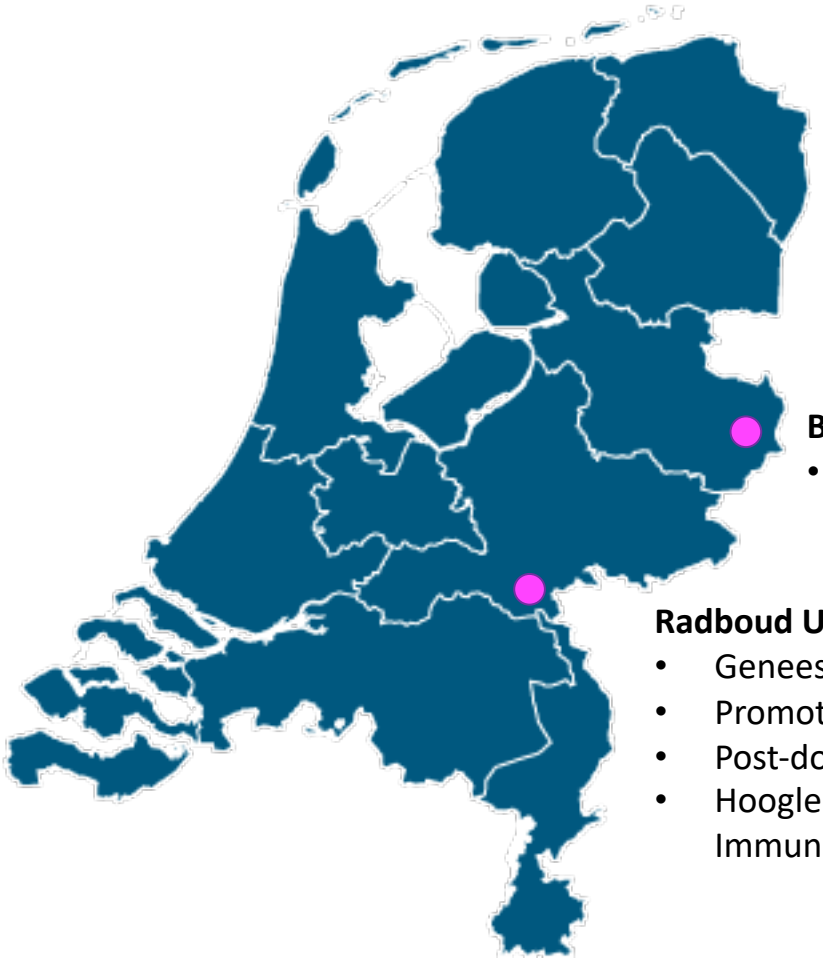
What you see is what you treat

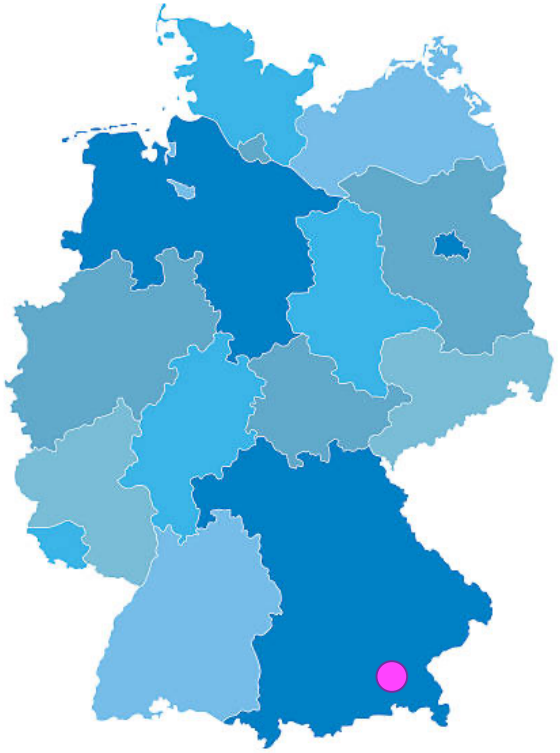
Sandra Heskamp
Afdeling Beeldvorming – Nucleaire Geneeskunde
Radboudumc, Nijmegen

Radboudumc

About me…



Nucleaire Geneeskunde



Bonhoeffer college, Enschede

- Atheneum (2003)

Radboud Universiteit/Radboudumc, Nijmegen

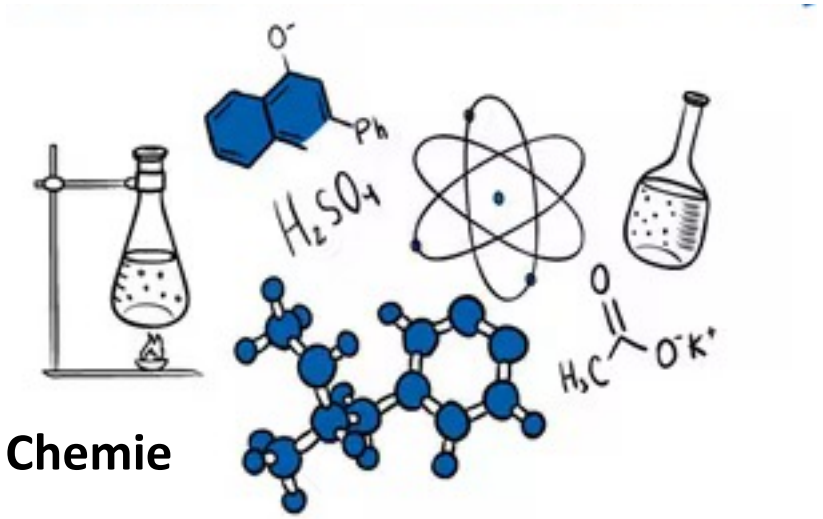
- Geneeskunde&Biomedische Wetenschappen (2009)
- Promotie onderzoek (2014)
- Post-doc/tenure track/universitair docent (2021)
- Hoogleraar ”Nucleaire Beeldvorming en Therapie in de Immuno-Oncologie (2021 – heden)

Technische Universiteit München

- Post-doc (2014)

Nucleaire Geneeskunde

Technologie



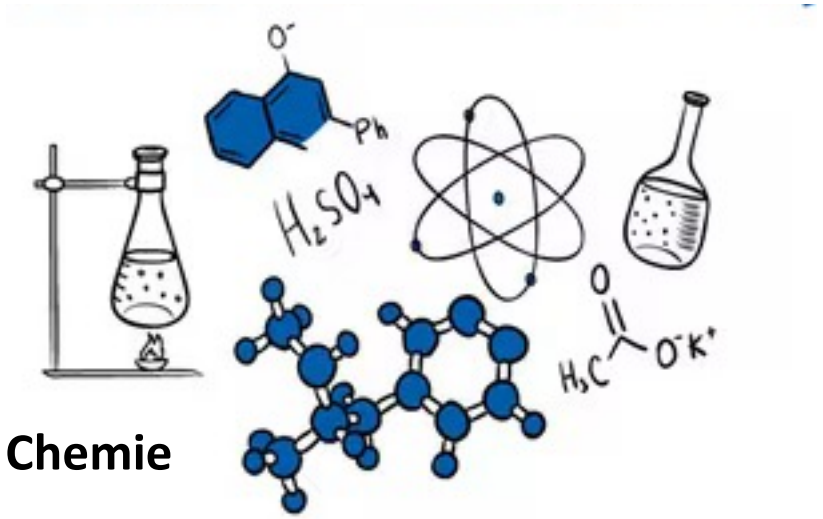
Chemie

Nucleaire Geneeskunde

Biologie

Nucleaire Geneeskunde

Technologie



Chemie

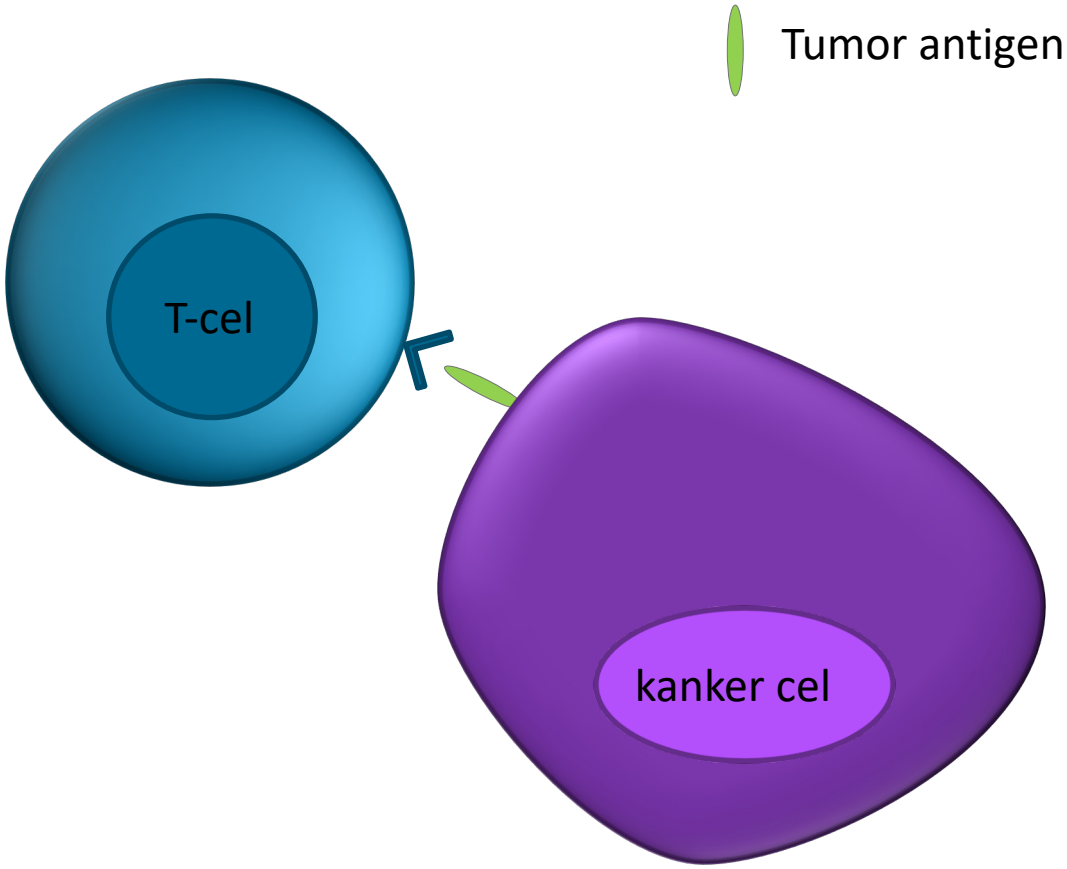
Nucleaire Geneeskunde

Immuno-oncologie

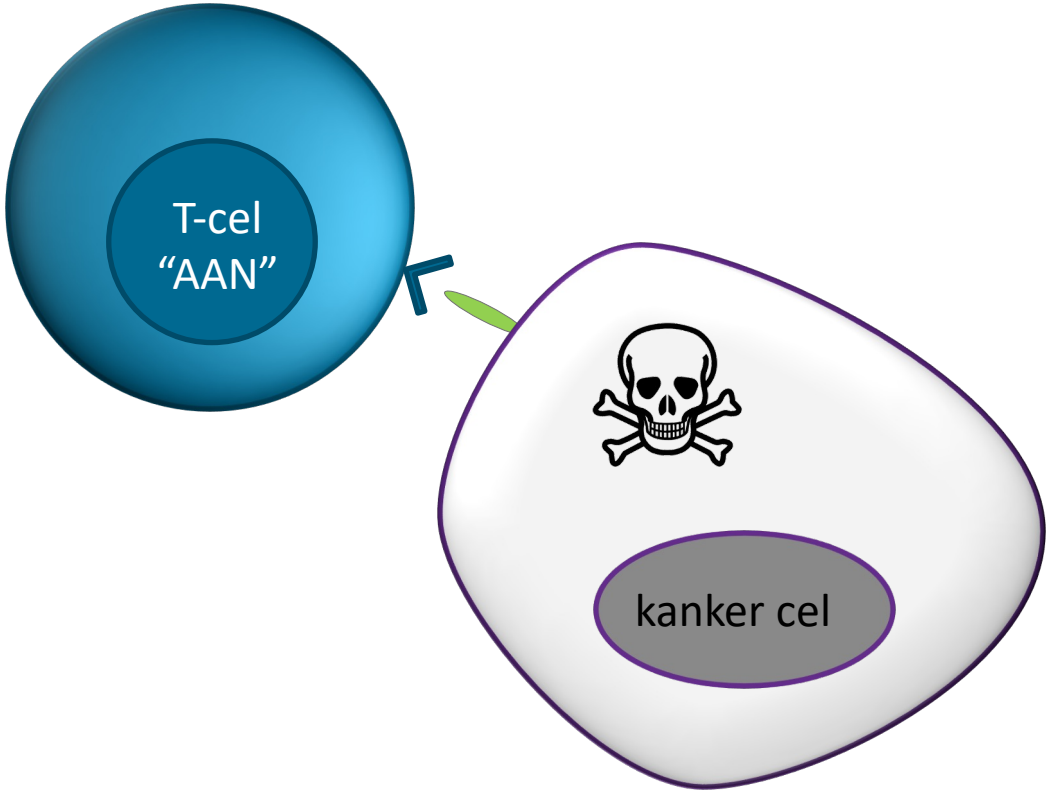
Outline

- Klinische context immunotherapie en kanker
- Technische aspecten
  - Radiotracers
  - Radionuclide beeldvorming
  - Radionuclide therapie
  - Dosimetrie
- Toepassingen binnen immuno-oncologie
- Maatschappelijke impact en conclusie

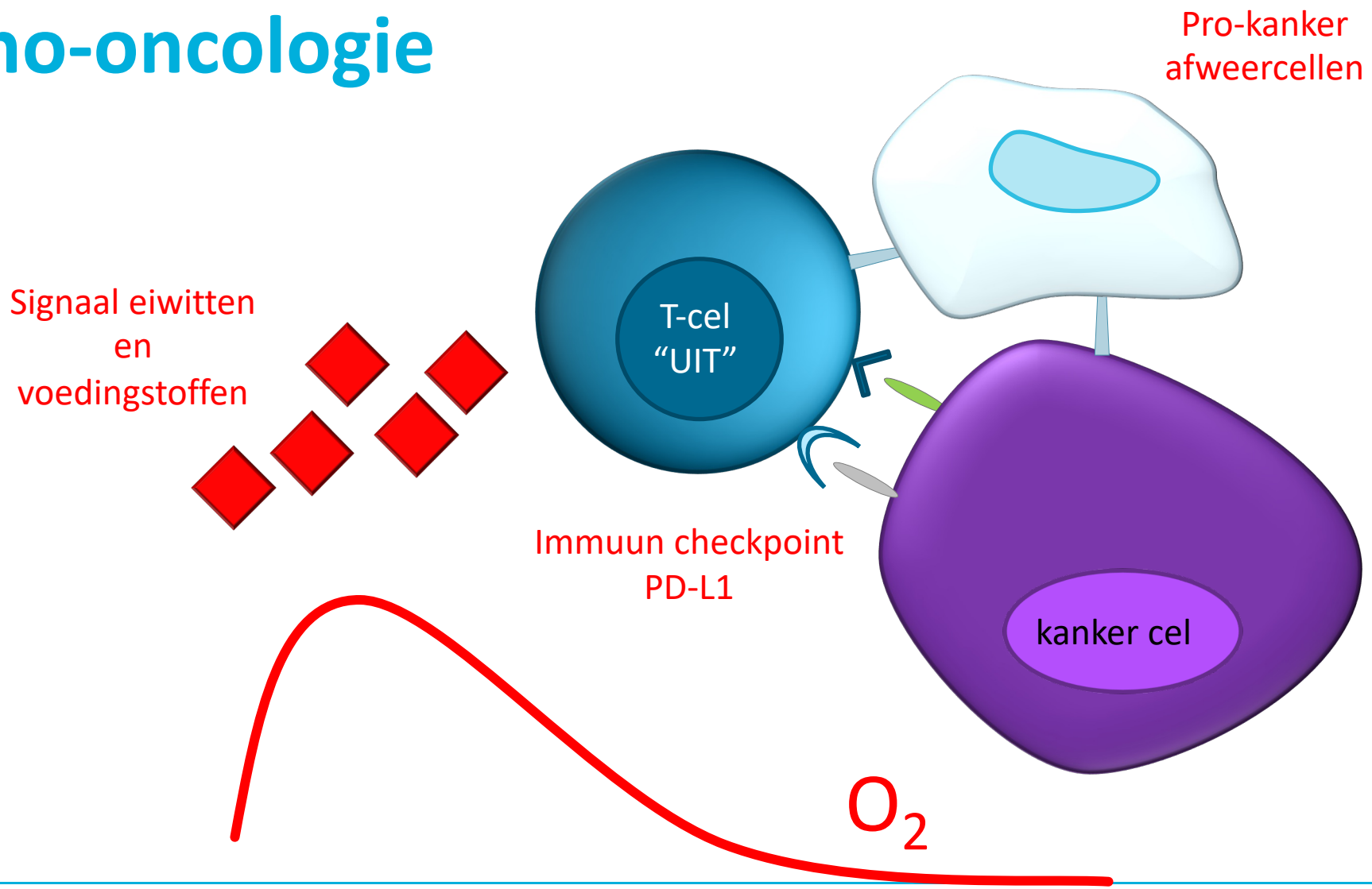
Immuno-oncologie



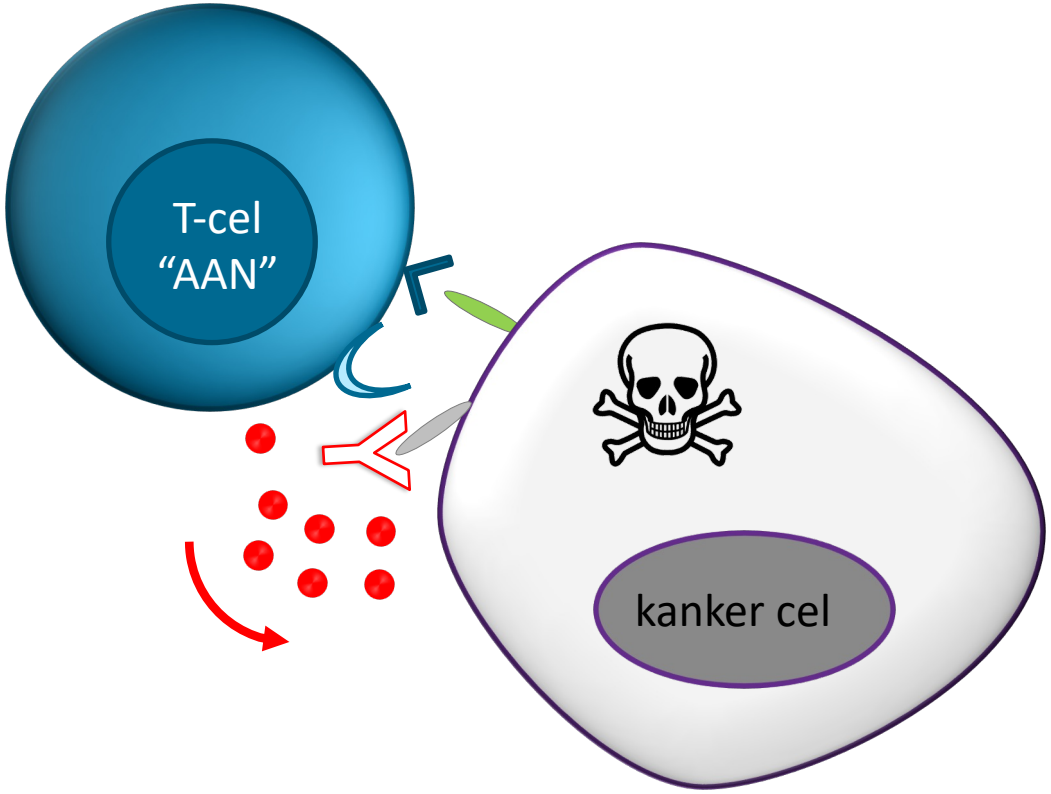
Immuno-oncologie



Immuno-oncologie



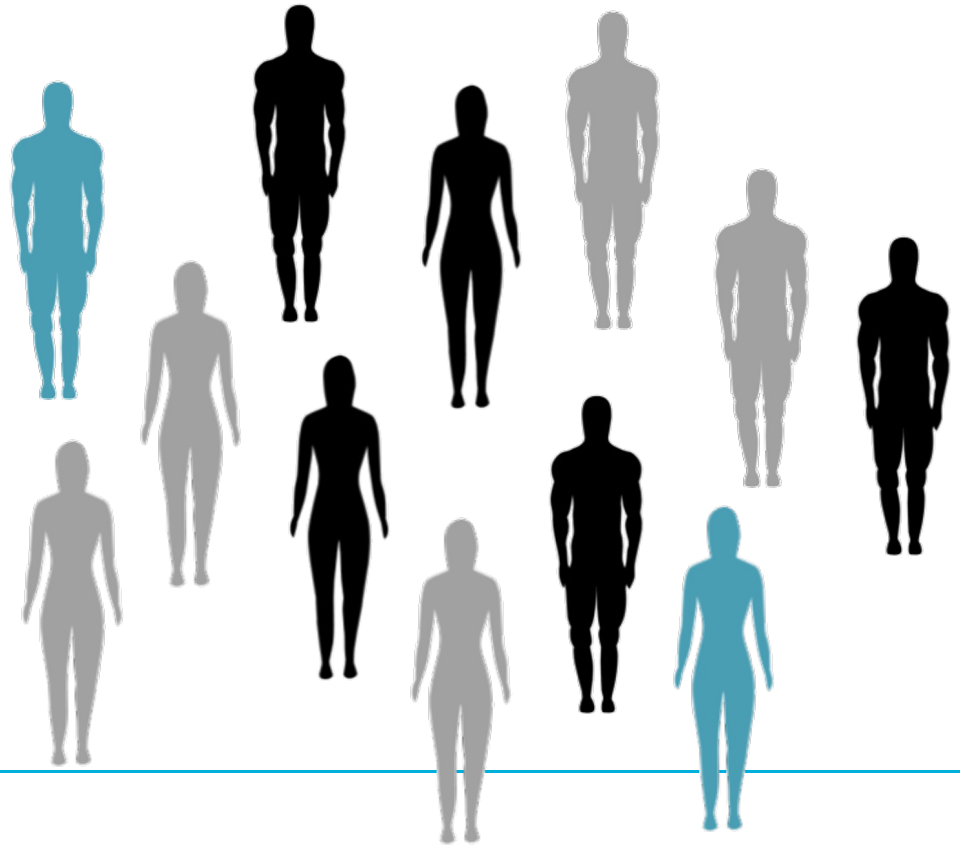
Immunotherapie



Immunotherapie

- Immuuntherapie (her)activeert het eigen afweersysteem om kankercellen op te ruimen en kan leiden tot aanzienlijke overlevingswinst

- Werkt niet voor iedereen
- Kans op ernstige bijwerkingen
- Hoge kosten



Belangrijke vragen

Kunnen we in een vroeg stadium de werking en veiligheid van (nieuwe) immuuntherapie voorspellen?

Radionuclide beeldvorming

Kunnen we met combinatie behandeling de respons op immuuntherapie verbeteren voor patiënten die nu geen baat hebben bij deze therapie?

Radionuclide therapie

Belangrijke vragen

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Radionuclide beeldvorming

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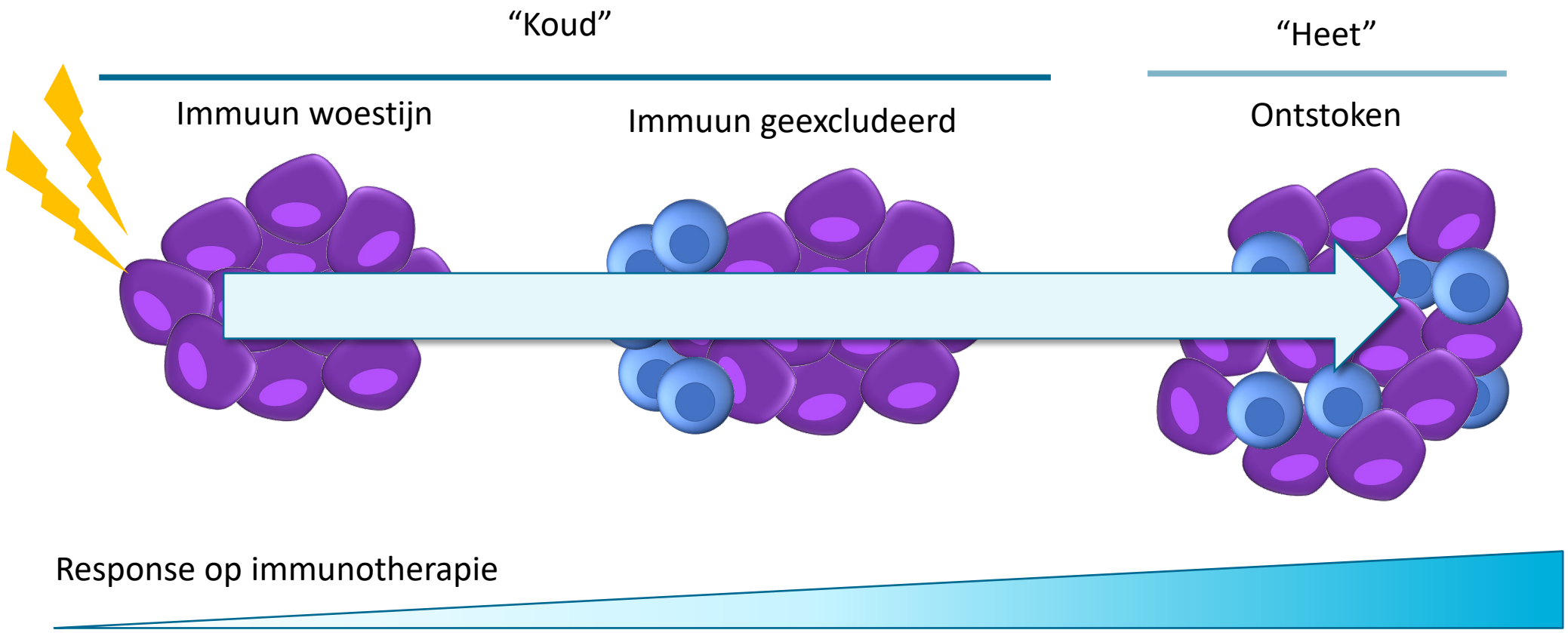
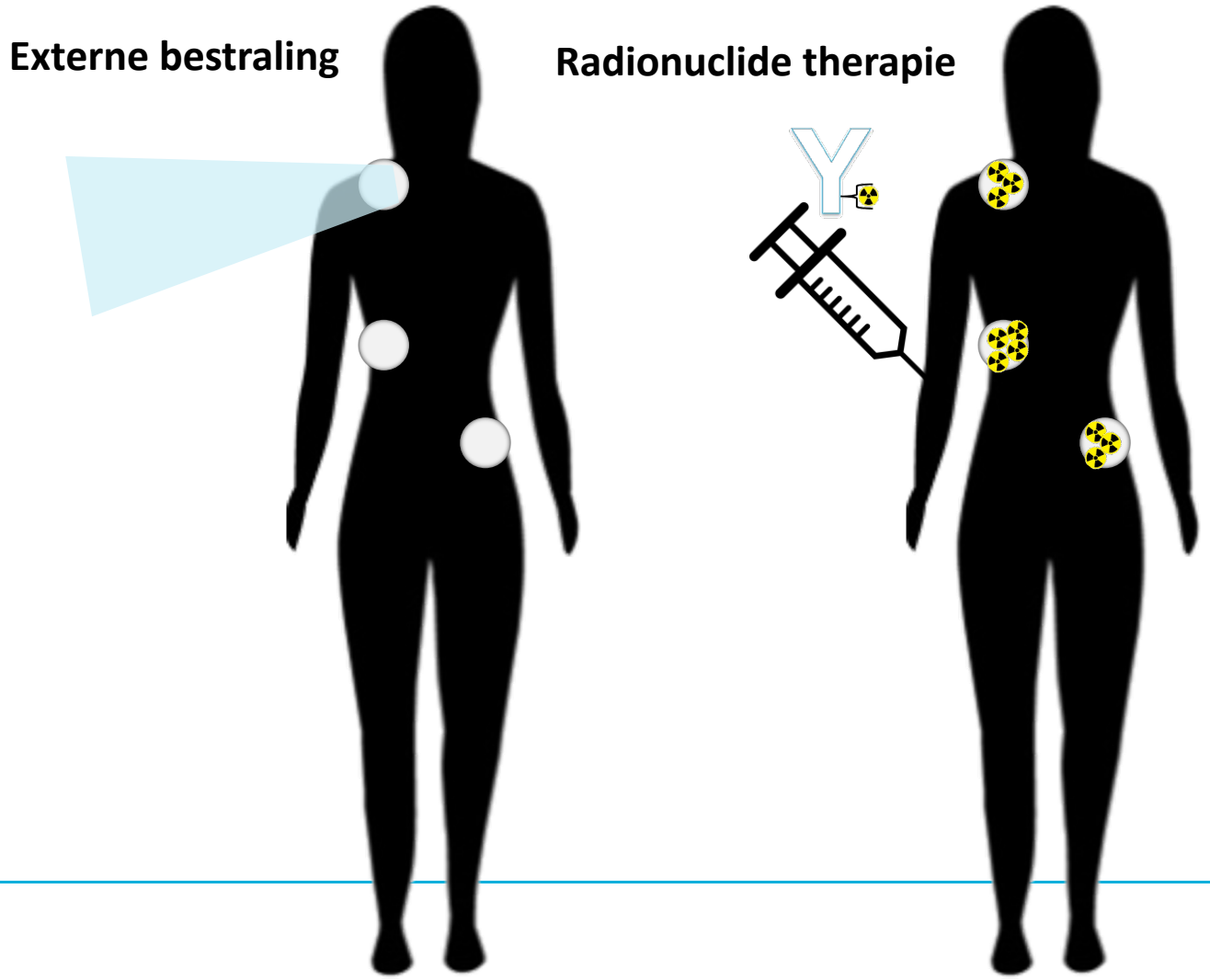
Radionuclide therapie

Immunologische verschillen tussen tumoren



Radionuclide therapie versus externe bestraling

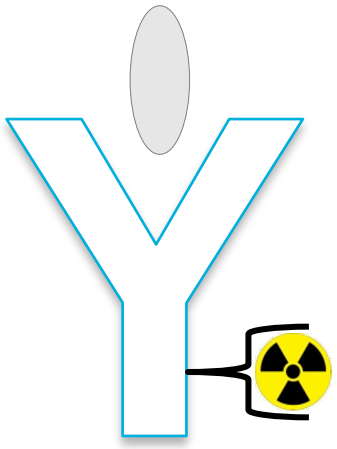


Voordelen radionuclide therapie

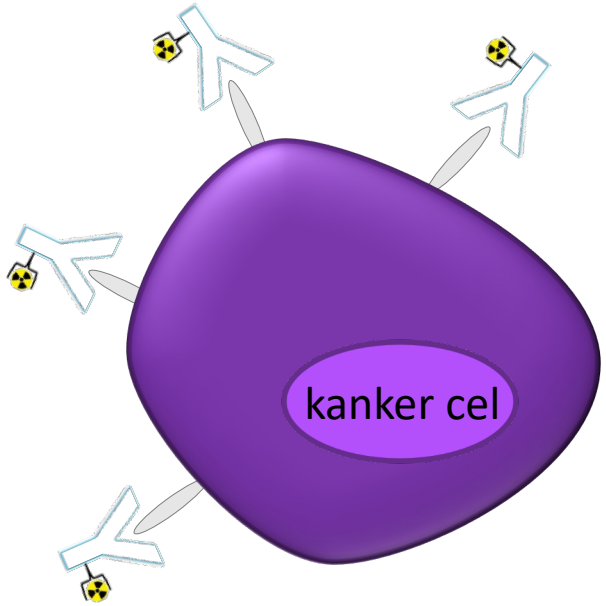
1. Meerdere uitzaaiingen
2. Type radioactieve deeltjes

Radiotracers

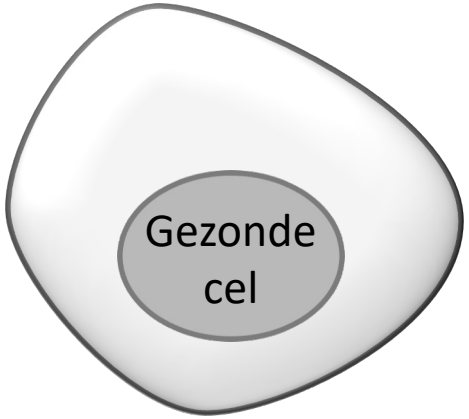
Tumor marker



Radiotracer

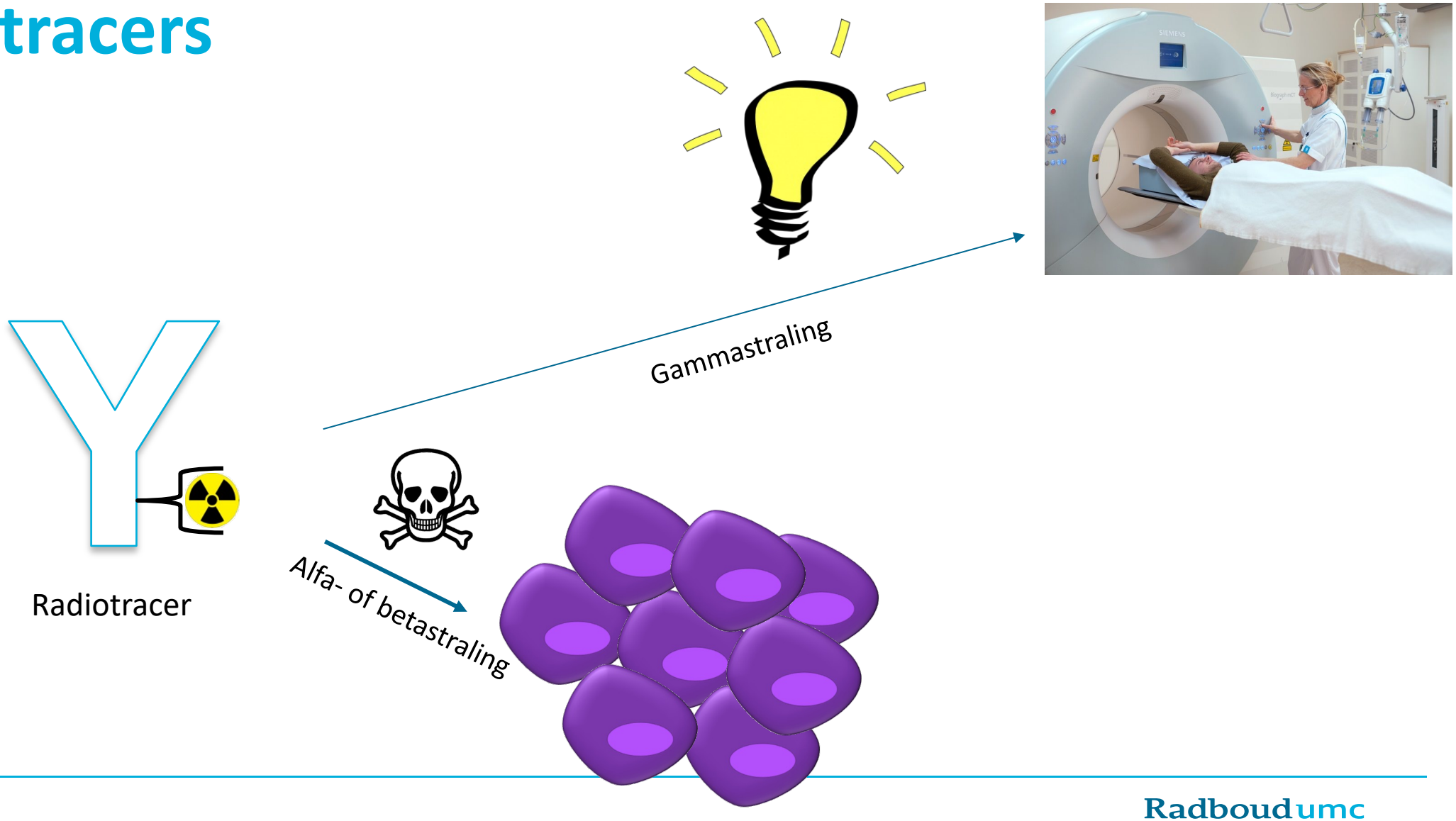


Tumor marker +

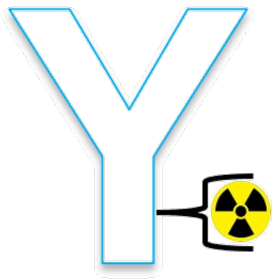


Tumor marker -

Radiotracers

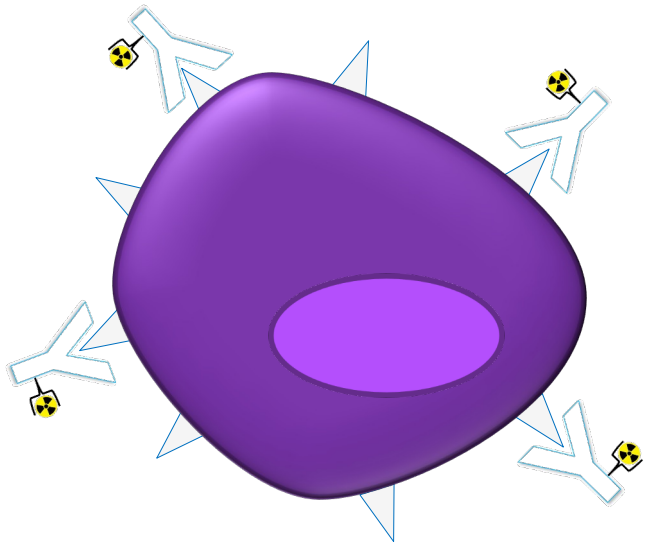


Radionuclide therapie prostaatkanker



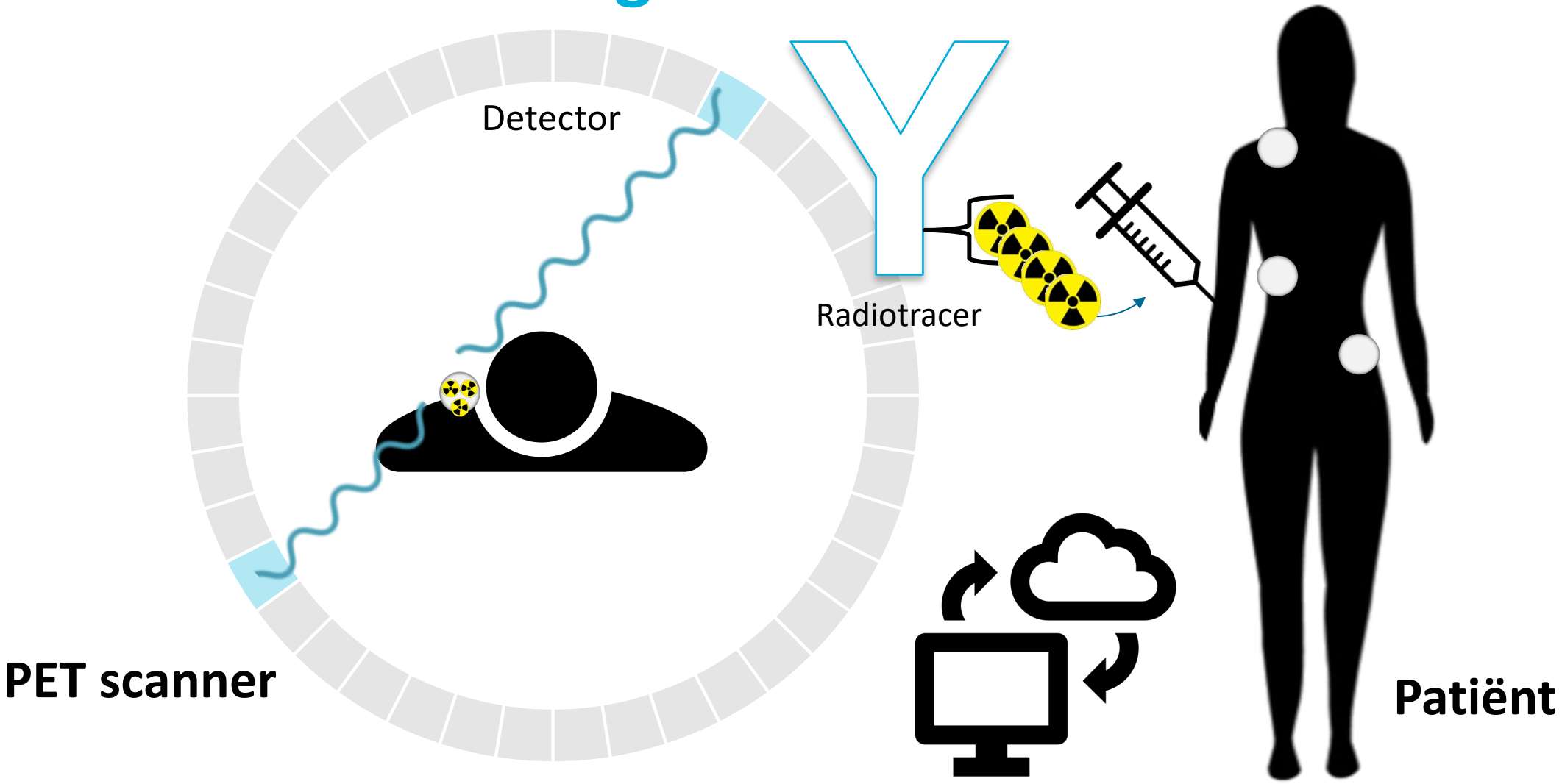
Prostaatkanker
Radiotracer
(PSMA)

Prostaatkankercel

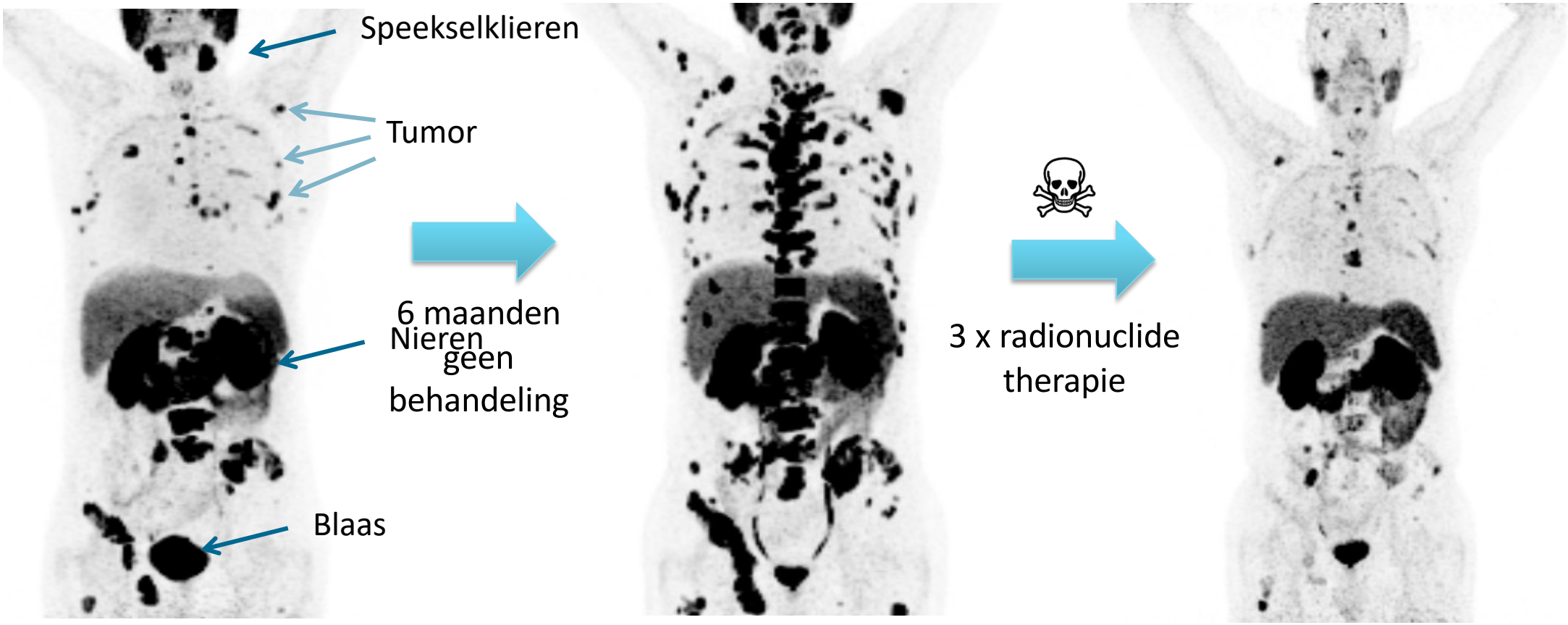


Tumor marker: PSMA

Nucleaire Beeldvorming



Radionuclide therapie prostaatkanker



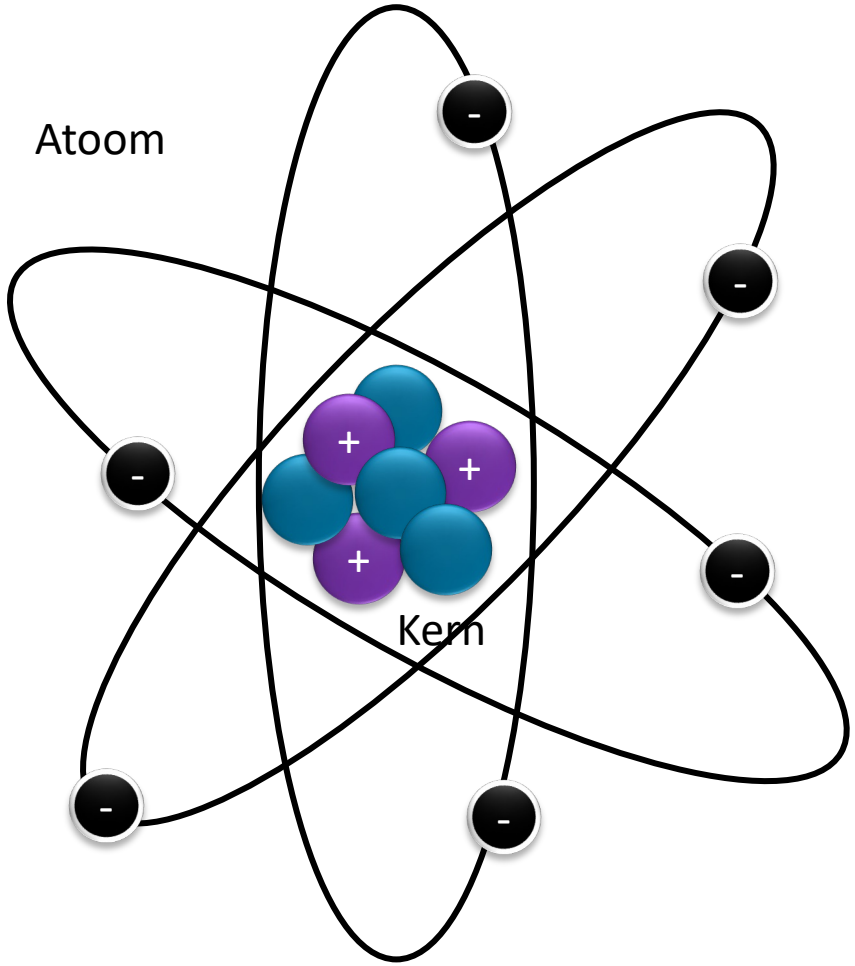
Radionuclide therapie prostaatkanker

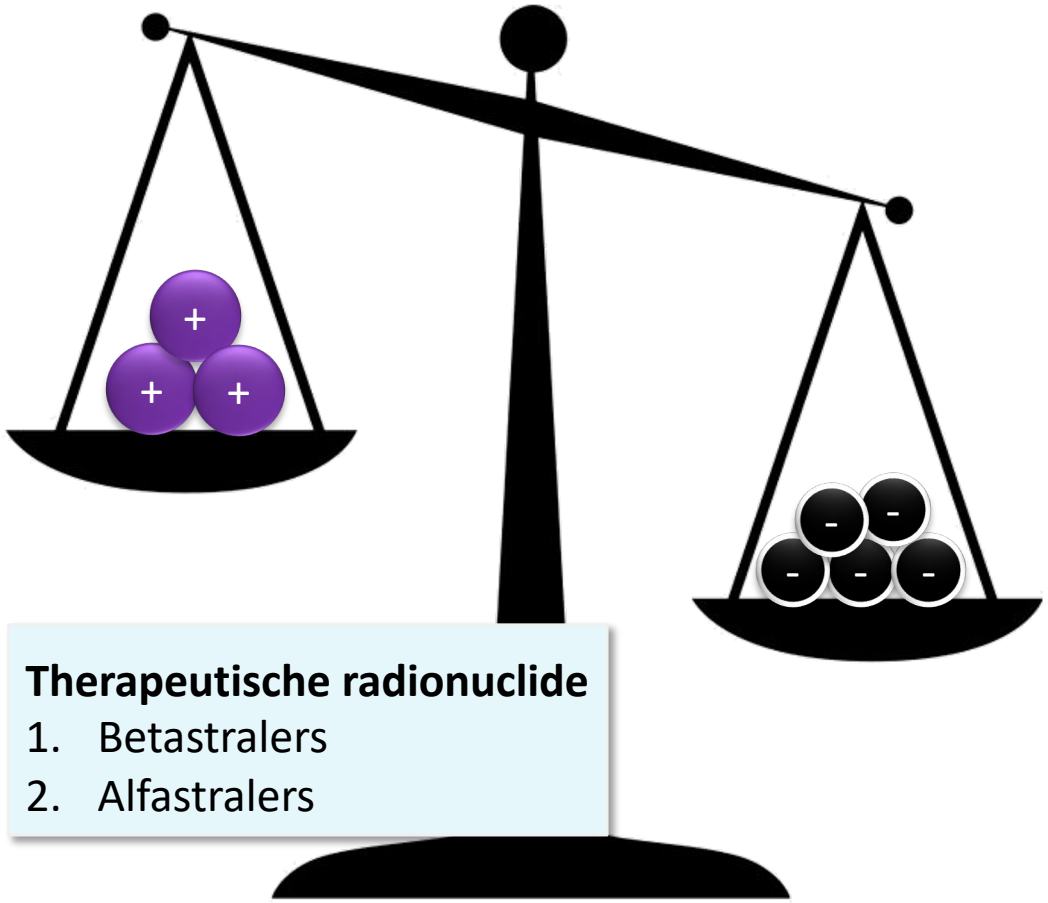
- Effectief bij 40-60% van de patienten
  - Overlevingswinst
  - Minder ziekteklachten
- Genezing in de meeste gevallen (nog) niet mogelijk
  - Type radionuclide? Alfa of beta?
  - Dosering?
  - Combinatietherapie met immunotherapie?

Inzoomen

1. Eigenschappen van radionucliden
2. Biologische effecten

Therapeutische radionucliden





Therapeutische radionuclide

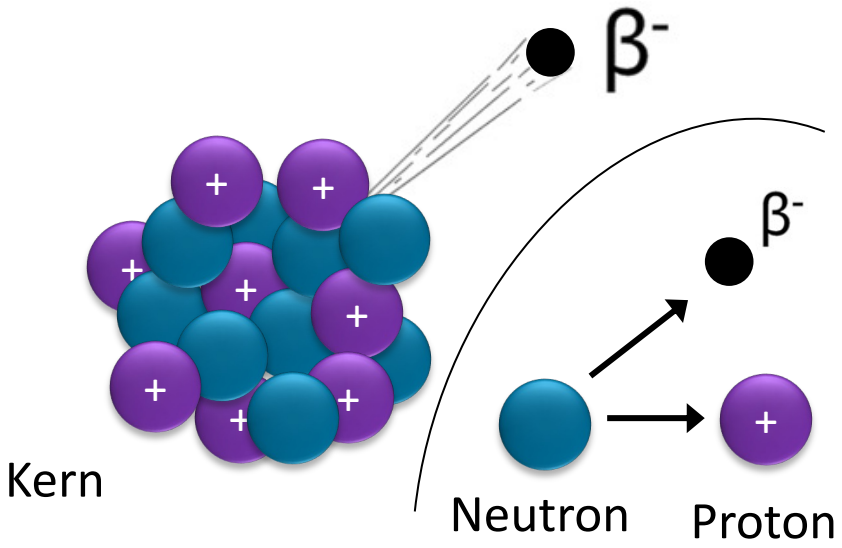
1. Betastralers
2. Alfastralers

Betastralers

- Kern met te weinig protonen
  - Transformatie van een neutron in een protron waarbij een electron wordt uitgezonden (**β^- emissie)**

- Eigenschappen
  - Voorbeeld radionuclide — Lutetium-177, Holmium-166
  - Dracht in weefsel — 2-10 mm
  - LET — Laag (0.1 – 1 keV/µm)

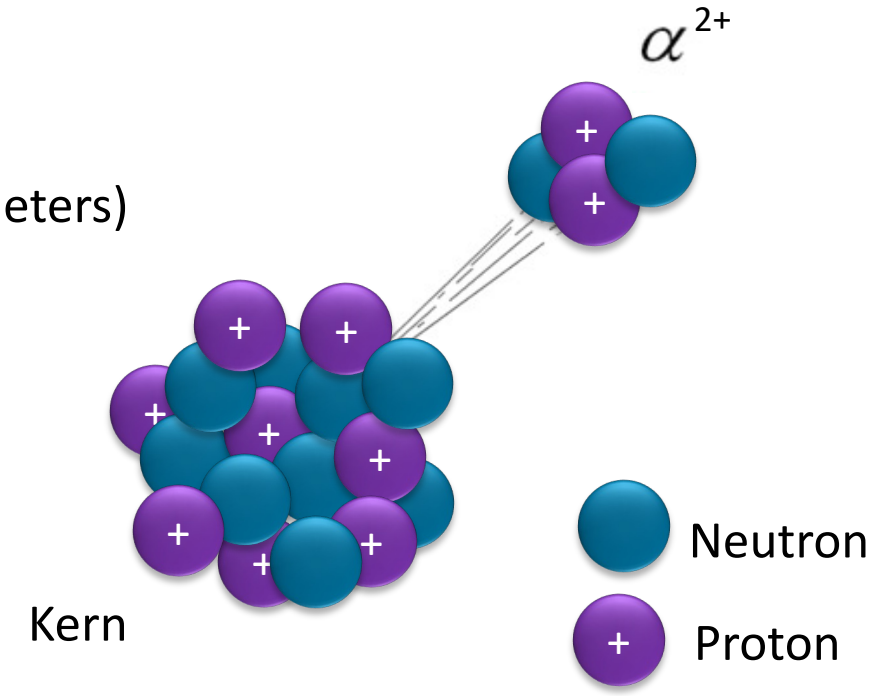
Linear energy transfer (LET)
LET beschrijft de hoeveelheid energie (keV) afgegeven door het deeltje over een bepaalde afstand (µm) in weefsel, uitgedrukt in keV/µm



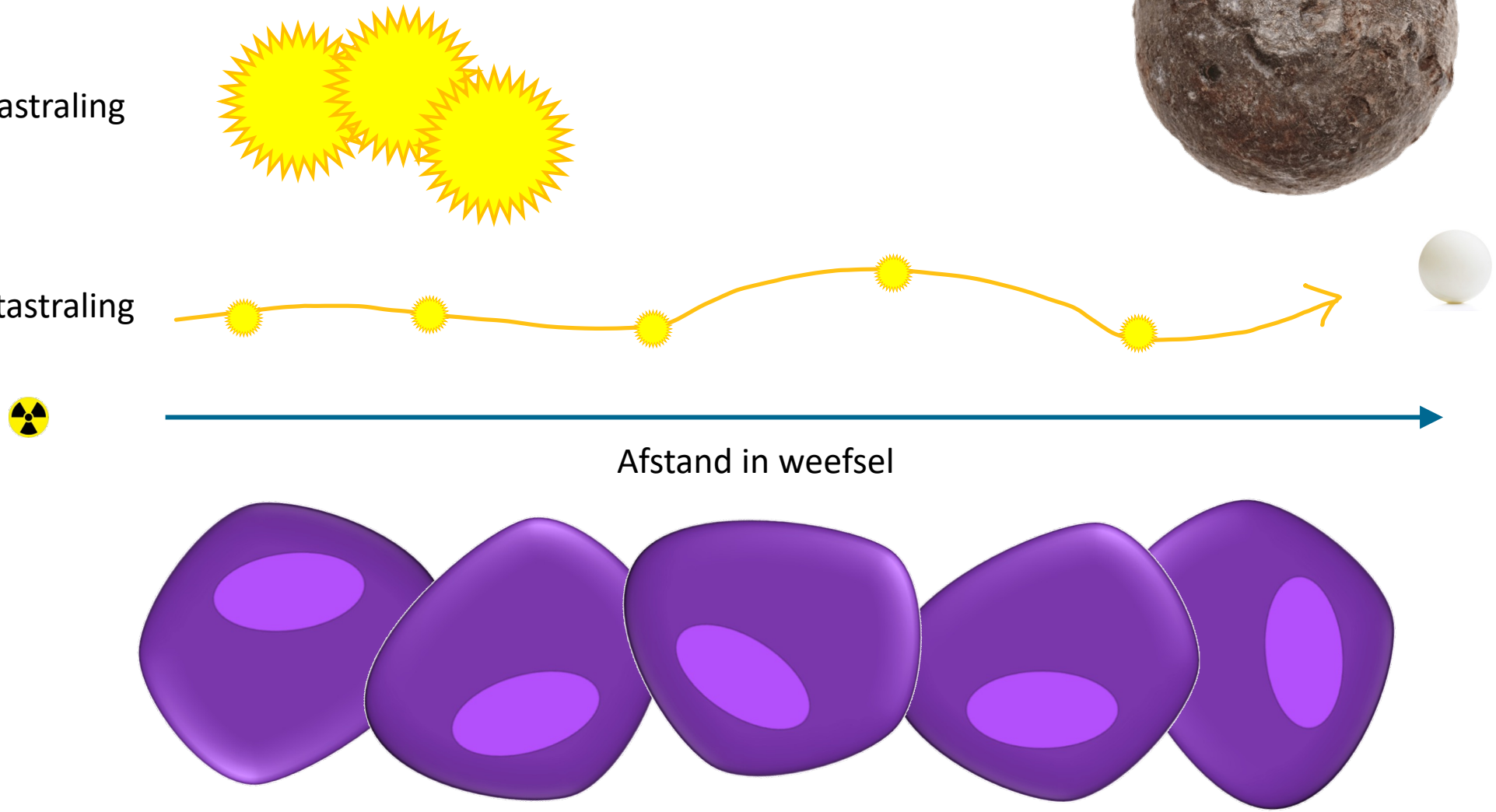
Alfastraling

- Grote nucleus, energetisch instabiel
  - Emissie van een helium nucleus, bestaande uit twee protonen en twee neutronen (**α emission**)

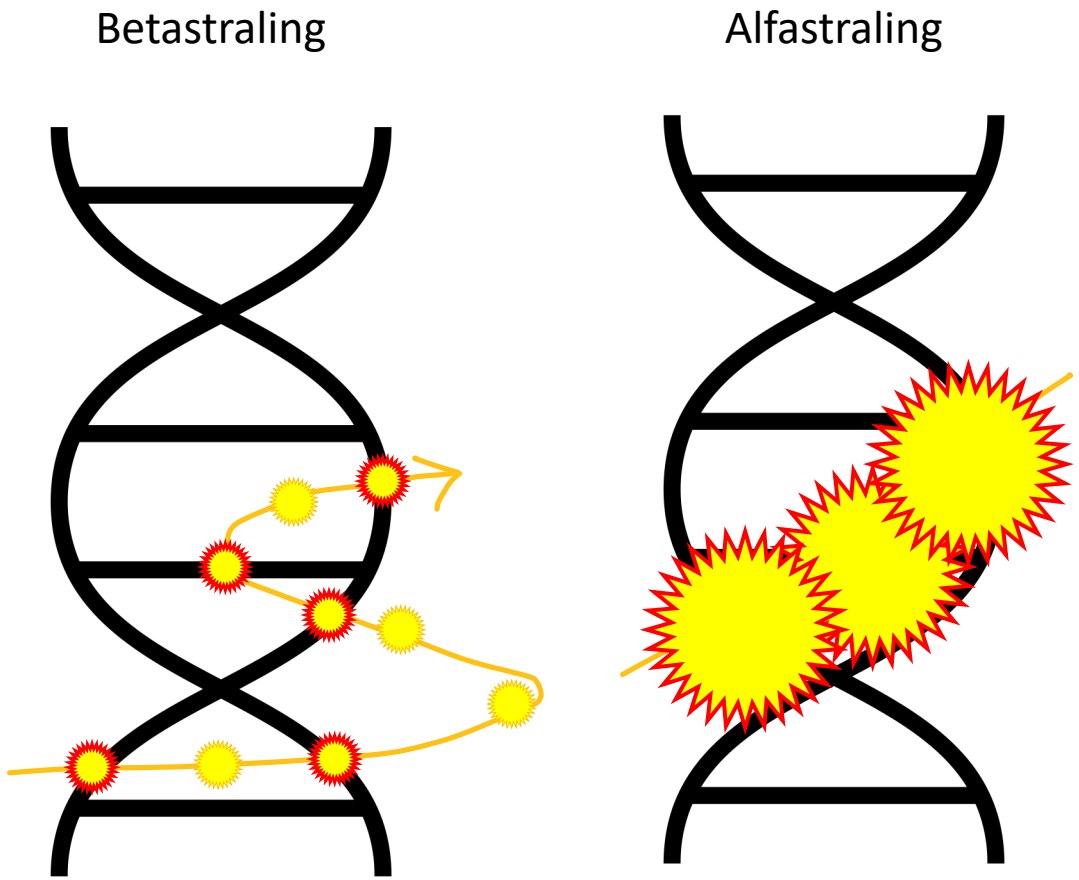
- Eigenschappen
  - Voorbeeld radionuclide — Actinium-225, Lood-212
  - Dracht in weefsel — 50 – 100 µm (5-10 cell diameters)
  - LET — Hoog (50 – 230 keV/µm)



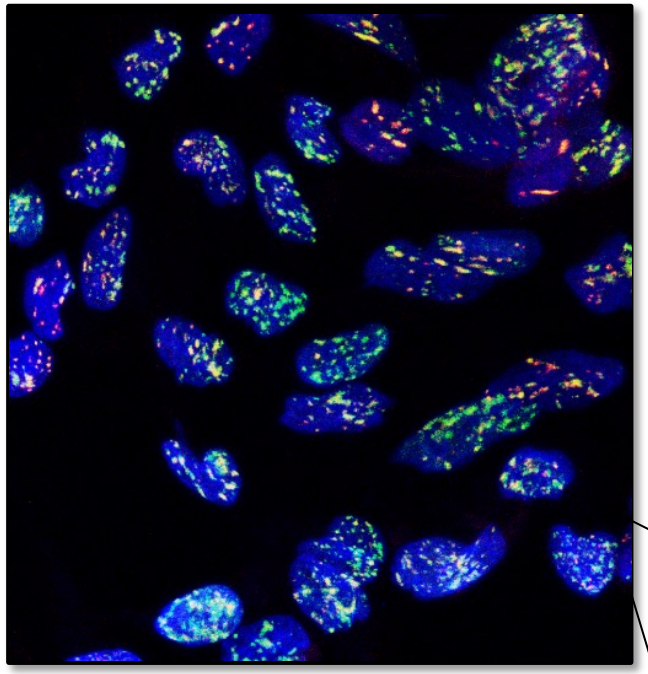
Alfa- versus betastraling – dracht/LET



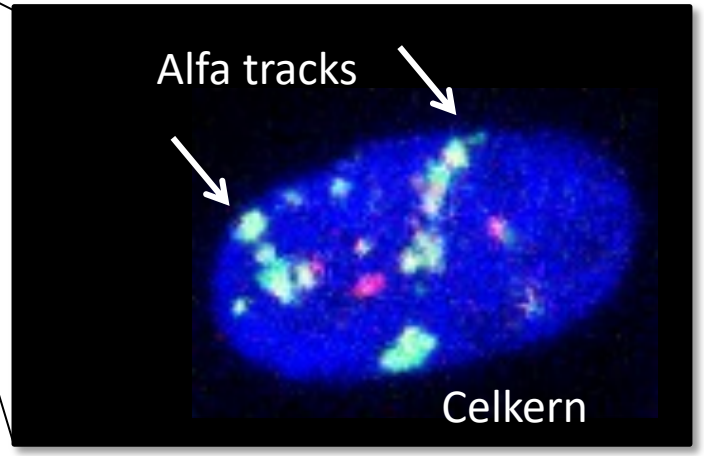
Lokale DNA schade



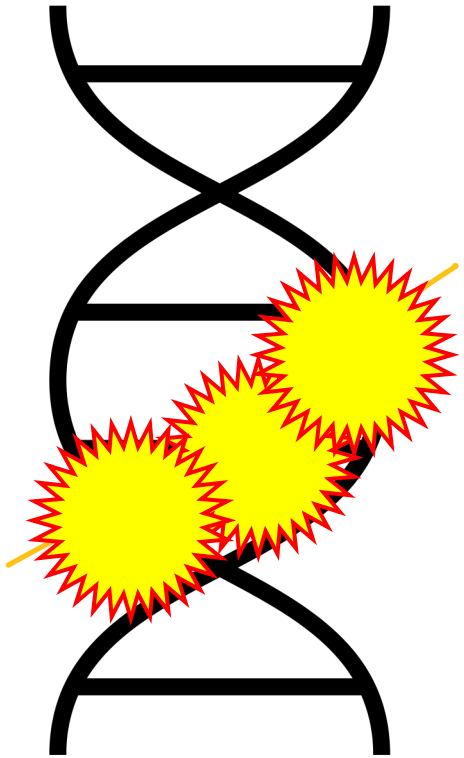
Lokale DNA schade



Prostaat kankercellen behandeld met alfastraling



Alfastraling



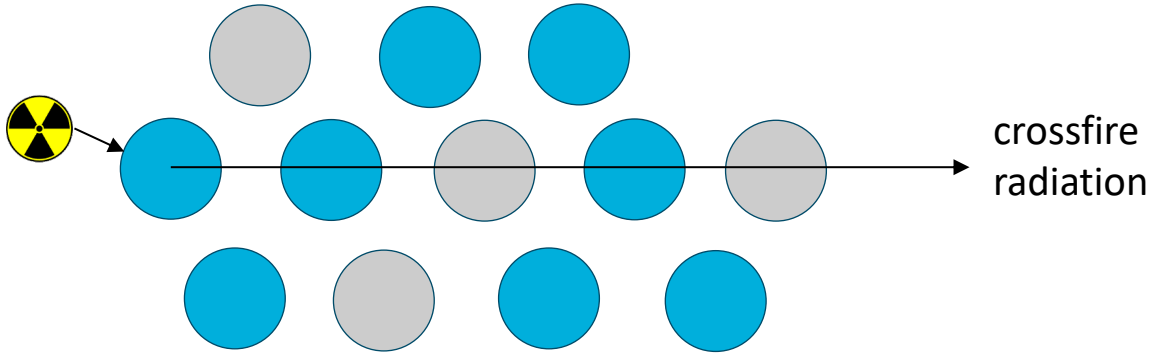
Alfa versus betastraling

- Is alfastraling altijd beter?

- **Voordelen**
  - Meer cytotoxisch
  - Effectiever in cellen resistent tegen conventionele of betastraling

- **Nadelen**
  - Minder cross-fire effect

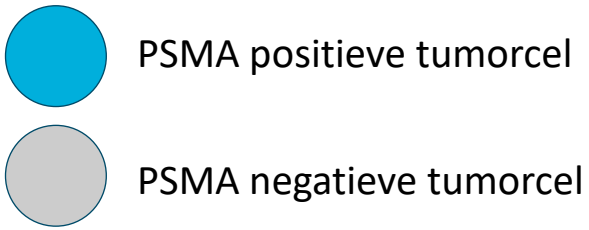
Cross-fire effect

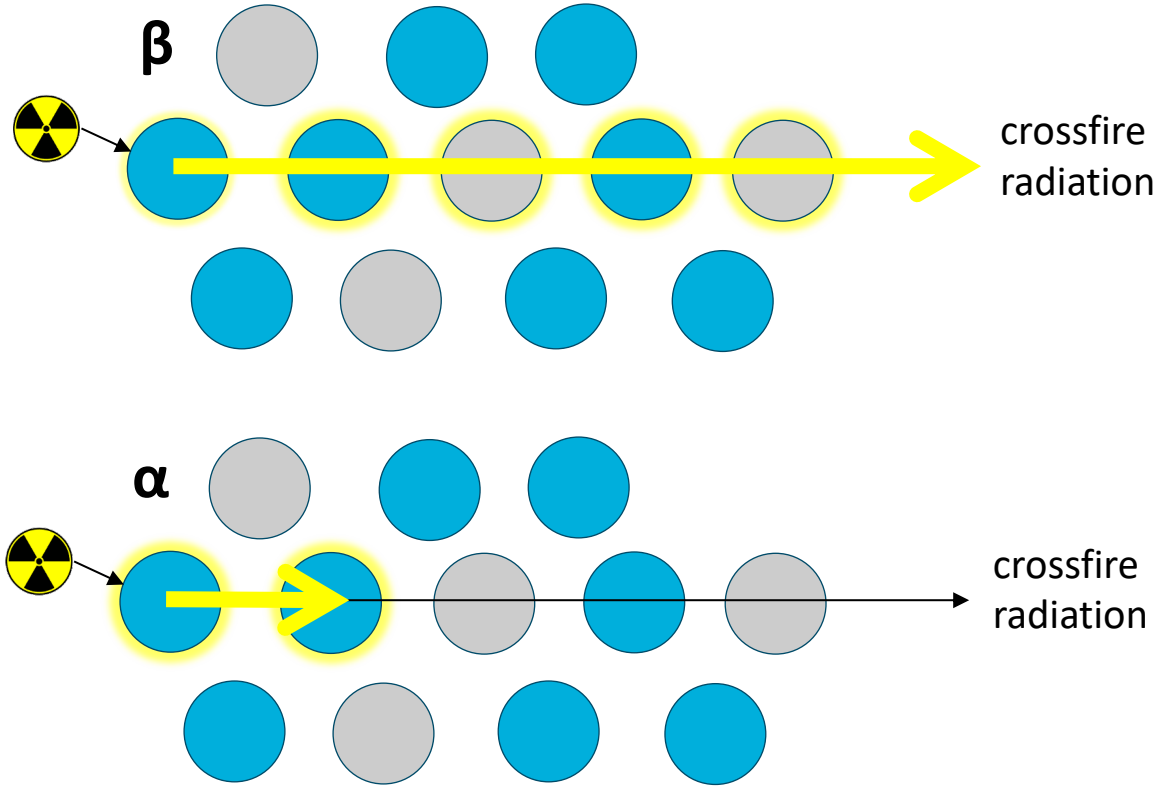


PSMA positieve tumorcel

PSMA negatieve tumorcel

Cross-fire effect





Alfa- versus betastraling

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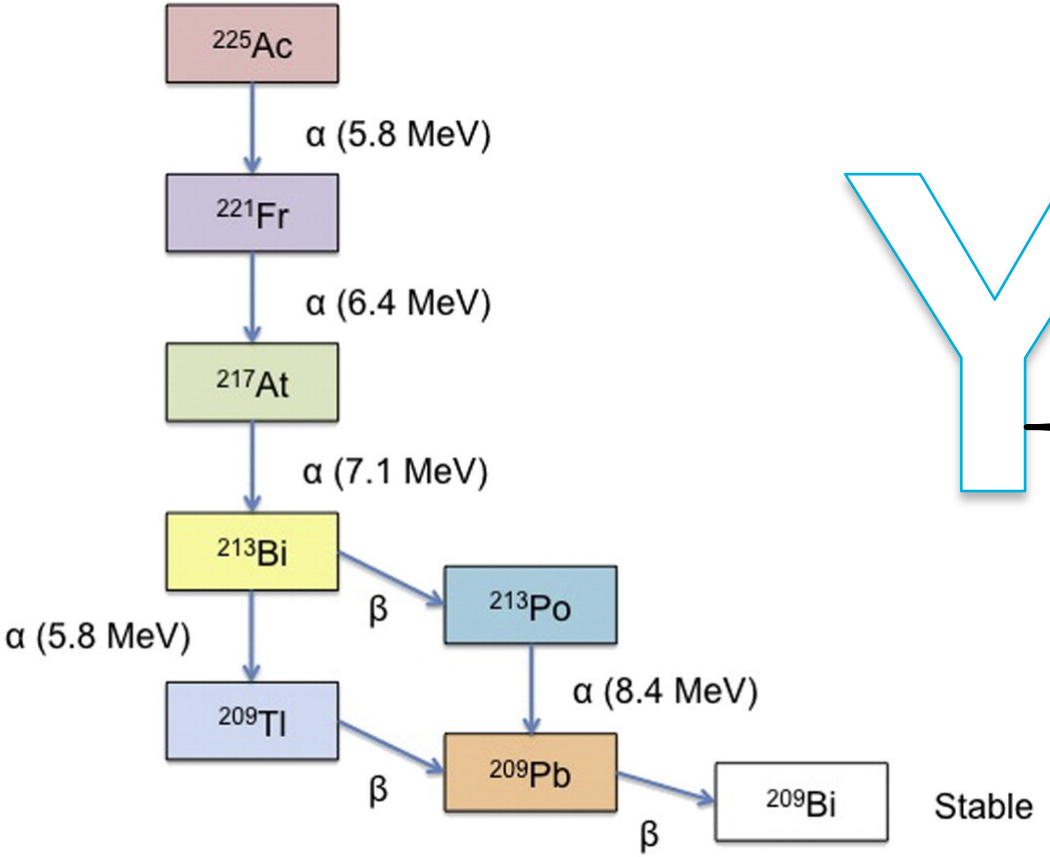
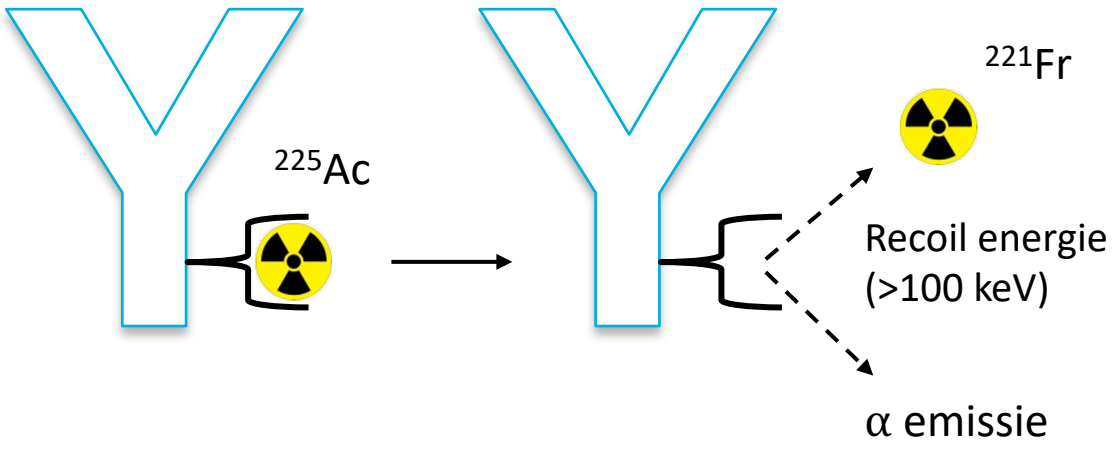
- **Voordelen**
  - Meer cytotoxisch
  - Effectiever in cellen resistent tegen conventionele of betastraling

- **Nadelen**
  - Minder cross-fire effect
  - Complex vervalschema

Complex verval en “recoil effect” alfastralers





Alfa- versus betastraling

- Is alfastraling altijd beter?

- **Voordelen**
  - Meer cytotoxisch
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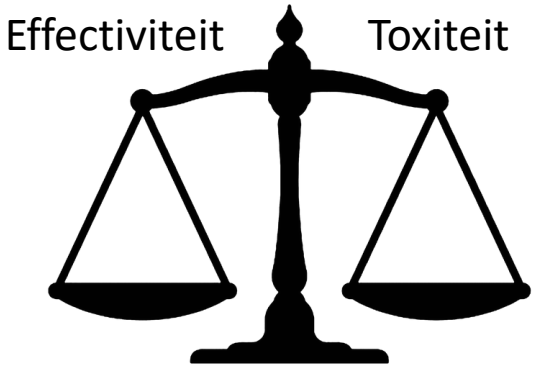
Effectiviteit

- **Nadelen**
  - Minder cross-fire effect
  - Complex vervalschema

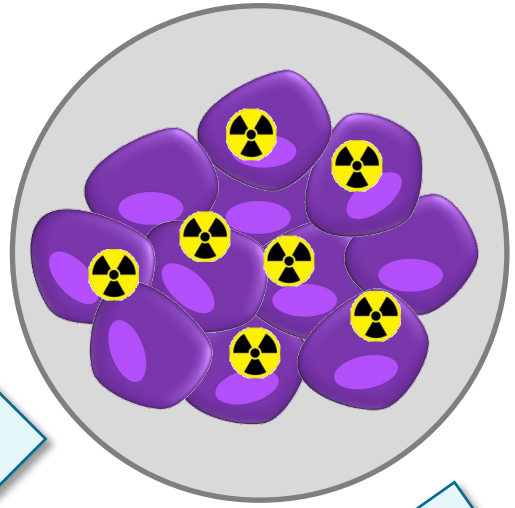
Effectiviteit
Toxiciteit



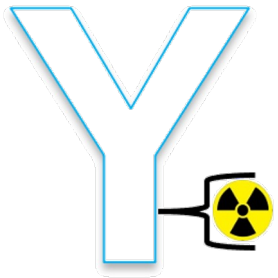
Dosimetrie!

Dosimetrie

Stralingsdosis in de tumor?



- Hoeveel?
- Hoelang?
- Biologische dosis-effect relatie?

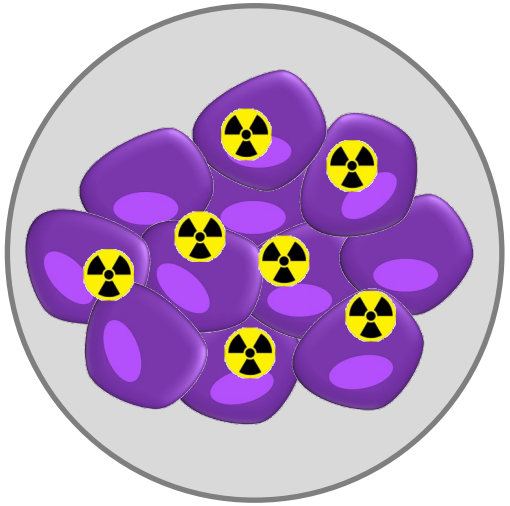


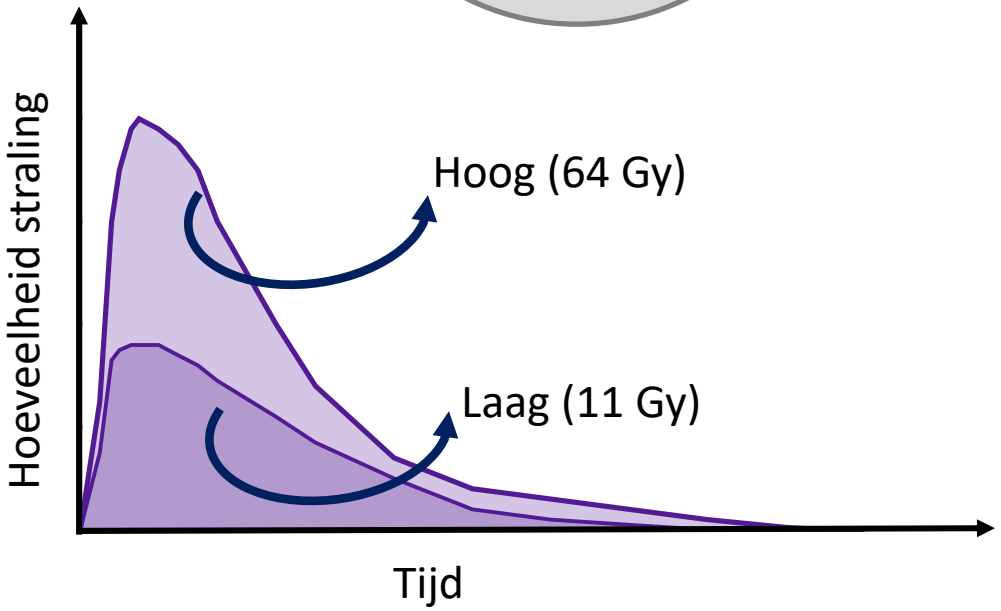
Gallium-68: $t_{1/2}$ = 68 minuten

Ontwikkeling nieuwe radiolabelingsreactie voor
Zirconium-89: $t_{1/2}$ = 3.3 dagen

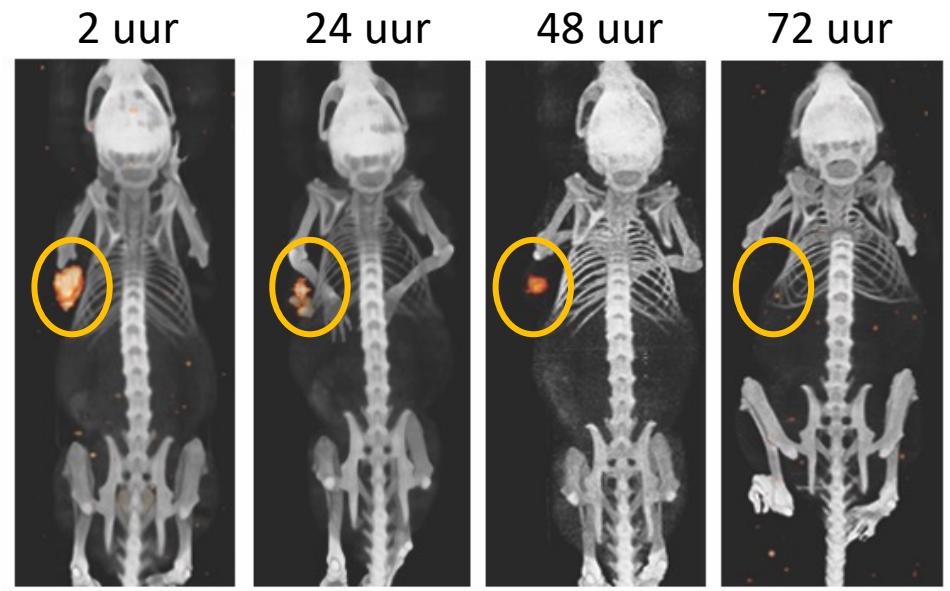
Dosimetrie

Stralingsdosis in de tumor?





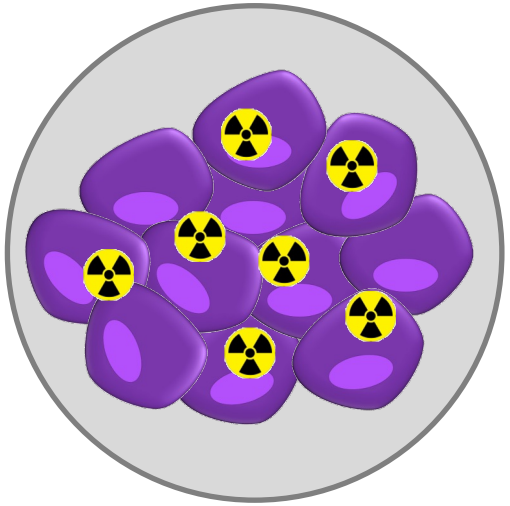
Zirconium-89 PSMA Beeldvorming

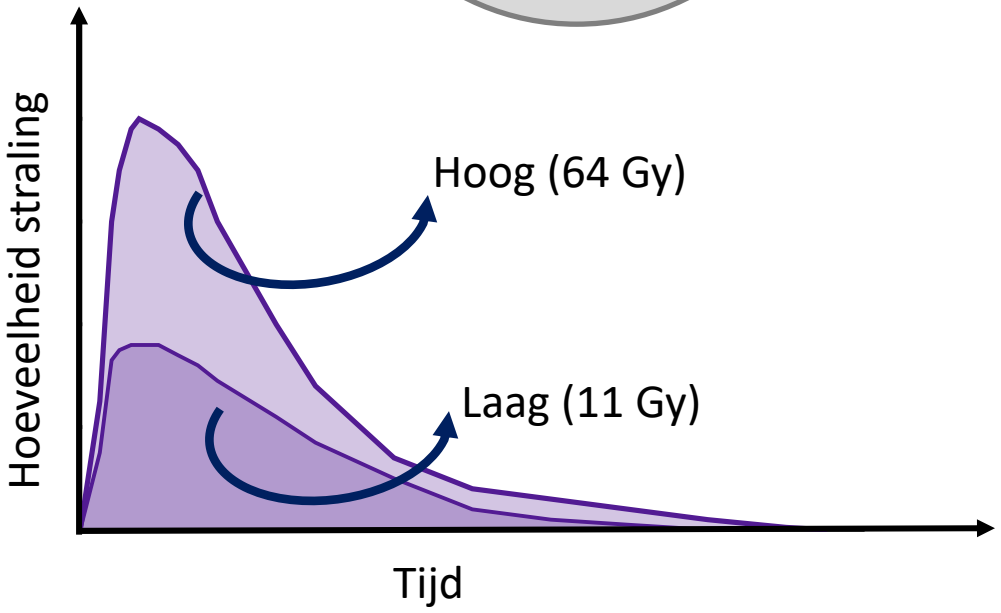


Dosimetrie

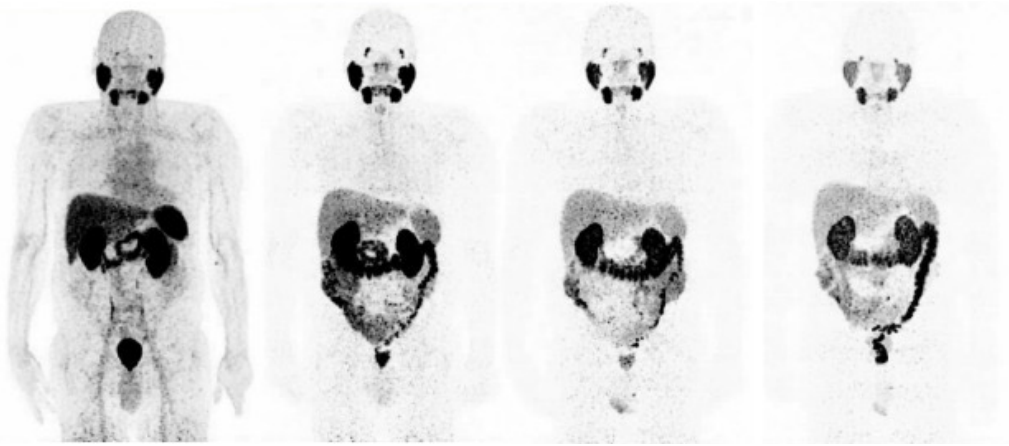
Dosimetrie

Stralingsdosis in de tumor?





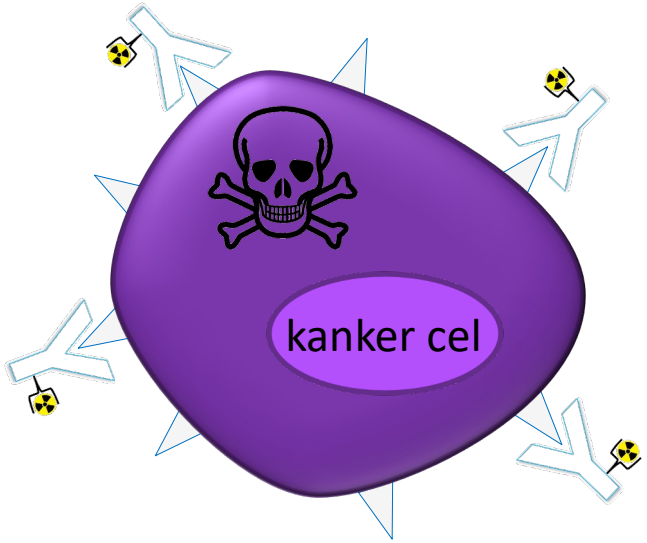
Zirconium-89 PSMA Beeldvorming



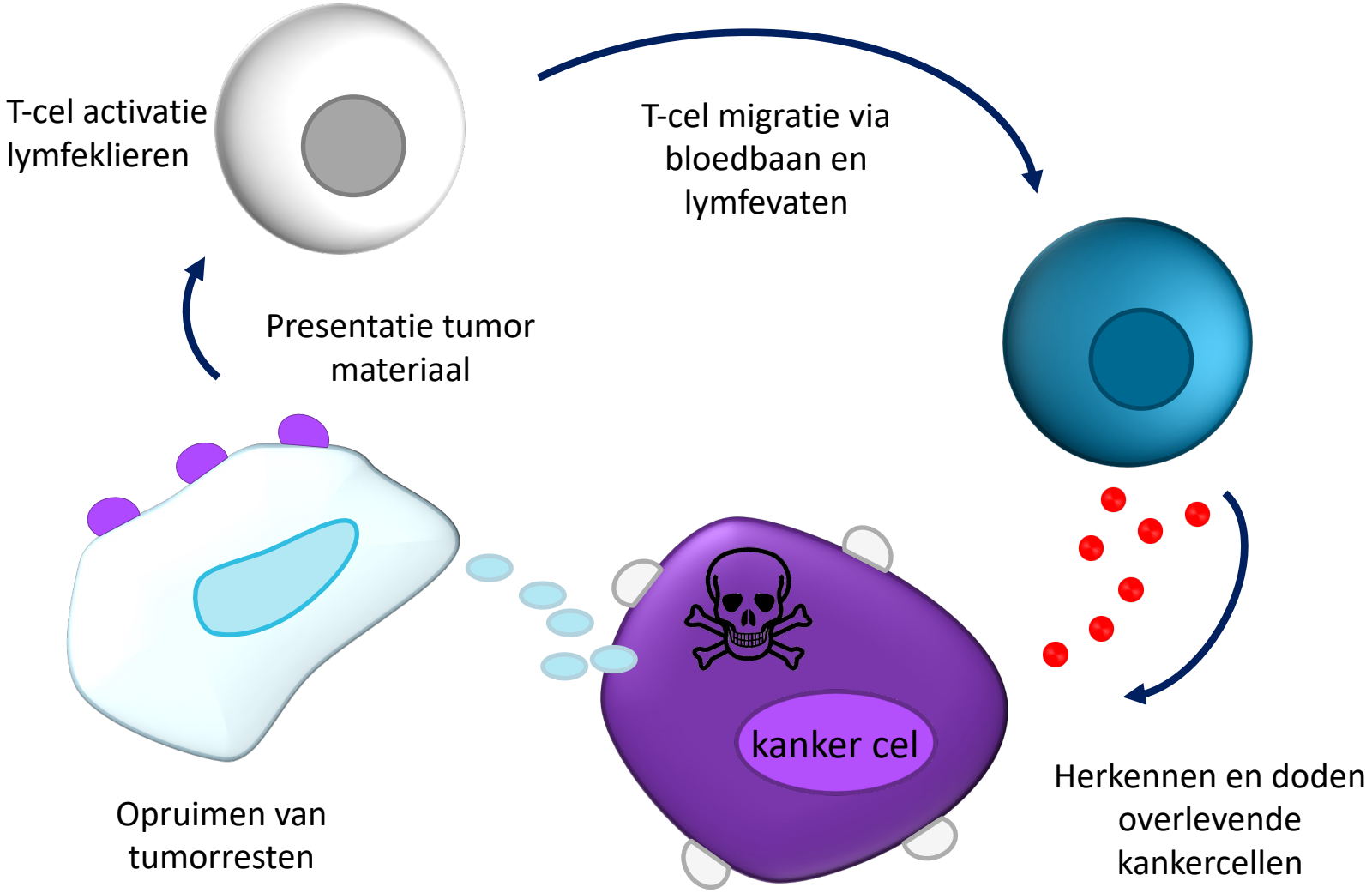
Dosis correleren aan biologische effecten!

Dosimetrie

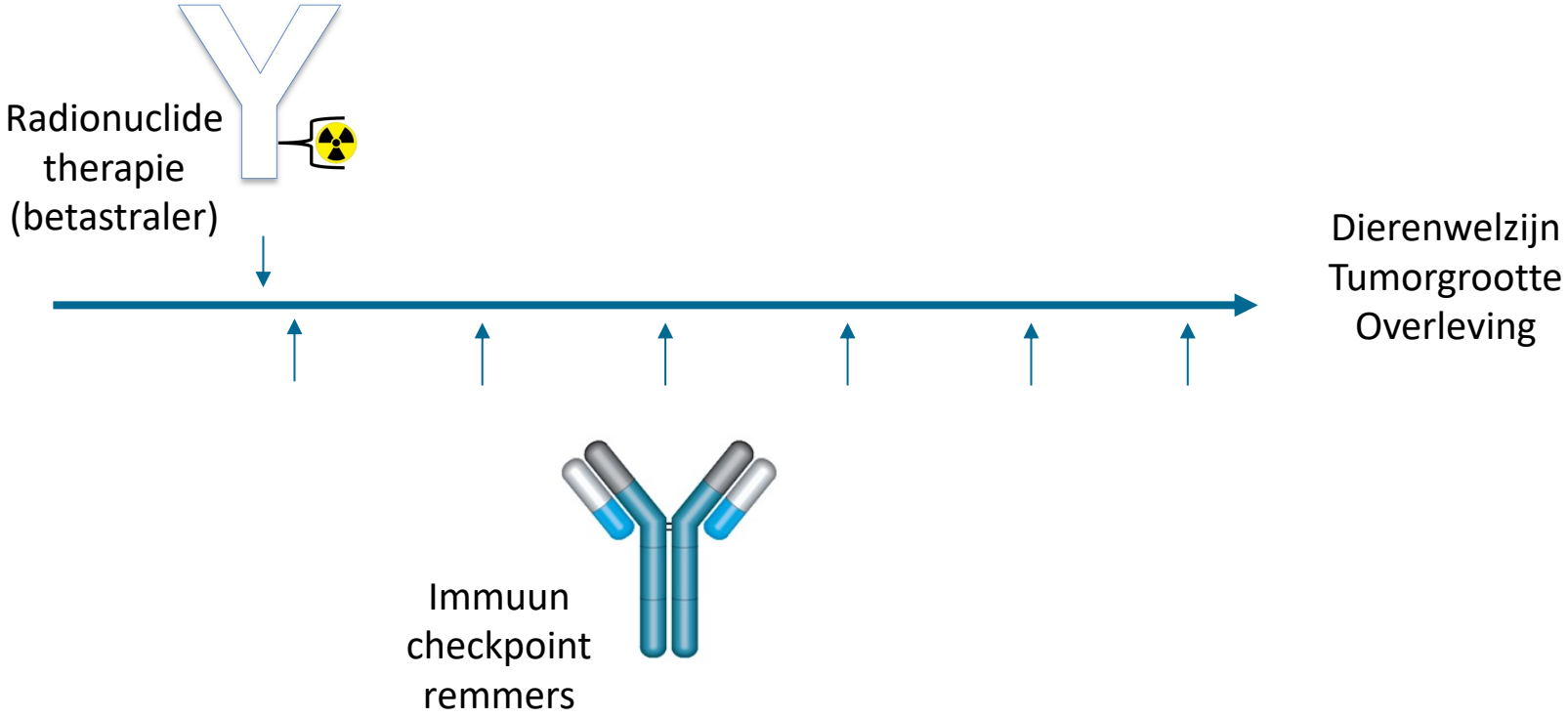
Systemische immuuneffecten



Systemische immuuneffecten

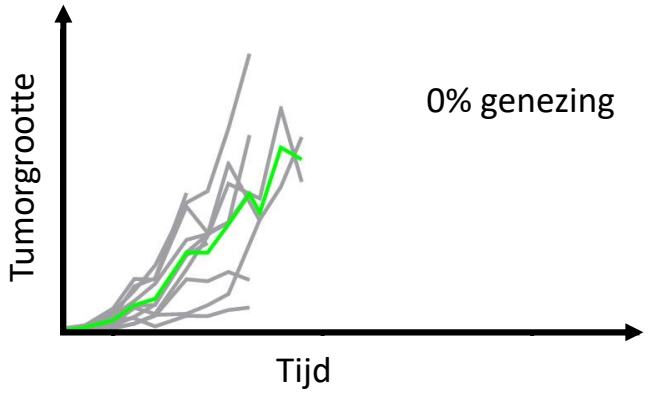


Radionuclide therapie + immunotherapie

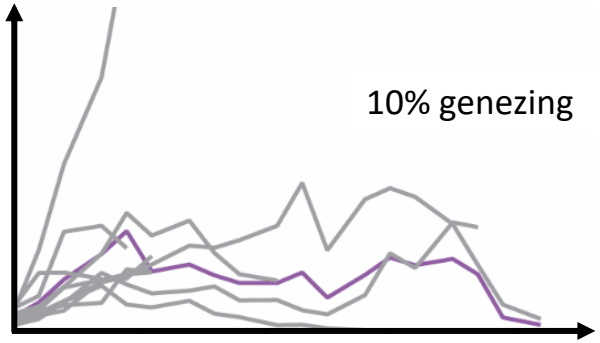


Radionuclide therapie + immunotherapie

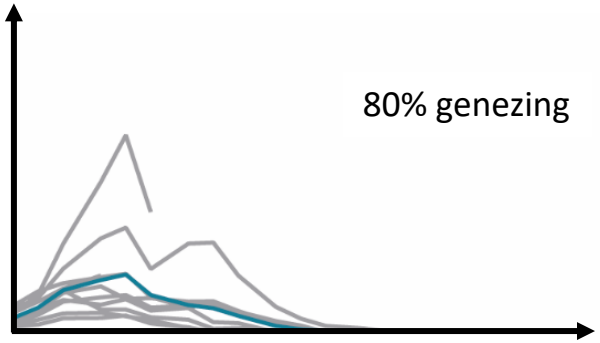
Geen behandeling



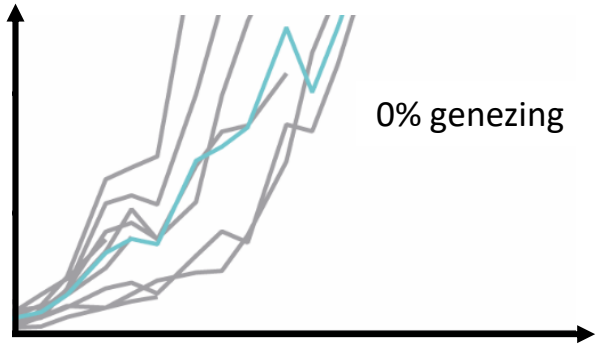
Immuun checkpoint remmers



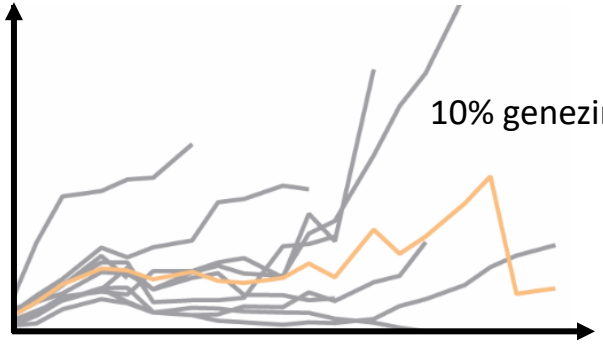
Lage dosis
radionuclide therapie (11 Gy)
+ immuun checkpoint remmers



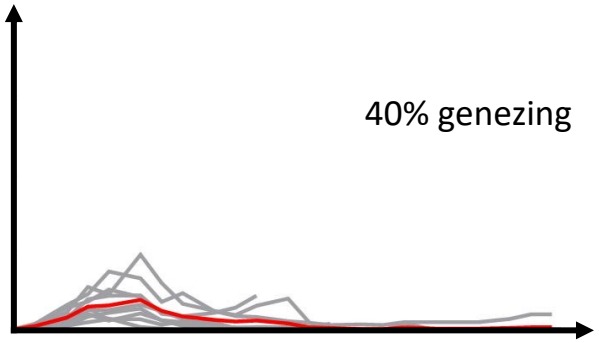
Lage dosis
radionuclide therapie (11 Gy)



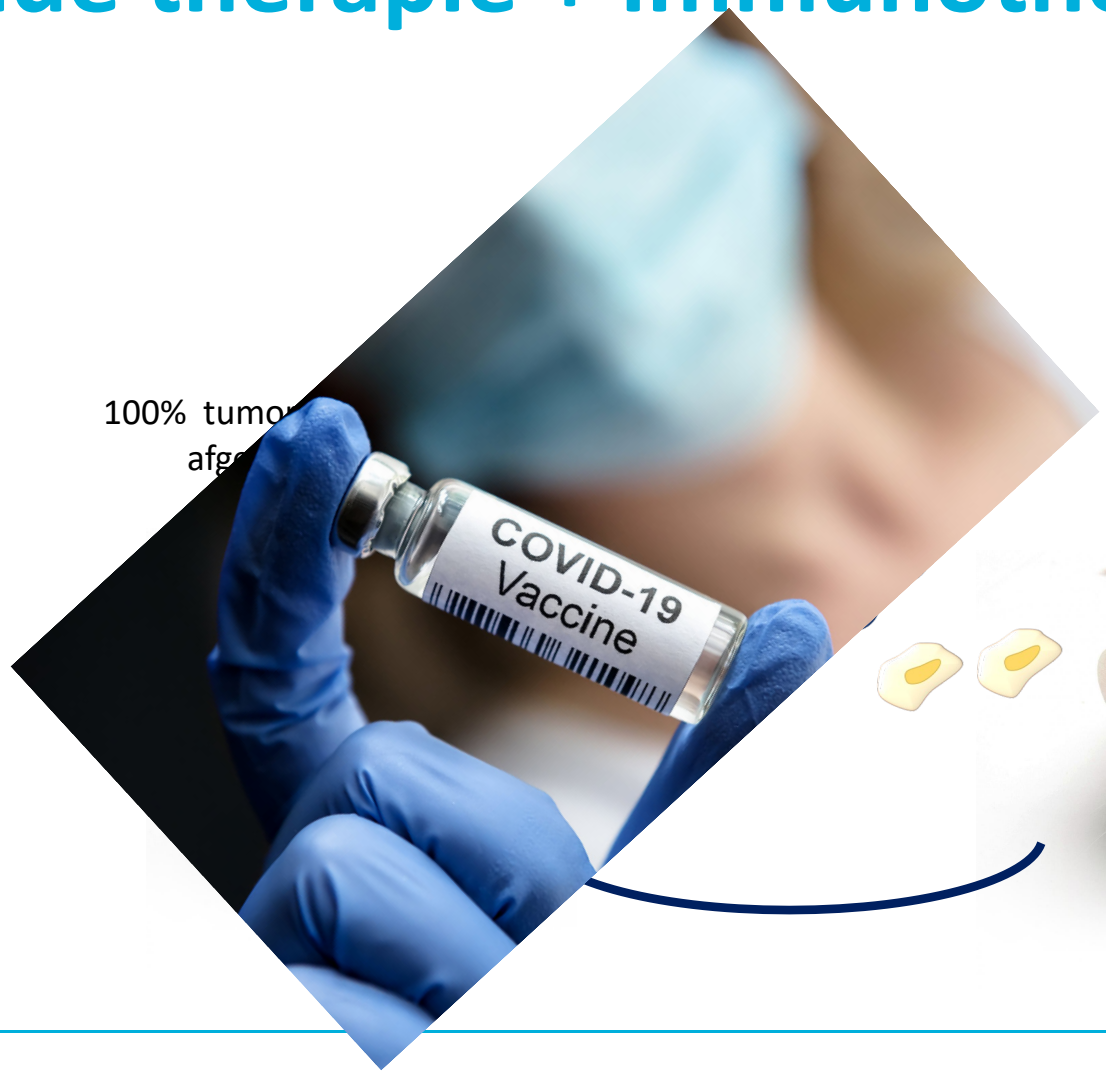
Medium dosis
radionuclide therapie (32 Gy)



Hoge dosis
radionuclide therapie (64 Gy)

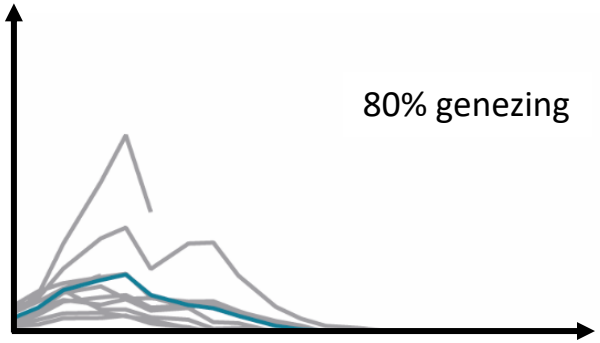


Radionuclide therapie + immunotherapie

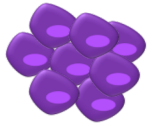


100% tumo
afg

Lage dosis
radionuclide therapie (11 Gy)
+ immuun checkpoint remmers



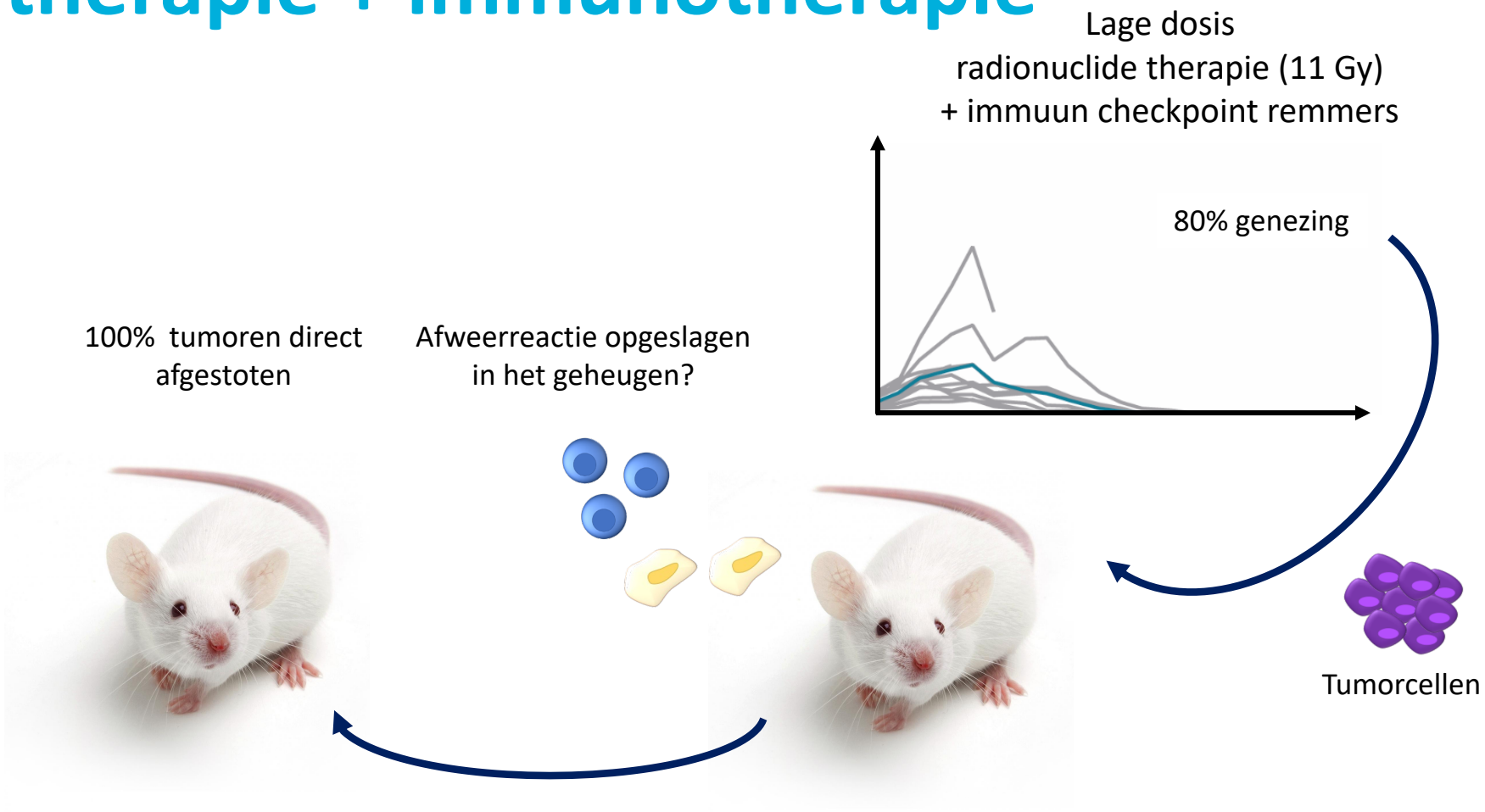
80% genezing



Tumorcellen

Radionuclide therapie + immunotherapie

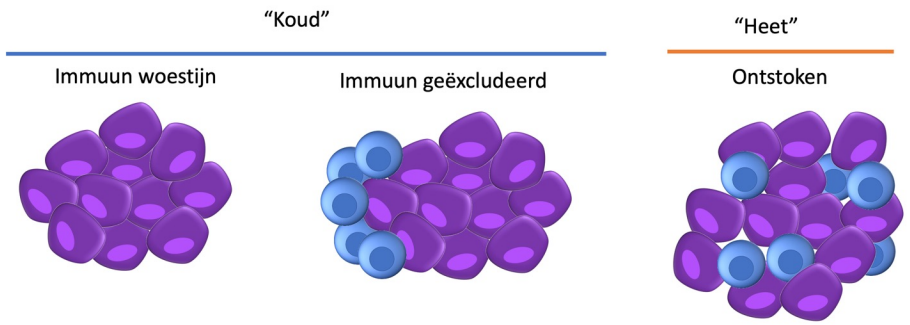
Wat bepaald deze goede respons?

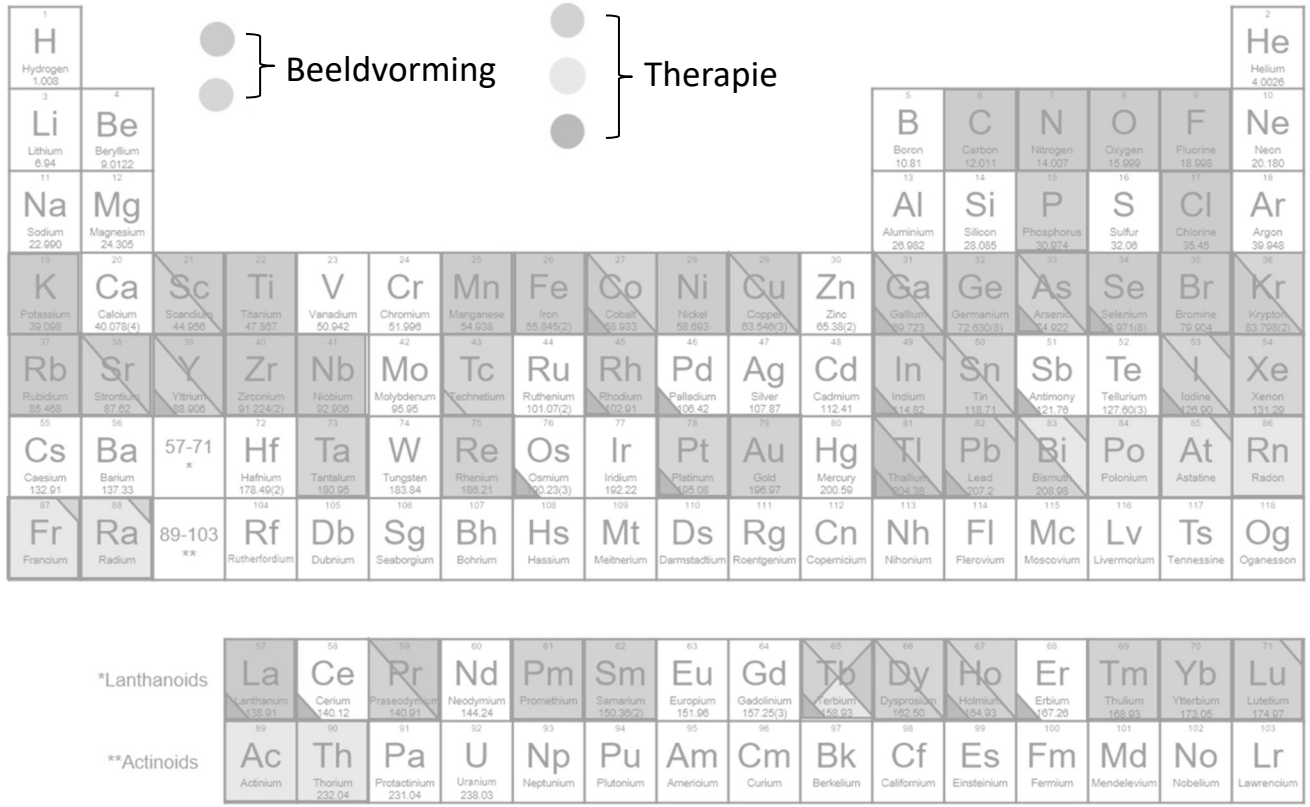


Radionuclide therapie + immunotherapie

- Wat bepaald deze goede respons?

  - Type radionuclide?
  - Stralingsdosis (dosimetrie)?
  - Tumor specifieke eigenschappen?





Toekomstig onderzoek

- **Fundamenteel onderzoek naar lokale en systemische effecten**
  - Verschillende type radionuclide
    - Alfa- versus betastraling
    - Korte versus lange halfwaardetijd
  - Dosis-effect relaties
  - Verschillende type tumoren

- **Betere klinische studies**
  - Effectieve en veilige combinatie van radionuclide en immuuntherapie

Maatschappelijke impact

NIEUWS

Jaarlijks 129 miljoen staatssteun voor nieuwe kernreactor in Petten, van belang voor kankerpatiënten

deVolkskrant

21 september 2022

Lighthouse - Kankerdiagnostiek zonder radioactief afval

Continue beschikbaarheid van belangrijke medische isotopen, zonder nucleair afval en zonder verrijkt uranium.

Ministerie van Economische Zaken en Klimaat

Samenvatting

- Voordelen van radionuclide therapie t.o.v. van externe bestraling
  - Behandeling meerdere metastasen
  - Andere type radioactieve deeltjes
    - Betastraling meest gebruikt in klinische praktijk
    - Alfastraling zeer effectief maar ook risico op bijwerking

- Radionuclide therapie kan de gevoeligheid van tumoren voor immunotherapie verhogen
  - Vervolg onderzoek naar de optimale combinatie:
    - Type radionuclide
    - Dosimetrie
    - Tumor specifieke eigenschappen

→ Effectieve en veilige combinatiebehandeling van radionuclide therapie + immunotherapie voor patiënten met kanker

Thank you for listening!

Questions?

Radboudumc

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