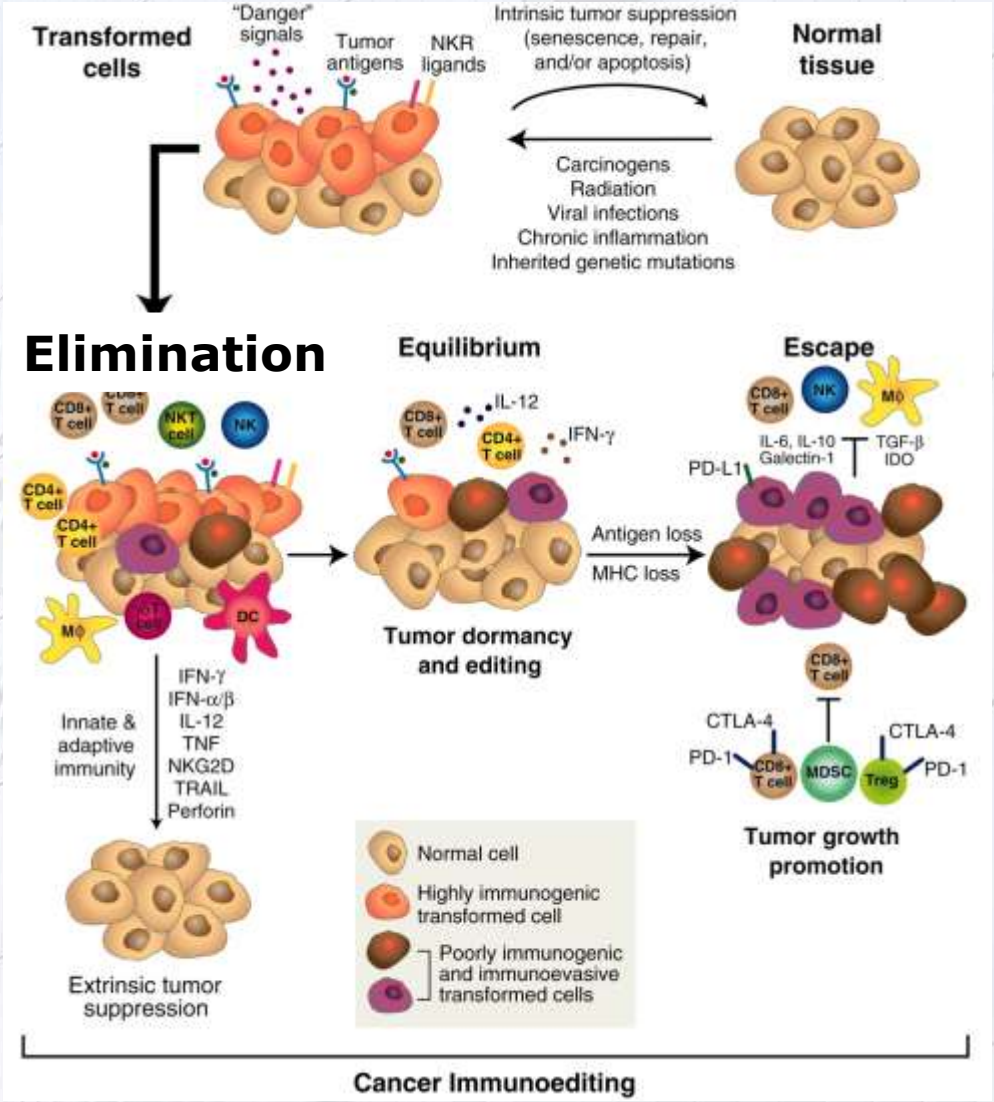
The cancer immunoediting concept



Schreiber RD et al. Science. 2011;33:1565-70

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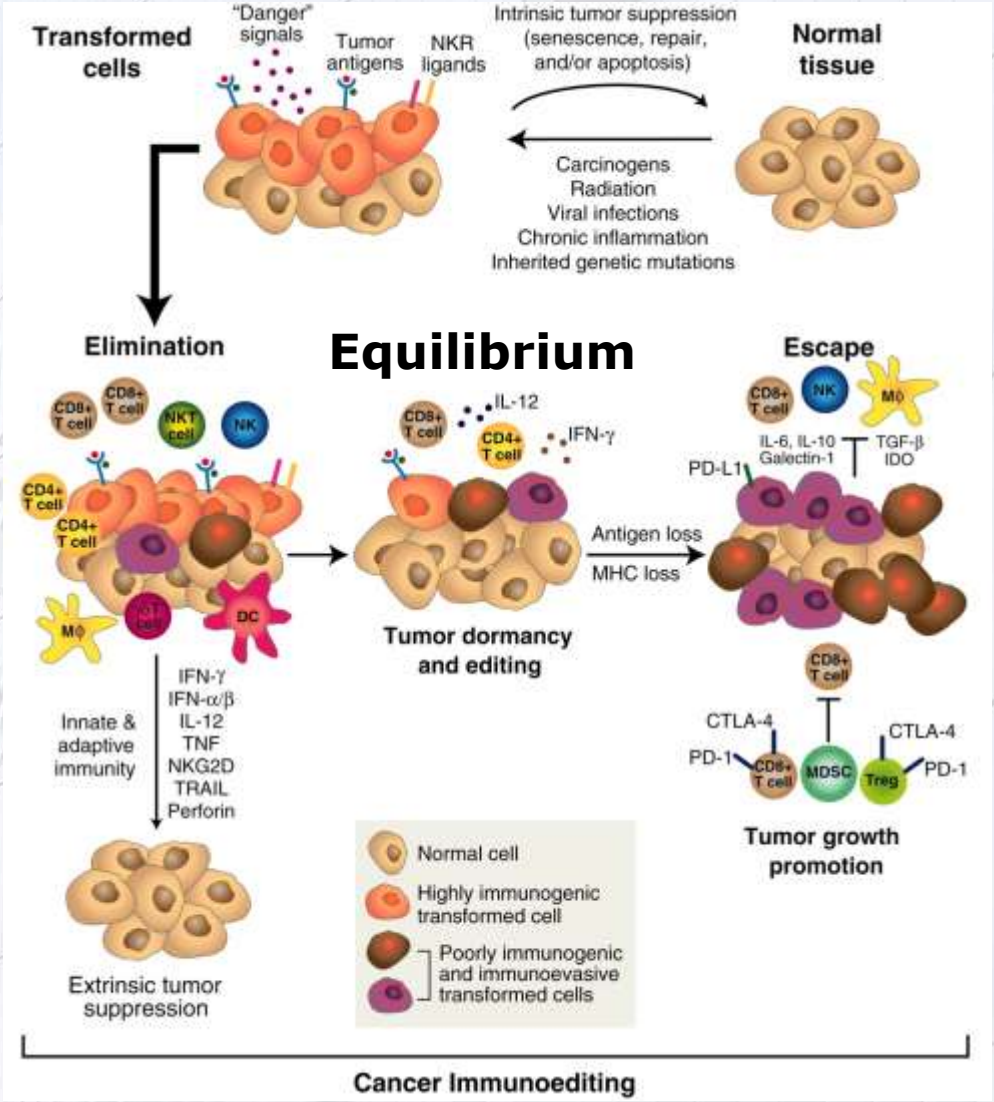

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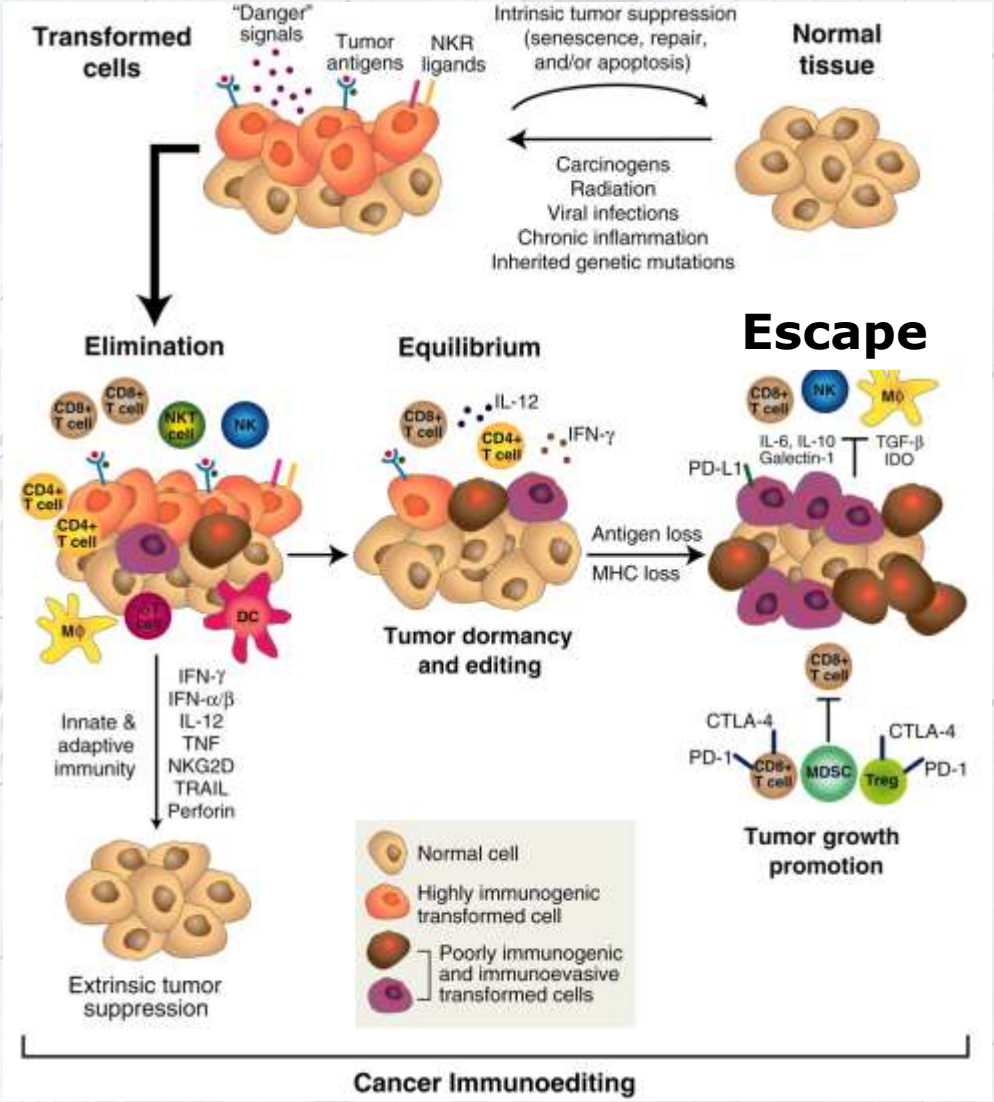

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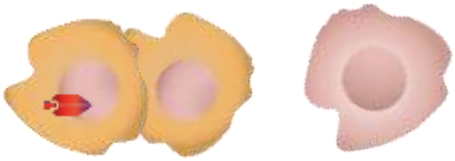
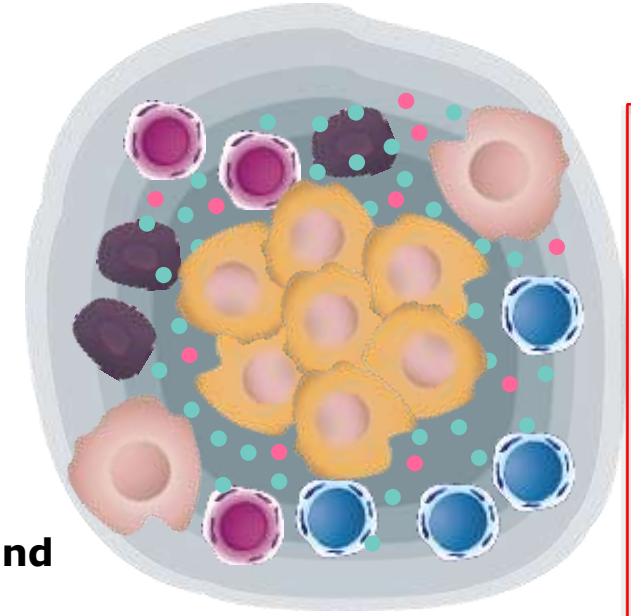
The cancer immunoediting concept

Reduced presentation of tumor antigens



Tumor cell APC

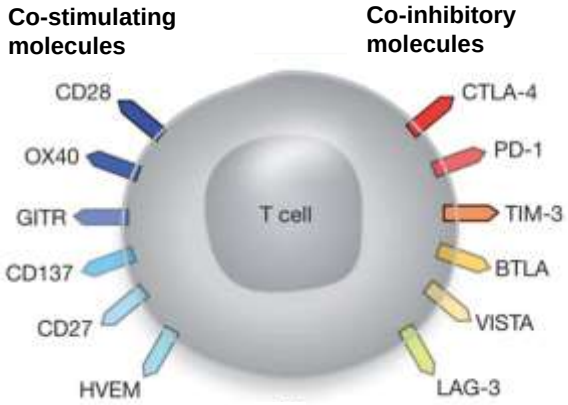


Recruitment of immunsuppressive cells and factors

Regulatory T cells Myeloid suppressor cells

Tumor microenvironment

T-Cell Immune-Checkpoint Modulation



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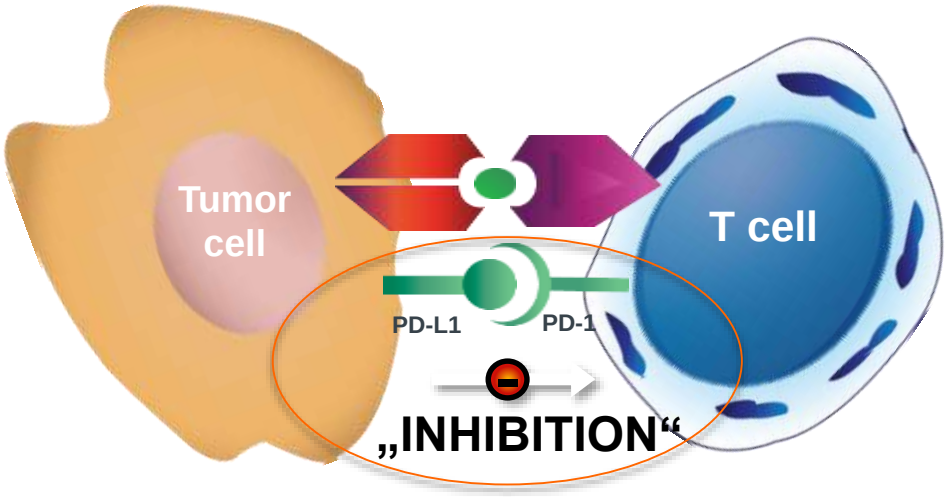
Innate and Adaptive Immunity

PD-1 pathway: inhibits the tumor specific immune response



Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264..

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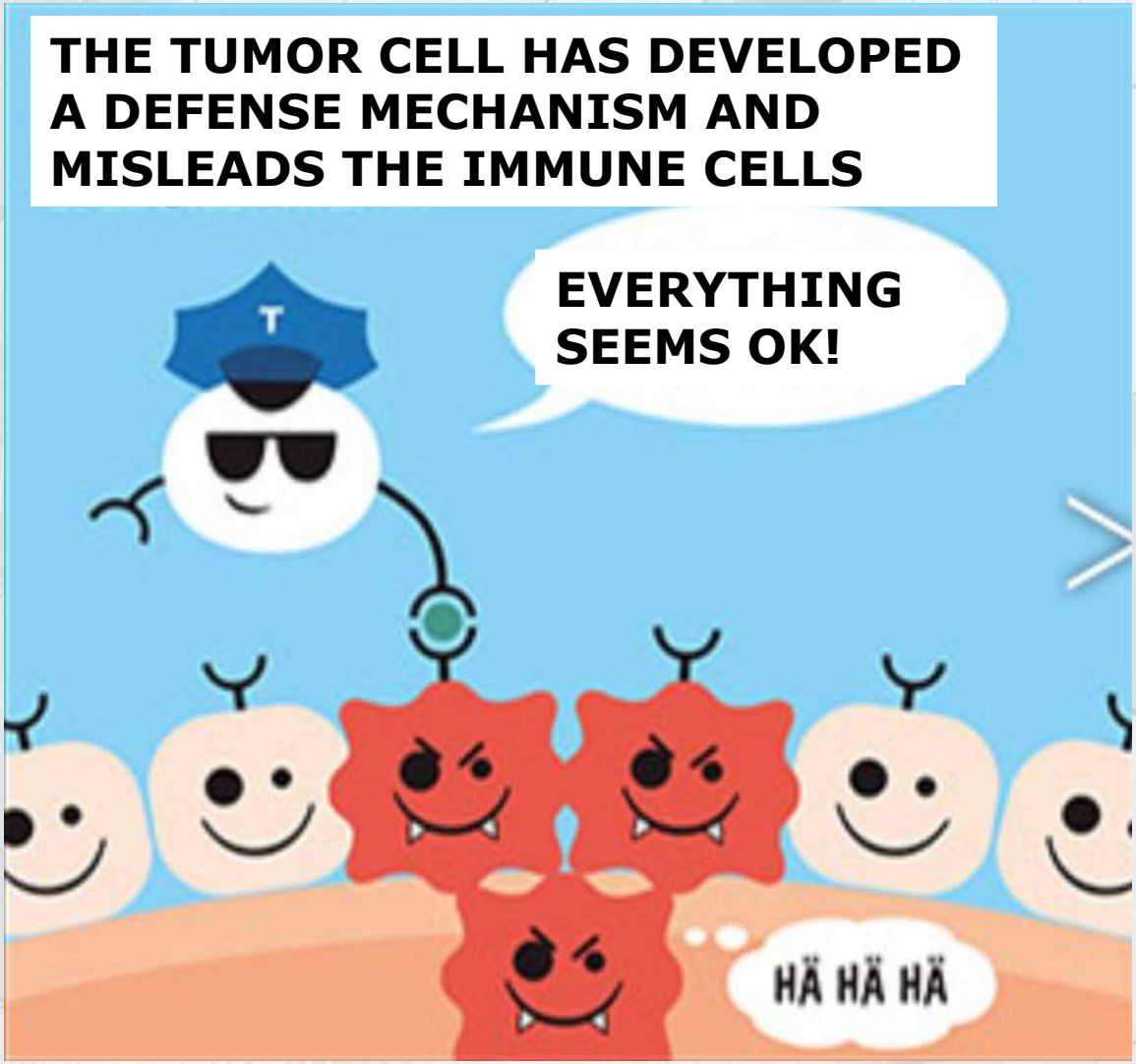
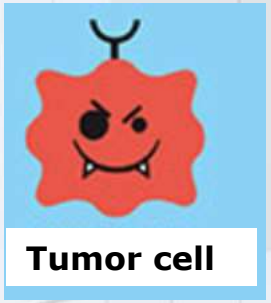
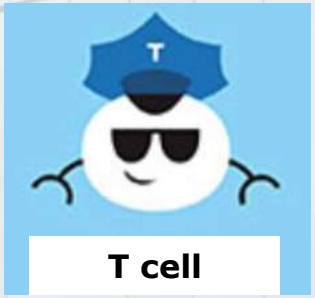
Innate and Adaptive Immunity



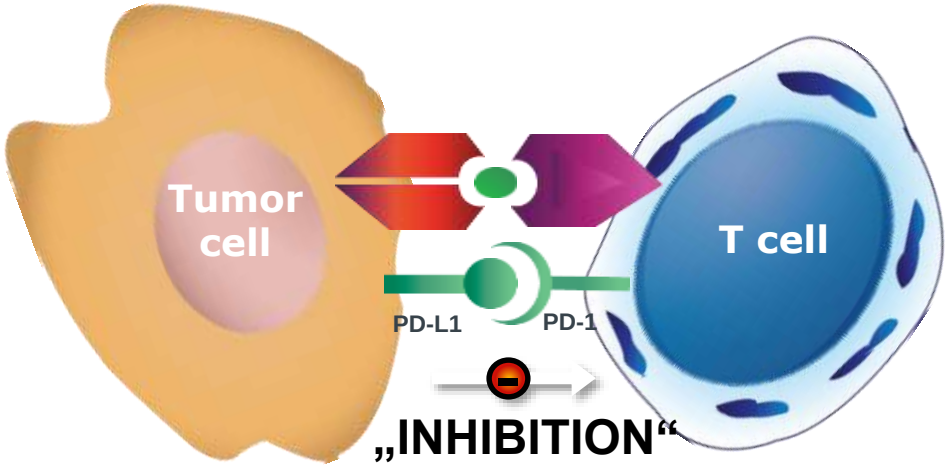




http://www.kampfgegenkrebs.ch/das-immunsystem-sagt-dem-krebs-den-kampf-an

Innate and Adaptive Immunity

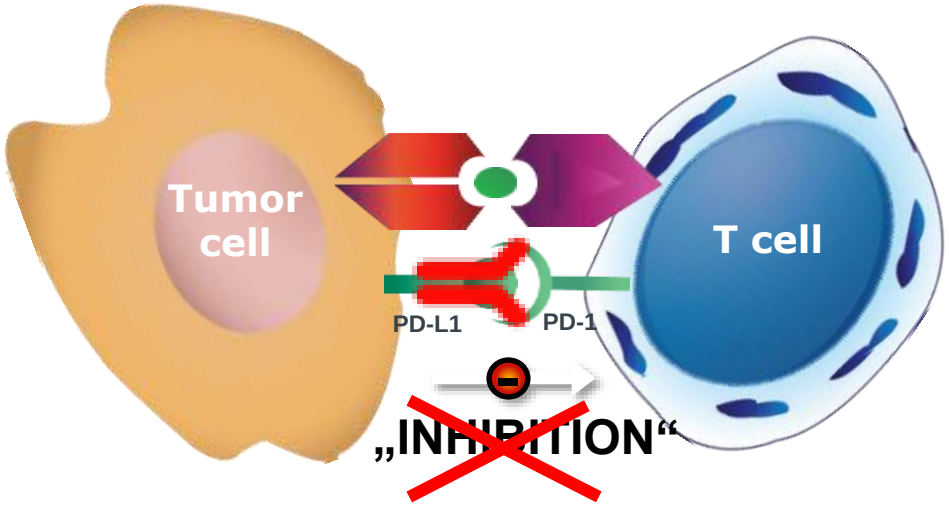
PD-1 pathway: the inhibition of the immune system can be reversed by immune checkpoint inhibitors



Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264..

Innate and Adaptive Immunity

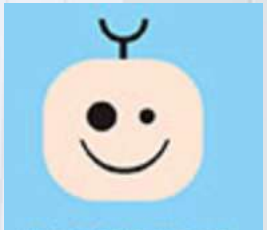
PD-1 pathway: the inhibition of the immune system can be reversed by immune checkpoint inhibitors



Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264..

Innate and Adaptive Immunity

DUE TO CHECKPOINT INHIBITORS IMMUNE CELLS CANNOT BE MISLEADED ANY MORE


Healthy cell


Tumor cell

T cell

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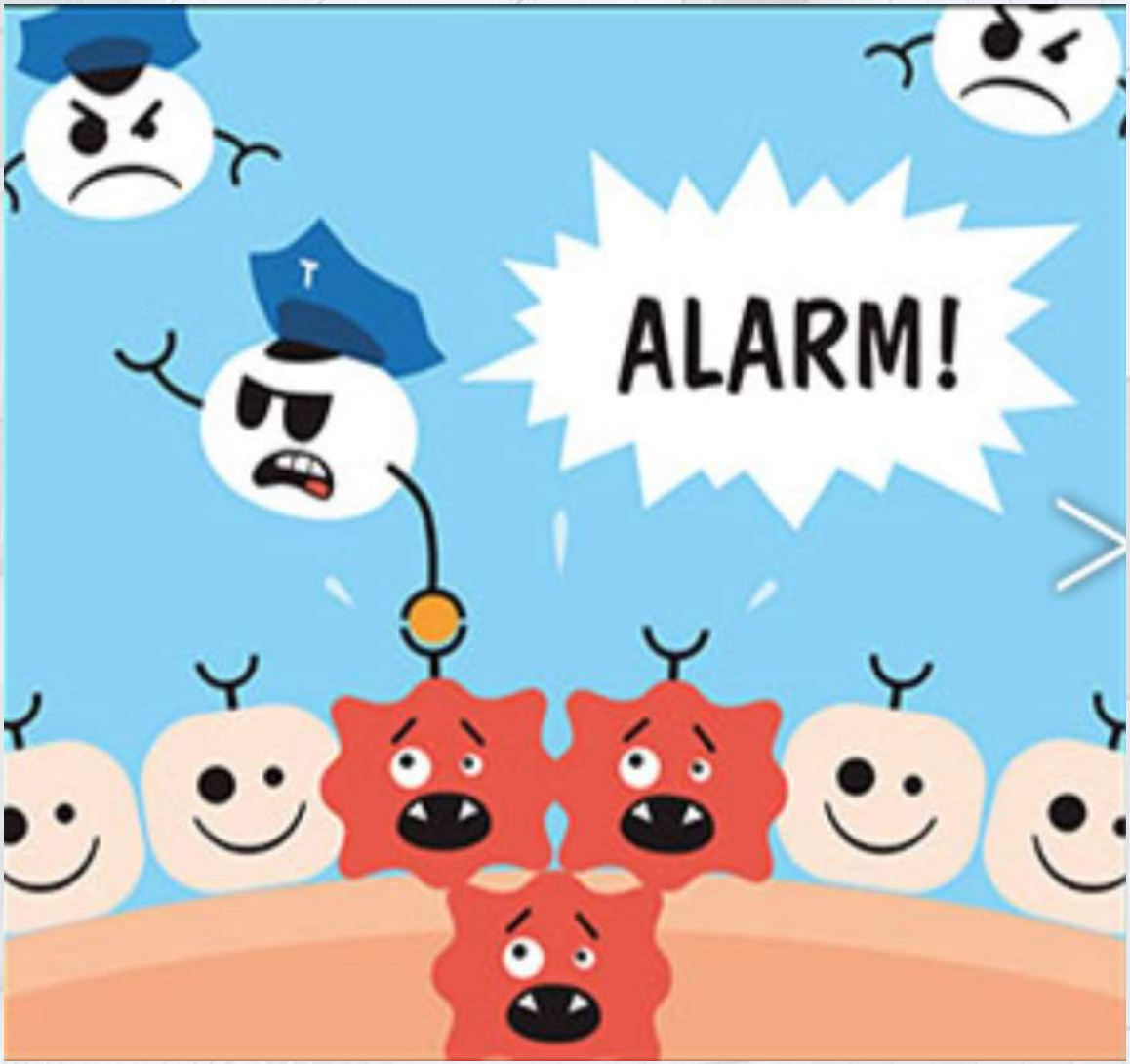
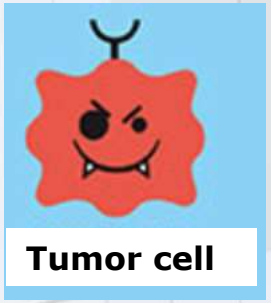
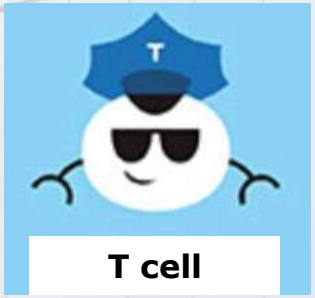
Innate and Adaptive Immunity




Healthy cell


Tumor cell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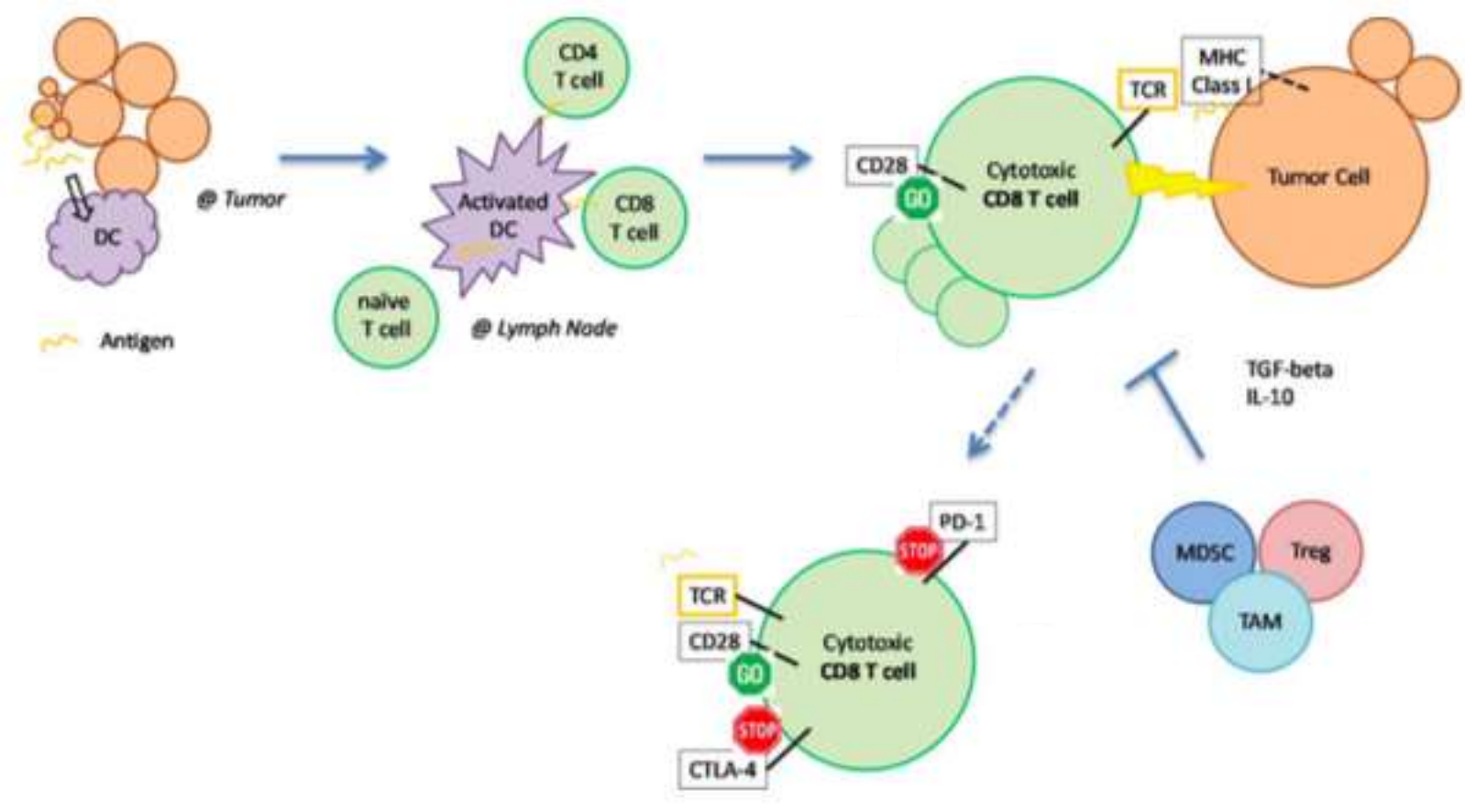
Adoptive T Cell Therapy and Immune Checkpoint Inhibitors



Tseng WW et al. Human Vaccines & Immunotherapeutics 10:11, 3117--3124

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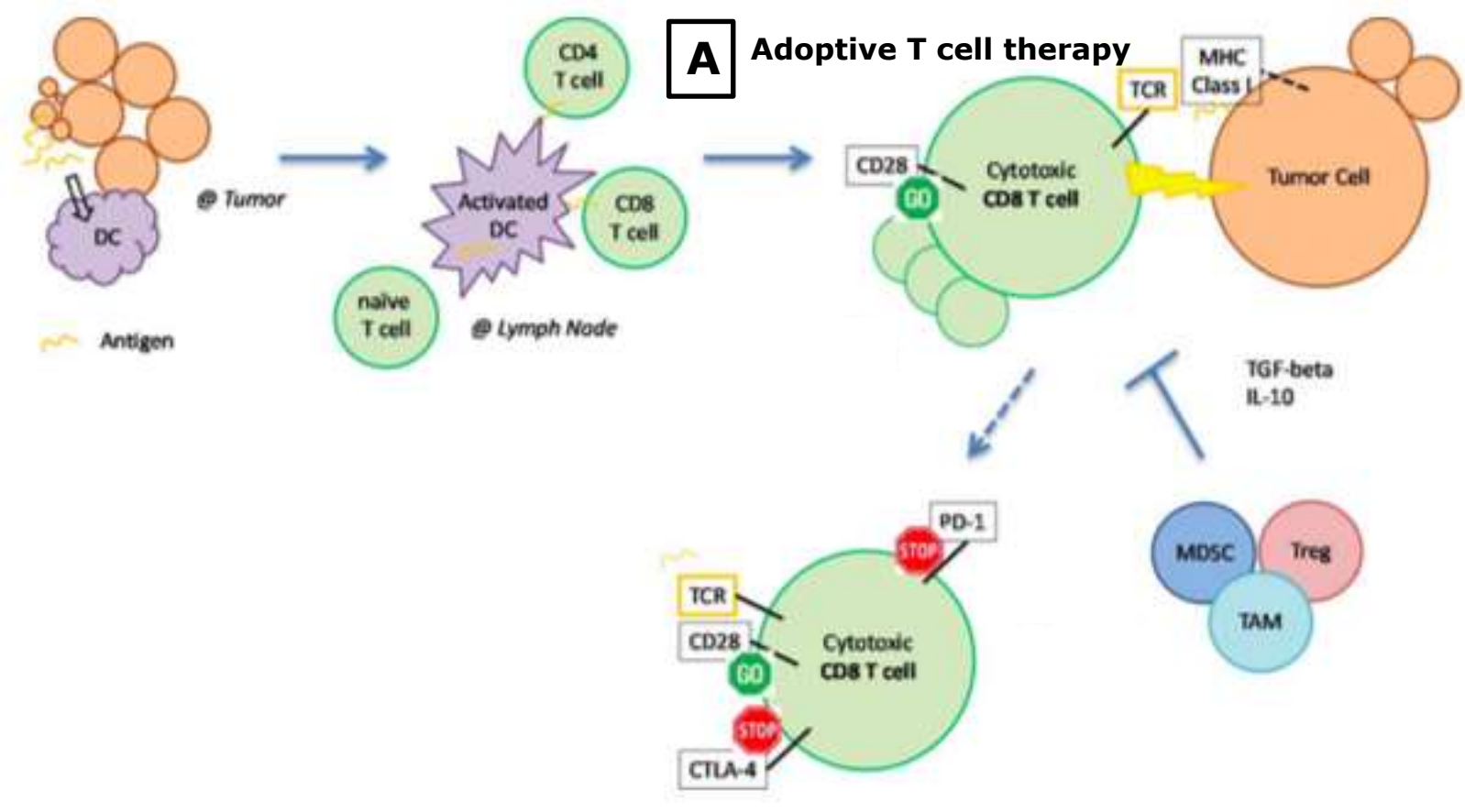

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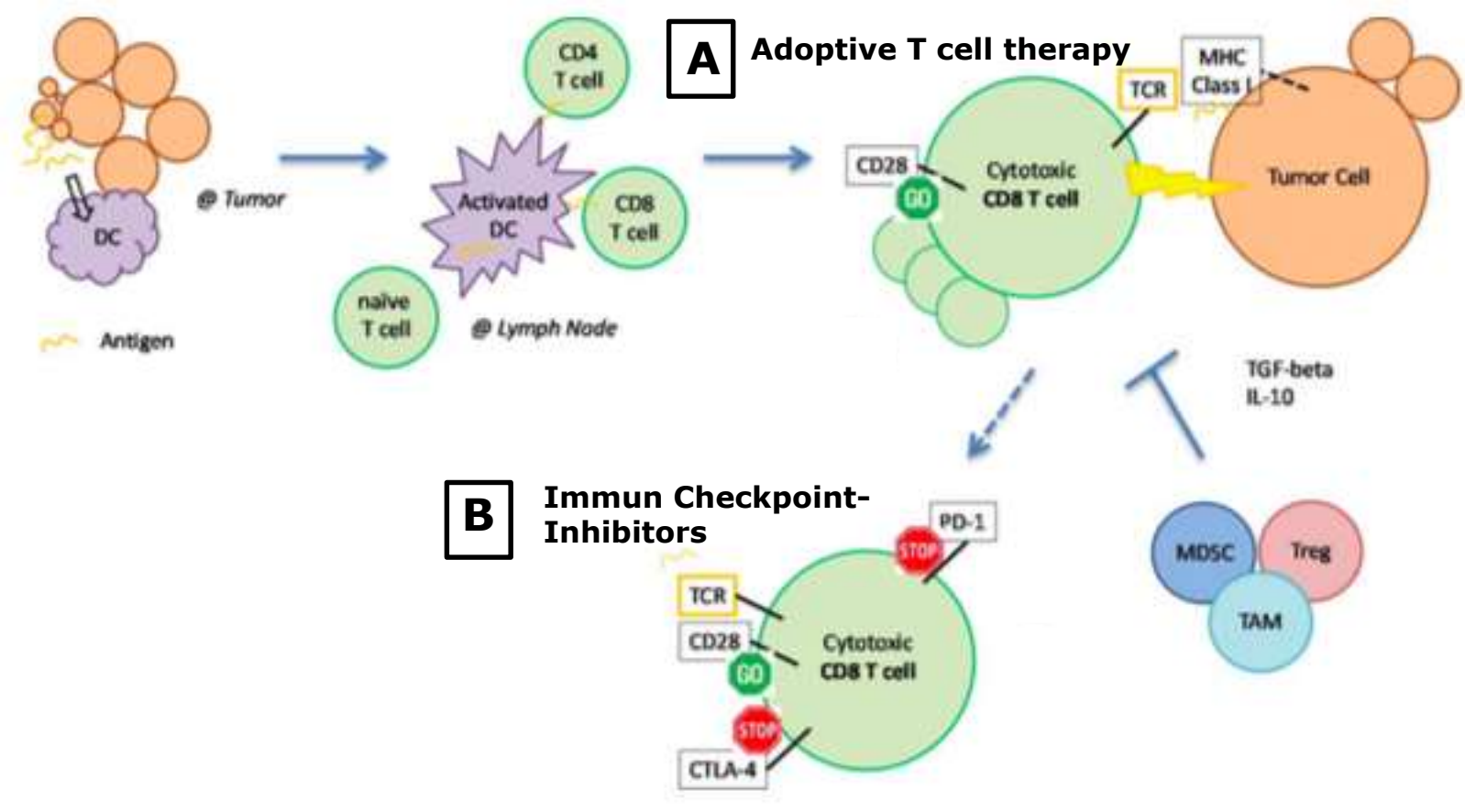

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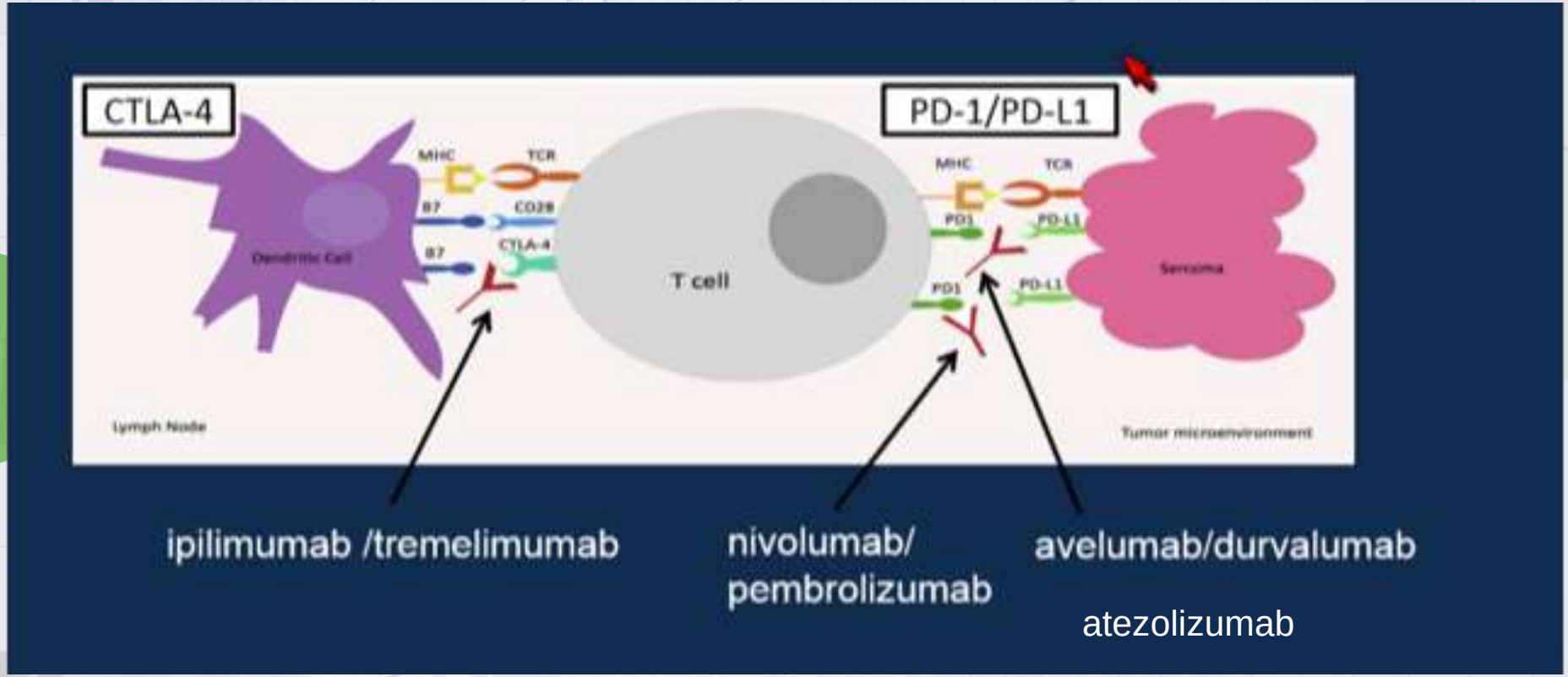
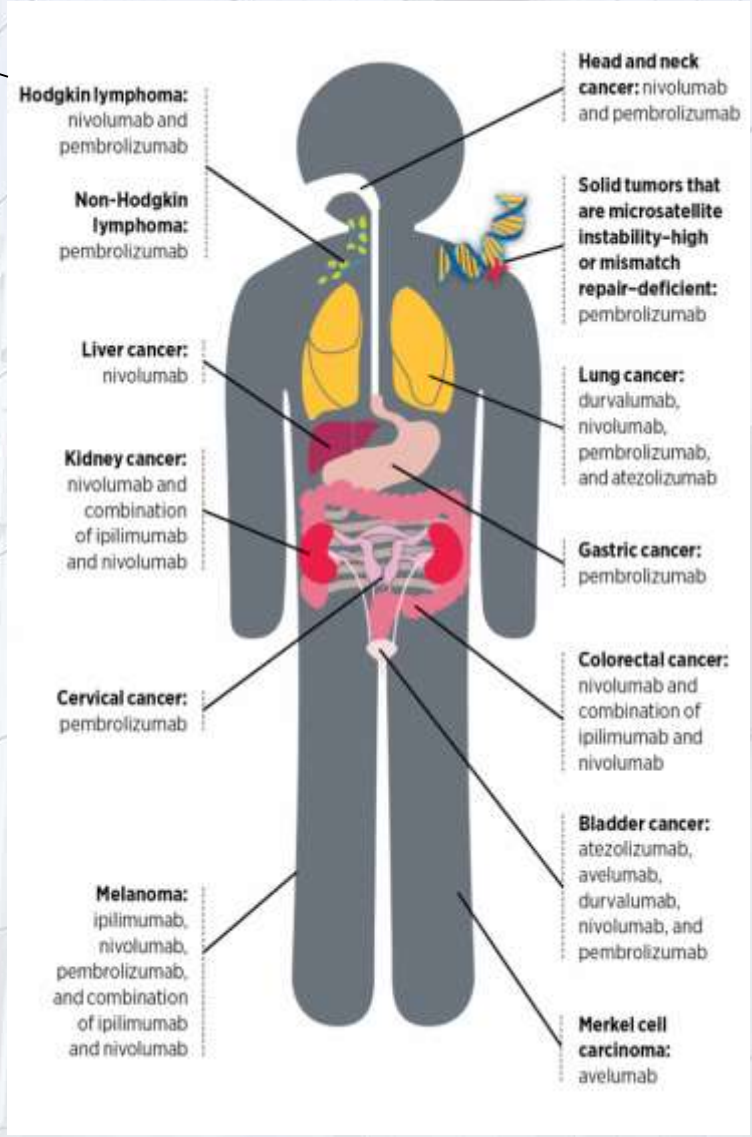
Immune Checkpoint Inhibitors



Immune Checkpoint Inhibitors

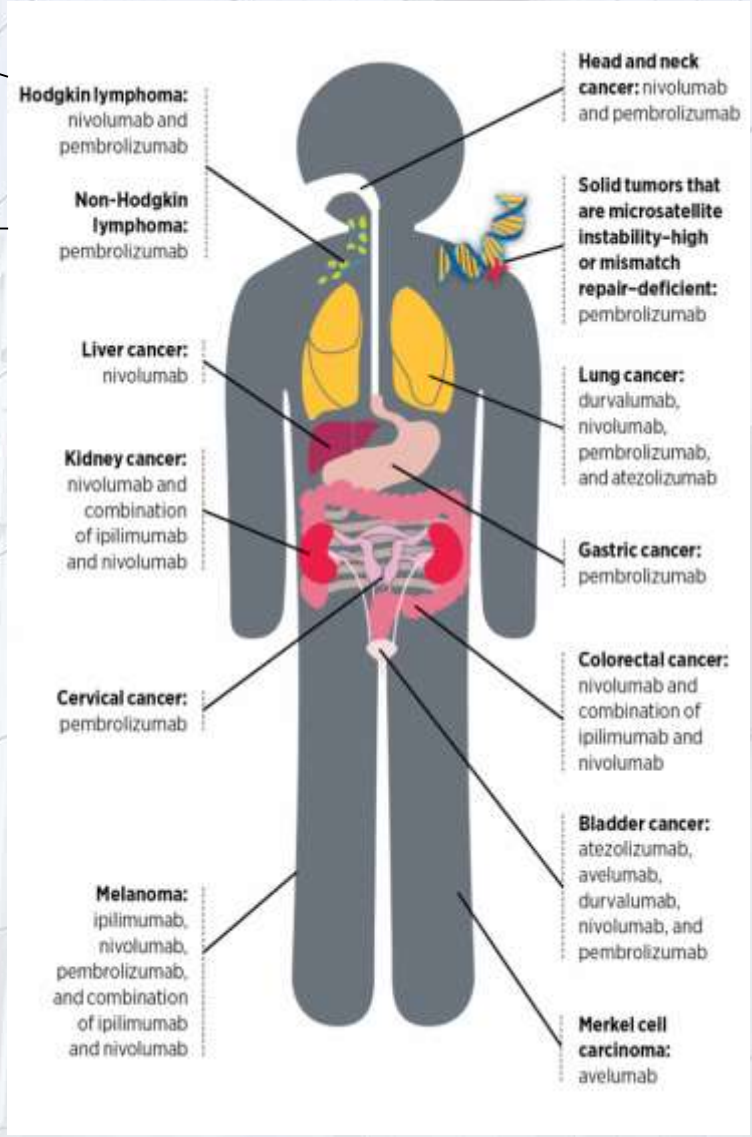
Hodgkin lymphoma



Immune Checkpoint Inhibitors

Hodgkin lymphoma

Non-Hodgkin lymphoma

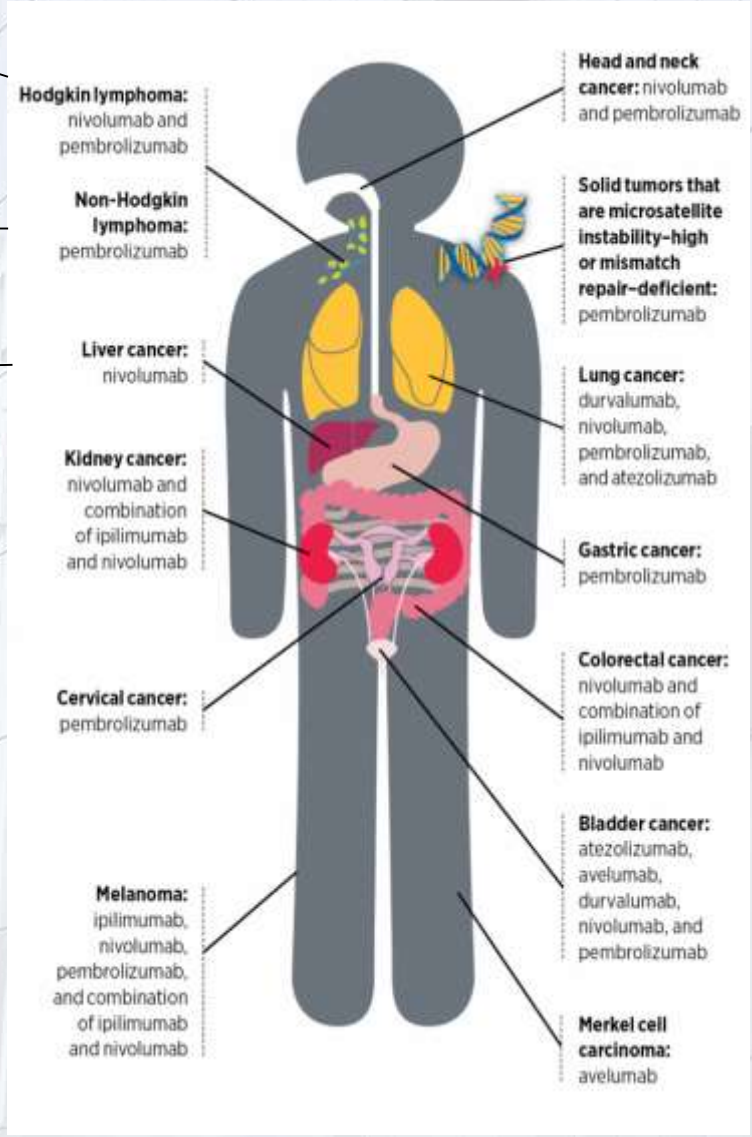


Immune Checkpoint Inhibitors

Hodgkin lymphoma

Non-Hodgkin lymphoma

Liver cancer



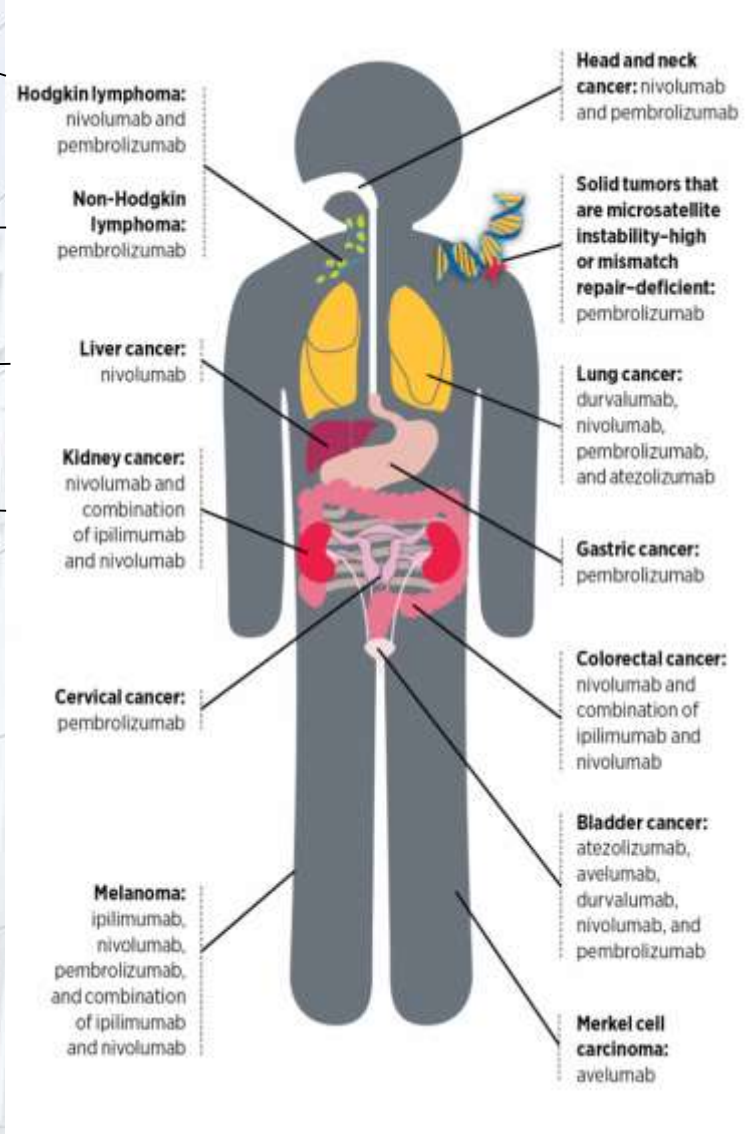
Immune Checkpoint Inhibitors

Hodgkin lymphoma

Non-Hodgkin lymphoma

Liver cancer

Kidney cancer



Immune Checkpoint Inhibitors

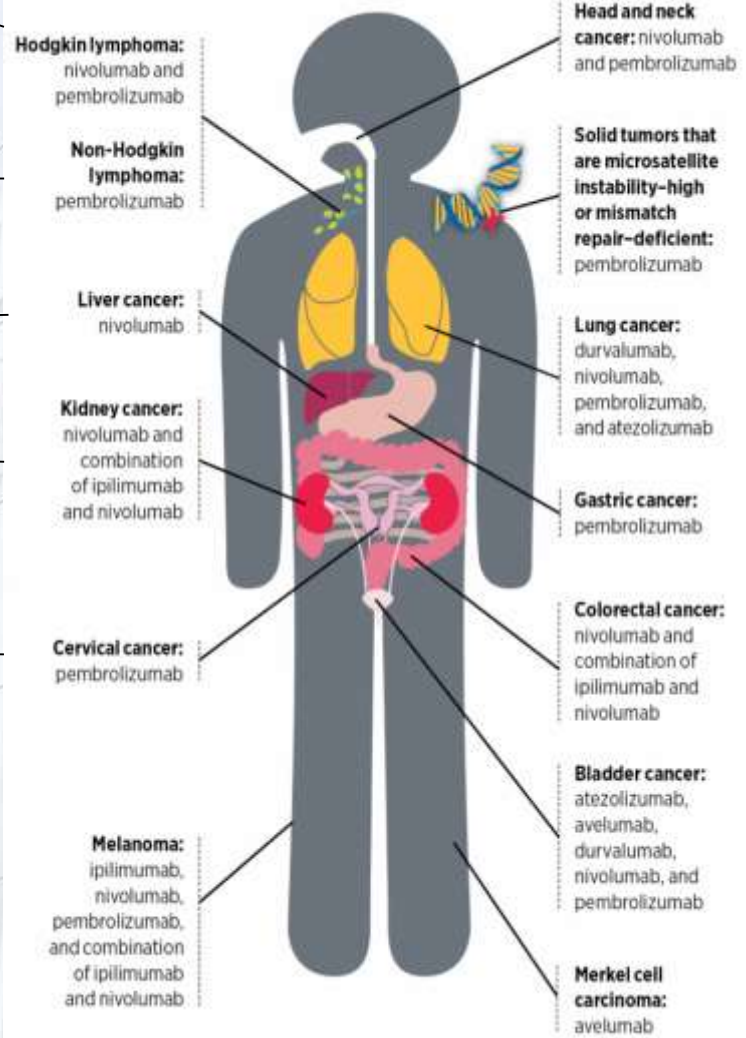
Hodgkin lymphoma

Non-Hodgkin lymphoma

Liver cancer

Kidney cancer

Cervical cancer



Immune Checkpoint Inhibitors

Hodgkin lymphoma

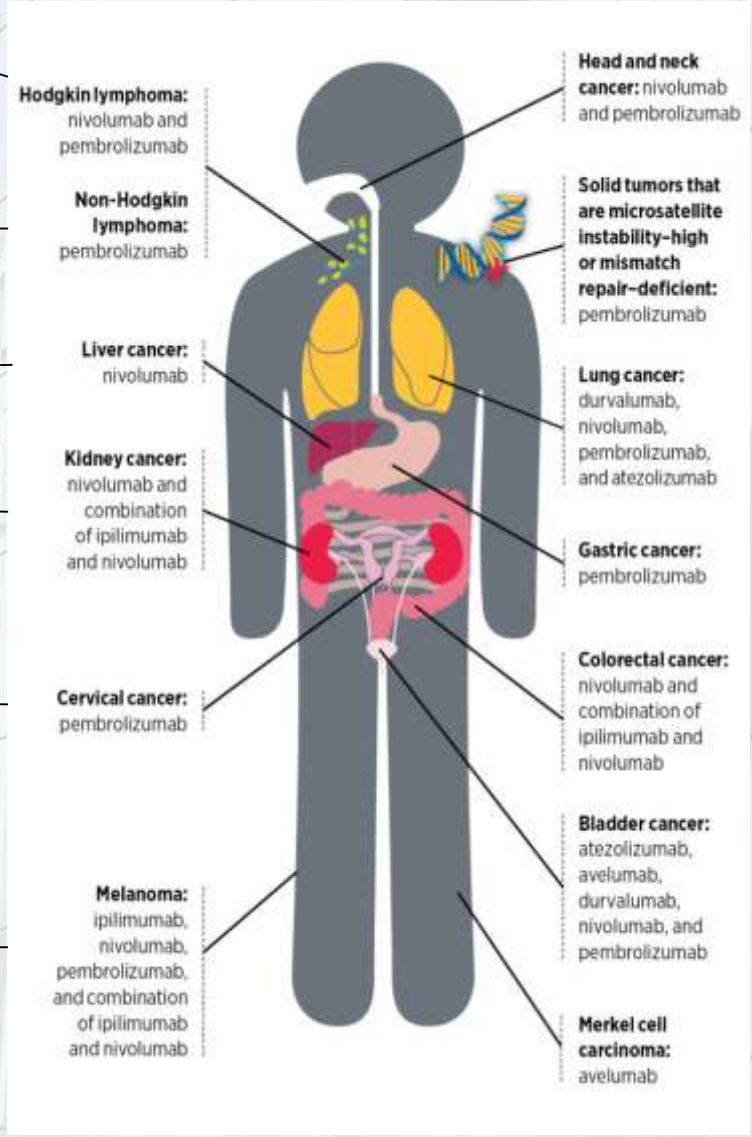
Non-Hodgkin lymphoma

Liver cancer

Kidney cancer

Cervical cancer

Melanoma



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Immune Checkpoint Inhibitors

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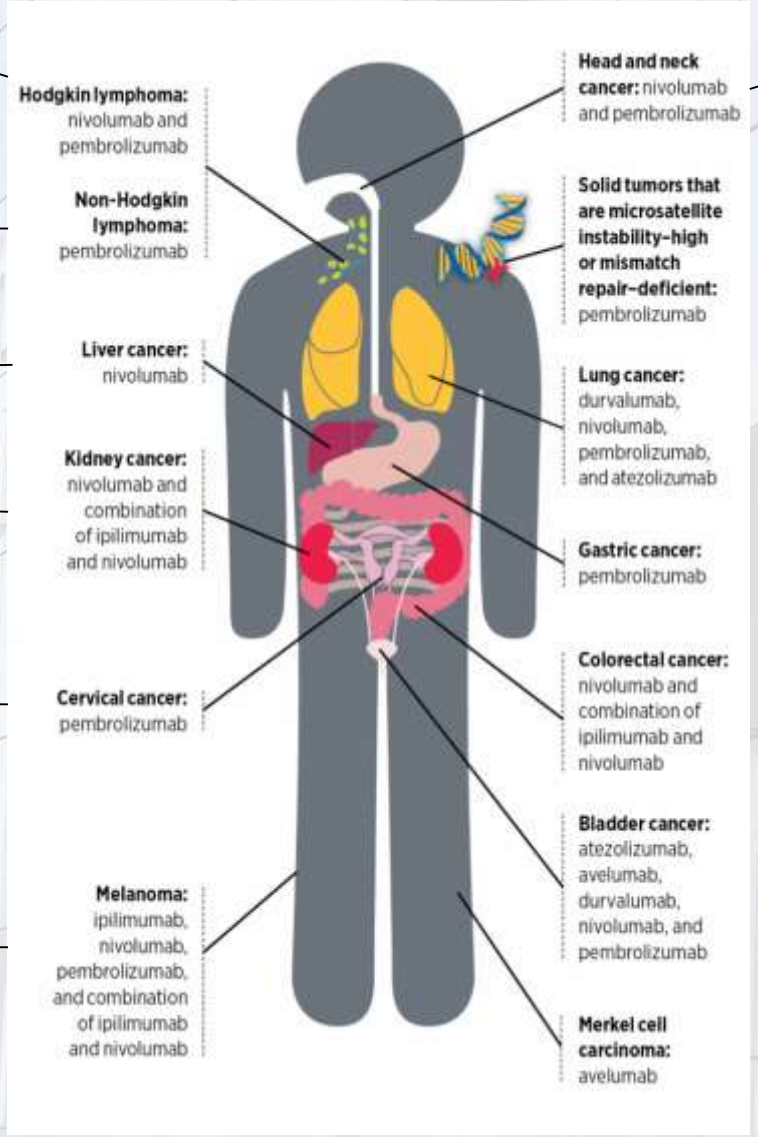

Head and neck cancer

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Immune Checkpoint Inhibitors

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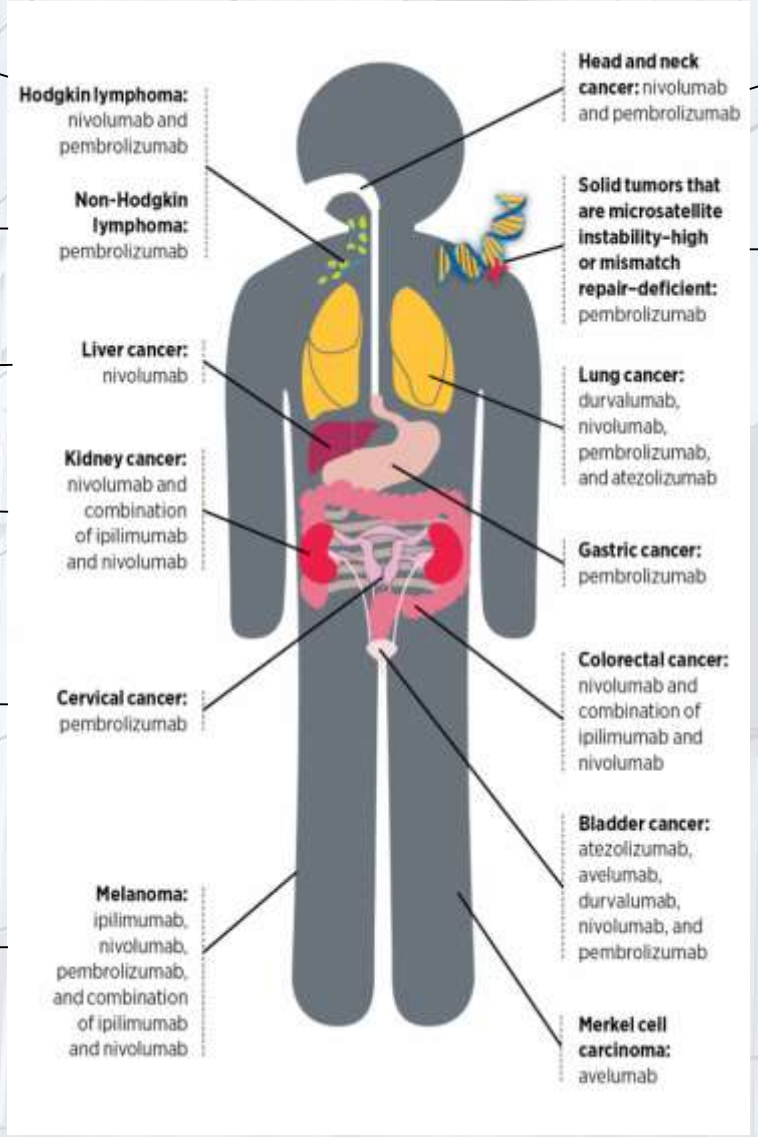
Melanoma



Head and neck cancer

Solid tumors that are microsatellite instability high or mismatch repair-deficient

Immune Checkpoint Inhibitors

Hodgkin lymphoma

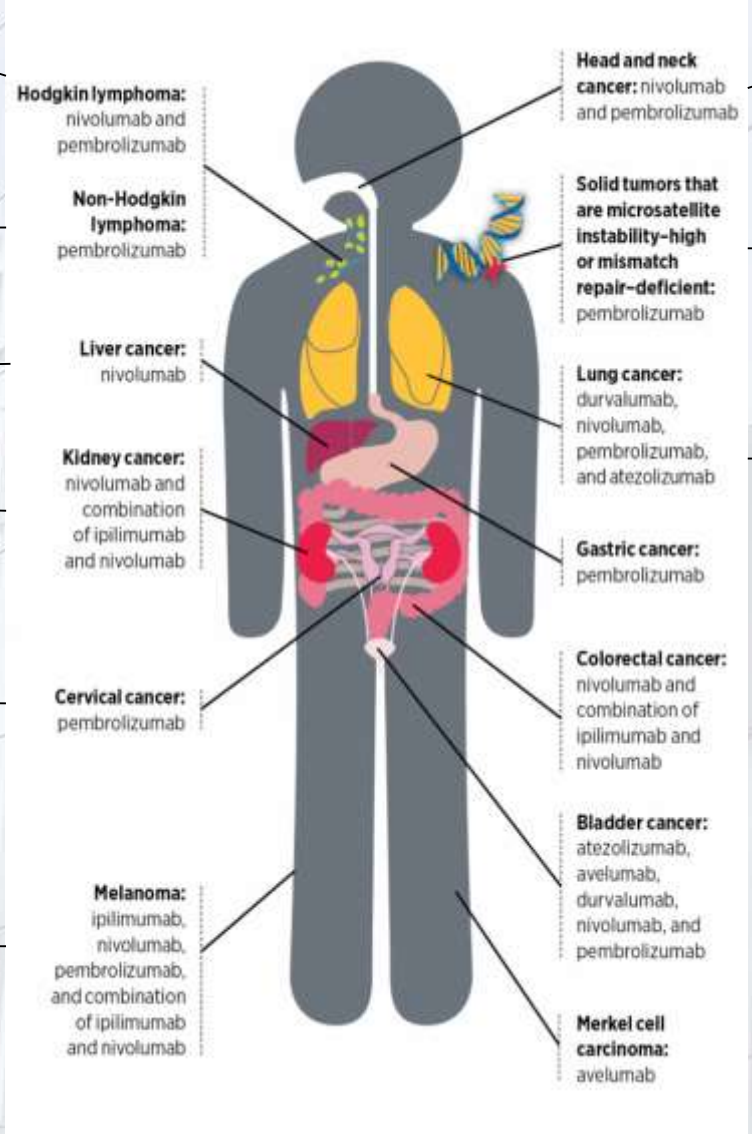
Non-Hodgkin lymphoma

Liver cancer

Kidney cancer

Cervical cancer

Melanoma



Head and neck cancer

Solid tumors that are microsatellite instability high or mismatch repair-deficient

Lung cancer

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Immune Checkpoint Inhibitors

Hodgkin lymphoma

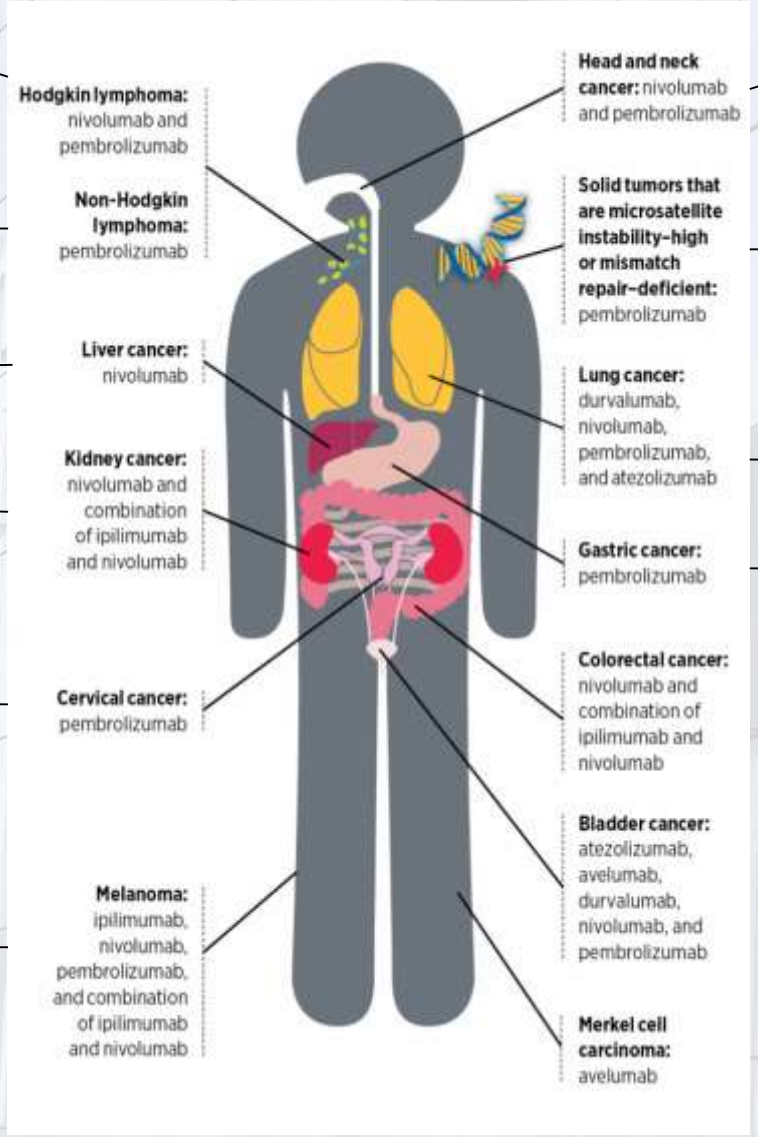
Non-Hodgkin lymphoma

Liver cancer

Kidney cancer

Cervical cancer

Melanoma



Head and neck cancer

Solid tumors that are microsatellite instability high or mismatch repair-deficient

Lung cancer

Gastric cancer

Immune Checkpoint Inhibitors

Hodgkin lymphoma

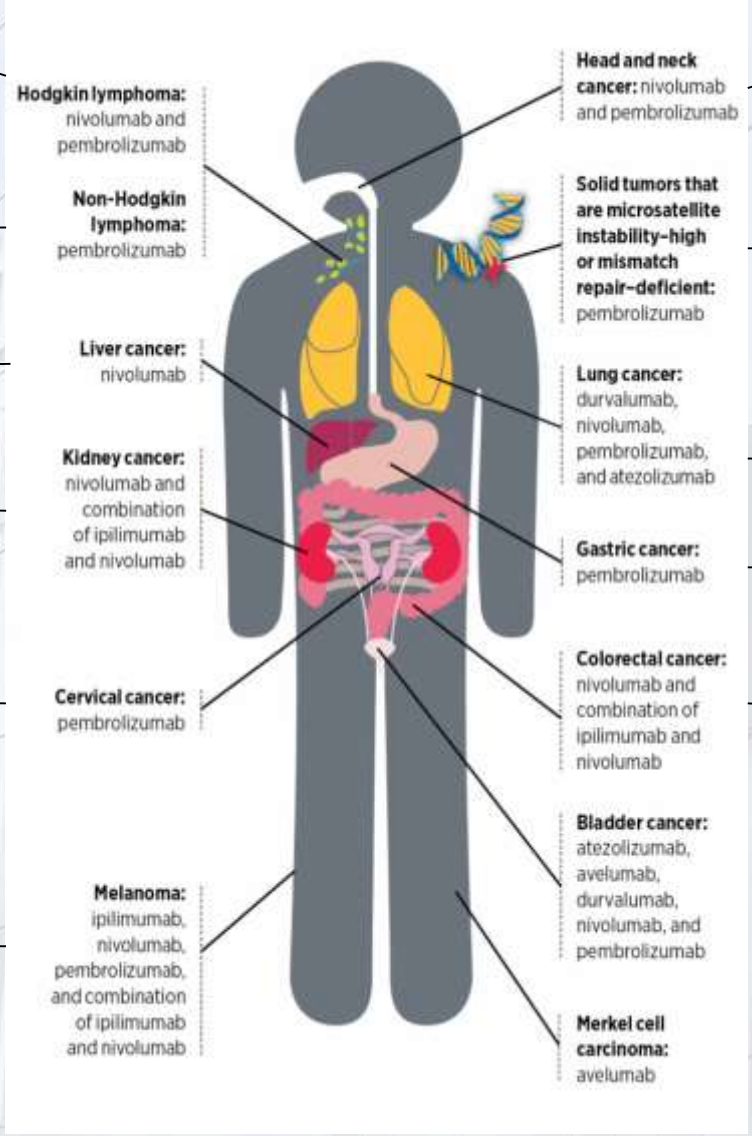
Non-Hodgkin lymphoma

Liver cancer

Kidney cancer

Cervical cancer

Melanoma



Head and neck cancer

Solid tumors that are microsatellite instability high or mismatch repair-deficient

Lung cancer

Gastric cancer

Colorectal cancer

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Immune Checkpoint Inhibitors

Hodgkin lymphoma

Non-Hodgkin lymphoma

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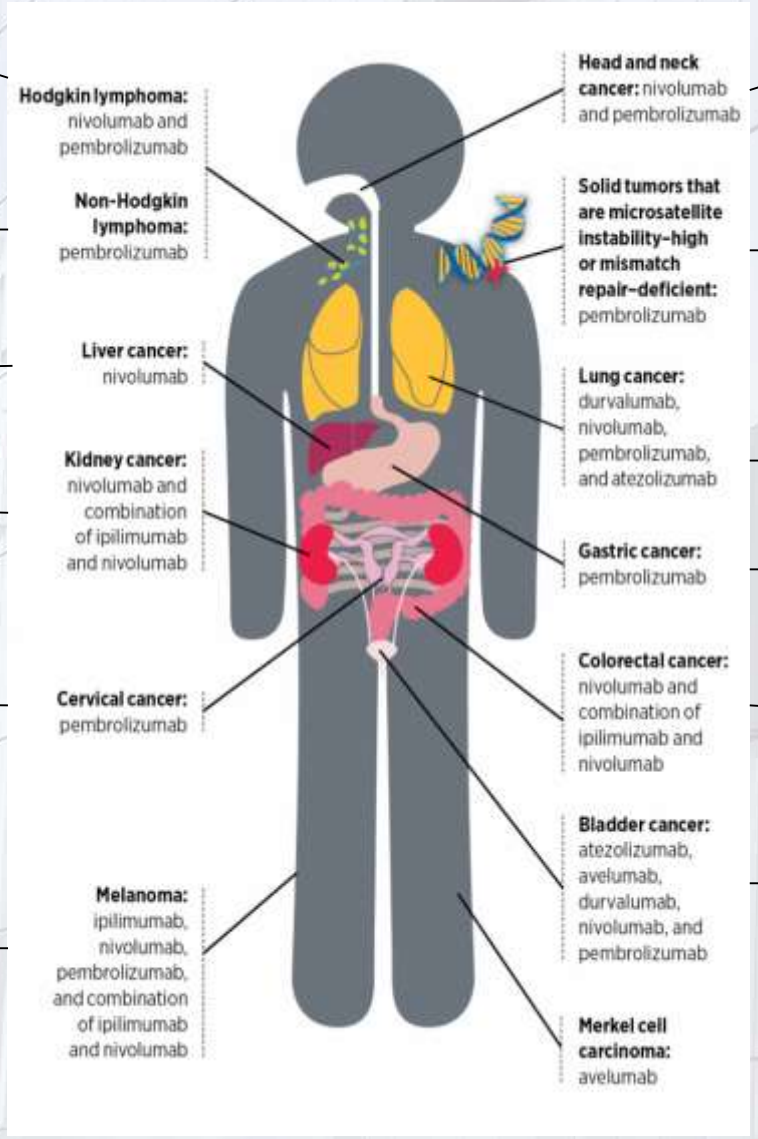

Head and neck cancer

Solid tumors that are microsatellite instability high or mismatch repair-deficient

Lung cancer

Gastric cancer

Colorectal cancer

Bladder cancer

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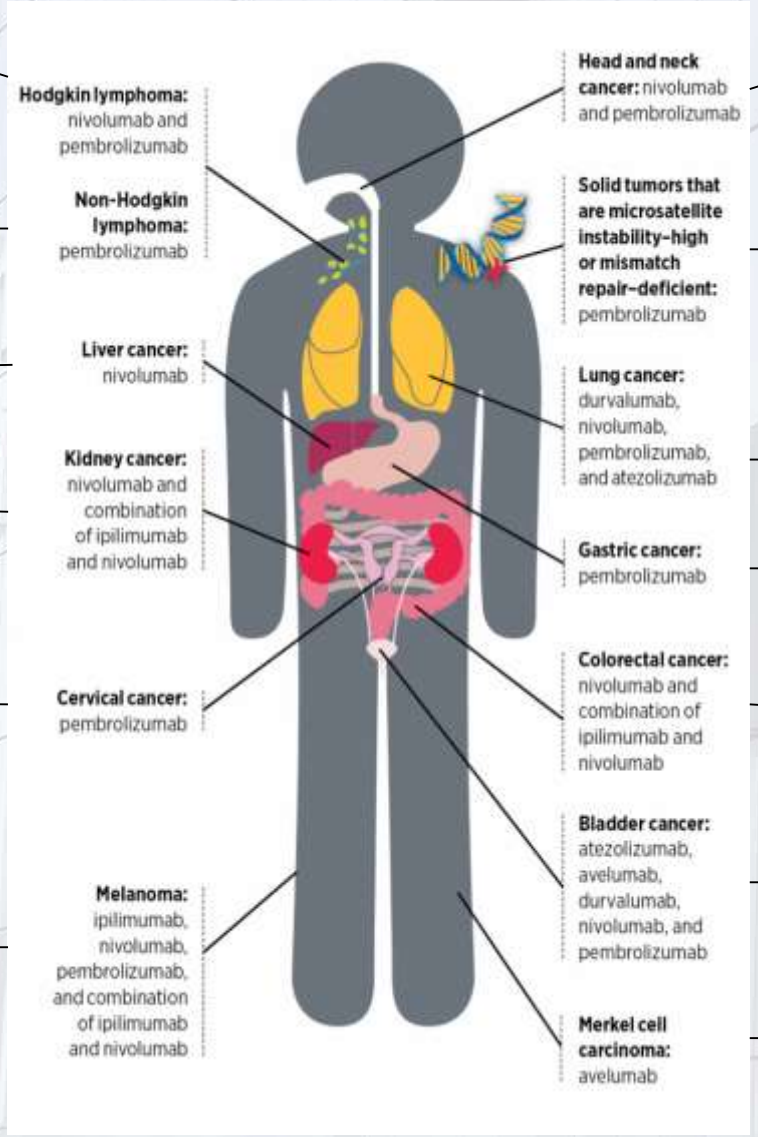
Immune Checkpoint Inhibitors



Hodgkin lymphoma

Non-Hodgkin lymphoma

Liver cancer

Kidney cancer

Cervical cancer

Melanoma

Head and neck cancer

Solid tumors that are microsatellite instability high or mismatch repair-deficient

Lung cancer

Gastric cancer

Colorectal cancer

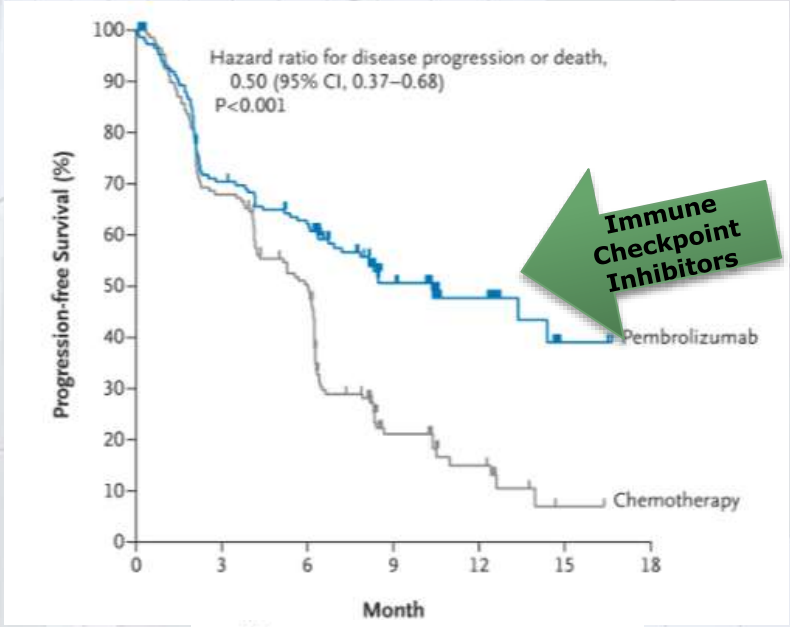
Bladder cancer

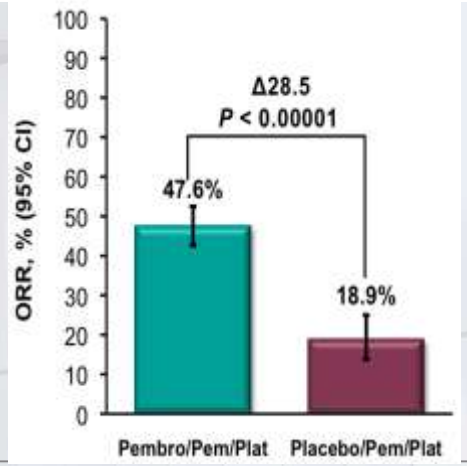
Merkel cell carcinoma

Immune Checkpoint Inhibitors

Lung cancer

- First line treatment in tumors with high PD-L1 expression
- Second line treatment after chemotherapy
- Combination with chemotherapy

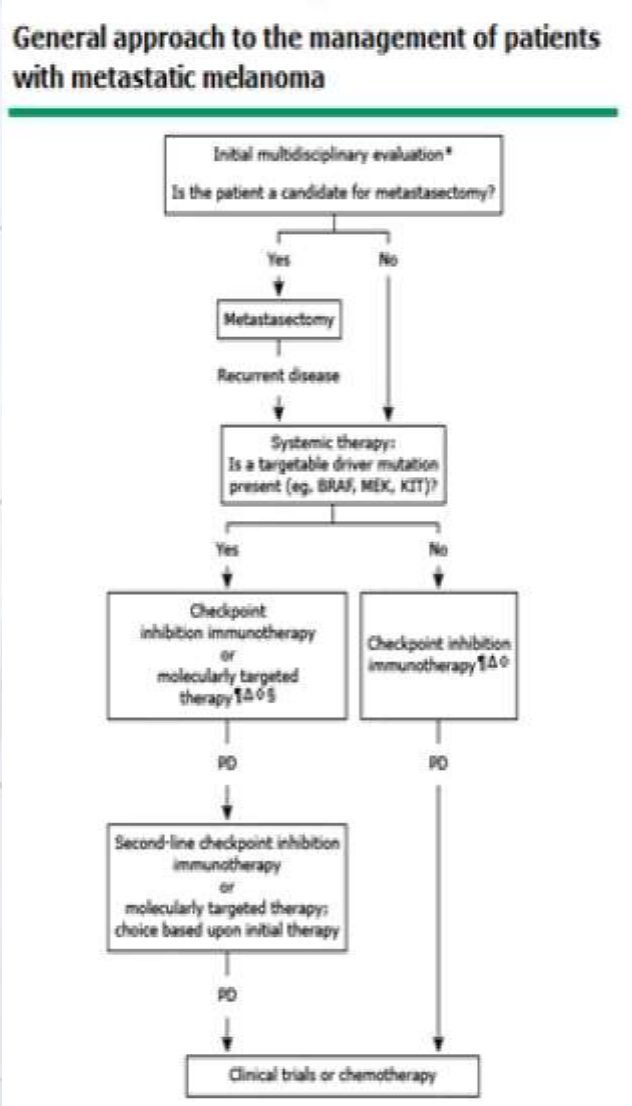




Immune Checkpoint Inhibitors

Melanoma

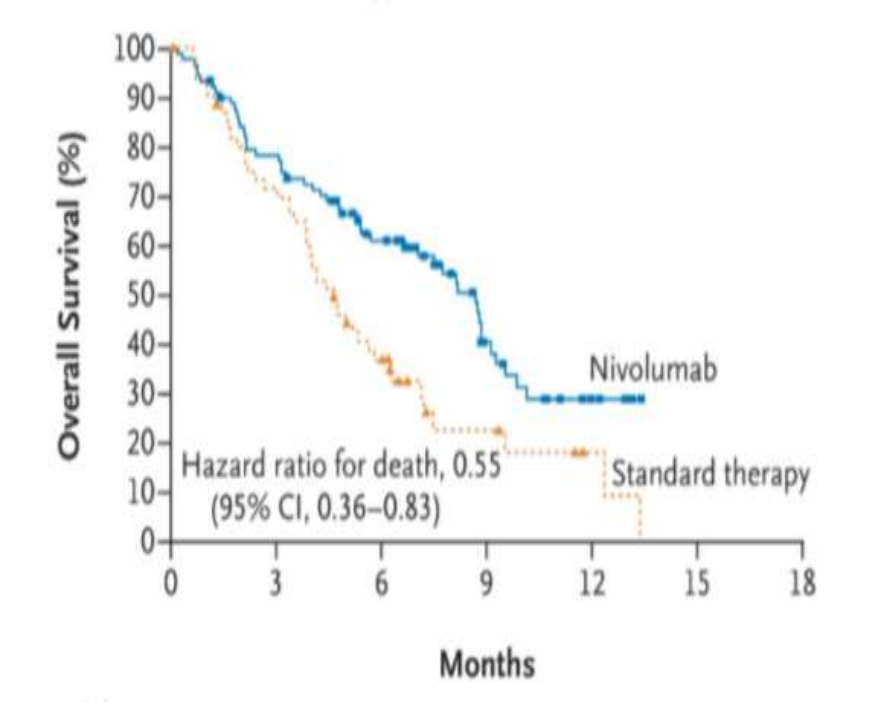
- **Standard treatment in metastatic melanoma**
- **Also approved in the adjuvant setting (after surgery)**



Immune Checkpoint Inhibitors

Head and Neck Cancer

- **Malignant tumors with squamous cell differentiation**
- **Approved as first line treatment in patients with high PD-L1 expression**
- **After disease progression in patients receiving chemotherapy**

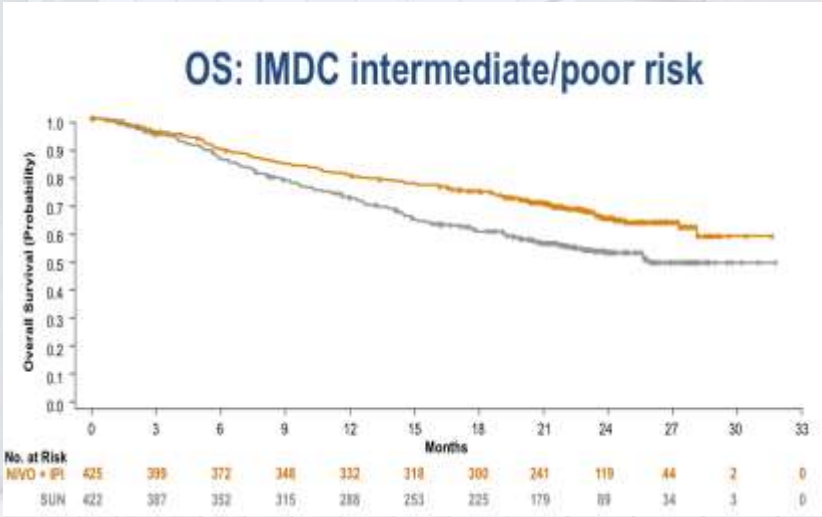


Ferris L et al. N Engl J Med 2016; 375:1856-1867

Immune Checkpoint Inhibitors

Renal Cell Carcinoma

- **Recommended in first and second line setting in specific patient subgroups**
- **They are approved as combination treatment with a Tyrosine Kinase Inhibitor**



Motzer RJ et al. N Engl J Med. 2018;378(14):1277-1290.

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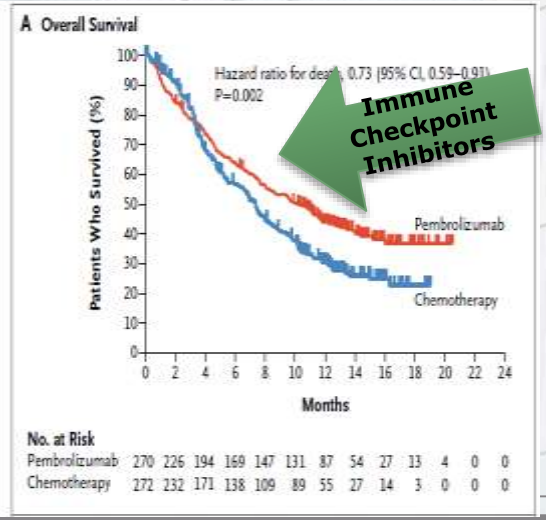
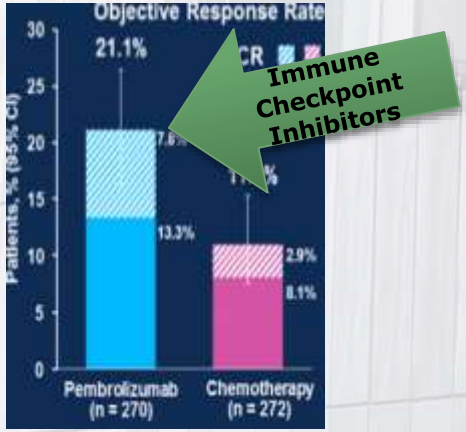
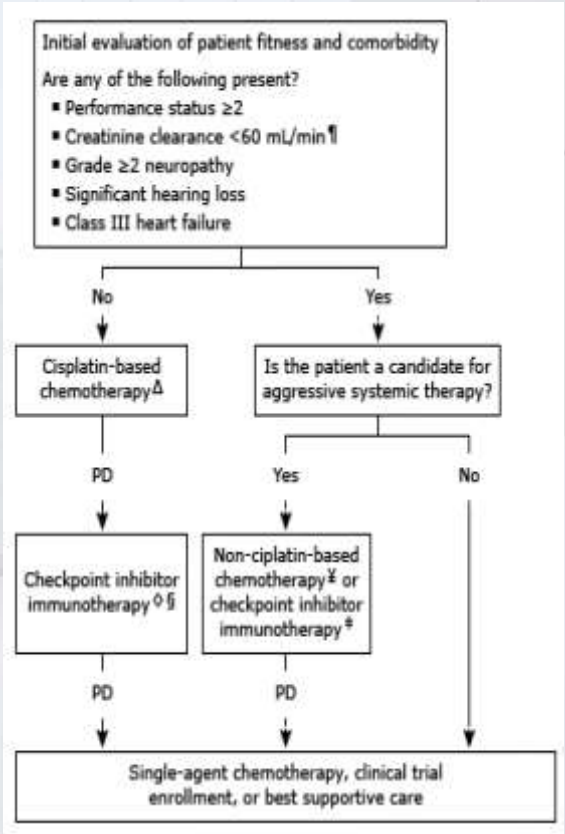
Immune Checkpoint Inhibitors

Bladder Cancer

- **Approved as first and second line therapy**
- **Depending on general condition, renal function, cardial function and biomarkers**





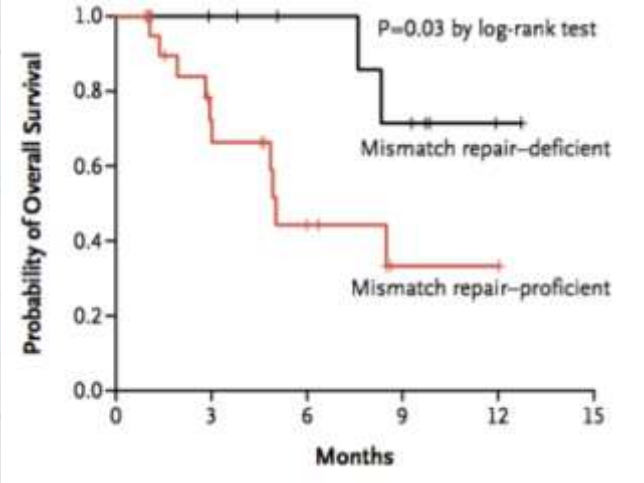


Bellmunt J et al. N Engl J Med. 2017;376(11):1015-1026

Immune Checkpoint Inhibitors

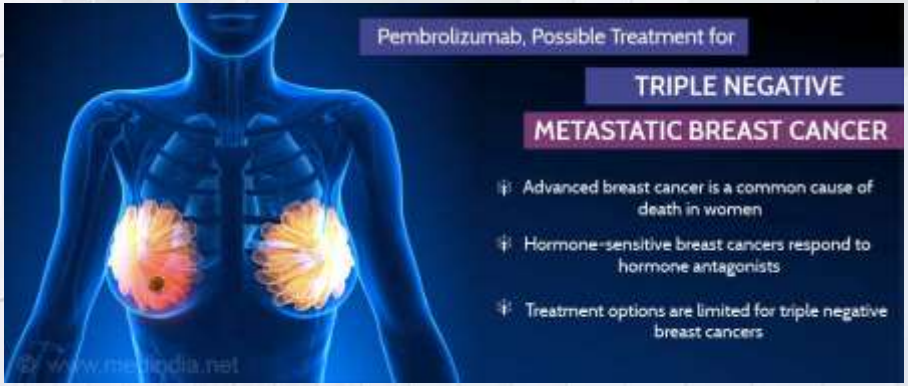
Colorectal Cancer

- Patients with a specific biomarker: MSI (microsatellite instability) high (15%)



Tripple Negative Breast Cancer

- Tripple negative and PD-L1 positive patients
- In combination with chemotherapy



Le DT et al. NEJM 2015; 372: 2509-20

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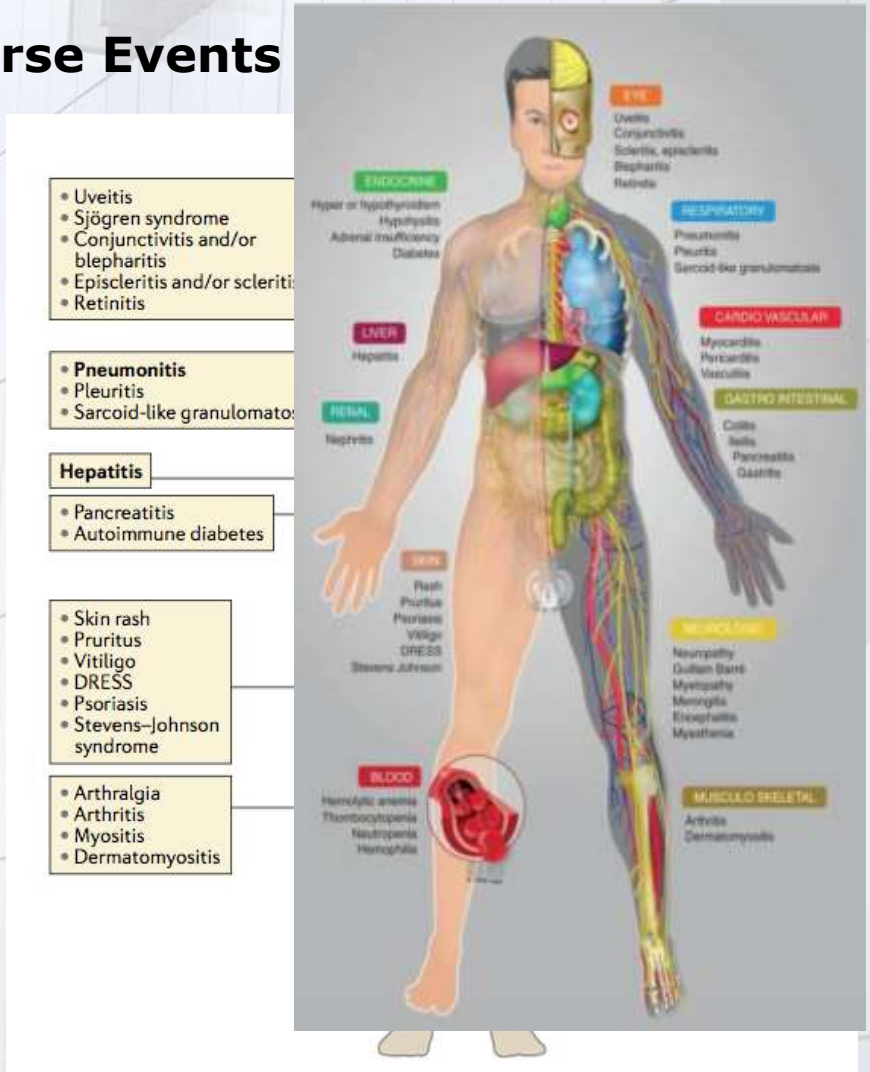
Immune Checkpoint Inhibitors

Adverse Events

- **Due to autoimmune reactions based on an overacting immune system**
- **Can affect all organs**
- **Severe adverse events are rare**
- **Possible symptoms are: cough, diarrhea, rash, hyper- or hypothyroidism**

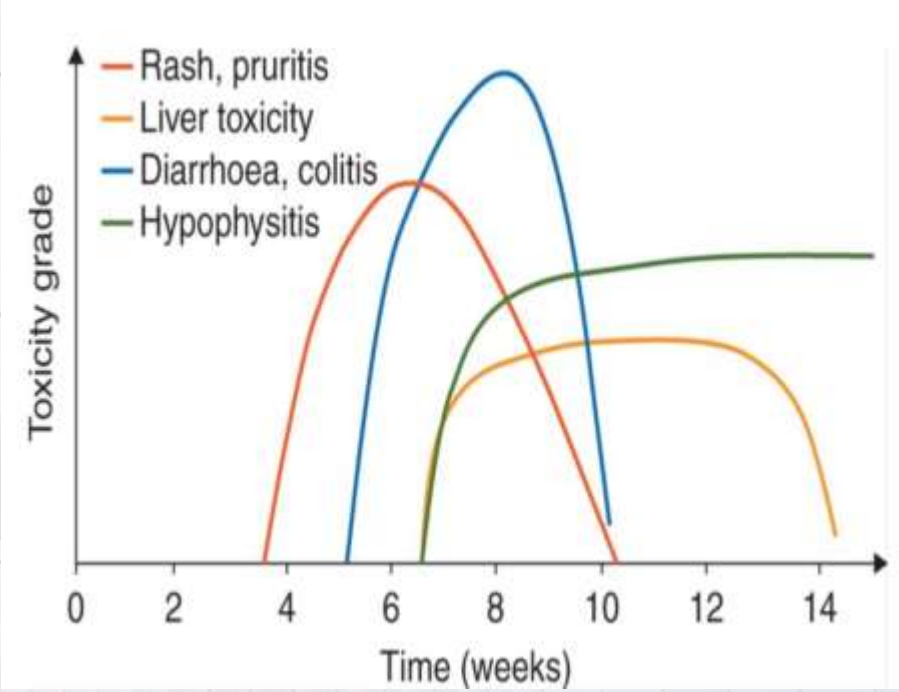


Martins F et al. Nat Rev Clin Oncol. 2019 Sep;16(9):563-580

Immune Checkpoint Inhibitors

Adverse Events

- **Can occur at the beginning of the treatment or at the end of the treatment with Immune Checkpoint Inhibitors**



Ann Oncol. 2015;27(4):559-574. doi:10.1093/annonc/mdv623

Immune Checkpoint Inhibitors

Adverse Events

- Management of adverse events depends on the degree of the severity
- Immune Checkpoint Inhibitors has to be stopped
- Treatment with Cortisone
- Local treatment
- Eventually additional specific treatment is needed

Adverse event	Incidence	Presentation/findings	Management
Rash and/or Pruritus	Most common: 50% with CTLA-4 inhibitors, 40% with PD-1 inhibitors and 60% with combination of inhibitors	Faintly erythematous, reticular, and maculopapular rash across the limbs and trunk Rare: Bullous pemphigoid, Stevens-Johnson syndrome and Sweet syndrome	Supportive care. Prednisone (in severe cases)
Diarrhea and/ or Colitis	Common	Diarrhea Abdominal computed tomography: Mild diffuse bowel thickening or segmental colitis	Antidiarrheal agents, fluids and electrolytes
Hepatitis	Common	Elevations in levels of aspartate transaminase, alanine transaminase and, occasionally, bilirubin	Prednisone
Hypophysitis (pituitary inflammation)	Common: 10% with CTLA-4 inhibitors, 1%-7% with PD-1 inhibitors	Fatigue, headache, hypogonadism, hypotension, hypoglycemia Brain magnetic resonance imaging: Enhancement and enlargement of the pituitary Blood tests: low adrenocorticotropic hormone, thyrotropin, luteinizing hormone, follicle-stimulating hormone, growth hormone, and/or prolactin levels	Prednisone and hormone replacement
Pneumonitis	Rare (<10%)	Upper respiratory infection, new cough, shortness of breath or hypoxia Chest computed tomography: bilateral consolidative, ground glass opacities predominantly in peripheral distribution and interlobular septal thickening in basilar and peripheral distribution	Prednisone. Bronchoscopy and hospitalization (in moderate-severe cases)
Pancreatitis	Rare	Pain, radiographic findings of an inflamed pancreas, or elevated amylase and lipase levels	Prednisone
Hematologic toxicities	Rare	Anemia, neutropenia, and pure red cell aplasia	Discontinuation of therapy, prednisone, and blood transfusion (if needed)
Neurologic Toxicities	Rare (<5%)	Sensory neuropathies, aseptic meningitis, temporal arteritis, myasthenia gravis and Guillain-Barré syndrome Blood test: high white blood cell count (increased lymphocytes)	High-dose methylprednisolone and/ or plasmapheresis. Discontinuation of therapy, intravenous immunoglobulin and/or supportive medications (in severe cases)

Fares J et al. Surg Neurol Int. 2019 Jan 25;10:9

Radiologic Response Criteria

	RECIST-Criteria	CHOI-Criteria
Complete remission (CR)	**Disappearance of all lesions**	**Disappearance of all lesions**
Partial remission (PR)	**≥30% decrease in the sum of the longest diameter of the lesions**	**≥10% decrease in tumor size or ≥15% decrease in tumor density**
Stable disease (SD)	**Neither PR nor PD**	**Neither PR nor PD**
Progressive disease (PD)	**≥20% increase in the sum of the longest diameter of the lesions or occurance of new lesions**	**≥10% increase in sum of longest diameters of lesions or ≥15% increase in tumor density or occurance of new lesions or new intratumoral nodules or an increase in the size of the existing intratumoral nodules**

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Immun Checkpoint Inhibitors

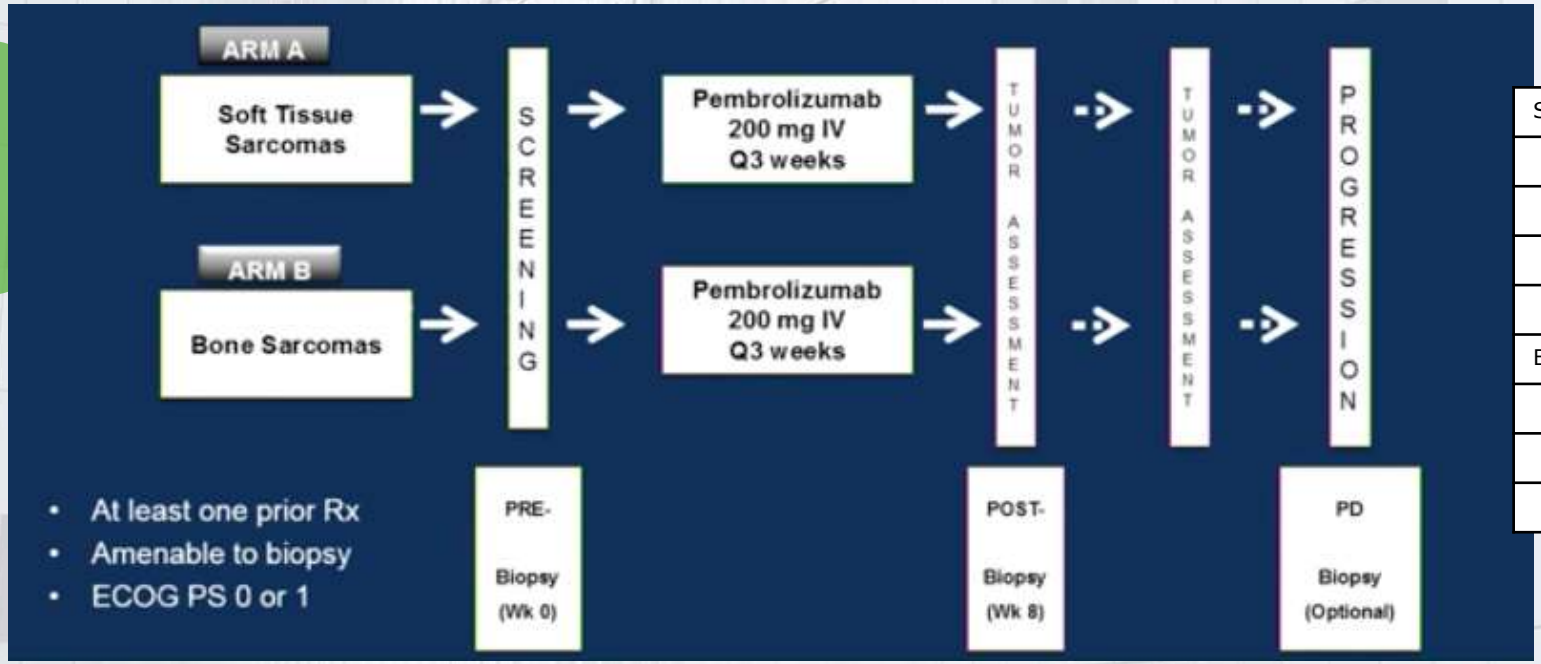
Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial

Hussein A Tawbi, Melissa Burgess, Vanessa Bolejack, Brian A Van Tine, Scott M Schuetze, James Hu, Sandra D'Angelo, Steven Attia, Richard F Riedel, Dennis A Priebat, Sujana Movva, Lara E Davis, Scott H Okuno, Damon R Reed, John Crowley, Lisa H Butterfield, Ruth Salazar, Jaime Rodriguez-Canales, Alexander J Lazar, Ignacio I Wistuba, Laurence H Baker, Robert G Maki, Denise Reinke, Shreyaskumar Patel

Lancet Oncol 2017; 18:1493-1501

Anti PD-1 Antibody

Study design (n=84)



Soft tissue sarcomas (n=40)
Leiomyosarcoma (n=10)
UPS (n=10)
LPS (n=10)
SS (n=10)
Bone sarcomas (n=40)
Chondrosarcoma (n=5)
Ewing´s sarcoma (n=13)
Osteosarcoma (n=22)

Tawbi HA et al. Lancet Oncol. 2017;18:1493-1501

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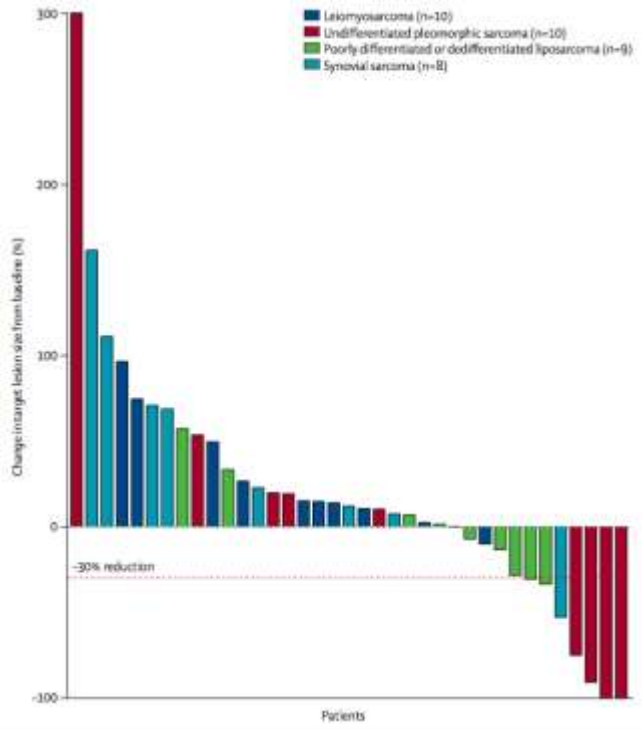
Lancet Oncol 2017; 18:1493-1501

Results soft tissue sarcoma (n=40)



UPS: undifferentiated pleomorphic sarcoma

LPS: liposarcoma

SS: synovial sarcoma

LMS: leiomyosarcoma

CR
- **UPS 1 (3%)**

PR
- **UPS 3 (8%)**
- **LPS 2 (5%)**
- **SS 1 (3%)**

SD
- **LMS 6 (15%)**
- **UPS 3 (8%)**
- **LPS 4 (10%)**
- **SS 2 (5%)**

PD
- **LMS 4 (10%)**
- **UPS 3 (8%)**
- **LPS 4 (10%)**
- **SS 7 (18%)**

Tawbi HA et al. Lancet Oncol. 2017;18:1493-1501

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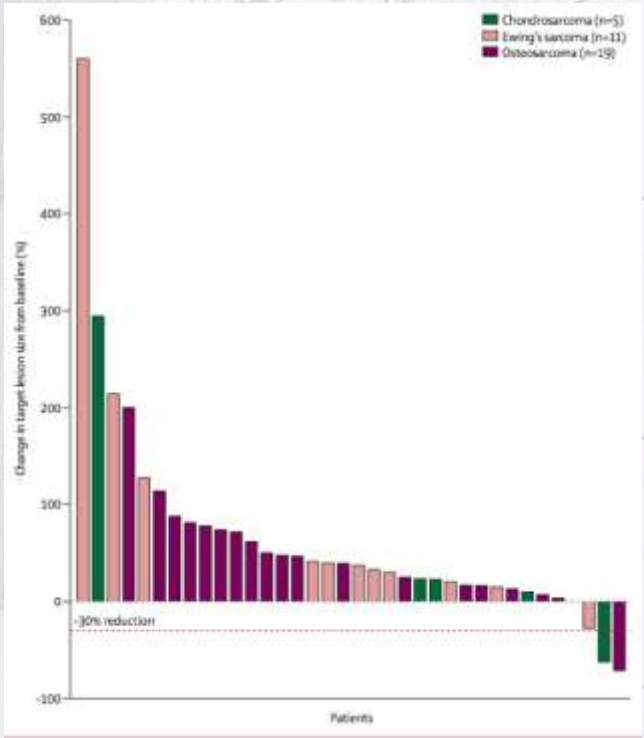
Lancet Oncol 2017; 18: 1493-1501

Results bone sarcoma (n=40)



PR
- **Chondrosarcoma 1 (3%)**
- **Osteosarcoma 1 (3%)**

SD
- **Chondrosarcoma 1 (3%)**
- **Ewing sarcoma 2 (5%)**
- **Osteosarcoma 6 (15%)**

PD
- **Chondrosarcoma 3 (8%)**
- **Ewing sarcoma 11 (28%)**
- **Osteosarcoma 15 (38%)**

Tawbi HA et al. Lancet Oncol. 2017;18:1493-1501

Immune Checkpoint Inhibitors

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Lancet Oncol 2017; 18: 1493-1501

Adverse events

- **Endocrine (adrenal insufficiency)**
- **Intestinal nephritis (protein in urine)**
- **Pneumonitis (specific changes in CT scan)**
- **Infectious pneumonia**
- **Bone pain**
- **Pulmonary embolism**

Tawbi HA et al. Lancet Oncol. 2017;18:1493-1501

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Immun Checkpoint Inhibitors

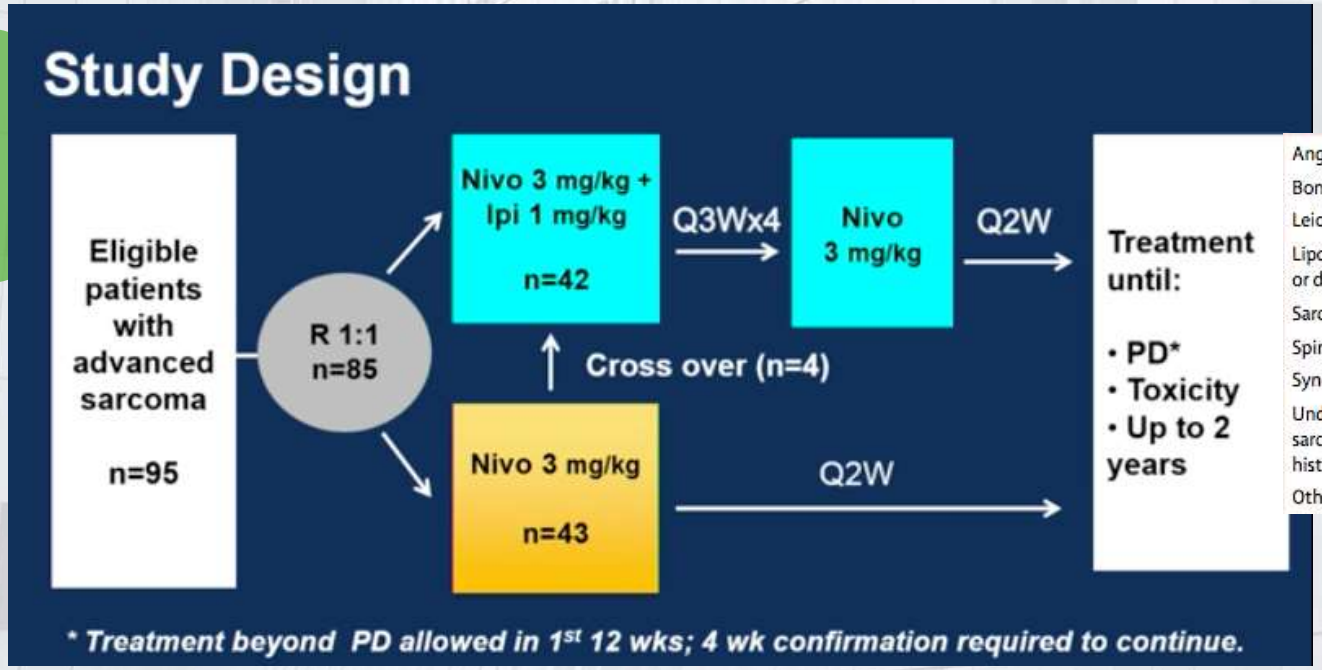
Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials

Sandra P D'Angelo, Michelle R Mahoney, Brian A Van Tine, James Atkins, Mohammed M Milhem, Balkrishna N Jahagirdar, Cristina R Antonescu, Elise Horvath, William D Tap, Gary K Schwartz, Howard Streicher

Lancet Oncol 2018; 19: 416–26

Anti PD-1 Antibodies
Anti CTLA4 Antibodies

Study design (n=85)



	Nivolumab	Nivolumab + Ipilimumab
Angiosarcoma	0	3 (7%)
Bone	5 (12%)†	4 (10%)‡
Leiomyosarcoma	15 (35%)	14 (33%)
Liposarcoma (well differentiated or dedifferentiated)	3 (7%)	2 (5%)
Sarcoma (not otherwise specified)	2 (5%)	1 (2%)
Spindle cell sarcoma	5 (12%)	6 (14%)
Synovial sarcoma	2 (5%)	2 (5%)
Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma	5 (12%)	6 (14%)
Other	6 (14%)†	4 (10%)‡

D´Angelo SP et al. Lancet Oncol. 2018;19:416-426.

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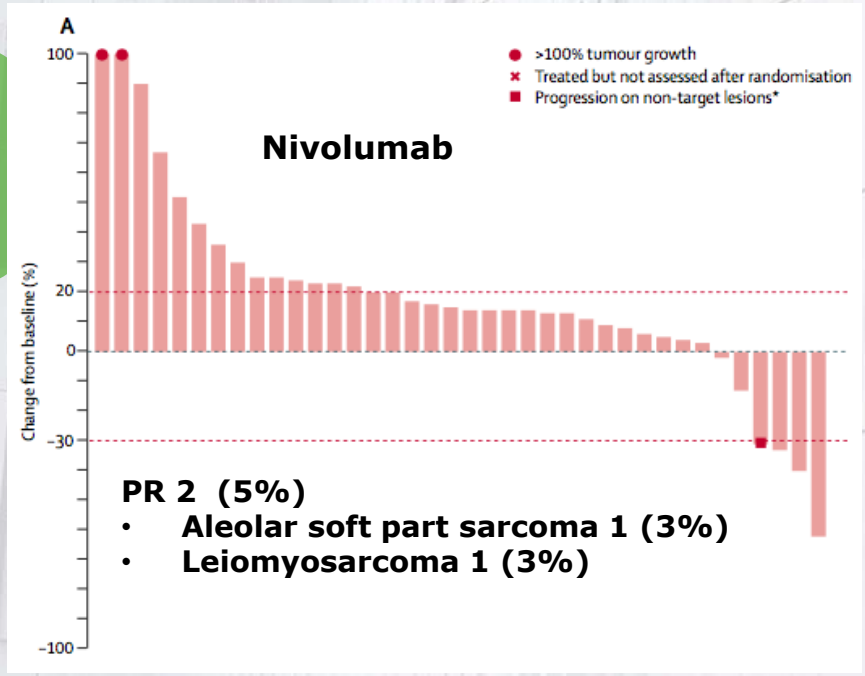
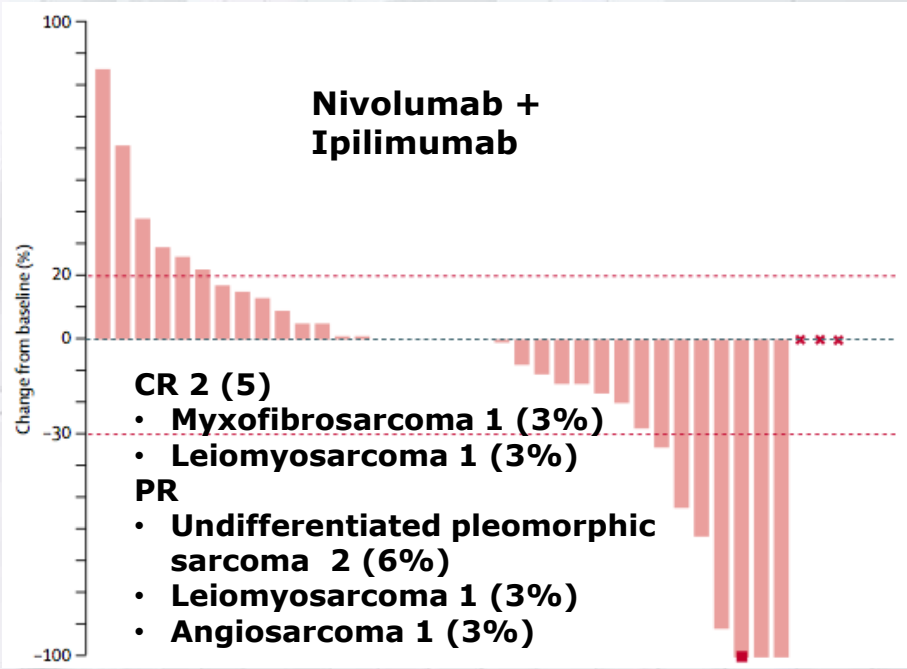
Lancet Oncol 2018; 19: 416–26

Results (n=38 in each treatment arm)



PR 2 (5%)
- **Aleolar soft part sarcoma 1 (3%)**
- **Leiomyosarcoma 1 (3%)**



CR 2 (5)
- **Myxofibrosarcoma 1 (3%)**
- **Leiomyosarcoma 1 (3%)**

PR
- **Undifferentiated pleomorphic sarcoma 2 (6%)**
- **Leiomyosarcoma 1 (3%)**
- **Angiosarcoma 1 (3%)**

D´Angelo SP et al. Lancet Oncol. 2018;19:416-426.

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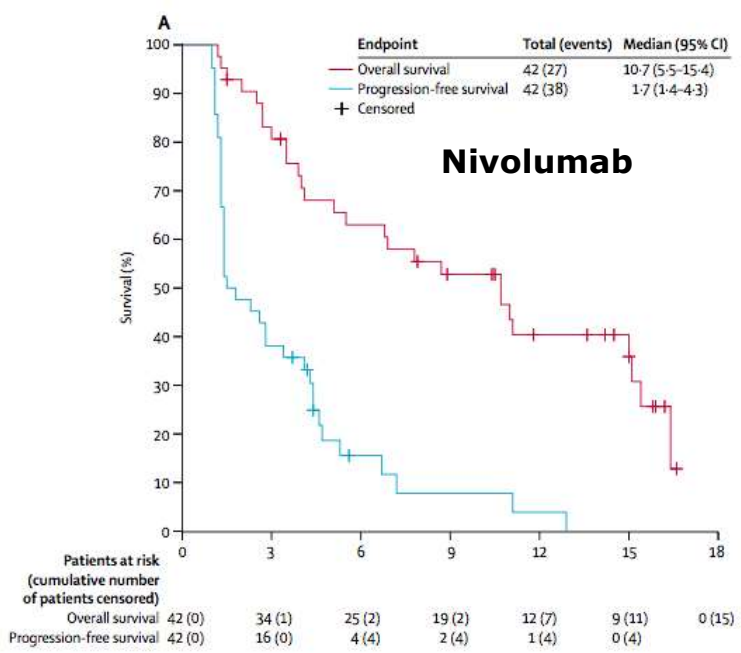
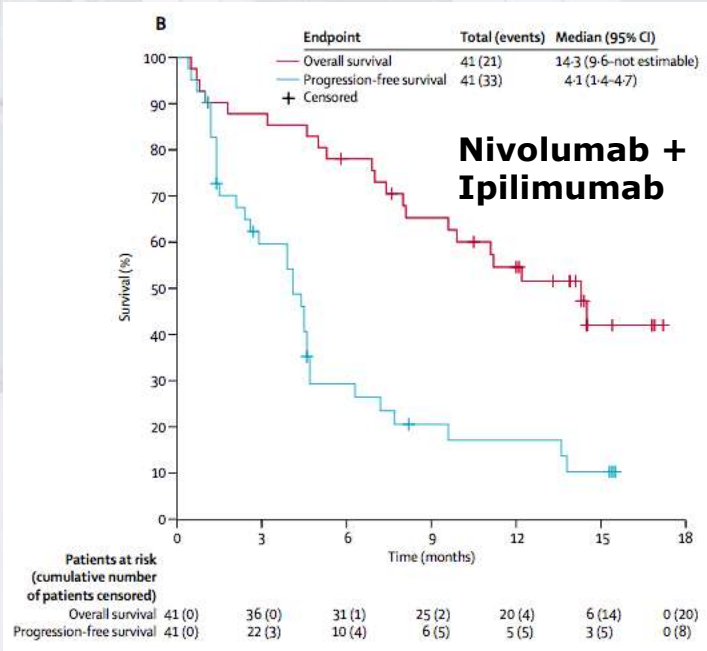
Lancet Oncol 2018; 19: 416–26

Results (n=38 in each study arm)





D´Angelo SP et al. Lancet Oncol. 2018;19:416-426.

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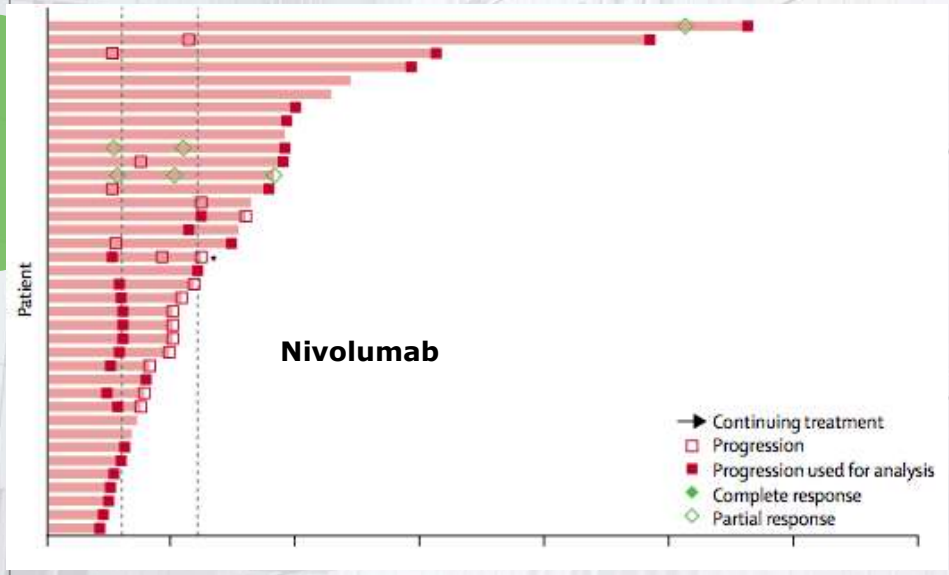

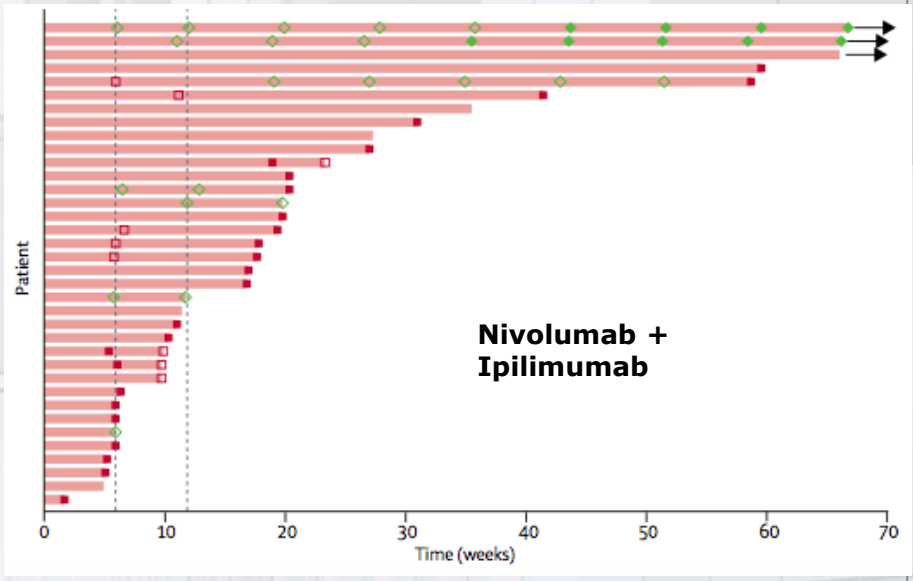

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Adverse events

- **Endocrine (adrenal insufficiency, hypofunction of the thyroid gland)**
- **Colitis with diarrhea**
- **Nausea**
- **Vomiting**
- **Rash**
- **Pneumonitis with dyspnea**
- **Nephritis**
- **Myositis with muscle pain**
- **Neuropathy**
- **Fever**
- **Mucositis**

D´Angelo SP et al. Lancet Oncol. 2018;19:416-426.

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Immune Checkpoint Inhibitors

Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial

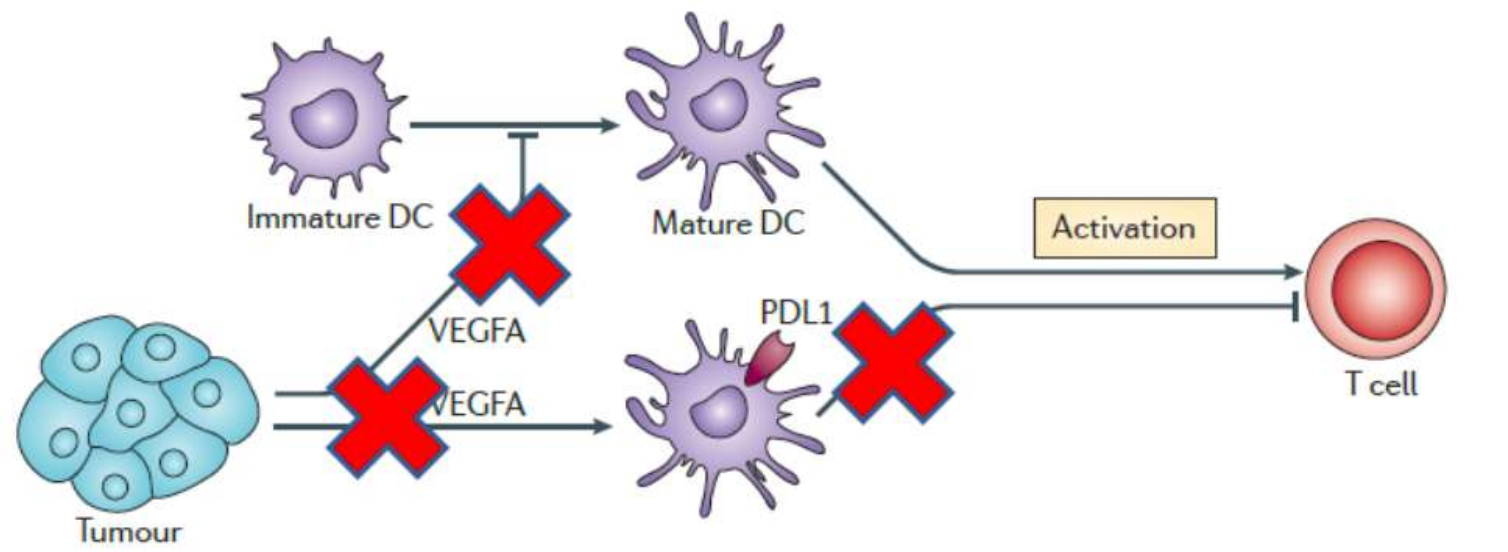
Breelyn A Wilky, Matteo M Trucco, Ty K Subhawong, Vaia Florou, Wungki Park, Deukwoo Kwon, Eric D Wieder, Despina Kolonias, Andrew E Rosenberg, Darcy A Kerr, Efrosyni Sfakianaki, Mark Foley, Jaime R Merchan, Krishna V Komanduri, Jonathan C Trent

Lancet Oncol 2019; 20: 837-48

Anti PD-1 antibody

TKI (Anti-VEGFR/PDGFR/c-KIT)

Rationale



Inhibition of angiogenesis increases the efficacy of immune-based tumor treatment

Wilky BA et al. Lancet Oncol. 2019;20:837-848.

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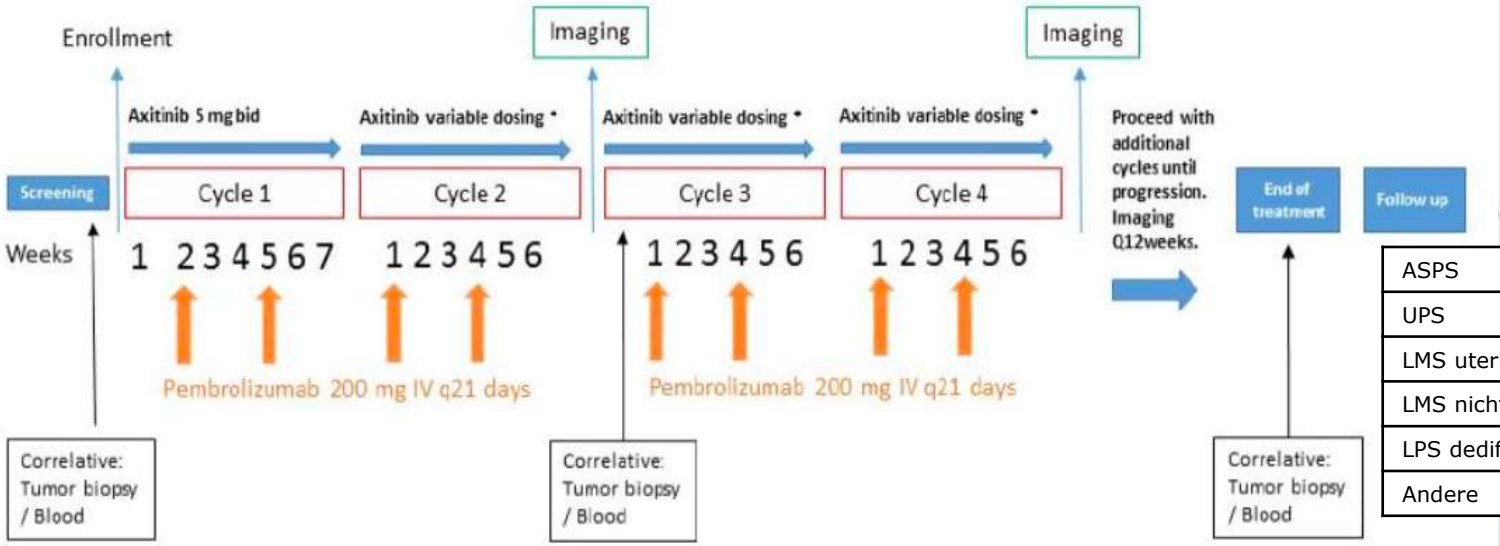
Lancet Oncol 2019; 20: 837-48

Study design (n=33)



ASPS	12 (36%)
UPS	5 (15%)
LMS uterin	4 (12%)
LMS nicht-uterin	2 (6%)
LPS dedifferentiert	2 (6%)
Andere	8 (24%)

Wilky BA et al. Lancet Oncol. 2019;20:837-848.

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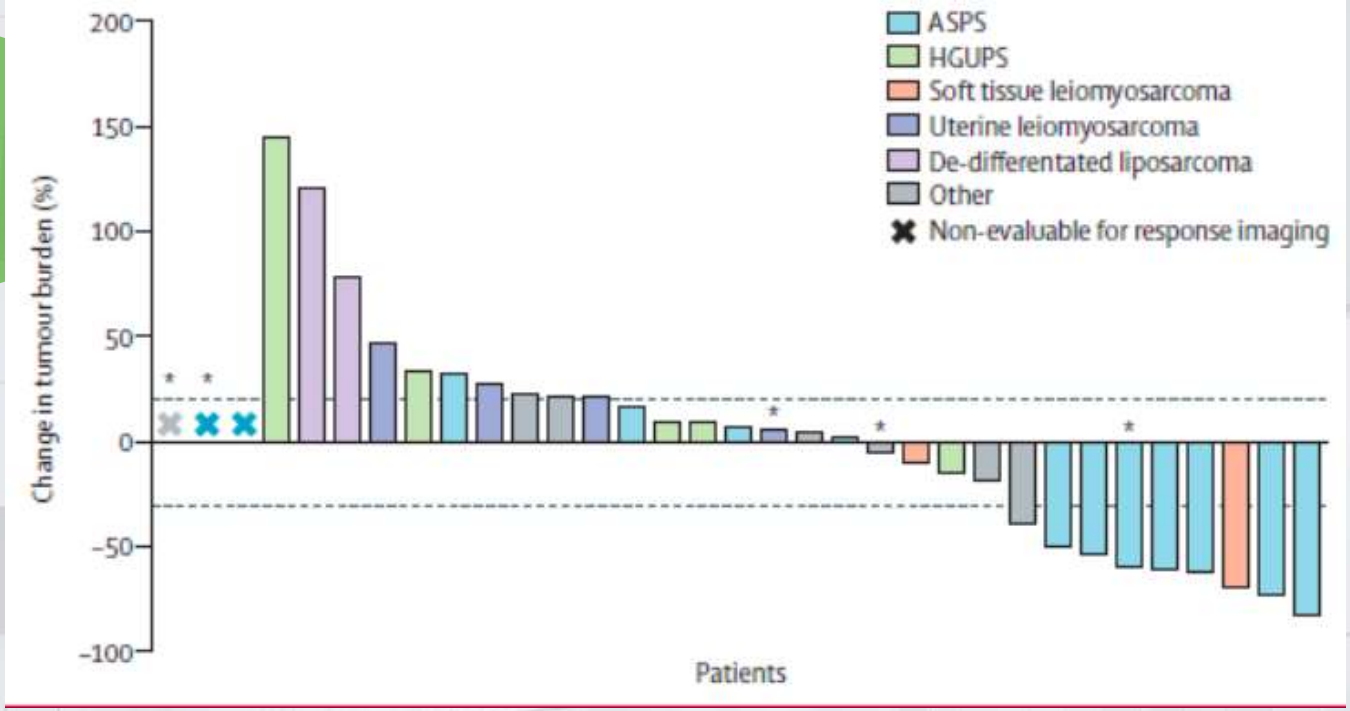
Lancet Oncol 2019; 20: 837-48

Results (n=32)



N=32	
CR	0 (0%)
PR	8 (25%)
SD	9 (28%)
PD	15 (47%)

Wilky BA et al. Lancet Oncol. 2019;20:837-848.

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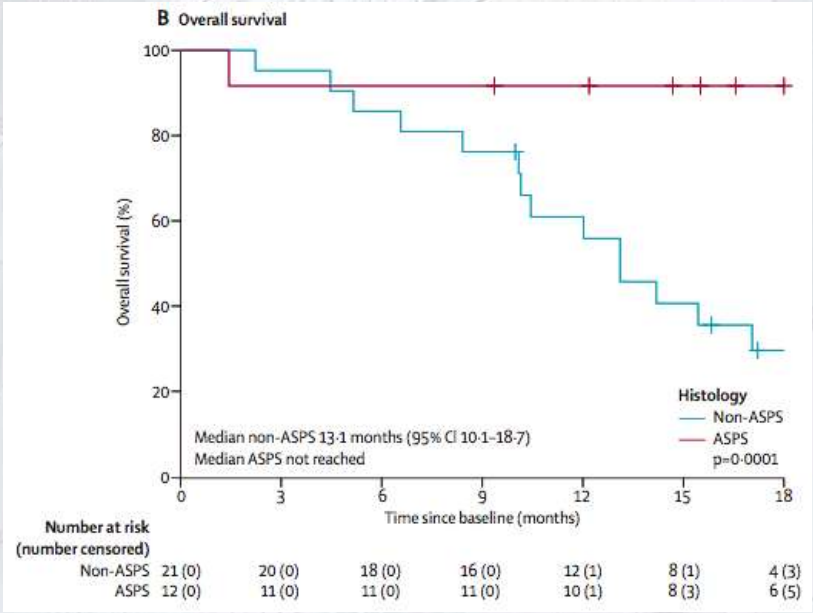
Lancet Oncol 2019; 20: 837-48

Results (subgroup analysis alveolar soft part sarcoma (ASPS))



ASPS n=12 (36%)
PR 6 (55%)
SD 2 (18%)

Wilky BA et al. Lancet Oncol. 2019;20:837-848.

Immune Checkpoint Inhibitors

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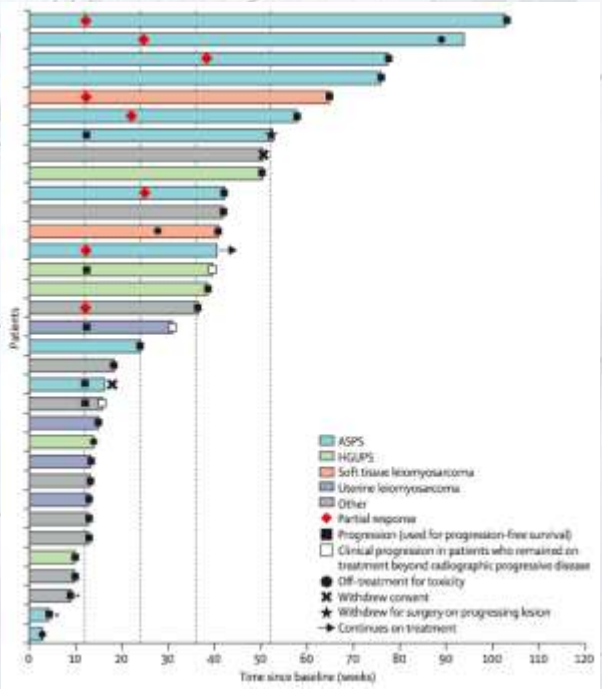
Lancet Oncol 2019; 20: 837–48

Results (subgroup analysis ASPS)



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Lancet Oncol 2019; 20: 837–48

Adverse events

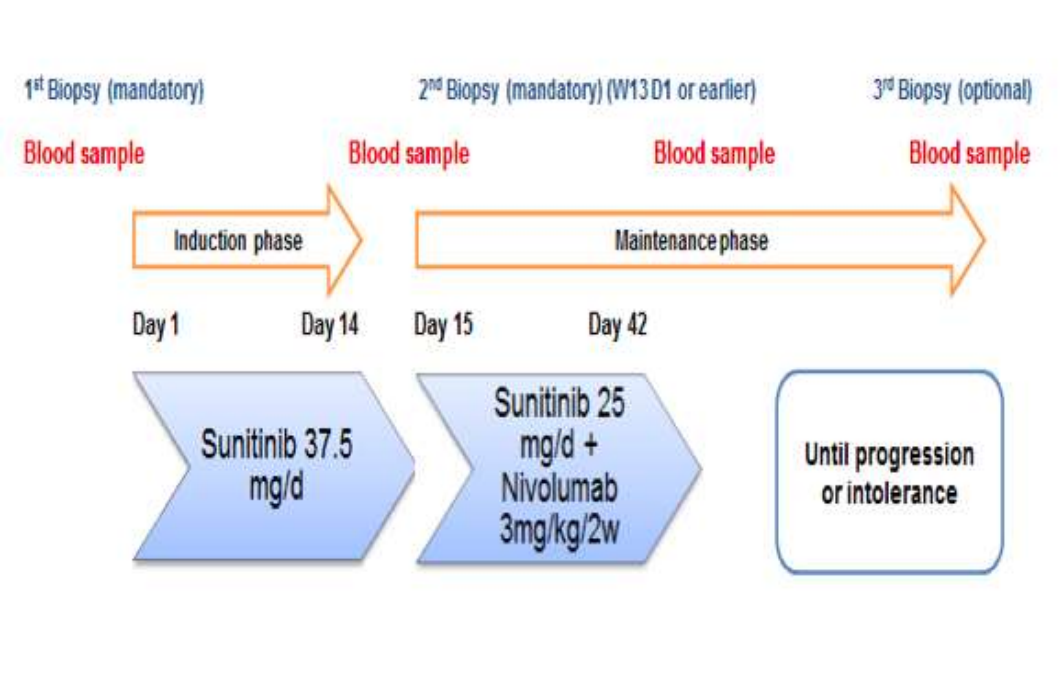
- **Fatigue**
- **Hypo- or hyperfunction of the thyroid gland**
- **Diarrhea**
- **Nausea**
- **Vomiting**
- **Abdominal pain**
- **Arthritis and Myositis**
- **Mucositis**
- **Palmar-plantar erythrodysesthesia syndrome**
- **Hypertension**
- **Weight loss**
- **Rash**
- **Autoimmune disorders**

Wilky BA et al. Lancet Oncol. 2019;20:837-848.

IMMUNOSARC: Phase II Trial of Sunitinib plus Nivolumab in advanced soft tissue sarcoma

Collaborative Spanish (GEIS) and Italian (ISG) sarcoma groups

Study design (n=50)



Anti PD-1 antibody

TKI (Anti-VEGFR/PDGFR/c-KIT)

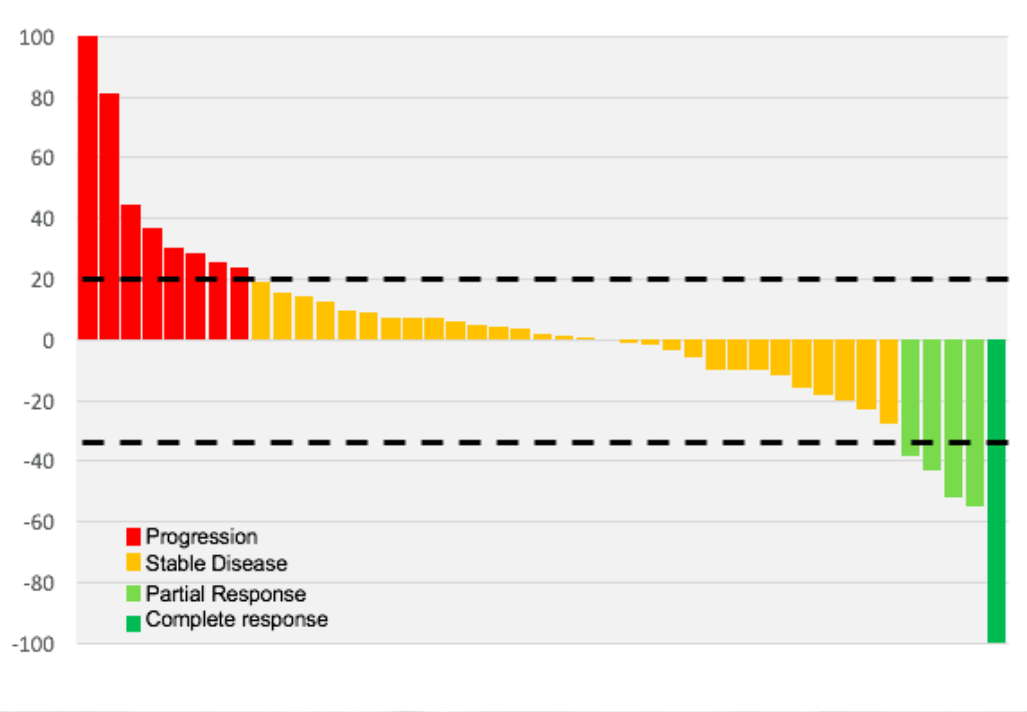
SS	9 (18)
Clear cell sarcoma	7 (14)
Solitary fibrous tumor	7 (14)
UPS	6 (12)
Epithelioid sarcoma	6 (12)
Angiosarcoma	5 (10)
Extraskeletal myxoid chondrosarcoma	4 (8)
ASPS	3 (6)
Other	3 (6)

Broto JM et al. CTOS 2019

IMMUNOSARC: Phase II Trial of Sunitinib plus Nivolumab in advanced soft tissue sarcoma

Collaborative Spanish (GEIS) and Italian (ISG) sarcoma groups

Results (RECIST) (n=46)



RESPONSE	N (%)
CR	1 (2%)
PR	4 (9%)
SD	28 (61%)
PD	13 (28%)

Responses were seen in:

- angiosarcoma
- extraskeletal myxoid chondrosarcoma
- SS
- ASPS

** SD: 11 patientsshowed a tumor shrinkage

Broto JM et al. CTOS 2019

IMMUNOSARC: Phase II Trial of Sunitinib plus Nivolumab in advanced soft tissue sarcoma

Collaborative Spanish (GEIS) and Italian (ISG) sarcoma groups

Results (CHOI) (n=46)

RES	N (%)
CR	1 (6%)
PR	23 (62%)
SD	9 (24%)
PD	4 (11%)

Responses were observed in:

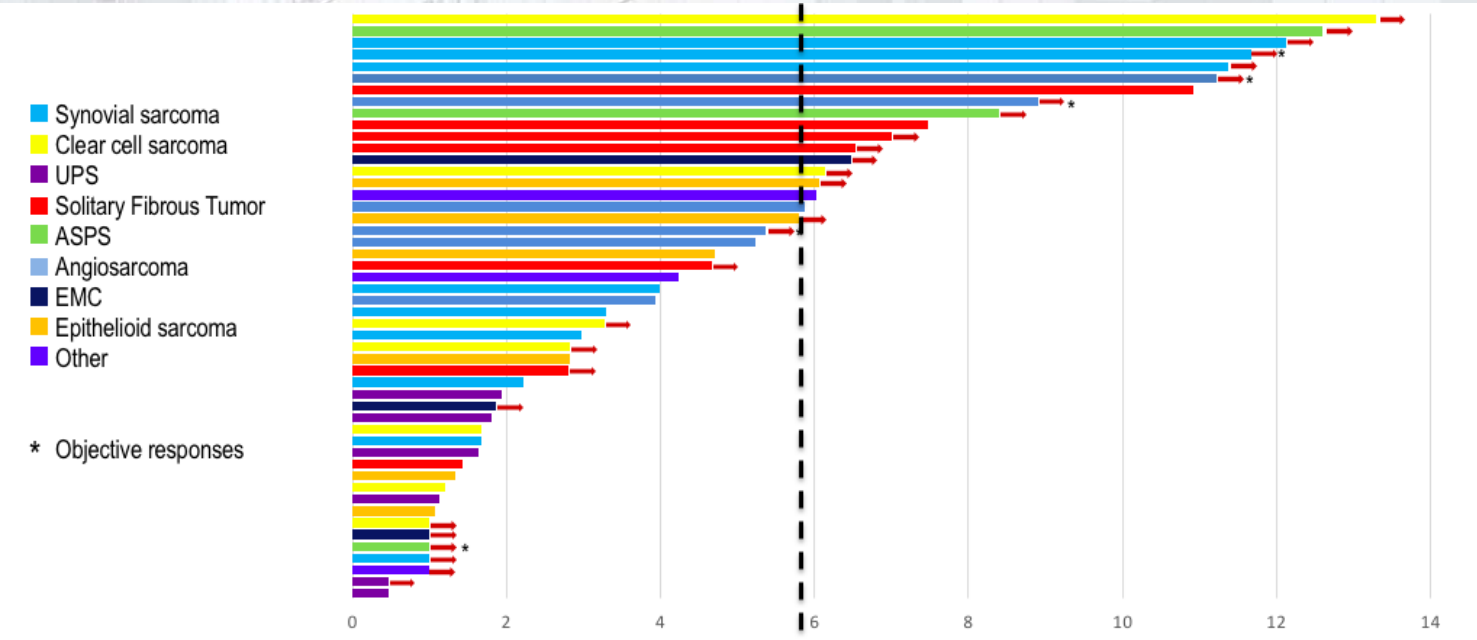
- Synovial sarcoma (4/7)
- Clear cell sarcoma (3/5)
- Solitary fibrous tumor (4/6)
- Undifferentiated pleomorphic sarcoma (3/6)
- Epithelioid sarcoma (1/4)
- Angiosarcoma (3/5)
- Extraskeletal myxoid chondrosarcoma (3/3)
- Alveolar soft-part sarcoma (2/3)

Broto JM et al. CTOS 2019

IMMUNOSARC: Phase II Trial of Sunitinib plus Nivolumab in advanced soft tissue sarcoma

Collaborative Spanish (GEIS) and Italian (ISG) sarcoma groups

Response duration in different subtypes (n=46)



Broto JM et al. CTOS 2019

IMMUNOSARC: Phase II Trial of Sunitinib plus Nivolumab in advanced soft tissue sarcoma

Collaborative Spanish (GEIS) and Italian (ISG) sarcoma groups

Adverse events

- **Fatigue**
- **Diarrhea**
- **Nausea**
- **Vomiting**
- **Arthralgia**
- **Myalgia**
- **Mucositis**
- **Hypertension**
- **Skin/hair hypopigmentation**
- **Weight loss**
- **Rash**
- **Neutropenia, thrombocytopenia, anemia**

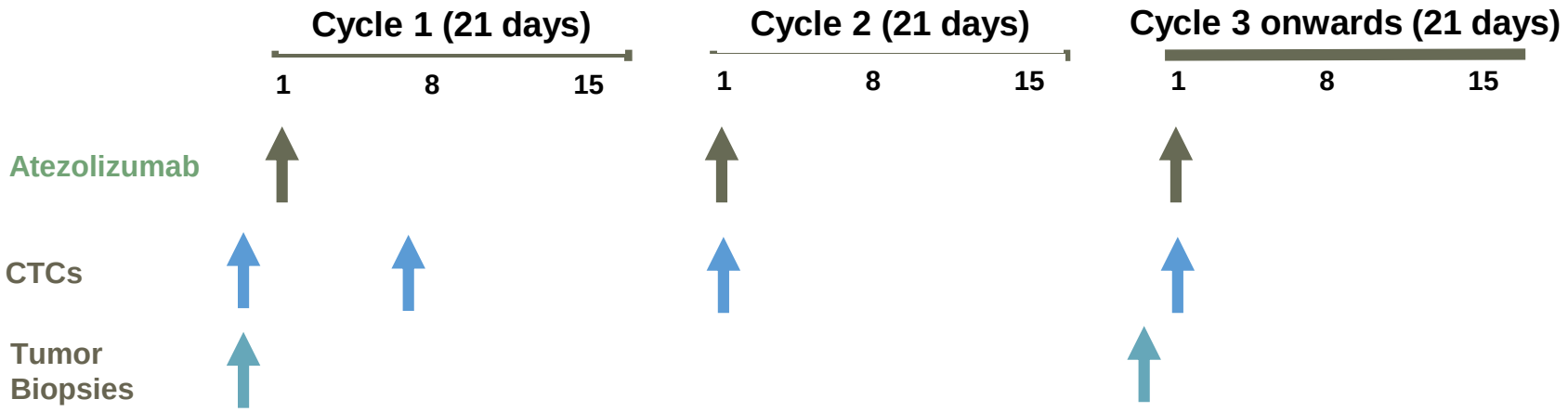
Broto JM et al. CTOS 2019

Atezolizumab in patients with alveolar soft part sarcoma (ASPS)

Phase II Study

Study design (n=34)

Anti PD-L1 Antibody



Circulating tumor cells (CTCs) (≥ 14 years) and biopsies (adult) will be collected for correlative studies

Atezolizumab (IV dose)

Adults	1200 mg
Pediatric ≥2 yrs	15 mg/kg *(1200 mg max)*

Chen A et al. CTOS 2019

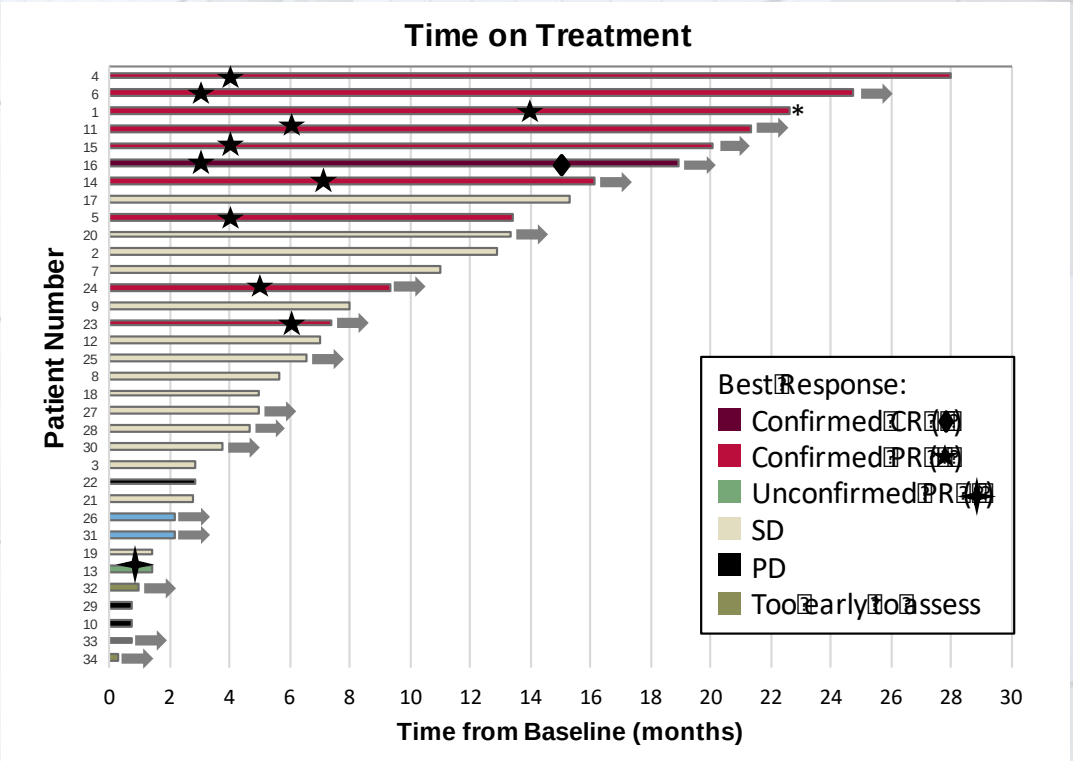
Atezolizumab in patients with alveolar soft part sarcoma (ASPS)

Phase II Study

Results (n=34)

Best Response	
CR	1 (3%)
PR	
confirmed	9 (27%)
unconfirmed	1 (3%)
SD	17 (50%)
PD	3 (9%)
Too Early to Assess	3 (9%)

- Median time to PR: **4.5 months** (range, 3-14 months)
- Duration of response: **≥15 Monate** in 50% of patients



Chen A et al. CTOS 2019

Atezolizumab in patients with alveolar soft part sarcoma (ASPS)

Phase II Study

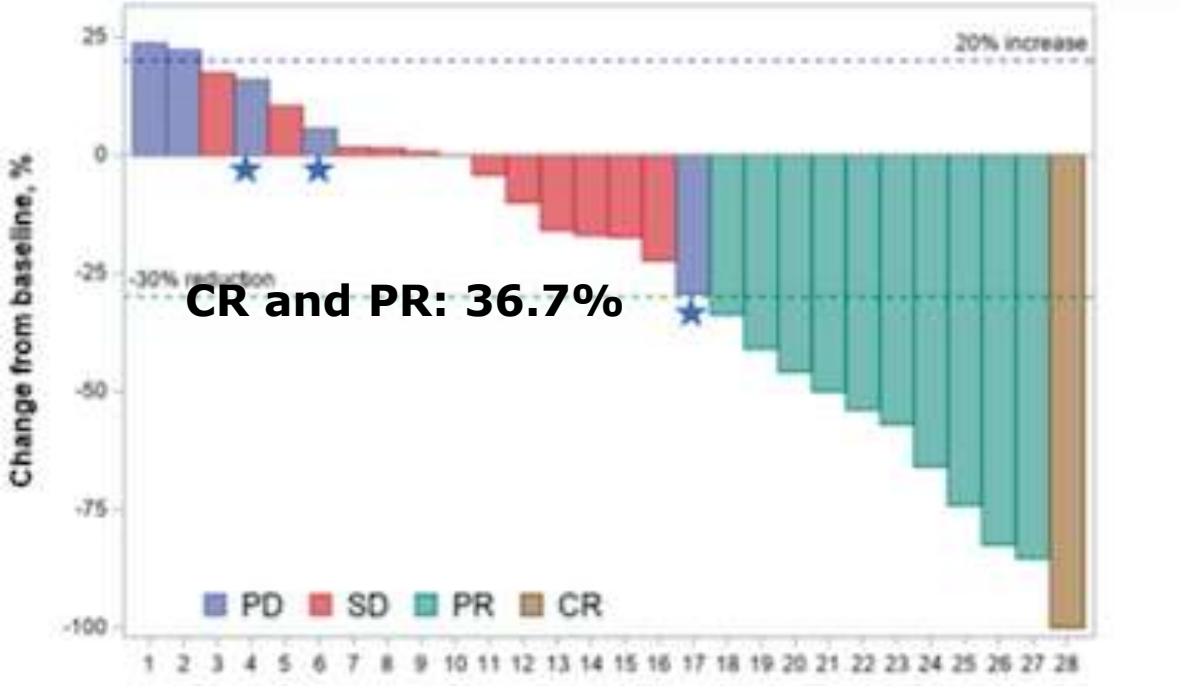
Adverse events

- **Fatigue**
- **Diarrhea**
- **Nausea**
- **Vomiting**
- **Arthralgia**
- **Myalgia**
- **Fever**
- **Pruritus**
- **Rash**
- **Decrease of white blood cell count**
- **Anemia**
- **Pain in extremity**

Chen A et al. CTOS 2019

Pembrolizumab and Doxorubicin in patients with advanced/metastatic sarcomas

Results (n=30)



CR and PR: 36.7%

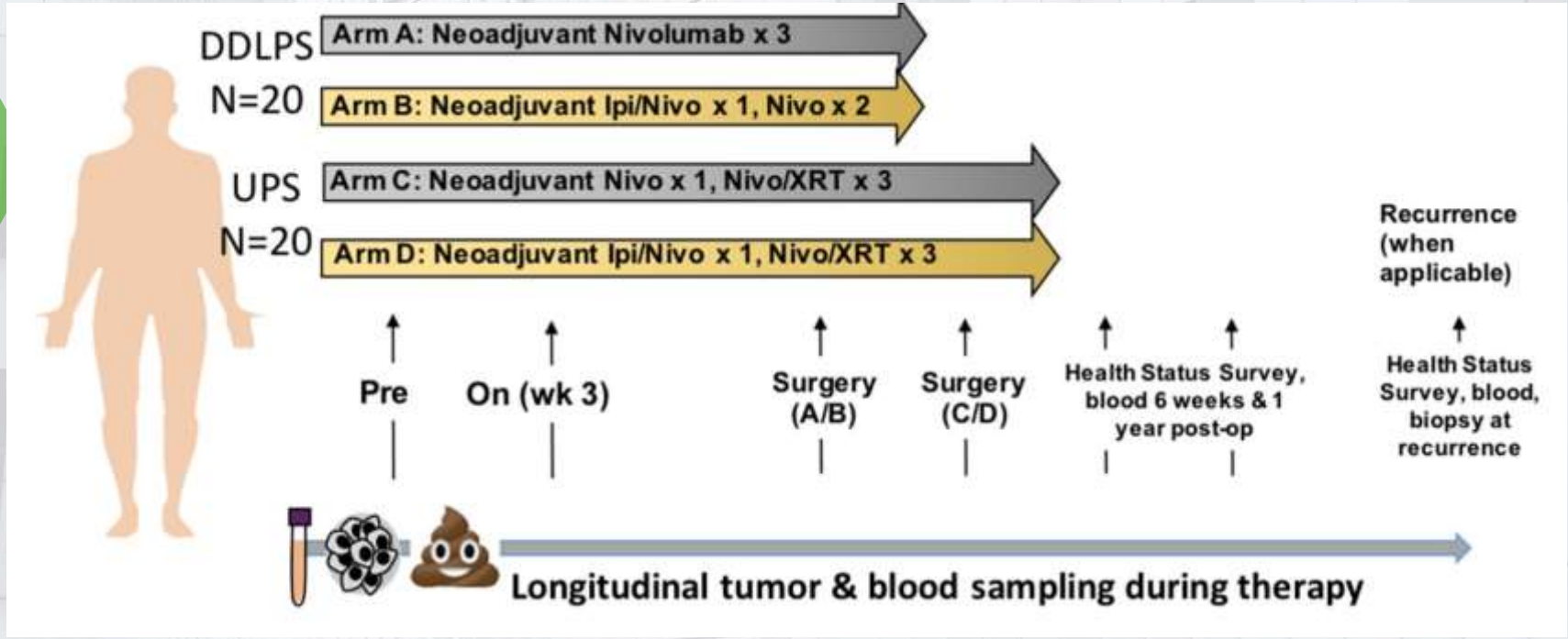
Histology	ORR N (%)
Liposarcoma (n = 7)	2 (28.6%)
Leiomyosarcoma (n = 10)	4 (40.0%)
Synovial sarcoma (n = 1)	0 (0.0%)
UPS (n = 3)	3 (100.0%)
Other (n = 9)	2 (22.2%)

Livingston MB et al. ASCO 2020

Neoadjuvant Checkpoint Blockade for surgically resectable undifferentiated pleomorphic sarcoma (USP) and dedifferentiated liposarcoma (DDLPS)

Phase II Study

Study design (n=40)

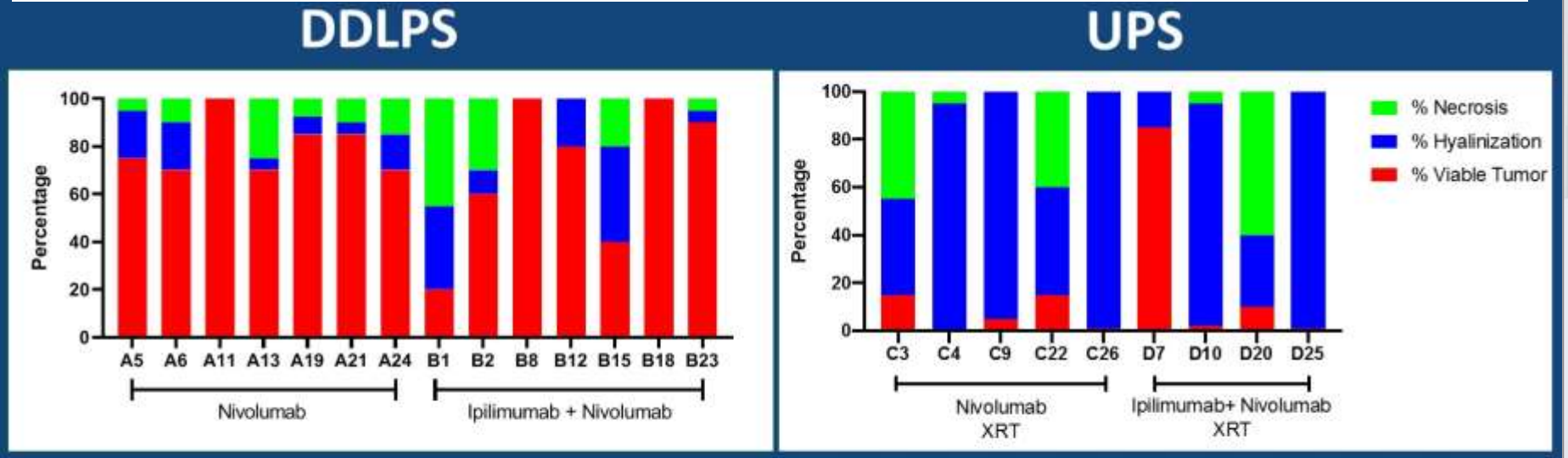


Roland C et al. ASCO 2020

Neoadjuvant Checkpoint Blockade for surgically resectable undifferentiated pleomorphic sarcoma (USP) and dedifferentiated liposarcoma (DDLPS)

Phase II Study

Results (n=24): Significant pathologic response in UPS patients



Median hyalinization: 8.75% (range 0-40)

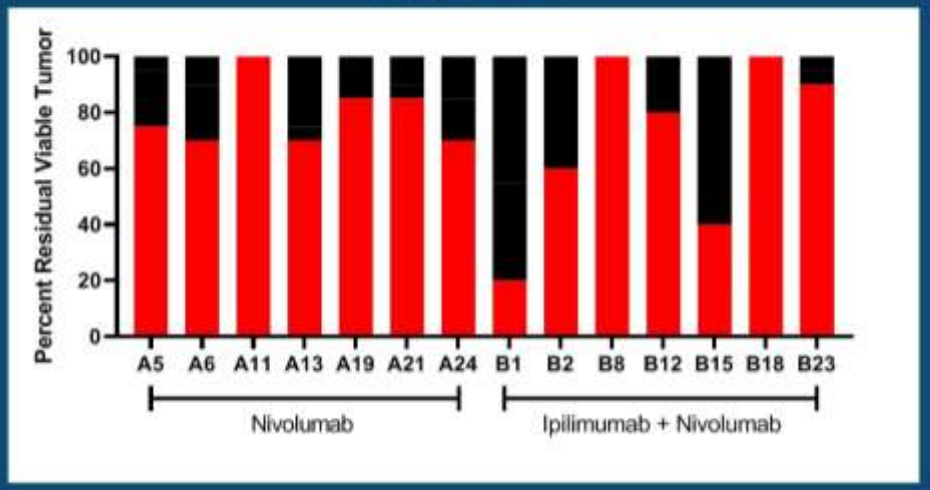
Median hyalinization: 93% (range 15-99)

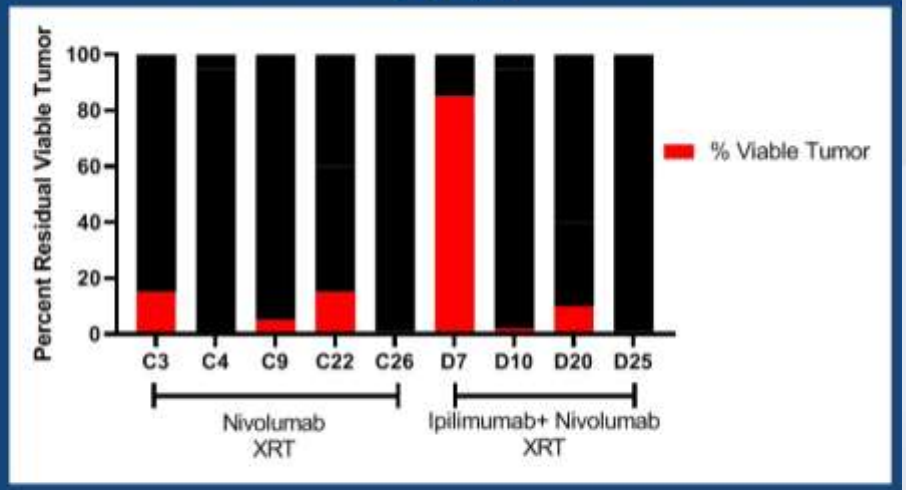
Roland C et al. ASCO 2020

Neoadjuvant Checkpoint Blockade for surgically resectable undifferentiated pleomorphic sarcoma (USP) and dedifferentiated liposarcoma (DDLPS)

Phase II Study

Results (n=24): Minimal residual viable tumor in UPS patients





Residual viable tumor: 77.5% (range 20-100)

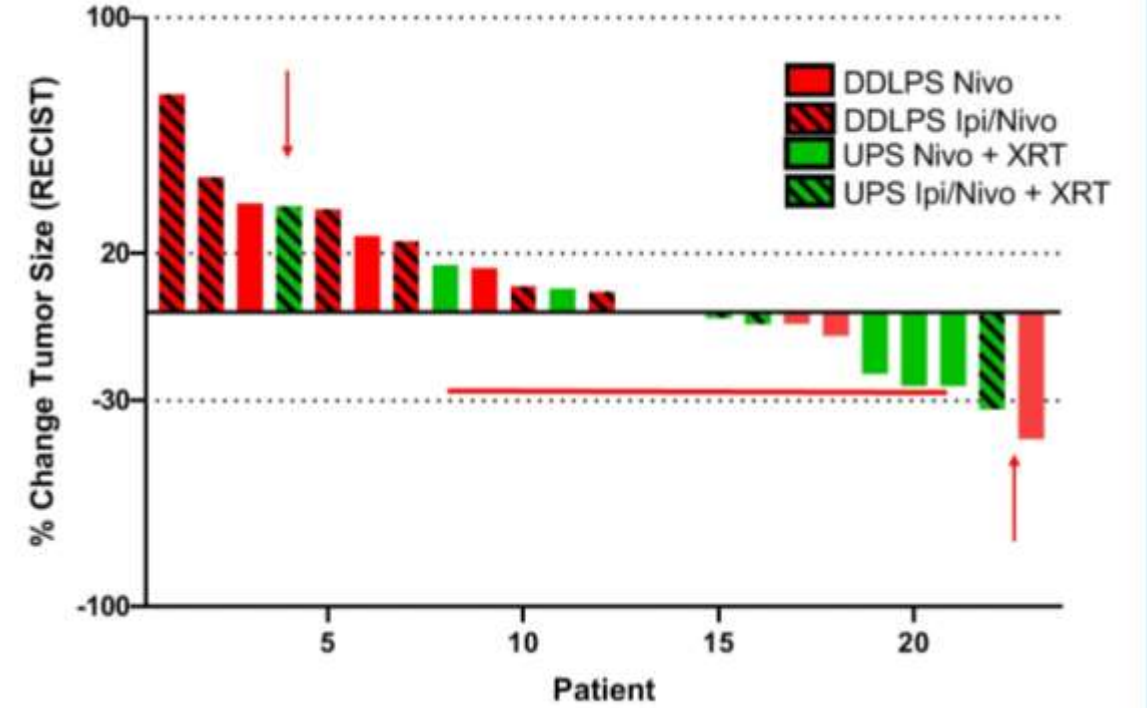
Residual viable tumor: 5% (range 0-85)

Roland C et al. ASCO 2020

Neoadjuvant Checkpoint Blockade for surgically resectable undifferentiated pleomorphic sarcoma (USP) and dedifferentiated liposarcoma (DDLPS)

Phase II Study

Results (n=24): RECIST response

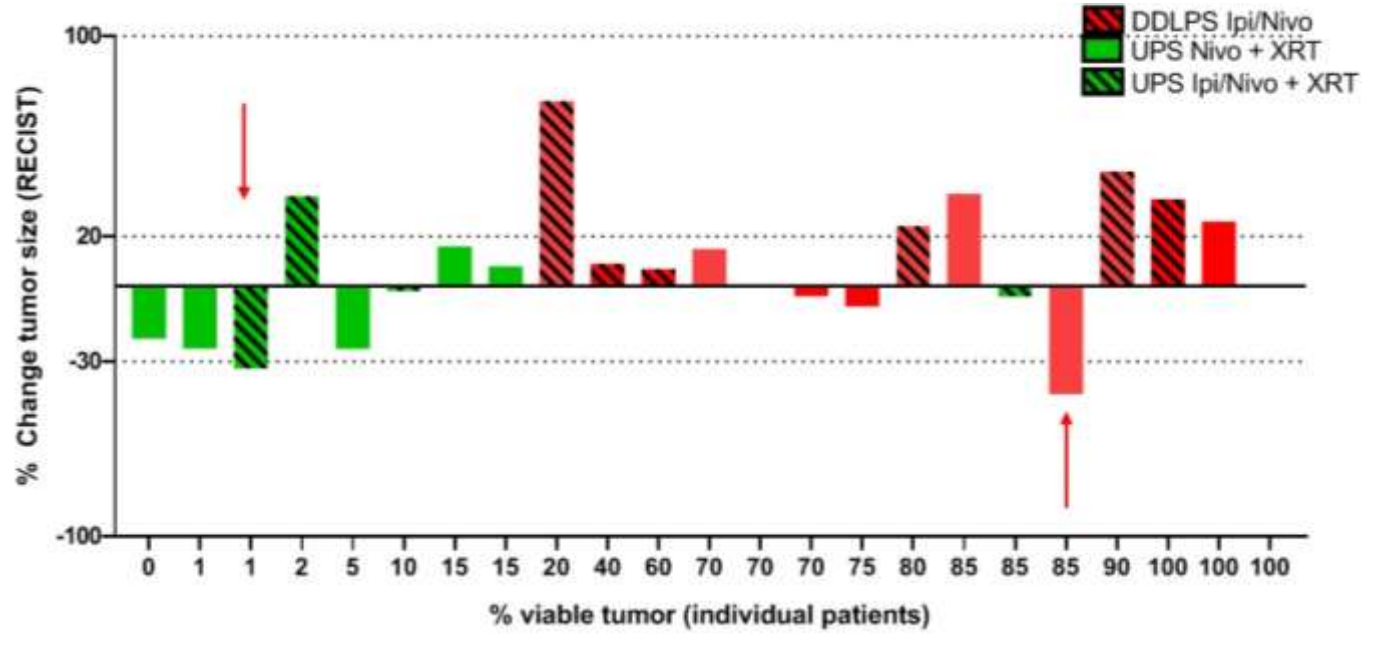


Roland C et al. ASCO 2020

Neoadjuvant Checkpoint Blockade for surgically resectable undifferentiated pleomorphic sarcoma (USP) and dedifferentiated liposarcoma (DDLPS)

Phase II Study

Response (n=24): no correlation between radiologic and pathological response



Roland C et al. ASCO 2020

Neoadjuvant Checkpoint Blockade for surgically resectable undifferentiated pleomorphic sarcoma (USP) and dedifferentiated liposarcoma (DDLPS)

Phase II Study

Adverse events

- **Diarrhea**
- **Renal failure**
- **Elevated white blood cell count**
- **Rash**
- **Hypofunction of the thyroid gland**

Roland C et al. ASCO 2020

TRAMUNE – Combination of Trabectedin and Durvalumab

Phase Ib Study

Study design

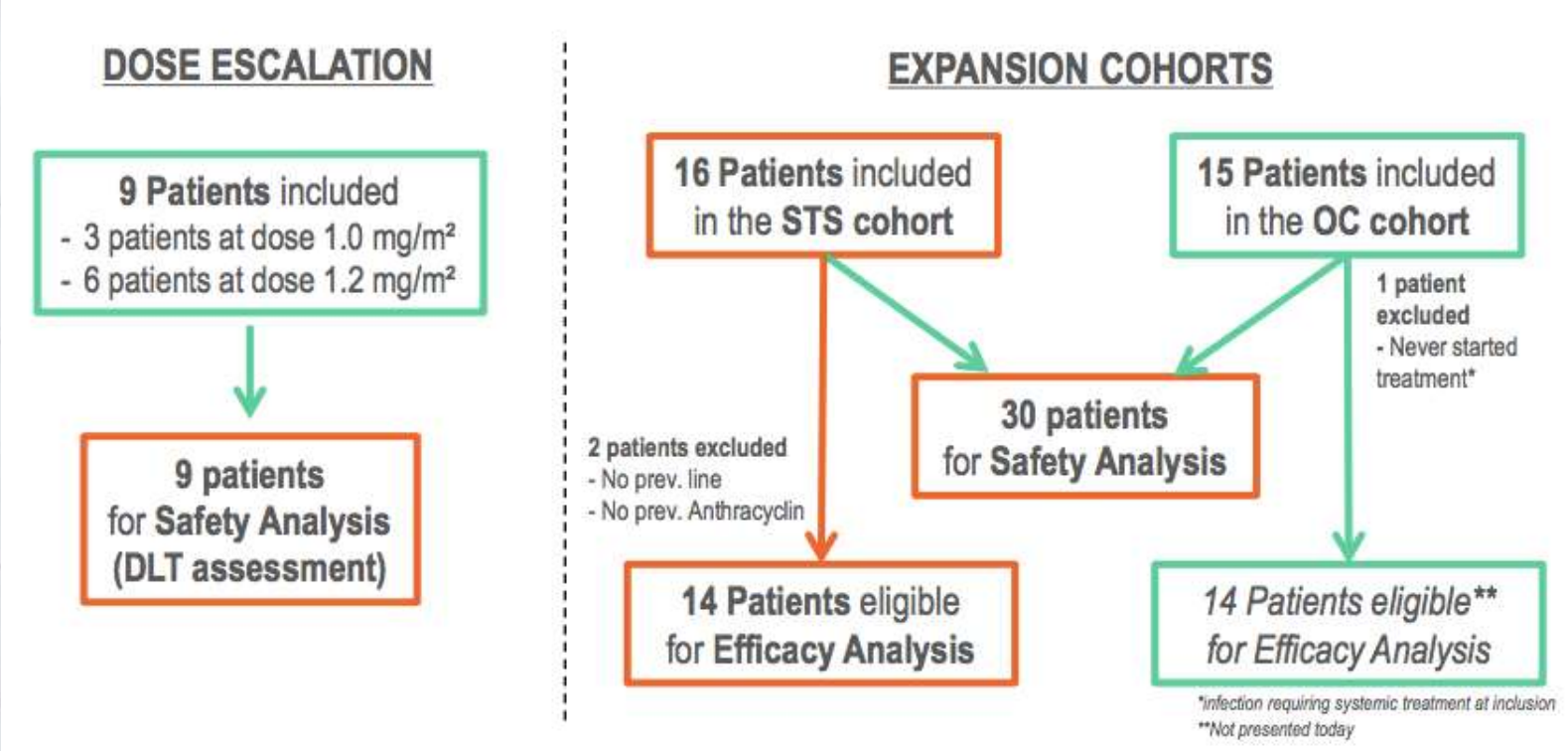
- **Dose Escalation Phase with 3 dose levels of Trabectedin:**
  1 mg/m^2, 1.2 mg/m^2, 1.5 mg/m^2
- **2 Expansion cohorts (soft tissue sarcomas (DD LPS, UPS, others) und ovarian cancer)**

Toulmonde M et al. ESMO 2020

TRAMUNE – Combination of Trabectedin and Durvalumab

Phase Ib Study

Study design (n=40)



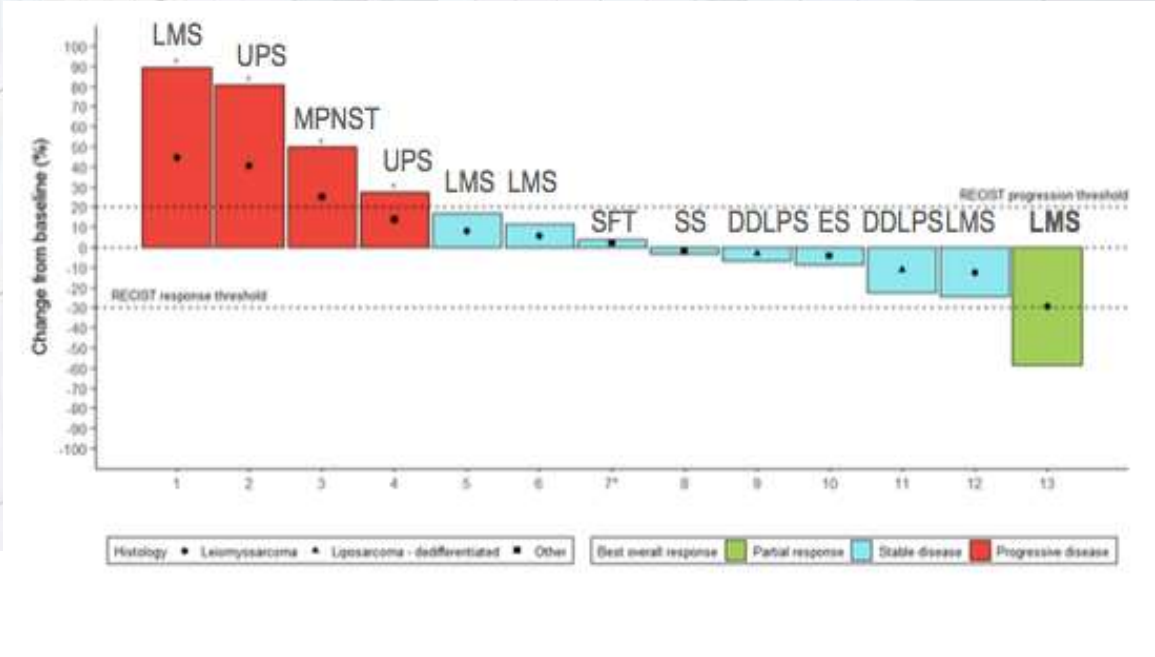
Toulmonde M et al. ESMO 2020

TRAMUNE – Combination of Trabectedin and Durvalumab

Phase Ib Study

Results STS (n=14)

Objective response	N = 14	
	n	%
Partial response	1	7%
Stable disease	8	57%
Progressive disease	4	29%
*Not evaluable**	*1*	7%



Tumor shrinkage in 6 patients (43%)

Toulmonde M et al. ESMO 2020

TRAMUNE – Combination of Trabectedin and Durvalumab

Phase Ib Study

Dose Escalation Phase

Trabectedin 1.2mg/m^2 + Durvalumab 1120mg every 3 weeks

Adverse events

- **Fatigue**
- **Nausea**
- **Decreased white blood cell count**
- **Myalgia**
- **Infections**
- **Cardiac failure**
- **Rash**
- **Renal failure**

Toulmonde M et al. ESMO 2020

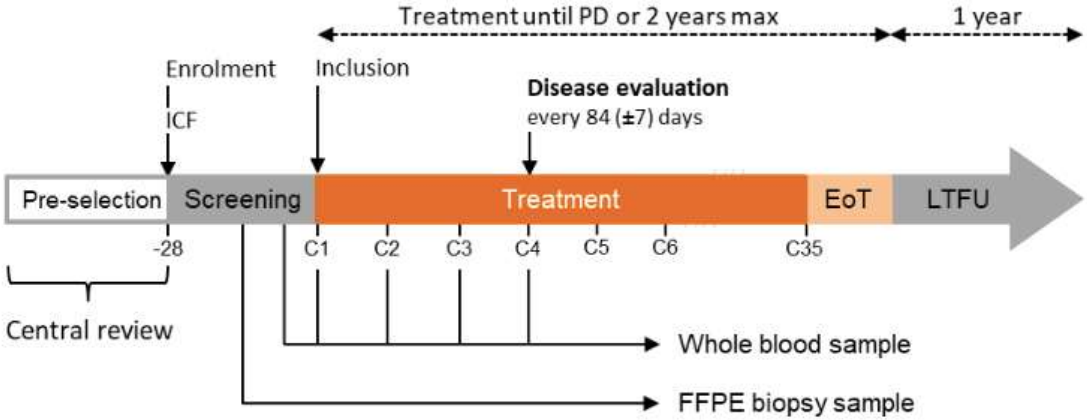
Pembrolizumab in selected rare sarcoma histotypes

AcSé Pembrolizumab

Phase II Study

Study design (n=81)

Subtypes:
24 chordoma
14 alveolar soft part sarcoma
5 desmoplastic round cell tumor (DSRCT)
6 smarca4-malignant rhabdoid tumor (SMBT)
32 other



Pembrolizumab 200 mg IV every 21 days until progression, unacceptable toxicity, physician or patient decision for a maximum of 24 months

Blay JY et al. ESMO 2020

Pembrolizumab in selected rare sarcoma histotypes
AcSé Pembrolizumab
Phase II Study

Results (n=81)

RECIST 1.1	Response at 84 days % (n/N=81)	Best Response % (n/N=81)
CR	0% (0)	0% (0)
PR	6% (5)	15% (12)
ORR (PR+CR)	6% (5)	15% (12)
DCR (SD+PR+CR)	48% (39)	52% (42)
PD	35% (28)	32% (26)

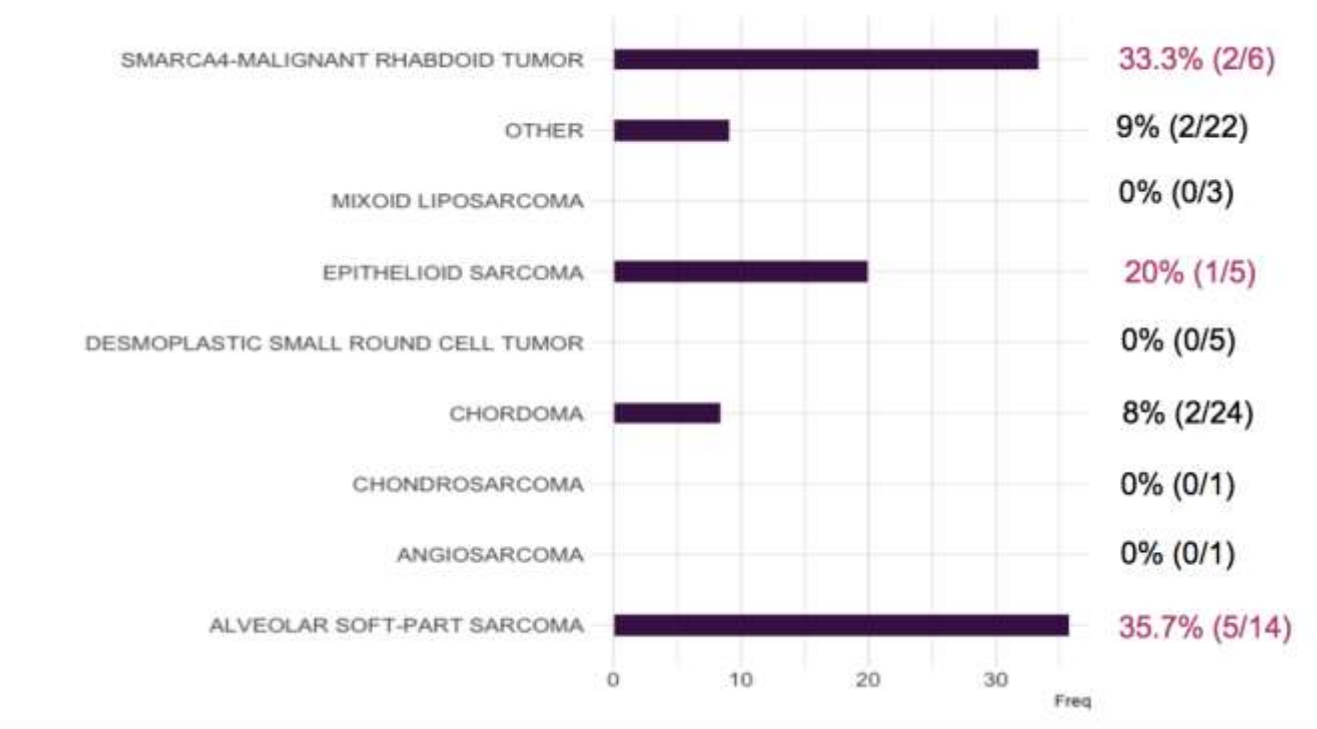
Blay JY et al. ESMO 2020

Pembrolizumab in selected rare sarcoma histotypes

AcSé Pembrolizumab

Phase II Study

Best response: % PR according to histology



Blay JY et al. ESMO 2020

OSCAR – Nivolumab in patients with advanced clear cell sarcoma (CCS) and alveolar soft part sarcoma (ASPS)

Phase II Study

Study design

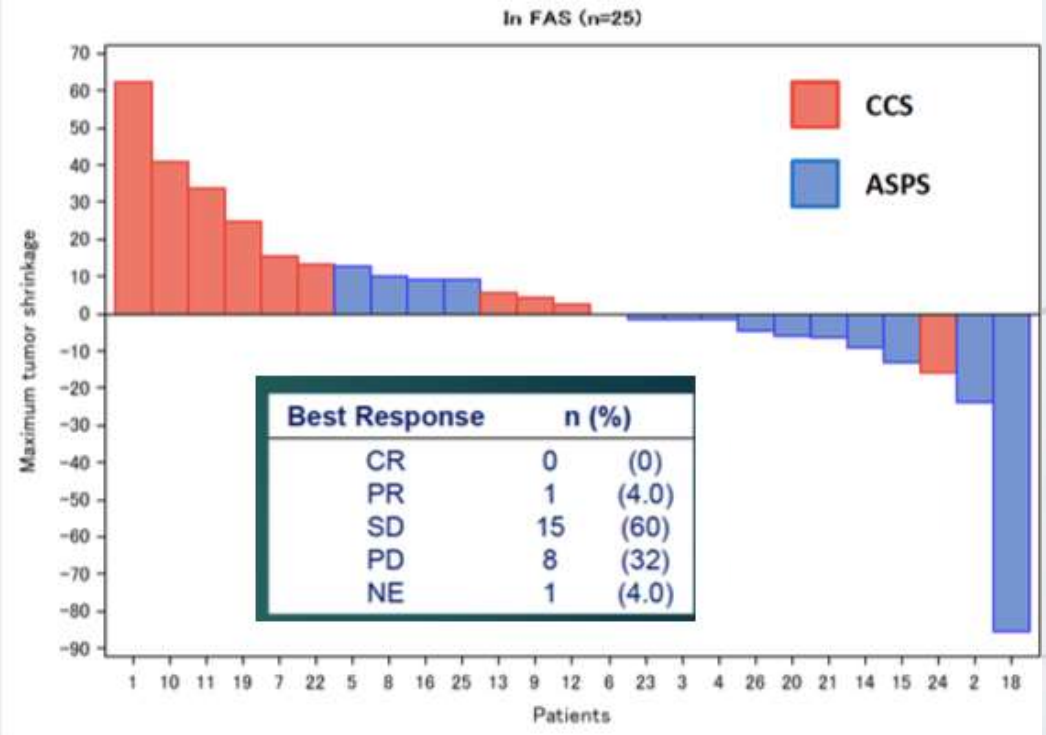
- **Clear cell sarcoma (CSS) (n=11), alveolar soft part sarcoma (ASPS) (n=14)**
- **Nivolumab 240mg every 2 weeks**
- **Advanced CCS oder ASPS, fusions approved in ~50%**

Kawai A et al. CTOS 2020

OSCAR – Nivolumab in patients with advanced clear cell sarcoma (CCS) and alveolar soft part sarcoma (ASPS)

Phase II Study

Results (n=25): Response rate



Kawai A et al. CTOS 2020

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Medizinische Universität & LKH-Univ. Klinikum

Immune Checkpoint Inhibitors

REGIMEN	n	mPFS (months)	3m-PFS	ORR (RECIST)	INCLUDED SUBTYPES	RESPONDING SUBTYPES	REF
Pembrolizumab (SARC 028) (Phase II)	42 (STS)	4.2	55%	7 (18%)	4 (UPS, LPS, LMS, SS)	UPS, LPS, SS	Tawbi
Nivolumab (Phase II)	43	1.7	+/- 35%	2 (5%)	> 10 (ASPS-1pt, UPS, LMS, LPS, ES, SS, MPNST…)	ASPS, LMS	D' Angelo
Nivolumab-Ipilimumab (Phase II)	42	4.1	+/- 60%	6 (16%)	> 10 (ASPS-1pt, UPS, LMS, LPS, ES, SS, MPNST…)	LMS, UPS, MFS, Angio	D' Angelo
Axitinib-Pembrolizumab (Phase II)	33	4.7	66%	8 (25%)	Several (ASPS 36%)	ASPS, LMS, ES	Wilky
Nivolumab-Sunitinib (Phase II)	50 (STS)	5.9	69%	5 (11%)	>10 (SS, ASPS, CCS, UPS, SFT, epitheloid sarcoma, Angio, extraskeletal myxoid chondrosarcoma)	Angio, extraskeletal myxoid chondrosarcoma, SS, ASPS	Martin-Broto

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Immune Checkpoint Inhibitors

REGIMEN	n	mPFS (months)	3m-PFS	ORR (RECIST)	INCLUDED SUBTYPES	RESPONDING SUBTYPES	REF
Atezolizumab (Phase II)	34	-	-	10 (32%)	ASPS	ASPS	Chen
Pembrolizumab –Doxorubicin	30	6.9	-	11 (36.7%)	LMS, LPS, UPS, SS, Other	LMS, LPS, UPS, Other	Livingston
Ipilimumab-Nivolumab neoadjuvant (Phase II)	23				DD LPS, UPS	UPS	Roland
Trabectedin-Durvalumab (Phase Ib)	40 (14)	2.3		1 (7.1%)	DD LPS, UPS, other		Toulmonde
Pembrolizumab in rare STS subtypes (Phase II)	81	7.9		12 (15%)	Chordoma, ASPS, DSRCT, SMBT, other	Chordoma, ASPS, DSRCT, SMBT	Blay
Nivolumab in CCS and ASPS (Phase II)	25	4.1 CCS 6 ASPS		0 (0%) CCS 1 (7.1%) ASPS	CCS, ASPS	ASPS	Kawai

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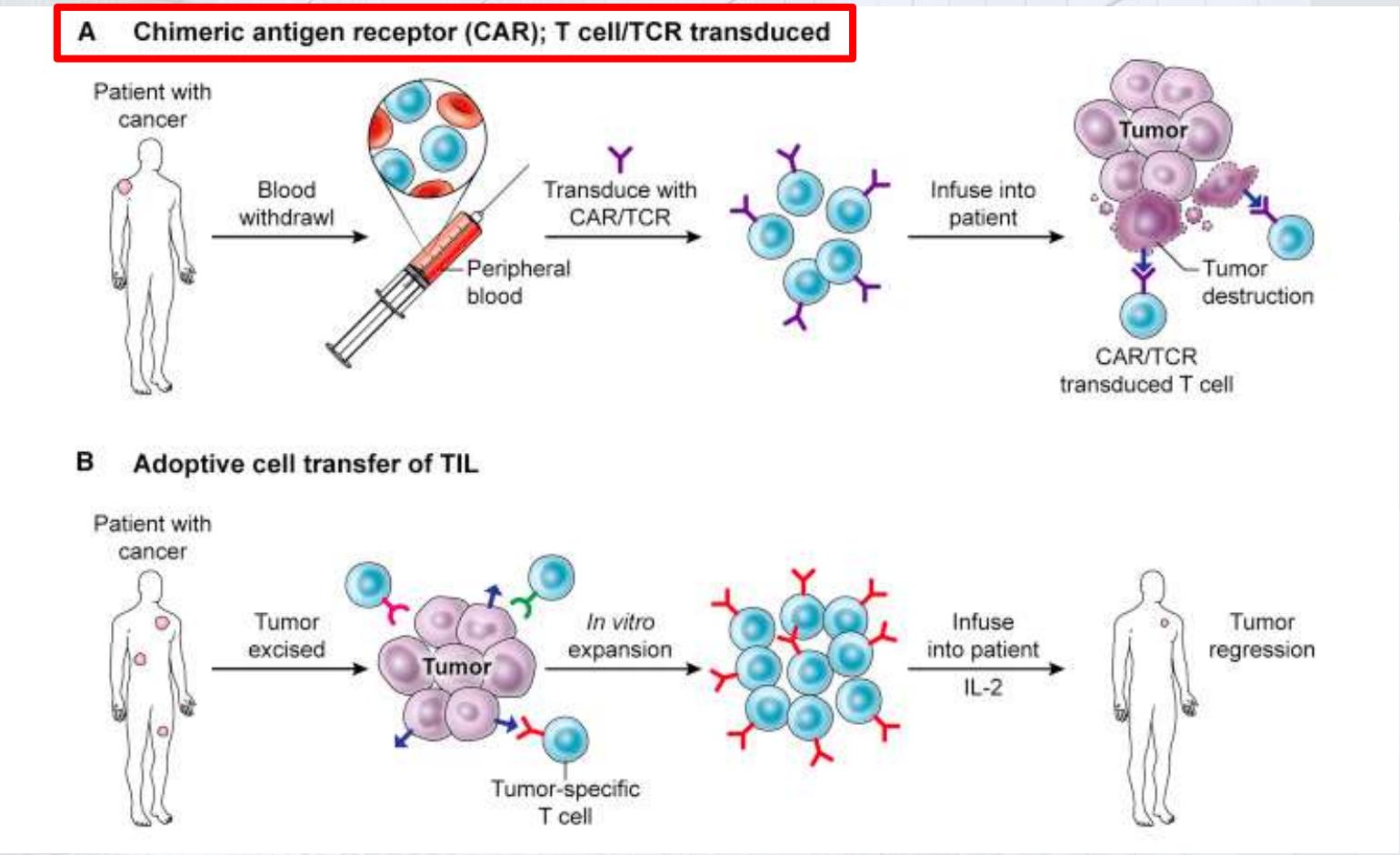
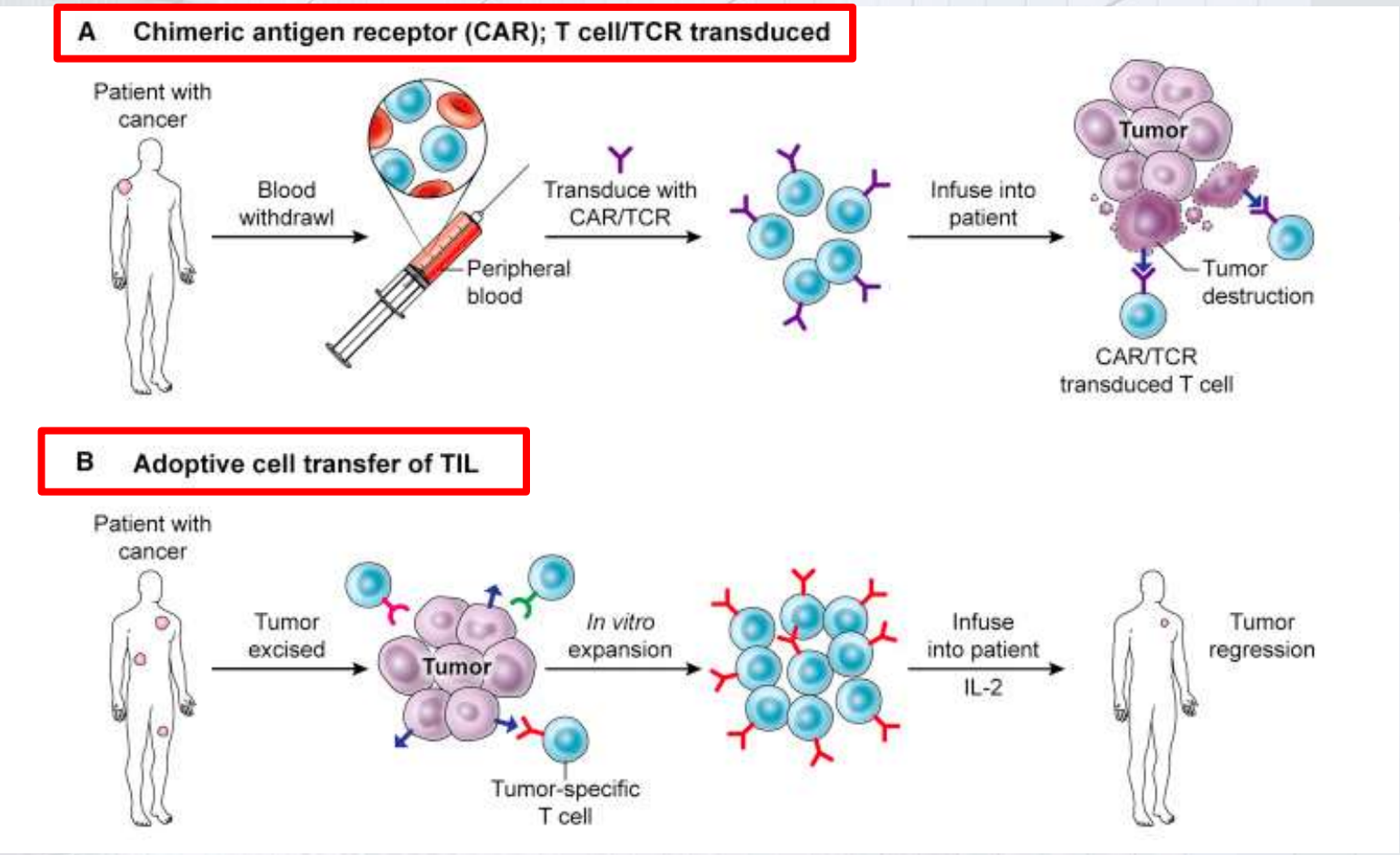
Adoptive T Cell Therapy



Kishton RJ et al., Cell Metab. 2017;26:94-109

Adoptive T Cell Therapy



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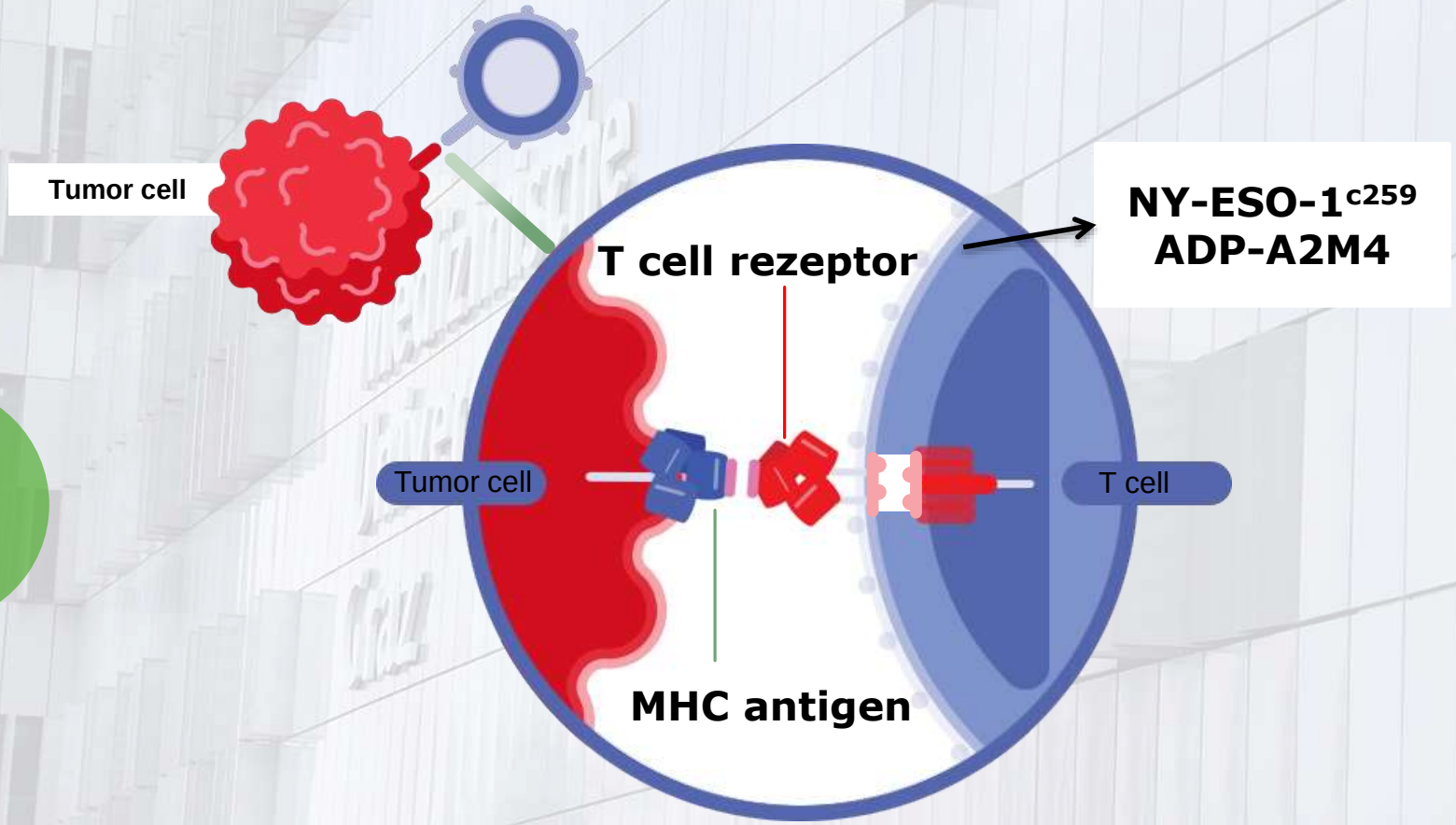
Adoptive T Cell Therapy



Brian A. Van Tine et al, 2019, CTOS 2019

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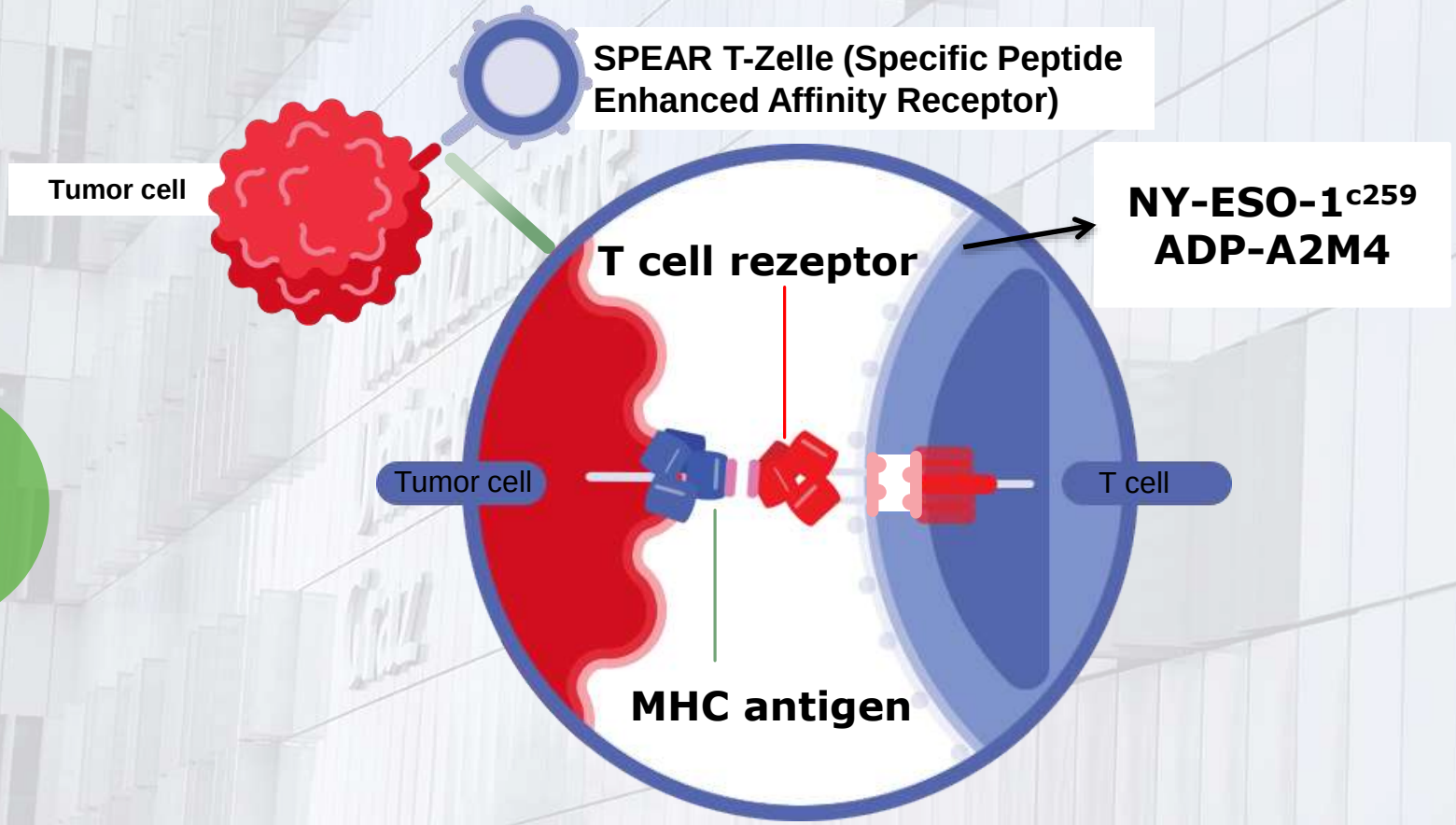
Adoptive T Cell Therapy



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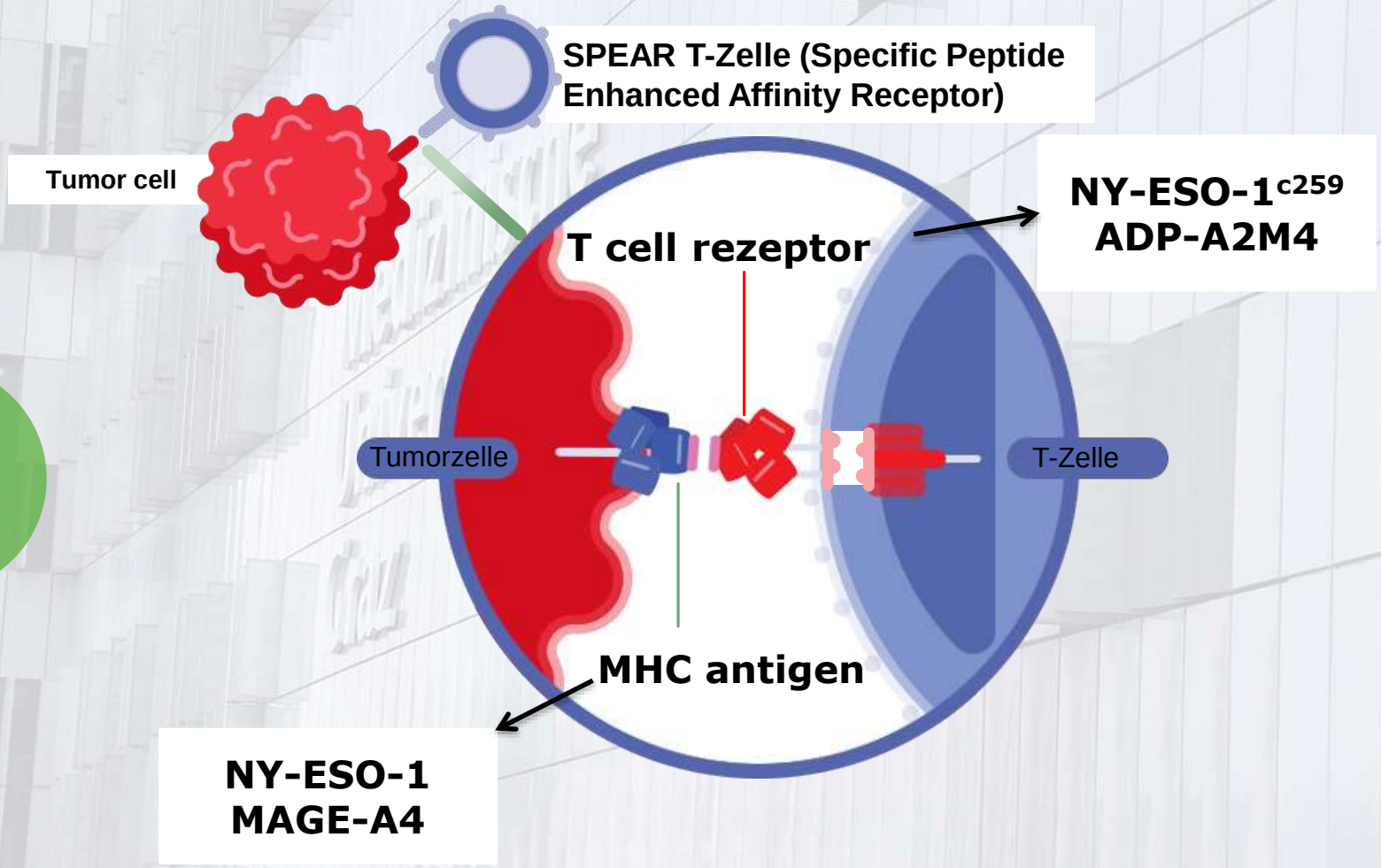
Adoptive T Cell Therapy



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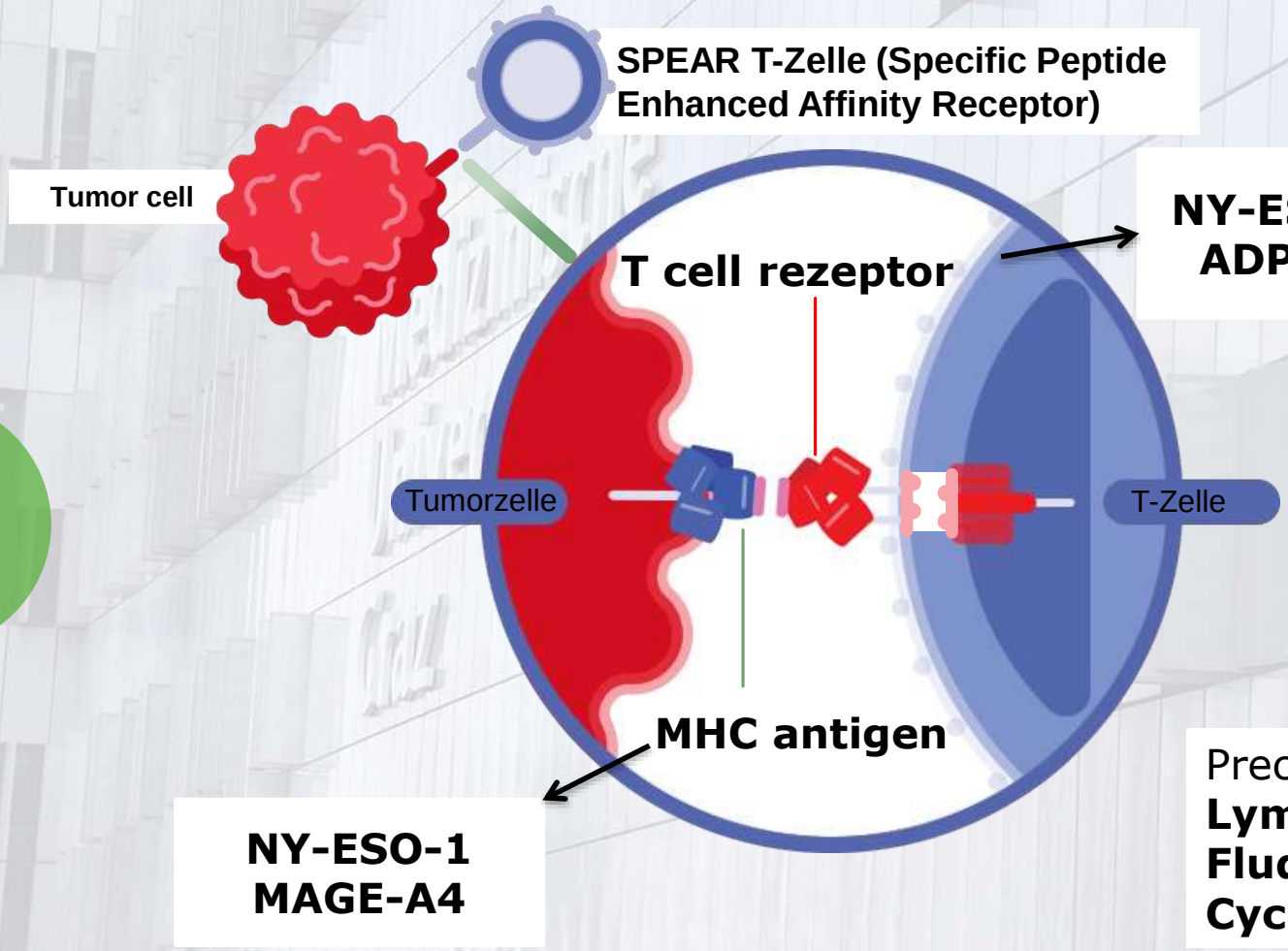
Adoptive T Cell Therapy



Precondition:
Lymphodepletion with Fludarabine and **Cyclophosphamid**

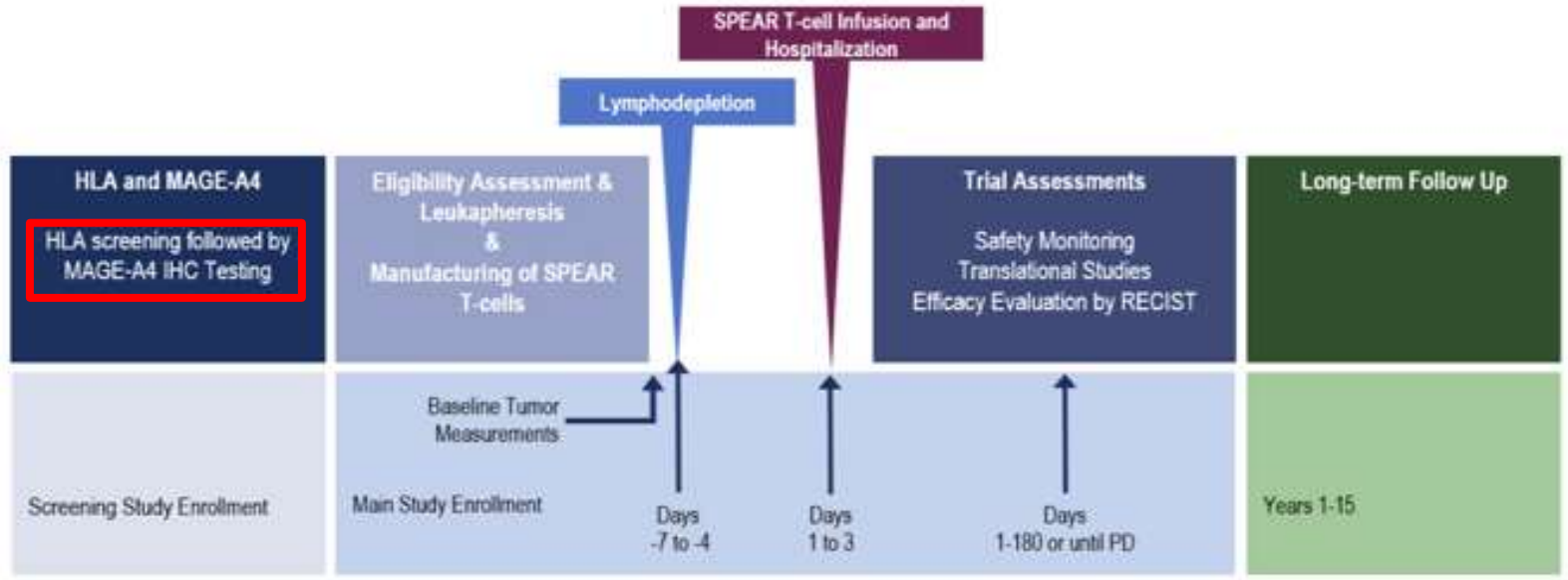
Brian A. Van Tine et al, 2019, CTOS 2019

Adoptive T Cell Therapy

Dose Escalation and Expansion Trial to assess Safety and Efficacy of ADP-A2M4 in Advanced Solid Tumors

Phase I Study

Study design (n=38)



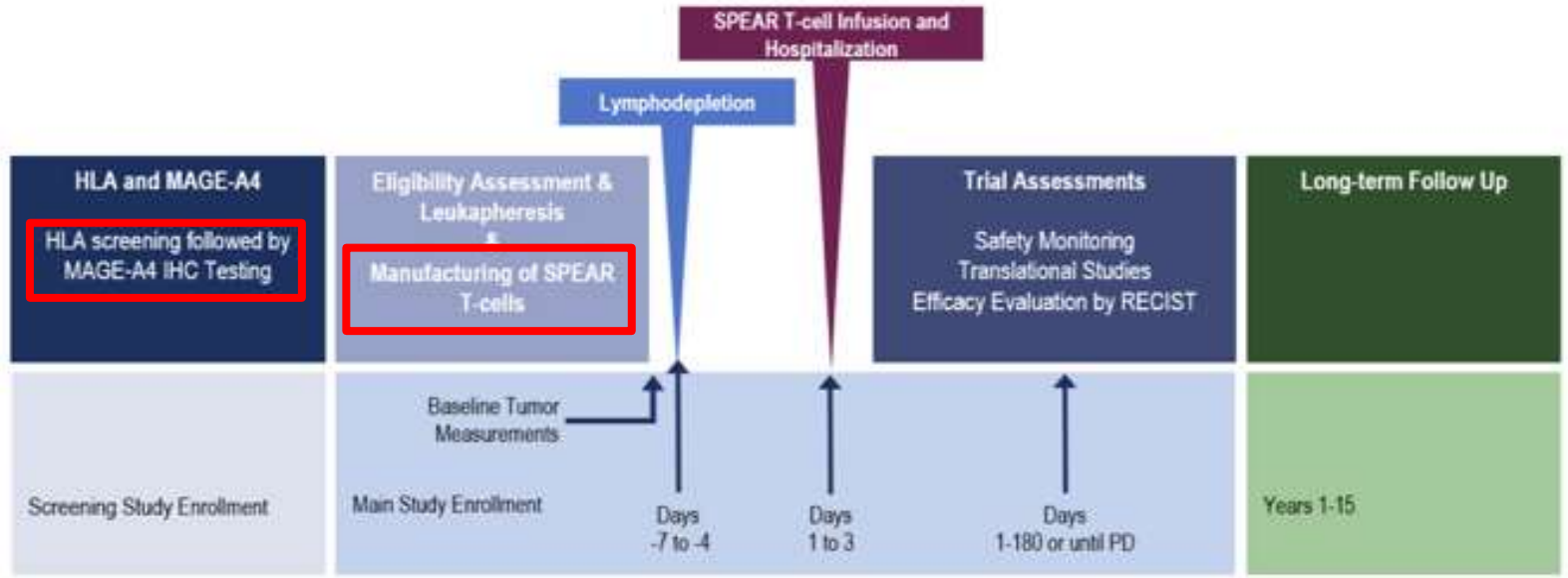
Hong D et al. ASCO 2020

Adoptive T Cell Therapy

Dose Escalation and Expansion Trial to assess Safety and Efficacy of ADP-A2M4 in Advanced Solid Tumors

Phase I Study

Study design (n=38)



Hong D et al. ASCO 2020

Adoptive T Cell Therapy

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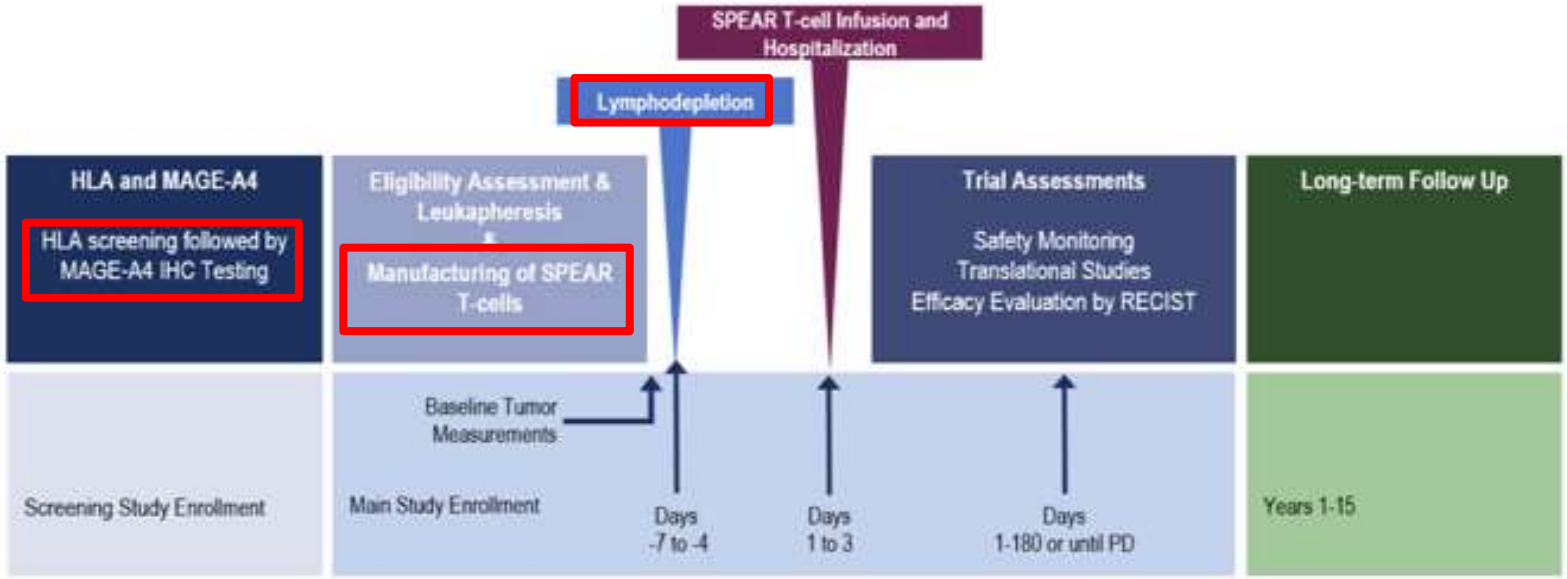
Phase I Study

Study design (n=38)



Hong D et al. ASCO 2020

Adoptive T Cell Therapy

Dose Escalation and Expansion Trial to assess Safety and Efficacy of ADP-A2M4 in Advanced Solid Tumors

Phase I Study

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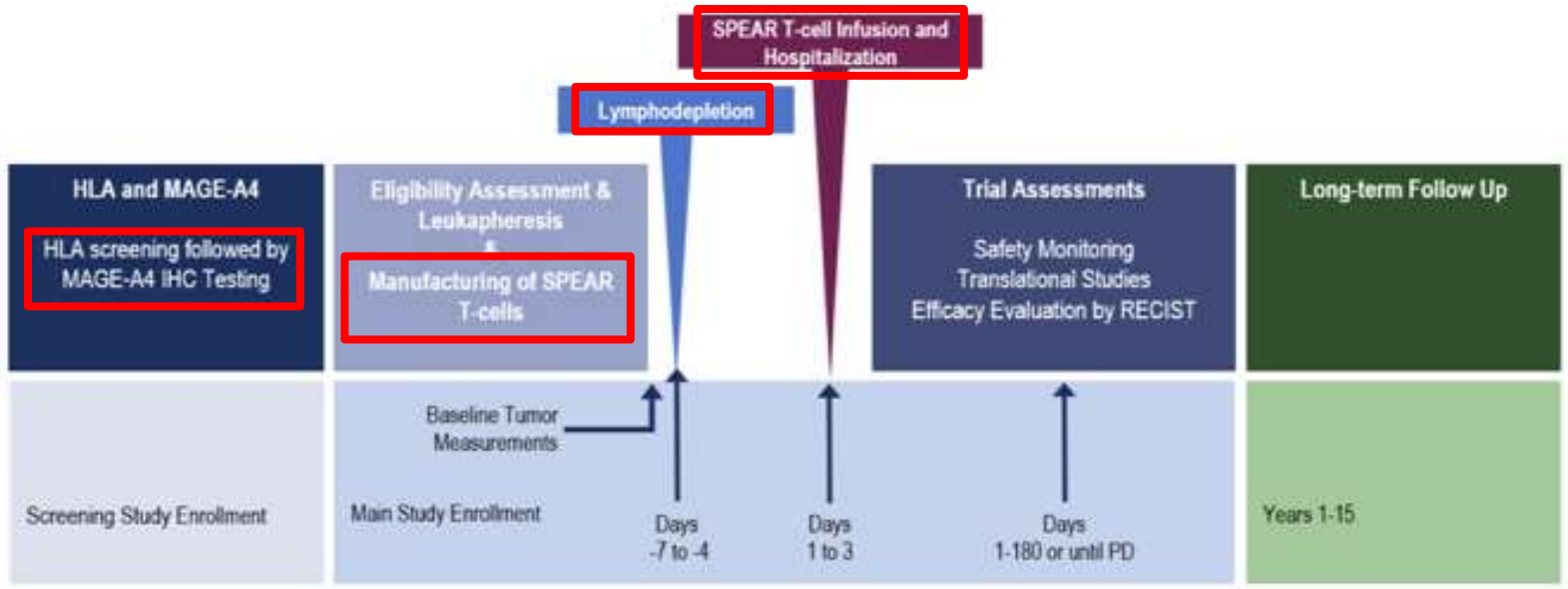

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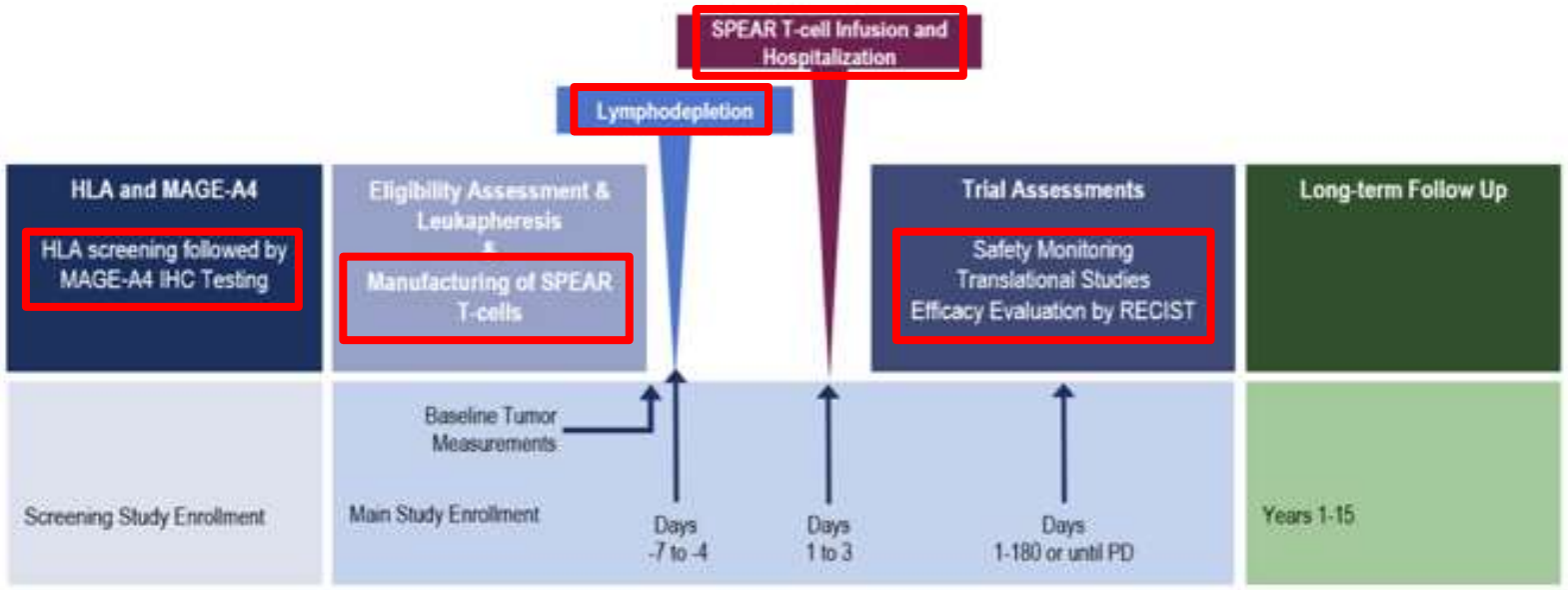
Adoptive T Cell Therapy

Dose Escalation and Expansion Trial to assess Safety and Efficacy of ADP-A2M4 in Advanced Solid Tumors

Phase I Study

Study design (n=38)



Hong D et al. ASCO 2020

Adoptive T Cell Therapy

Dose Escalation and Expansion Trial to assess Safety and Efficacy of ADP-A2M4 in Advanced Solid Tumors

Phase I Study

Results (n=38; ORR RECIST):

	Overall	Synovial sarcoma	Non-sarcoma	Head & neck	Lung
n	38[1]	16	22	3	2
BOR partial response (%)	9 (23.7)	7 (43.8)	2 (9.1)	1 (33.3)	1 (50.0)
BOR stable disease (%)	18 (47.4)	7 (43.8)	11 (50.0)	1 (33.3)	0
BOR progressive disease (%)	7 (18.4)	1 (6.3)	6 (27.3)	1 (33.3)	1 (50.0)
Unknown or missing (%)	4 (10.5)	1 (6.3)	3 (13.6)	0	0
ORR (%)	23.7	43.8	9.1	33.3	50.0

Response in different tumor types:
synovial sarcoma, head and neck carcinoma, lung cancer

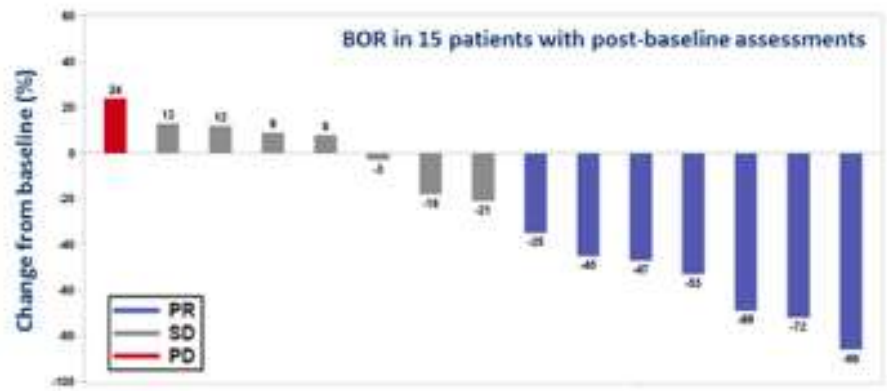
Hong D et al. ASCO 2020

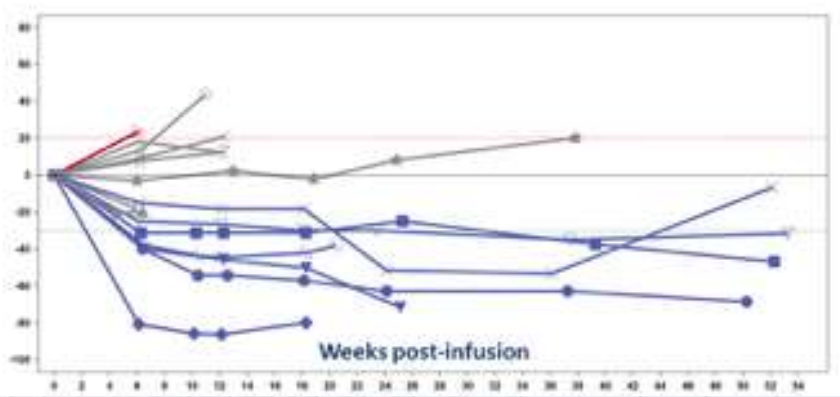
Adoptive T Cell Therapy

Dose Escalation and Expansion Trial to assess Safety and Efficacy of ADP-A2M4 in Advanced Solid Tumors

Phase I Study

Results in synovial sarcoma (n=16): durable responses





PR in 44% patients
Duration of response: m28 weeks (range 12-54 weeks)

Hong D et al. ASCO 2020

Dose Escalation and Expansion Trial to assess Safety and Efficacy of ADP-A2M4 in Advanced Solid Tumors

Phase I Study

Adverse events:

- **Pancytopenia (leukopenia, lymphopenia, neutropenia, anemia, thrombopenia)**
- **Fatigue**
- **Nausea**
- **Vomiting**
- **Fever**
- **Cytokine release syndrome (CRS)**
- **Diarrhea**
- **Decreased appetite**
- **Dyspnea**
- **Hypotension**

Hong D et al. ASCO 2020

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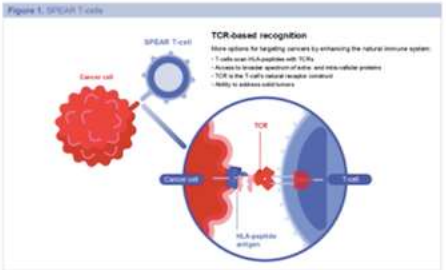
Adoptive T Cell Therapy

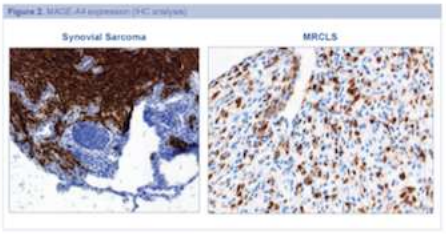
ADP-A2M4 SPEAR T Cells in Patients with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

Phase II Study

Background

- ADP-A2M4 SPEAR T-cells target MAGE-A4+ tumors (**Figure 1**)
- MAGE-A4 is highly expressed in synovial sarcoma and myxoid/round cell liposarcoma (MRCLS) in the context of HLA-A*02 (**Figure 2**)
- This Phase 2 trial was initiated based on the favorable benefit:risk profile of ADP-A2M4 observed in a Phase 1 trial (NCT03132922), which demonstrated compelling clinical responses in patients with synovial sarcoma





SPEAR T-cell mechanism of action video can be viewed by clicking here:
https://youtu.be/zdl8IGXxQd0

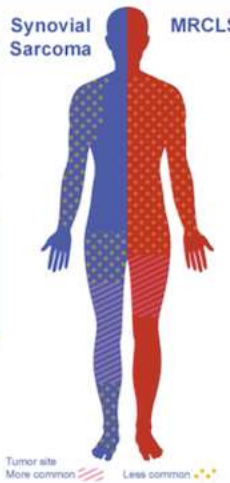
Full trial details from ClinicalTrials.gov can be viewed by clicking here:
https://clinicaltrials.gov/ct2/show/NCT04044768

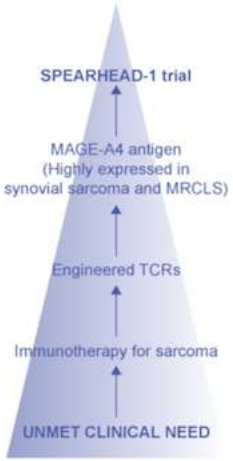
Soft tissue sarcomas

- >50 subtypes, including liposarcoma and synovial sarcoma
- Prognosis in advanced disease remains unfavorable

Synovial Sarcoma
- ~800–1000 new cases/year in the United States
- Often occurs in patients aged <40 years
- High metastatic potential

MRCLS
- ~750 new cases/year in the United States
- Typically presents at 35–55 years of age
- One-third MRCLS become metastatic





SPEARHEAD-1 trial (NCT04044768)

- Recruiting 45 patients from North America and Europe
- Advanced synovial sarcoma or MRCLS, prior chemotherapy, HLA-A*02 and MAGE-A4 positive

Trial Details

- Primary objective is to evaluate the efficacy of ADP-A2M4 in patients with synovial sarcoma or MRCLS
  - Determined by the Overall Response Rate, defined as incidence of complete or partial responses as assessed by independent RECIST v1.1 review
- We are currently recruiting trial participants
  - Total of 20 sites open: 14 in the US, 1 in Canada, 2 in France, and 3 in Spain
- Trial design and engineered T-cell pathway are shown below (**Figure 3** and **Figure 4**)

Principal investigator details:
- Dejka M. Araujo, MD
- (+1) 713-792-3626
- daraujo@mdanderson.org

Abbreviations

ASCO Annual Meeting, May 29-June 2, 2020 (Virtual Format)

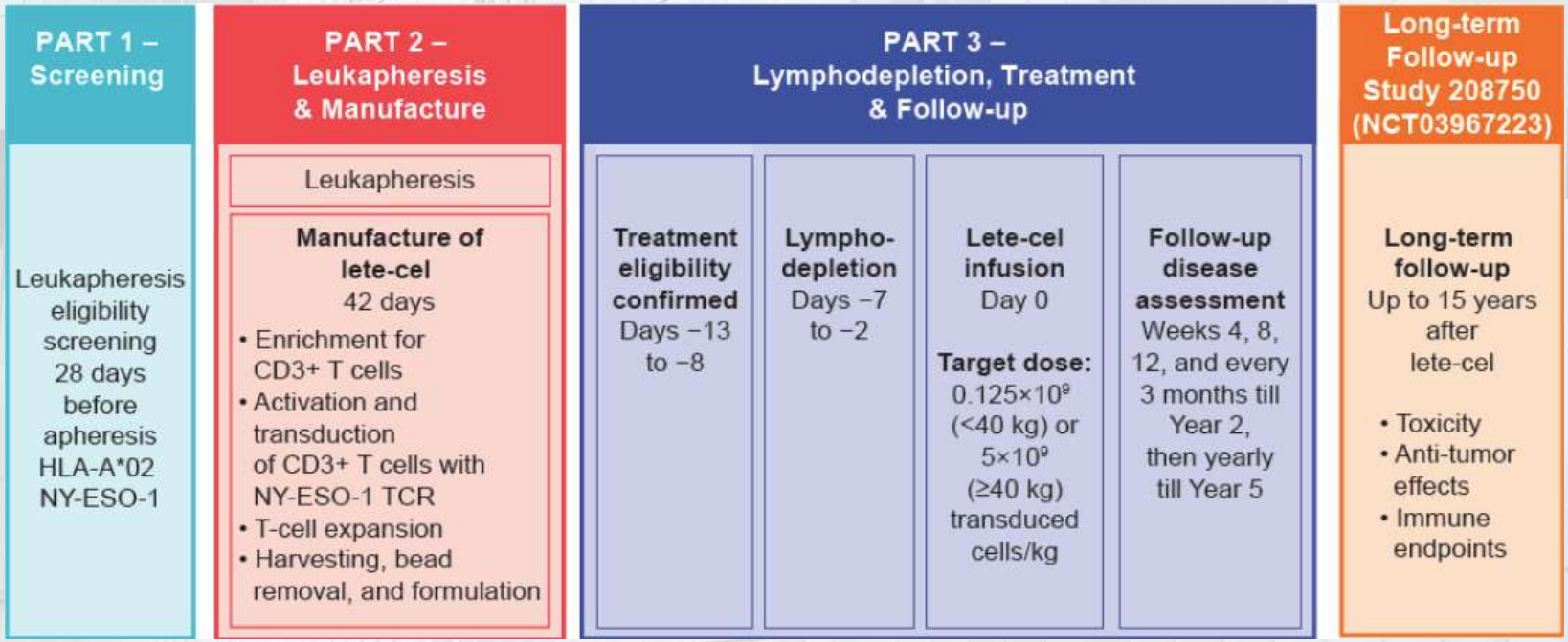
Araujo D et al. ASCO 2020

Adoptive T Cell Therapy

Final Analysis of NY-ESO-1 specific T Cell Receptor (TCR) T Cell Therapy in Patients with advanced Synovial Sarcoma (SS)

Phase I Study

Study design



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Adoptive T Cell Therapy

Final Analysis of NY-ESO-1 specific T Cell Receptor (TCR) T Cell Therapy in Patients with advanced Synovial Sarcoma (SS)

Phase I Study

Cohort 1 from the pilot study and additional cohort 2, 3 and 4:

Cohort	NY-ESO-1 expression	Lymphodepletion regimen
1 (n=12)	**HIGH** IHC score 2+ or 3+ in ≥50% of tumor cells	**HIGH** doses of fludarabine and cyclophosphamide *Fludarabine 30 mg/m² IV x 4 days[a]* *Cyclophosphamide 1800 mg/m² IV x 2 days[b]*
2 (n=13)	**LOW** IHC score ≥1+ in ≥1% cells but not exceeding 2+ or 3+ in ≥50% cells	**HIGH** doses of fludarabine and cyclophosphamide *Fludarabine 30 mg/m² IV x 4 days[a]* *Cyclophosphamide 1800 mg/m² IV x 2 days[b]*
3 (n=5)	**HIGH** IHC score 2+ or 3+ in ≥50% of tumor cells	**HIGH** dose of cyclophosphamide only *Cyclophosphamide 1800 mg/m² IV x 2 days[b]*
4 (n=15)	**HIGH** IHC score 2+ or 3+ in ≥50% of tumor cells	**LOW** doses of fludarabine and cyclophosphamide *Fludarabine 30 mg/m² IV x 3 days[c]* *Cyclophosphamide 600 mg/m² IV x 3 days[c]*

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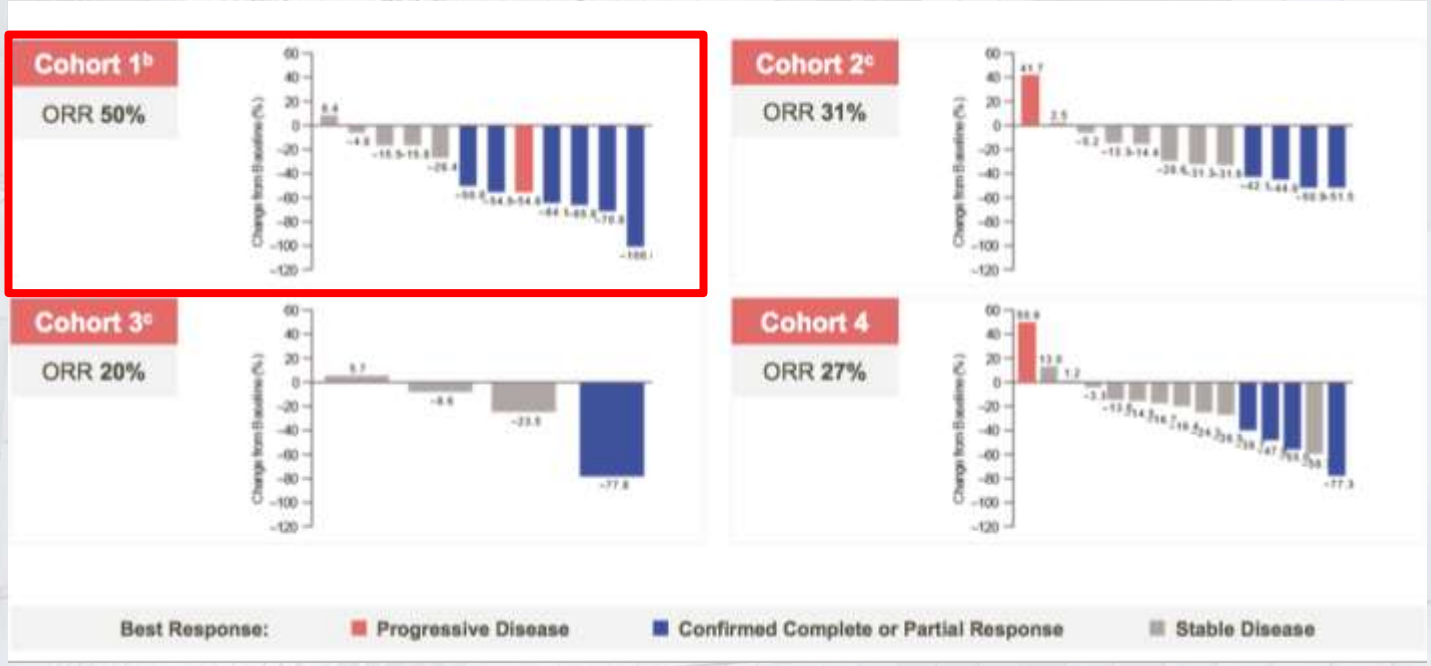
Phase I Study

Results (n=45): Response rate



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Adoptive T Cell Therapy

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Phase I Study

Adverse events:

- **Cytopenia (leukopenia, lymphopenia, neutropenia, anemia, thrombopenia)**
- **Febrile neutropenia**
- **Dyspnoea**
- **Hyponatremia**

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Conclusio

- **Immune Checkpoint Inhibitors** show **efficacy** in **specific histologic STS subtypes** such as **dedifferentiated liposarcoma**, **undifferentiated pleomorphic sarcoma** and **alveolar soft part sarcoma**

- **Identification of biomarkers** to predict the response of **STS** to **Immune Checkpoint Inhibitors** is **essential**

- **Kombination strategies** (**Checkpoint Inhibitores + Tyrosine Kinase Inhibitors**, **2 Checkpoint Inhibitors**, **Checkpoint Inhibitors + Chemotherapy**) is **more effective** than **Monotherapies** with **Checkpoint Inhibitors**

Conclusio

- The **complex therapeutic modell** of adoptive **T cell transfer** seems to work, at least in patients with **synovial sarcoma**
- **Response duration** has to be **further evaluated**
- **High costs/long hospitalization!**
- **Long term adverse events** remain to be seen

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