Στρογγυλό Τραπέζι
Ανοσοθεραπεία

Εξελίξεις της ανοσοθεραπείας στους συμπαγείς όγκους και στις ανοσολογικές ανεπιθύμητες ενέργειες

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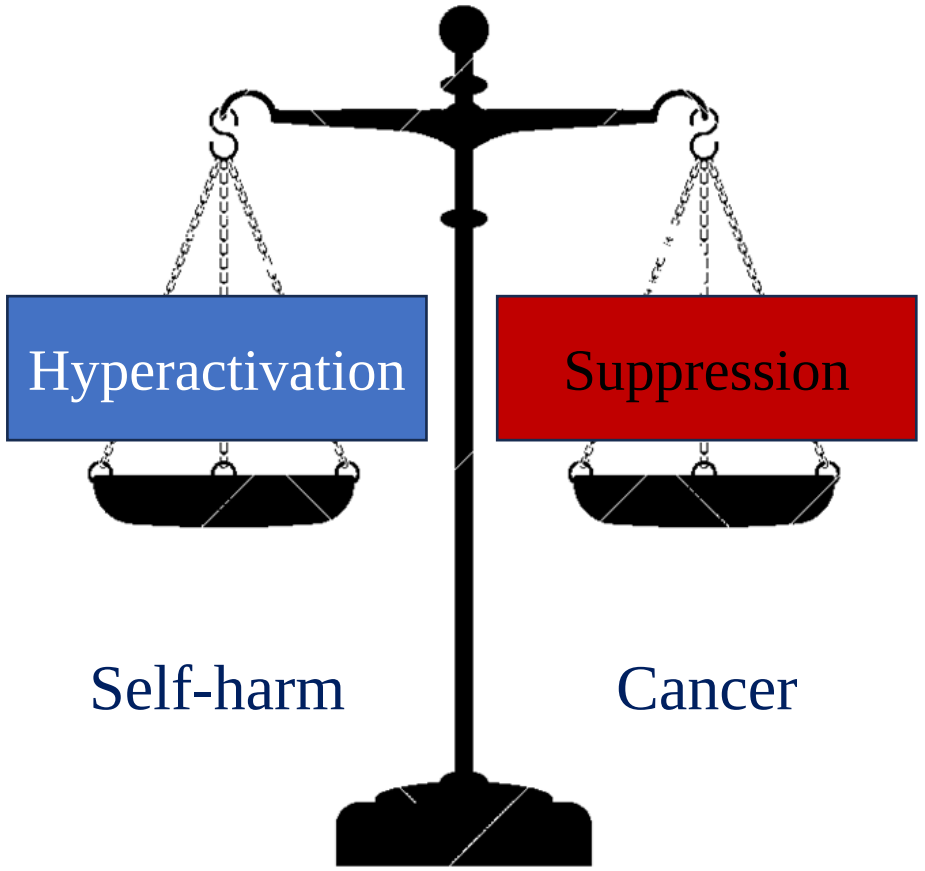
OCTOBER 03, 2025

Conflicts of interest

None

Immune System

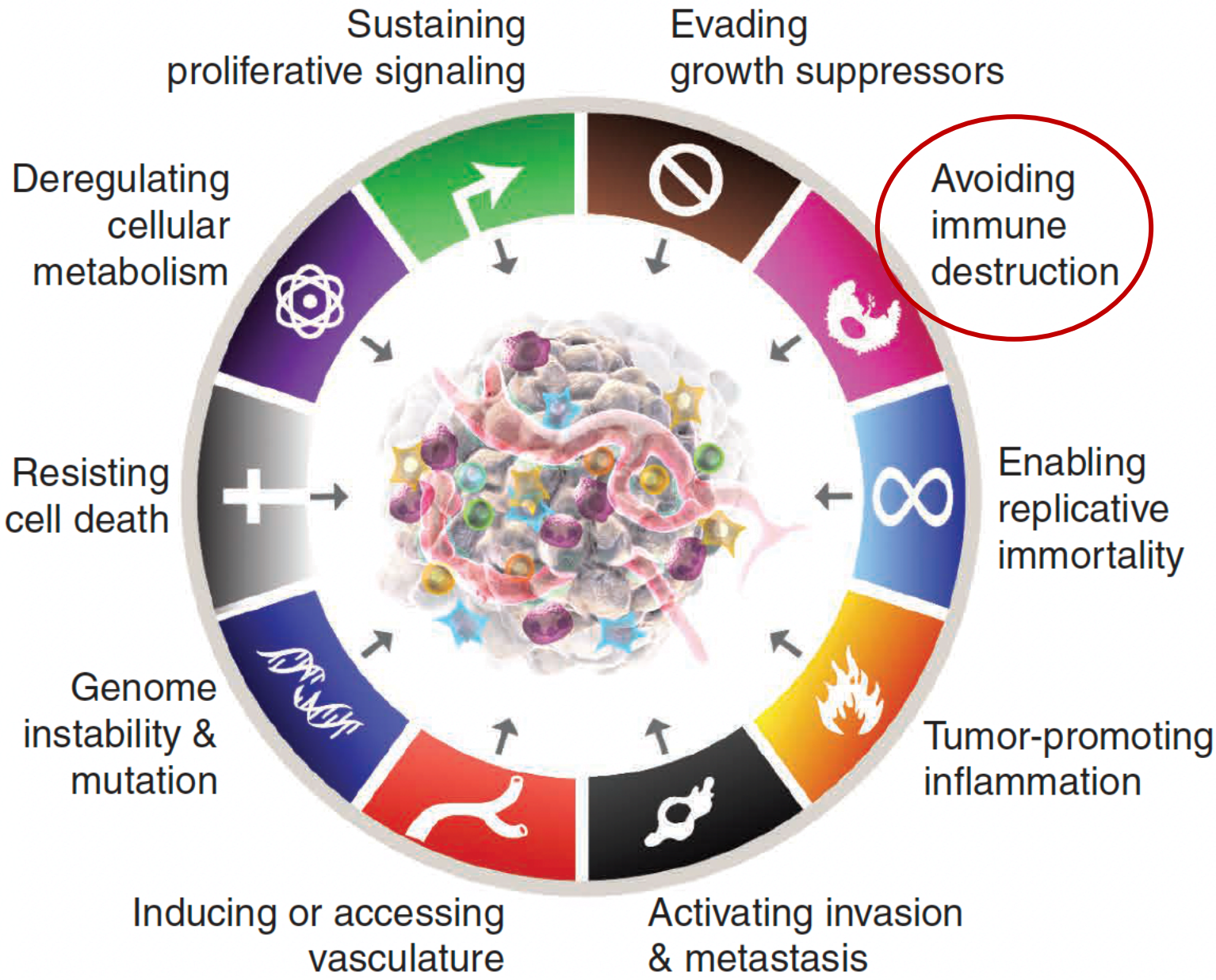


Self-harm

Cancer

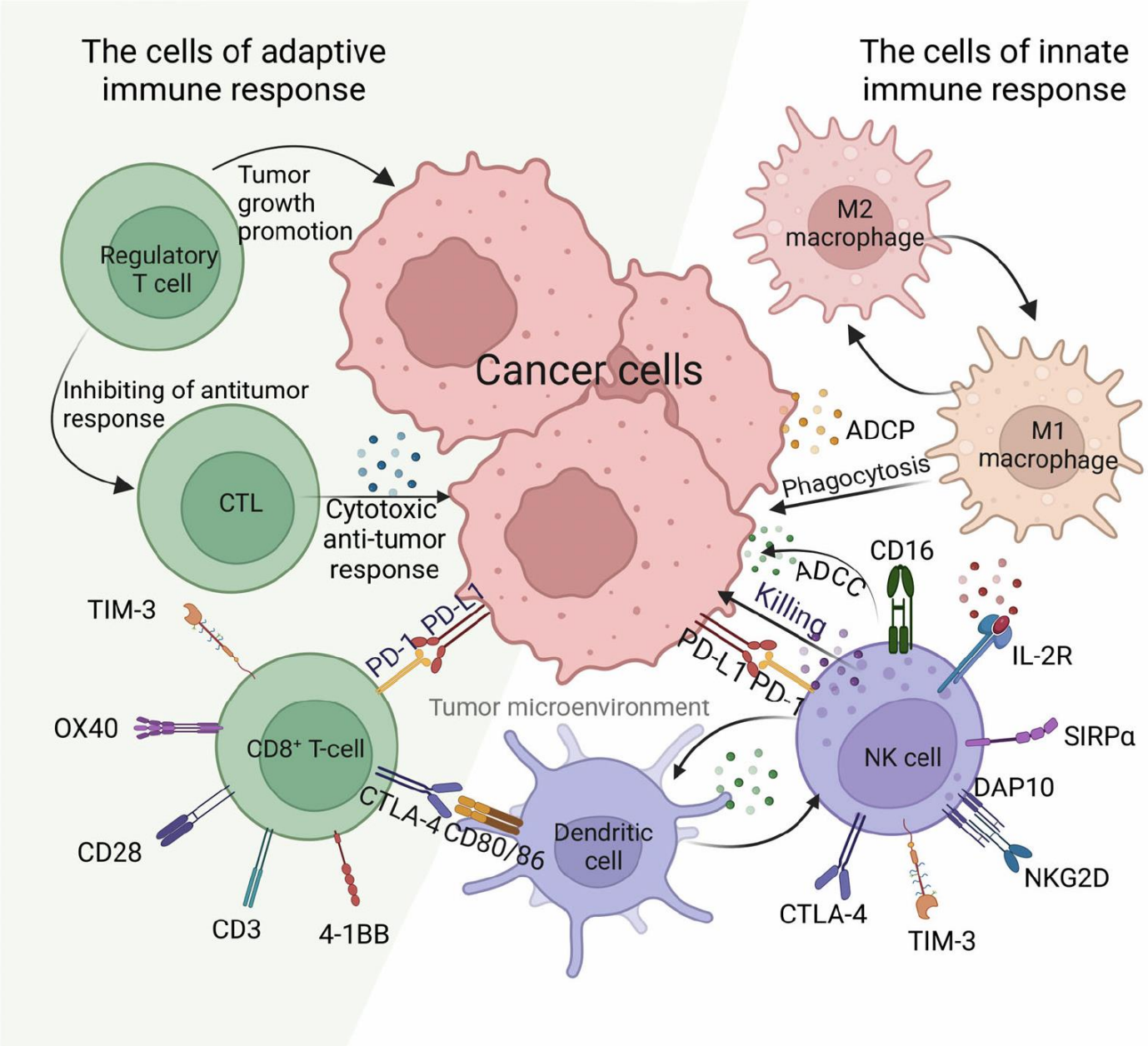
Germs

Hallmarks of cancer



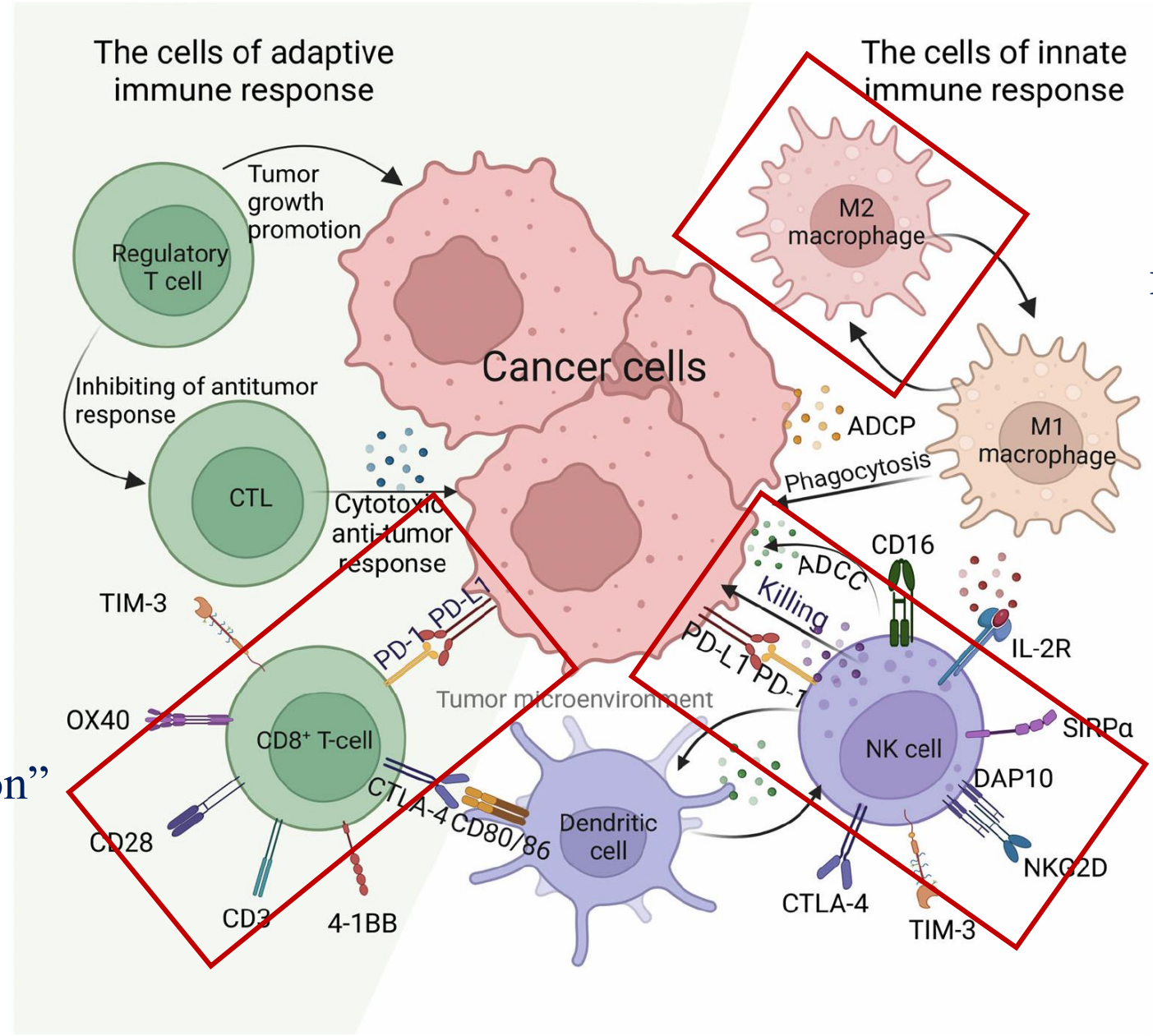
Weinberg and Hanahan

The immune landscape of a solid tumor



Kuznetsova, 2024

Immune tolerance within the tumor microenvironment (TME)



1

T-cell “exhaustion”

2

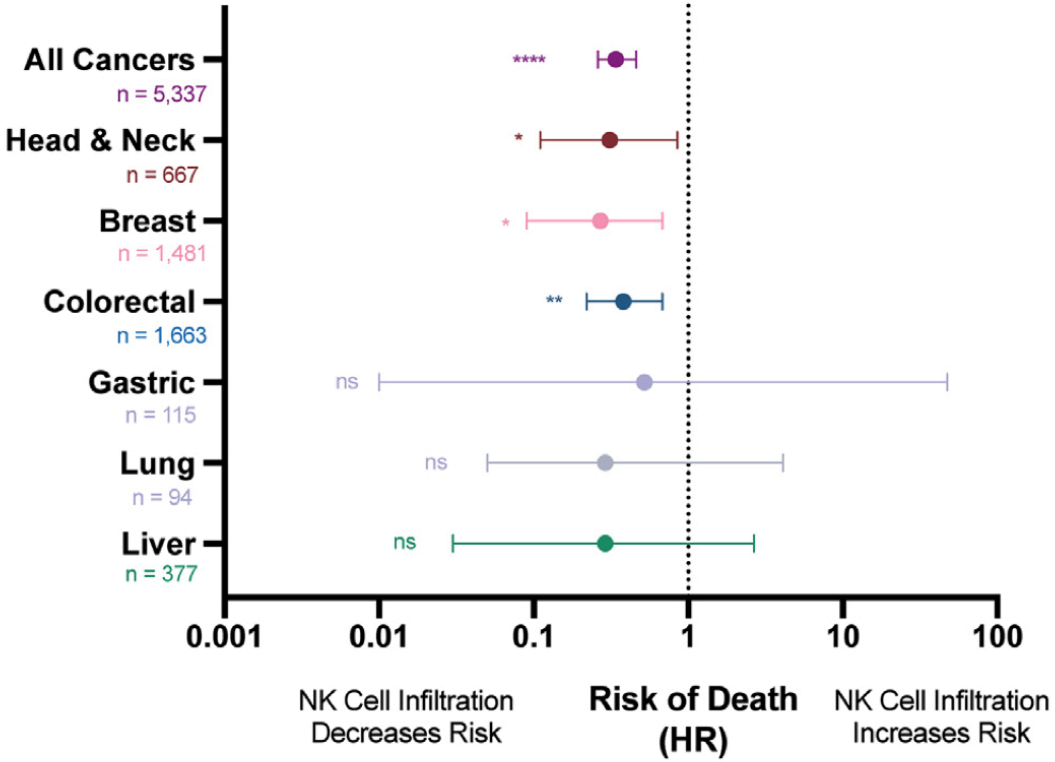
NK-cell “dormancy”

3

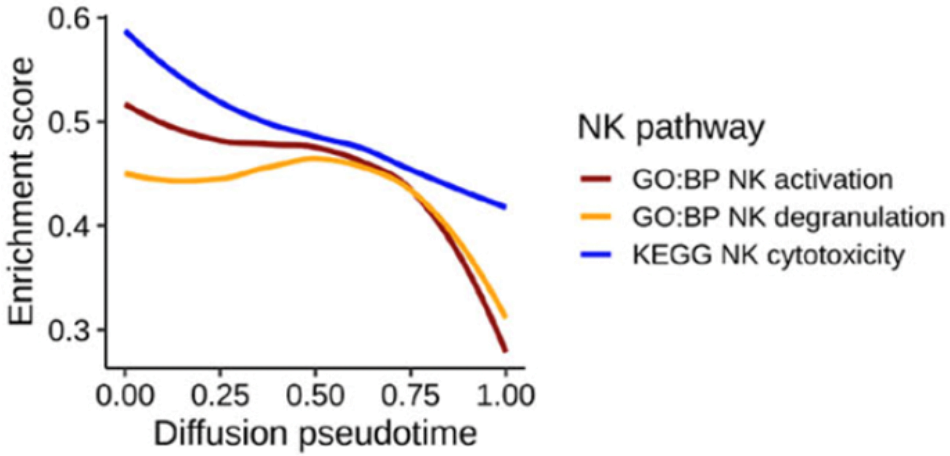
Predominance of immunosuppressive macrophages (TAMs)

Kuznetsova, 2024

Modulation of immune cells by the TME - the example of NK cells

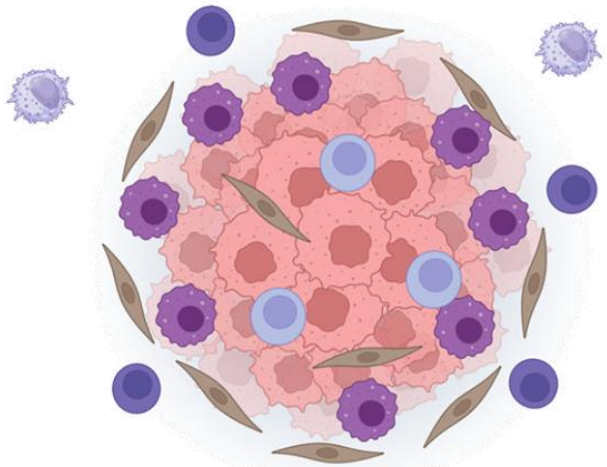


TME induces loss of NK cell effector functions with time



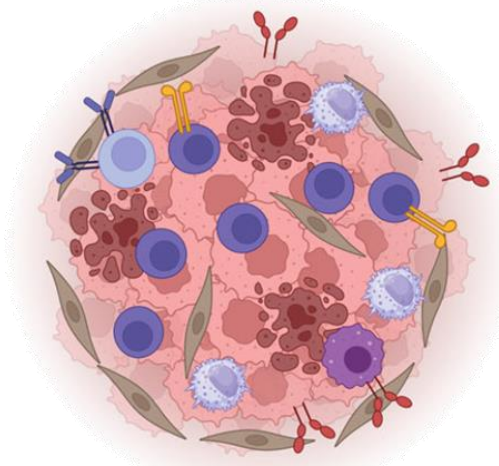
Nersesian, 2021; Dean, 2024

Cold tumor

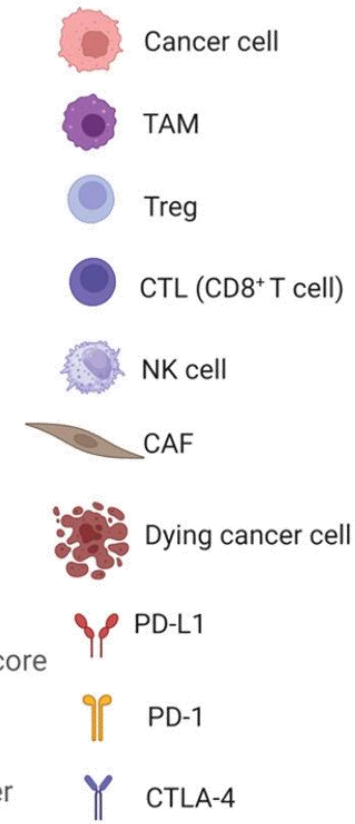


- Non-immunogenic tumors
- Immunosupressive immune cells in tumor (TAMs and Treg)
- Exclusion of CTLs ($CD8^+$ T cells) and NK cells from the tumor core
- CTLs present along periphery of the tumor, where they contact with TAMs
- Poor prognosis and response to immunotherapy

Hot tumor



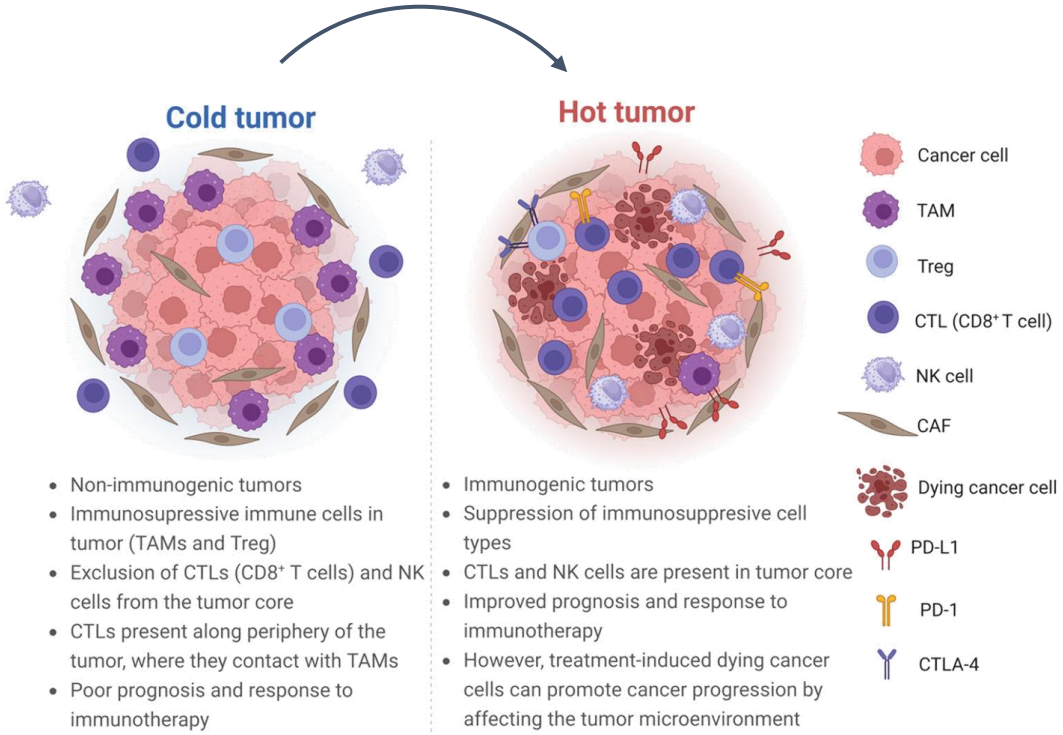
- Immunogenic tumors
- Suppression of immunosuppresive cell types
- CTLs and NK cells are present in tumor core
- Improved prognosis and response to immunotherapy
- However, treatment-induced dying cancer cells can promote cancer progression by affecting the tumor microenvironment



Kuznetsova, 2024

Goals of immunotherapy

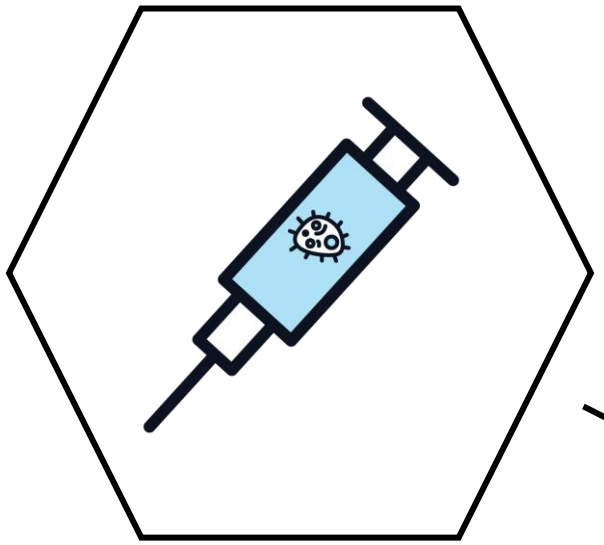
- Improve the infiltration of CTLs, NK cells, M1 macrophages
- Inhibit the infiltration of Tregs, MDSCs, TAMs (M2 macrophages)
- Enhance the effector function of infiltrating immune cells
- Generate immunological memory



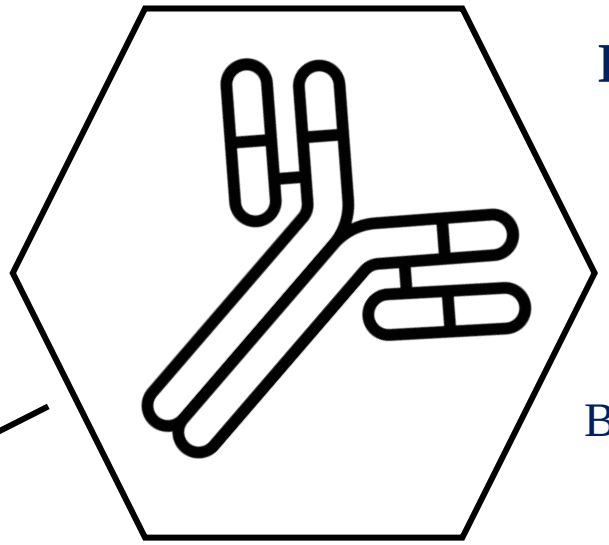
Kuznetsova, 2024

Modes

Cancer vaccines



Monoclonal antibodies

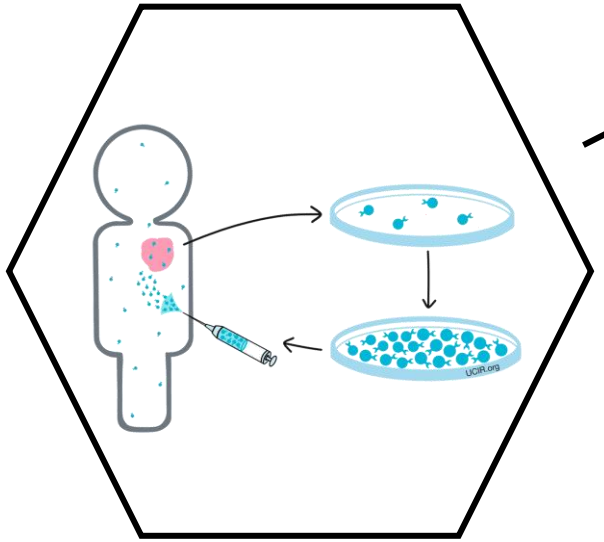


Immune Checkpoint Inhibitors (ICIs)

Antibody-Drug Conjugates (ADCs)

Bi- or Tri-specific Immune Cell Engagers (ICEs)

Adoptive cell transfer (ACT)



(TCR) T-cells

CAR-T/NK/M cells

CART.BiTE

Oncolytic viruses

T-VEC©

Adstiladrin©

Immune checkpoint inhibitors (ICIs) in solid tumors

Cancer survival in the era of ICIs

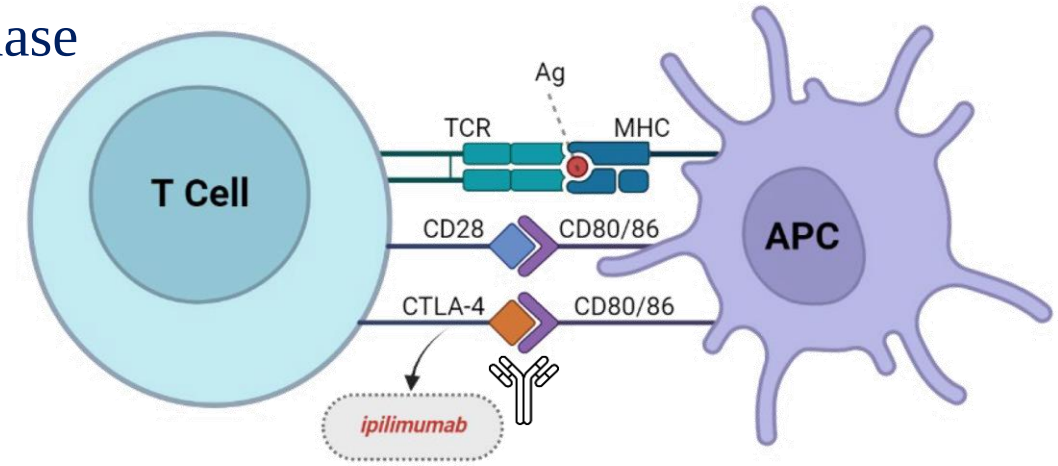
Immune-related adverse events (ir-AEs)

Future challenges

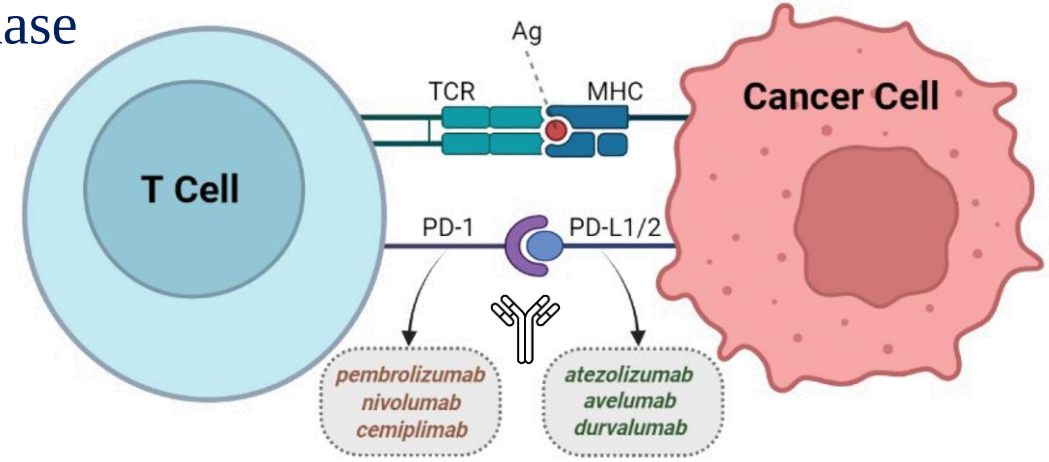
ICIs


ALLIED
CHECK POINT
MILITARY
POLICE
US ARMY
YOU ARE LEAVING
THE AMERICAN SECTOR
VOUS SORTEZ
DU SECTEUR AMERICAIN

Priming Phase



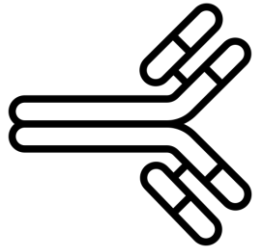
Effector Phase



- PD-1 ↔ PD-L1
- CTLA-4 ↔ CD80/CD86

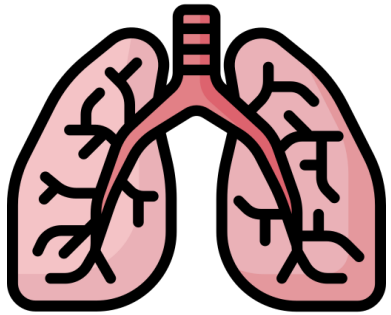
Other targetable immune checkpoints
- LAG-3
- TIM-3
- TIGIT
- CD73
- VISTA
- BTLA
- NKG_{2A}

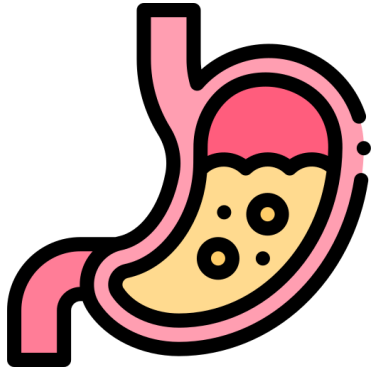
Basudan, 2023

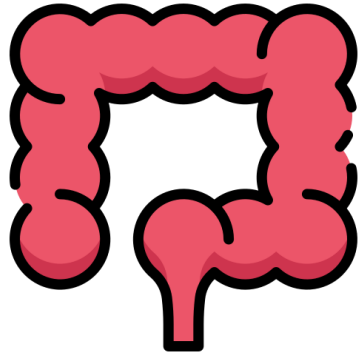
ICI 

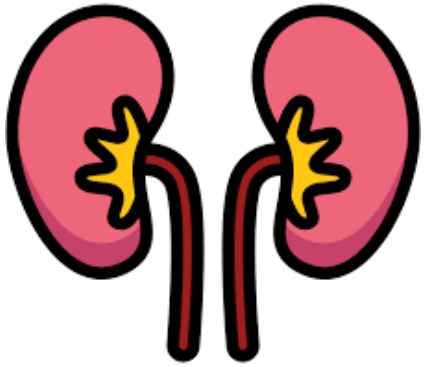
PD-L1 / PD-1	CTLA-4	LAG-3
Pembrolizumab	Ipilimumab	Relatlimab
Nivolumab		
Durvalumab		
Atezolizumab		

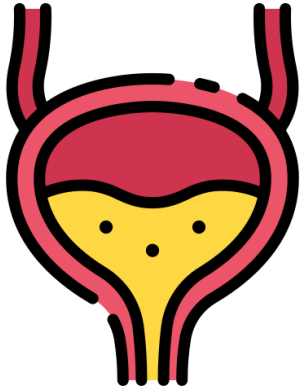
ICIs











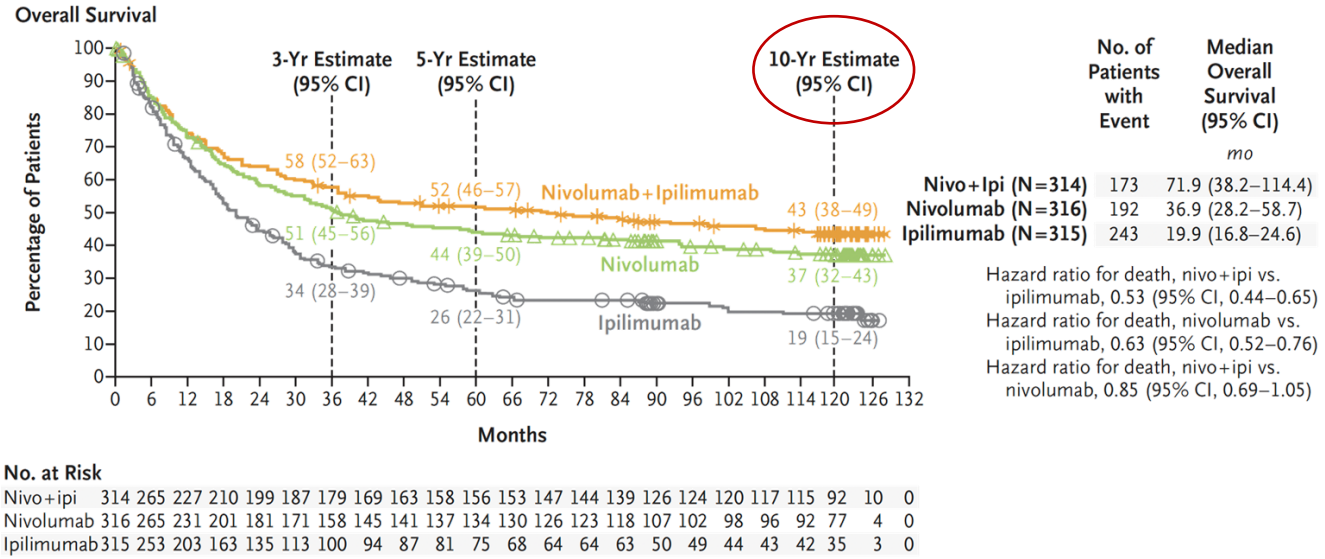
The example of advanced melanoma

Before ICI

Median OS*:
6-9 months

*OS: Overall Survival

ICI era



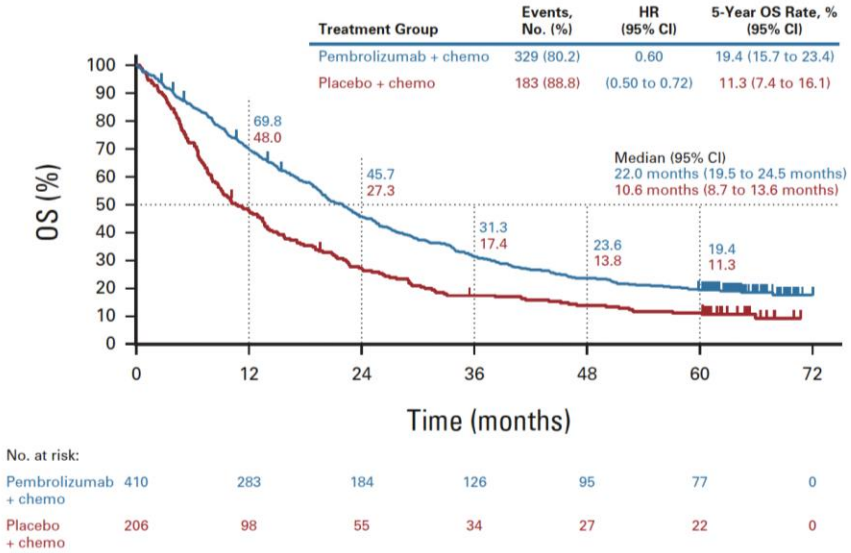
	No. of Patients with Event	Median Overall Survival (95% CI)
		mo
Nivo+Ipi (N=314)	173	71.9 (38.2–114.4)
Nivolumab (N=316)	192	36.9 (28.2–58.7)
Ipilimumab (N=315)	243	19.9 (16.8–24.6)

Hazard ratio for death, nivo+ipi vs. ipilimumab, 0.53 (95% CI, 0.44–0.65)
Hazard ratio for death, nivolumab vs. ipilimumab, 0.63 (95% CI, 0.52–0.76)
Hazard ratio for death, nivo+ipi vs. nivolumab, 0.85 (95% CI, 0.69–1.05)

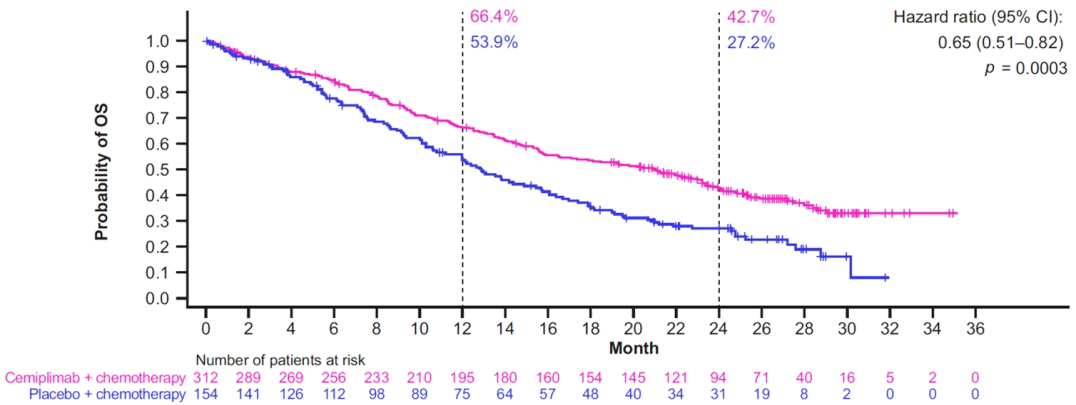
Wolchok, 2025

The example of advanced non-small cell lung cancer

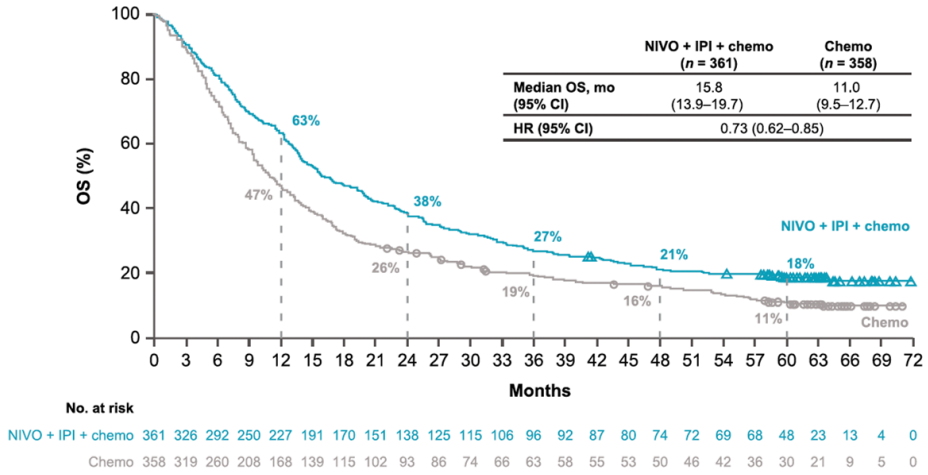
KEYNOTE-189

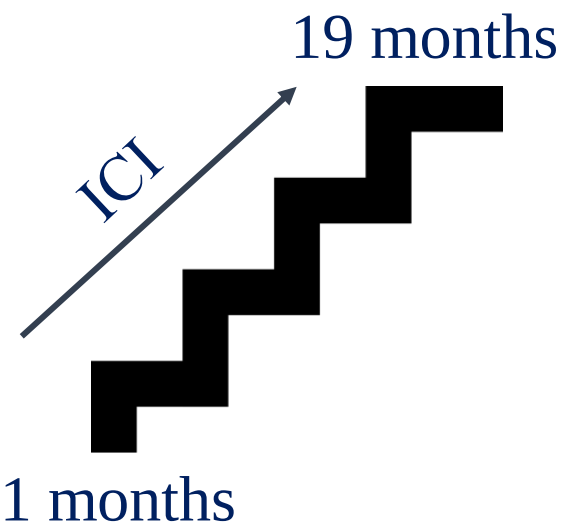


EMPOWER-Lung 3



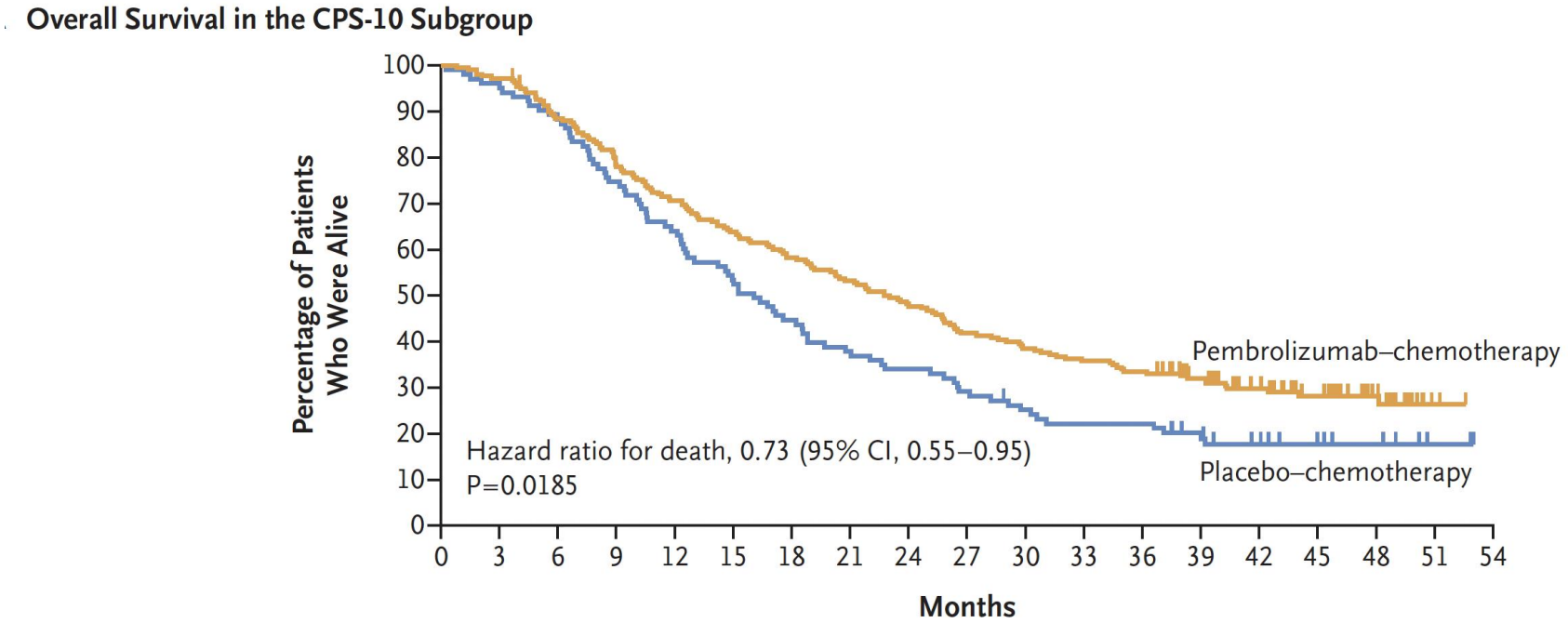
CheckMate 9LA





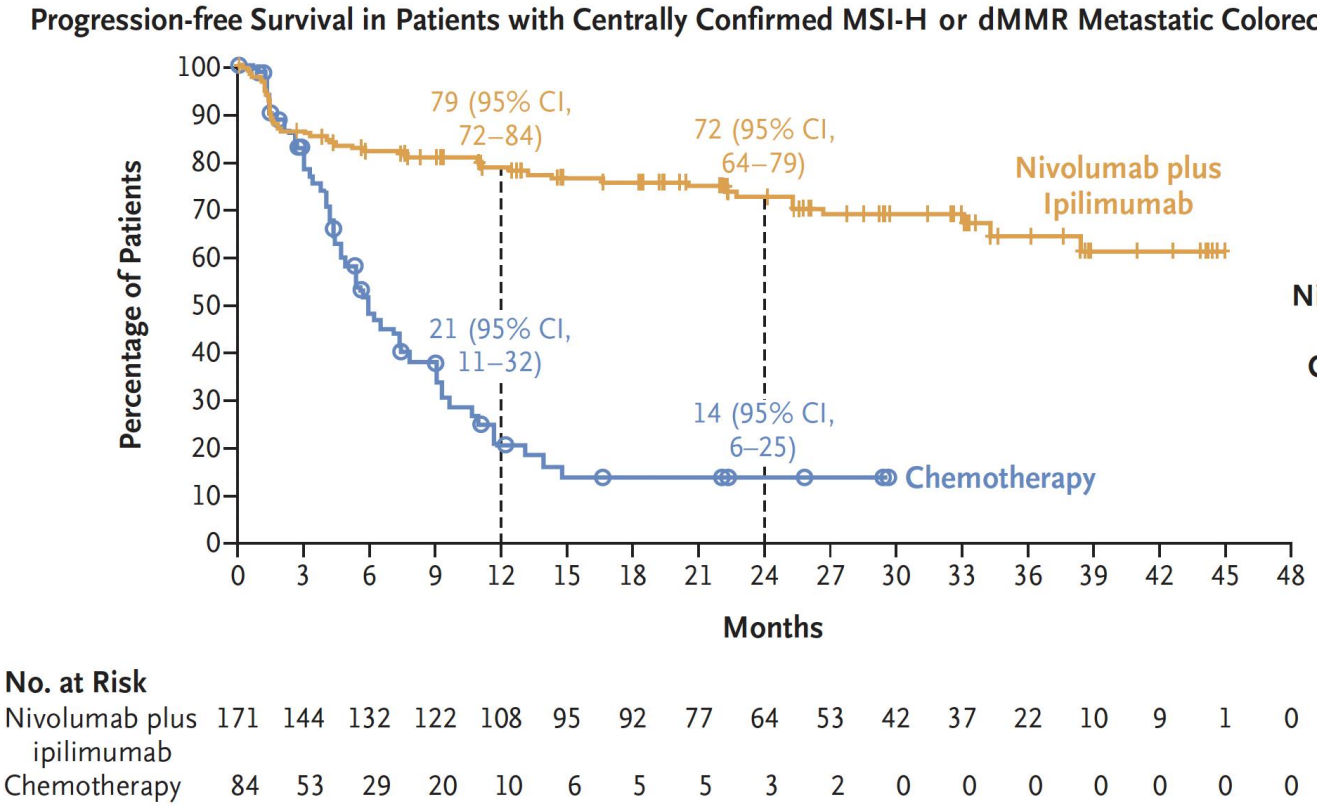
Garassino, 2023; Makharadze, 2023; Reck, 2024

The example of advanced, triple-negative breast cancer



Cortes, 2022

The example of advanced, MSI-H colorectal cancer

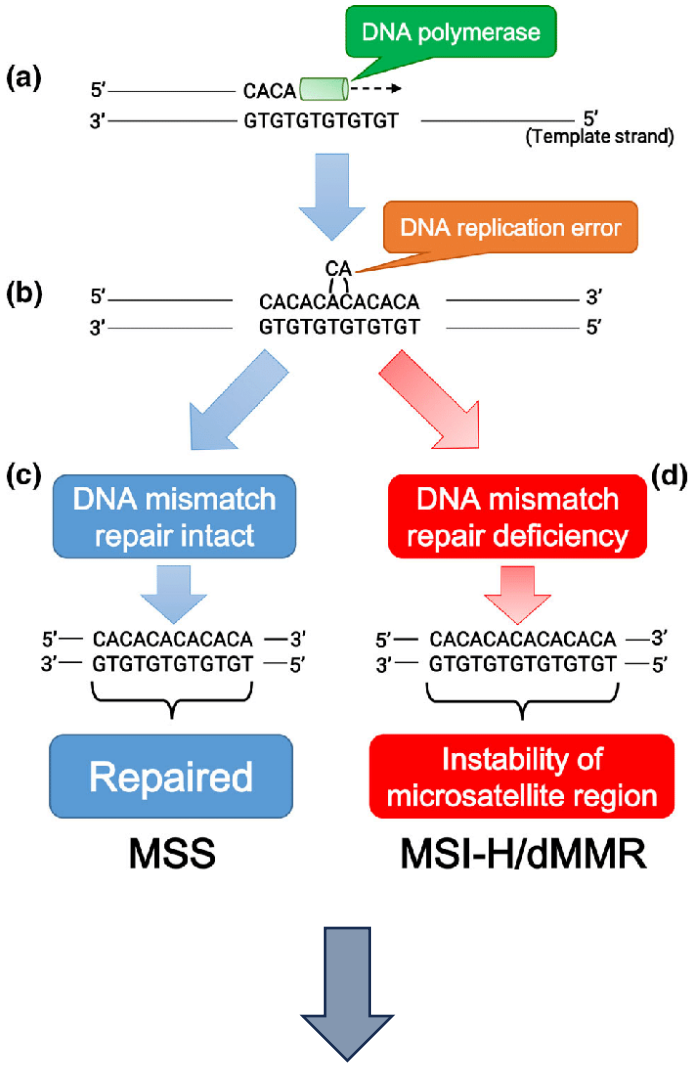


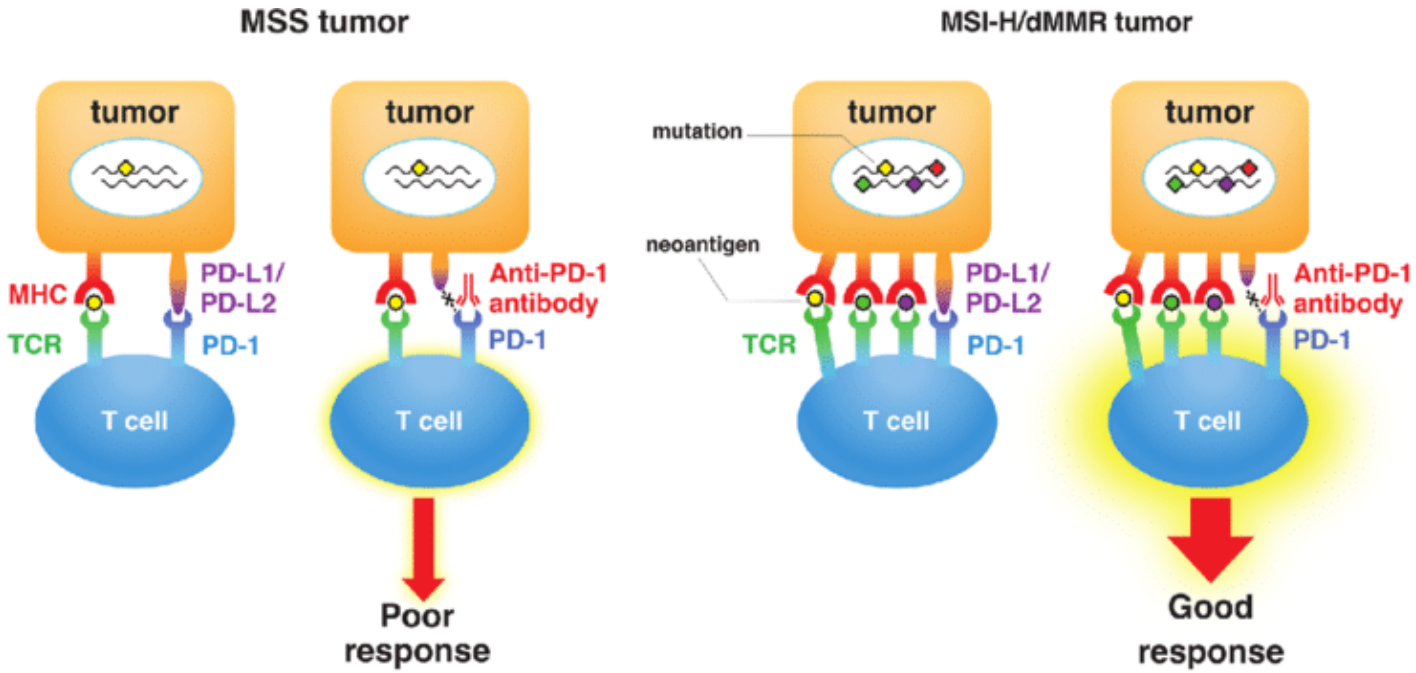
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab plus Ipilimumab	48/171	NR (38.4–NE)
Chemotherapy	52/84	5.9 (4.4–7.8)

Adjusted difference in restricted mean survival time at 24 mo, 10.6 mo (95% CI, 8.4–12.9)
P<0.001 with the use of a two-sided stratified log-rank test

André, 2024

Tumor-agnostic indication (MSI-H/dMMR tumors)





Increased mutation burden

Eso, 2019

Tumor-agnostic indication - Pembrolizumab (MSI-H/dMMR tumors)

Article | March 29, 2023

FDA Grants Full Approval to Pembrolizumab for Select Patients With MSI-H or dMMR Solid Tumors

Author(s): Kristi Rosa

The FDA has granted full approval to pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability–high or mismatch repair–deficient solid tumors that have progressed following previous treatment and who have no satisfactory alternative options.

FDA

The FDA has granted full approval to pembrolizumab (Keytruda) for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) solid tumors that have progressed following previous treatment and who have no satisfactory alternative options.[1]

Trial ID	No. of Patients	Previous lines of therapy
KEYNOTE-158	373	≥ 1
KEYNOTE-164	124	≥ 1
KEYNOTE-051	7 (pediatric)	

ORR: 33%

Source: fda.gov

Mechanisms of ICI resistance

Tumor-intrinsic

- Loss of neoantigens
- Defective antigen presentation
- Tumor cell phenotypic changes
- Metabolic antagonism

Tumor-extrinsic

- Upregulation of alternative immune checkpoints
- Immunosuppressive immune cell infiltration
- “Irreversible” T cell exhaustion
- Gut microbiome

Alsaafeen, 2025

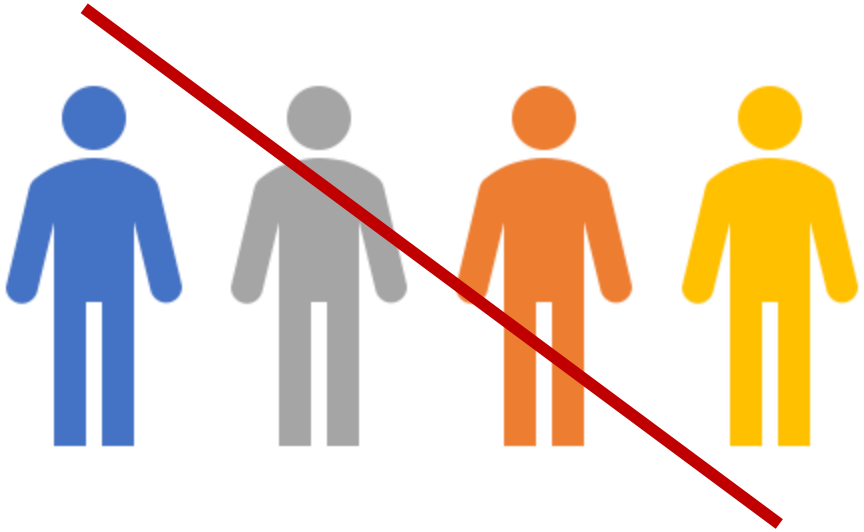
Side effects of ICIs

Flare of a pre-existing autoimmune disease

De novo immune-related adverse events resembling autoimmune diseases

ICI use in patients with a pre-existing autoimmune disease

13.5%-25% of patients diagnosed with lung cancer may have a concomitant autoimmune disorder

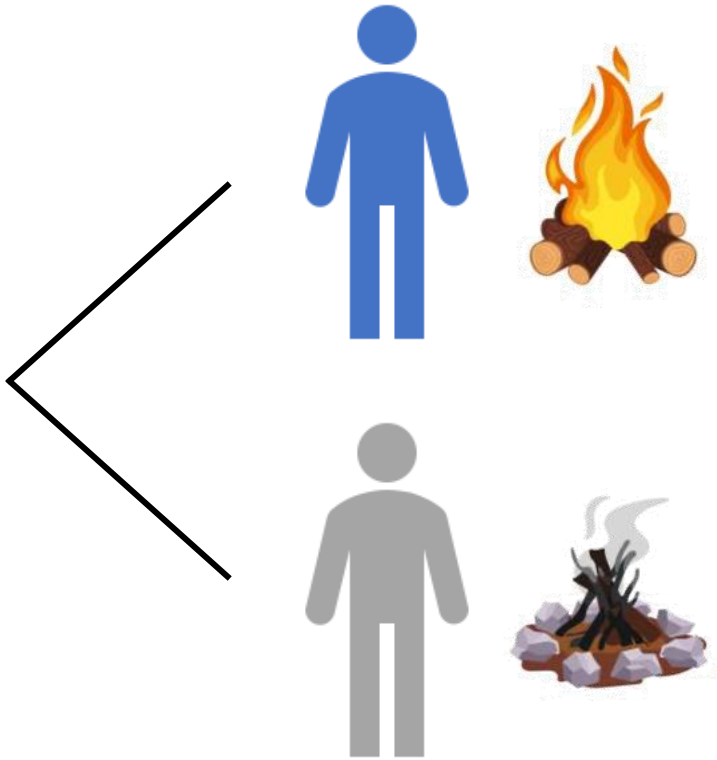


Excluded from clinical trials of immunotherapy

ICI use in patients with pre-existing autoimmune diseases

Patients with a history of ADs.[7] Patients with a history of AD have an increased chance for a flare of the AD following initiation of ICI. One can distinguish patients with an active AD requiring IS treatment and patients with a history of AD who are asymptomatic without treatment. The latter group may undergo treatment with ICI therapy, but patients should be fully aware of the risks and should report immediately when AD symptoms start.

ESMO Clinical Practice Guidelines, 2022



Systematic Review

- N = 123 pts.
- 83.5%: prior treatment for autoimmune disease
  46.2%: active autoimmune disease with ongoing symptoms
  43.6%: concomitant immunosuppressive treatment at initiation of ICI
- 75% reported adverse events
  - 41%: exacerbation of pre-existing autoimmune disease
  - 25%: de novo ir-AEs
  - 9%: both
- 17.1% discontinued immunotherapy permanently due to adverse events
- No difference in occurrence for patients with active *vs.* inactive autoimmune disease
- Trend for fewer adverse events in patients receiving any therapy for autoimmune disease at initiation of ICI

Abdel-Wahab, 2018

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

Autoimmune diseases and immune-checkpoint inhibitors for cancer therapy: review of the literature and personalized risk-based prevention strategy

J. Haanen[1], M. S. Ernstoff[2], Y. Wang[3], A. M. Menzies[4,5], I. Puzanov[2], P. Grivas[6], J. Larkin[7], S. Peters[8], J. A. Thompson[6,9] & M. Obeid[10,11*]

[1]Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; [2]Roswell Park Comprehensive Cancer Center, Buffalo; [3]Department of Gastroenterology, Hepatology & Nutrition, University of Texas MD Anderson Cancer Center, Houston, USA; [4]Melanoma Institute Australia, The University of Sydney, Sydney; [5]Royal North Shore and Mater Hospitals, Sydney, Australia; [6]University of Washington, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, USA; [7]Royal Marsden NHS Foundation Trust, London, UK; [8]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV) and Lausanne University, Lausanne, Switzerland; [9]National Cancer Institute/NIH, Bethesda, USA; [10]Department of Medicine, Service of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne; [11]Vaccine and Immunotherapy Center, Centre Hospitalier Universitaire Vaudois (CHUV), Centre d'Immunothérapie et de Vaccinologie, Lausanne, Switzerland

Available online 17 March 2020

Patients who are receiving IS for their AD could, depending on the IS and dose (non-specific or targeted), undergo tapering of the IS (e.g. to prednisone 10 mg) or switch to a biological disease-modifying antirheumatic drug before ICI treatment is initiated. This treatment could be continued during ICI therapy to keep the AD and a potential flare under control.

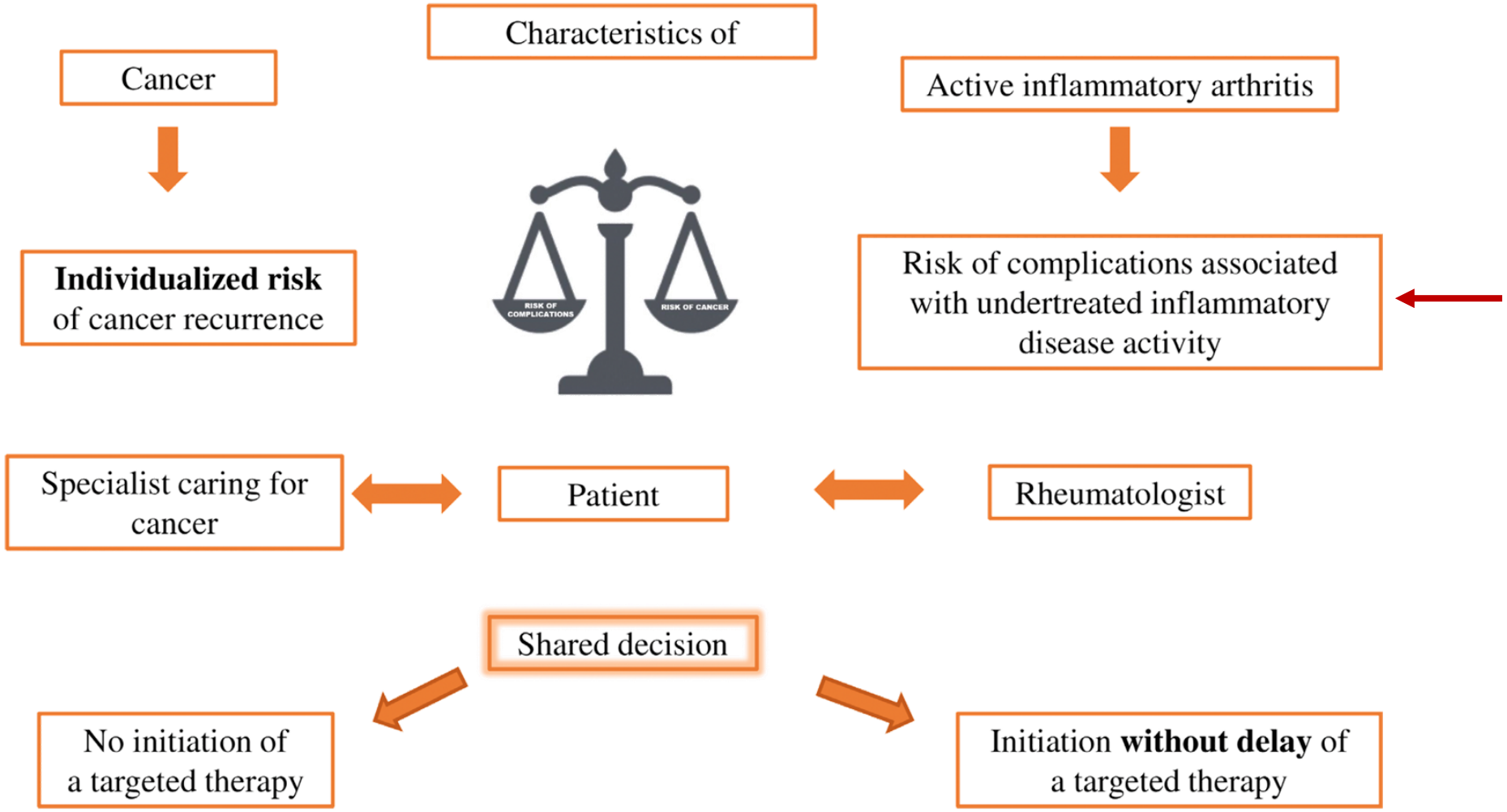
Haanen, 2022

Recommendation

OPEN ACCESS

2024 EULAR points to consider on the initiation of targeted therapies in patients with inflammatory arthritis and a history of cancer

Eden Sebbag [1], Kim Lauper [2], Juan Molina-Collada [3], Daniel Aletaha [4], Johan Askling [5], Karolina Gente,[6] Heidi Bertheussen,[7] Samuel Bitoun [8], Ertugrul Cagri Bolek [9], Gerd R Burmester [10], Helena M Canhão,[11] Katerina Chatzidionysiou [5], Jeffrey R Curtis,[12] Francois-Xavier Danlos [13,14], Vera Guimarães,[15] Merete Lund Hetland [16,17], Florenzo Iannone [18], Marie Kostine [19], Tue Wenzel Kragstrup [20,21], Tore K Kvien [22], Anne Constanze Regierer [23], Hendrik Schulze-Koops [24], Lucía Silva-Fernández,[25] Zoltan Szekanecz,[26] Maya H Buch [27], Axel Finckh [2], Jacques-Eric Gottenberg [1]

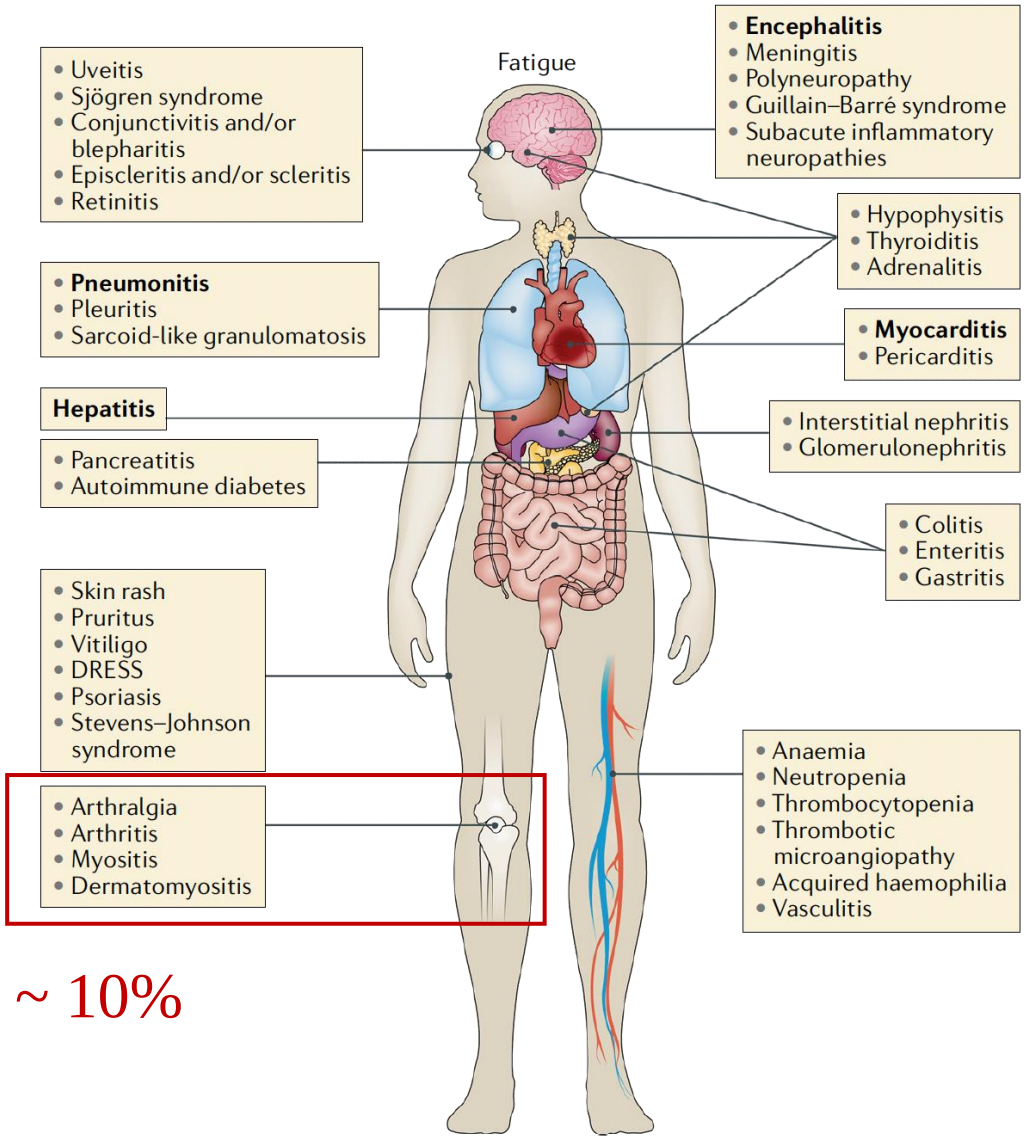

Characteristics of
Cancer
Active inflammatory arthritis
Individualized risk of cancer recurrence
RISK OF COMPLICATIONS
RISK OF CANCER
Risk of complications associated with undertreated inflammatory disease activity
Specialist caring for cancer
Patient
Rheumatologist
Shared decision
No initiation of a targeted therapy
Initiation without delay of a targeted therapy

Sebbag, 2024

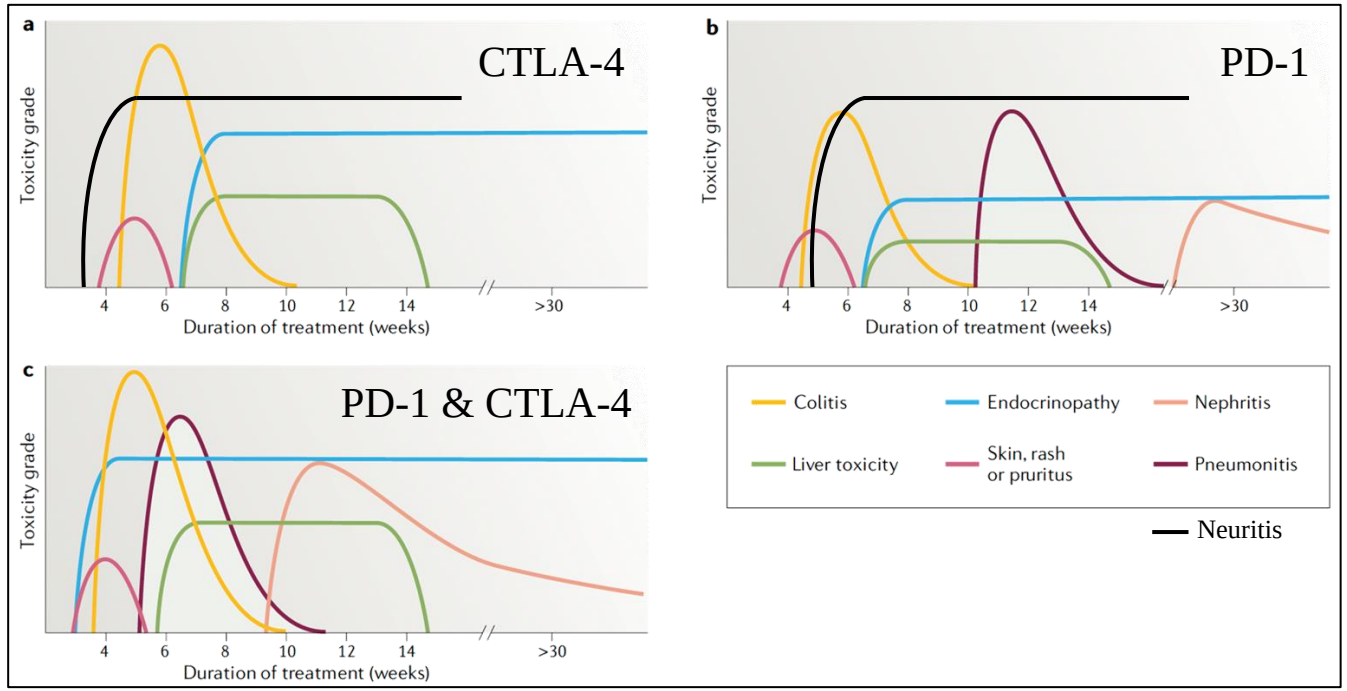
Our own anecdotal experience (PAGNI)

	Disease flare
Rheumatoid Arthritis	✗
SLE	✓ ✗
IBD	✓
Psoriasis	✓

De novo immune-related adverse events

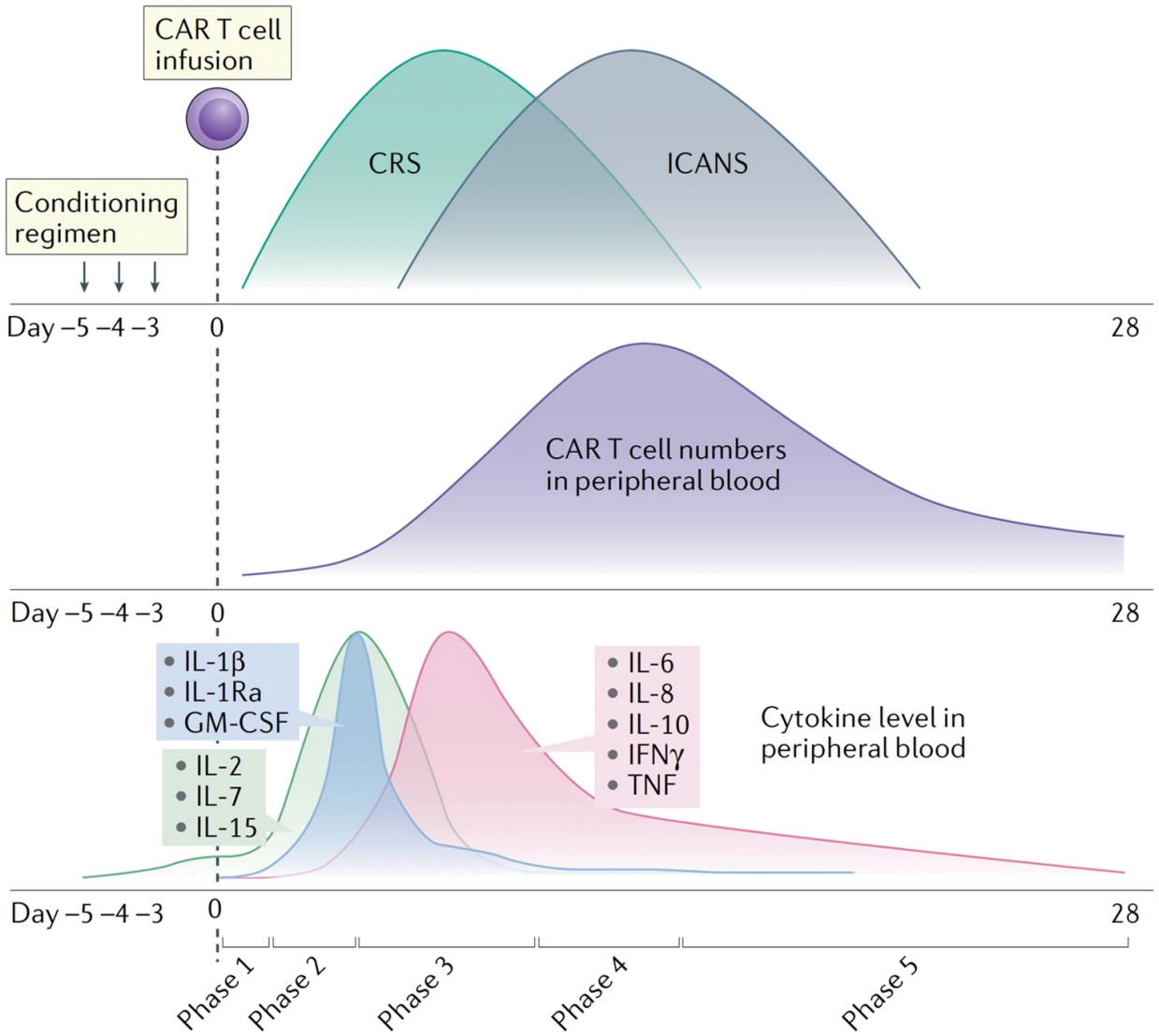


~ 10%



Martins, 2019

Cytokine Release Syndrome (CRS) / ICANS / GVHD

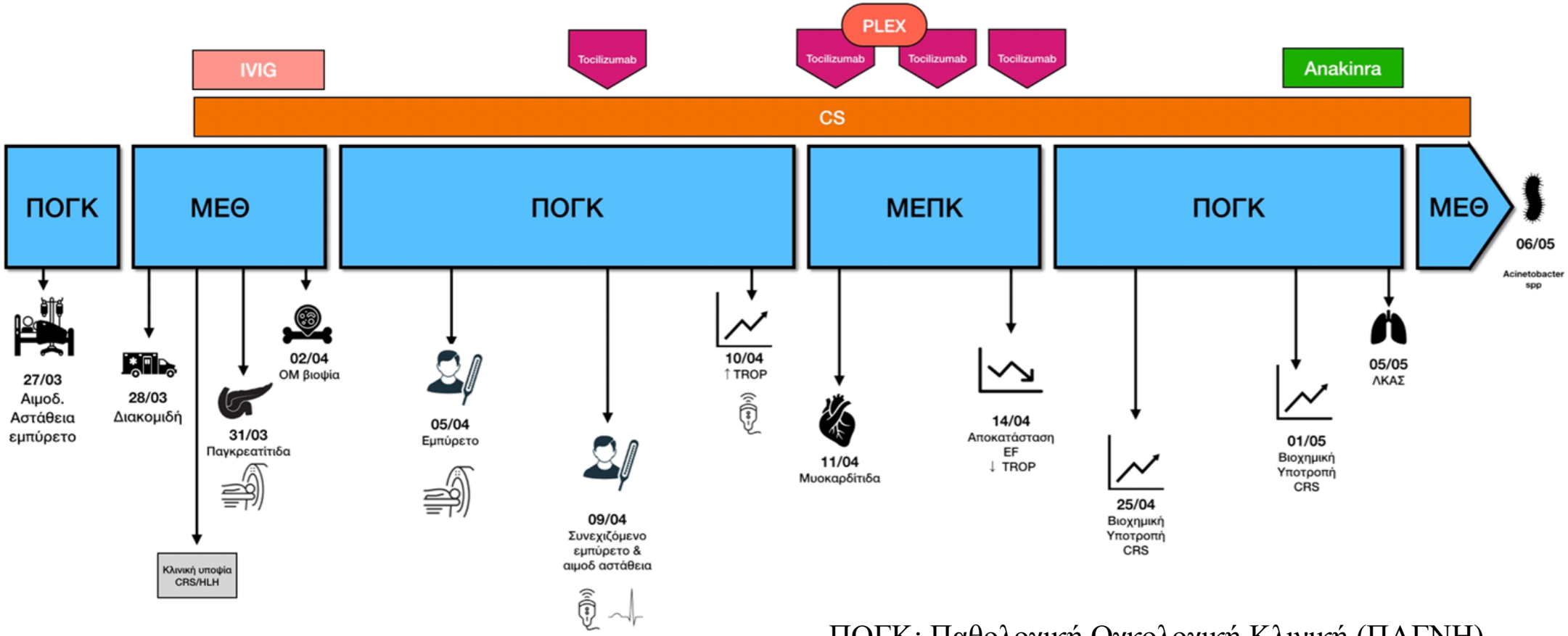


CRS symptoms
- Cardiac
- Pulmonary
- Hepatic
- Renal
- Gastrointestinal

ICANS symptoms
- Confusion
- Slurred speech / aphasia
- Seizures
- Cerebral oedema
- Coma (!)

Morris, 2021

A rare example of fatal ir-AEs



ΠΟΓΚ: Παθολογική Ογκολογική Κλινική (ΠΑΓΝΗ)

Courtesy of: Michail Papadakis, MD

Arthralgia / Myalgia

- Incidence rates: 1-43%, 2-20%
- Differential diagnosis: paraneoplastic, induced by other cancer therapies (e.g. hormones)
- Needs to be ruled out (!): myalgia secondary to myositis
- Treatment: analgesics +/- NSAIDs

ir-inflammatory arthritis and polymyalgia rheumatica (PMR)

- Incidence rate: 5-10%
- First-line treatment: steroids
- Consider early referral to a rheumatologist (≥ grade 2) before starting steroids or if switching to DMARDs
- ICI treatment continuation evaluated on an individual basis

ir-sicca syndrome

- Incidence rate: 5-24% (hard to precisely define)
- Differential diagnosis: RT-related, drug-related (opioid), oral candidiasis
- Treatment: symptomatic treatment, pilocarpine, hydrochloroquine

ir-myositis

- Incidence rate: ~ 1%

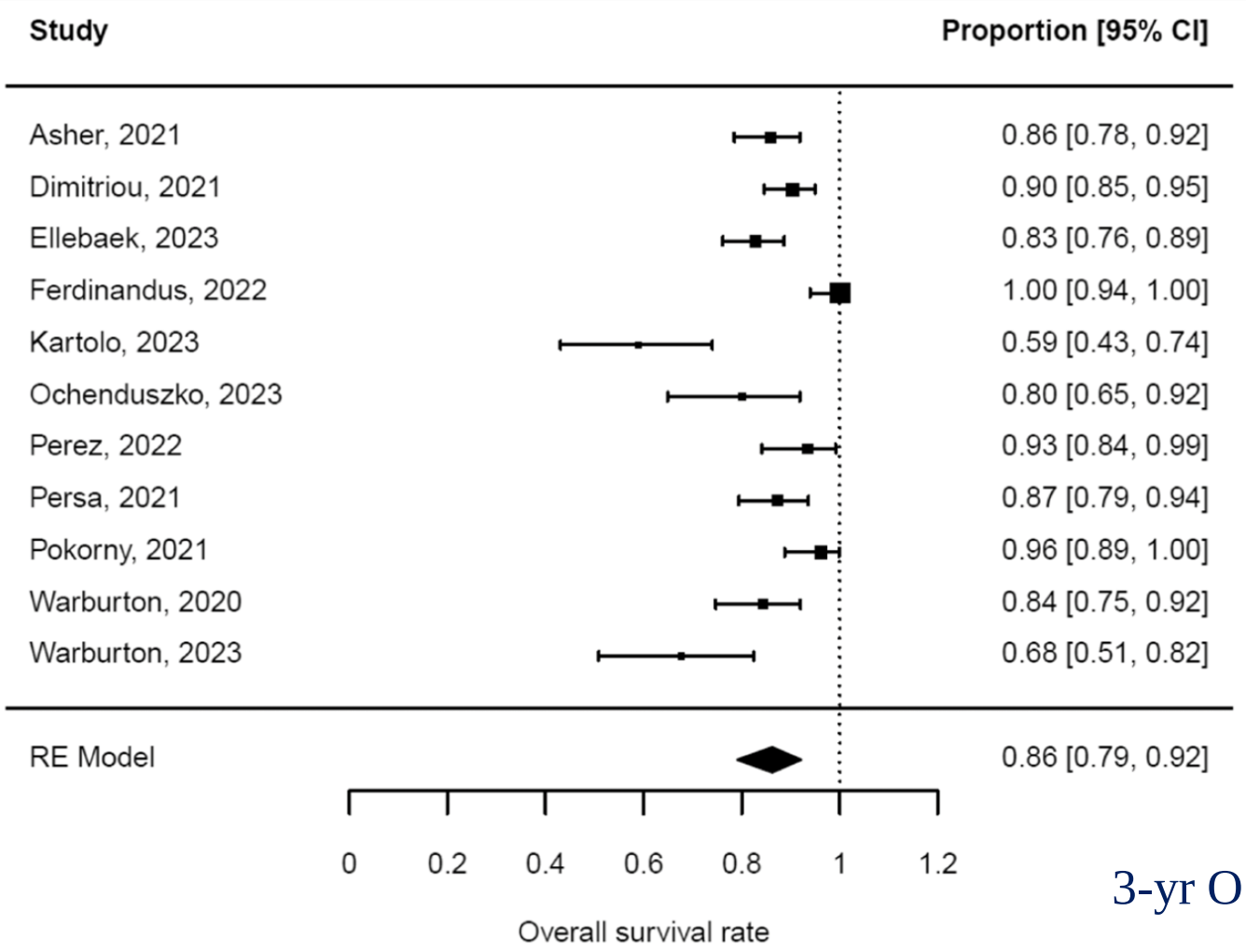
- Clinical Presentation: myalgia, axial, limb-girdle, bulbar, oculomotor weakness / secondary myocarditis (myasthenia-myocarditis-myositis)

- Treatment: (mild) steroids (0.5-1 mg/kg per day prednisone)
  (severe) steroid pulses, IVIG, plasma exchange, IL-6R inhibitors

Other ir-rheumatologic manifestations (rare)

- Vasculitis
- Scleroderma-like reaction
- Lupus

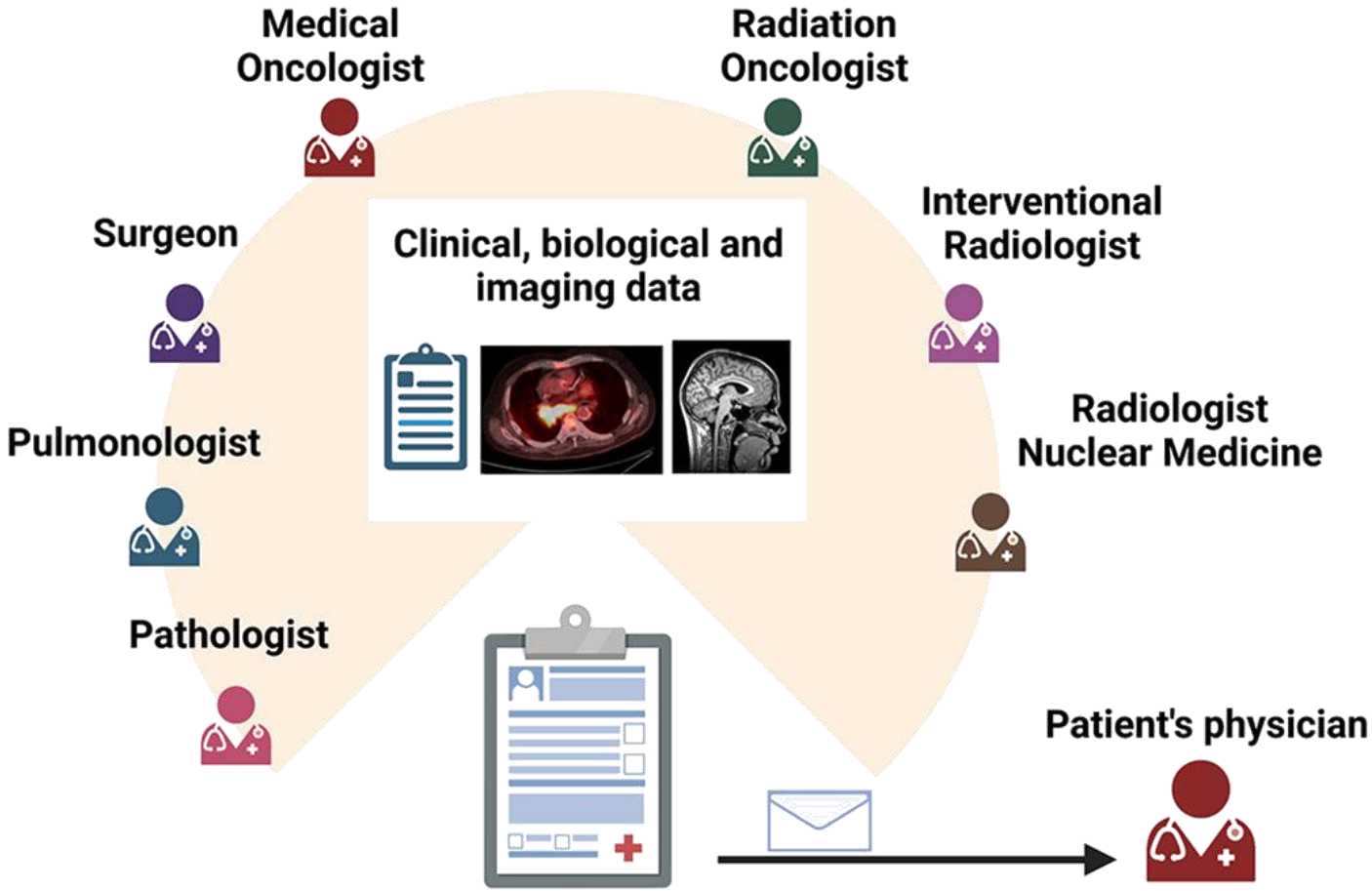
The long-lasting effects of ICIs



3-yr OS after ICI discontinuation (melanoma)

Mayer, 2025

Immunotherapy-related toxicity tumor board (ImmunoTox Board)



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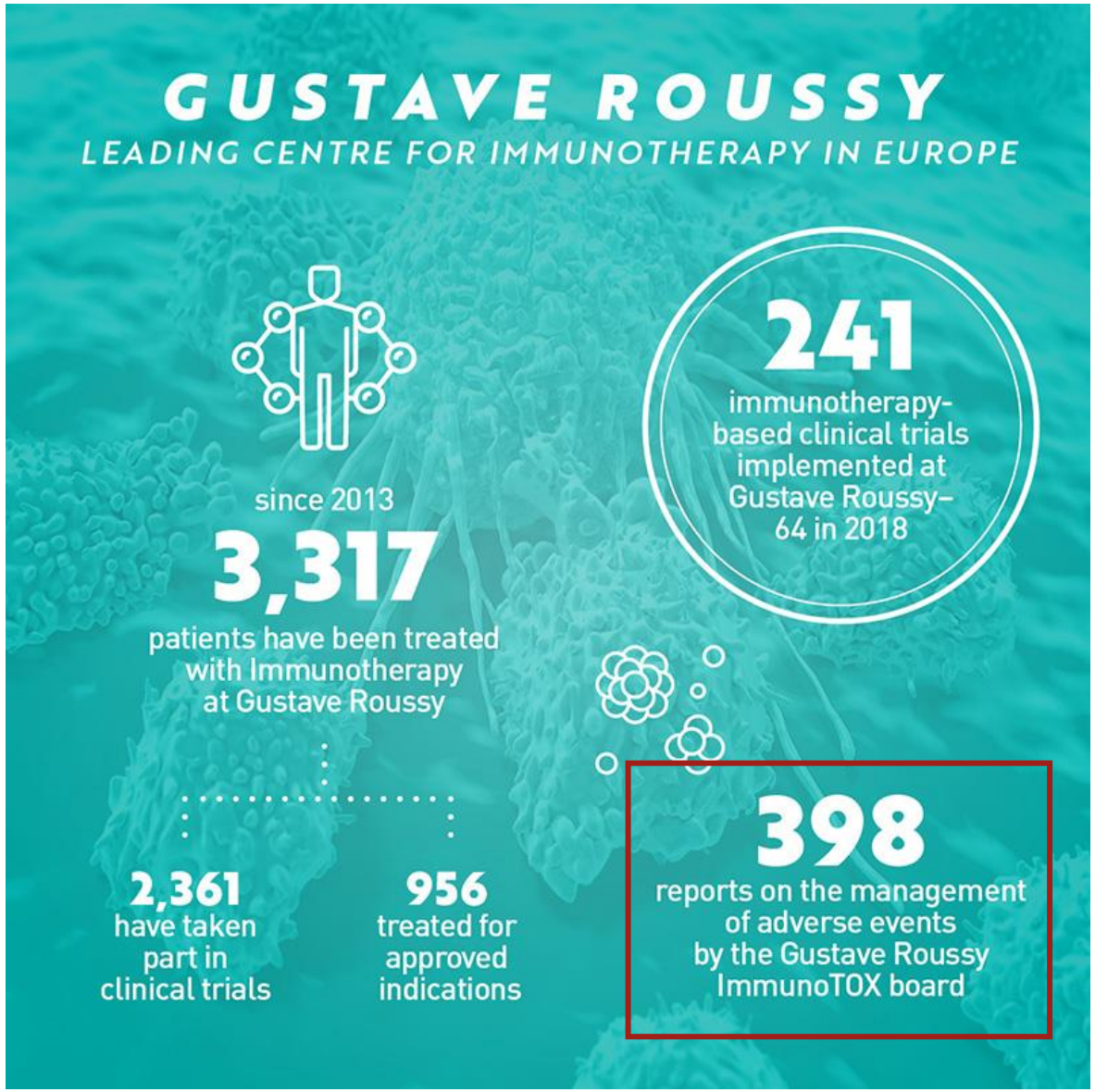
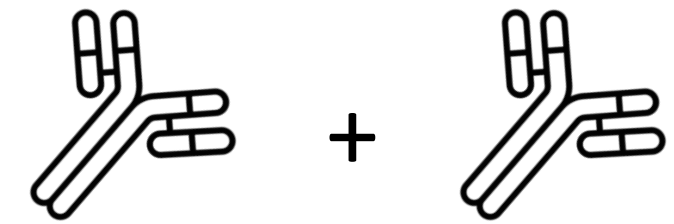
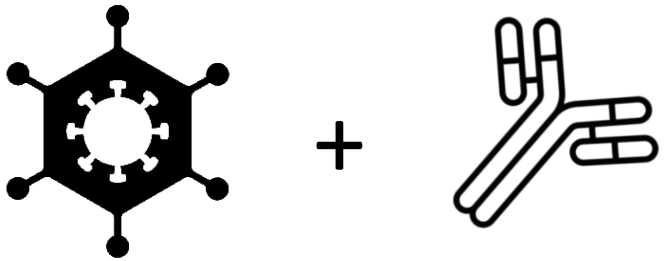
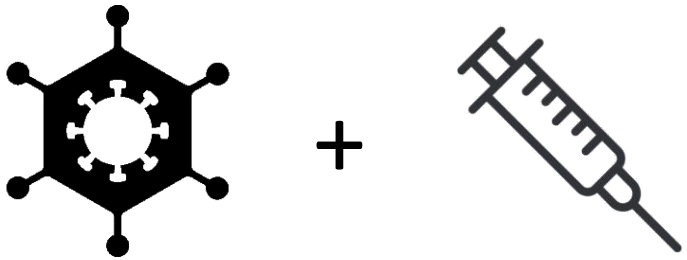


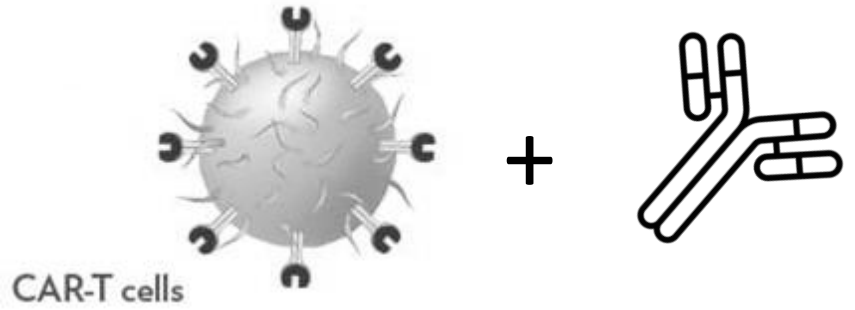
Source: Gustave Roussy

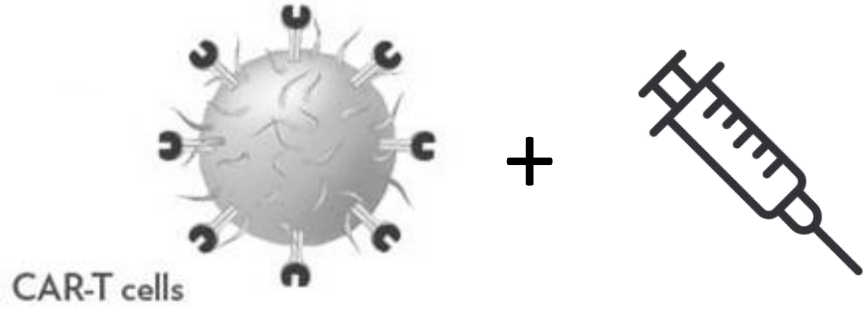
Future Challenges











Familiarity and early recognition of ir-AEs necessary!

THANK YOU