



Meld je aan met de **QR-code**



Practopics

Praktische topics voor de huisarts

Of klik op de link in de Q&A rechtsboven.





Practopics

Praktische topics voor de huisarts

Nieuwe en toekomstige oncologische behandelingen

Aandachtspunten, nevenwerkingen en management van toxiciteit

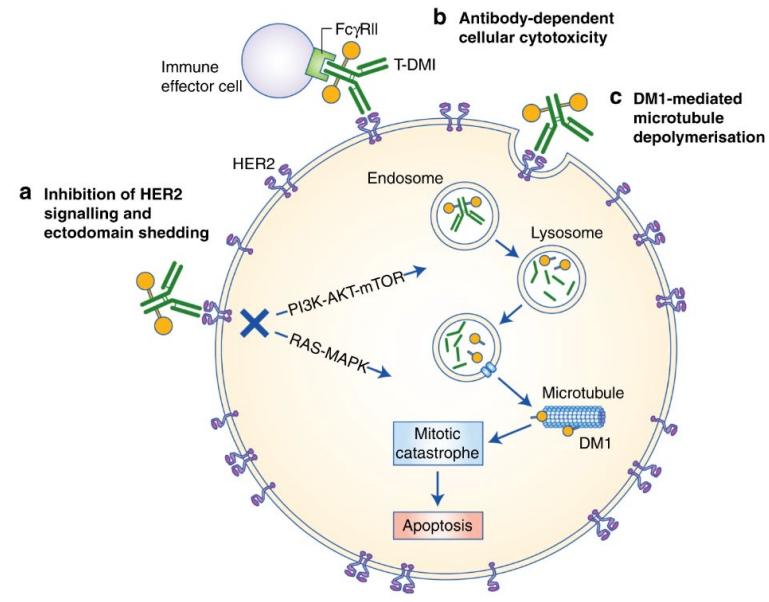
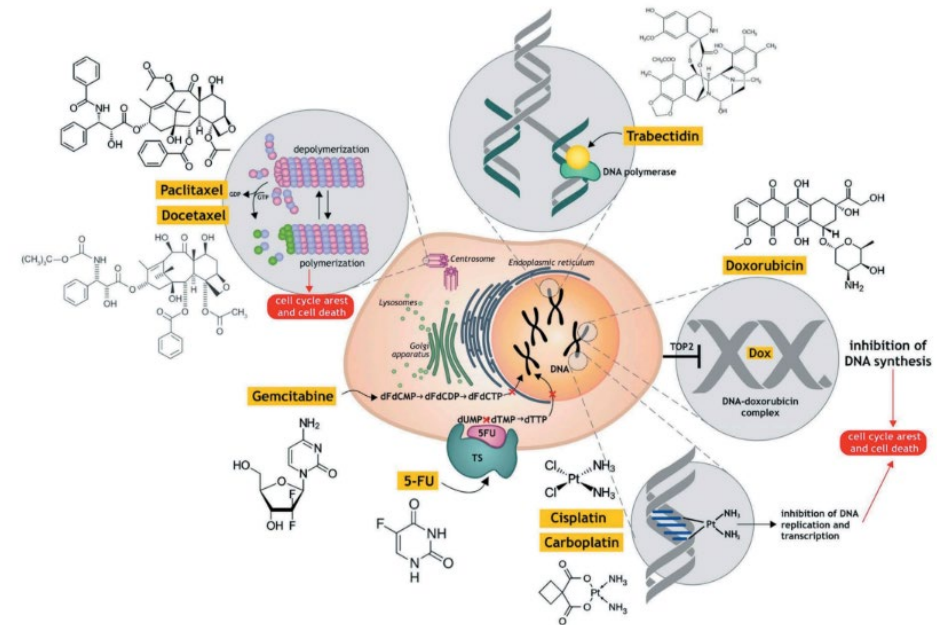
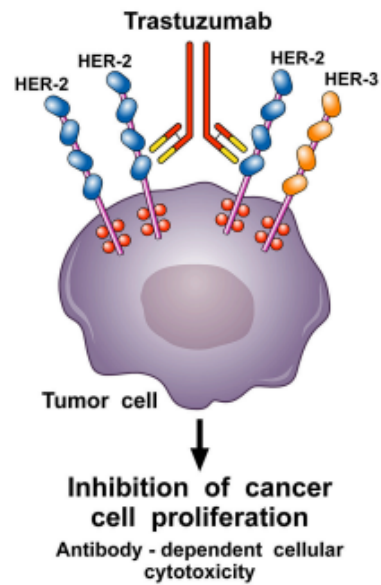
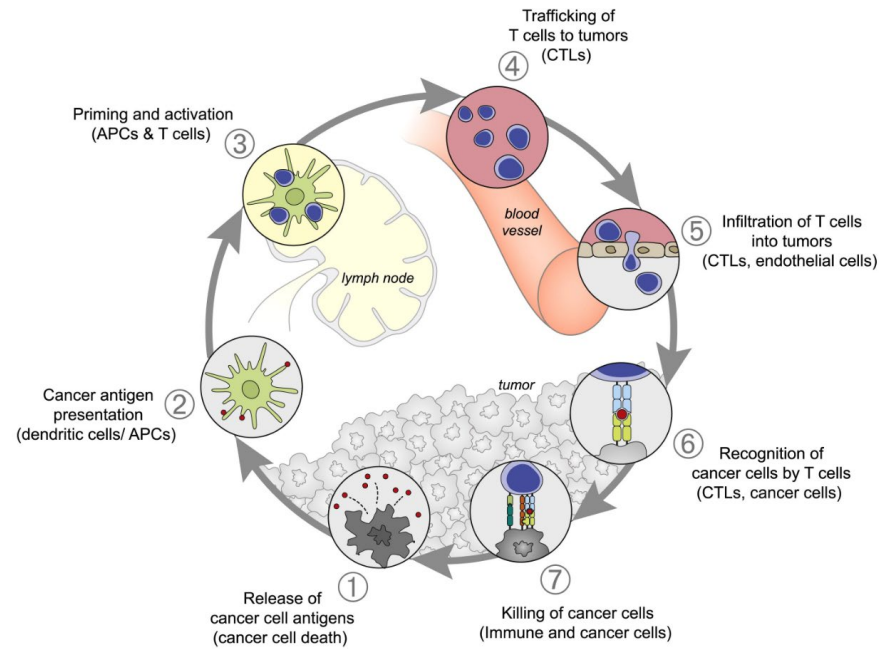


Tom Van den Mooter
Michiel Strijbos

Het huidige landschap

Klassieke arsenaal

- Cytotoxische chemotherapie (anti-mitotisch)
 - Doxorubicine, cisplatinum, methotrexaat, etc.
- Doelgerichte therapie
 - TKI: imatinib, axitinib, osimertinib, etc.
 - mAb: trastuzumab, bevacizumab, cetuximab, etc.
 - Anti-lichaamdrug conjugaat: T-DMI, T-DxD, EV, etc
- Immunotherapie (checkpoint inhibitie)
 - Anti-PD(L)-I: pembrolizumab, nivolumab, avelumab, etc
 - Anti-CTLA4: ipilimumab, tremelimumab
- Anti-hormonale therapie



Typische toxiciteiten

- Chemotherapie
 - Nausea, myelosuppressie, alopecia, polyneuropathie
- Doelgerichte therapie
 - Afh van doelwit: hypertensie, hypothyroïdie, diarree, huidtoxiciteit
 - CAVE: cardiale en pulmonale toxiciteit
- Checkpoint inhibitie
 - Auto-immuniteit (voornamelijk huidtoxiciteit en endocrinopathie, CAVE colitis, hepatitis en andere)
 - Frequenter/ernstiger in combinatie

BITOX



NEUROLOGIC

- Posterior Reversible Encephalopathy
- Neuropathy
- Guillian-Barre Syndrome
- Myelopathy
- Autoimmune Encephalitis
- Aseptic Meningitis
- Myasthenia gravis
- Transverse Myelitis
- Non-specific symptoms: headache, tremor, lethargy, memory disturbance, seizure

RESPIRATORY

- Cough/dyspnea
- Laryngitis
- Pneumonitis
- Bronchitis
- Pleuritis
- Sarcoid-like granulomatosis

RENAL



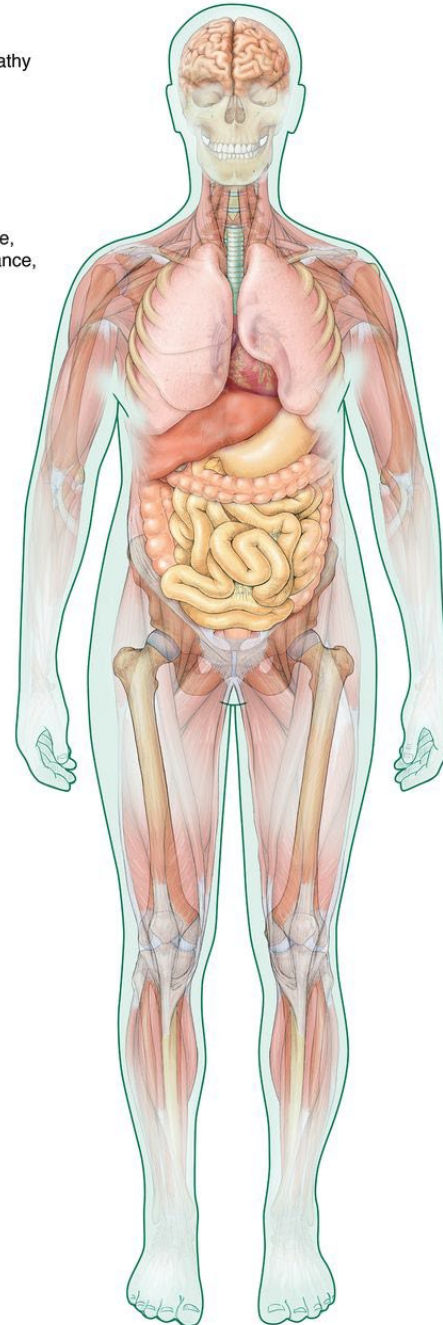
- Tubulointerstitial nephritis
- Acute renal failure
- Lupus nephritis
- Granulomatous lesions
- Thrombotic microangiopathy

HEMATOLOGIC

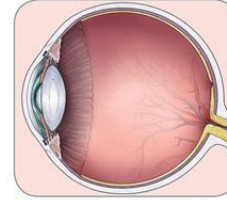
- Autoimmune hemolytic anemia
- Red cell aplasia
- Thrombocytopenia
- Leukopenia/Neutropenia
- Acquired hemophilia
- Myelodysplasia

DERMATOLOGIC

- Rash/Pruritis
- Mucositis
- Psoriasis
- Vitiligo
- Bullous pemphigoid
- Steven-Johnson syndrome
- DRESS syndrome



OCULAR



- Uveitis
- Conjunctivitis
- Scleritis, episcleritis
- Optic neuritis
- Blepharitis
- Retinitis
- Peripheral ulcerative keratitis
- Vogt-Koyanagi-Harada

CARDIOVASCULAR

- Myocarditis
- Pericarditis
- Pericardial effusion
- Arrhythmia
- Hypertension
- Congestive heart failure

ENDOCRINE

- Hyper or hypothyroidism
- Hypophysitis
- Adrenal insufficiency
- Diabetes

GASTROINTESTINAL

- Diarrhea
- Gastritis
- Colitis
- Ileitis
- Pancreatitis
- Hepatitis

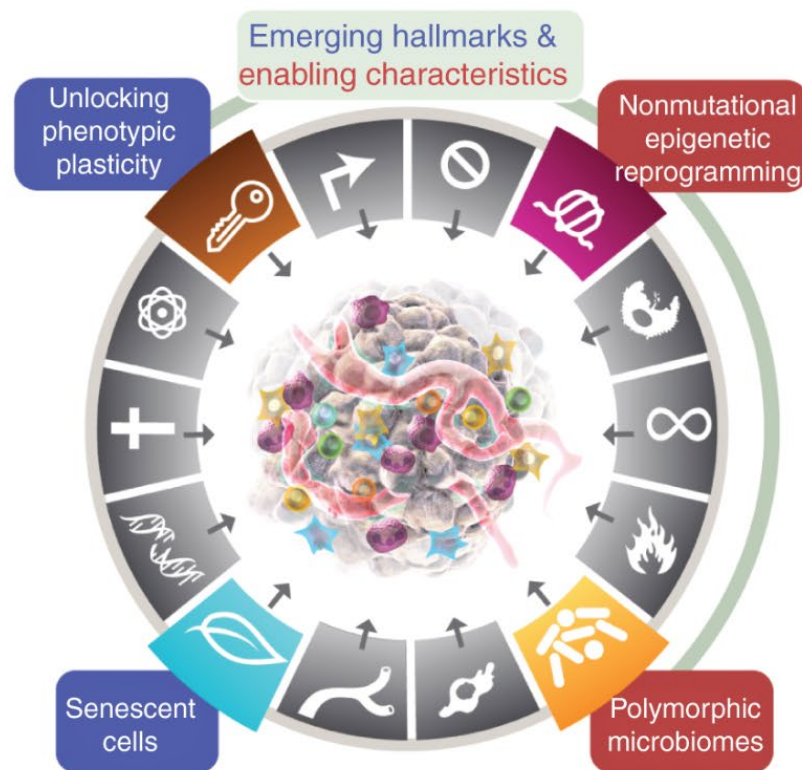
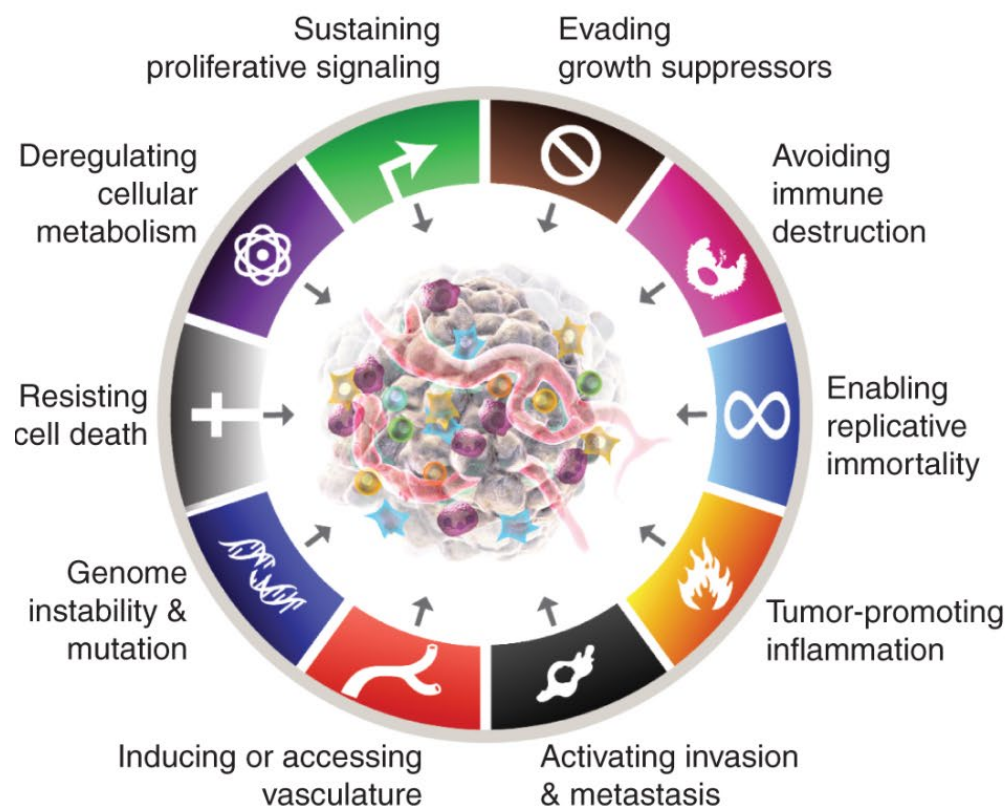
RHEUMATOLOGIC

- Arthralgias/Myalgias
- Inflammatory Polyarthritis
- PMR-like
- Psoriatic Arthritis
- Oligoarthritis
- Vasculitis
- Sicca Syndrome
- Sarcoidosis
- Inflammatory myositis
- Resorptive bone lesions and fractures

Nood aan nieuwe middelen

- Onvoldoende effectiviteit therapie
 - Genetische diversiteit ziekte
 - Verworven/intrinsieke resistent
- Excessieve toxiciteit bestaande therapie
 - Vaak idiosyncrasie
- One size does not fit all
 - Zelfde ziekte, wisselende effectiviteit

Nood aan nieuwe middelen



Hanahan D., Cancer Discovery 2022

Wat brengt de toekomst?

Gemiddeld is er nood aan 14 jaar
ontwikkeling alvorens beschikbaar¹

Klinische Studies

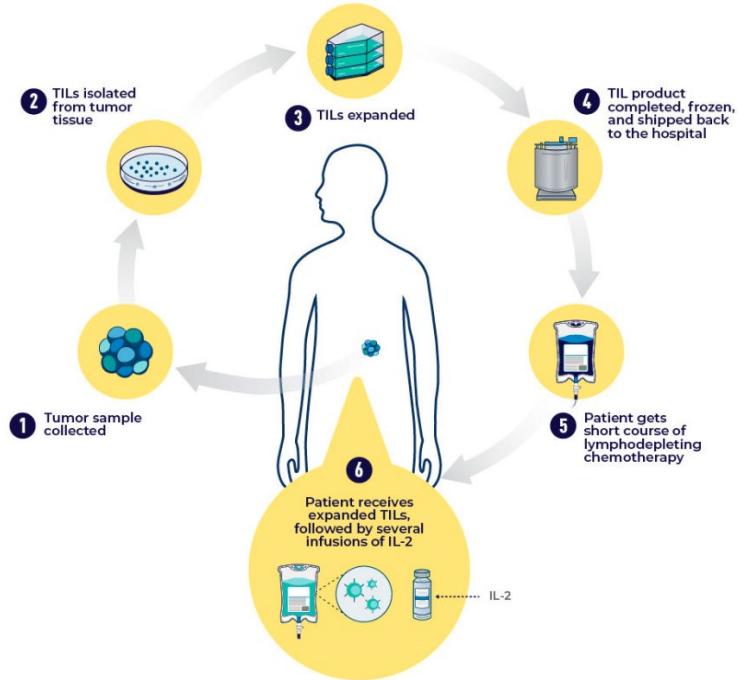
- **Fase 1**
 - Zoeken naar MTD, PK/PD, veiligheid, kleine groep patiënten, geen placebo, geen selectie
 - FIH
 - Nieuwe combinaties
 - Interactiestudies
- **Fase 2**
 - Grotere groep, iedereen behandeling, geen placebo, meer kans om zeldzamere nevenwerkingen te zien.
- **Fase 3**
 - Gecontroleerde studie, vaak gerandomiseerd en dubbel blind (RCT)

Nieuwe Therapeutische Opties

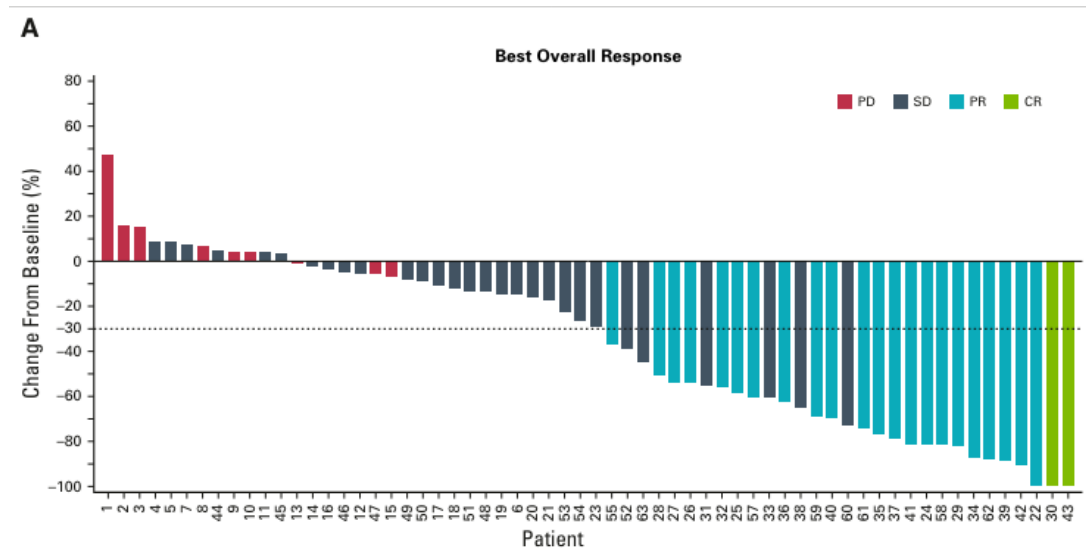
- Cellulaire therapieën of adoptieve cel therapie
 - Tumor-infiltrating lymphocyte (TIL) therapie
 - Chimerisch antigen receptor (CAR) T cel therapie (CAR-T)
 - Engineerd T Cell receptor (TCR) therapie
 - Natural killer (NK) cel therapie
- Cancervaccins
- Radionuclides
- BiSpecific T-cell Engager (BiTe)
- CRISPR-technieken
- Verdere uitbreiding van klassieke antikankerebehandelingen

TIL

TUMOR-INFILTRATING LYMPHOCYTE (TIL) THERAPY



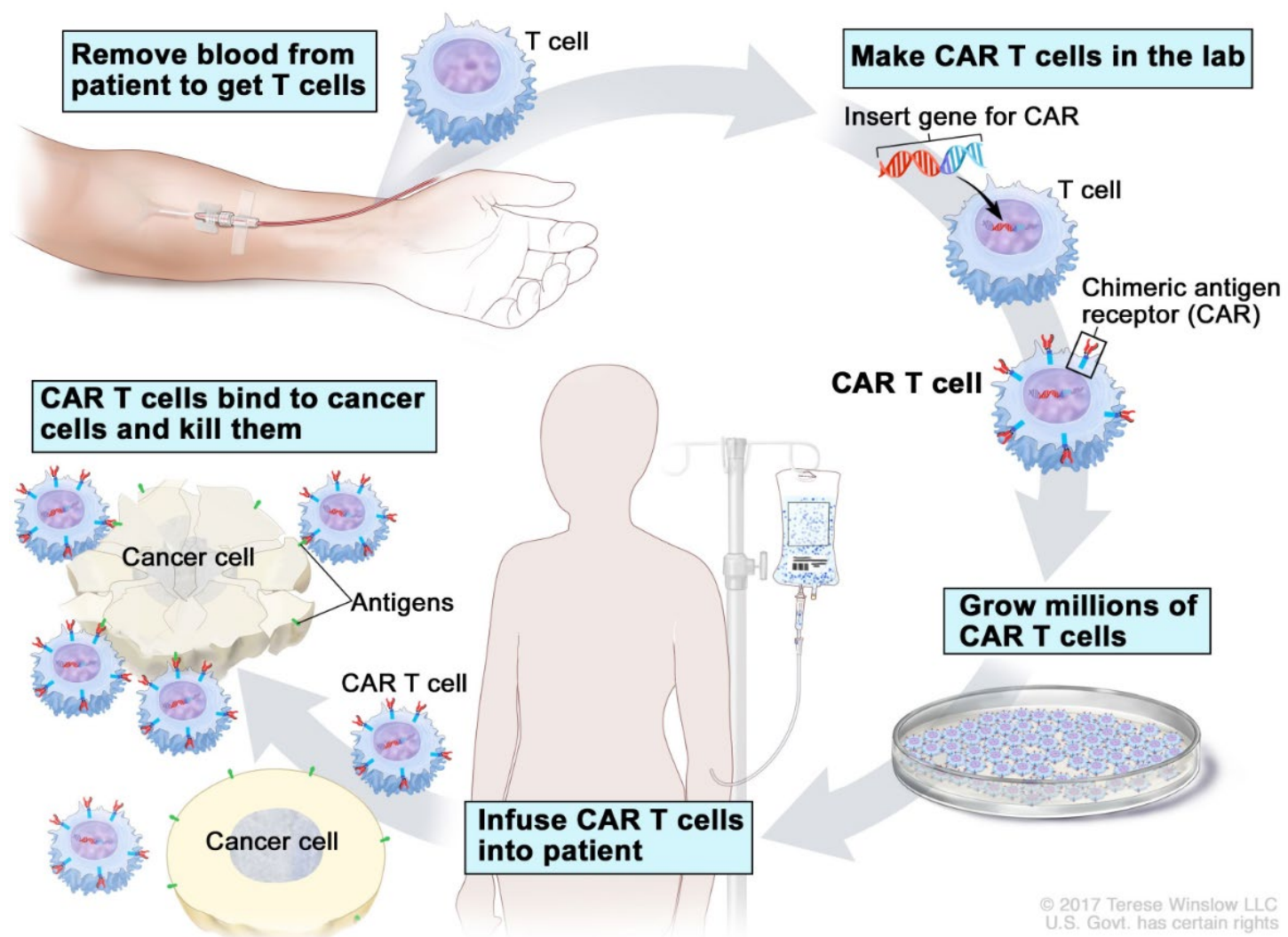
02/2024: Lifileucel: FDA-goedkeuring in de behandeling van gevorderde melanomen met progressieve ziekte na voorgaande behandelingen.



[Amod A. Sarnaik et al. JCO 39, 2656-2666\(2021\).](#)

CAR-T

CAR T-cell Therapy



Onderzoek naar CAR-NK
lopende

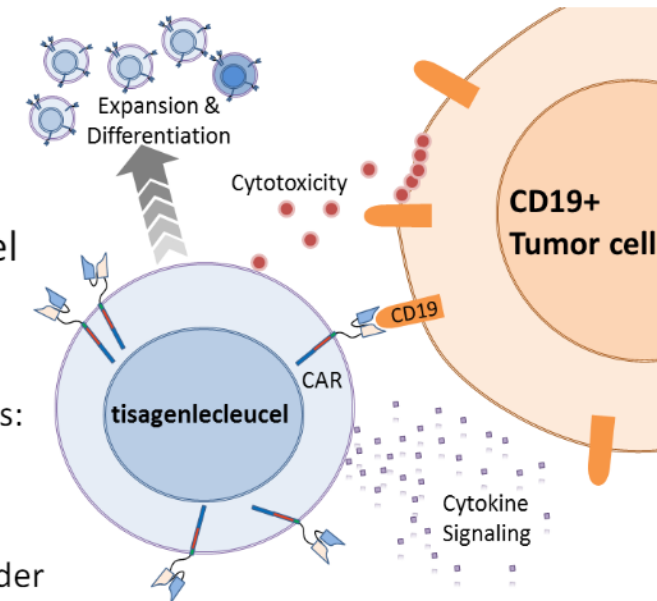
Indicatie: acute B-cel leukemie

- 2017: FDA-goedkeuring voor tisagenlecleucel autologe anti-CD19 chimeric antigen receptor (CAR) T-cell therapy

Mechanism of action



- CAR scFv binds to CD19 on B cell tumors
 - Not restricted by HLA
- Binding of CAR to CD19 activates tisagenlecleucel
 - Promotes cell expansion and differentiation
 - Triggers effector functions:
 - Lysis of CD19⁺ cells
 - Cytokine signaling
 - Stimulation of bystander immune cells



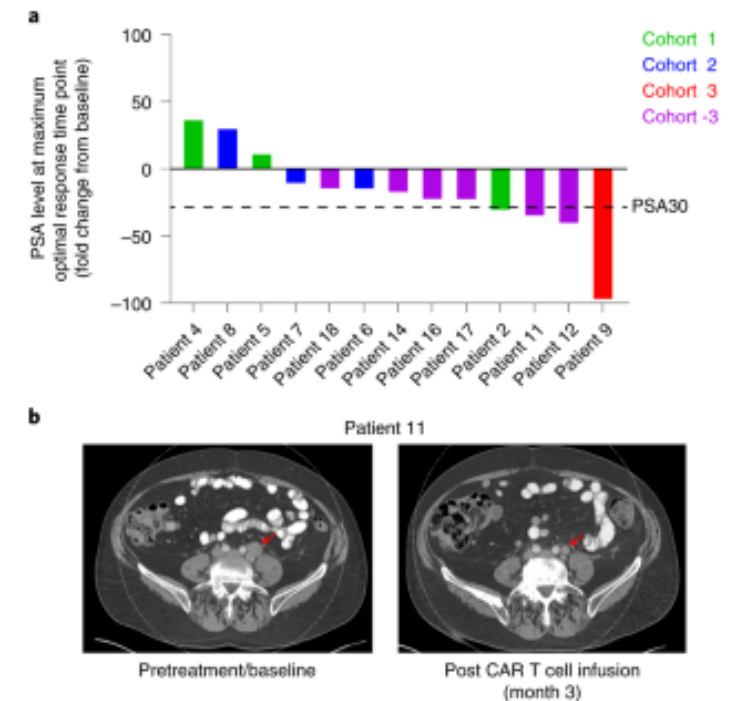
www.fda.gov

5

CAR-T: toekomst in soliede tumoren?

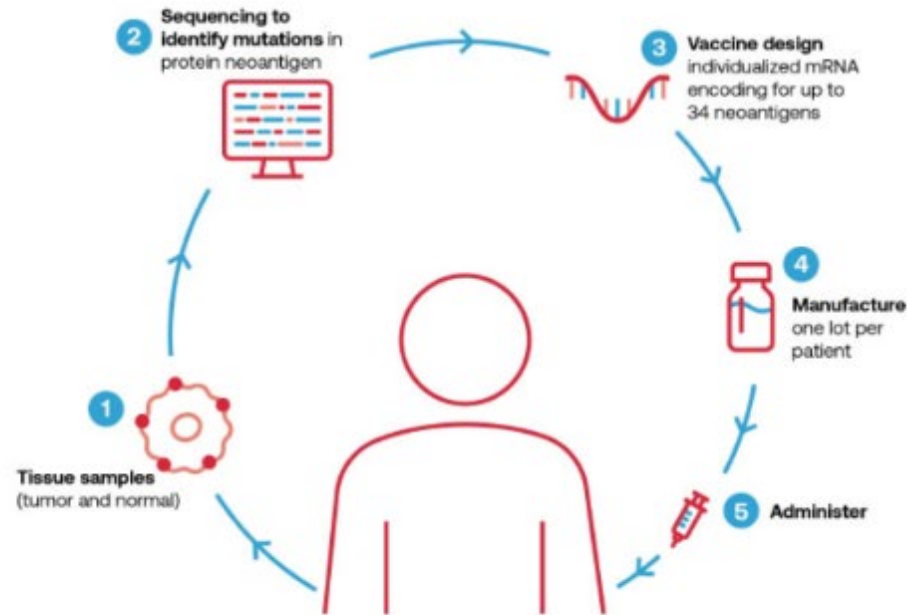
- Beperkingen:
 - beperkte tumorale celproliferatie
 - tumorale infiltratie
 - tumoromgeving
- Eerste resultaten komende (voorlopig nog fase I)

Fig. 3: Pathological and radiologic evaluations following CART-PSMA-TGF β RDN cell infusion.



Kankervaccin

mRNA-4157/V940: Designed to target an individual patient's unique tumor mutations



Advantages of mRNA-based Cancer Therapies

Speed and efficiency

Needle-to-needle generation of personalized treatments can be produced in just a few weeks.

Integrated Manufacturing

Opportunities to scale and optimize within Moderna's existing Massachusetts manufacturing facility

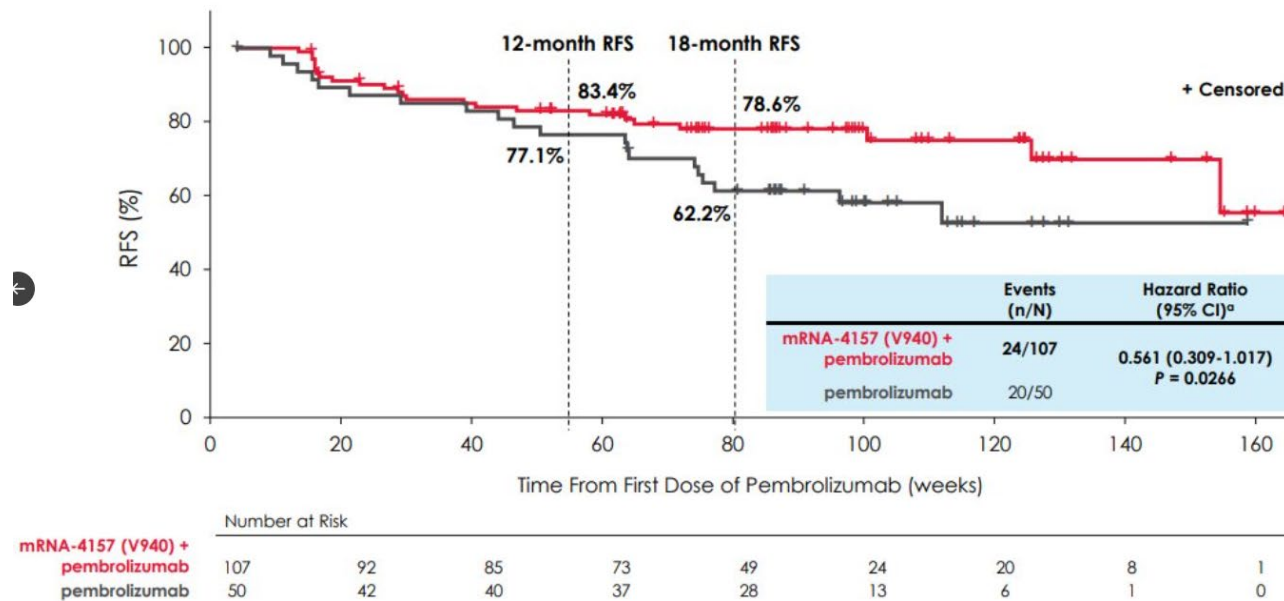
Customizable

Identify and encode multiple patient-specific neoantigens to design an individualized treatment

moderna

Klinische Resultaten - Melanoom

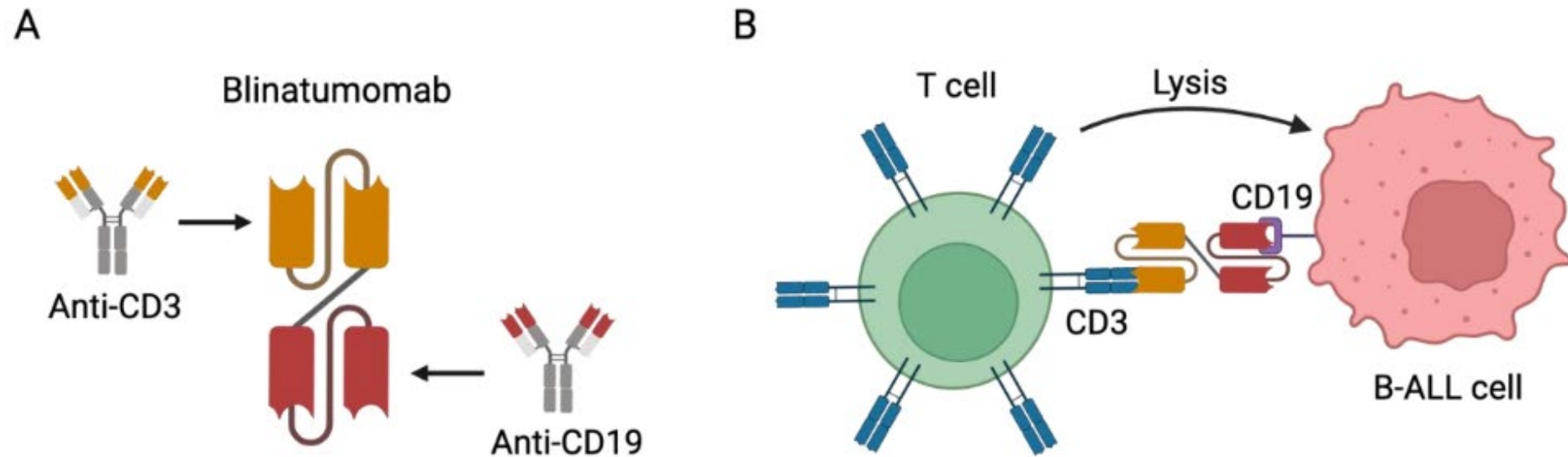
mRNA-4157 (V940) and pembrolizumab demonstrated an improvement in recurrence-free survival (RFS) vs pembrolizumab



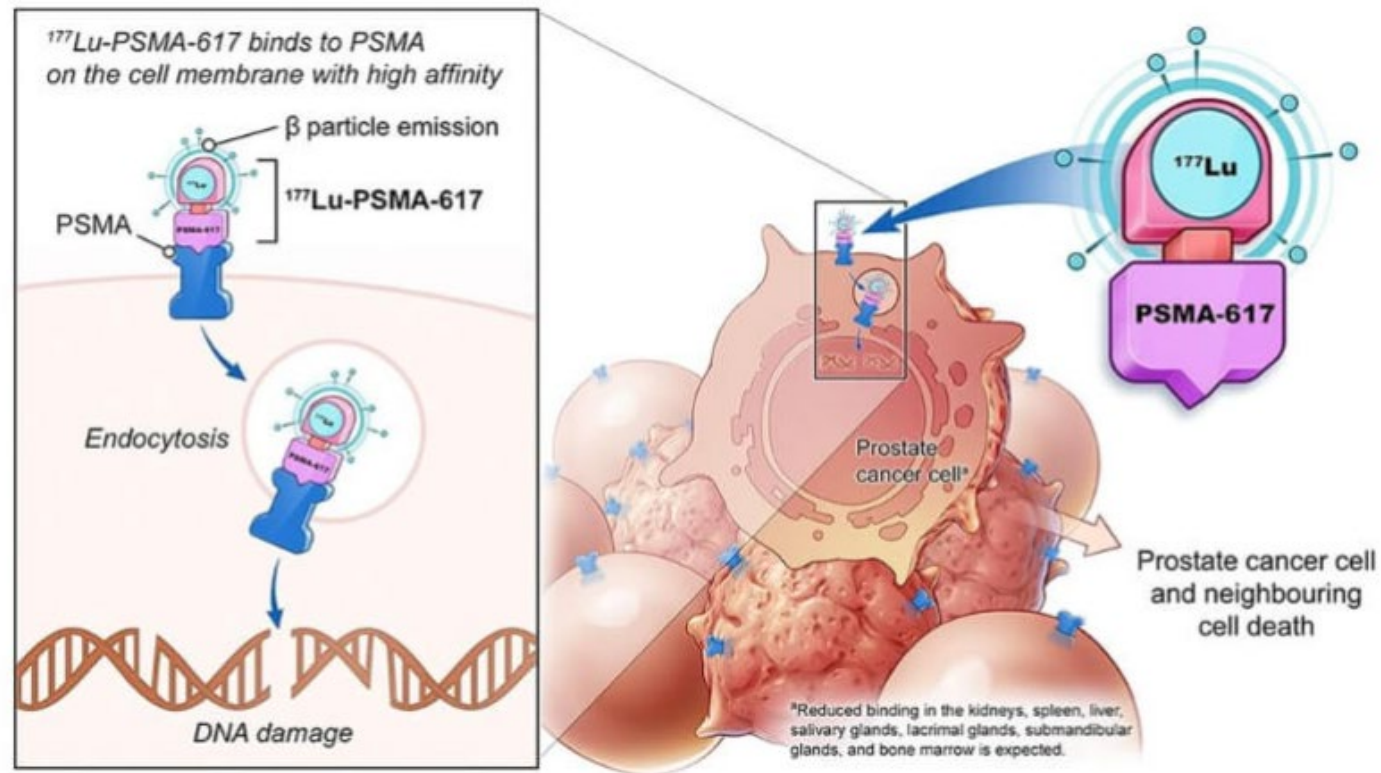
CI, confidence interval; mRNA, messenger RNA; RFS, recurrence-free survival.

^aThe hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The P value is based on a 1-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization.

Bispecific T-cell Engagers (BiTe)



Radionuclides



Bijzonder toxiciteiten

- CRS:
 - Suprafysiologische respons op immuuntherapie met activering/betrokkenheid van endogene of geïnfundeerde immuuneffectorcellen
- ICANS
 - Toxische encephalopathie met woordvindingsmoeilijkheden, confusie, dysfasie, afasie, somnolentie en fijne motoriekstoornissen

CRS



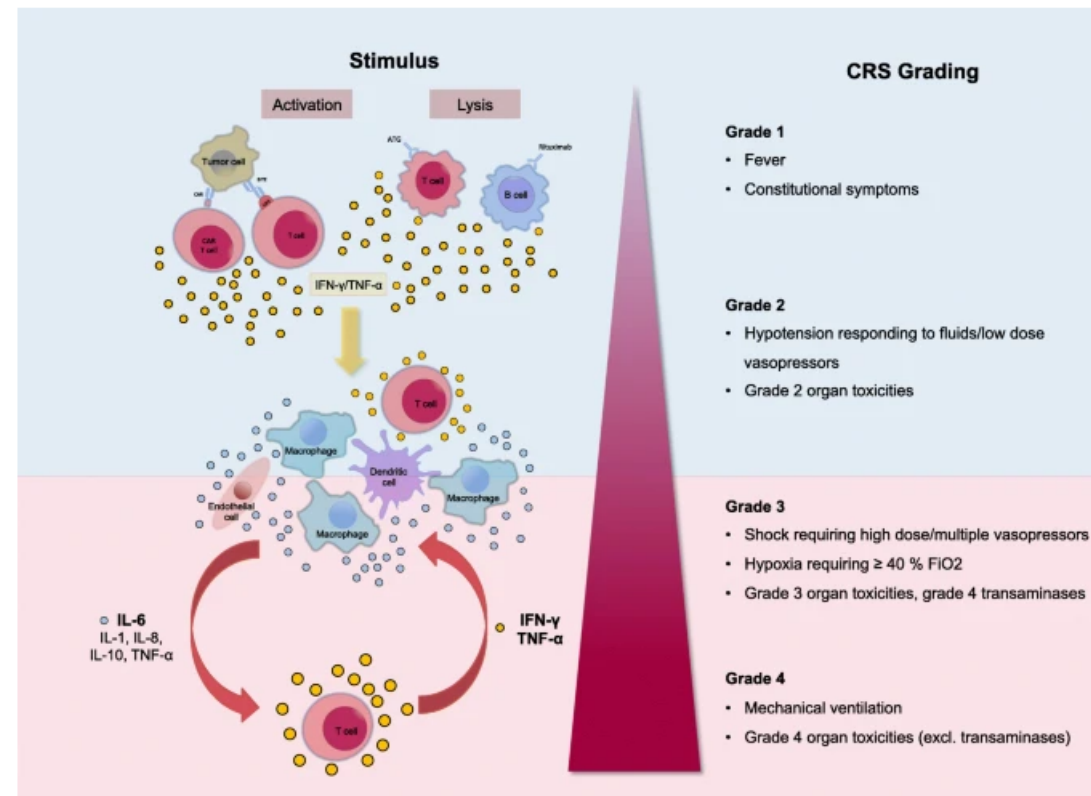
Beschrijving: syndroom met koorts en milde griepachtige klachten reikende tot levensbedreigende problematiek.



Start: tijdens infusie immuuntherapie tot meerdere uren en/of dagen nadien



Symptomen: rillingen, hoofdpijn, duizeligheid, verwardheid, vermoeidheid, nausea en braken, diarree, hoest, spier- en gewrichtspijnen, huiduitslag en in meer ernstige gevallen hypotensie, dyspnee, oedeem en desaturatie.



Proposed pathomechanism of CRS. Activation of mainly T cells or lysis of immune cells induces a release of interferon gamma (IFN- γ) or tumor necrosis factor alpha (TNF- α). This leads to the activation of macrophages, dendritic cells, other immune cells and endothelial cells. These cells further release proinflammatory cytokines. Importantly, macrophages and endothelial cells produce large amounts of interleukin 6 (IL-6) which in a positive feedback loop manner activates T cells and other immune cells leading to a cytokine storm. Abbreviations: CAR: chimeric antigen receptor; FiO_2 : fraction of inspired oxygen; IL-6: interleukin 6; IFN- γ : interferon gamma; TNF- α : tumor necrosis factor alpha

CRS

DD

- Allergische reactie
- Reactie op infusie
- Infectieuze complicaties: pneumonie, sepsis
- Hemofagocytair syndroom
- Macropaagactivatiesyndroom

Behandeling: ifv gradatie

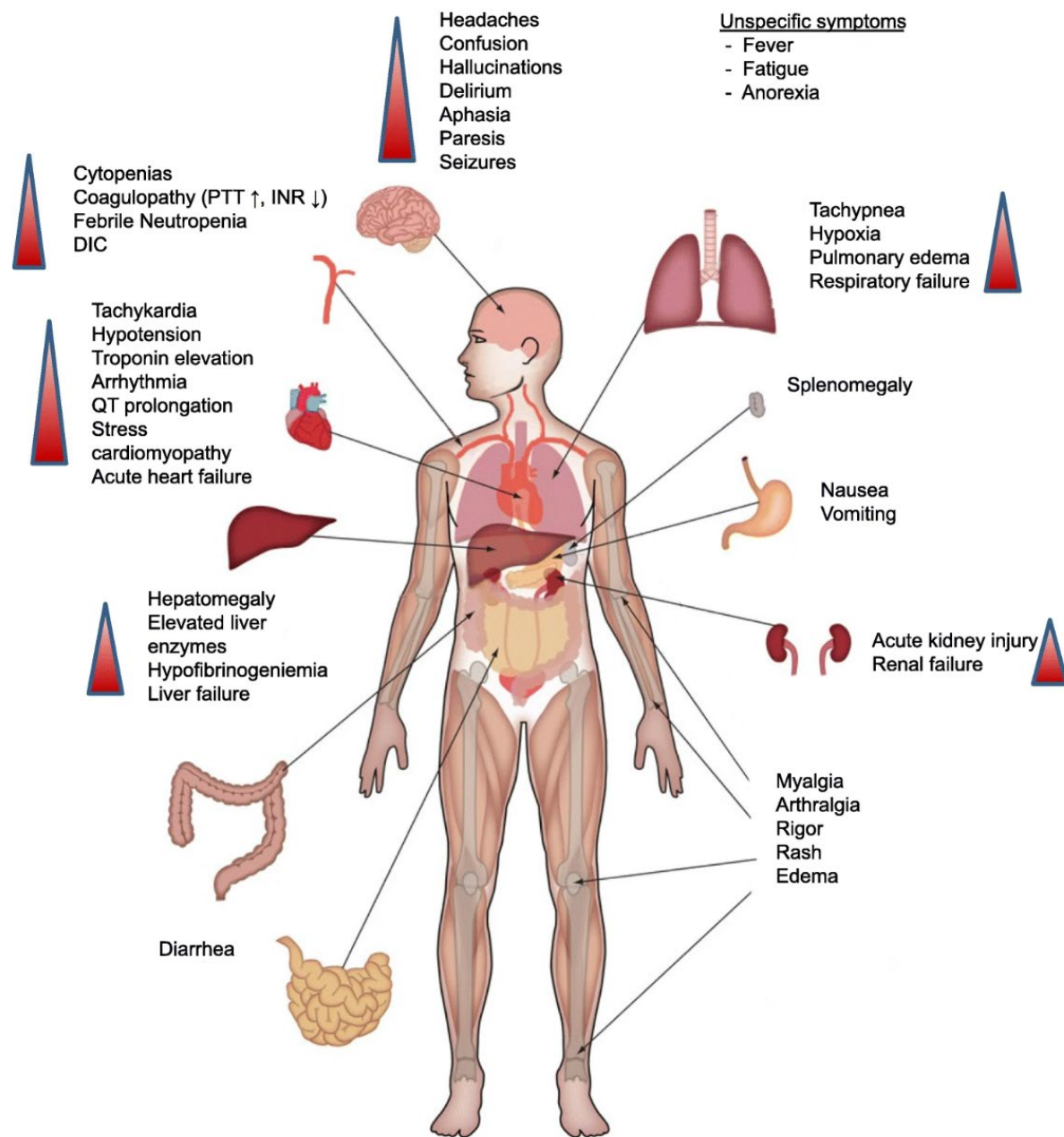
- Supportieve zorgen: hydratatie, antihistaminica, antipyretica, zuurstoftherapie, analgesie, uitzonderlijk opname intensieve zorgen
- Corticoiden: al dan niet hoge dosis
- In extreme gevallen anti-IL6 therapie

Table. ASTCT Consensus Grading for Cytokine Release Syndrome

Clinical Parameter	Grade 1	Grade 2 ^a	Grade 3 ^a	Grade 4 ^a
Fever	≥38 C	≥38 C	≥38 C	≥38 C
Hypotension	None	No vasopressors	Vasopressor 3 vasopressin	Requires multiple vasopressors (not vasopressin)
Hypoxia	None	Low-flow nasal cannula or blow-by	High-flow nasal cannula, face mask, non-rebreather, Venturi mask	CPAP, BiPAP, mechanical ventilation

^a In grades 2 to 4, inclusion is fever plus hypotension and/or hypoxia.

ASTCT, American Society for Blood and Marrow Transplantation; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure
Adapted from reference 12.



ICANS

DD
Intracraniële metastasen
Epilepsie
Cerebrovasculair accident
Infectie/Sepsis
Iatrogeen: Supportieve medicatie
(morfine-derivaten of pijnmedicatie)

Klinisch beeld encefalopathie met beeld van wakkere, afatische patiënt zonder verbale of fysieke respons. Andere symptomen: delier, lethargie, concentratiestoornissen, agitatie, tremor, epileptisch insult, cerebraal oedeem (zeldzaam), hoofdpijn (aspecifiek)

ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness [†]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings [‡]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging [§]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[†] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

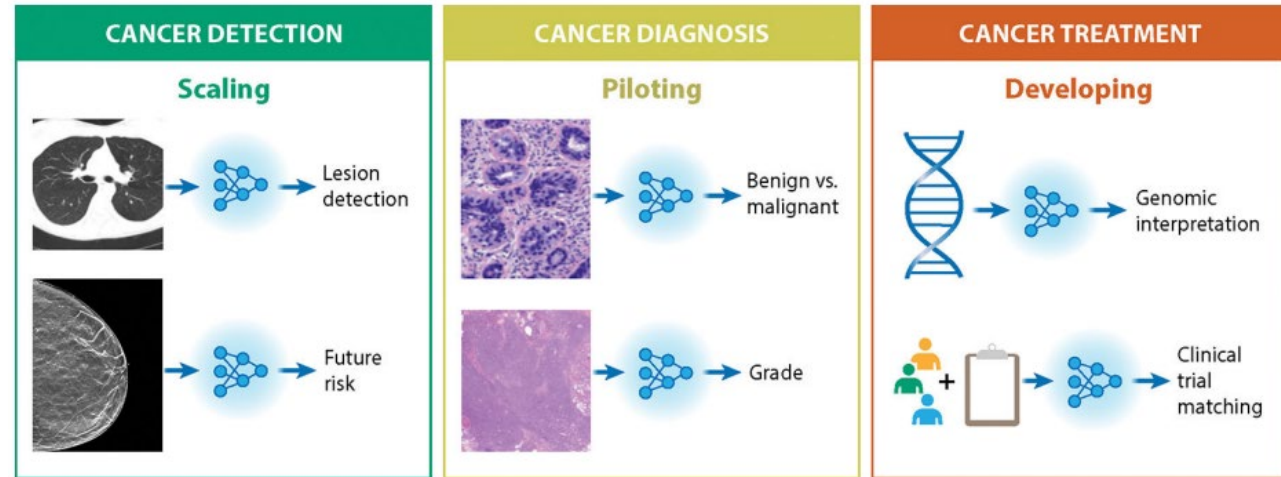
[‡] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[§] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

AI in de oncologie

AI

- Shifts naar AI
 - Deep learning
 - Gebruik van elektronische dossiers

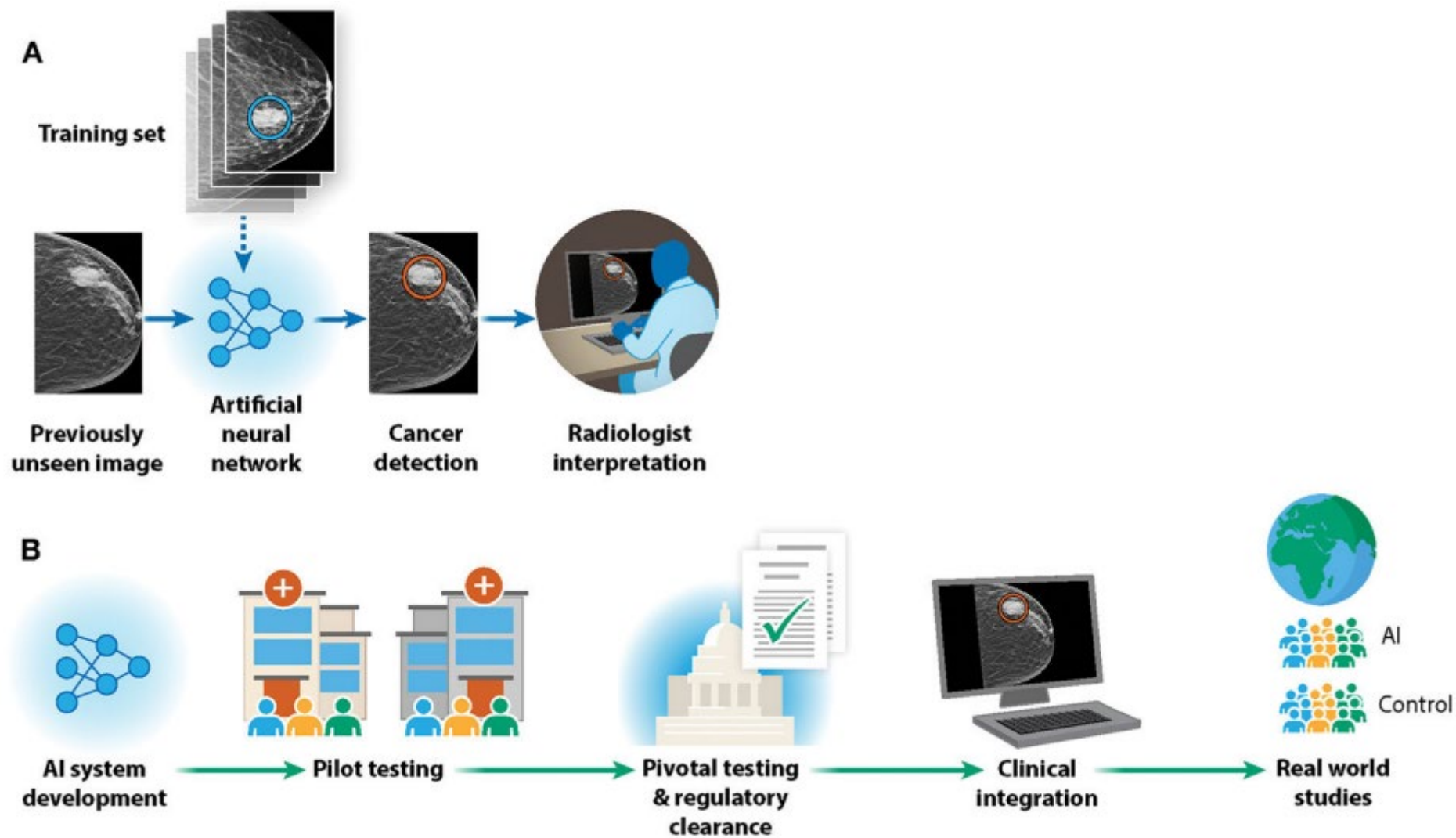


Lotter et al, 2024

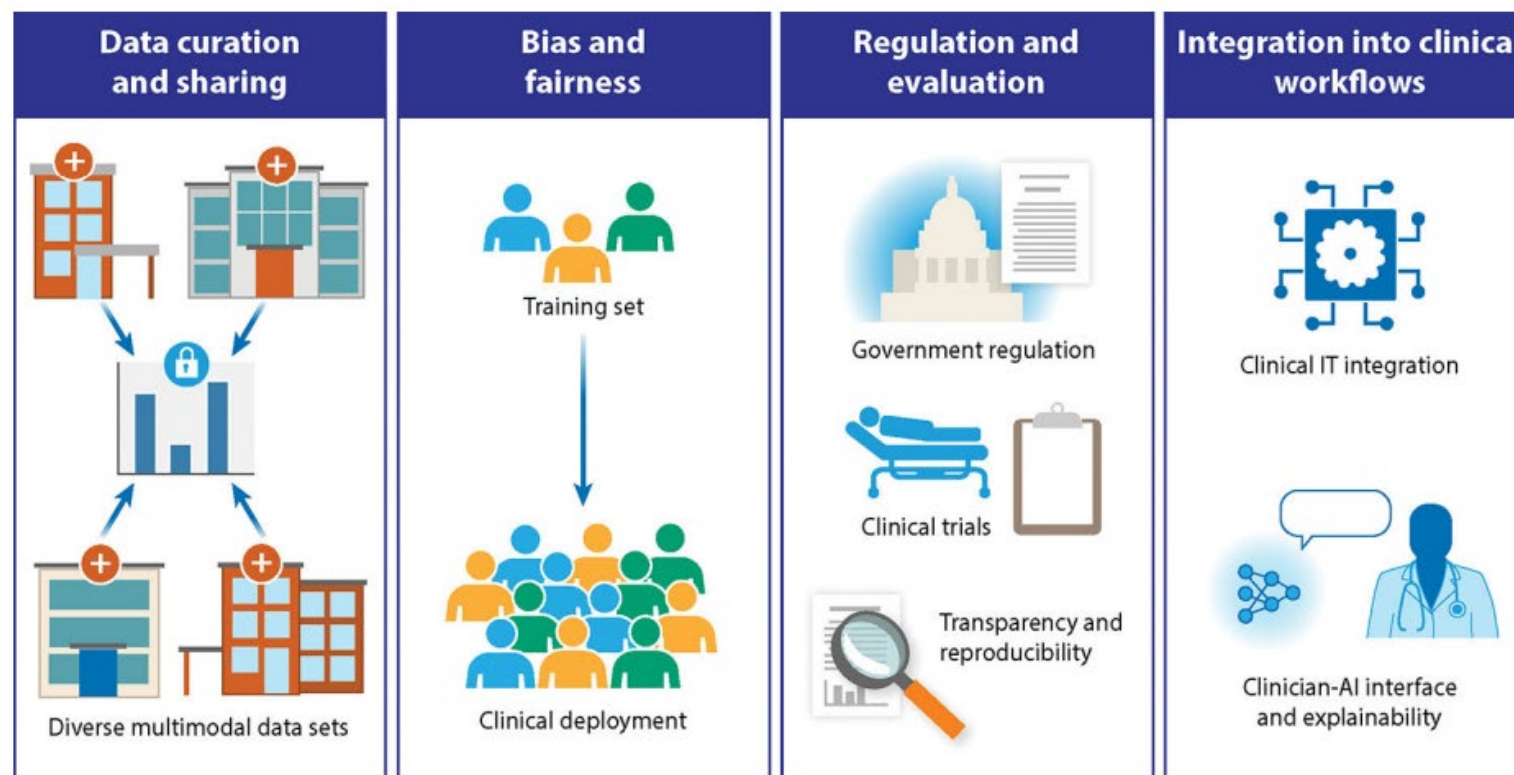
- Huidig gebruik in oncologie:
 - Analyse beeldvorming
 - Analyse pathologisch staal
 - Hulp bij keuze behandeling
 - Drug discovery targets
 - Drug-drug interacties

Chemistry Nobel goes to developers of AlphaFold AI that predicts protein structures

This year's prize celebrates computational tools that have transformed biology and have the potential to revolutionize drug discovery.



Moeilijkheden

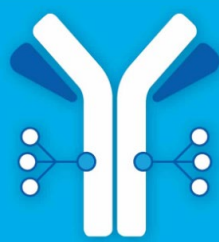


Wat brengt de toekomst

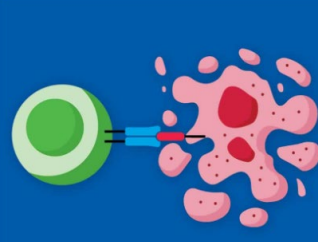
Vraag aan 5 experts in kankeronderzoek naar toekomstige evoluties in kankergeneeskunde



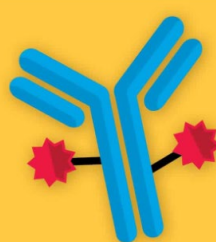
ctDNA Applications to Guide Dose Optimization, Clinical Trial Decisions



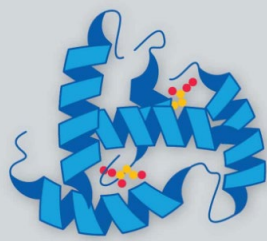
Antibody-drug Conjugates and Newer Classes of Therapeutics



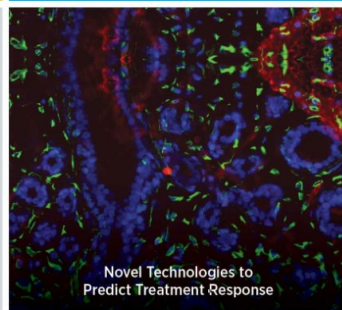
Expanding Cancer Vaccines to More Cancer Types



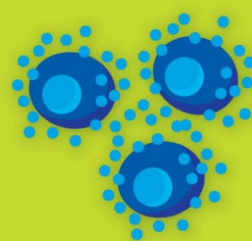
Novel Targets for Antibody-drug Conjugates



Next-generation Molecules for "Undruggable" Targets



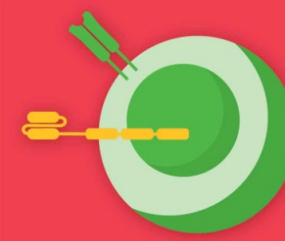
Novel Technologies to Predict Treatment Response



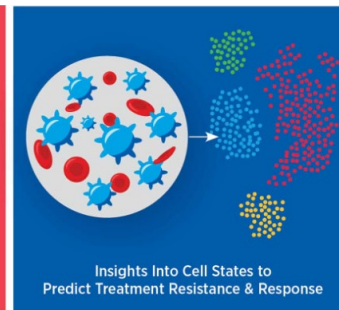
Expanding Cellular Therapies to More Cancer Types



Developing Off-the-shelf Cancer Vaccines and Cellular Therapies



Advances in Logic-gated and Allogeneic CAR T Therapies



Insights Into Cell States to Predict Treatment Resistance & Response



Structural and Social Drivers of Health



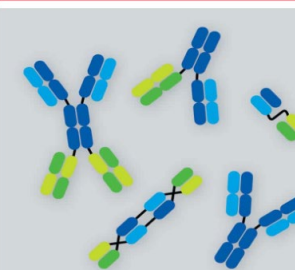
Multidisciplinary Team Science



Advances in Predicting Future Risk of Cancer



Multimodal Analysis of Data



Bispecific Antibodies



Early Detection Through cfDNA Methylation-Based Methods



Understudied Environmental Exposures



Increased Focus on Understudied Distinct Populations



Molecular Modeling for Rapid Drug Development



Predicting Optimal Treatments for Patients

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Practopics

Praktische topics voor de huisarts

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