Immunotherapies in Cancer

Session: Current concepts in cancer "immunotherapy"

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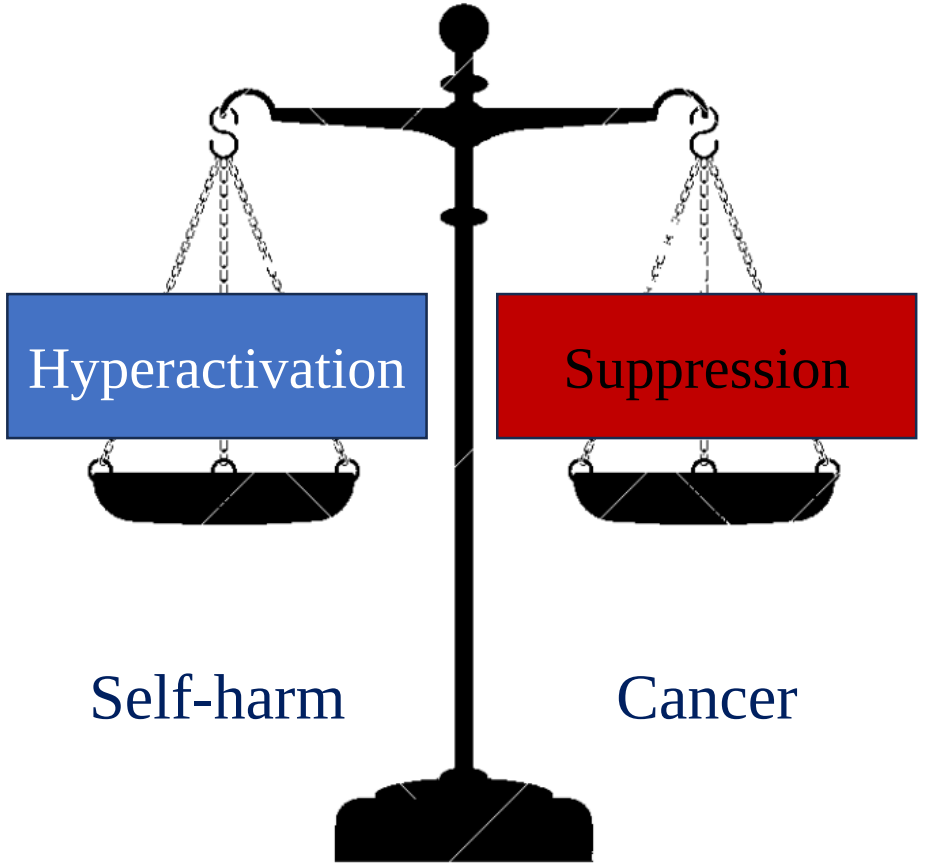
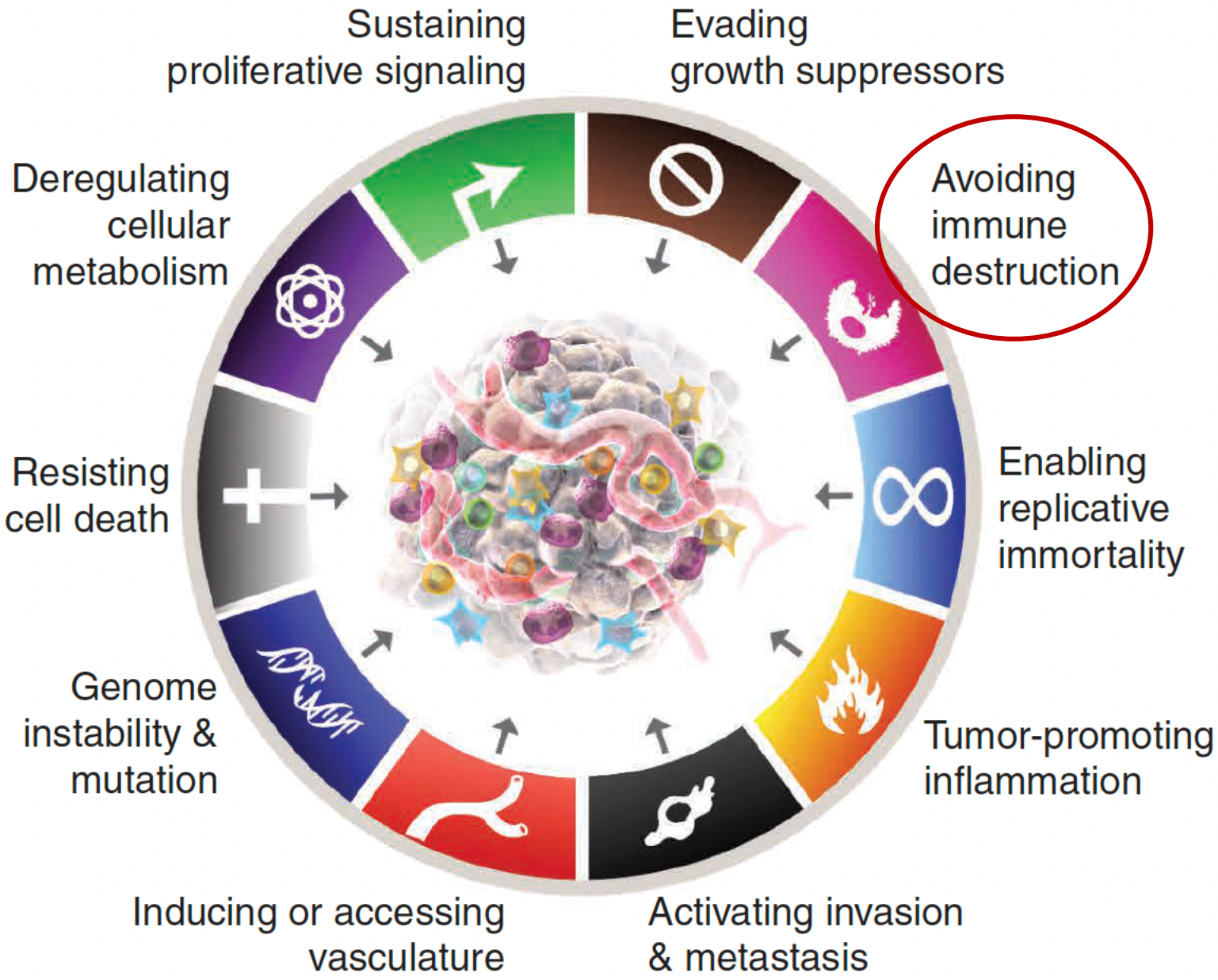
MAY 31, 2025

Immune System



Hallmarks of cancer



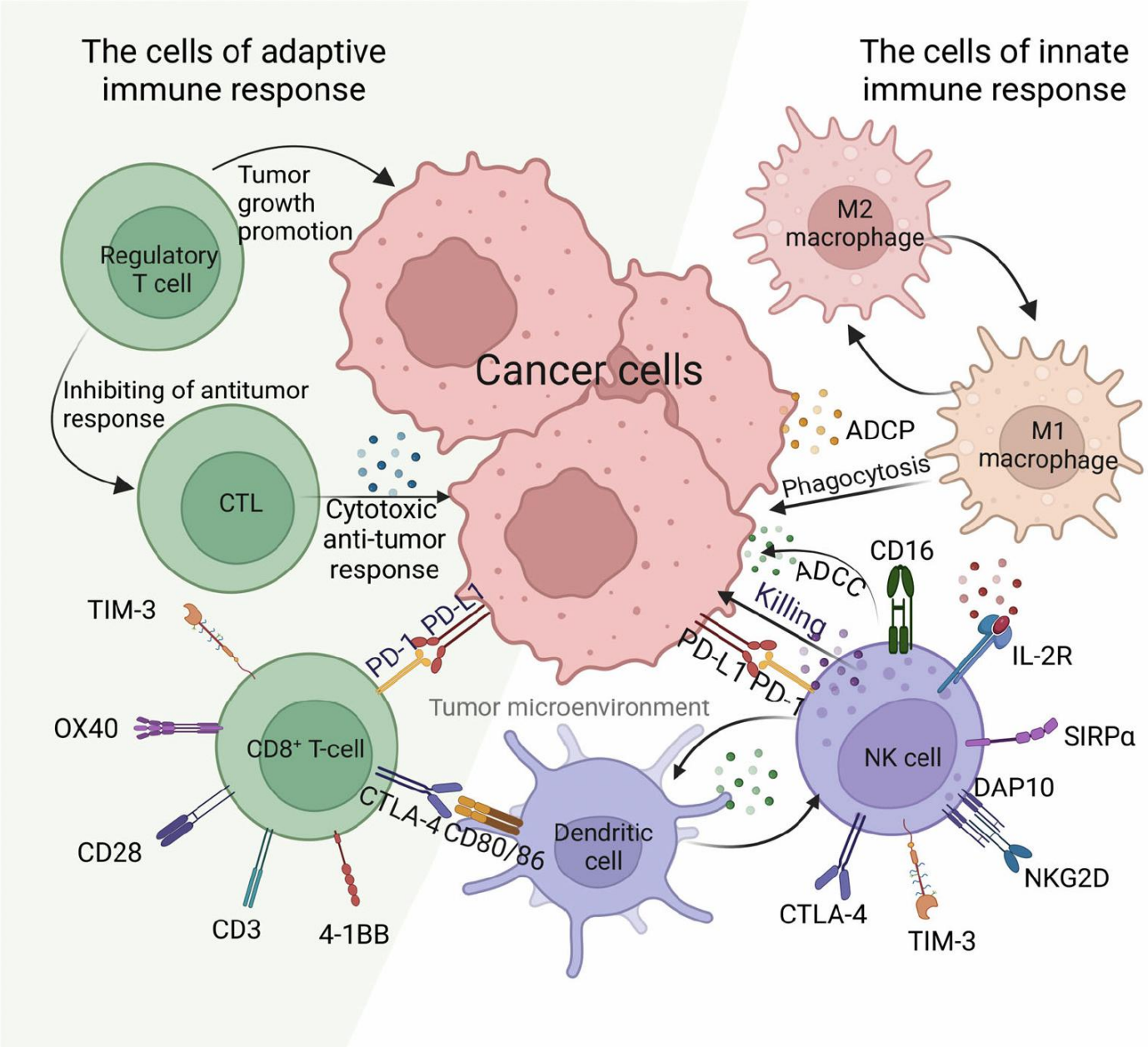
Weinberg and Hanahan

Modes of immunotherapy in solid tumors

Cancer survival in the era of immunotherapy

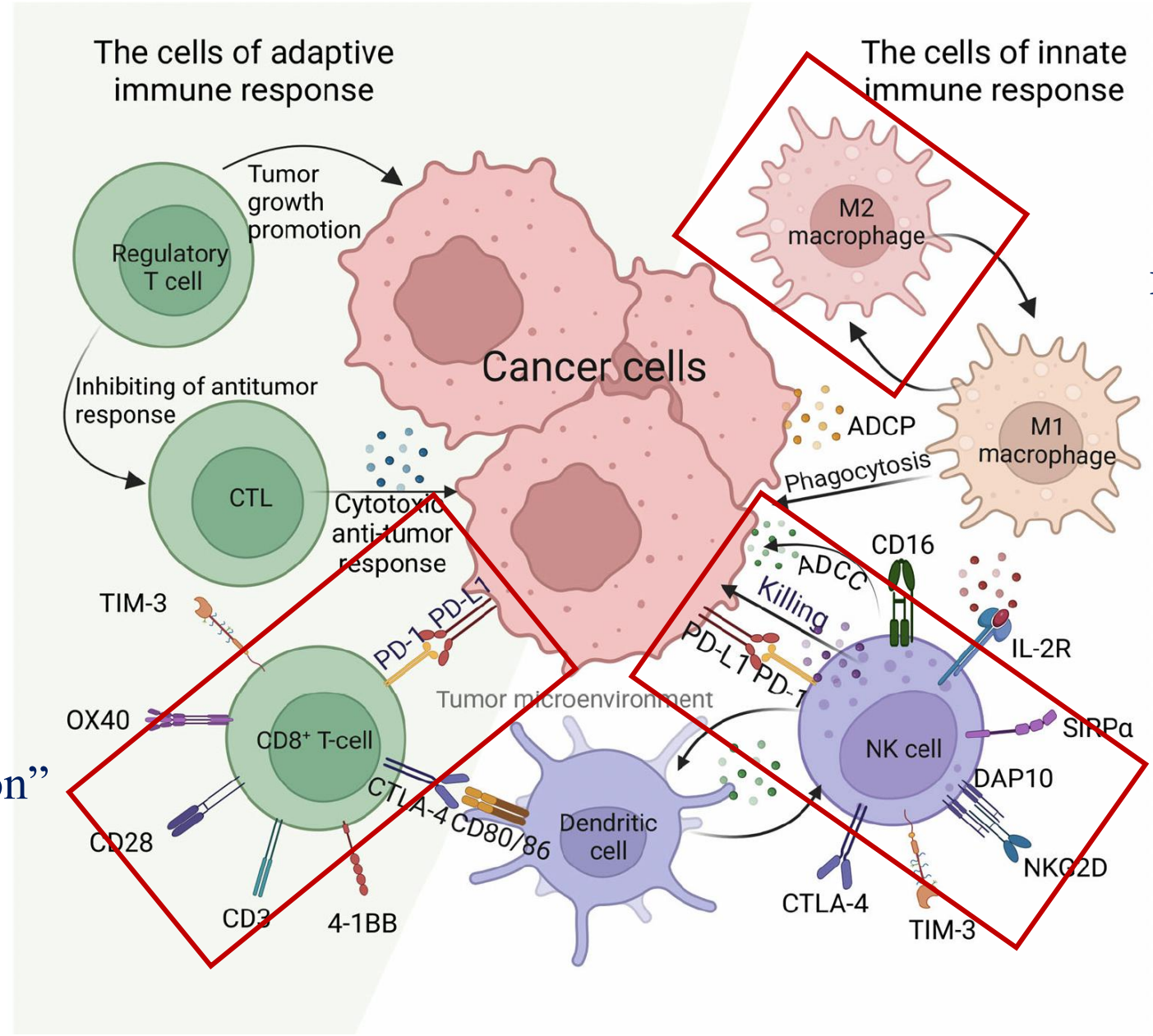
Future directions

The immune landscape of a solid tumor



Kuznetsova, 2024

Immune tolerance within the tumor microenvironment (TME)



1

T-cell “exhaustion”

2

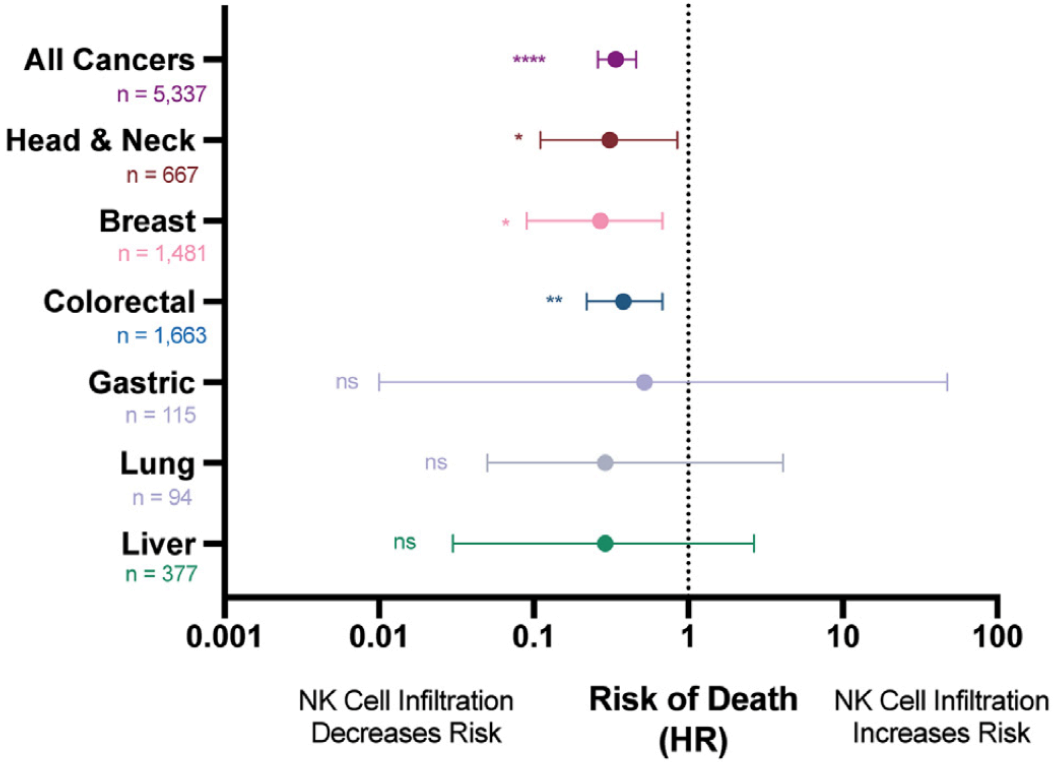
NK-cell “dormancy”

3

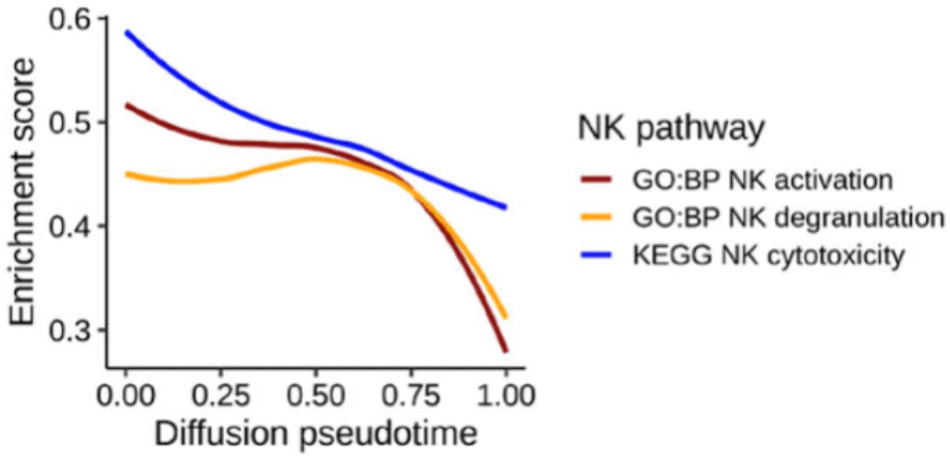
Predominance of immunosuppressive macrophages (TAMs)

Kuznetsova, 2024

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

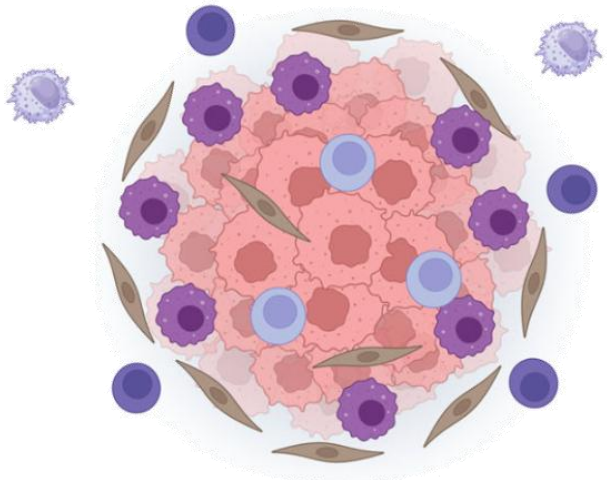


TME induces loss of NK cell effector functions



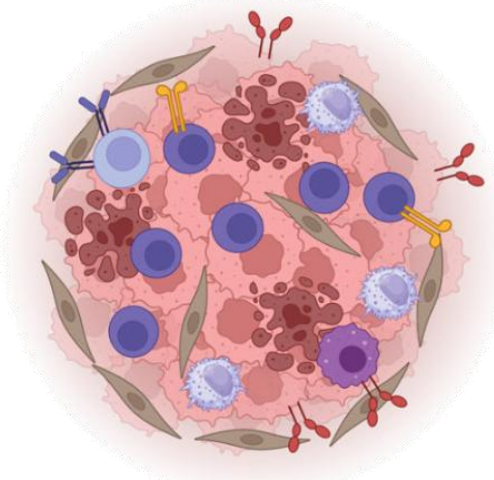
Nersesian, 2021; Dean, 2024

Cold tumor

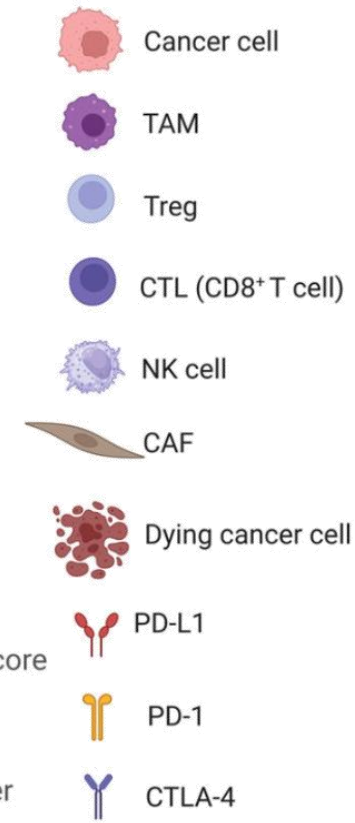


- Non-immunogenic tumors
- Immunosupressive immune cells in tumor (TAMs and Treg)
- Exclusion of CTLs ($CD8^+$ T cells) and NK cells from the tumor core
- CTLs present along periphery of the tumor, where they contact with TAMs
- Poor prognosis and response to immunotherapy

Hot tumor



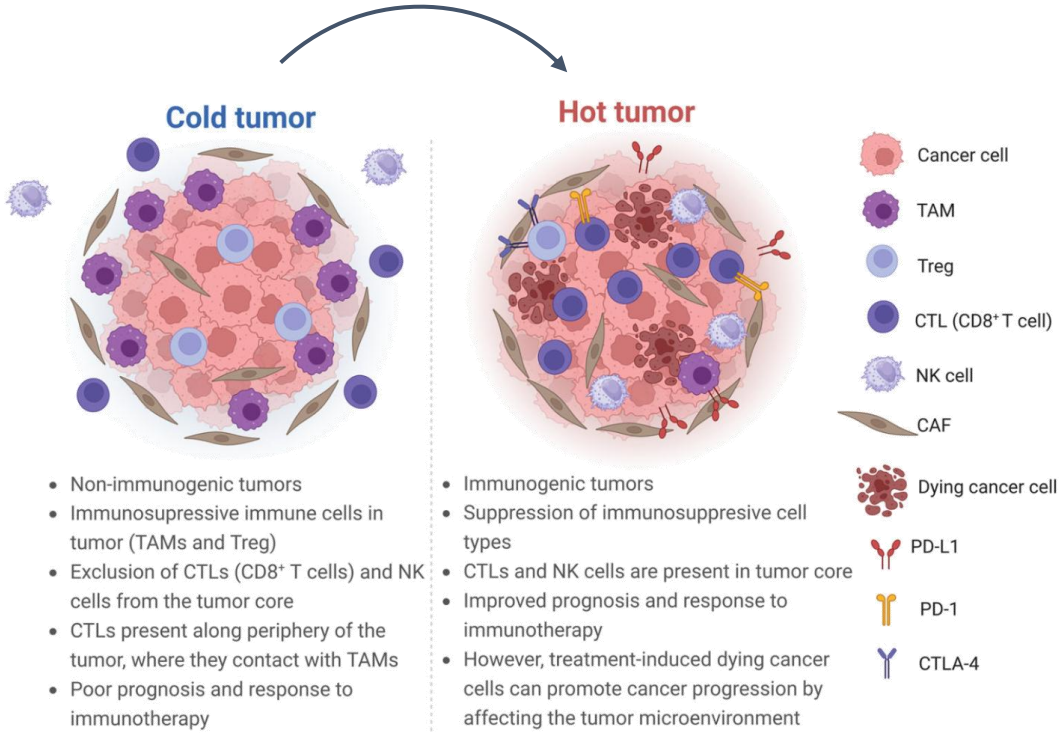
- Immunogenic tumors
- Suppression of immunosuppresive cell types
- CTLs and NK cells are present in tumor core
- Improved prognosis and response to immunotherapy
- However, treatment-induced dying cancer cells can promote cancer progression by affecting the tumor microenvironment



Kuznetsova, 2024

Goals of immunotherapy

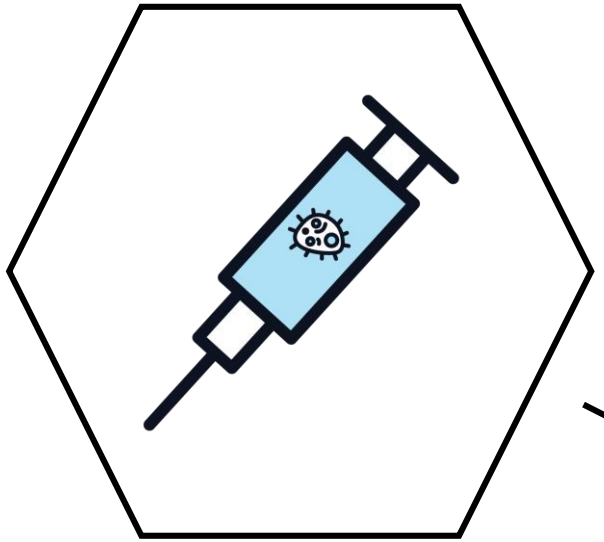
- Improve the infiltration of CTLs, NK cells, M1 macrophages
- Inhibit the infiltration of Tregs, MDSCs, TAMs (M2 macrophages)
- Enhance the effector function of infiltrating immune cells
- Generation of immunological memory



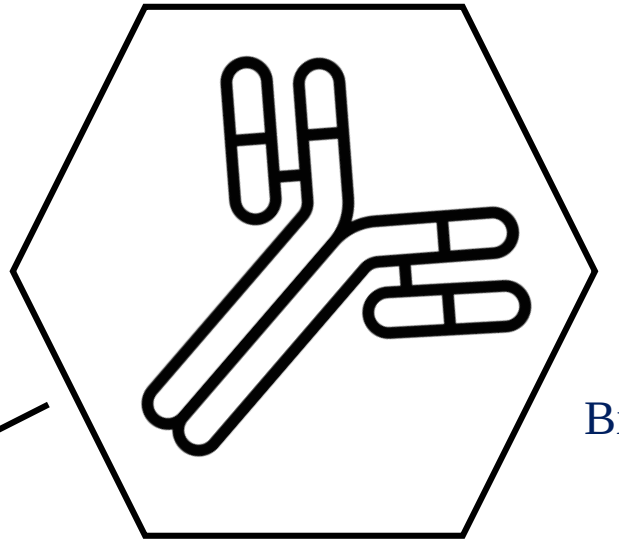
Kuznetsova, 2024

Modes

Cancer vaccines



Monoclonal antibodies

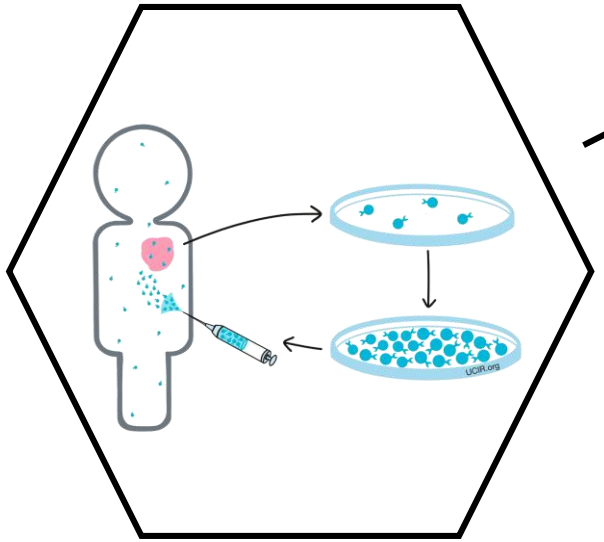


Immune Checkpoint Inhibitors (ICIs)

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

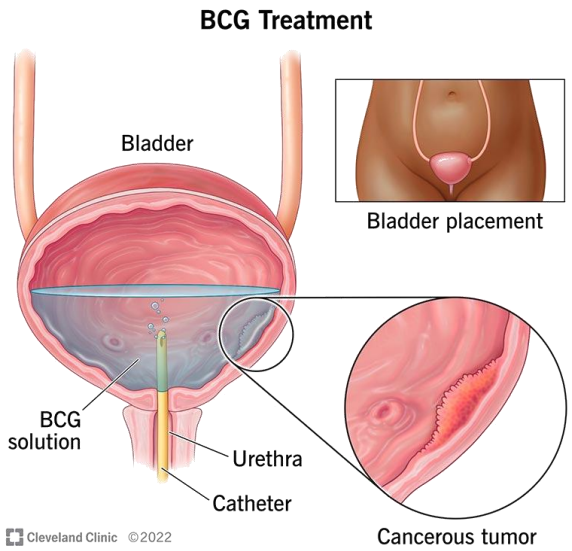
Oncolytic viruses

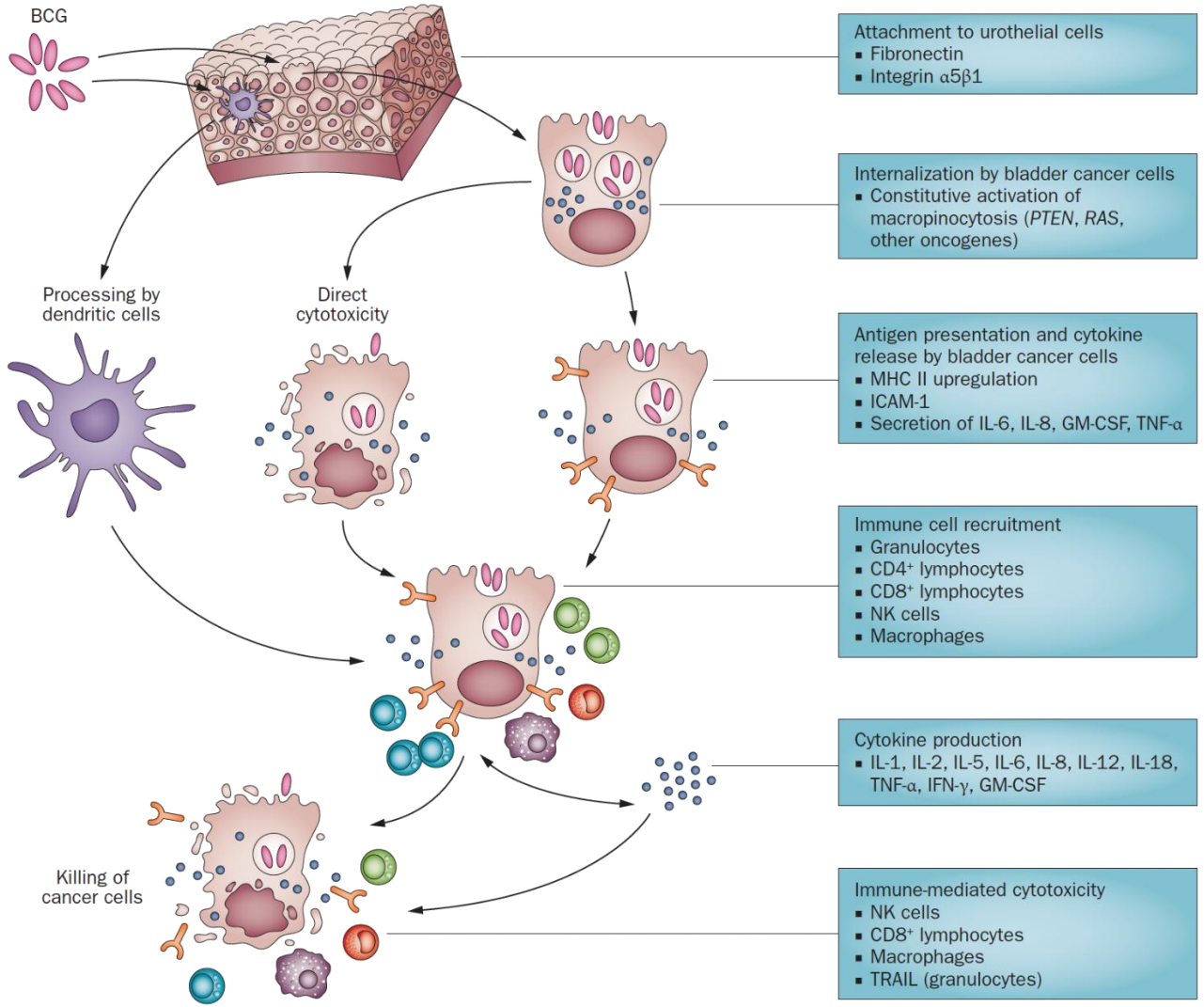
T-VEC©

Adstiladrin©

BCG infusions (1976 -)

Bladder cancer (non-muscle invasive)



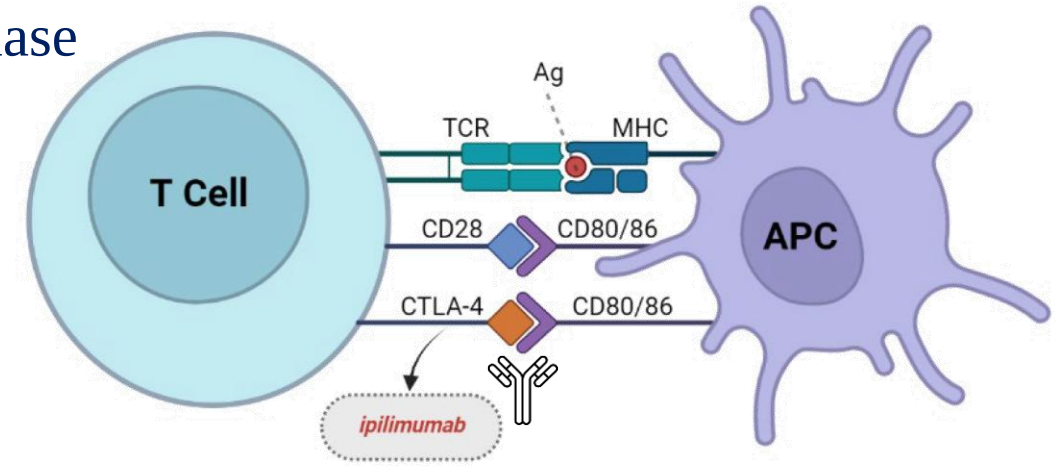


Redelman-Sidi, 2014

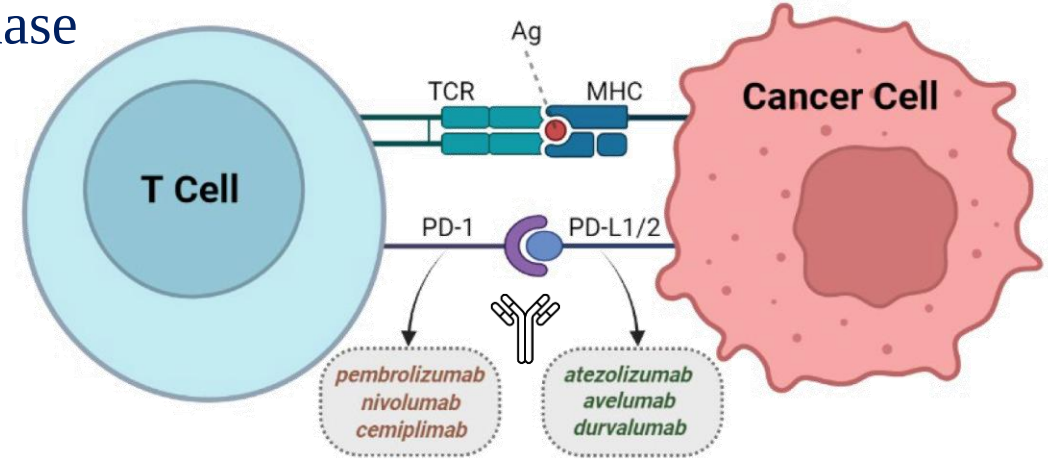
ICIs


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

Priming Phase



Effector Phase

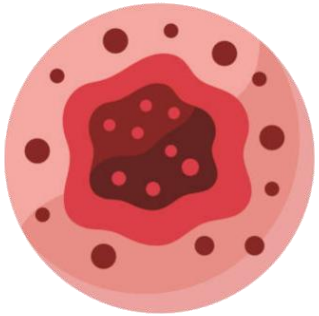


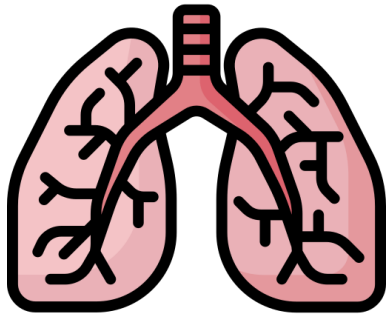
- PD-1 ↔ PD-L1
- CTLA-4 ↔ CD80/CD86

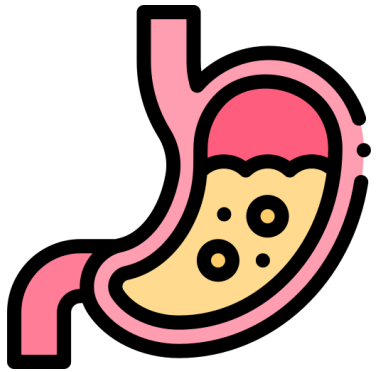
Other targetable immune checkpoints
- LAG-3
- TIM-3
- TIGIT
- CD73
- VISTA
- BTLA
- NKG_{2A}

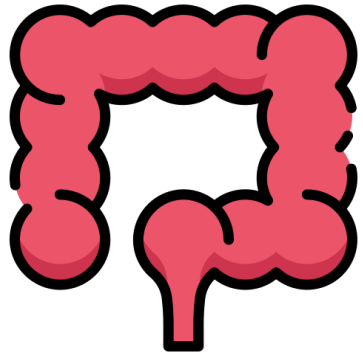
Basudan, 2023

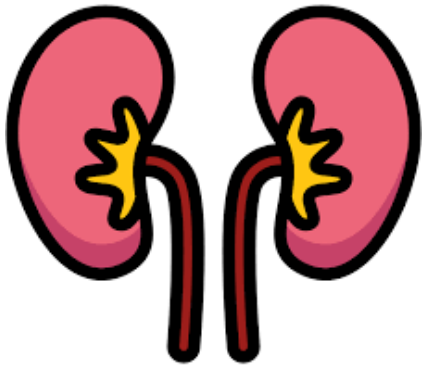
ICIs

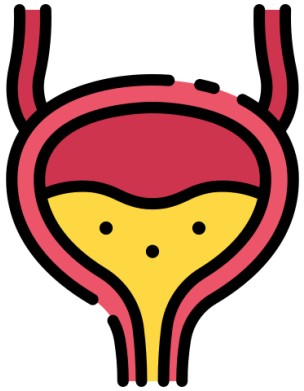








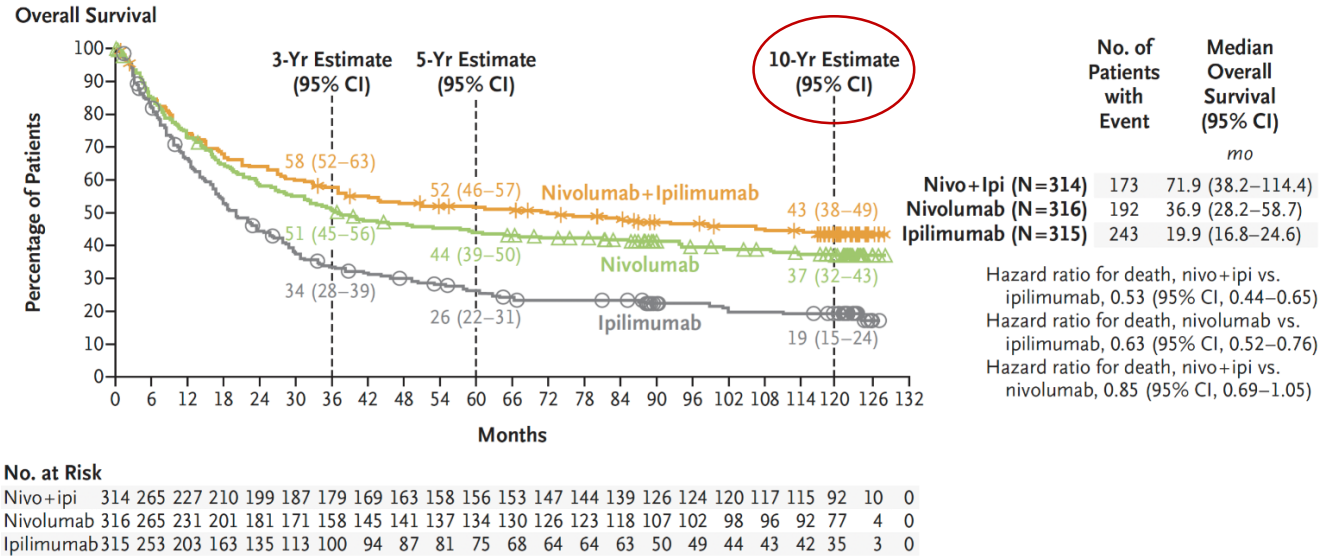




The example of advanced melanoma

Before ICI

Median OS*:
6-9 months

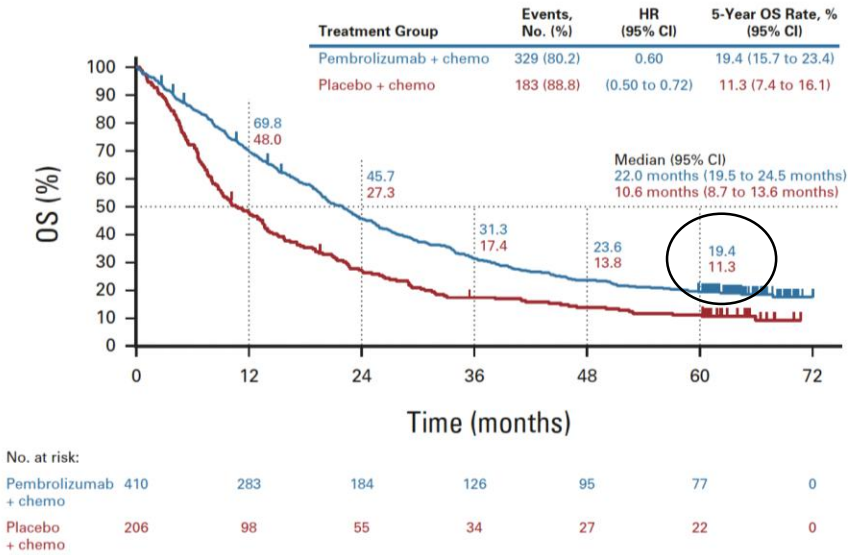


*OS: Overall Survival

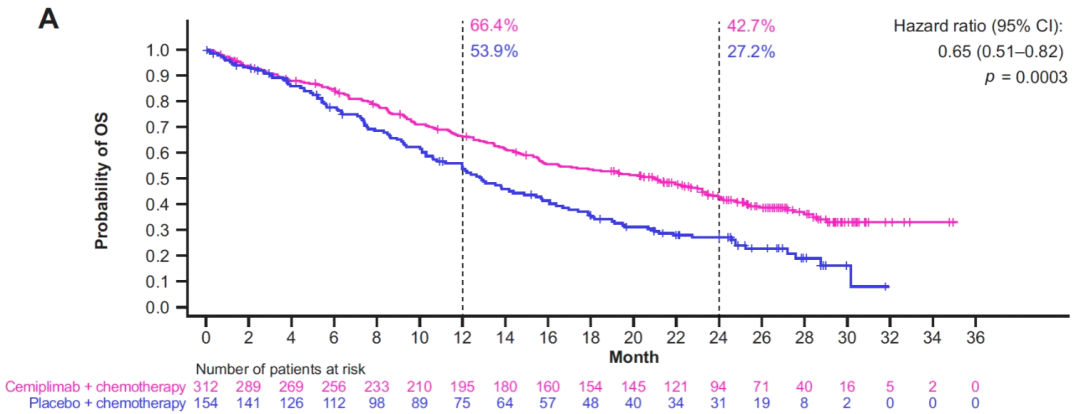
Wolchok, 2025

The example of advanced non-small cell lung cancer

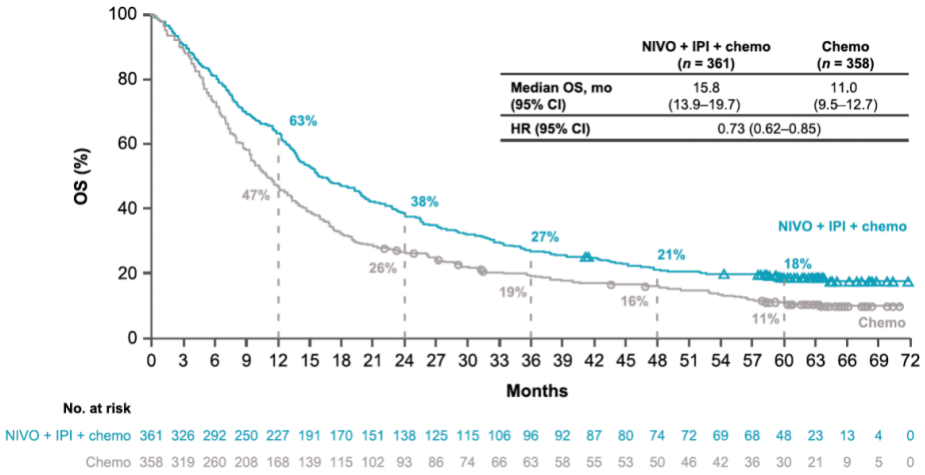
KEYNOTE-189

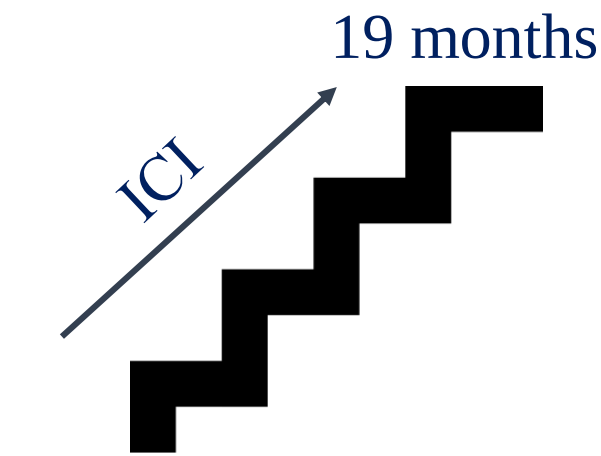


EMPOWER-Lung 3



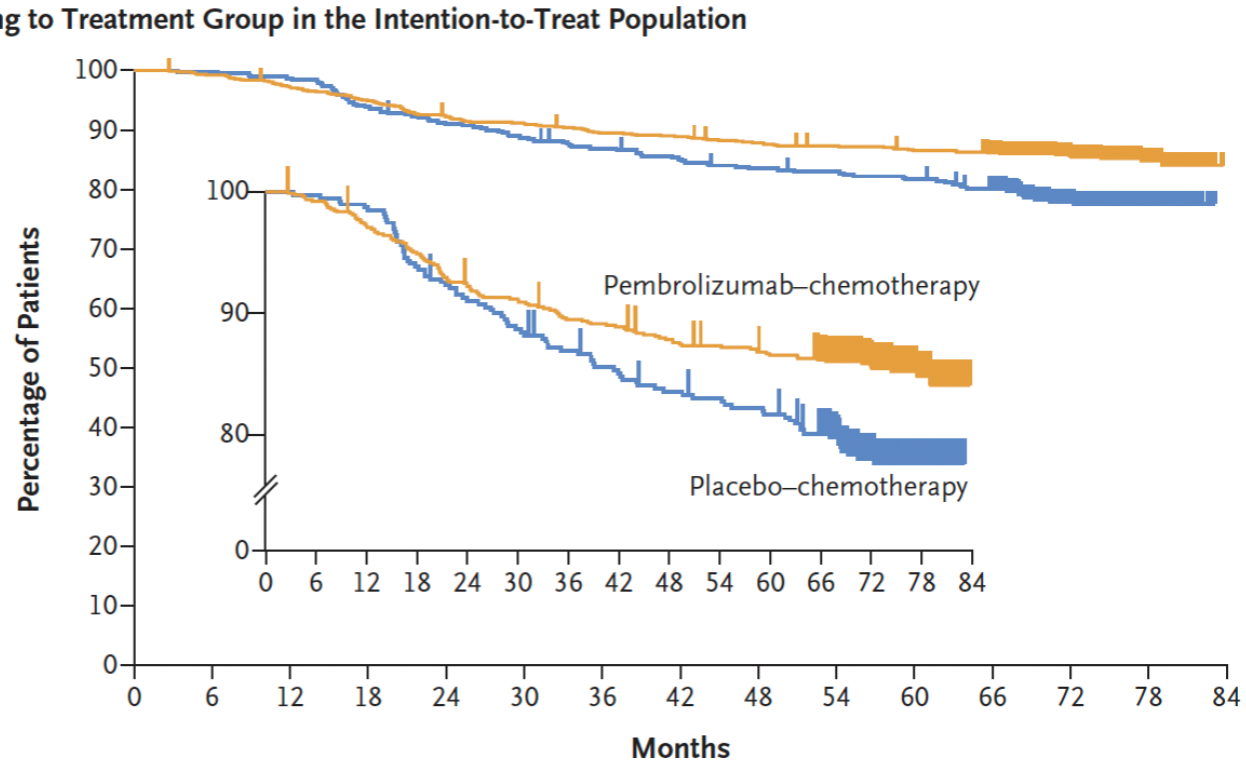
CheckMate 9LA





Garassino, 2023; Makharadze, 2023; Reck, 2024

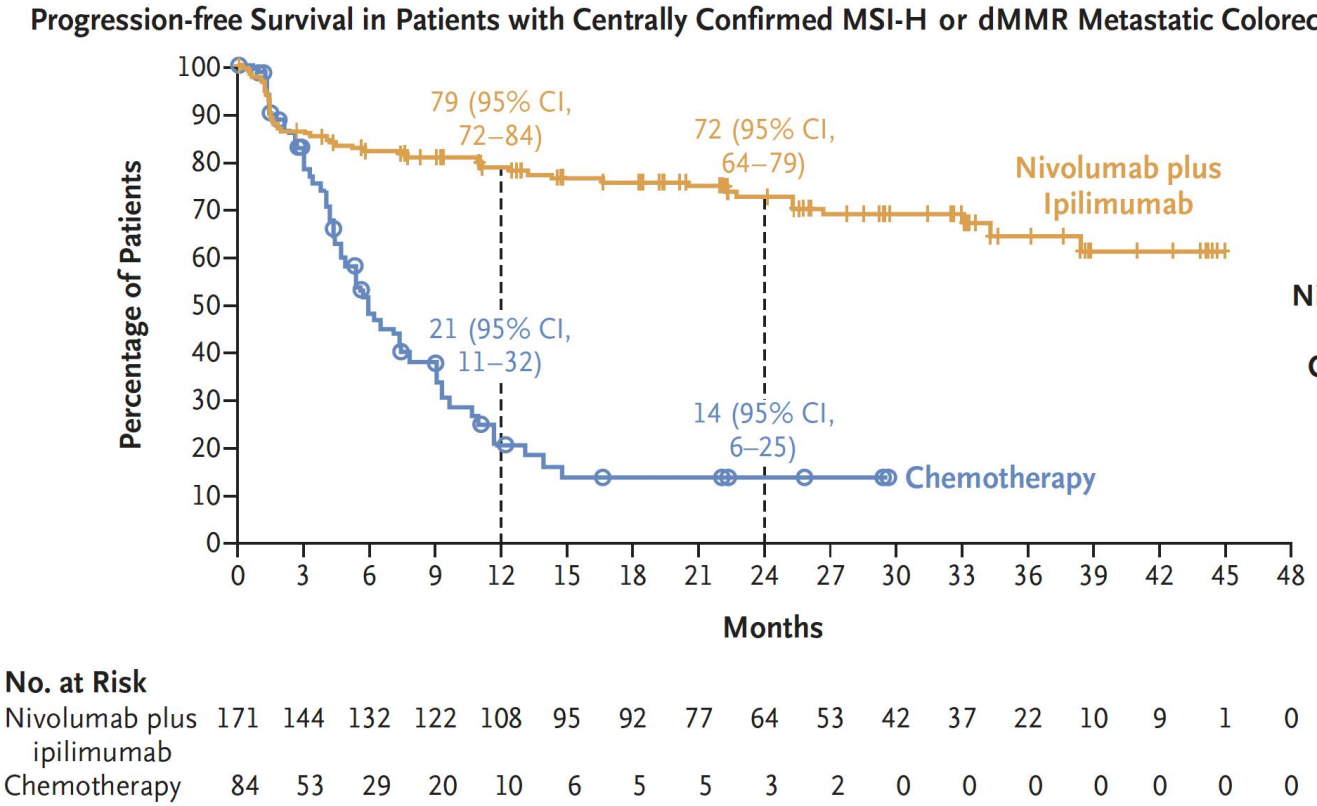
The example of early-stage, triple-negative breast cancer



No. at Risk															
Pembrolizumab–chemotherapy	784	777	760	742	720	712	698	693	683	677	670	656	448	176	0
Placebo–chemotherapy	390	389	385	366	354	345	336	328	321	318	313	300	199	82	0

Schmid, 2024

The example of advanced, MSI-H colorectal cancer

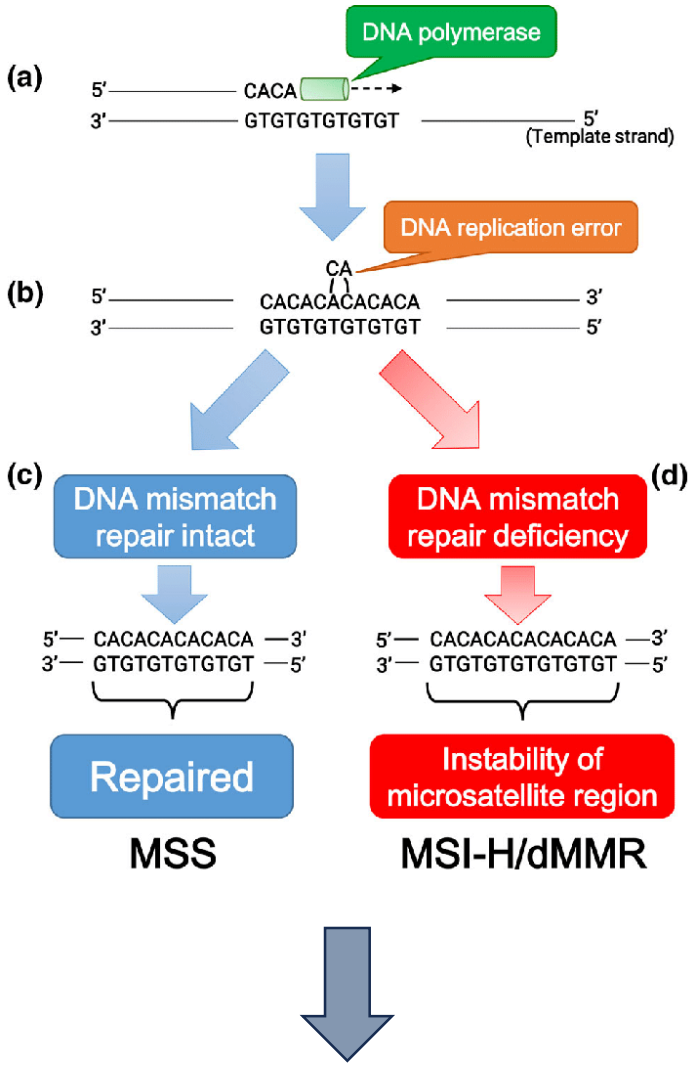


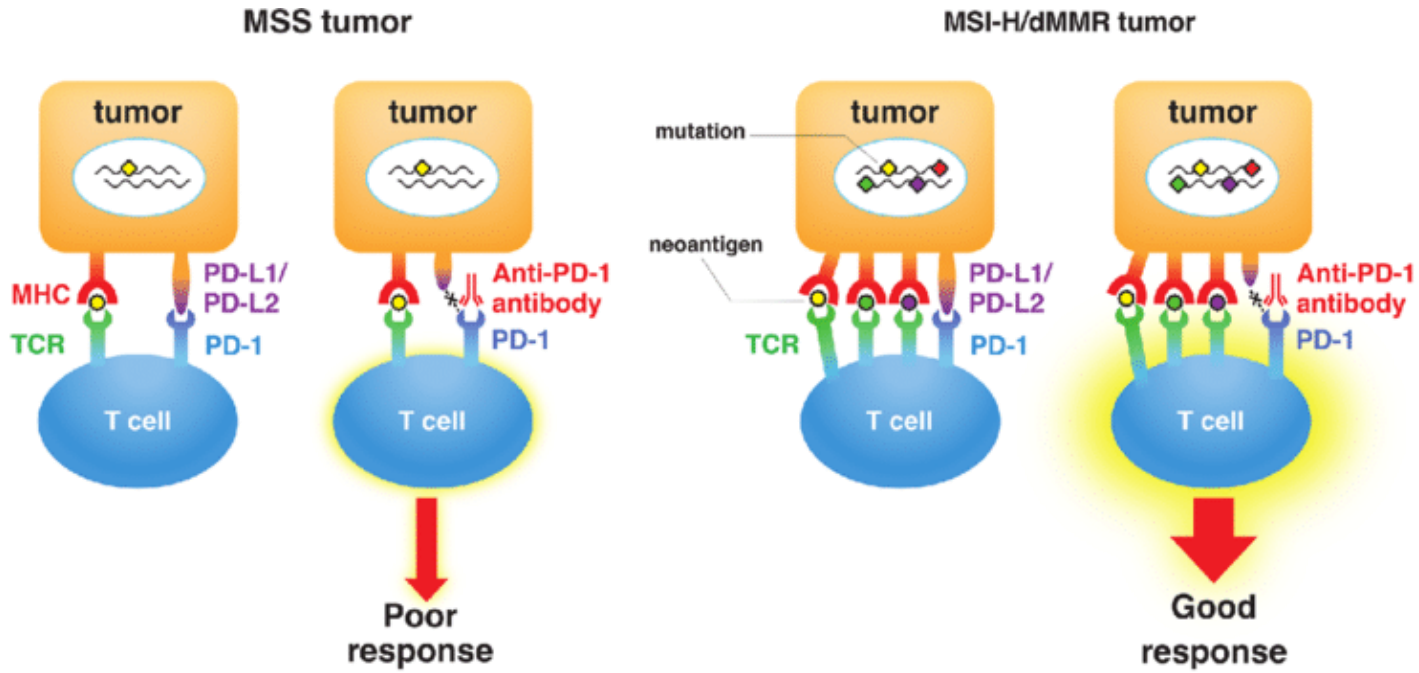
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab plus Ipilimumab	48/171	NR (38.4–NE)
Chemotherapy	52/84	5.9 (4.4–7.8)

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

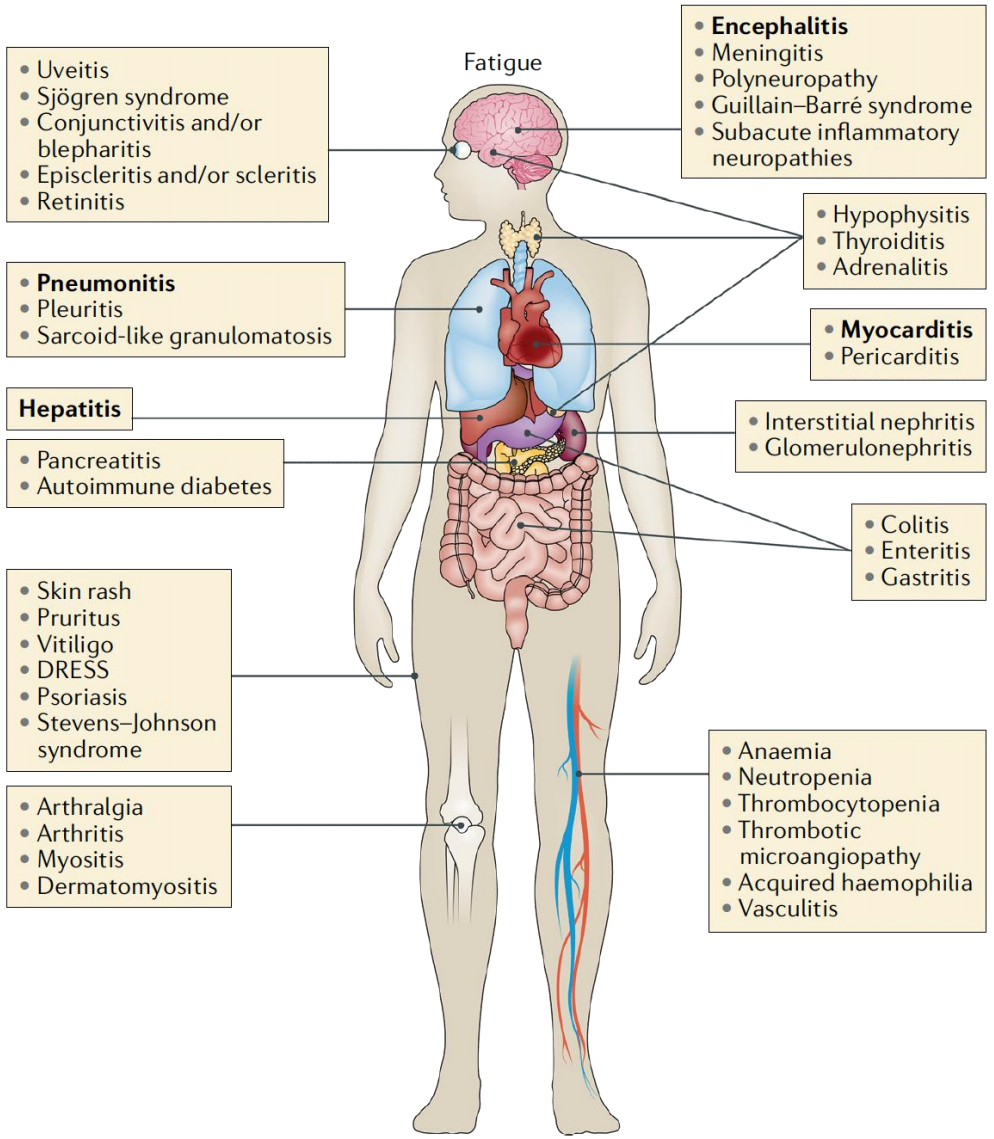
- Loss of neoantigens
- Defective antigen presentation
- Tumor cell phenotypic changes
- Metabolic antagonism

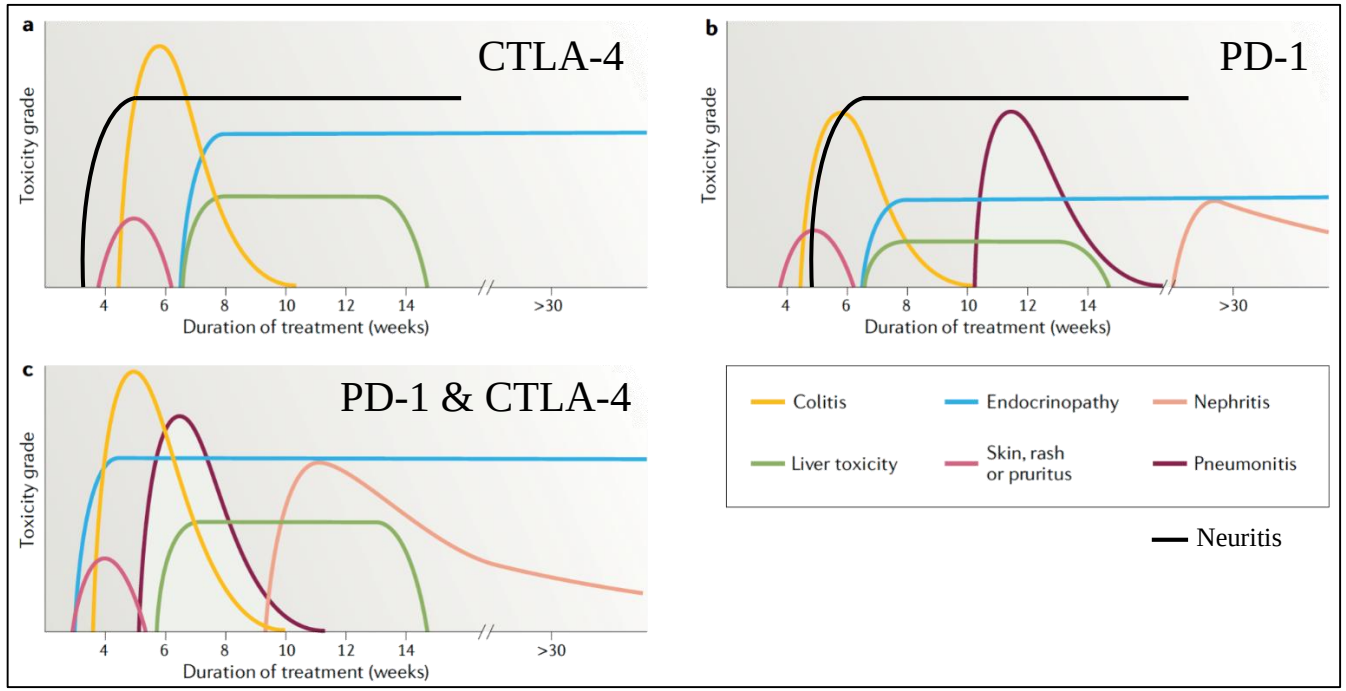
Tumor-extrinsic

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

Alsaafeen, 2025

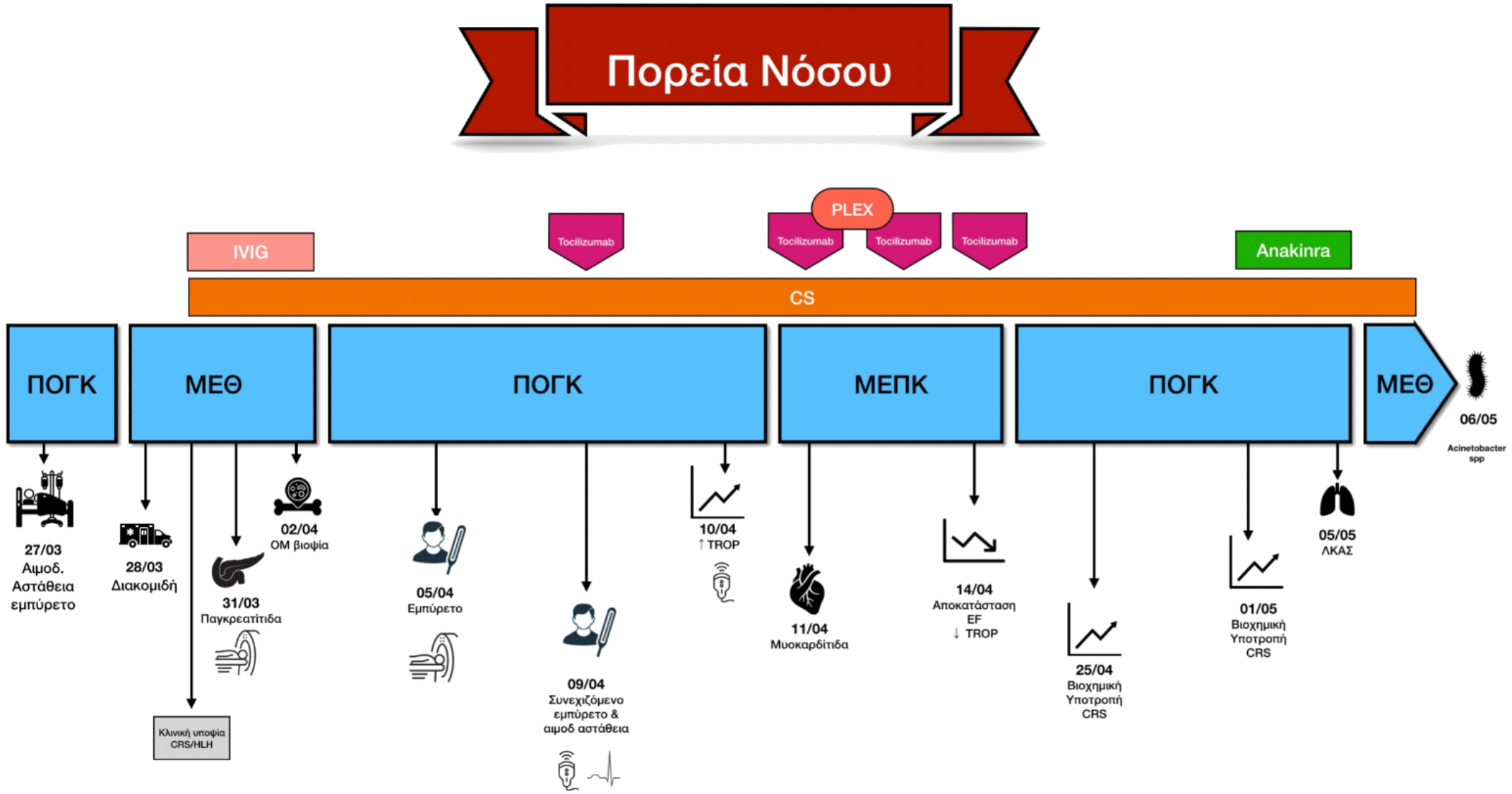
Side effects of ICIs (immune-related adverse events)





Martins, 2019

A rare example of fatal ICI-related adverse events



Courtesy of: Michail Papadakis

ICIs and 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.

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.

ESMO Clinical Practice Guidelines, 2022

Usually excluded from clinical trials

Rheumatoid Arthritis 

SLE 

IBD 

Psoriasis 

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

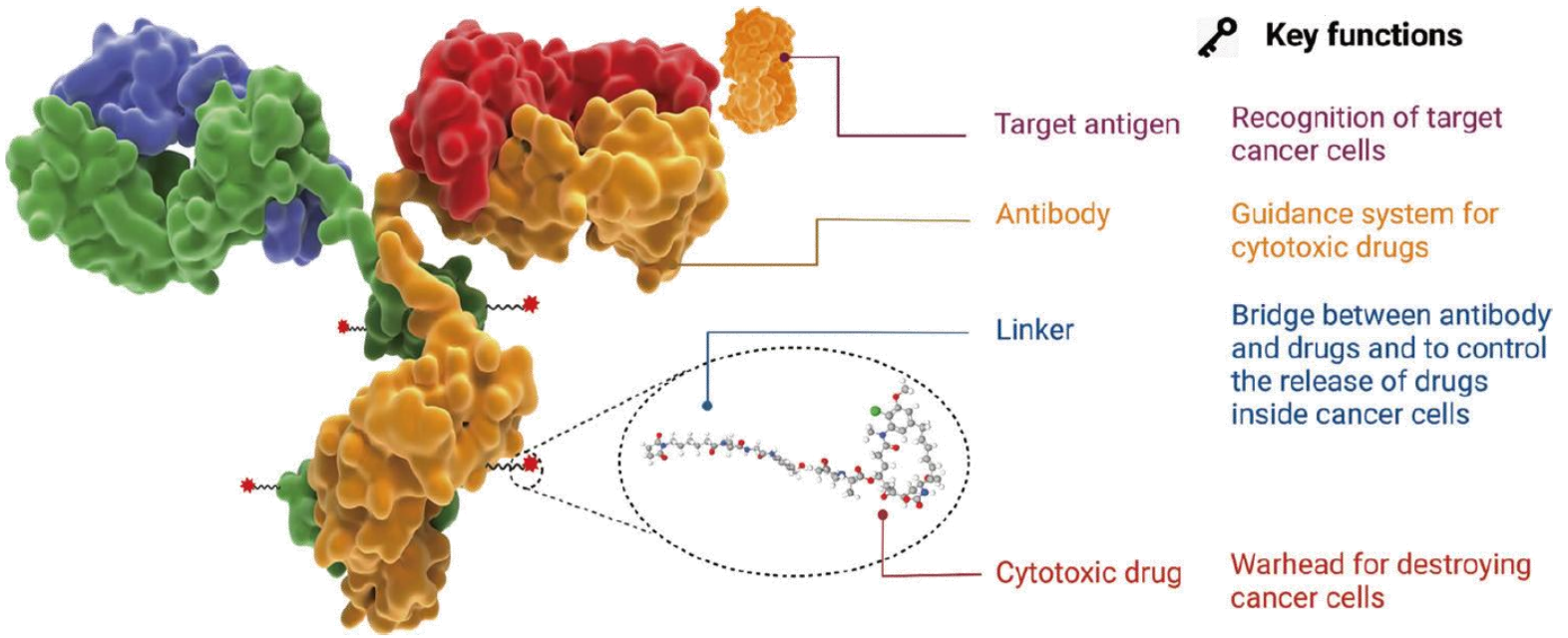
Recommendation

OPEN ACCESS

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

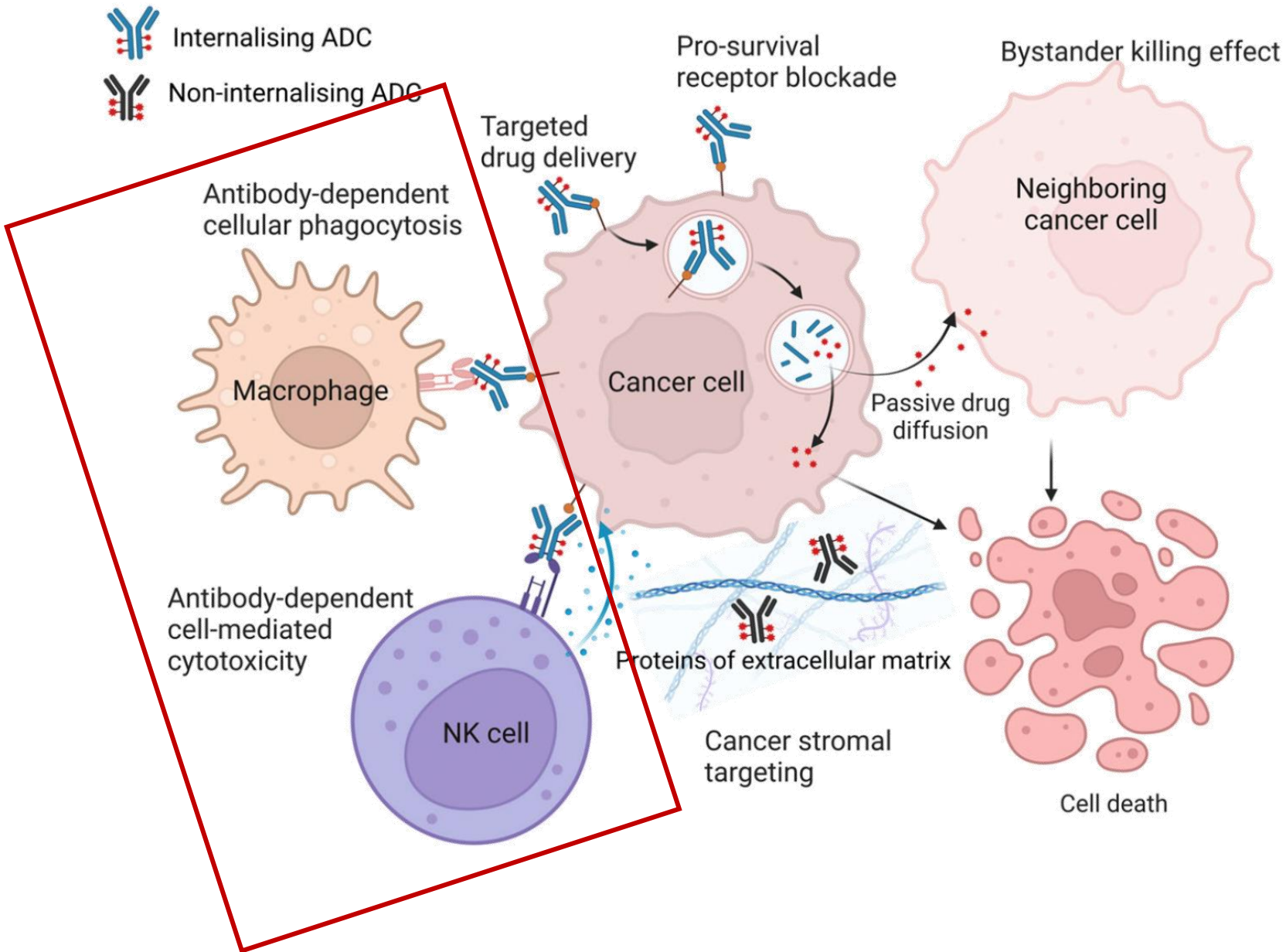
Eden Sebbag [1], Kim Lauper [2], Juan Molina-Collada [3], Daniel Aletaha [4], Johan Askling [5], Karolina Gente,[6] Heidi Bertheussen,[7] Samuel Bitoun [8], Ertugrul Cagri Bolek [9], Gerd R Burmester [10], Helena M Canhão,[11] Katerina Chatzidionysiou [5], Jeffrey R Curtis,[12] Francois-Xavier Danlos [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]

Antibody-Drug Conjugates (ADCs)



Fu, 2022

Antibody-Drug Conjugates (ADCs)

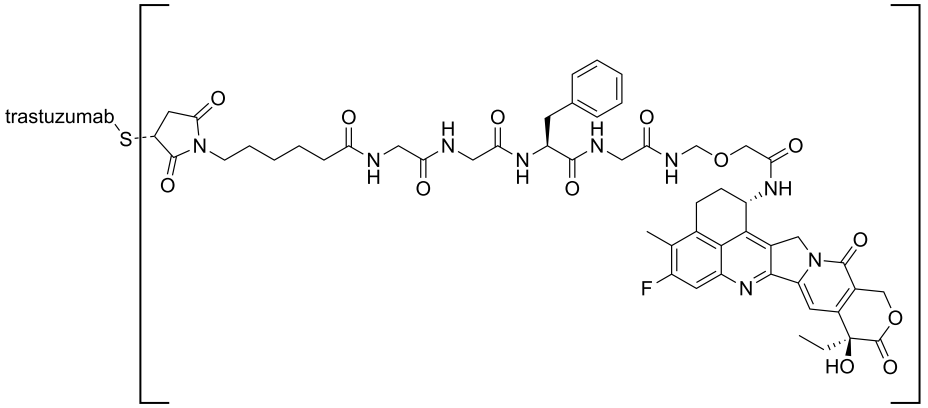


Kuznetsova, 2024

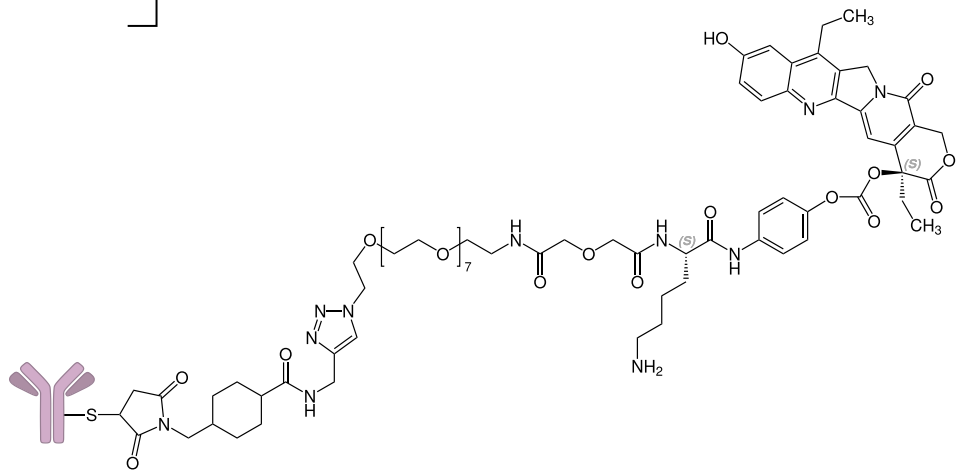
ADCs

	First-generation ADC	Second-generation ADC	Third-generation ADC
Antibodies	Mouse-original or chimeric humanized antibodies	Humanized antibodies	Fully humanized antibodies or Fabs
Linkers	Unstable	Improved stability: cleavable and non-cleavable linkers;	Stable in circulation; precise control drugs release into tumor sites
Payloads	Low potency, including calicheamicin, duocarmycin and doxorubicin	Potency, such as auristatins and mytansinoids	High potency, such as PBDs, and tubulysin, and novel payloads like immunomodulators
Conjugation methods	Random lysines	Random lysines and reduced interchain cysteines	Site-specific conjugation
DAR	Uncontrollable (0–8)	4–8	2–4
Representative drugs	Gemtuzumab ozogamicin and inotuzumab ozogamicin	Brentuximab vedotin and ado-trastuzumab emtansine	Polatuzumab vedotin, enfortumab vedotin, and fam-trastuzumab deruxtecan
Advantages	• Specific targeting • Increase therapeutic window to some extent	• Improved targeting ability • More potent payloads • Lower immunogenicity	• Higher efficacy though in cancer cells with low antigen; • Improved DAR along with improved stability and PK/PD; • More potent payloads; • Less off-target toxicity
Disadvantages	• Heterogeneity; • Lack of efficacy; • Narrow therapeutic index; • Off-target toxicity as premature drug loss; • High immunogenicity	• Heterogeneity; • Fast clearance for high DARs; • Off-target toxicity as premature drug loss; • Drug resistance	• Possible toxicity due to highly potent payloads; • Catabolism may be different across species • Drug resistance

Fu, 2022

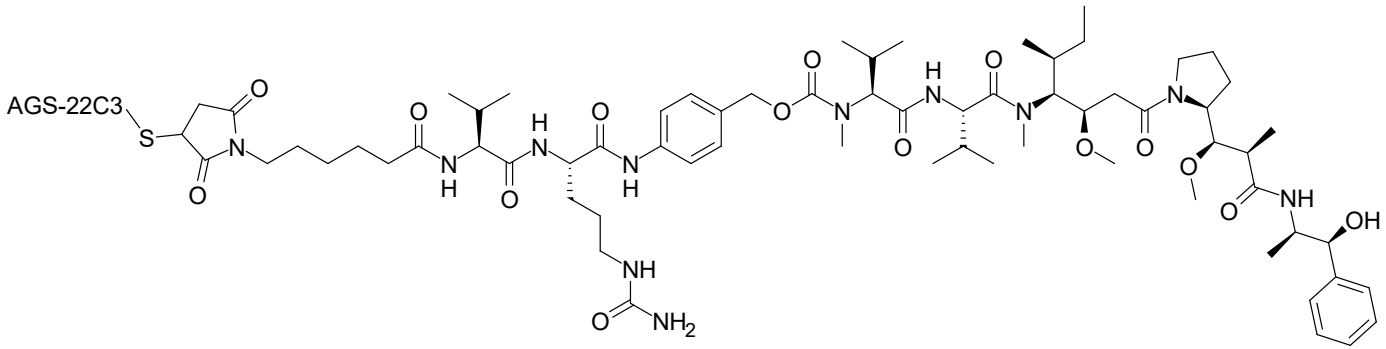


Trastuzumab deruxtecan (HER2) – Breast Cancer

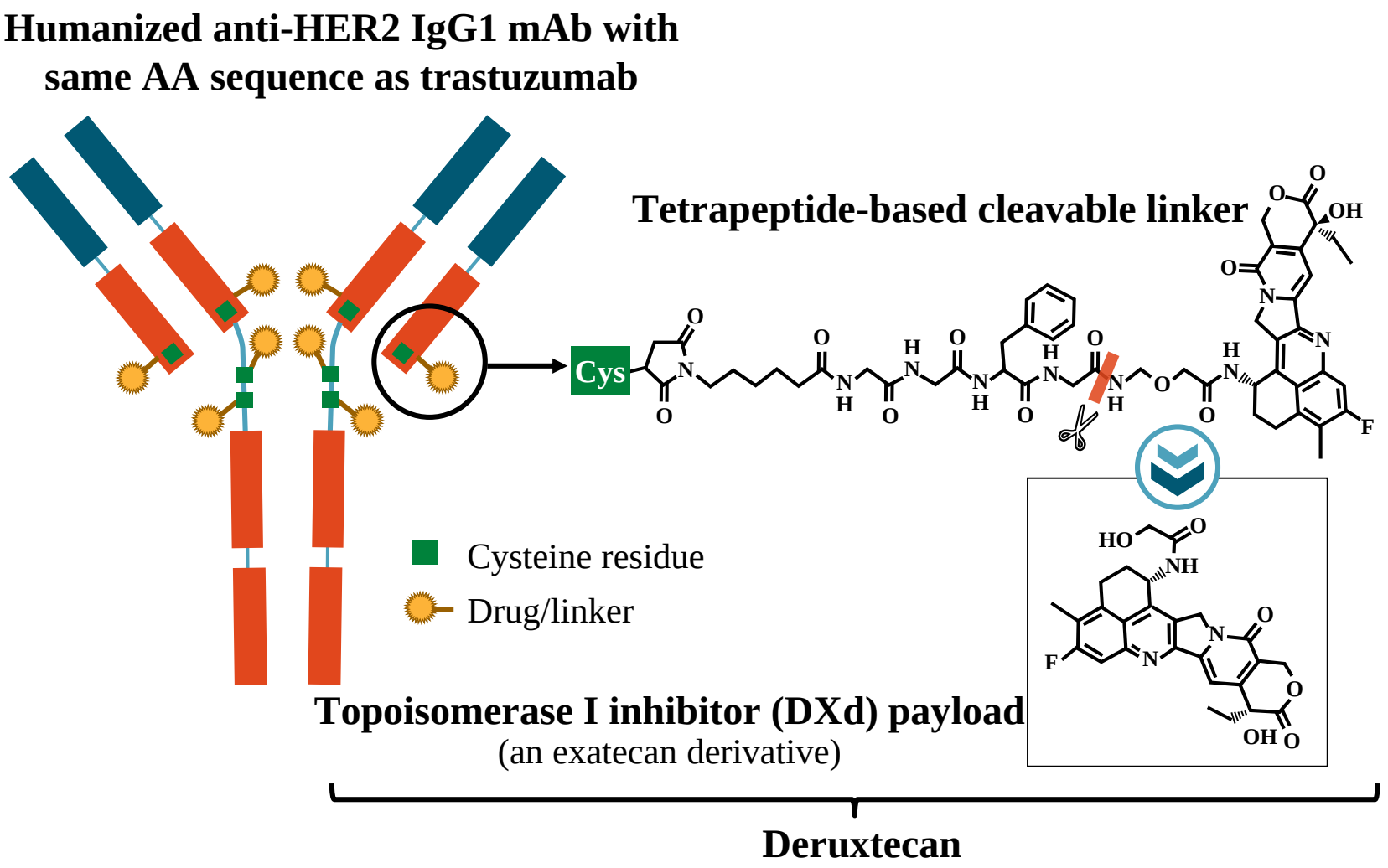


Sacituzumab govitecan (Trop-2) – Breast Cancer

Enfortumab vedotin (Nectin-4) – Bladder Cancer



Trastuzumab deruxtecan (*Enhertu*®)



- High drug:antibody ratio: ~8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect
- CNS permeability

Slide credit: clinicaloptions.com

Second Line Treatment

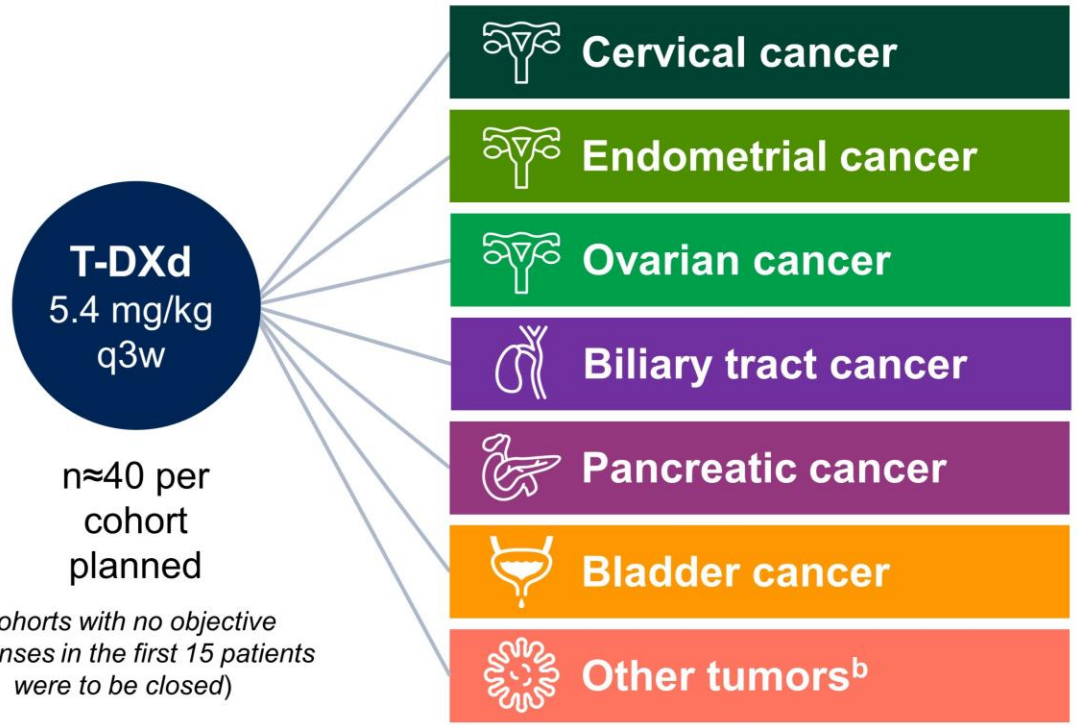
- HER2+ disease: mOS = 52.6 months
(*vs.* T-DM1: 42.7 months)

- HER2-low disease: mOS = 23.9 months
(*vs.* chemotherapy: 17.5 months)

DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



n≈40 per cohort planned

(*Cohorts with no objective responses in the first 15 patients were to be closed*)

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

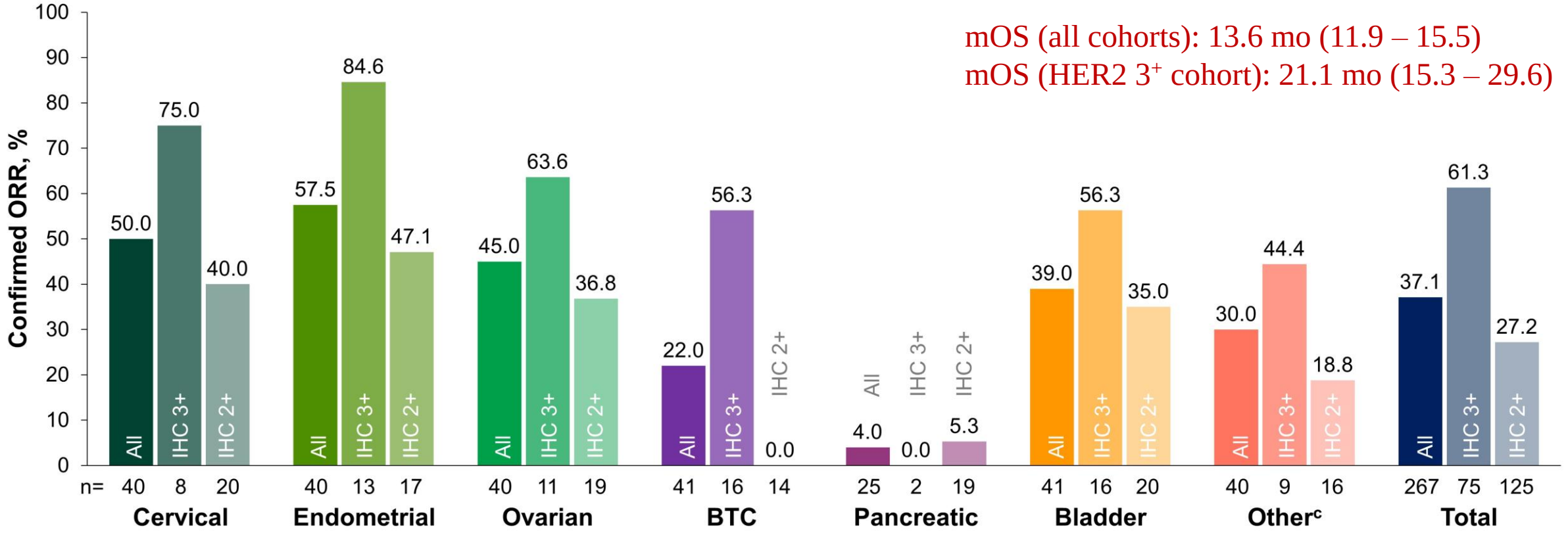
- Nov 16, 2022

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer.
[c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.
2L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

1. Hofmann M, et al. *Histopathology 2008*;52(7):797–805.

Objective Response Rate by HER2 status

mOS (all cohorts): 13.6 mo (11.9 – 15.5)
mOS (HER2 3+ cohort): 21.1 mo (15.3 – 29.6)



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

Resources for Information | Approved Drugs

Oncology (Cancer)/Hematologic Malignancies Approval Notifications

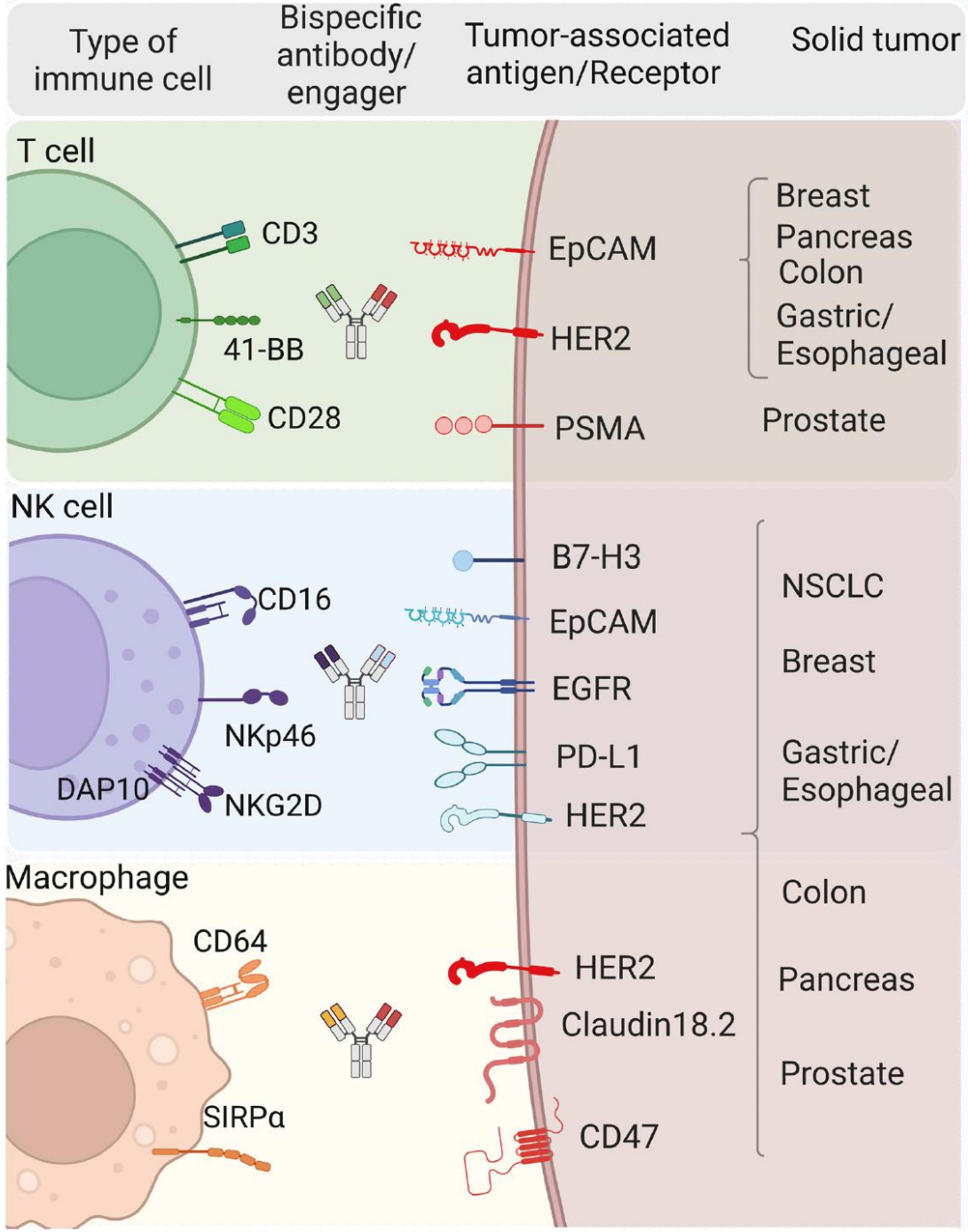
On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

Full prescribing information for Enhertu will be posted here.

Content current as of:
04/05/2024

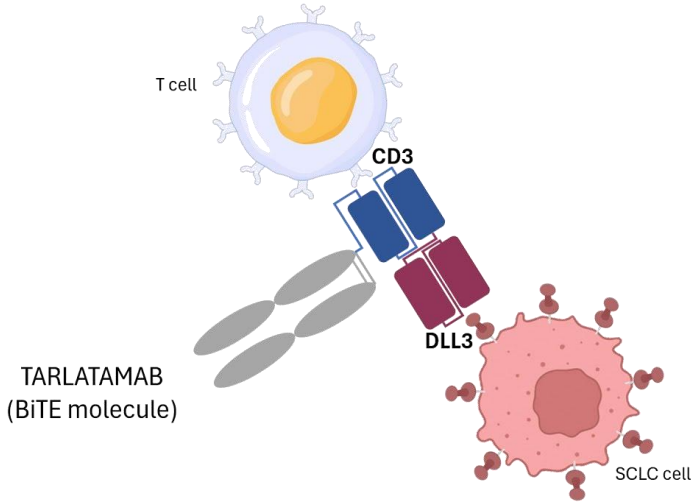
Source: fda.gov

BiTEs

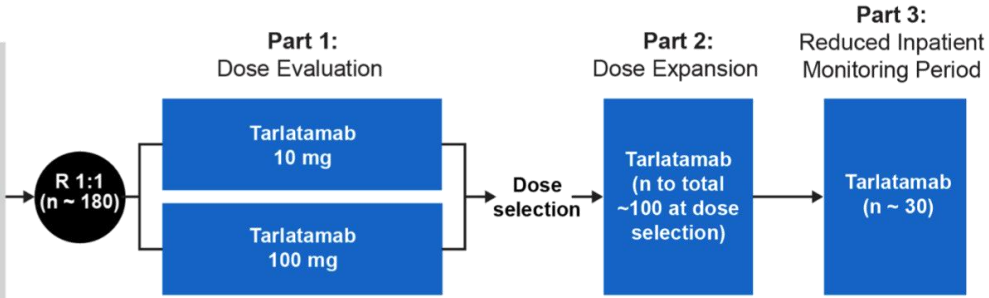


Kuznetsova, 2024

A promising new BiTE for refractory small cell lung cancer



Key Inclusion Criteria
- ES-SCLC
- Previous treatment with ≥ 2 lines (including platinum-doublet)
- ECOG PS 0–1
- Available tumor tissue
- Measurable disease
- Treated and stable brain metastases allowed



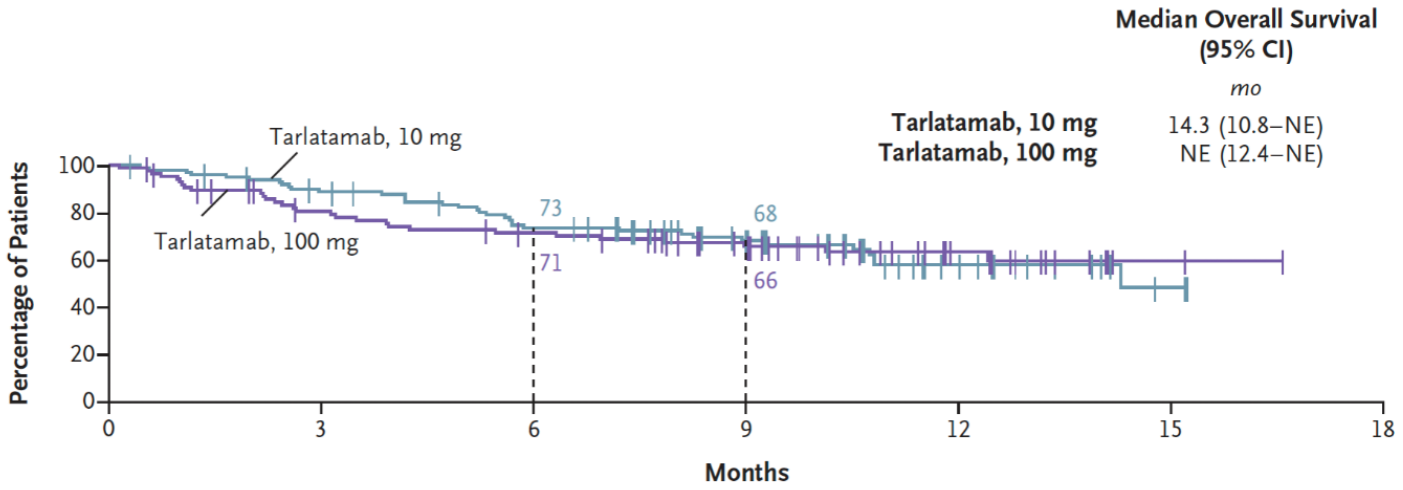
Endpoints

Primary: Objective response rate per RECIST v1.1 by BICR, incidence of adverse events, serum concentrations of tarlatamab

Secondary: Duration of response, disease control rate, duration of disease control, progression-free survival as per RECIST v1.1 by BICR, overall survival; and incidence of anti-tarlatamab antibody formation

BICR: blinded independent central review; ECOG PS: Eastern Cooperative Oncology Group performance status scale; ES-SCLC: extensive stage-small cell lung cancer; R: randomization; RECIST: Response Evaluation Criteria in Solid Tumors.

Overall Survival



No. at Risk

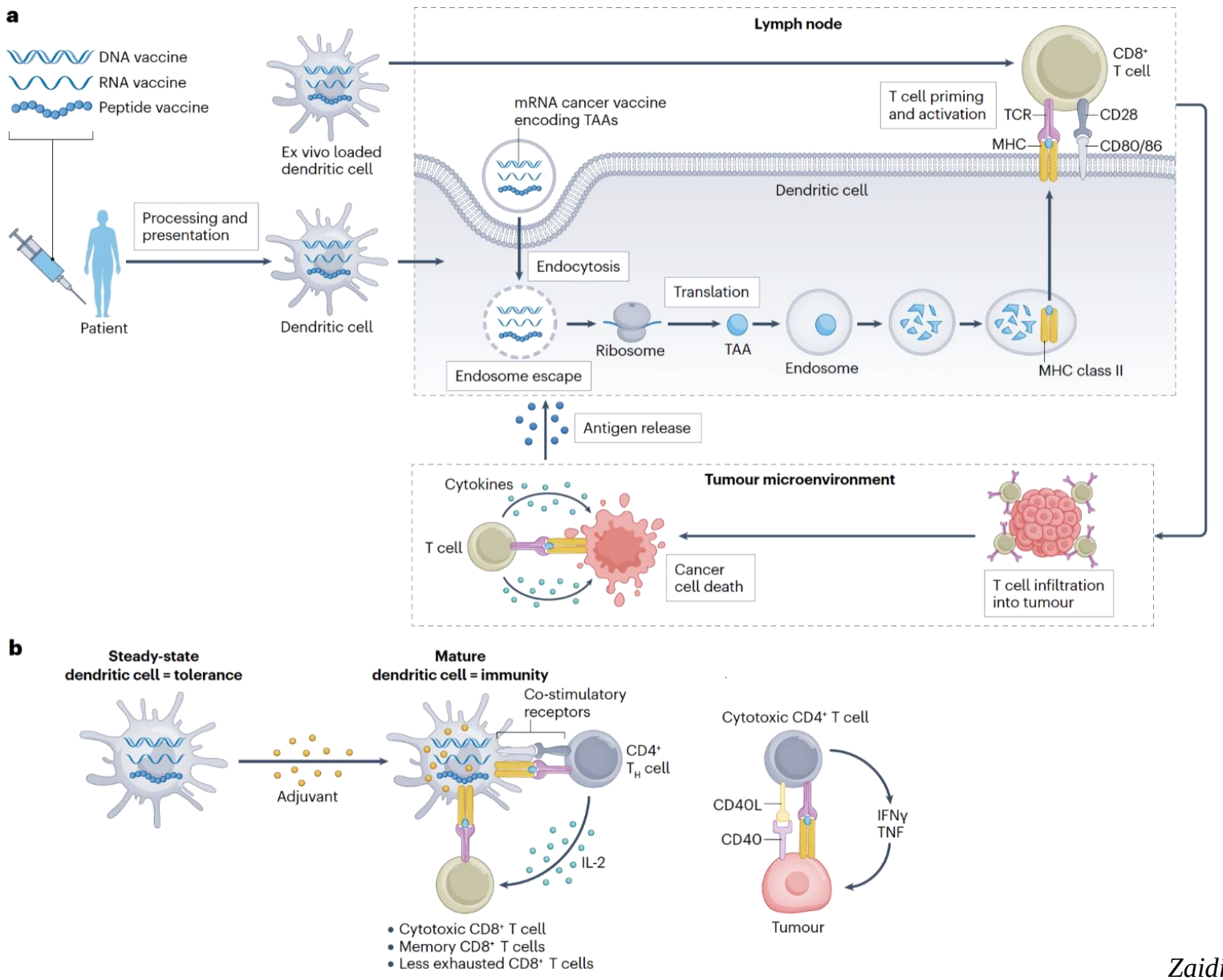
Tarlatamab, 10 mg	100	84	67	44	17	3	0
Tarlatamab, 100 mg	88	62	53	39	16	2	0

Comparator OS:
< 6 months

Ahn, 2023

Therapeutic cancer vaccines

- Peptide-based
- Nucleic acid-based
- Cell-based



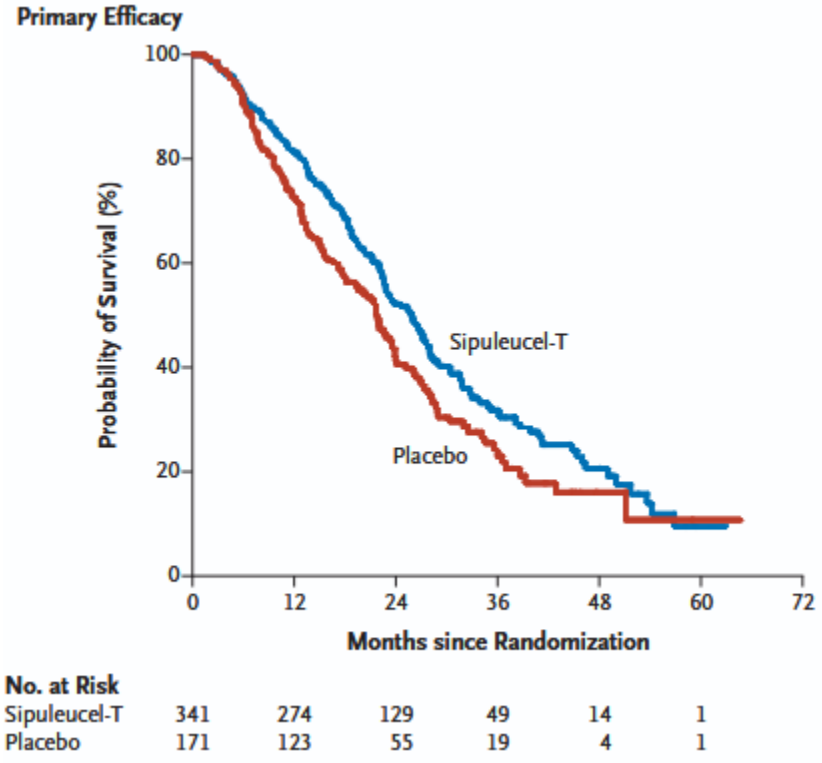
Zaidi, 2025

Therapeutic cancer vaccines

Prostate Cancer

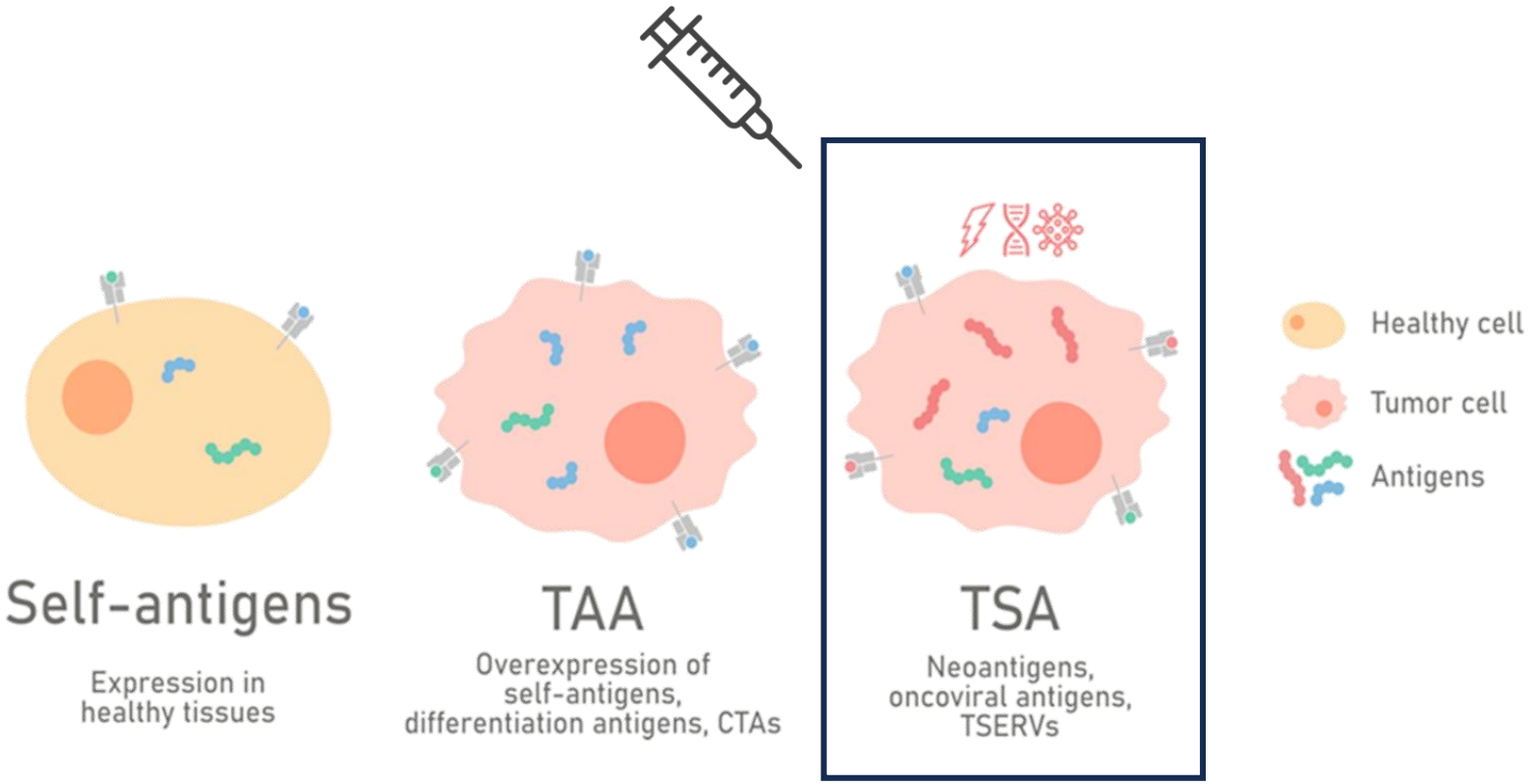
IMPACT (phase III)

Sipuleucel-T (FDA, 2010)



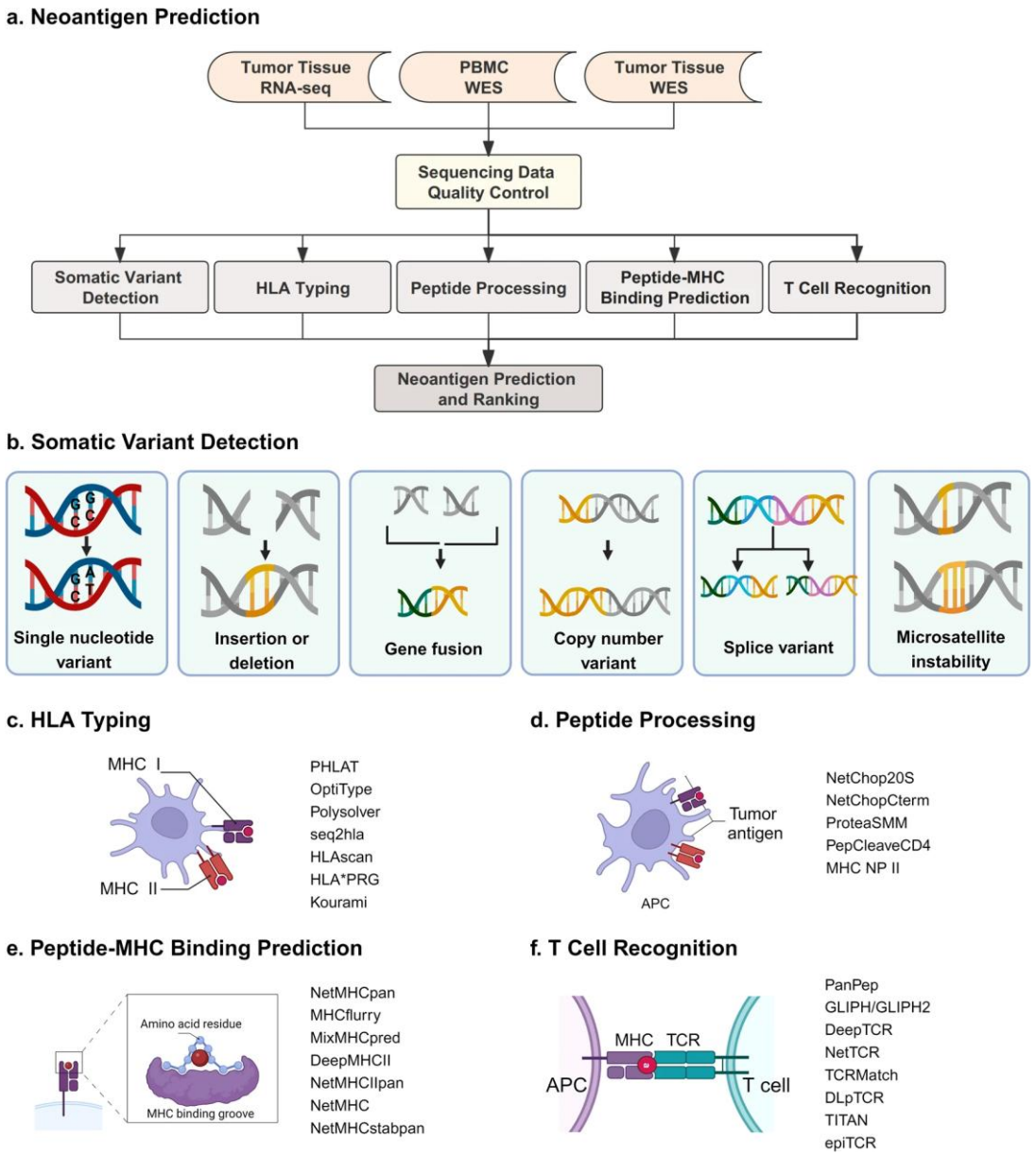
Kantoff, 2010

Therapeutic cancer vaccines



Feola, 2020

Prediction of neoantigen candidates: a challenging task



Fan, 2023

Therapeutic cancer vaccines

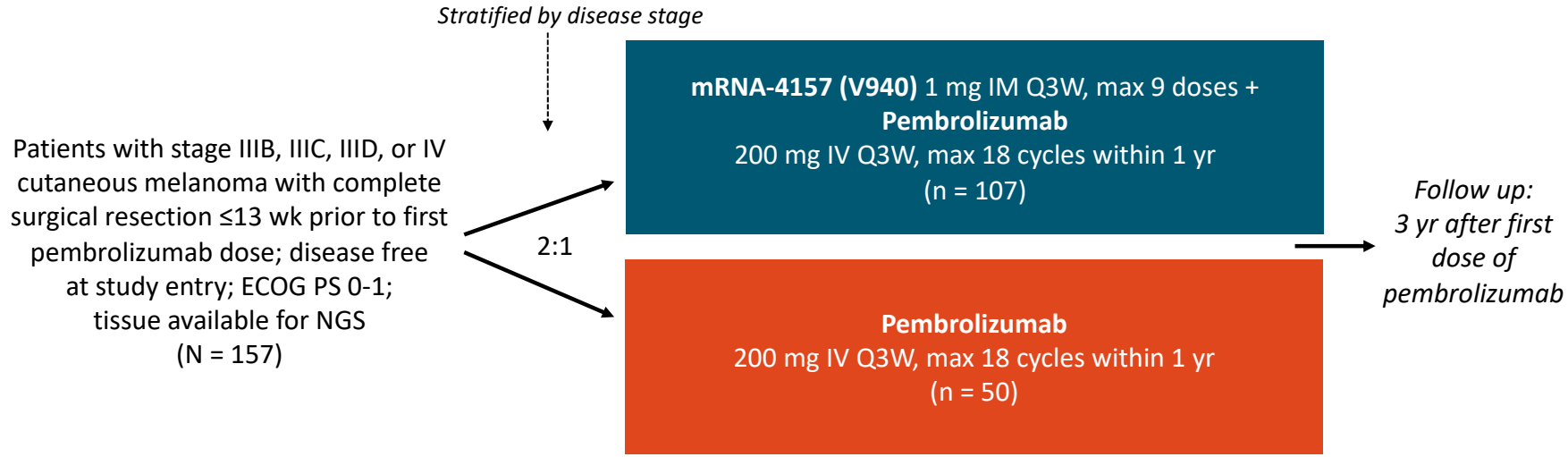
Melanoma

KEYNOTE-942 (Phase II)

mRNA-4157 (V940)
(up to 34 individ. neoantigens)

(FDA, 2023)

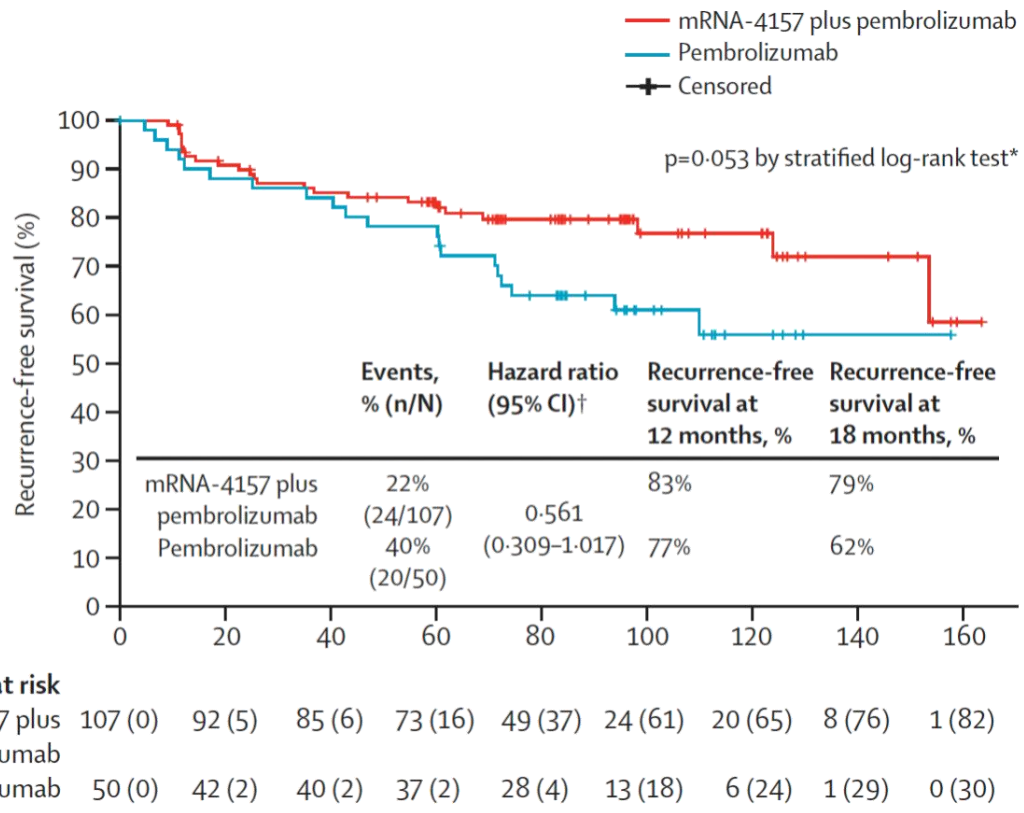
- Randomized, open-label phase II trial



- **Primary endpoint:** RFS
- **Secondary endpoints:** DMFS, safety, tolerability

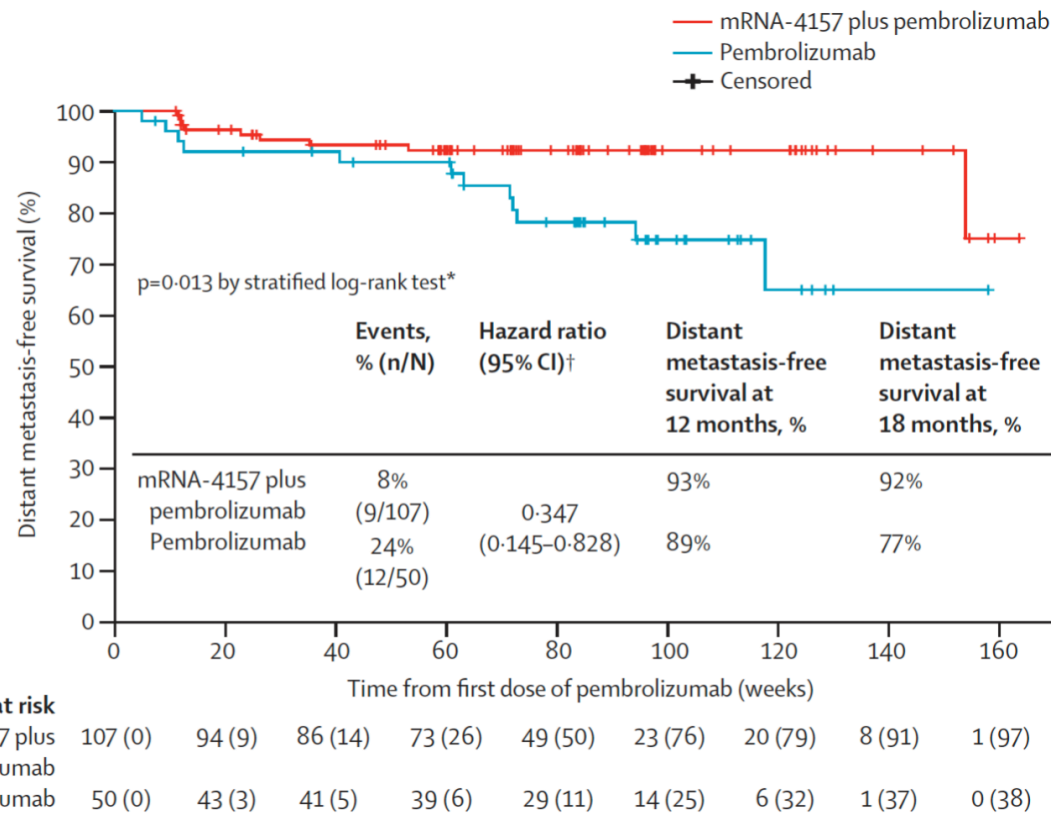
Khattak. ASCO 2023. Abstr LBA9503.

Slide Credit: CCO powered by cea



	Events, % (n/N)	Hazard ratio (95% CI)†	Recurrence-free survival at 12 months, %	Recurrence-free survival at 18 months, %
mRNA-4157 plus pembrolizumab	22% (24/107)	0·561 (0·309–1·017)	83%	79%
Pembrolizumab	40% (20/50)		77%	62%

Number at risk									
mRNA-4157 plus pembrolizumab	107 (0)	92 (5)	85 (6)	73 (16)	49 (37)	24 (61)	20 (65)	8 (76)	1 (82)
Pembrolizumab	50 (0)	42 (2)	40 (2)	37 (2)	28 (4)	13 (18)	6 (24)	1 (29)	0 (30)



	Events, % (n/N)	Hazard ratio (95% CI)†	Distant metastasis-free survival at 12 months, %	Distant metastasis-free survival at 18 months, %
mRNA-4157 plus pembrolizumab	8% (9/107)	0·347 (0·145–0·828)	93%	92%
Pembrolizumab	24% (12/50)		89%	77%

Number at risk									
mRNA-4157 plus pembrolizumab	107 (0)	94 (9)	86 (14)	73 (26)	49 (50)	23 (76)	20 (79)	8 (91)	1 (97)
Pembrolizumab	50 (0)	43 (3)	41 (5)	39 (6)	29 (11)	14 (25)	6 (32)	1 (37)	0 (38)

Weber, 2024

Therapeutic cancer vaccines

Table 1 | Ongoing randomized, phase II and phase III clinical trials of neoantigen-specific vaccines

Vaccine	Vaccine target	Combination therapy[a] (target)	Phase	Study population and clinical setting	Primary end-point	Trial number
Adagloxad simolenin (OBI-822)/OBI-821	Off-the-shelf vaccine targeting TAA (Globo H)	Standard of care (observation off-therapy, or chemotherapy)	Randomized phase III	Adjuvant Globo H-positive triple-negative breast cancer	DFS	NCT03562637 (ref. 129)
Autogene cevumeran	Personalized neoantigen	Pembrolizumab	Randomized phase II	Untreated advanced melanoma	PFS	NCT03815058 (ref. 130)
Autogene cevumeran	Personalized neoantigen	Nivolumab	Randomized phase II	High-risk muscle-invasive urothelial carcinoma	DFS	NCT06534983 (ref. 131)
Autogene cevumeran	Personalized neoantigen	Atezolizumab	Randomized phase II	Adjuvant pancreatic adenocarcinoma	DFS	NCT05968326 (ref. 132)
ELI-002	Off-the-shelf vaccine targeting mutant KRAS	None	Randomized phase II	PDAC	DFS	NCT05726864 (ref. 133)
IO102-IO103	Off-the-shelf vaccine targeting TAAs (PDL1/IDO1)	Pembrolizumab	Randomized phase III	Advanced melanoma	PFS	NCT05155254 (ref. 134)
OSE2101	Off-the-shelf vaccine targeting TAAs (HER2, CEA, MAGE 2, MAGE 3 and p53)	None	Randomized phase III	Advanced NSCLC with secondary resistance to an ICI	OS	
V940	Personalized neoantigen	Pembrolizumab	Randomized phase III	Adjuvant melanoma	RFS	NCT05933577 (ref. 135)
V940	Personalized neoantigen	Pembrolizumab	Randomized phase III	Adjuvant NSCLC	RFS	NCT06077760 (ref. 117)
V940	Personalized neoantigen	Pembrolizumab	Randomized phase III	Adjuvant NSCLC in patients who received neoadjuvant anti-PD1 without complete response	DFS	NCT06623422 (ref. 128)
V940	Personalized neoantigen	Pembrolizumab	Randomized phase II/III	Locally advanced cutaneous squamous cell carcinoma	EFS	NCT06295809 (ref. 136)
V940	Personalized neoantigen	Pembrolizumab	Randomized phase II	Adjuvant RCC	DFS	NCT06307431 (ref. 137)
V940	Personalized neoantigen	Pembrolizumab	Randomized phase II	Adjuvant high-risk muscle-invasive urothelial carcinoma	DFS	NCT06305767 (ref. 138)

Zaidi, 2025

> Lung Cancer. 2025 May:203:108516. doi: 10.1016/j.lungcan.2025.108516. Epub 2025 Mar 30.

ARTEMIA phase 3 study: A randomized, open-label trial comparing the efficacy and safety of OSE2101 versus docetaxel in HLA-A2 positive patients with metastatic non-small cell lung cancer and secondary resistance to immune checkpoint inhibitors

S V Liu [1], R Dziadziuszko [2], S Viteri [3], F Cappuzzo [4], S Comis [5], V Gabarre [5], C Chevalier [5], T Vandewalle [5], F Montestruc [6], B Vasseur [5], J Remon [7], B Besse [7]

Affiliations + expand

PMID: 40174385 DOI: 10.1016/j.lungcan.2025.108516

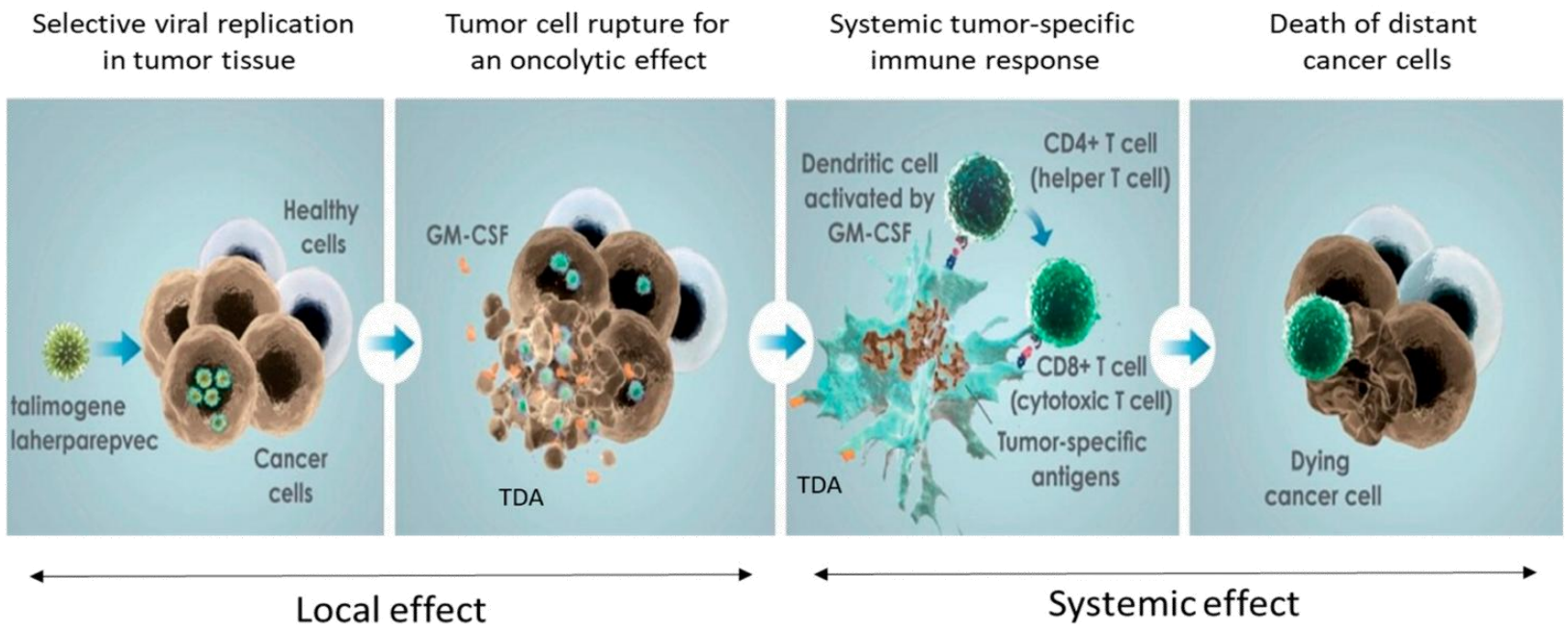
No abstract available

PubMed Disclaimer

Oncolytic viruses

Melanoma: T-VEC

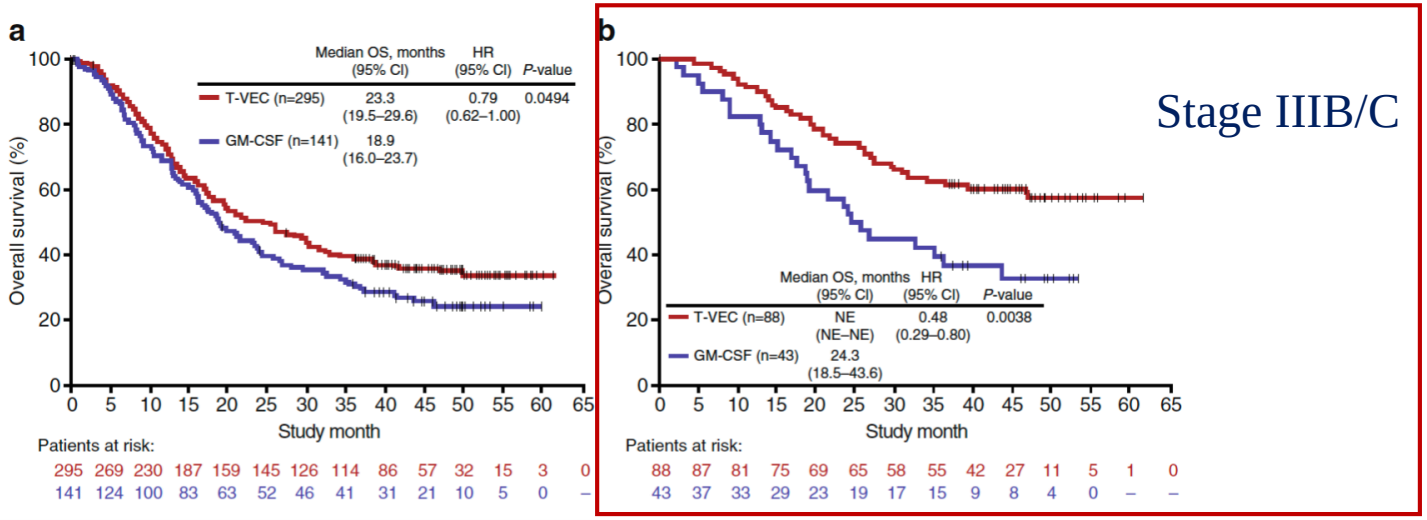
(Vector: HSV)



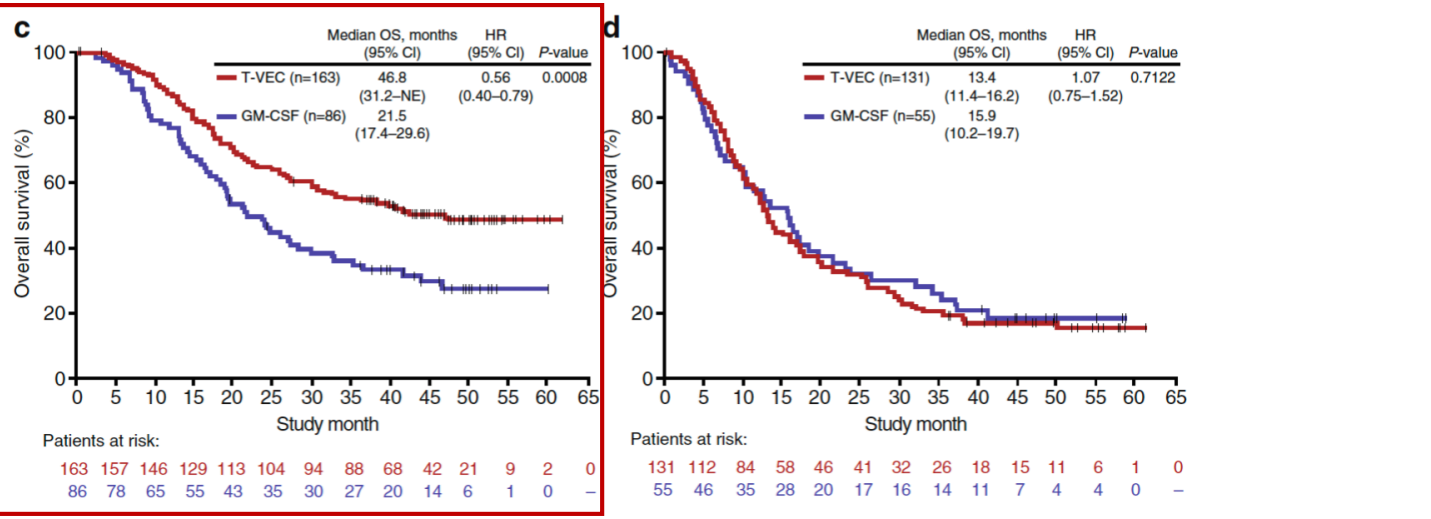
Ferrucci, 2021

Oncolytic viruses

Unresectable melanoma (low tumor burden)



Stage IIIB/C

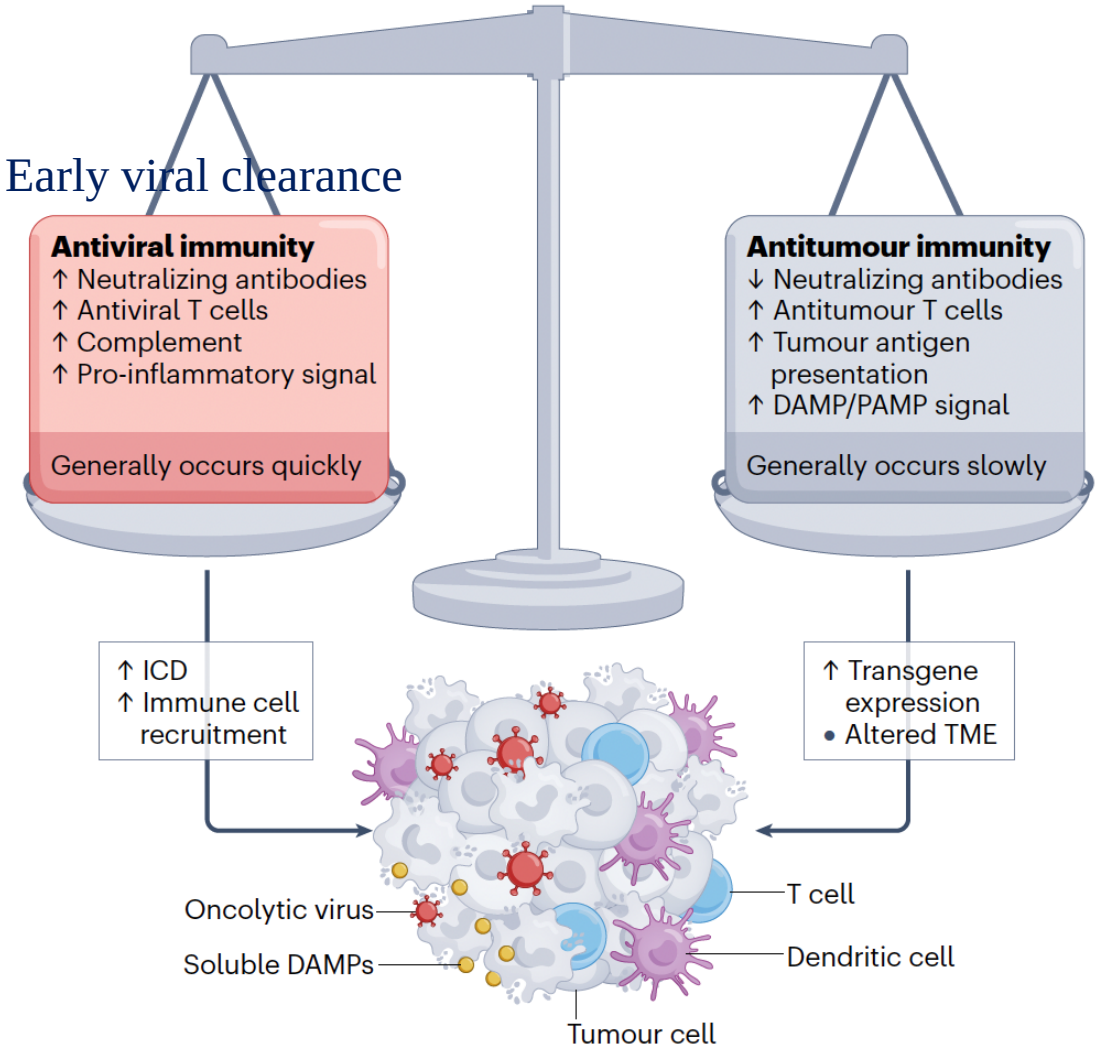


Stage IIIB-IVM1a

Andtbacka, 2019

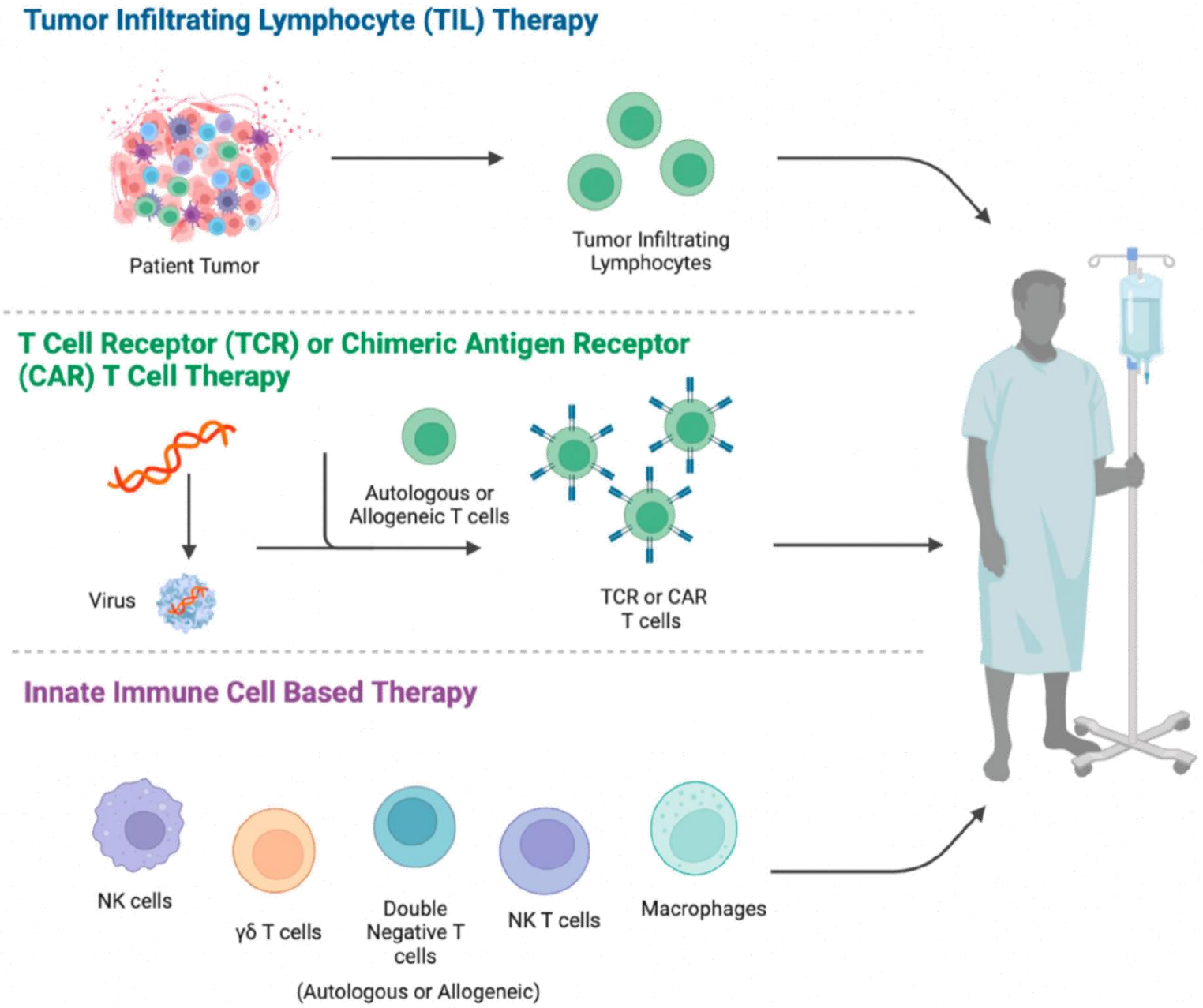
Oncolytic viruses

Challenges in clinical development



Shalhout, 2023

Adoptive Cell Therapy

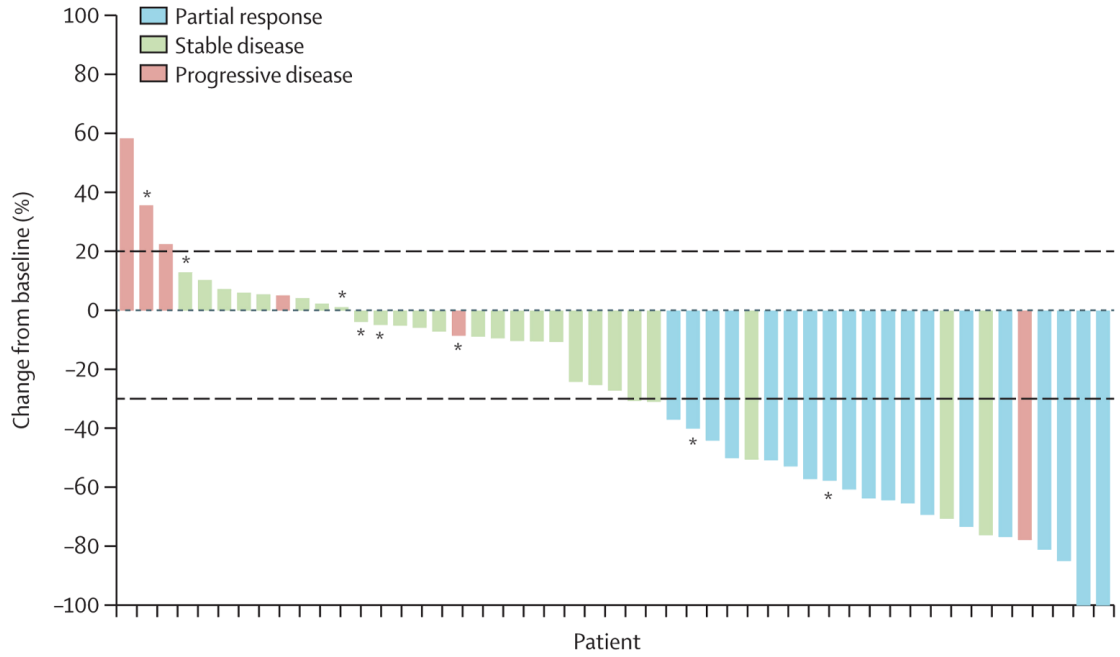


Fang, 2023

TCR T-cell therapy

First approval (FDA, 2024): afami-cel (autologous T cells)

Chemo-resistant synovial sarcoma
→ HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P (+)
→ MAGE-A4 (+)



D'Angelo, 2024

CAR-T cells

FDA approval: B-cell malignancies

- CD19-targeting
- BCMA-targeting

None for solid tumors (!)

|

Unfavorable factors

- Complex TME in solid tumors
- Difficulty choosing appropriate TAAs
- Heterogeneous target antigen expression
- "Tumor antigen escape"

Potential solutions

- Bi-specific CAR T-cells
- Intratumoral delivery

Table 1. Clinical trials of CAR-T cell therapy in solid tumors.

CAR-T Product	Target Antigen	Generation of CAR-T Cell Structure	Cancer	Trial Phase	Status	NCT Number
HER2-E-CART cells	HER-2	2nd-generation	HER-2-positive and refractory advanced solid tumors	I	Not yet recruiting	NCT05745454
Mesothelin/GPC3/GUCY2C-CAR-T Cells	Mesothelin	2nd-generation (secreting a fusion protein of IL21 and scFv against PD1)	Pancreatic cancer	I	Recruiting	NCT05779917
CART-TnMUC1 cells; Cyclophosphamide; Fludarabine	TnMUC1	2nd-generation	Advanced TnMUC1-positive solid tumors (triple negative breast cancer, epithelial ovarian cancer, pancreatic cancer, and non-small cell lung cancer), and advanced TnMUC1-positive multiple myeloma	I	Terminated	NCT04025216
LeY-CAR-T	Lewis Y Antigen (LeY)	2nd-generation	LeY antigen-expressing advanced solid tumors	I	Completed	NCT03851146
GPC3/Mesothelin/Claudin18.2/GUCY2C/B7-H3/PSCA/PSMA/MUC1/TGFβ/HER2/Lewis-Y/AXL/EGFR-CAR-T Cells	GPC3, Mesothelin, Claudin18.2, GUCY2C, B7-H3, PSCA, PSMA, MUC1, TGFβ, HER2, Lewis-Y, AXL, or EGFR	3rd-generation	Lung cancer	I	Recruiting	NCT03198052
Anti-HLA-G CAR-T cells (IVS-3001); Fludarabine phosphate; Cyclophosphamide	Human leukocyte antigen (HLA-G)	3rd-generation	Previously treated, locally advanced, or metastatic solid tumors that are HLA-G positive	I/IIa	Recruiting	NCT05672459
EGFR-IL12-CART Cells	EGFR	4th-generation (IL12 expressing)	Metastatic colorectal cancer	I/II	Unknown status	NCT03542799
anti-CTLA-4/PD-1 expressing EGFR-CAR-T	EGFR	4th-generation (CTLA-4 and PD-1 antibodies expressing)	EGFR-positive advanced solid tumor	I/II	Unknown status	NCT03182816
4SCAR-GD2 T-cells	GD2	4th-generation (with an inducible caspase 9 suicide gene)	Solid tumor	I/II	Unknown status	NCT02992210
C7R-GD2.CART Cells	GD2	4th-generation (IL7 expressing)	Relapsed or refractory neuroblastoma and other GD2 positive cancers (sarcoma, uveal melanoma, phyllodes breast tumor, or another cancer)	I	Active, not recruiting	NCT03635632
CAR-T therapy	Nectin4/FAP	4th-generation (IL7 and CCL19, or IL12 expressing)	Nectin4-positive solid tumors such as non-small cell lung cancer, breast cancer, ovarian cancer, bladder cancer, or pancreatic cancer, and FAP-positive CAFs in the tumor-associated stroma	I	Unknown status	NCT03932565
GPC3/TGFβ-CART cells	GPC3/soluble TGFβ	3rd/4th-generation	Hepatocellular carcinoma with GPC3 expression, squamous cell lung cancer	I	Unknown status	NCT03198546

Kuznetsova, 2024

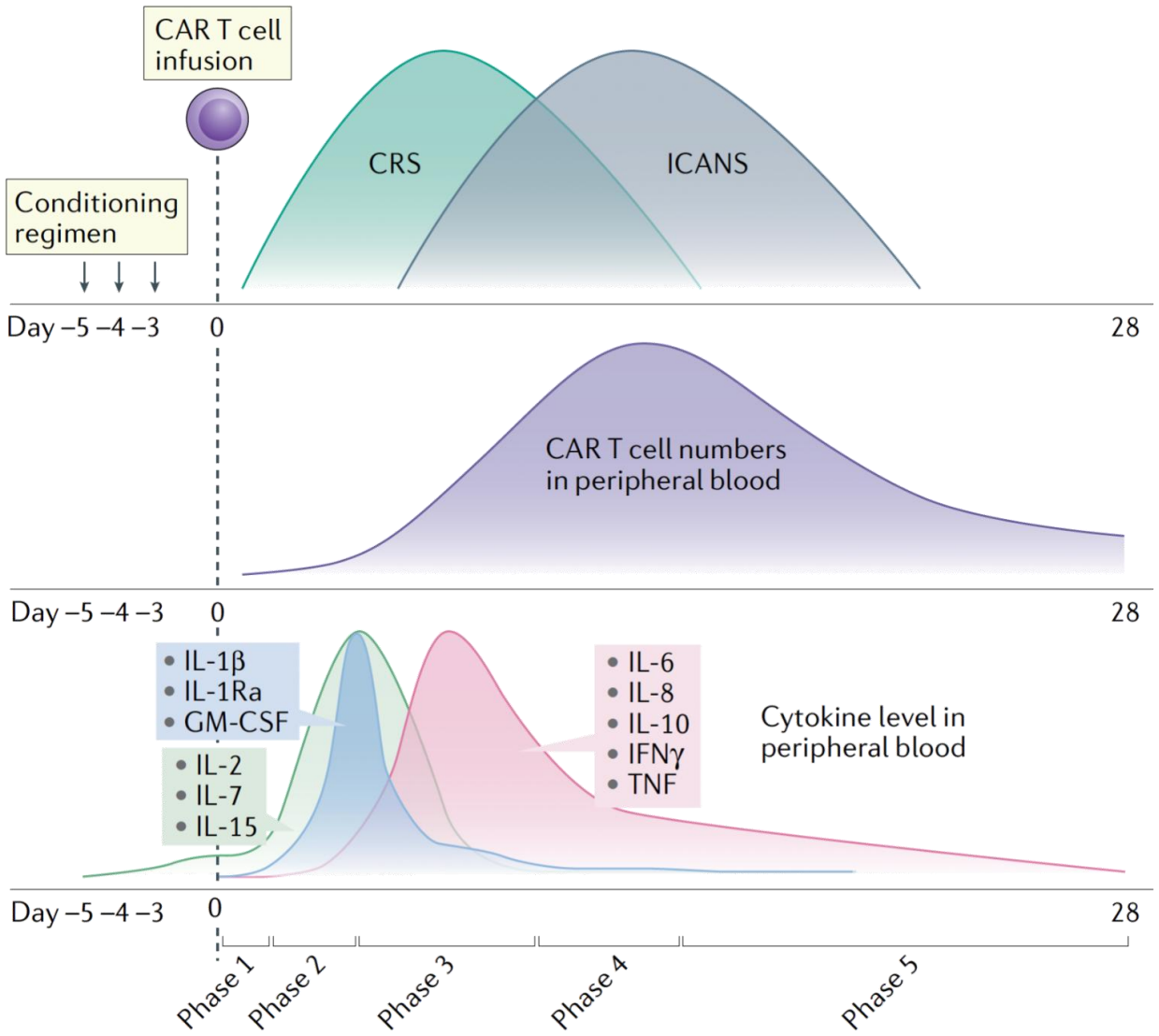
CAR-NK cells

Table 3. Examples of clinical trials with CAR-NK cells for the treatment of solid tumor.

Target Antigen	NK Cell Source	Targeted Disease	Trial Phase	Status	NCT Number
MUC1	Placental HSC-derived	Solid tumors (colorectal, gastric, pancreatic, NSCLC, breast, and glioma)	I/II	Unknown	NCT02839954
ROBO1	NK-92 cell line	Pancreatic cancer	I/II	Unknown	NCT03941457
ROBO1	Human primary NK cells	Solid tumors	I/II	Unknown	NCT03940820
NKG2D	Patient derived or donor NK cells	Metastatic solid tumors (e.g., colorectal cancer)	I	Unknown	NCT03415100
5T4 oncofoetal trophoblast glycoprotein (5T4)	Undisclosed	Advanced solid tumors	I	Unknown	NCT05194709
Claudin6, GPC3, Mesothelin, or AXL	Human primary NK cells	Advanced solid tumors (ovarian cancer and others)	I	Recruiting	NCT05410717
PD-L1	haNK	Solid tumors	I	Active, not recruiting	NCT04050709
PD-L1	haNK	Pancreatic cancer	I/II	Recruiting	NCT04390399

Kuznetsova, 2024

Cytokine Release Syndrome (CRS) / ICANS / GVHD

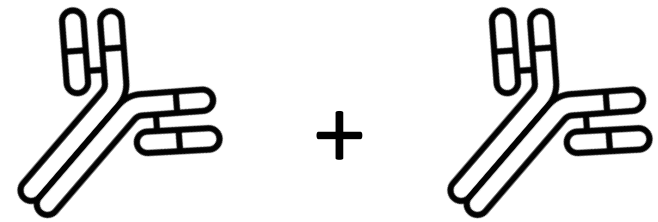


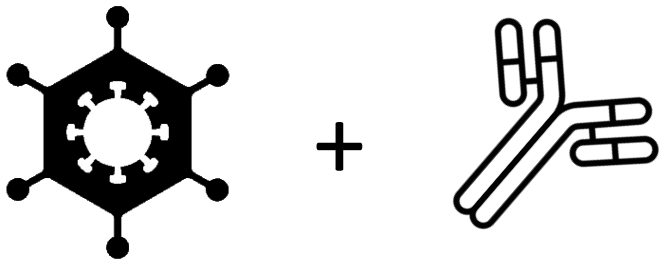
CRS symptoms
- Cardiac
- Pulmonary
- Hepatic
- Renal
- Gastrointestinal

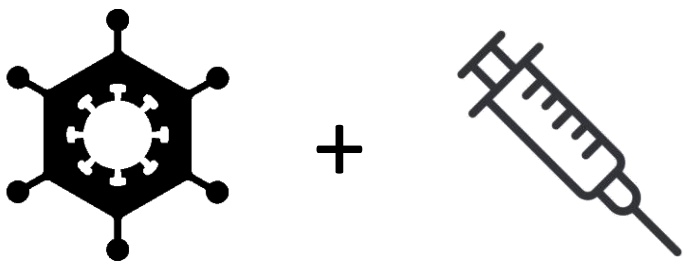
ICANS symptoms
- Confusion
- Slurred speech / aphasia
- Seizures
- Cerebral oedema
- Coma (!)

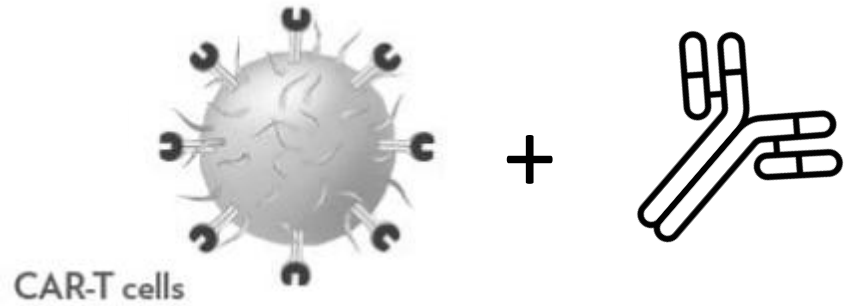
Morris, 2021

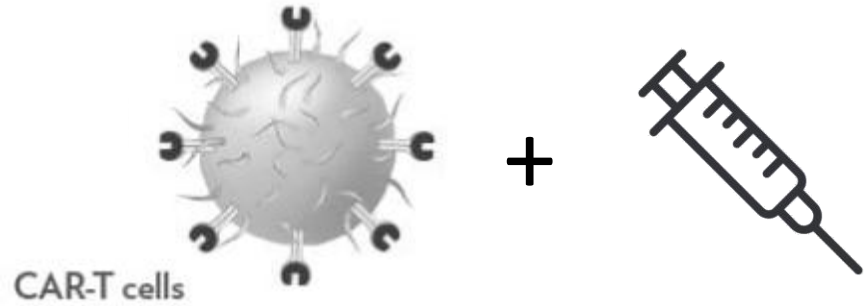
Future Directions



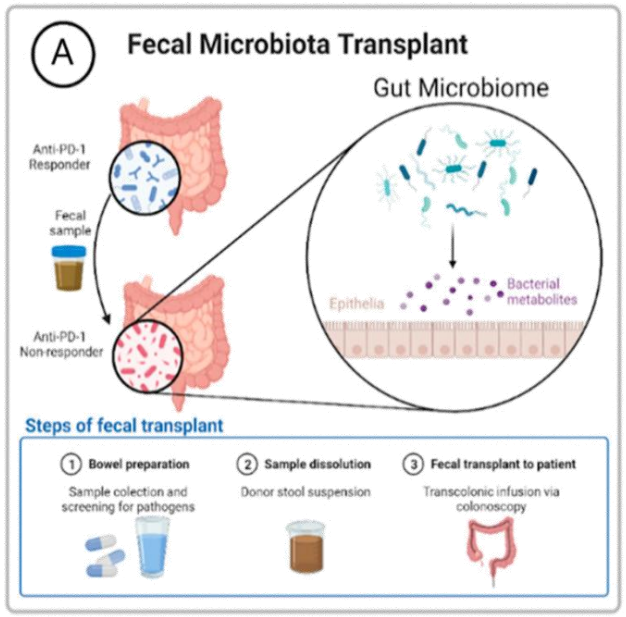


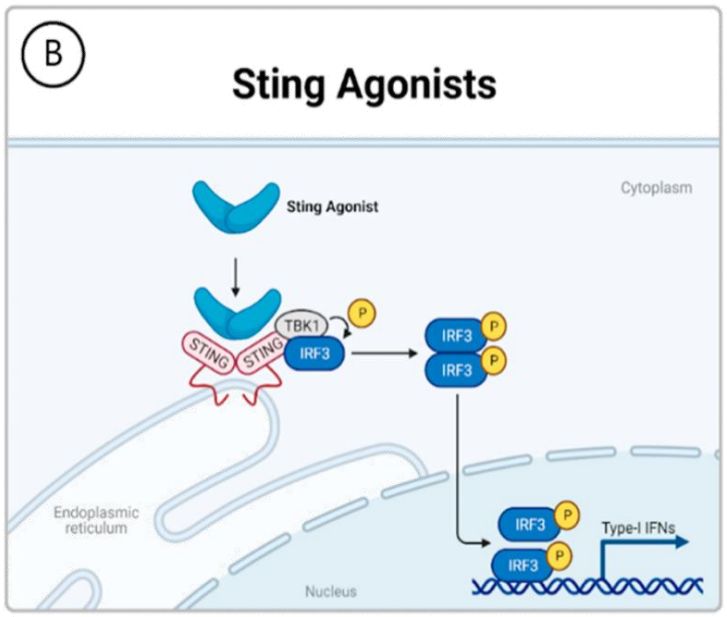


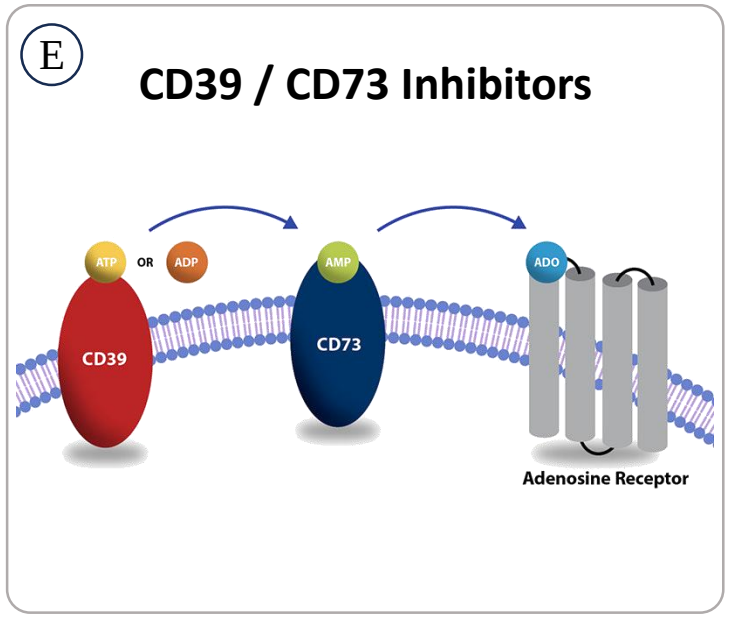

CAR-T cells

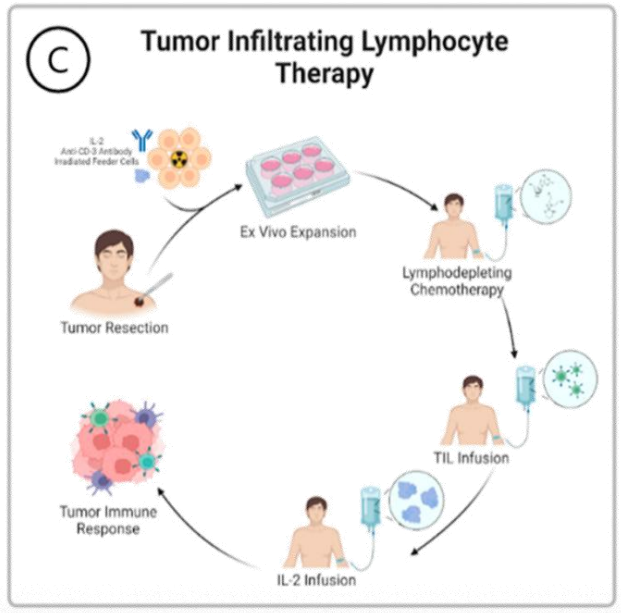

CAR-T cells

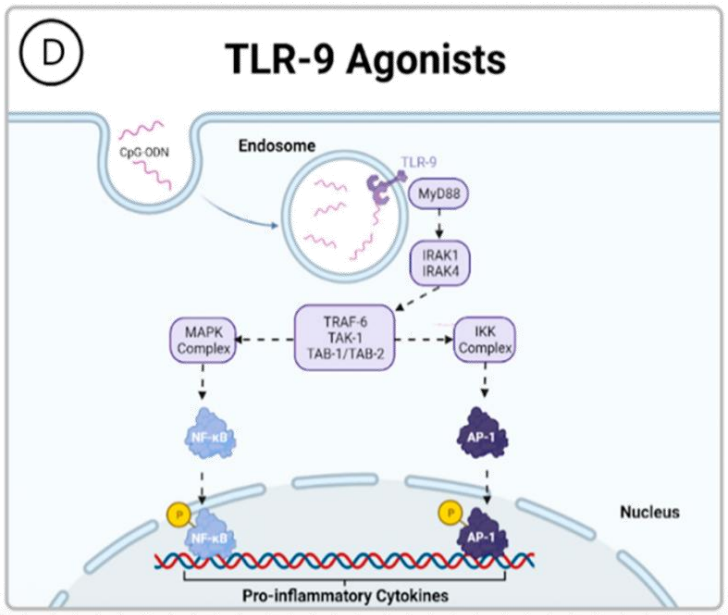
Novel immunotherapy approaches











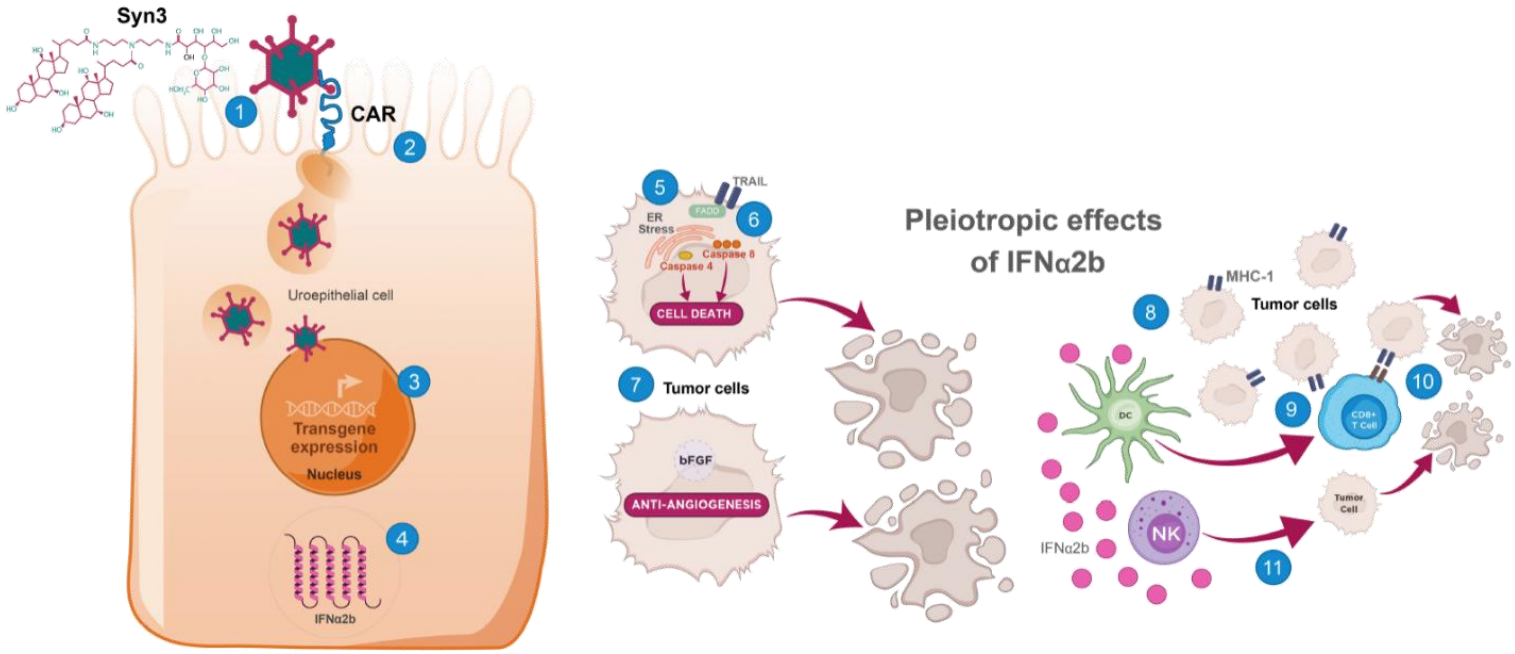
Sade-Feldman, 2018; Knight, 2023

THANK YOU

Oncolytic viruses

High-risk, BCG-unresponsive, non-muscle invasive bladder Ca: Nadofaragene firadenovec-vncg

(Vector: adenovirus)



Alternative:

Narayan, 2024

Oncolytic viruses

High-risk, BCG-unresponsive, non-muscle invasive bladder Ca: Nadofaragene firadenovec-vncg

(Vector: adenovirus)

Complete response and freedom from high-grade recurrence in the efficacy population

	Carcinoma in situ cohort (n=103)	High-grade Ta or T1 cohort (n=48)	All patients (n=151)
Patients with complete response at month 3 *	55 (53·4%; 43·3–63·3)	35 (72·9%; 58·2–84·7)	90 (59·6%; 51·3–67·5)
Duration of complete response † or high-grade recurrence-free survival ‡, months	9·69 (9·17-NE)	12·35 (6·67-NE)	7·31 (5·68–11·93)
Patients who were free from high-grade recurrence			
Month 6	42 (40·8%; 31·2–50·9)	30 (62·5%; 47·4–76·0)	72 (47·7%; 39·5–56·0)
Month 9	36 (35·0%; 25·8–45·0)	28 (58·3%; 43·2–72·4)	64 (42·4%; 34·4–50·7)
Month 12	25 (24·3%; 16·4–33·7)	21 (43·8%; 29·5–58·8)	46 (30·5%; 23·2–38·5)

Data are n (%; 95% CI) or median (95% CI). NE=not estimable.

* Patients with a complete response included all patients who had both a complete response reported by the study investigator.

† Patients in the carcinoma in situ cohort.

‡ Patients in the high-grade Ta or T1 cohort.

Boorjian, 2022