Practopics-Plus

Innovaties in de Radiotherapie, Medische Oncologie en Hematologie
Iridium Netwerk en Oncologisch Centrum GZA
25/3/2022

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Practopics-Plus

- **Dr Carole Mercier MD + Prof Dr Ines Joye MD, PhD, Radiotherapeuten-Oncologen:**
  - Nieuwigheden binnen de Radiotherapie
- **Dr Tom Van den Mooter MD, Internist-Medisch Oncoloog:**
  - Klinische studies in de Oncologie
- **Dr Jan Lemmens MD, Internist-Hematoloog:**
  - Nieuwe moleculen in de Hematologie

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PRACTOPICS:

INNOVATIES IN RADIOTHERAPIE

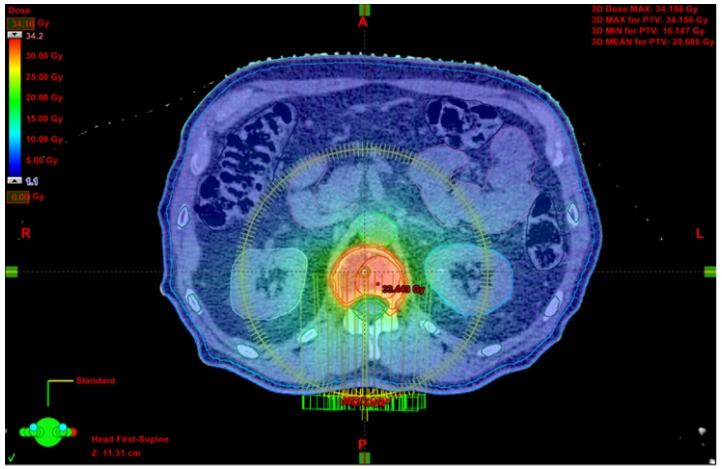
Dr. Ines Joye
Dr. Carole Mercier

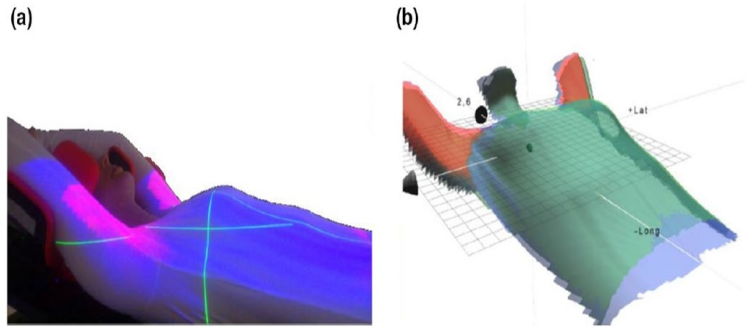
netwerk iridium
Topzorg in radiotherapie

25-03-2022

Voornaamste trends binnen moderne radiotherapie

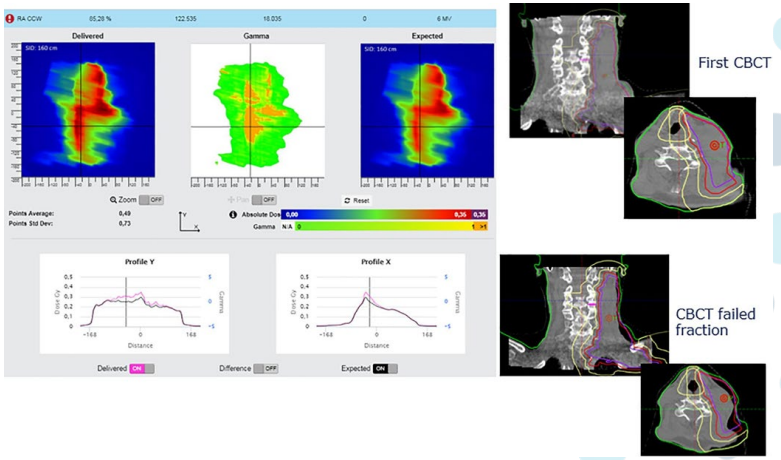
Stereotactische radiotherapie





Surface guided positionering & monitoring

Automatisering & Artificiële Intelligentie

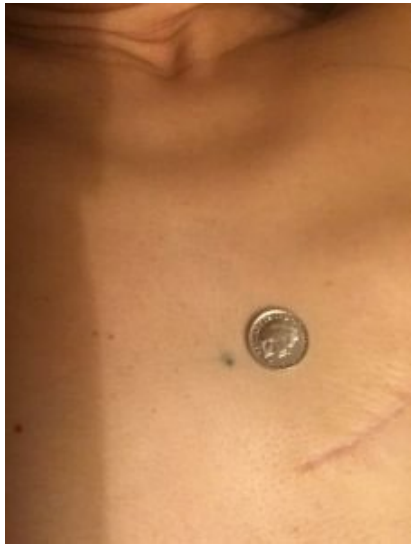


Radiotherapie: patiententraject

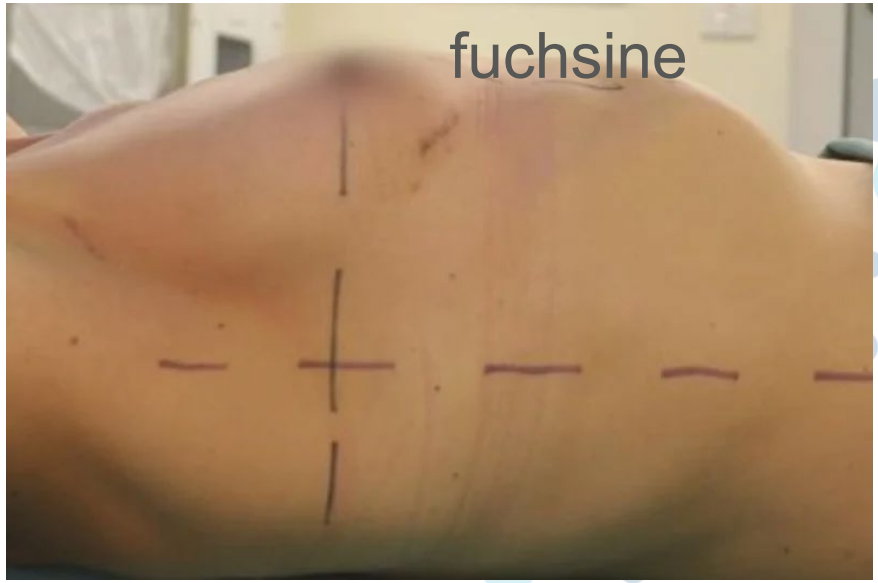
Verwijzing voor RT: status gesprek

SIMULATIE → INTEKENING → PLANNING → BESTRALING

Simulatie

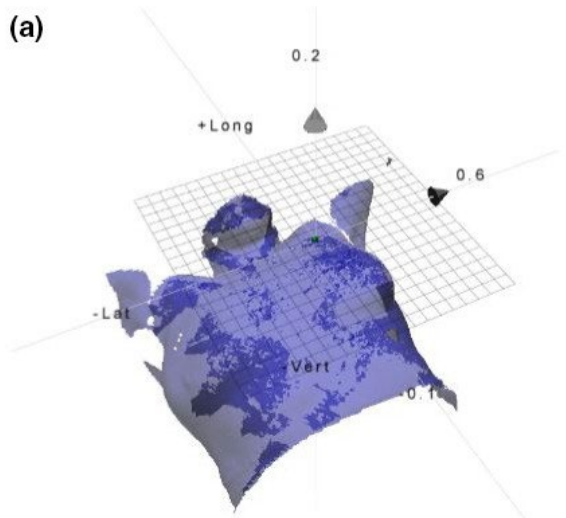


tatoeages

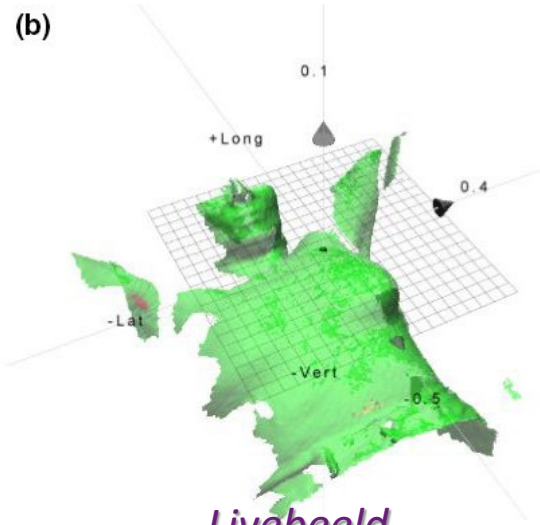


fuchsine

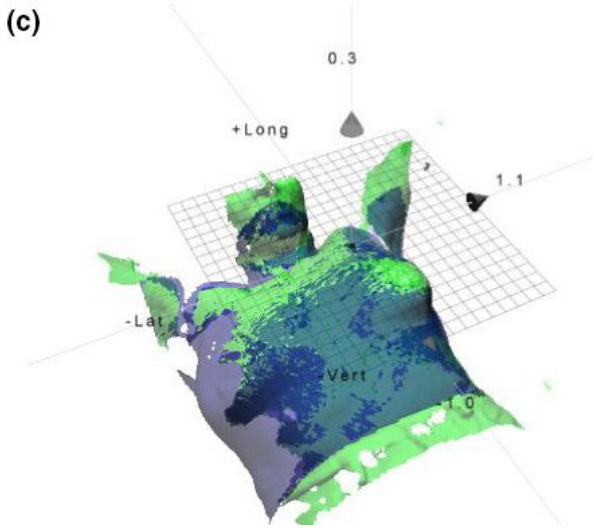
SURFACE GUIDED RADIOTHERAPIE



Referentiebeeld



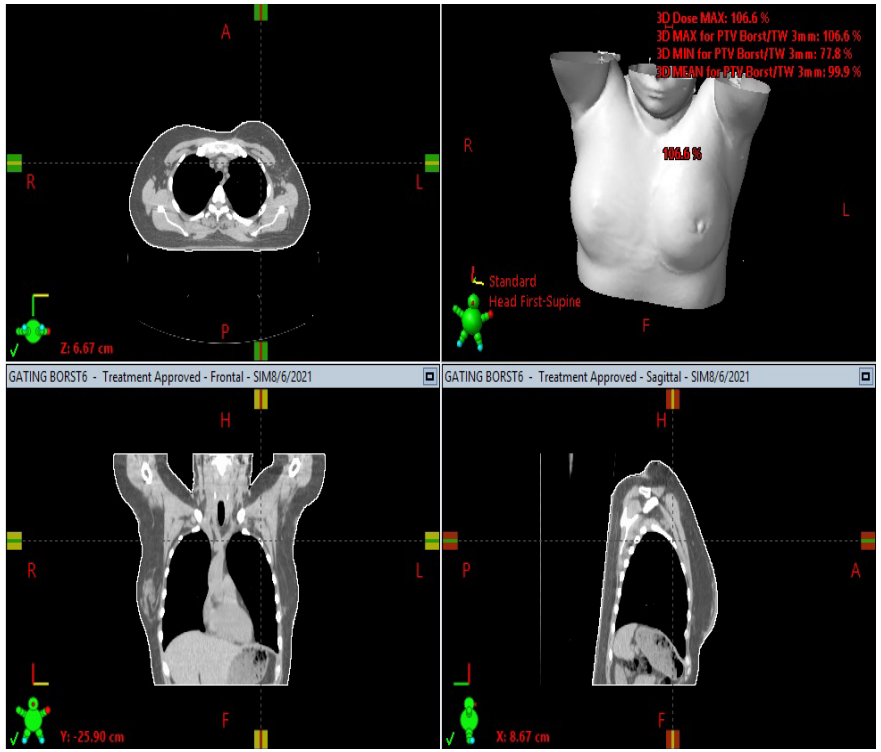
Livebeeld



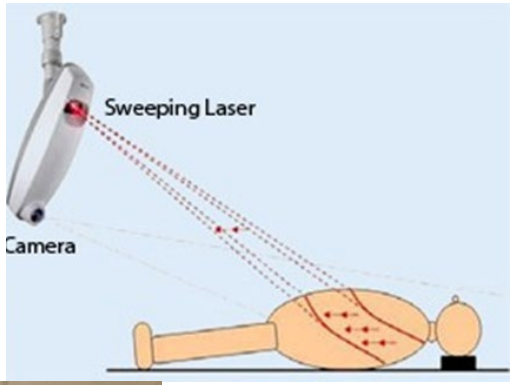
Vergelijking

= Surface van houding **op simulatie**

1. vanuit de planning



2. Bodyscan van op simulatie



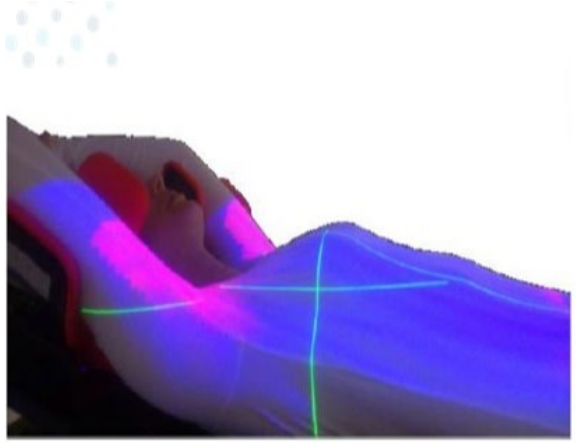
SURFACE GUIDED RADIOTHERAPIE

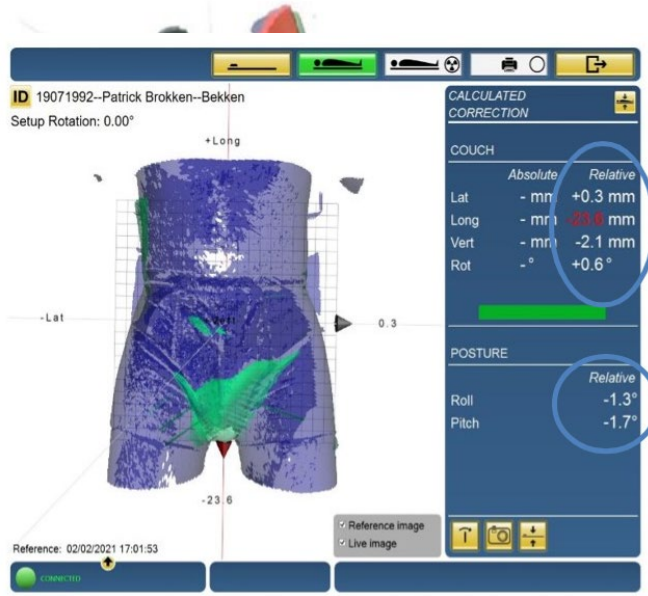
= Surface **tijdens de behandeling**

Camera bestaat uit 2 componenten:

- Projector van LED-licht
  ➔ uitzenden van licht
- CCD (charge coupled device) camera
  ➔ opvangen van licht

Livebeeld



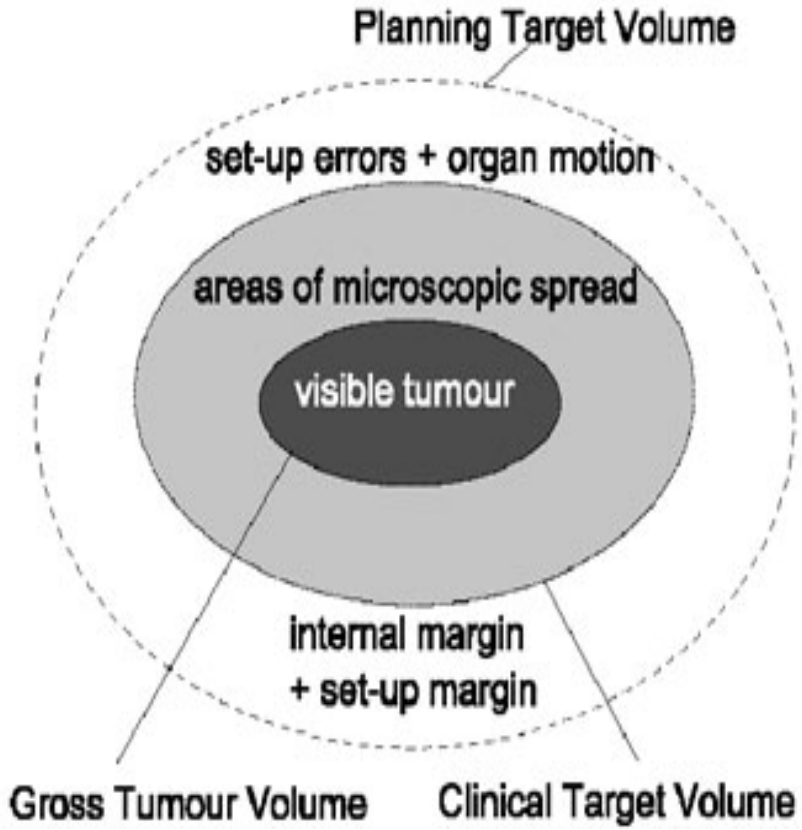


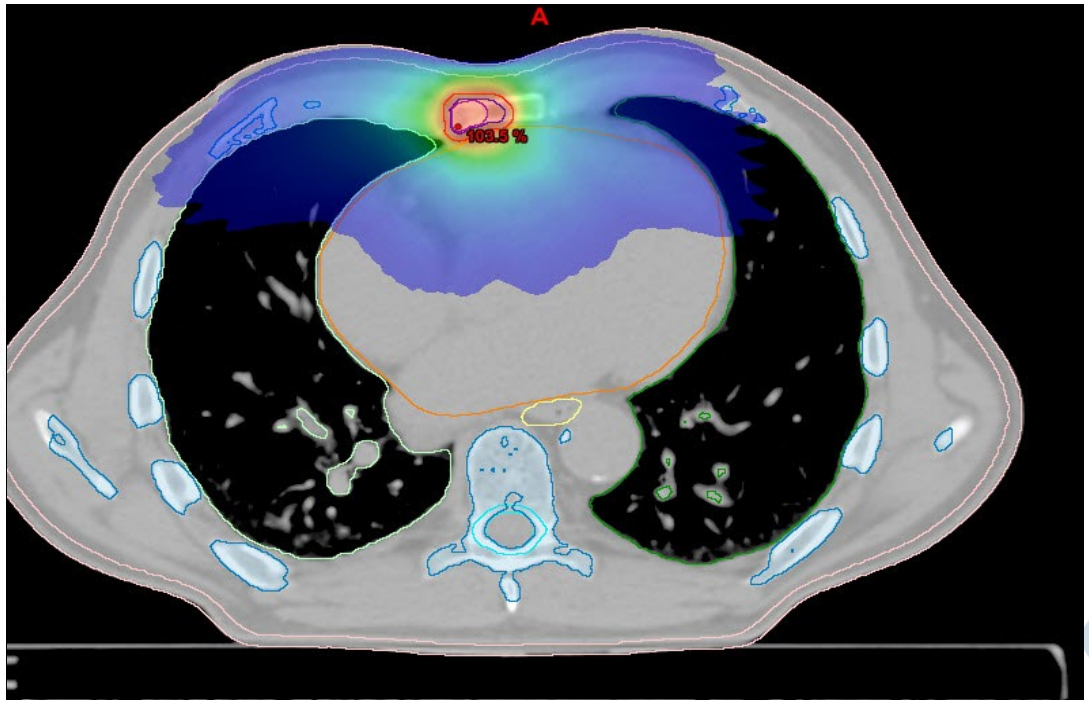
Radiotherapie: patiententraject

Verwijzing voor RT: status gesprek

SIMULATIE → INTEKENING → PLANNING → BESTRALING

Doelvolume bepaling





Radiotherapie: patiententraject

Verwijzing voor RT: status gesprek

SIMULATIE → INTEKENING → **PLANNING** → BESTRALING

Planning

2D-RT 1990 3D-CRT 2000 IMRT 2010 VMAT

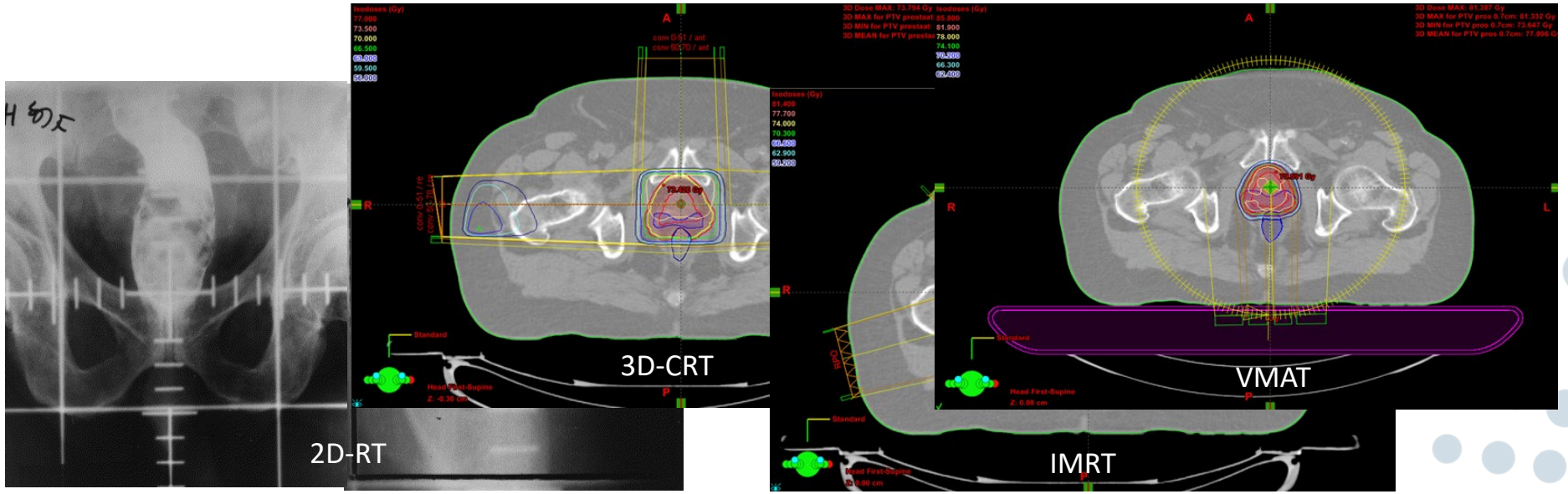
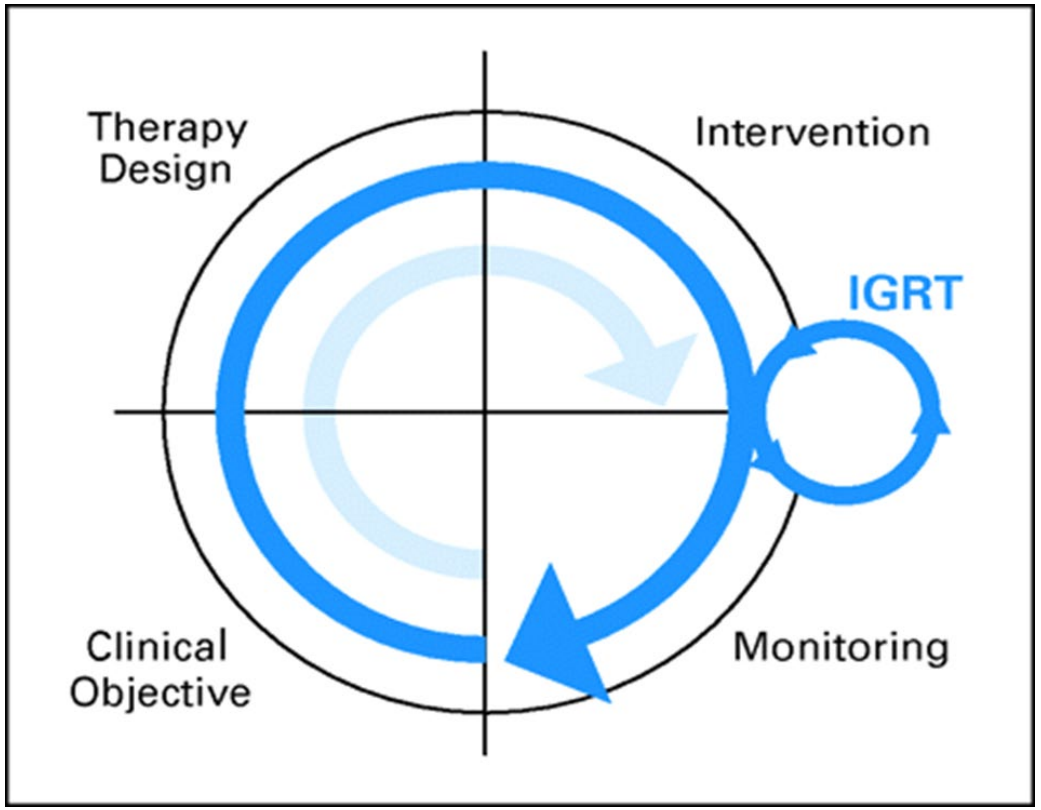
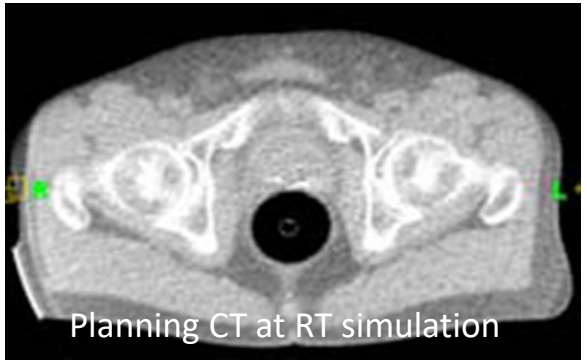
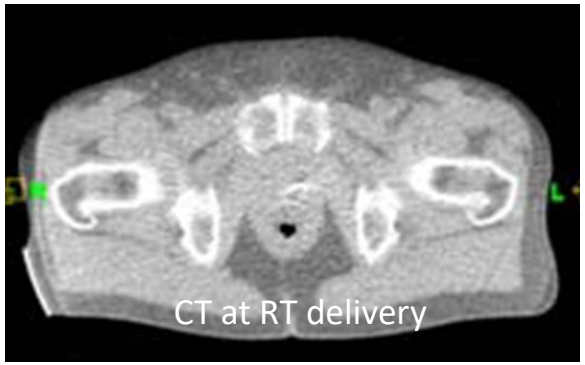


Image guided radiotherapie

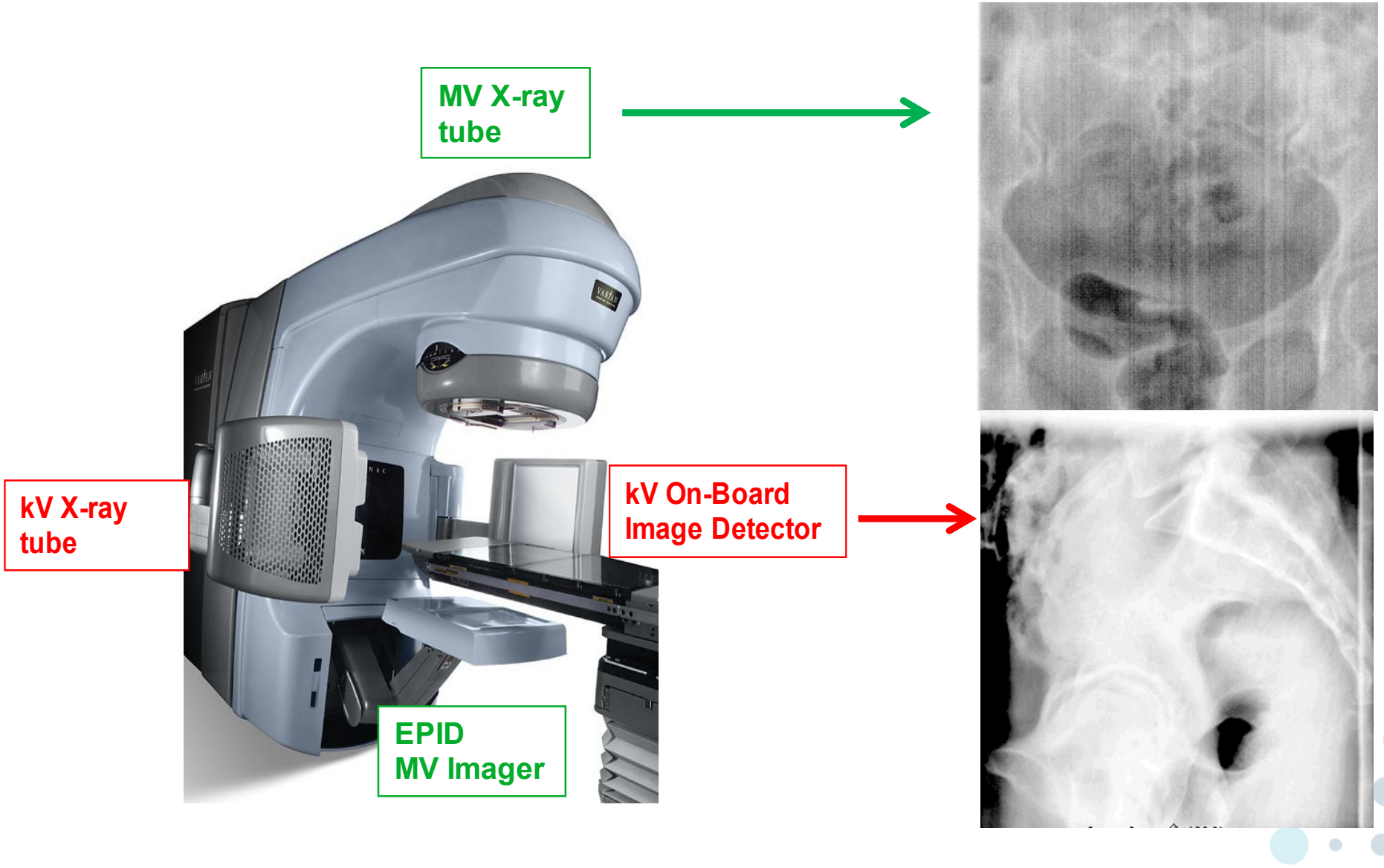




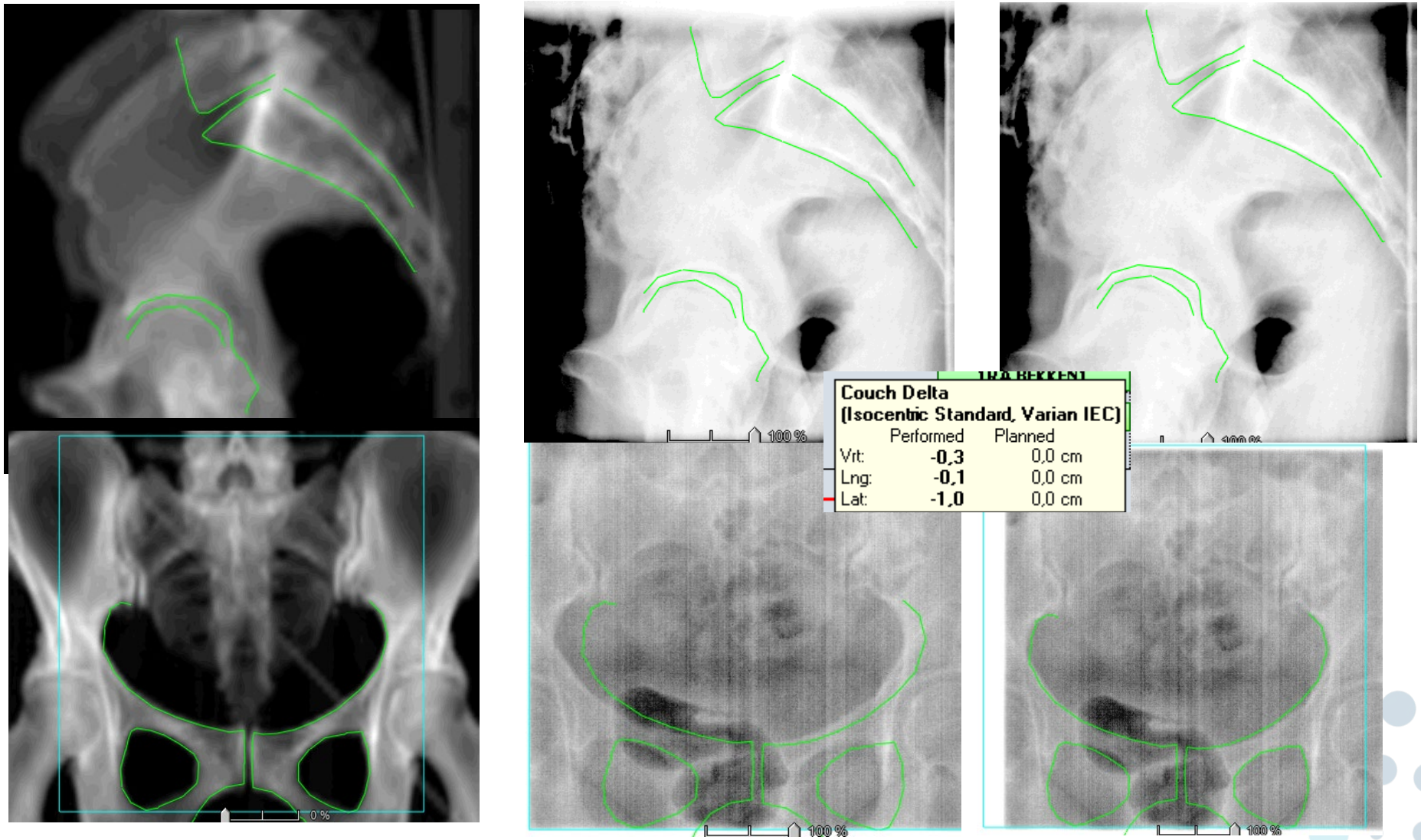


IGRT = making sure that treatment is delivered as planned

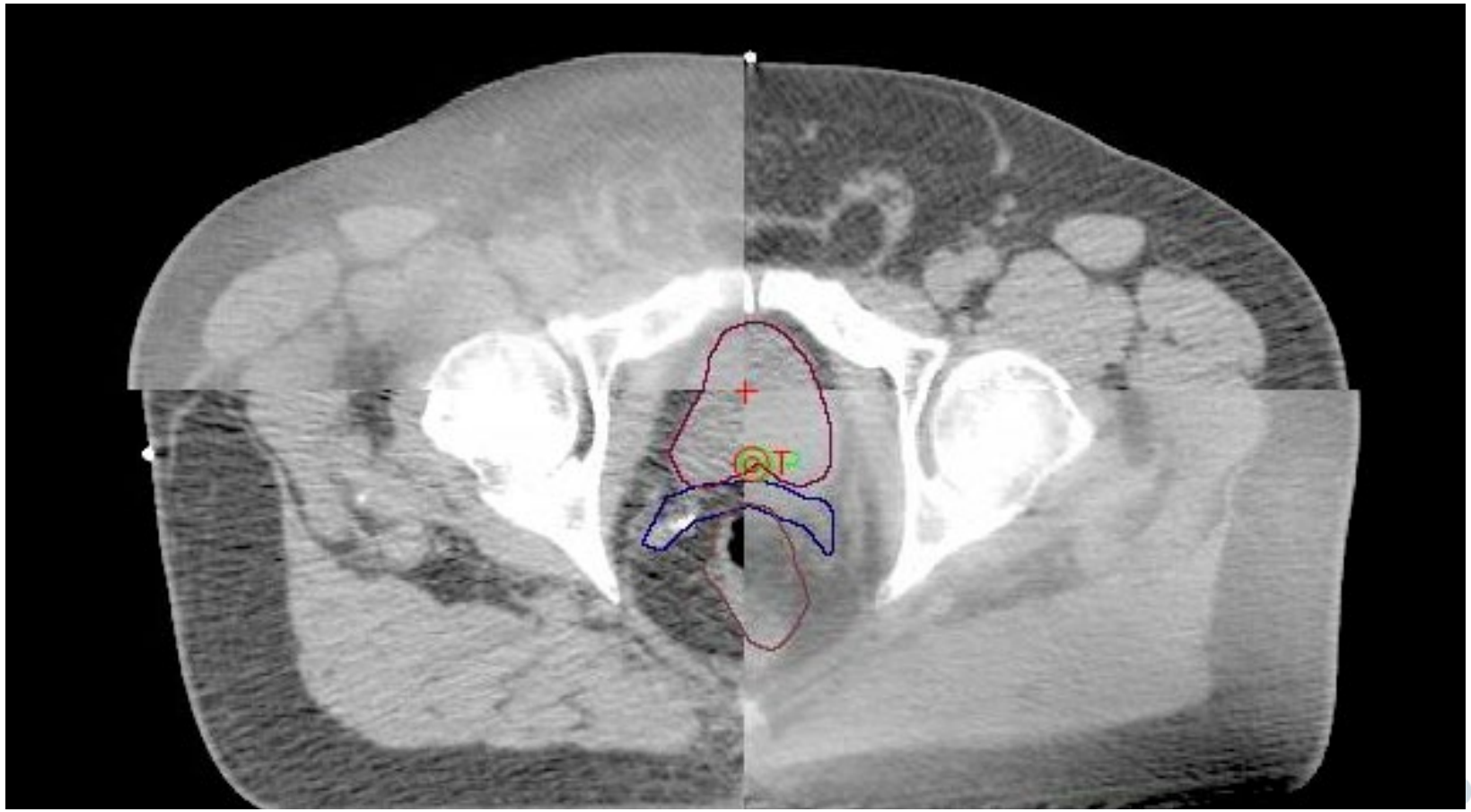
On-board Imaging (OBI)



kV-MV “matching” on bony anatomy



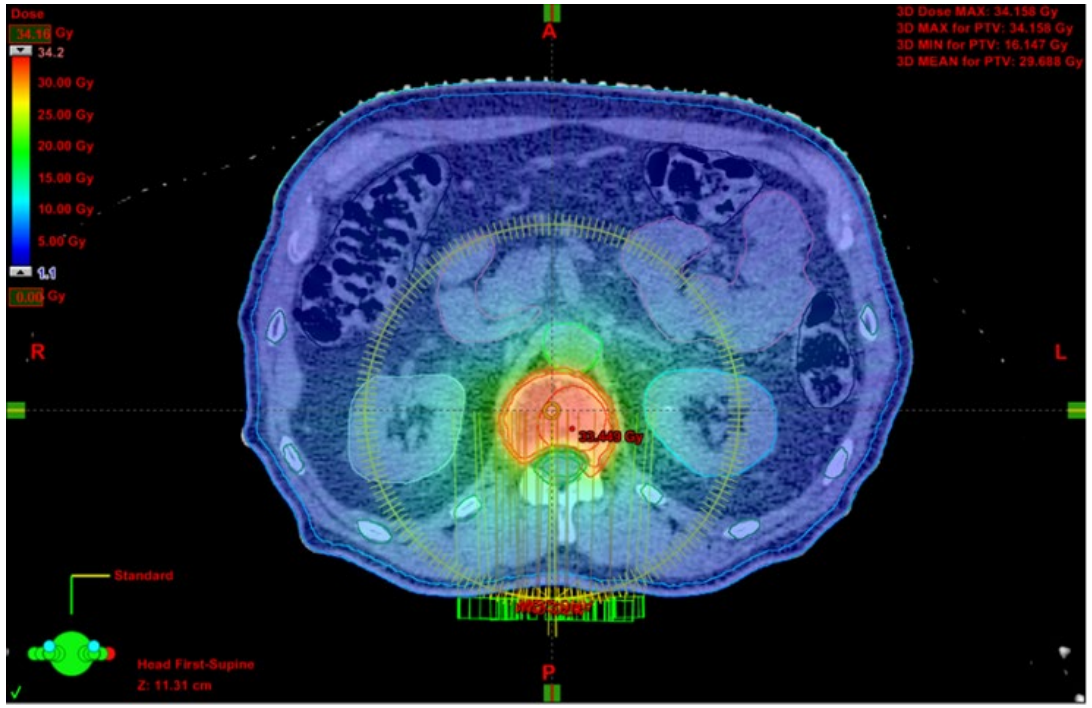
CBCT on soft tissue



Stereotactische bestraling

Dankzij

1. Intensiteits-gemoduleerde RT
2. Image-guided RT

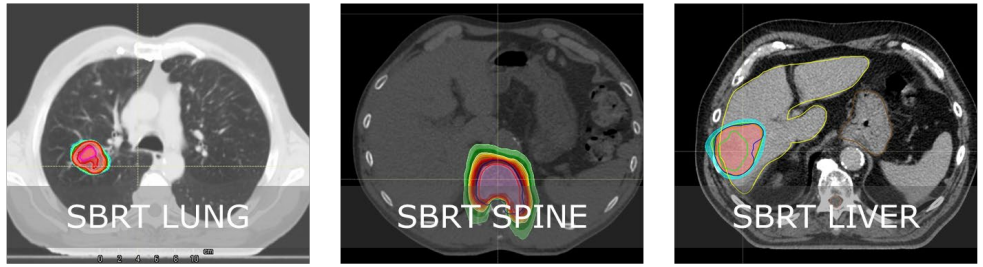


- kleinere marges rondom doelvolume
- hypofractionatie: minder fracties, hogere dosis/fractie

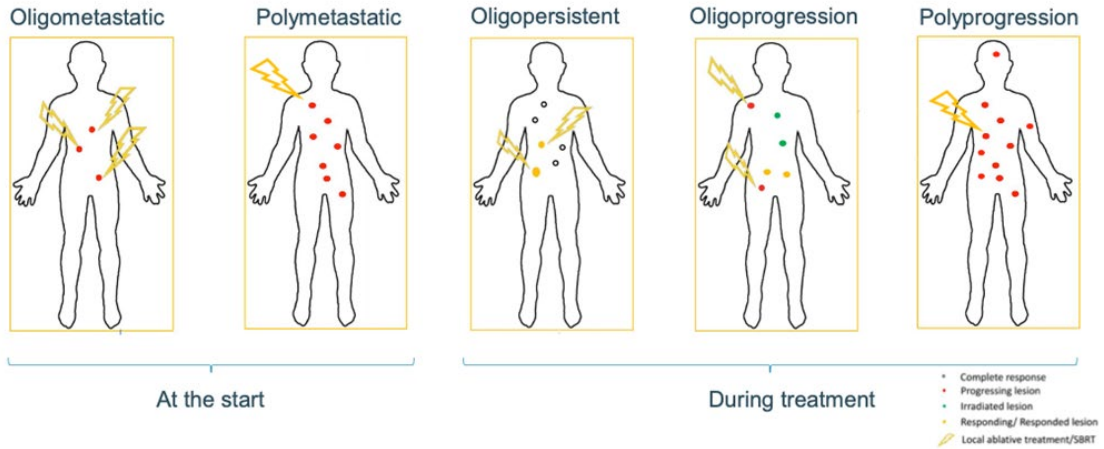
Minder nevenwerkingen, meer effect

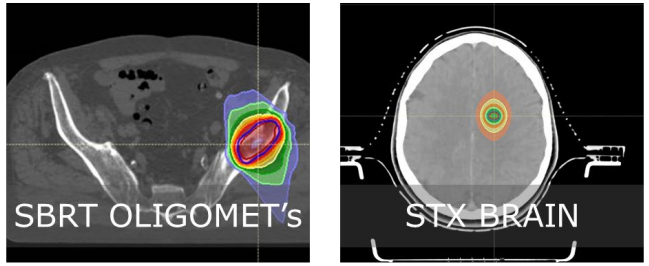
Indicaties stereotactische radiotherapie

1. **Primaire tumoren, o.a.**
- Long
- Prostaat
- Pancreas (KOTK project)

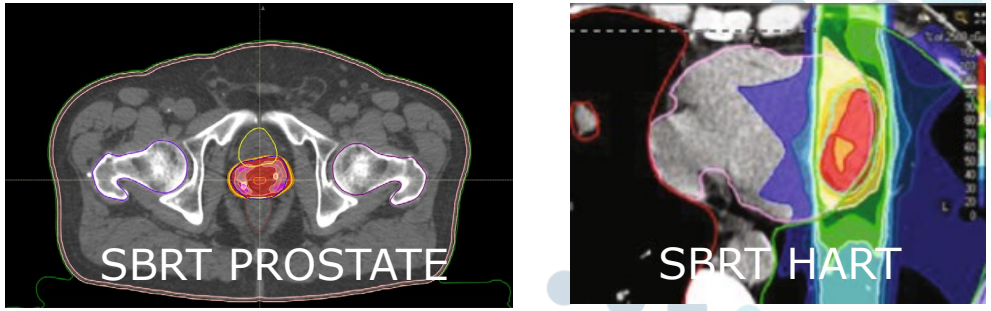


2. **Oligometastasen**





3. Symptomatische metastasen, o.a.
- pijnlijke botmetastasen (ROBOMET-studie)
- myelumcompressie (SABR MESCC studie)



4. Ventriculaire tachycardie (CASTAR-studie)

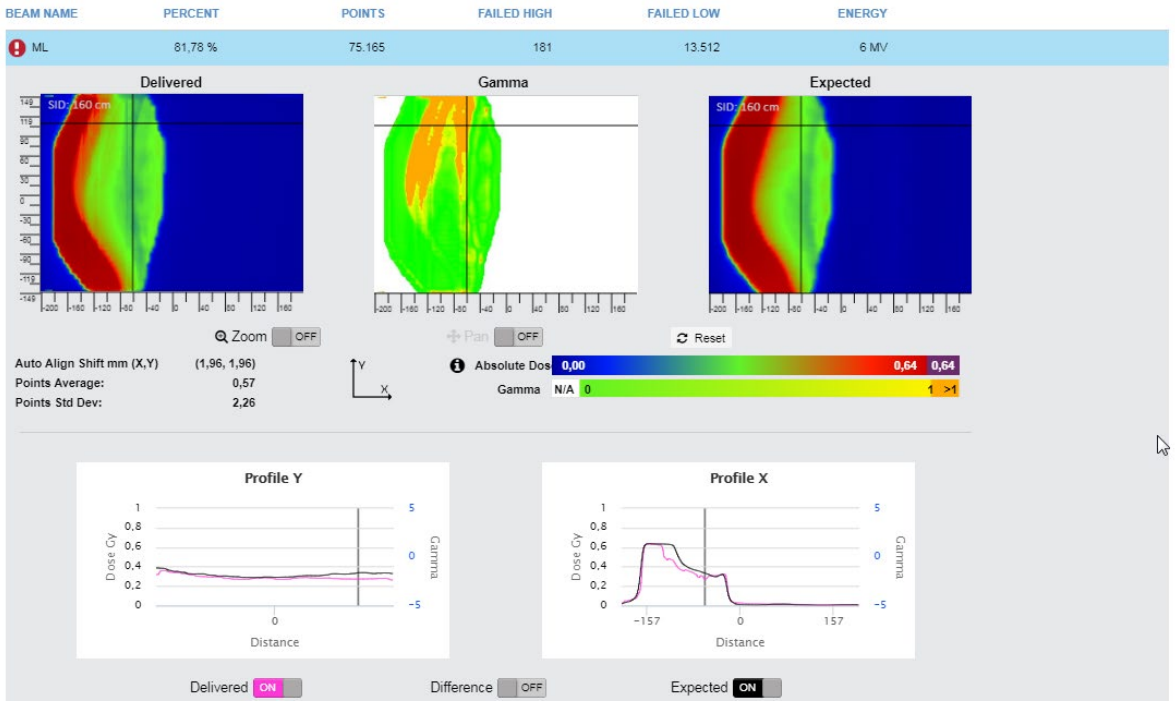
Radiotherapie: patiententraject

Verwijzing voor RT: status gesprek

SIMULATIE → INTEKENING → PLANNING →

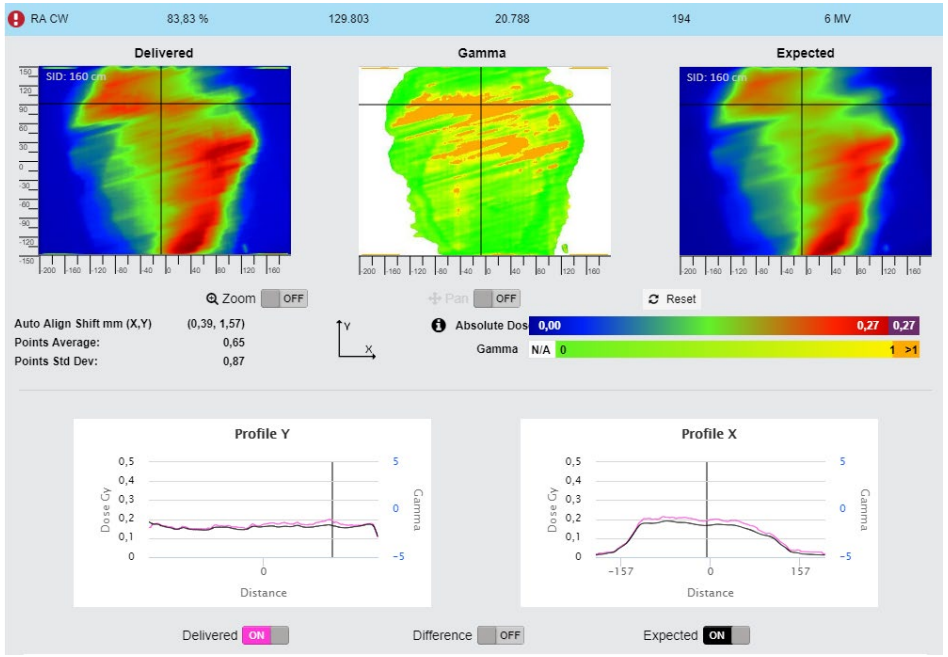
In vivo dosimetrie voor Quality Assurance

PLAN	PRE-TREATMENT QA	IN-VIVO MONITORING	RECENT ACTIVITY
RA HH3	✓	✓ 10 ! 1	✓ 11 FEB 2021
ERA SLKDRM#23	✓	✓ 3	✓ 10 FEB 2021
RA SLOKD8	✓	✓ 2	✓ 05 FEB 2021
LEFTULOBE3	✓	✓ 7 ! 1	✓ 08 FEB 2021
RA GYN SIB3	✓	✓ 16	✓ 12 FEB 2021
RA PROST2	✓	✓ 33 ! 2	✓ 08 FEB 2021
EVAL HER 9FR	✓	✓ 7	✓ 10 FEB 2021
RA HH HER	✓	✓ 20 ! 1	✓ 01 FEB 2021
RA PROST8	✓	✓ 14	✓ 11 FEB 2021
RA LONGEV	✓	✓ 9	✓ 13 JAN 2021
RA LONG1	✓	✓ 19 ! 4	! 15 DEC 2020
AIP LI PUBIS1	✓	✓ 1	✓ 11 FEB 2021
AIP CWZ	✓	✓ 1	✓ 11 FEB 2021

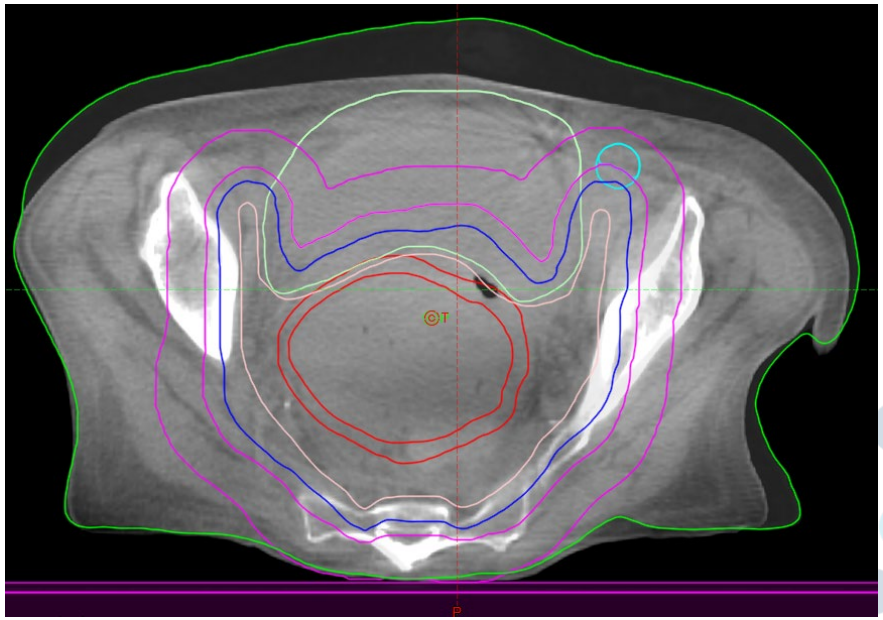


Voorbeelden

Gewichtsverlies, al in eerste fractie

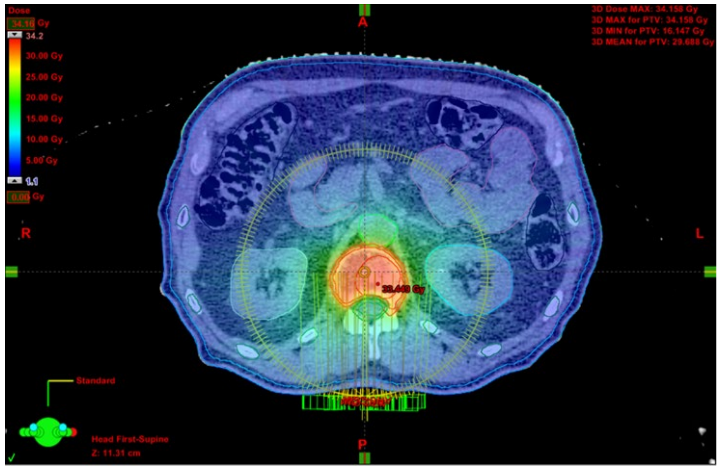


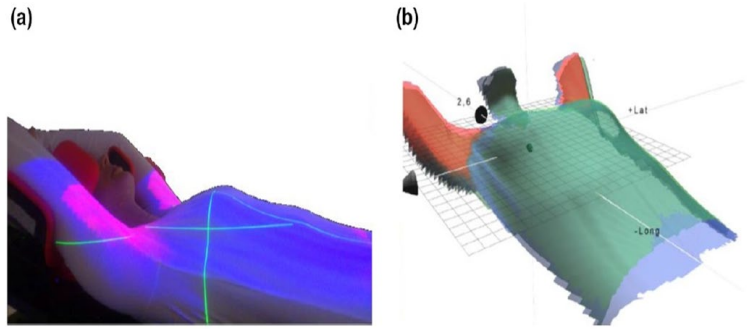
CBCT na slechte meting PerFRACTION



Voornaamste trends binnen moderne radiotherapie

Stereotactische radiotherapie





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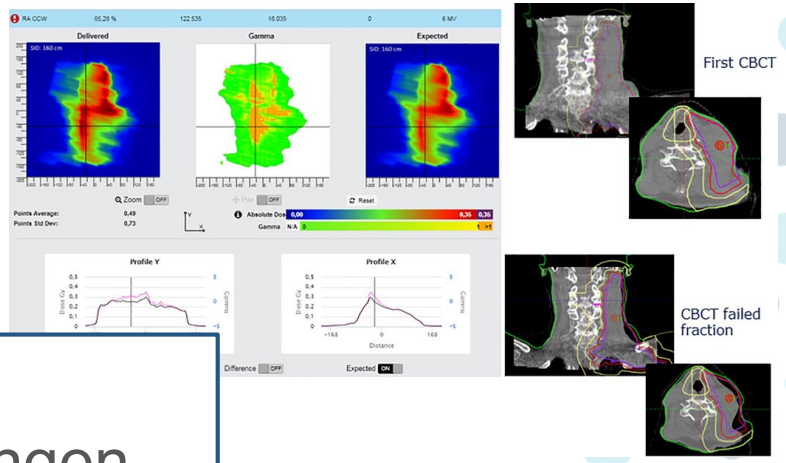

Efficiënter
Minder nevenwerkingen

Klinische studies

Dr. Tom Van den Mooter
Medisch Oncoloog
Oncologisch centrum, GZA ziekenhuizen

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

Declaratie van Helsinki

Inleiding

- Klinische studies in de oncologie hebben in de laatste decenia gezorgd voor een exponentiële groei aan nieuwe, goedgekeurde diagnostische middelen en behandelingsmogelijkheden
- Gemiddeld is er nood aan 14 jaar ontwikkeling alvorens beschikbaarheid[1]

[1]: bron FAGG

Table 1. The following list of ADCs that have been approved by the FDA as of July 2021.

Drug	Trade name	Maker	Condition	Approval Year
Gemtuzumab ozogamicin	Mylotarg	Pfizer/Wyeth	relapsed acute myelogenous leukemia (AML)	2000, 2017
Brentuximab vedotin	Adcetris	Seattle Genetics, Millennium/Takeda	relapsed HL and relapsed sALCL	2011
Trastuzumab emtansine	Kadcyla	Genentech, Roche	HER2-positive metastatic breast cancer (mBC)	2013
Inotuzumab ozogamicin	Besponsa	Pfizer/Wyeth	CD22-positive B-cell precursor acute lymphoblastic leukemia	2017
Moxetumomab pasudotox	Lumoxiti	Astrazeneca	hairy cell leukemia (HCL)	2018
Polatuzumab vedotin-piiq	Polivy	Genentech, Roche	diffuse large B-cell lymphoma (DLBCL)	2019
Enfortumab vedotin	Padcev	Astellas/Seattle Genetics	urothelial cancer	2019
Trastuzumab deruxtecan	Enhertu	AstraZeneca/Daiichi Sankyo	HER2-positive breast cancer	2019
Sacituzumab govitecan	Trodelvy	Immunomedics	triple-negative breast cancer (mTNBC)	2020
Belantamab mafodotin-blmf	Blenrep	GlaxoSmithKline (GSK)	multiple myeloma	2020
Loncastuximab tesirine-lpyl	Zynlonta	ADC Therapeutics	Large B-cell lymphoma	2021

Zhong, L *et al.* Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. *Sig Transduct Target Ther* **6,** 201 (2021).
https://broadpharm.com/web/blog.php?post=adc-approval-2021-antibody-conjugates

Inleiding

Situatie België

- Einde proces > 1/10 vergunning
- België is in Europa één van de landen waar meeste klinische proeven per inwoner worden uitgevoerd.

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Basisregels klinische studies

Declaratie van Helsinki

- Eerste versie 1964 (7 updates, laatste oktober 2013)
- Statement betreffende ethische principes over medisch onderzoek waar menselijke individuen betrokken zijn (incluis menselijk materiaal en data)
- Gekoppeld aan kerndocument medische ethiek: Declaratie van Geneve (1948): *De gezondheid van mijn patiënt zal mijn eerste overweging zijn*
- Gekoppeld aan International Code of Medical Ethics: *een arts zal handelen binnen de patiënts best interest wanneer een medische behandeling gekozen wordt*

https://www.wma.net/

Basisregels klinische studies

Good Clinical Practice (GCP)

Code van internationale standaards betreffende design, uitvoeren, monitoren, auditen, opslaan, analyseren en rapporteren van klinische studies.

GCP verzekert dat studieresultaten waardevol en accuraat zijn en de rechten en confidentialiteit van de deelnemers beschermd

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32005L0028

Basisregels klinische studies

COMMISSION DIRECTIVE 2005/28/EC

of 8 April 2005

laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use ([1]), and in particular Article 1(3), Article 13(1) and Article 15(5) thereof,

Whereas:

(1) Directive 2001/20/EC requires the adoption of principles of good clinical practice and detailed guidelines in line with those principles, minimum requirements for authorisation of the manufacture or importation of investigational medicinal products, and detailed guidelines on the documentation relating to clinical trials to verify their compliance with Directive 2001/20/EC.

(2) The principles and guidelines for good clinical practice should be such as to ensure that the conduct of clinical trials on investigational medicinal products, as defined in Article 2(d) of Directive 2001/20/EC, is founded in the protection of human rights and the dignity of the human being.

(3) Manufacturing requirements to be applied to investigational medicinal products are provided for by Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use ([2]). Title IV of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use ([3]) contains the provisions applied for the authorisation for the manufacture of medicinal products as part of the requirements needed for the application for a marketing authorisation. Article 3(3) of that Directive establishes that these requirements are not applicable for medicinal products intended for research and development trials. It is therefore necessary to lay down minimal requirements regarding applications for and management of authorisations to manufacture or import investigational medicinal products, as well as for the granting and the content of the authorisations, in order to guarantee the quality of the investigational medicinal product used in the clinical trial.

(4) With regard to the protection of trial subjects and to ensure that unnecessary clinical trials will not be conducted, it is important to define principles and detailed guidelines of good clinical practice whilst allowing the results of the trials to be documented for use in a later phase.

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Basisregels klinische studies

Ik doe mee aan een klinische proef, wat zijn mijn rechten?
Als deelnemer/deelneemster hebt u het recht:

- om vrijwillig deel te nemen, zonder dwang of gevolgen als u niet deelneemt;
- om de proef op elk moment te verlaten;
- op gratis behandeling met het onderzochte geneesmiddel, en gewoonlijk op gratis medische onderzoeken in het kader van de klinische proef;
- op een eventuele onkostenvergoeding die door de ethische comités wordt geëvalueerd en een compensatie vormt voor gemaakte onkosten en voor de tijd die wordt gespendeerd om deel te nemen aan de proef; de onkostenvergoeding wordt niet bepaald in functie van het mogelijke risico;
- op alle informatie nodig om uw instemming te kunnen geven vóór elke procedure;
- op duidelijke en begrijpelijke antwoorden op uw vragen;
- onmiddellijk te worden geïnformeerd, zelfs na de start van de proef, in het geval dat er nieuwe gegevens zijn die een impact kunnen hebben op de beslissing om deel te nemen;
- op zorgen die in alle veiligheid worden toegediend, met inachtneming van uw overtuigingen;
- op een vertrouwelijke en anonieme behandeling van uw gegevens;
- op een verzekering die door de opdrachtgever van de proef wordt betaald (no-fault verzekering)

https://www.fagg.be/nl/menselijk_gebruik/geneesmiddelen/geneesmiddelen/onderzoek_ontwikkeling/klinische_proeven/rechten_en

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Basisregels klinische studies

Ik doe mee aan een klinische proef, wat zijn mijn plichten?
Als deelnemer/deelneemster verbindt u uzelf ertoe:

- om waarheidsgetrouwe en volledige informatie te verstrekken over uw gezondheidstoestand en medische voorgeschiedenis en de eventuele behandelingen die u kreeg;
- om het protocol van de klinische proef na te leven en samen te werken met het medisch personeel;
- om de bezoeken en bijkomende evaluaties, die intensief kunnen zijn, op te volgen.

https://www.fagg.be/nl/menselijk_gebruik/geneesmiddelen/geneesmiddelen/onderzoek_ontwikkeling/klinische_proeven/rechten_en

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Basisregels klinische studies

Belgische regulator: Federaal agentschap voor geneesmiddelen en gezondheidsproducten

De experten van het FAGG evalueren de kwaliteit en veiligheid van de experimentele geneesmiddelen die in de klinische proeven worden gebruikt. Het FAGG garandeert u een gepaste bescherming tijdens uw deelname aan een klinische proef.

In samenwerking met de ethisch comités gaat het FAGG na of door de sponsor een adequate bescherming wordt geboden aan elke deelnemer aan de klinische proef.

Het FAGG staat ook in voor de inspectie van de klinische proef gedurende het volledige proces en waakt over de naleving van de goede klinische praktijken.

Basisregels klinische studies

Geïnformeerde toestemming (ICF):

- Noodzakelijk voor start klinische studie
- Geen contract (steeds “withdrawl” mogelijk)
- Oplijsting van onderzoeksvra(a)g(en), procedures, te verwachten toxiciteit, mogelijk te vewachten effect…
- Verplicht up-to-date te houden (nieuwe bevindingen binnen studie, eventueel nieuwe onderzoeksvragen)

Basisregels klinische studies

1. Waarom wordt de deelnemer gevraagd om deel te nemen? Wat is het doel van de studie? Vermeld tevens de ziekte van de deelnemer, en indien van toepassing, zijn beperkte levensverwachting.
2. Wat is het doel van dit document?
3. Zal de deelnemer voordeel halen uit de studie?
4. Hoe zal het studiegeneesmiddel worden toegediend?
5. Welke belangrijkste (meest frequent, meest pijnlijke) onderzoeken zal de patiënt moeten ondergaan?
6. Wat is de duur van de studie?
7. Zal het studiegeneesmiddel bijwerkingen hebben?
8. Werd er een verzekering afgesloten in geval er iets mis gaat in de studie?
9. Kan de deelnemer (of zijn partner) zwanger worden tijdens de studie?
10. Wie betaalt de studiespecifieke kosten en wat moet de deelnemer al dan niet zelf betalen?
11. Worden de gegevens confidentieel behandeld?
12. Staat het de deelnemer vrij om deel te nemen aan de studie?
13. Wie heeft de studiedocumenten nagekeken?
14. Zal de deelnemer na zijn/haar deelname aan de studie, verder kunnen behandeld worden met het studiegeneesmiddel?
15. Wat wordt er verwacht van de deelnemer? Gelieve volgende verwachtingen te vermelden:
    - ermee akkoord gaan dat de onderzoeker de behandelende artsen op de hoogte brengt van de deelname aan de studie
    - niet gelijktijdig aan een andere klinische studie deelnemen
    - relevante informatie meedelen over zijn/haar gezondheidstoestand, andere medicatie of ondervonden symptomen
    - de "in-geval-van-nood-kaart", steeds bijhebben
16. Wie zal de deelnemer meer informatie geven over de studie?

Onderverdeling klinische studies

Klinische studies

- Interventionele studie (*clinical trial*)
- Observationele studie

Clinical trial: specifieke interventie volgens specifiek onderzoeksprotocol of –plan

- Interventie= medicatie, apparaat, procedure of veranderingen in gewoonte (voeding)
- Kan eventueel vergeleken worden met beschikbaar product, placebo of geen interventie

klinische studies

Fasen in productontwi

- Preklinische studies:

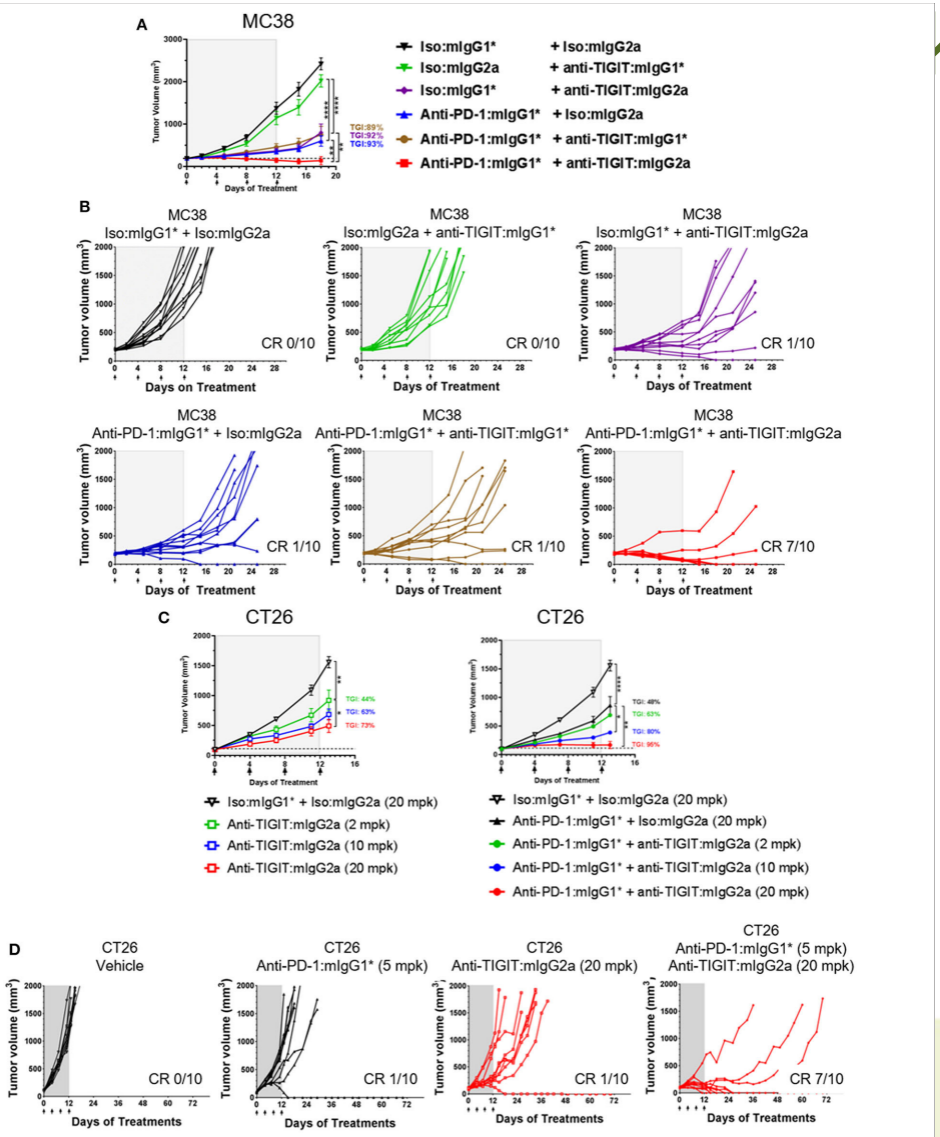

FIGURE 1 | Anti-TIGIT antibody induces anti-tumor response with a certain isotype. **(A,B)** Large (average 190 mm^3), established MC38-bearing mice were enrolled in each group (n=10 per group) and injected with antibodies i.p. every 4 days for times as indicated. **(C,D)** Antibody treatments for *in vivo* titration of anti-TIGIT:mIgG2a (2, 10, or 20 mpk) as a monotherapy or as a combination with anti-PD-1 (5 mpk) have been initiated when CT26 tumor was formed at average 98 mm^3 subcutaneously (n = 10 per group). Dotted lines in **(A,C)** indicate the average tumor volumes at which the antibody treatments had been initiated. Data are representative of at least 3 independent experiments. *$p < 0.05$; **$p < 0.01$; ****$p < 0.001$.

Han J-H et al Effective Anti-tumor Response by TIGIT Blockade Associated With FcγR Engagement and Myeloid Cell Activation. Front. Immunol. 11:573405. doi: 10.3389/fimmu.2020.573405

https://preclinicaltrials.eu/

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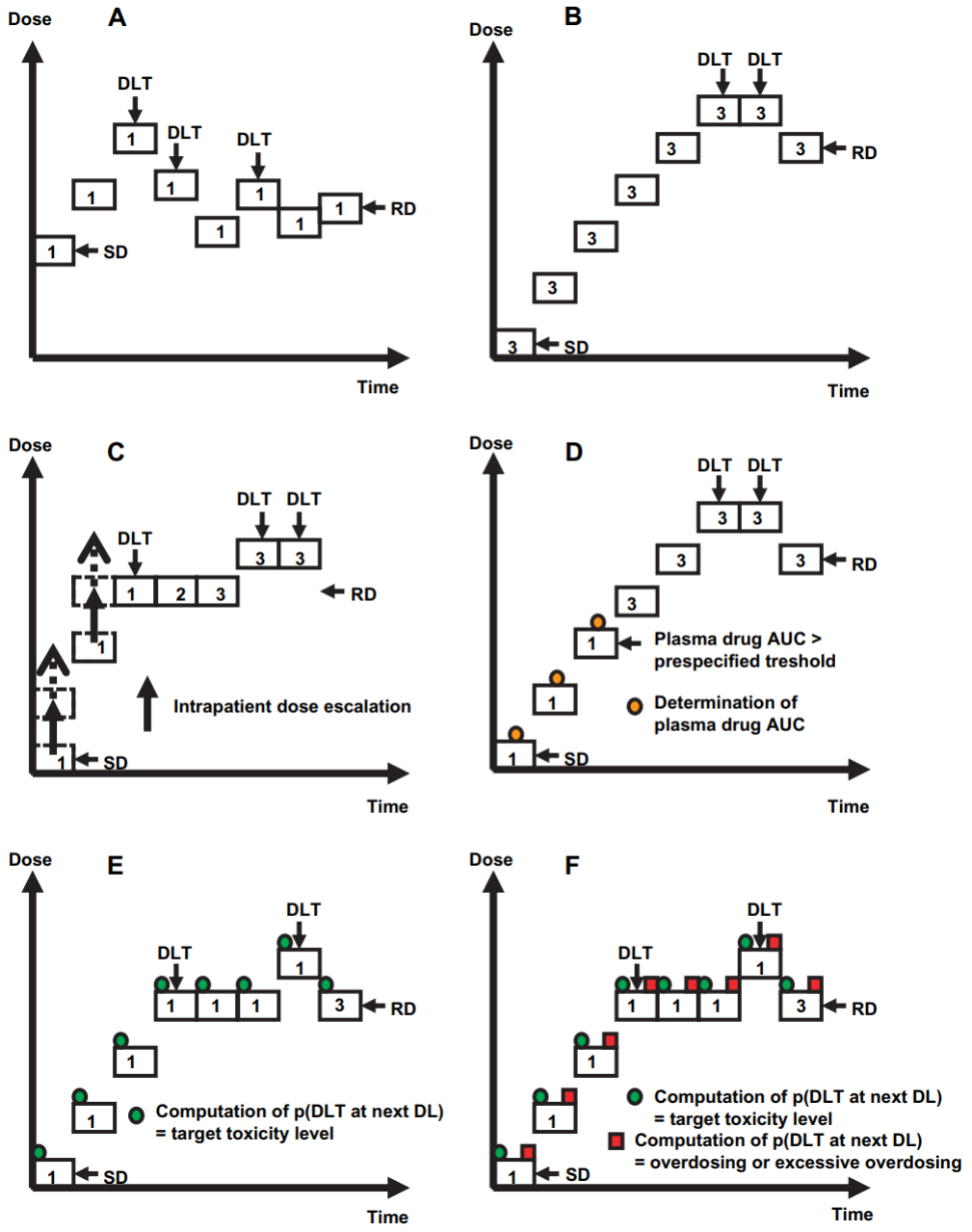
Onderverdeling klinische studies

Fase 1-studie

- Onderzoekssituaties: First in Human (FIH), nieuwe combinatie, interactiestudie…
- Hoofddoelen: zoeken naar MTD/RP2D (optimale dosis), PK/PD, veiligheid (tolerantie en toxiciteit)
- Doelgroep: kleine groep patiënten, geen placebo, (vaak) geen selectie
- Opmerking: early phase 1 (vroeger Fase 0): kleine hoeveelheid (microdosis) in kleine groep vrijwilligers (PK/PD): geen therapeutisch effect te verwachten, geen nevenwerkingen te verwachten

PK = pharmacokinetiek > wat lichaam met product doet (absorptie, metabolisatie, excretie); PD = pharmacodynamiek > wat product met lichaam doet (NADIR, moleculaire tellingen, …); MTD = maximum tolerated dose; RP2D = recommended phase 2 dose



Le Tourneau et al, J Natl Cancer Inst 2009

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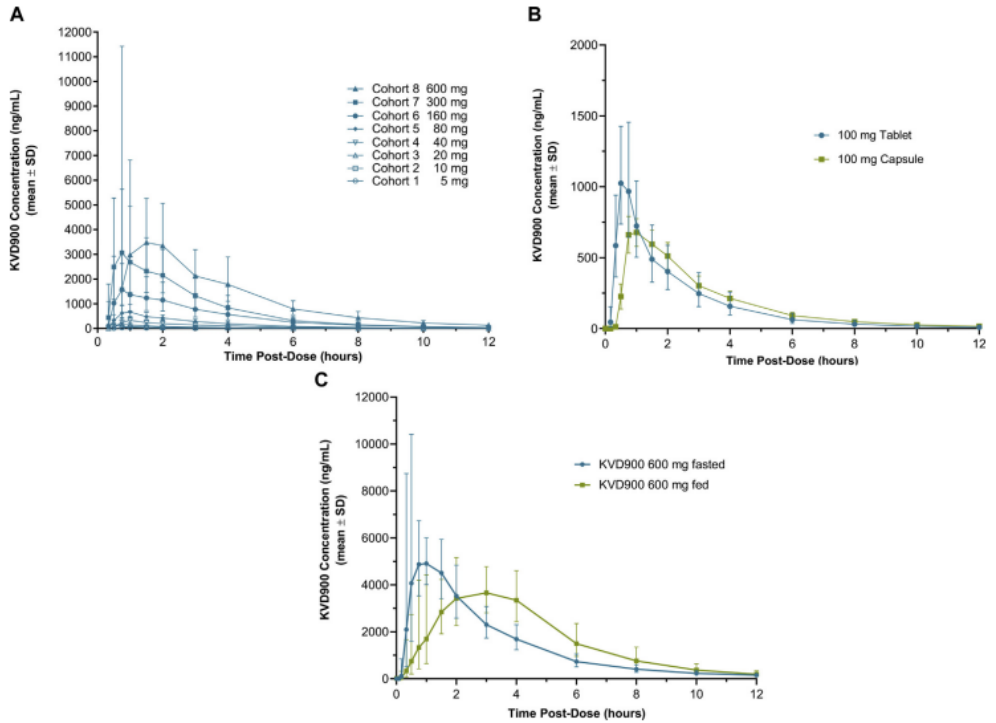


FIG 2. Study 101, KVD900 plasma concentration over time. Single PIC administrations in increasing strengths from 5 mg to 600 mg (**A**), single dose of 100 mg as PIC (*green*) or tablet (*blue*) under fasted conditions (**B**), and single dose of 600 mg as tablet under fasted (*blue*) and fed (*green*) conditions (**C**) (geometric mean ± SD, linear scale).

TABLE III. Estimated PK parameters of KVD900

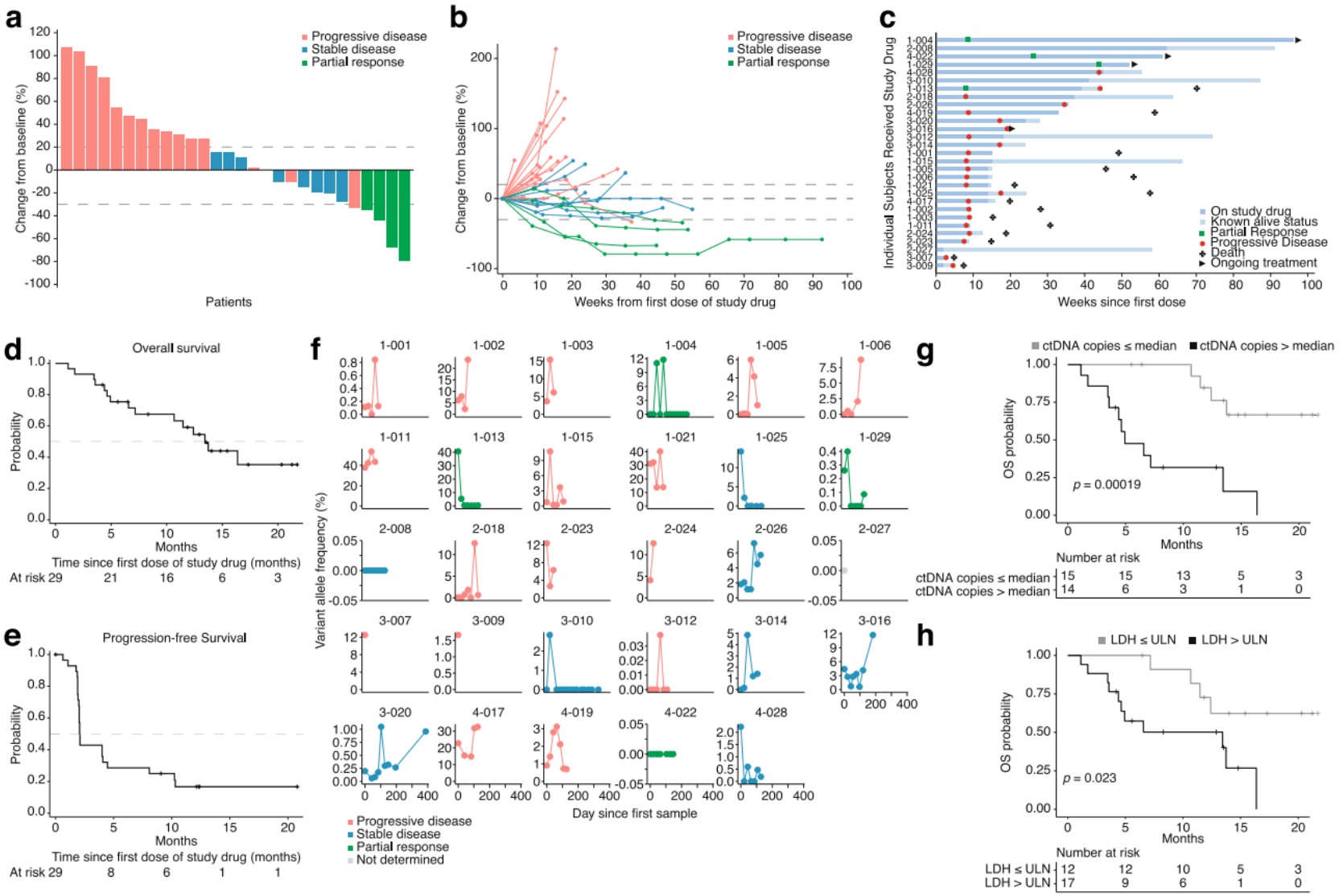
		Part A (PIC single)								Part B (bridging)		Part C (food effect)	
PK variable	Statistical parameter	5 mg (n = 6)	10 mg (n = 6)	20 mg (n = 6)	40 mg (n = 6)	80 mg (n = 6)	160 mg (n = 6)	300 mg (n = 6)	600 mg (n = 6)	100 mg PIC (n = 8)	100 mg tablet (n = 8)	600 mg tab fed (n = 12)	600 mg fasted (n = 12)
C_{max} (ng/mL)	Geometric mean (CV%)	38.7 (28.4)	80.7 (23.6)	169 (31.2)	357 (35.6)	684 (36.1)	1970 (46.5)	3910 (59.6)	4830 (21.9)	772 (34.8)	1180 (30.5)	4550 (22.5)	6460 (22.0)
$AUC_{0\text{-}24}$ (h·ng/mL)	Geometric mean (CV%)	84.3 (29.9)	209 (27.1)	387 (18.5)	995 (62.9)	1970 (27.5)	5500 (37.2)	9220 (43.4)	15,900 (27.4)	1990 (47.7)	2140 (41.5)	21,100 (22.9)	18,600 (22.5)
$AUC_{0\text{-}t}$ (h·ng/mL)	Geometric mean (CV%)	82.9 (30.0)	206 (27.0)	384 (18.5)	992 (64.2)	1990 (27.4)	5540 (37.0)	9260 (43.3)	16,500 (26.7)	2000 (47.6)	2140 (41.5)	21,100 (22.9)	18,600 (22.5)
$AUC_{0\text{-}inf}$ (h·ng/mL)	Geometric mean (CV%)	87.1 (30.5)	210 (26.6)	388 (18.6)	1000 (63.9)	2010 (26.5)	5560 (37.0)	9280 (43.2)	16,800 (25.2)	2010 (47.4)	2150 (41.5)	21,200 (23.0)	19,800 (22.7)
$AUC_{\%extrap}$ (%)	Geometric mean (CV%)	4.78 (18.7)	1.69 (28.6)	1.10 (27.1)	0.707 (46.2)	0.573 (158.3)	0.334 (76.2)	0.130 (79.1)	0.843 (168.1)	0.464 (56.0)	0.377 (62.9)	0.389 (40.6)	2.75 (163)
T_{max} (hours)	Median (range)	0.750 (0.75-1.0)	0.875 (0.5-1.0)	0.750 (0.5-1.5)	1.000 (0.75-2.0)	1.000 (0.75-1.0)	0.625 (0.5-1.5)	0.750 (0.5-2.0)	0.625 (0.5-2.0)	0.875 (0.75-2.0)	0.500 (0.38-0.75)	2.500 (1.0-4.0)	0.500 (0.33-1.5)
K_{el} (1/h)	Geometric mean (CV%)	0.346 (17.5)	0.358 (11.5)	0.344 (20.9)	0.241 (34.5)	0.152 (57.9)	0.123 (48.0)	0.145 (31.0)	0.0594 (37.8)	0.179 (43.6)	0.219 (37.8)	0.213 (16.0)	0.111 (48.7)
$t_{½}$ (hours)	Geometric mean (CV%)	2.01 (17.7)	1.94 (12.4)	2.01 (25.5)	2.88 (41.8)	4.55 (161.7)	5.64 (50.3)	4.79 (31.8)	11.70 (57.4)	3.86 (51.3)	3.16 (68.2)	3.26 (16.1)	6.24 (111)

Maetzel et al, J Allergy Clin Immunol 2022

Onderverdeling klinische studies

Fase 2

- Onderzoekssituaties: verder onderzoek na fase 1
- Hoofddoel: doeltreffendheid, meer kans om zeldzamere nevenwerkingen mogelijk zichtbaar.
- Doelgroep: grotere groep, iedereen krijgt behandeling, geen placebo



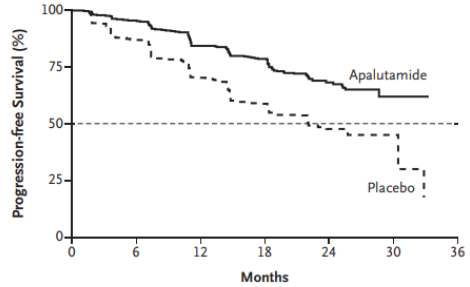
Ny L. et al, Nature communications, 2021

Onderverdeling klinische studies

Fase 3

- Onderzoekssituaties: aftoetsen effectiviteit en veiligheid/verdraagzaamheid aan de klinische situatie.
- Hoofddoel: doeltreffendheid (vaak registratie/autorisatie doeleinden).
- Doelgroep: zeer grote groep, randomisatie in onderzoeksbehandeling of placebo/standaard/geen behandeling (best supportive care)

A Radiographic Progression–free Survival



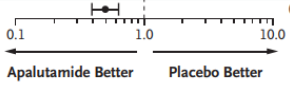
No. at Risk							
Apalutamide	525	469	389	315	89	2	0
Placebo	527	437	325	229	57	3	0

	No. of Patients	Median Radiographic Progression–free Survival (95% CI) *mo*	Patients with Radiographic Progression–free Survival at 24 Mo (95% CI) %
Apalutamide	525	NE	68.2 (62.9–72.9)
Placebo	527	22.1 (18.5–32.9)	47.5 (42.1–52.8)

Hazard ratio for radiographic progression or death, 0.48 (95% CI, 0.39–0.60)
P<0.001

B Subgroup Analysis

Subgroup	Apalutamide *no. of events/no. of patients*	Placebo *no. of events/no. of patients*	Apalutamide *median radiographic progression–free survival (mo)*	Placebo *median radiographic progression–free survival (mo)*	Hazard Ratio for Radiographic Progression or Death (95% CI)
All patients	134/525	231/527	NE	22.1	0.49 (0.40–0.61)
Baseline ECOG performance status					
0	79/328	142/348	NE	30.5	0.52 (0.39–0.68)
1	55/197	89/178	28.7	15.0	0.42 (0.30–0.59)
Geographic region					
North America and European Union	32/173	67/173	NE	30.5	0.43 (0.28–0.66)
Other	102/352	164/354	NE	21.4	0.51 (0.40–0.65)
Bone metastasis only at baseline					
Yes	49/289	102/269	NE	32.9	0.38 (0.27–0.54)
No	85/236	129/258	NE	18.2	0.60 (0.46–0.80)
Visceral disease and bone metastasis at baseline					
Yes	25/56	38/72	23.7	14.9	0.71 (0.43–1.18)
No	109/469	193/455	NE	23.0	0.46 (0.37–0.59)
Gleason score at diagnosis					
≤7	41/174	65/169	NE	30.5	0.53 (0.36–0.78)
>7	93/351	166/358	NE	18.6	0.48 (0.37–0.61)
Previous docetaxel use					
Yes	10/58	19/55	NE	22.1	0.47 (0.22–1.01)
No	124/467	212/472	NE	22.0	0.49 (0.39–0.62)
Age					
<65 yr	40/149	85/182	NE	18.4	0.45 (0.31–0.66)
65–74 yr	61/243	105/232	NE	22.0	0.47 (0.34–0.64)
≥75 yr	33/133	41/113	NE	32.9	0.65 (0.41–1.03)
Baseline PSA above median					
Yes	92/285	119/241	NE	15.4	0.51 (0.39–0.67)
No	42/240	112/286	NE	30.5	0.39 (0.27–0.56)
Baseline LDH above ULN					
Yes	21/60	30/60	22.4	14.6	0.57 (0.33–1.00)
No	109/443	191/442	NE	23.0	0.48 (0.38–0.61)
Baseline ALP above ULN					
Yes	69/177	98/180	22.4	14.7	0.54 (0.40–0.74)
No	64/346	133/345	NE	30.5	0.42 (0.31–0.57)
Disease volume					
High	109/325	173/335	NE	14.9	0.53 (0.41–0.67)
Low	25/200	58/192	NE	30.5	0.36 (0.22–0.57)
Metastasis stage at initial diagnosis					
M0	17/85	23/59	NE	NE	0.41 (0.22–0.78)
M1	108/411	196/441	NE	22.0	0.49 (0.39–0.63)



Kim N. et al, NEJM, 2019

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Onderverdeling klinische studies

- Speciale situaties
  - Fase 4: postautoristatiestudie met als doel levenskwaliteitsgegevens (quality of life, QoL) en kosteneffectiviteit of bijkomende effectiviteitsgegevens
  - Soms worden 2 fasen gecombineerd (Fase 1/2 of 2/3) om sneller resultaten te bekomen met minder patiënte
  - Belangrijk! Na autorisatie en terugbetaling meldingen blijven maken van nevenwerkingen via FAGG (https://www.fagg.be/nl/bijwerking)

Veiligheidsonderzoek stopt nooit

Praktische kant

Sponsor: initiatiefnemer voor klinische studie

- Farmaceutische bedrijven (61% in EEA[1])
- Niet-commercieel (39% in EEA[1])
  - Academische centra
  - Vrijwilligersgroepen
  - Andere

CRA

- Ondersteunt, superviseert en monitort administratie en progressie klinische studie in naam van sponsor (outsourcing)

Gegevens EU

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Praktische kant

On-site research team

- Medisch team: principal investigator (PI) en subinvestigators (SI's).
- Zorgteam: studycoordinator (SC), studynurses (SN's) en projectmanagers
- Ondersteunende diensten: juridisch departement (contractonderhandelingen), radiologie, …

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Ons Team

- CTO (Clinical Trials Office) GZA
  - Overkoepelen organisatie voor studies binnen zowel medische oncologie, hematologie als radiotherapie

https://www.gzaziekenhuizen.be/clinical-trials-oncology-cto

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Praktische kant

- Wat moet sponsor doen om studie te kunnen opstarten?

We zitten heden in een overgangsfase tussen het Clinical Trials Directive (CTD) en Clinical Trials Regulation (CTR) > EU wetgeving

Doel van beide (en het CTR bij voornaam) is de *aantrekkelijkheid en favorabele omgeving te verbeteren voor het uitvoeren van klinische research op grote schaal met hoge graad van transparantie en veiligheid voor de deelnemers*

Praktische kant

FAGG

Een klinische proef kan pas van start gaan na een gunstig advies van een erkend Ethisch Comité en als de bevoegde overheid, de afdeling Onderzoek en Ontwikkeling (menselijk gebruik) van het FAGG, geen grote tekortkomingen heeft vastgesteld binnen de wettelijke termijn zoals bepaald in de wet van 7 mei 2004 inzake experimenten op de menselijke persoon

CTR: een aanvraag via informaticasysteem (CTIS of clinical trials information system) voor alle landen in EU en EER.

- Ondersteunen informatie-uitwisseling en collectieve beslissingen
- Verhogen transparantie van informatie in klinische studies
- Verzekeren hoge veiligheid voor alle patiënten in EU-clinical trials

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Praktische kant

- Nieuw sinds 31 januari 2022: bruikbaar vanaf 31 januari 2022 (nog geen verplichting)
- Overgangsperiode van 3 jaar (eerste jaar nog geen verplichting van gebruik CTIS, einde 3 jaar ook oudere trials via CTIS)
- Transparantie:
  - Alle gegevens publiekelijk beschikbaar behalve:
    - Persoonlijke gegevens (gebonden aan GDPR en EU Data protection regulation)
    - Commerciële confidentiële informatie (voornamelijk marktautorisatie)
    - Vertrouwelijke informatie tussen EU-staten gedurende evaluatie
    - Supervisie klinische trials door EU lidstaten
- Onderhoud: EMA, EU en EEA-leden en regulatoren

EU Clinical Trials Register

Help

Home & Search | Joining a trial | Contacts | About | News update

Clinical trials

The European Union Clinical Trials Register allows you to search for protocol and results information on:

- interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA);
- clinical trials conducted outside the EU / EEA that are linked to European paediatric-medicine development.

Learn more about the EU Clinical Trials Register including the source of the information and the legal basis.

The EU Clinical Trials Register currently displays **41854** clinical trials with a EudraCT protocol, of which **6883** are clinical trials conducted with subjects less than 18 years old.
The register also displays information on **18700** older paediatric trials (in scope of Article 45 of the Paediatric Regulation (EC) No 1901/2006).

Phase 1 trials conducted solely in adults and that are not part of an agreed PIP are not public in the EU CTR (refer to European Guidance 2008/C 168/02 Art. 3 par. 2 and Commission Guideline 2012/C 302/03, Art. 5) .

Clinical Trials marked as "Trial now transitioned" were transitioned to the Clinical Trial Regulation 536/2014 and can be further followed in the Clinical Trial Information System

Please enter search term... X Search

Examples: Cancer AND drug name. Pneumonia AND sponsor name.
How to search [pdf]

Advanced Search: Search tools

For support, visit the EMA Service Desk , log in using your EMA account and open a ticket specifying "EU CTR" in your request.
If you do not have an account, please visit the EMA Account management page page click on "Create an EMA account" and follow the instructions.

https://www.clinicaltrialsregister.eu/

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Clinical Trials

English EN | CTIS log in

About | Search clinical trials and reports | CTIS for sponsors | CTIS for authorities | Support

Clinical trials in the European Union

This website supports the undertaking and oversight of clinical trials in the European Union (EU) and European Economic Area (EEA).

It is part of a broad initiative to transform the EU/EEA clinical trials environment in support of large clinical trials in multiple European countries, to the benefit of medical innovation and patients.

A clinical trial is a study performed to investigate the safety or efficacy of a medicine. For human medicines, these studies are carried out in human volunteers.

Learn more about this website →

CTIS for sponsors

Clinical trial sponsors and other organisations involved in running clinical trials can apply to run a trial and can manage an ongoing trial in up to 30 countries in the European Union and European Economic Area via the Clinical Trials Information System (CTIS).

CTIS for authorities

Regulatory authorities, such as national competent authorities and ethics committees of EU Member States and European Economic Area countries can participate in the assessment, authorisation or oversight of a trial.

http://euclinicaltrials.eu/

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Accelerating clinical trials in the EU (ACT EU)

3. Objectives

To deliver on these recommendations it is proposed to establish ACT EU as an EC-HMA-EMA co-led European initiative.

Proposed initiative objectives are:

1. Optimise the EU environment for clinical research in Europe, whilst maintaining high-level participant protection, data robustness and transparency, by:

Verdere ontwikkeling EU als competitief centrum voor innovatieve research

2. Strengthening clinical trials that deliver decisional evidence for unmet medical needs, rare diseases, and on vaccines and therapeutics for public health crises and pandemics, ensuring support for HTA bodies as well as for academic and SME sponsors.

3. Heighten the impact of European clinical trials through excellent and coordinated scientific advice as a complement to trial authorisation and to support marketing authorisation and access throughout the medicine lifecycle.

4. Engage all stakeholders to proactively deliver inclusive patient-oriented medicines development and delivery across populations.

5. Ensure a clear and unified European position on clinical trials in strategic matters at the international level.

6. Build capacity in all aspects of drug development and regulatory science through, amongst others, research collaboration and training with academia.

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/accelerating-clinical-trials-eu-act-eu-delivering-eu-clinical-trials-transformation-initiative_en.pdf

Opzoeken klinische studies

- FAGG: https://databankklinischeproeven.be/nl
- CTR: https://www.clinicaltrialsregister.eu/
- NIH: ClinicalTrials.gov
- WHO: Trialsearch.who.int

Na trials

CHMP: Committee for Medical Products for Human Use

- Voert een evaluatie uit bij humane medicijnen waar een EU-wijde marktautorisatie gevraagd wordt.
- Maakt gebruik van data uit klinische studies

CTG: commissie tegemoetkoming geneesmiddelen (onderdeel RIZIV) vormt advies naar minister van volksgezondheid > eindbeslissing

Perspectief naar (nabije) toekomst

- Heden heel wat trials lopende met vooruitzichten naar toekomst
  - Verbreden van het immuuntherapiespectrum (heden toch nog steeds gedomineerd door PD(-L)1- en CTLA4-remmers)
    - LAG3-inhibitie, TIGIT-inhibitie, CD47-remmers, TIM3-remmer, andere (goedkopere) PD1/PD-L1- en CTLA4-remmers
  - Radiopharmaceuticals (gerichte “radiotherapeutische” behandeling) > radium223 en Lutathera
    - Lu-PSMA > reeds terugbetaald in België, nieuwe doelwitten (FAP en NTSR1)
  - Aangepaste modulering immuuncel (van autologe CAR-T naar allogene?)
  - Bispecifieke antilichamen (therapie voornamelijk binnen hematologie)

Take home messages

- In de behandeling van kanker is een studiebehandeling steeds een optie (onafhankelijk welke fase van de ziekte, dus niet enkel in laatste fase)
- Geen start in klinische studie zolang geen geïnformeerde toestemming voor handen
- Geïnformeerde toestemming bevat alle noodzakelijke informatie voor deelnemer, zo toch bijkomende vragen kunnen deze steeds gesteld worden aan de PI of SI.
- Uiteindelijk heeft patiënt steeds mogelijkheid tot terugtrekking zo hij wenst

Nieuwe Moleculen in de Hematologie

Practopics-Plus

25.03.022

Dr J. Lemmens

Nieuwe Moleculen in de Hematologie

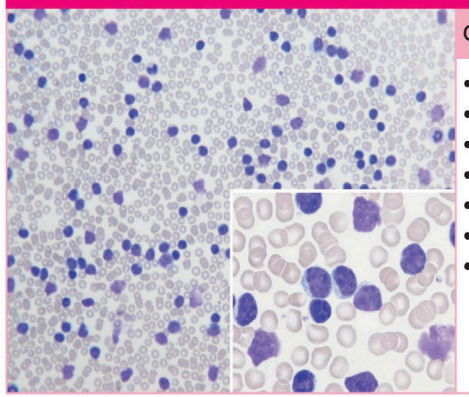
CLL: acalabrutinib (Calquence)

MDS: luspatercept (Reblozyl)

ITP: avatrombopag (Doptelet)

CLL: inleiding

Morphology of CLL



Courtesy: Dr C. Brusselmans, UZ Leuven

CLL cell characteristics

- small
- mature
- narrow border of cytoplasm
- dense nucleus with partially aggregated chromatin
- no discernible nucleoli
- Gumprecht nuclear shadows or smudge cells
- < 55% prolymphocytes

Microscopy blood smear: easy, rapid and inexpensive

MBL-CLL type vs. SLL vs. CLL

Monoclonal B cell lymphocytosis	Small Lymphocytic Lymphoma	Chronic Lymphocytic Leukemia
Clonal B cells < 5000/µl	Clonal B cells < 5000/µl	**Clonal B cells > 5000/µl**
	Lymph-adenopathies +	Lymph-adenopathies +/-
	Organomegaly +/-	Organomegaly +/-
	Cytopenia due to marrow infiltration +/-	Cytopenia due to marrow infiltration +/-
	Constitutional symptoms +/-	Constitutional symptoms +/-

Low-count MBL	High-count MBL
<500/µl	500-5000/µl

Hallek et al. Blood 2018, Swerdlow et al. Blood 2016

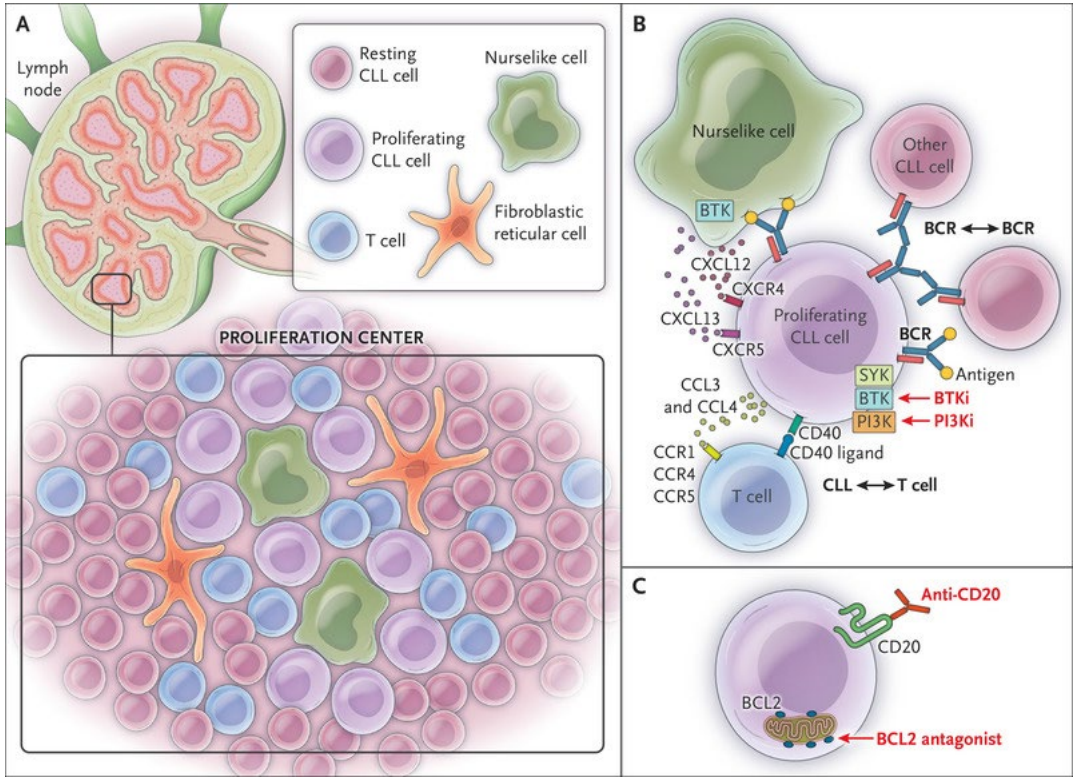
CLL: inleiding

CLL - International Prognostic Index (CLL-IPI) for treatment naïve patients			
Variable		**HR**	**Grading**
17p del/p53 mut	No or Yes	4.2	4
IGV_H	Mut or Unmut	2.6	2
B2 microglobulin	≤ or > 3.5 mg/dl	2	2
Stage	Rai 0 vs 1-4 Binet A vs B-C	1.6	1
Age	≤ or > 65y	1.7	1

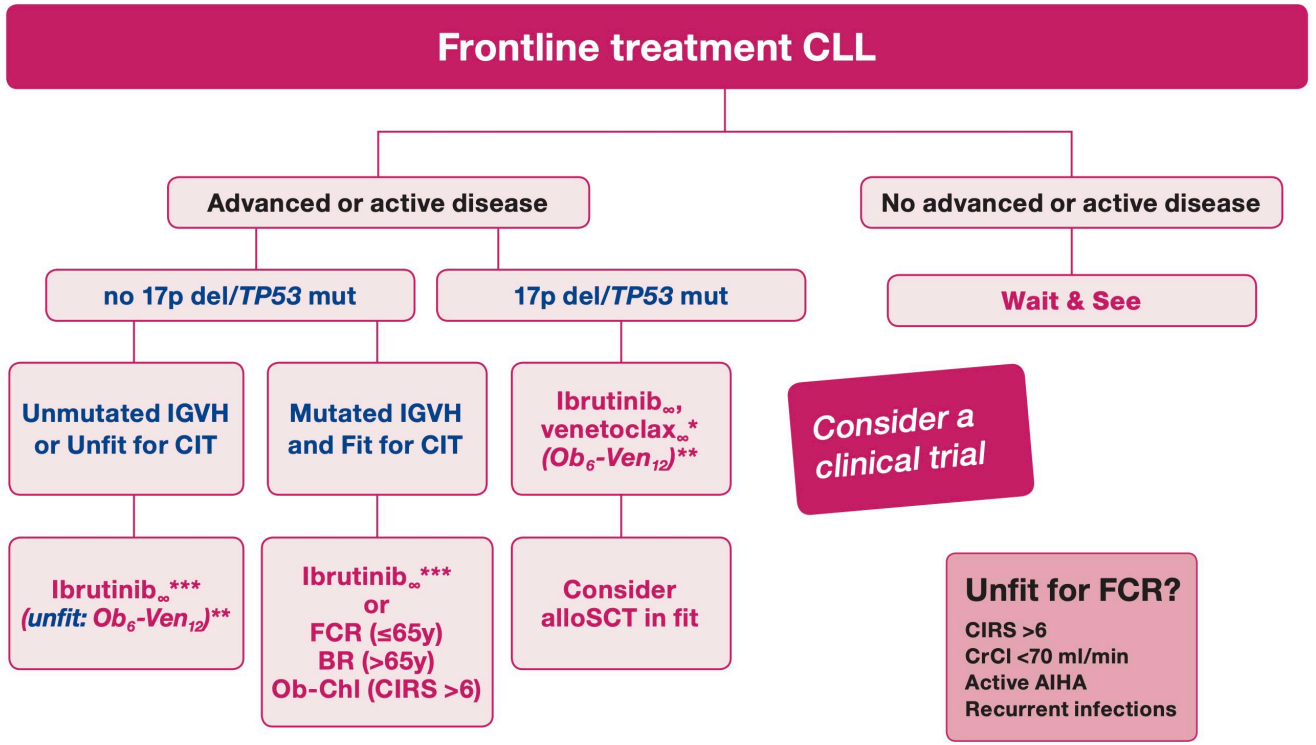
Risk group		**%**	**5y TTFT**	**5y OS**
low	0-1	47	80%	94%
intermediate	2-3	33	47%	91%
high	4-6	18	29%	68%
very high	7-10	3	19%	21%

Indications for treatment (advanced and/or active disease)	
High tumorload	• Rai 3-4 or Binet C
Disease progression	• Lymphocyte doubling time of less than 6 months • Massive (>6 cm below costal margin) or progressive or symptomatic splenomegaly • Massive (>10cm) or progressive or symptomatic lymphadenopathy • Progressive marrow failure leading to cytopenia • Symptomatic functional extranodal disease
Auto-immune problems	• AIHA, AITP, PRCA poorly responsive to corticosteroids
Disease related problems	• 10% weight loss in 6 months • Fatigue (PS≥2) • Fever >38°C for >2w without infection • Night sweats >1m

CLL: inleiding



CLL: therapie



CLL: therapie

		dosage	route	Days(d)/weeks(w)	Cycles (C)
1	**FCR** Fludarabine Cyclophosphamide Rituximab*	 25 mg/m^2 250 mg/m^2 375 (C1)-500(C2-6) mg/m^2	 IV IV IV (SC)	 d1-3 d1-3 d1	 6
2	**BR** Bendamustine Rituximab*	 90 (Frontline)-70 (Relapse) mg/m^2 375 (C1)-500(C2-6) mg/m^2	 IV IV (SC)	 d1-2 d1	 6
3	**Ob-Chl** Obinutuzumab Chlorambucil	 100(d1)-900 (d2)-1000 (d8-15) mg (C1) 1000 mg (C2-6) 10 mg/m^2 or 0.5 (till 0.8) mg/kg	 IV oral	 d1-2-8-15 d1 d1-7 d1 & 15	 6 6 (12) 6 (12)
4	**Ibrutinib$_\infty$**	420 mg	oral	once daily	Continuous treatment
5	**Venetoclax$_\infty$**	Ramp up 20-50-100-200 mg 400 mg	oral	w1-2-3-4 once daily from w5 once daily	Continuous treatment
6	**R$_6$-Ven$_{24}$** Venetoclax Rituximab*	 Ramp up 20-50-100-200 mg 400 mg 375 (C1=w5)-500(C2-6) mg/m^2	 oral IV (SC)	 w1-2-3-4 once daily from w5 once daily w5-9-13-17-21-25	 24 6
7	**Ob$_6$-Ven$_{12}$**** Obinutuzumab Venetoclax	 100(d1)-900 (d2)-1000 (d8-15) mg (C1) 1000 mg (C2-6) Ramp up 20-50-100-200 mg 400 mg	 IV oral	 d1-2-8-15 d1 w1-2-3-4 once daily From w5 once daily	 6 12

**: Rituximab sc 1600mg fixed dose from the cycle following a cycle wihout any infusion reaction (reimbursed 2018)*
***: Ob$_6$-Ven$_{12}$ not indicated and reimbursed in Belgium 02-2020*

8: Acalabrutinib 2x100mg/d PO, continu

CLL: acalabrutinib

Acalabrutinib Is a Highly Selective, Potent, Next-Generation BTK Inhibitor[1,2]

- Fast, near complete and sustained BTK occupancy at the recommended oral dose of 100 mg BID[1]
- High selectivity for BTK with limited off-target activity[1]

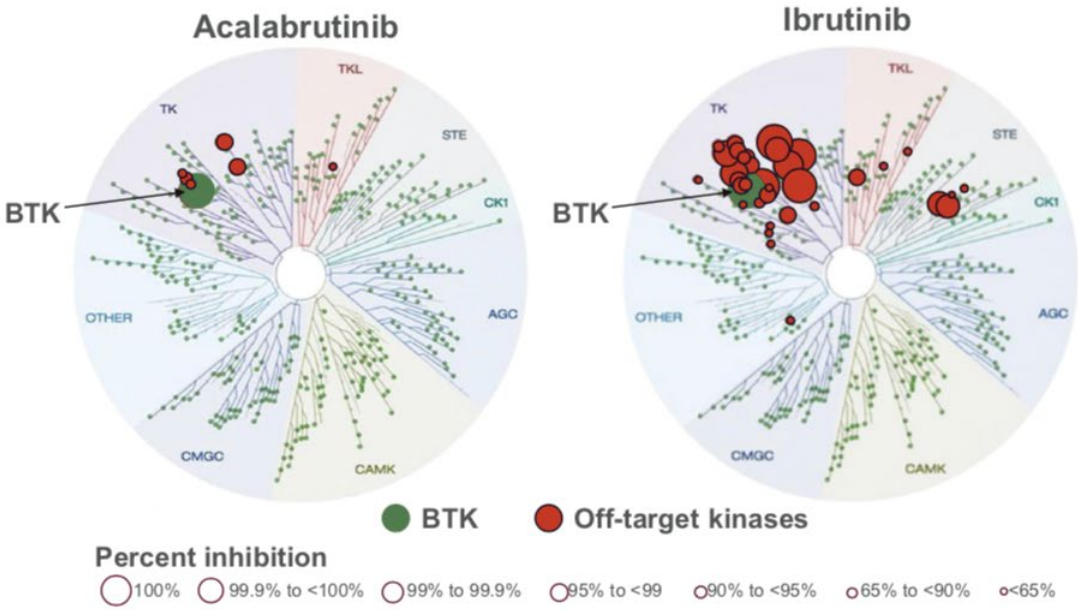


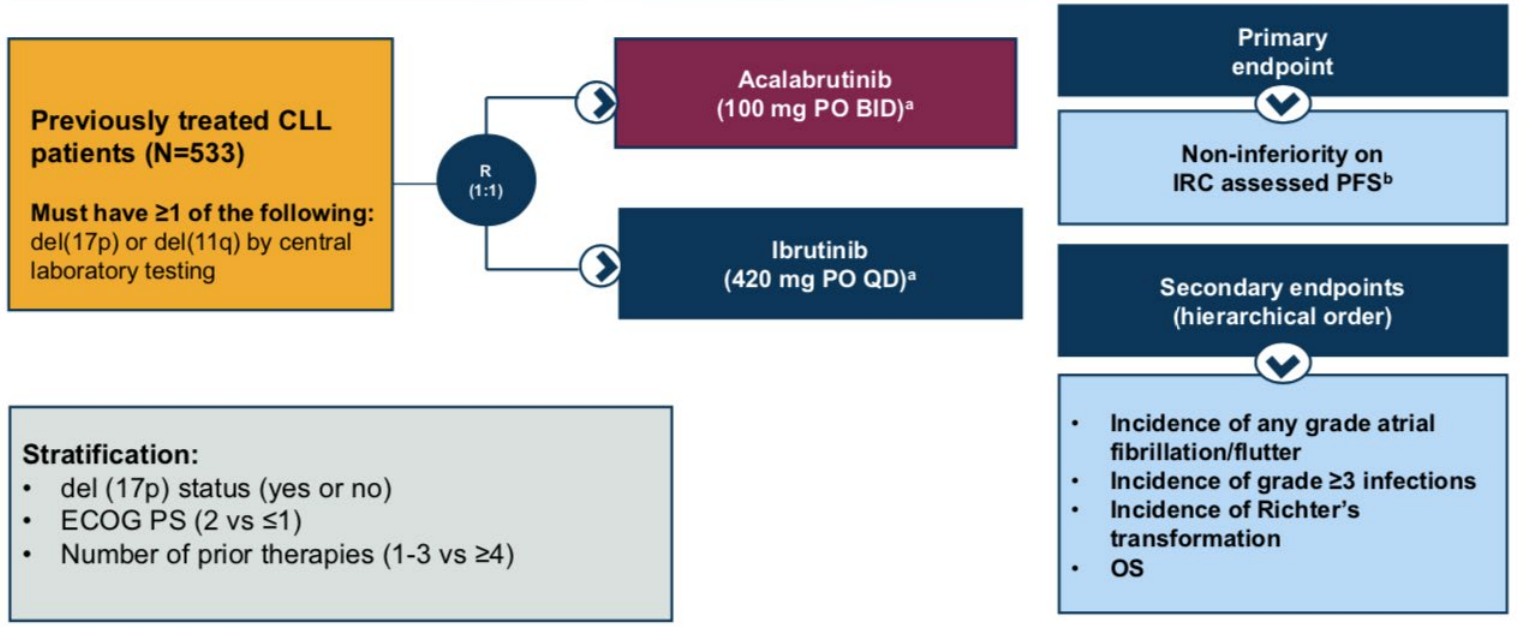
Figure adapted from Barf T et al. *J Pharmacol Exp Ther.* 2017;363(2):240-252.

AGC, containing PKA, PKC, PKG families; BID, twice daily; BTK, Bruton tyrosine kinase; CAMK, calcium/calmodulin-dependent protein kinase; CK1, casein kinase 1; CMGC, containing CDK, MAPK, GSK3, CLK families; STE, homologues of yeast Sterile 7, Sterile 11, Sterile 20 kinases; TK, tyrosine kinase; TKL, tyrosine kinase-like.
Note: The images represent the profile of CALQUENCE and ibrutinib in a competitive binding assay of more than 450 human kinases and disease-relevant mutants when tested at a single concentration of 1 μM. The degree of inhibition vs untreated control is represented by circle size.

1. Barf T et al. *J Pharmacol Exp Ther.* 2017;363(2):240-252. **2.** Bond DA, Woyach JA. *Curr Hematol Malig Rep.* 2019;14(3):197-205.

CLL: acala vs ibrutinib

Study Design



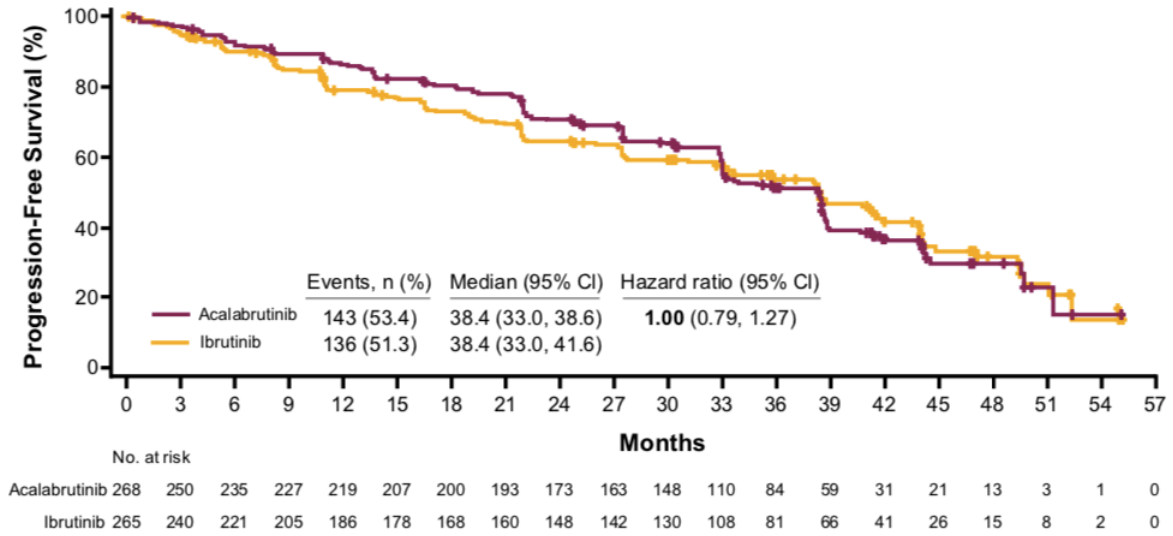
[a]Continued until disease progression or unacceptable toxicity. [b]Conducted after enrollment and accrual of ~250 IRC-assessed PFS events.

BID = twice daily; CLL = chronic lymphocytic leukemia; ECOG PS = eastern cooperative oncology group performance status; IRC = independent review committee; OS = overall survival; PFS = progression-free survival; PO = orally; R = randomization; QD = once daily.

CLL: acala vs ibrutinib

Non-inferiority met on IRC-Assessed PFS (Primary Endpoint)

- At a median follow-up of 40.9 months (range 0.0–59.1), acalabrutinib was non-inferior to ibrutinib with a median PFS of 38.4 months in both arms (HR: 1.00; 95% CI 0.79–1.27)



CLL: acala vs ibrutinib

Events of Clinical Interest

	Any grade		Grade ≥3	
Events, n (%)	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

Higher incidence indicated in **bold** for terms with statistical differences.
*Two-sided *P*-value for event comparisons <0.05 without multiplicity adjustment.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter. [b]Includes events with preferred terms torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia. [c]Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased. [e]Most common grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
ILD = interstitial lung disease; NMSC = nonmelanoma skin cancer; SPMs = second primary malignancies; UTI = urinary tract infection.

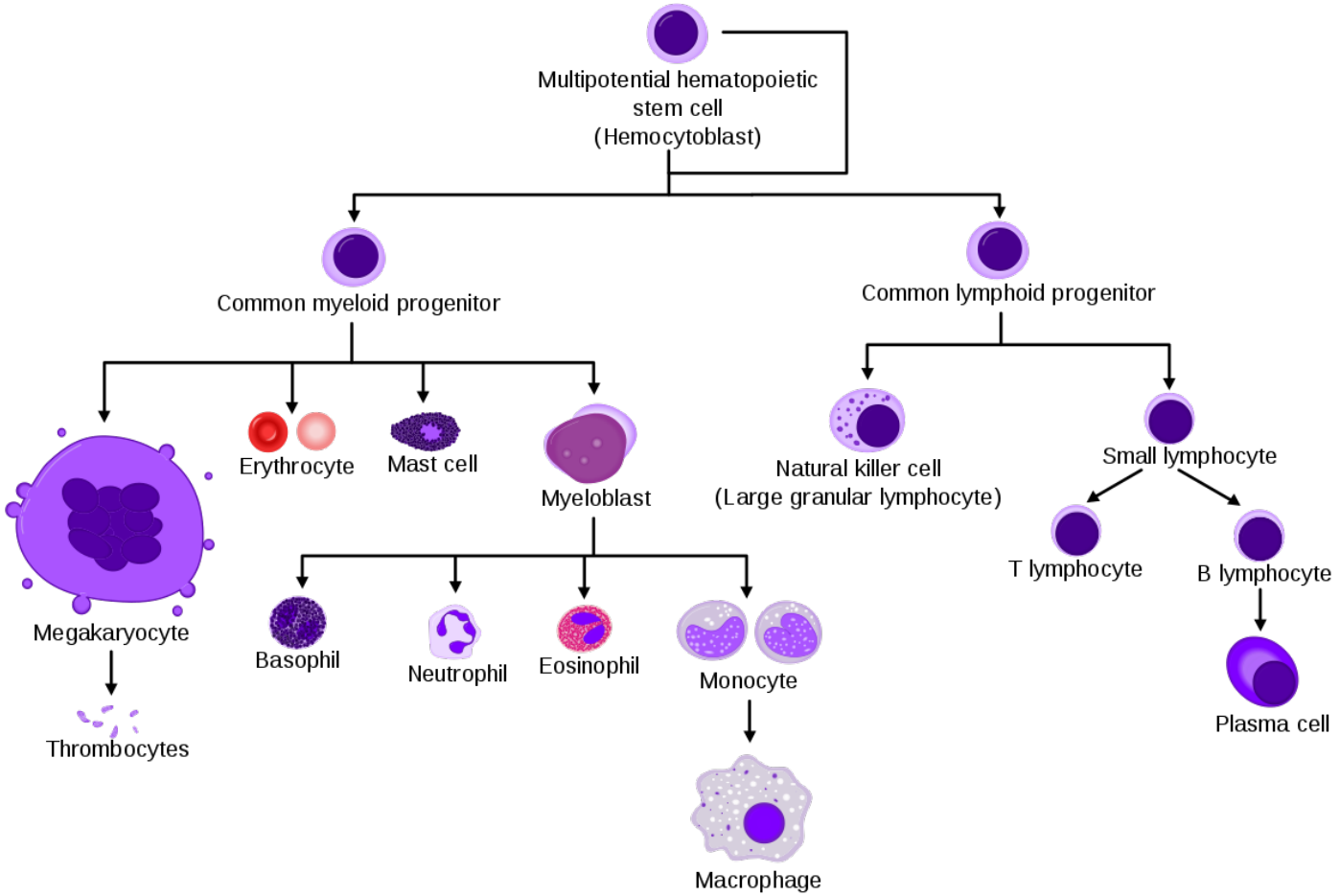
CLL: acalabrutinib

Recommendations regarding use of Calquence with CYP3A inhibitors or inducers and gastric acid reducing agents are provided in Table 2 (see section 4.5).

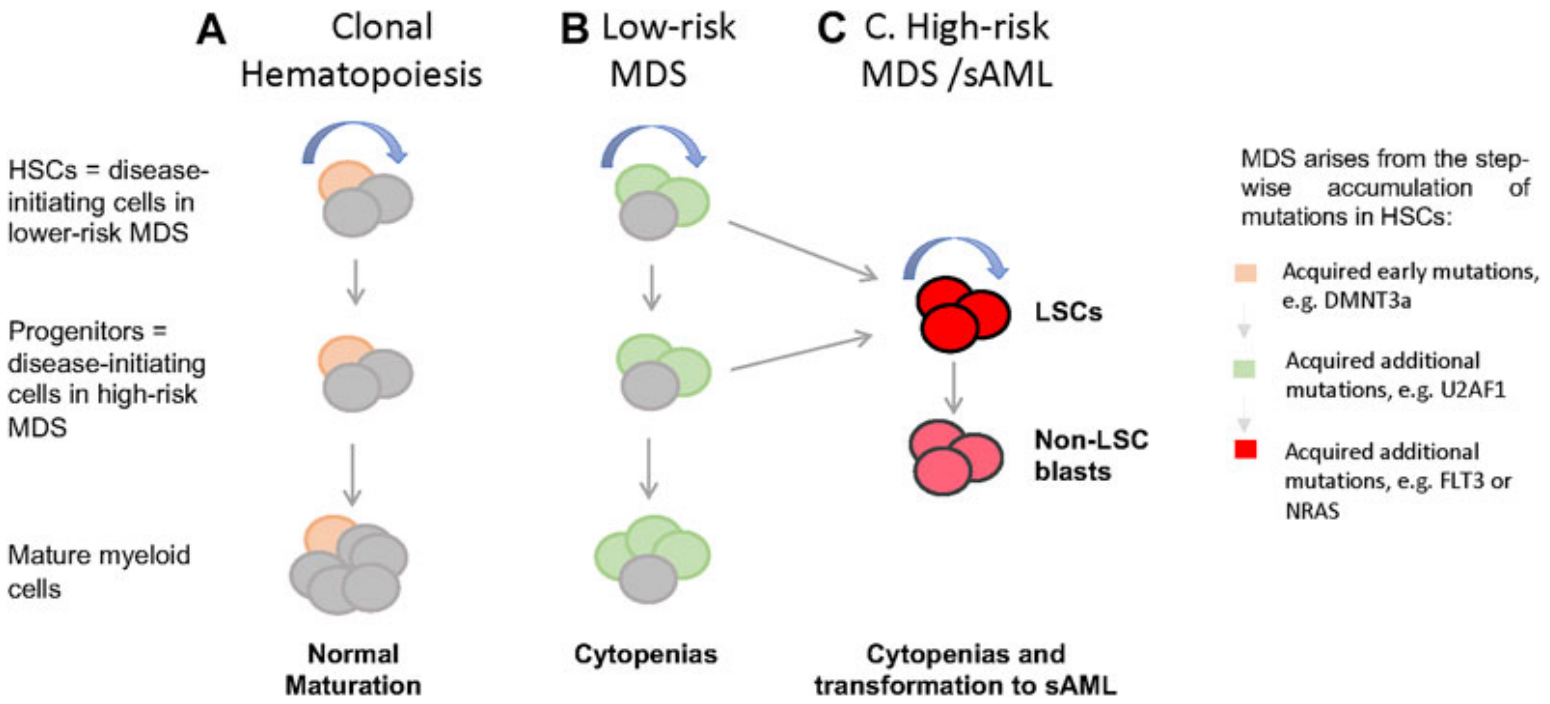
Table 2. Use with CYP3A inhibitors or inducers and gastric acid reducing agents

	Co-administered medicinal product	Recommended Calquence use
CYP3A inhibitors	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt Calquence.
	Moderate CYP3A inhibitor	No dose adjustment. Monitor patients closely for adverse reactions if taking moderate CYP3A inhibitors.
	Mild CYP3A inhibitor	No dose adjustment.
CYP3A inducers	Strong CYP3A inducer	Avoid concomitant use.
Gastric acid reducing agents	Proton pump inhibitors	Avoid concomitant use.
	H2-receptor antagonists	Take Calquence 2 hours before (or 10 hours after) taking a H2-receptor antagonist.
	Antacids	The interval between taking the medicinal products should be at least 2 hours.

MDS: inleiding



MDS: inleiding



MDS: inleiding

Table 2. IPSS-R in MDS: Survival and AML Evolution

Prognostic Variable	Score						
	0	0.5	1	1.5	2	2.5	3.0
Cytogenetics[a]	Very good	—	Good	—	Intermediate	Poor	Very poor
Bone marrow blasts, %	≤2	—	>2 to <5	—	5-10	>10	—
Hemoglobin, g/dL	≥10	—	8 to <10	<8	—	—	—
Platelets, cells/mcL	≥100	50 to <100	<50	—	—	—	—
ANC, cells/mcL	≥0.8	<0.8	—	—	—	—	—

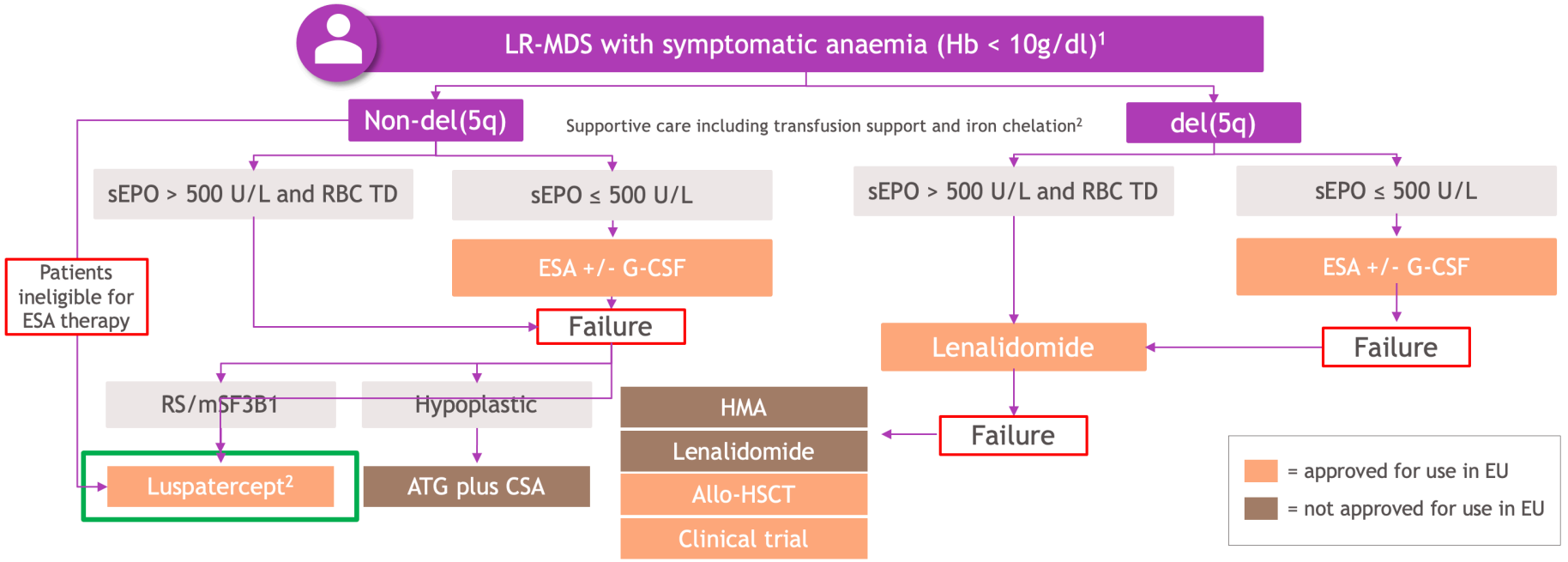
Risk Group	IPSS-R Risk Score	Median OS, y	Median Time to 25% AML Evolution, y
Very low	≤1.5	8.8	Not reached
Low	>1.5 to 3	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
Very high	>6	0.8	0.7

[a] *Very good:* -Y, del(11q), *Good:* normal, del(5q), del(12p), double including del(5q); *Intermediate:* del(7q), +8, +19, i(17q); any other single or double independent clones; *Poor:* -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex (3 abnormalities); *Very poor:* complex (>3 abnormalities).

ANC, absolute neutrophil count; **IPSS-R,** Revised International Prognostic Scoring System; **MDS,** myelodysplastic syndromes; **—,** not applicable; **OS,** overall survival

Adapted from reference 2.

MDS: therapie



Patients who fail ESA treatment face unmet medical needs due to lack of available treatment options

Allo-HSCT, allogeneic haematopoietic stem cell transplantation; ATG, anti-thymocyte globulin; CSA, cyclosporine; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factors; Hb. haemoglobin; HMA, hypomethylating agent; LR-MDS, lower-risk myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblasts; sEPO, serum erythropoietin; TD, transfusion dependent. 1. Platzbecker U, et al. Blood. 2019;133:1096-107; 2. Luspatercept. SmPC. 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/reblozyl-epar-product-information_en.pdf.

MDS: therapie met EPO

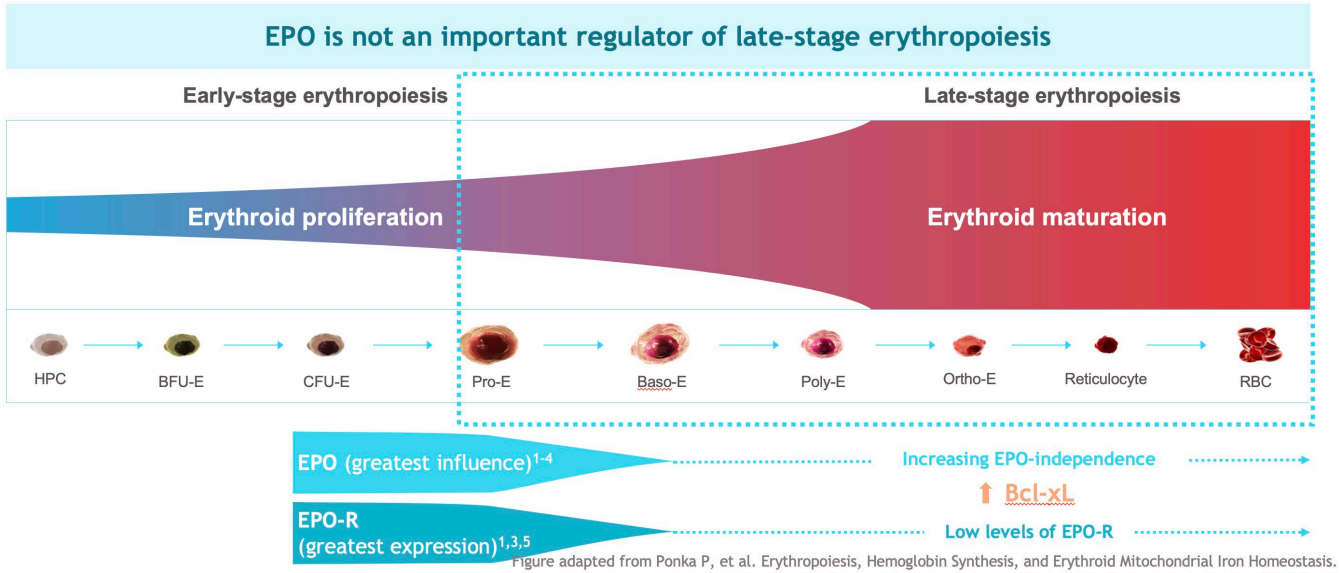


Figure adapted from Ponka P, et al. Erythropoiesis, Hemoglobin Synthesis, and Erythroid Mitochondrial Iron Homeostasis. In: The Handbook of Porphyrin Science; 2014:41-84; Zivot A, et al. Mol Med 2018;24:11

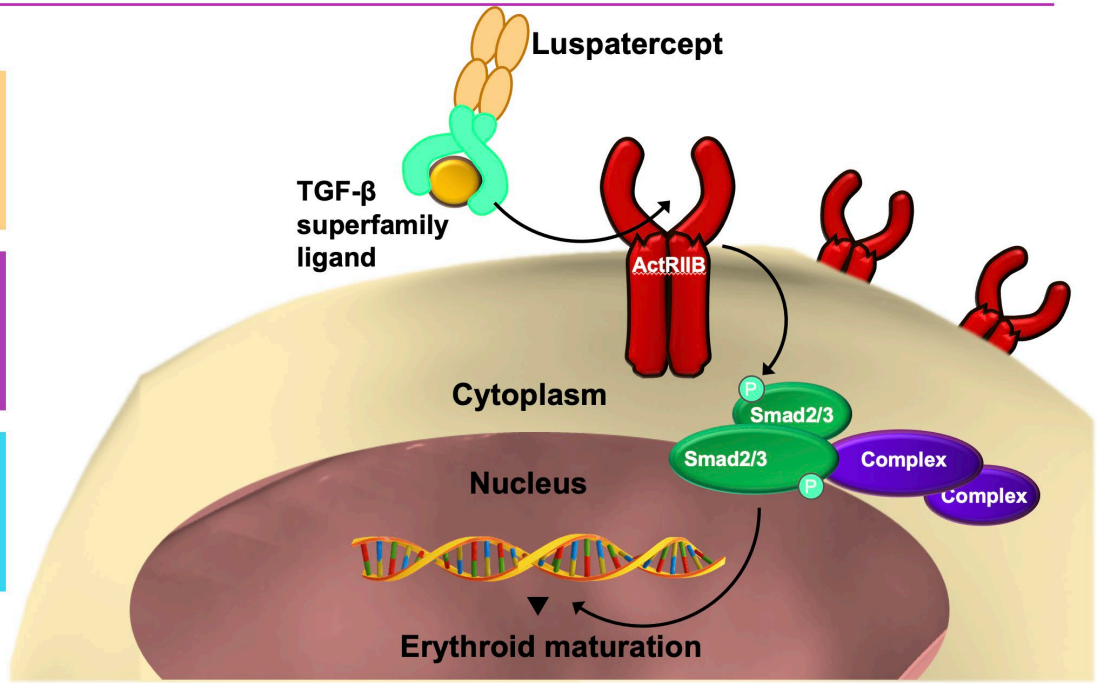
1. Valent P, et al. Haematologica 2018;103:1593-6; 2. Koury MJ, et al. Curr Opin Hematol 2002;9:93-100; 3. Papayannopoulou T, et al. In: Hoffman R et al, eds. Hematology Basic Principles and Practice; 2018:297-320; 4. Higgs DR, et al. In: Hoffbrand AV, et al., eds. Erythropoiesis. Postgraduate Haematology; 2016:314-31; 5. Koury MJ. Blood Rev 2014;28:49-66

Luspatercept addresses ineffective erythropoiesis

Luspatercept binds to select TGF-β superfamily ligands[1]

… inhibiting ActRIIB activation and reducing Smad2/3 signaling[1]

Inhibition of aberrant Smad2/3 signaling enhances erythroid maturation in late-stage erythropoiesis[2]

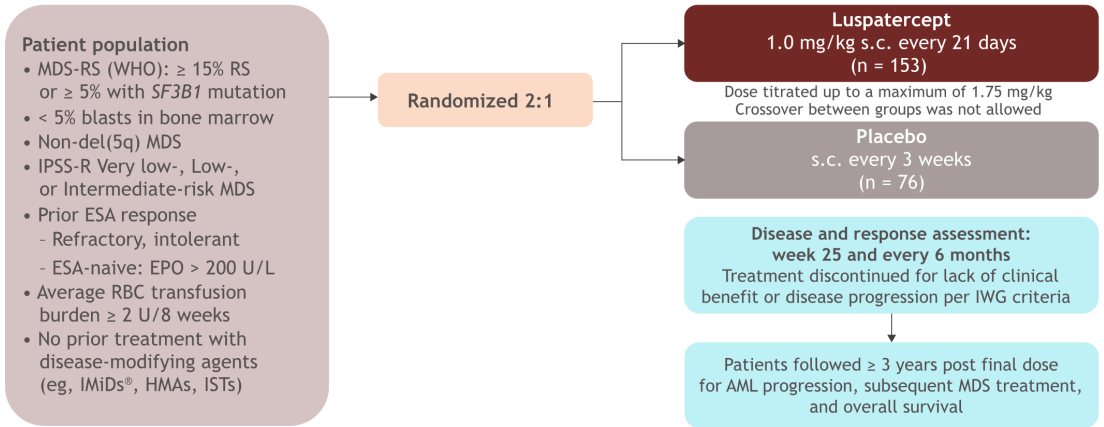


1. Attie KM, et al. *Am J Hematol* 2014;89:766-70; 2. Suragani RN, et al. *Nat Med* 2014;20:408–14; 3. Suragani RN, et al. *Blood* 2014;123:3864–72

MDS: luspatercept vs placebo

MEDALIST study design

- Randomized, double-blind, phase 3 trial (**Figure 1**)

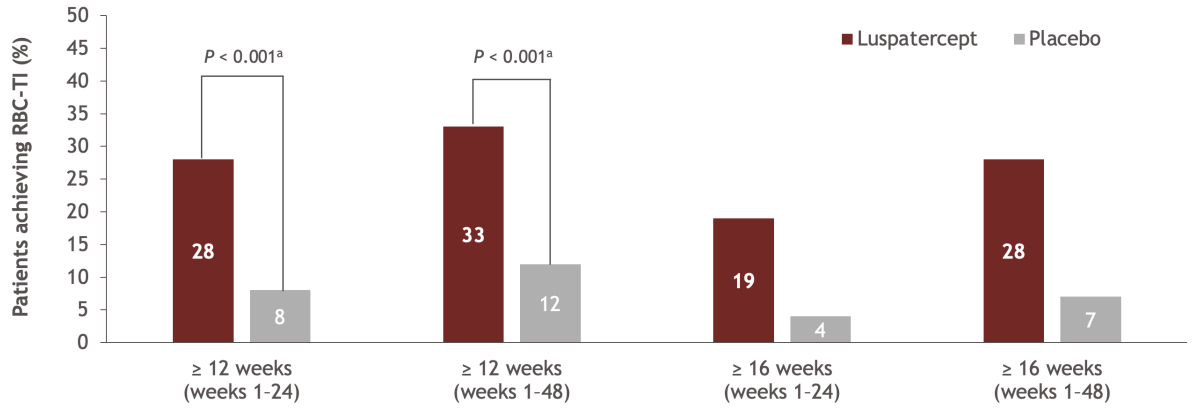


HMA, hypomethylating agent; IMiD, immunomodulatory imide drug; IPSS-R, Revised International Prognostic Scoring System; IST, immunosuppresive therapy; IWG, International Working Group; s.c., subcutaneous; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

Platzbecker et al, Presented at ASH 2021. Poster Presentation number 1524

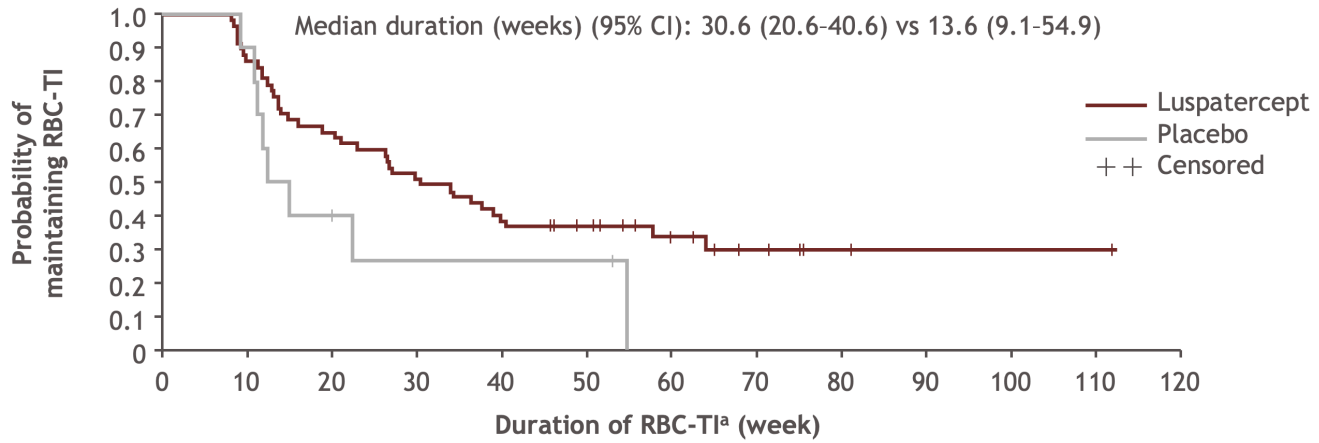
MDS: luspatercept vs placebo

- A **greater proportion of patients in the luspatercept arm achieved** the key secondary endpoint (**RBC-TI ≥ 12 weeks**), as well as **RBC-TI ≥ 16 weeks**, compared with those in the placebo arm



[a]Determined using a Cochran-Mantel-Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 vs < 6 units/8 weeks) and baseline IPSS-R score (Very low or Low vs Intermediate).
IPSS-R, International Prognostic Scoring System-Revised; RBC, red blood cell; TI, transfusion independence.
Fenaux P et al. *N Engl J Med*. 2020;382:140-151.

MDS: luspatercept vs placebo: duur van effect



Number of patients												
Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

[a]During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.
RBC, red blood cell; TI, transfusion independence.
Fenaux P et al. Presentation at the ASH 60th Annual Meeting and Exposition; December 1-4, 2018; San Diego, CA.

MDS: luspatercept: neveneffecten

TEAEs (≥ 2% incidence in either treatment arm) by category, n (%)	Luspatercept (n = 153)		Placebo (n = 76)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	10 (6.5)	0	5 (6.6)	0
Neutropenia	2 (1.3)	3 (2.0)	5 (6.6)	1 (1.3)
Fall	7 (4.6)	0	2 (2.6)	0
Fatigue	7 (4.6)	0	2 (2.6)	0
Syncope	5 (3.3)	0	1 (1.3)	0
Hypertension	5 (3.3)	0	3 (3.9)	0
Asthenia	4 (2.6)	0	0	0
Iron overload	3 (2.0)	0	1 (1.3)	0
Back pain	3 (2.0)	0	0	0
Increased ALT	3 (2.0)	0	0	0
Urinary tract infection	2 (1.3)	0	3 (3.9)	0
Pneumonia	1 (0.7)	0	2 (2.6)	0
Hip fracture	1 (0.7)	0	3 (3.9)	0
Arthralgia	1 (0.7)	0	2 (2.6)	0

Startdosis 1,33mg/kg SC/3w

Als Hb >2g/dl na 3w: reduceer dosis (maar 0,8mg is minimale dosis)

Evt toediening interval >

Als Hb niet stijgt: verhoog 1,75mg/kg/3w

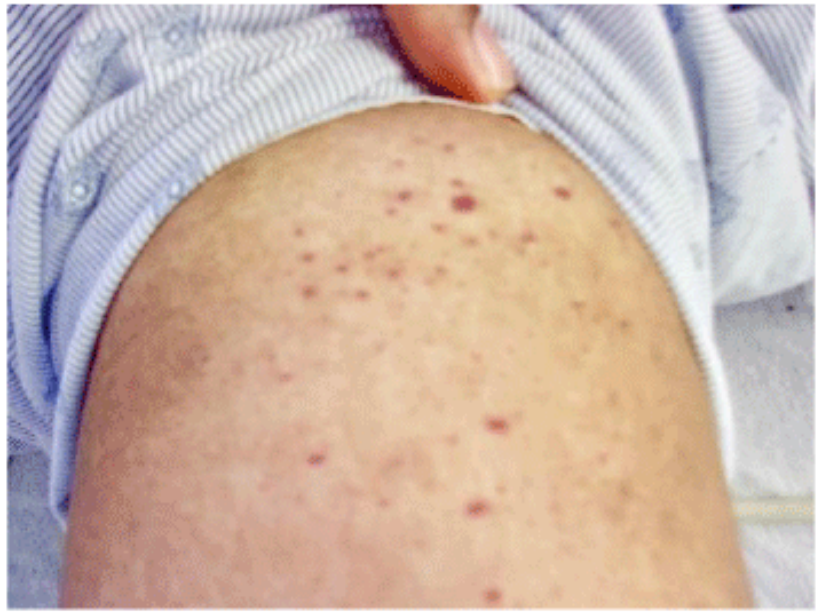
Stop therapie na 6 w zo geen effect

Dose Reductions for MDS

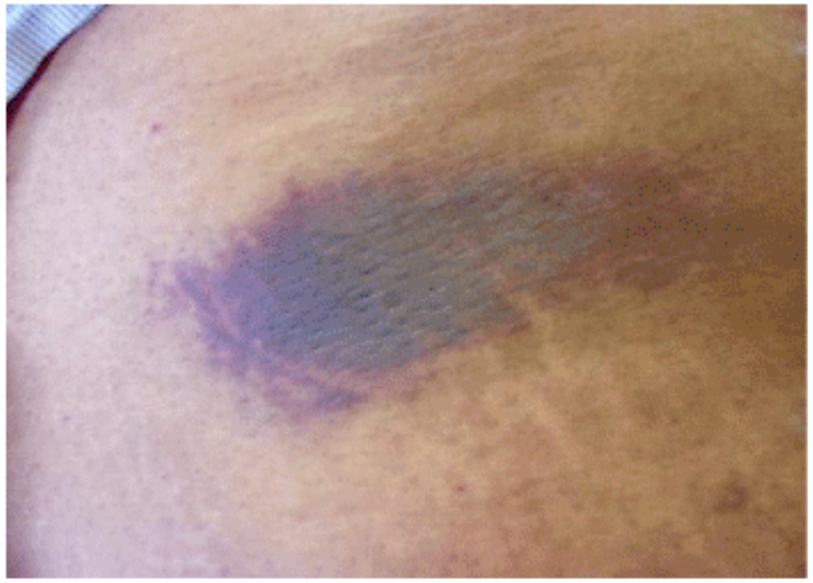
Current Dose	Dose Reduction
1.75 mg/kg	1.33 mg/kg
1.33 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg

ITP: inleiding

(a)



(b)



ITP: inleiding

Immuungemedieerde plaatjes afbraak

Incidentie 5/100000

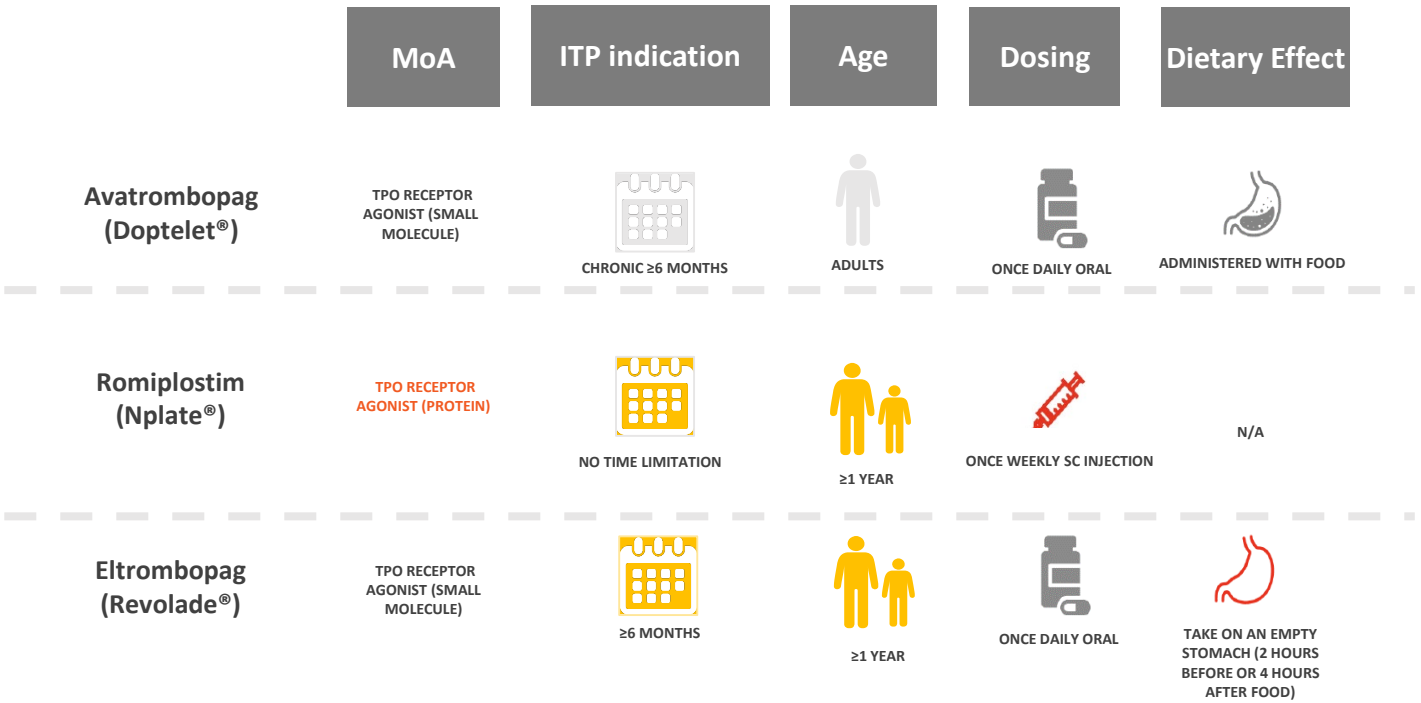
Oorzaak meestal postviraal

Initiële therapie dexamethasone 40mg PO/dx4d (evt plus IV immuunglobulines)

2/3 bekomen remissie, 1/3 hervalt

Tweede lijnstherapie: rituximab, splenectomie, TPO-RA

ITP: therapie met TPO-RA's



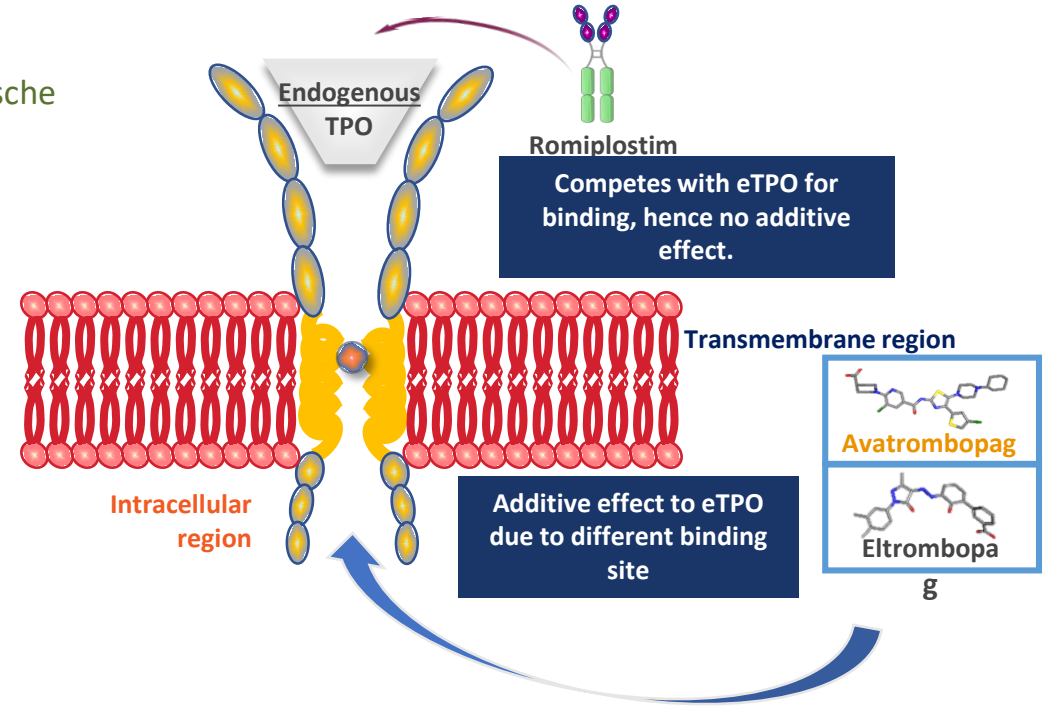
- [a]Occuring in ≥1/10 patients[1-3]; [b]Durable response: Last 6–8 weeks with PC ≥50 x 10^9 /L[1-3].
- AE, adverse event; ALT, alanine aminotransferase; ITP, immune thrombocytopenia; MoA, mechanism of action; N/A, not applicable; PBO, placebo; TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist; SC, subcutaneous.**1.** EMA. Doptelet SmPC 2021 **2.** EMA. Nplate SmPC 2021 **3.** EMA. Revolade SmPC 2021 **4.** Jurczak et al. *Br J Haematol* 2018 **5.** Kuter et al. *Lancet* 2008 **6.** Cheng et al. *Lancet* 2011.

ITP: Avatrombopag: werkingsmechanisme

Avatrombopag is een thrombopoïetine receptor agonist (TPO-RA) vergelijkbaar met en additief aan biologische effecten van TPO *in vitro* en *in vivo*[2]

Stimuleert de maturatie van megakaryocyten van haematopoïetische stamcellen, waardoor verhoogde plaatjes productie[1,2]

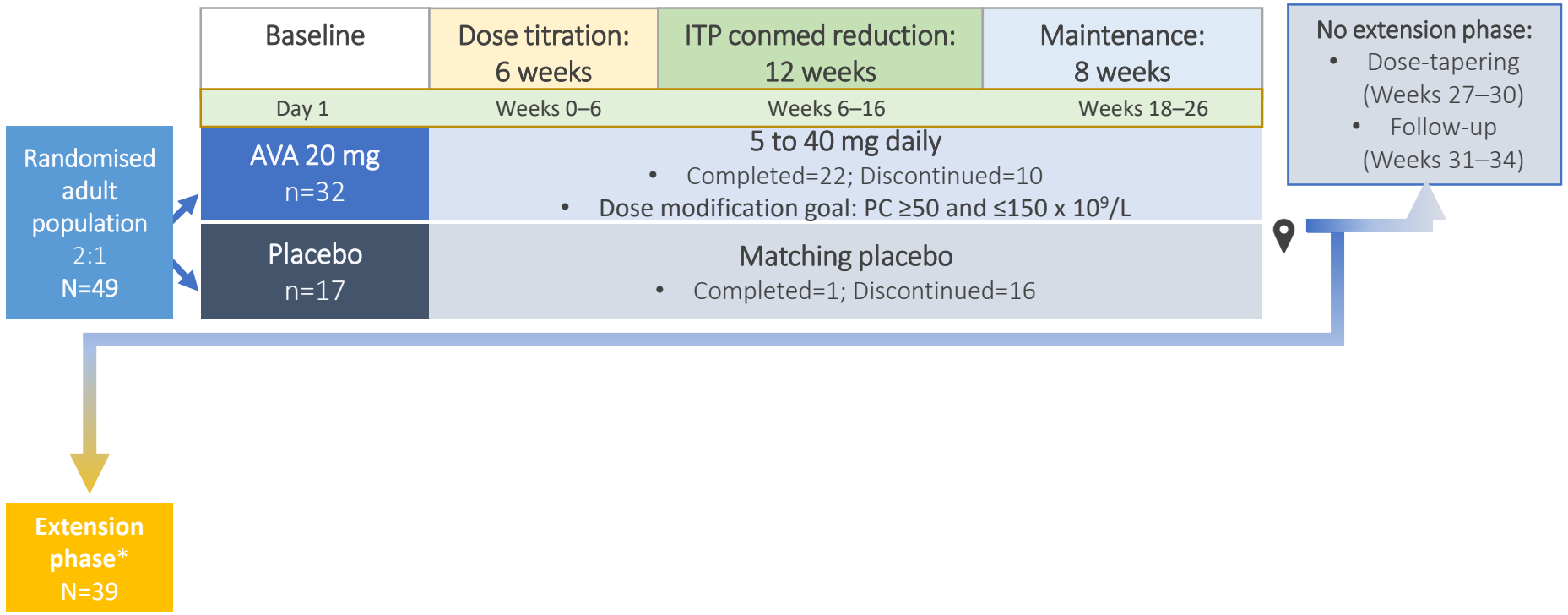
Effect is zichtbaar na 3-5 dagen



- eTPO, endogenous thrombopoietin; PK / PD, pharmacokinetic / pharmacodynamic; TPO, thrombopoietin.

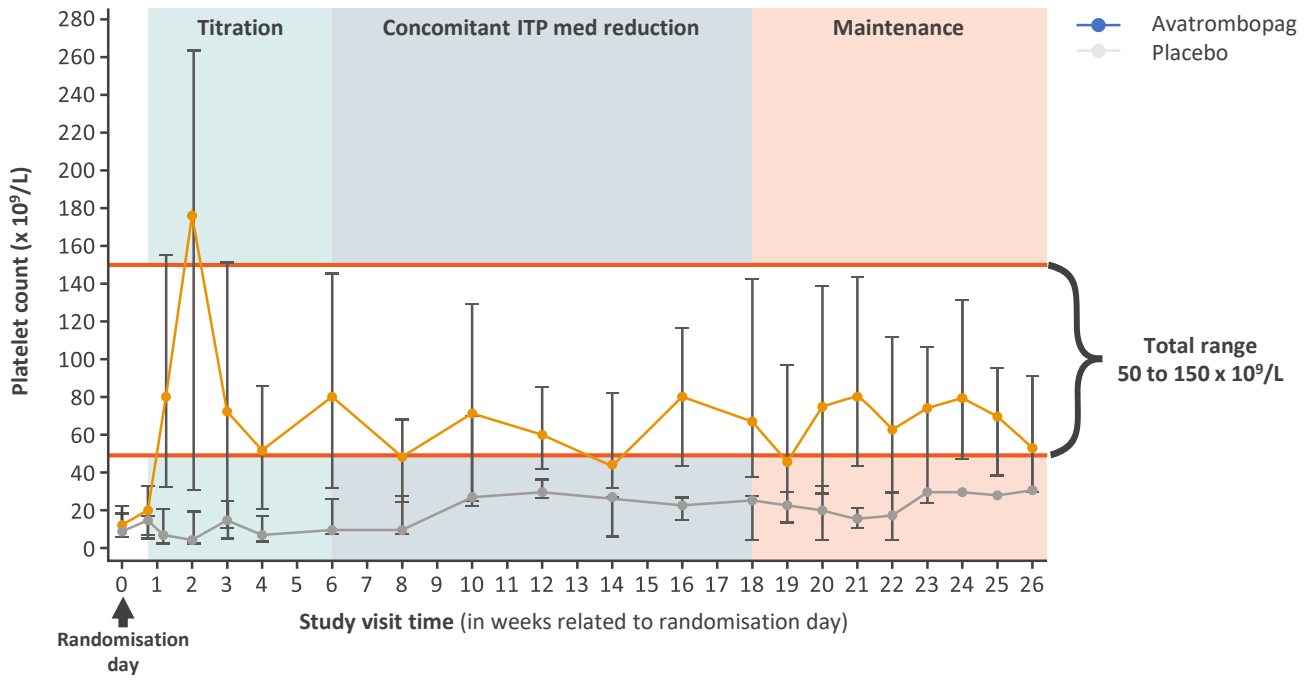
1. EMA. Doptelet SmPC 2021 **2.** Fukushima-Shintan et al. *Exp Hematol* 2008 **3.** FDA. Doptelet PI 2020. **4.** Rodeghiero & Carli *Ann Hematol.* 2017; **5.** Kuter & Begley *Blood* 2002 **6.** Fanucchi et al. *N Engl J Med* 1997
7. Wang et al. *Clin Pharmacol Ther.* 2004 **8.**. Revolade SmPC 2015 **9.** Garzon & Mitchell *Front Pediatr.* 2015

ITP: Avatrombopag vs placebo



- *Patients joined the extension phase if they had completed maintenance phase of the core study, had no significant safety or tolerability concerns, or discontinued from core study due to lack of effect.
  AVA, avatrombopag; conmed; concomitant medication; ITP, immune thrombocytopenia; PC, platelet count.
- **1.** Jurczak et al. *Br J Haematol* 2018.

ITP: Avatrombopag vs placebo



- ITP, immune thrombocytopenia.

1. Jurczak et al. *Br J Haematol* 2018.