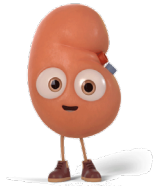
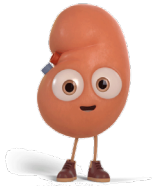
Intérêt du TDM en Transplantation Rénale: exemple du **belatacept**



@dommibertrand

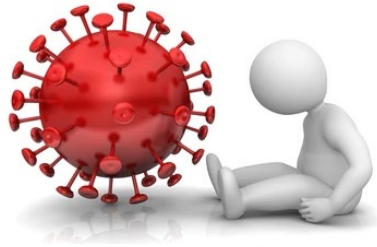


Mardi 1er Octobre 2024

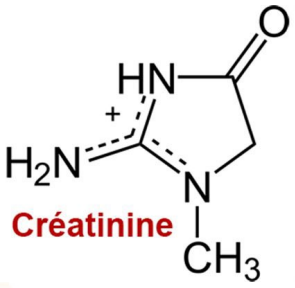
Dominique Bertrand (Néphrologue CHU Rouen)

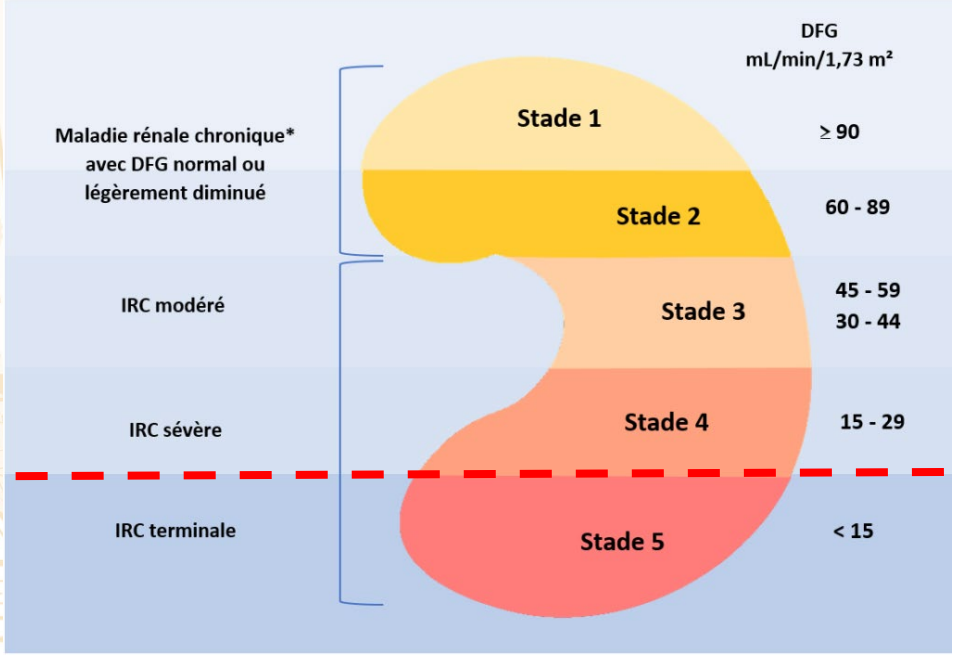
CHU ROUEN NORMANDIE

Centres SPIESSER ASTRE



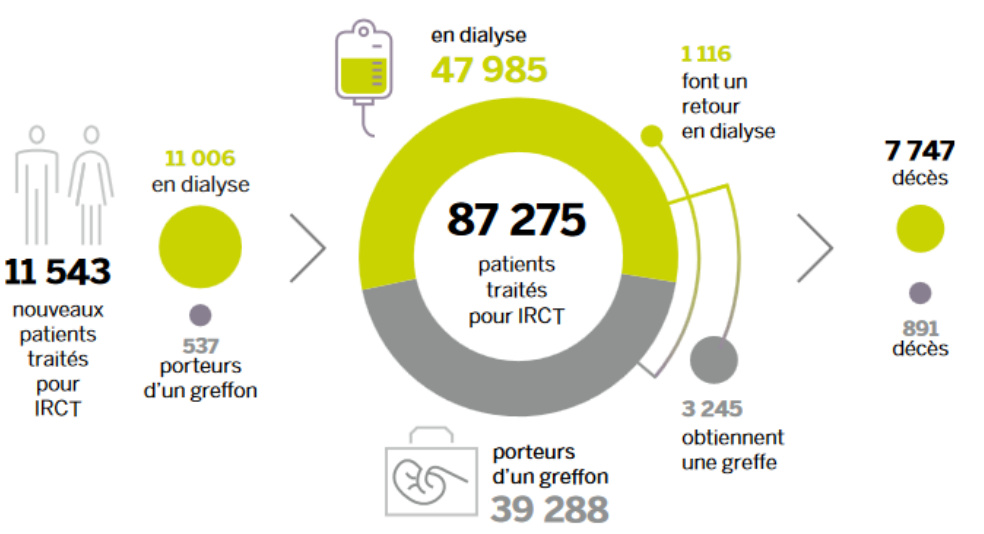
Quand a-t-on besoin d'une greffe rénale?



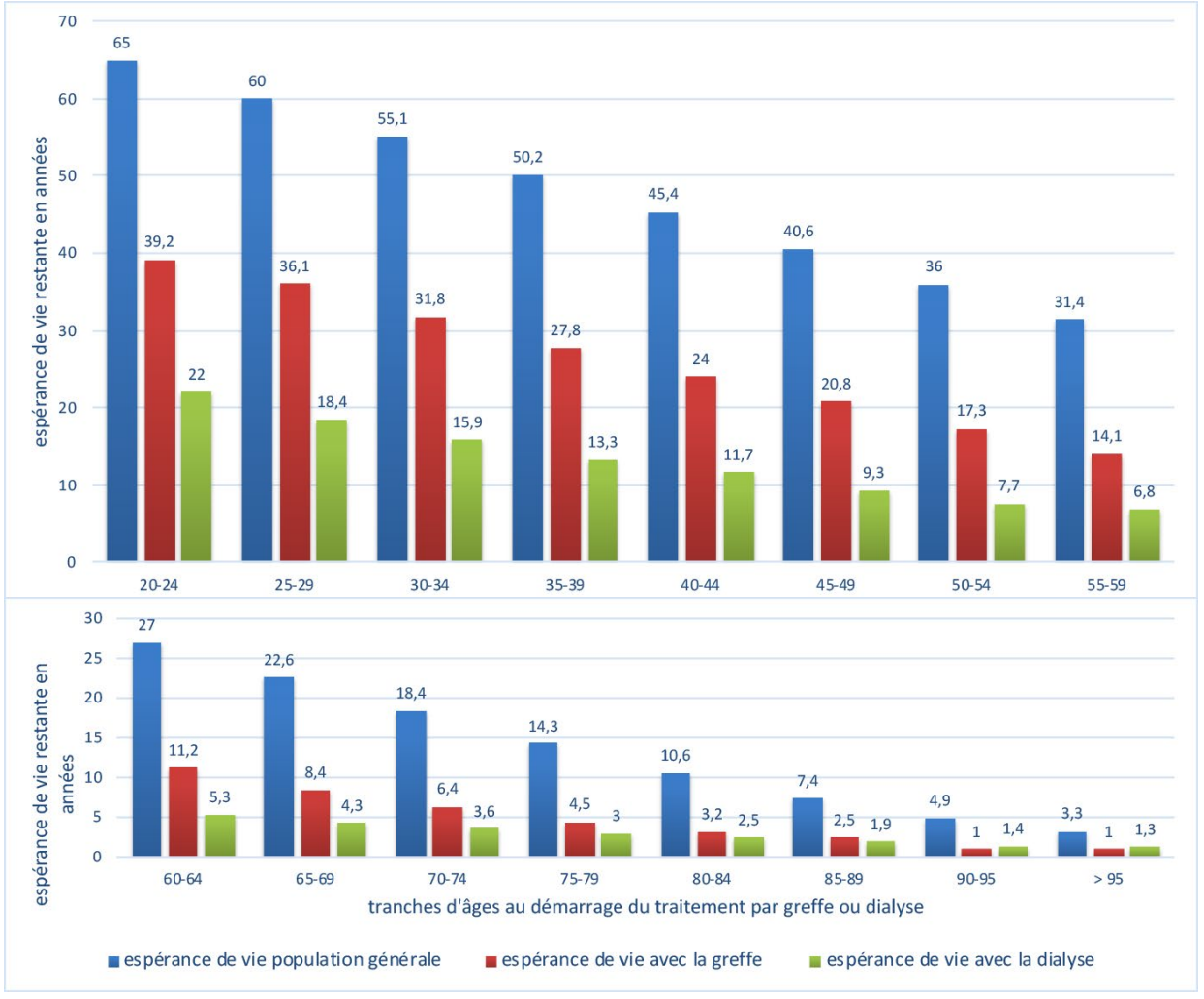


Patients en dialyse

Greffe préemptive (avant la dialyse)

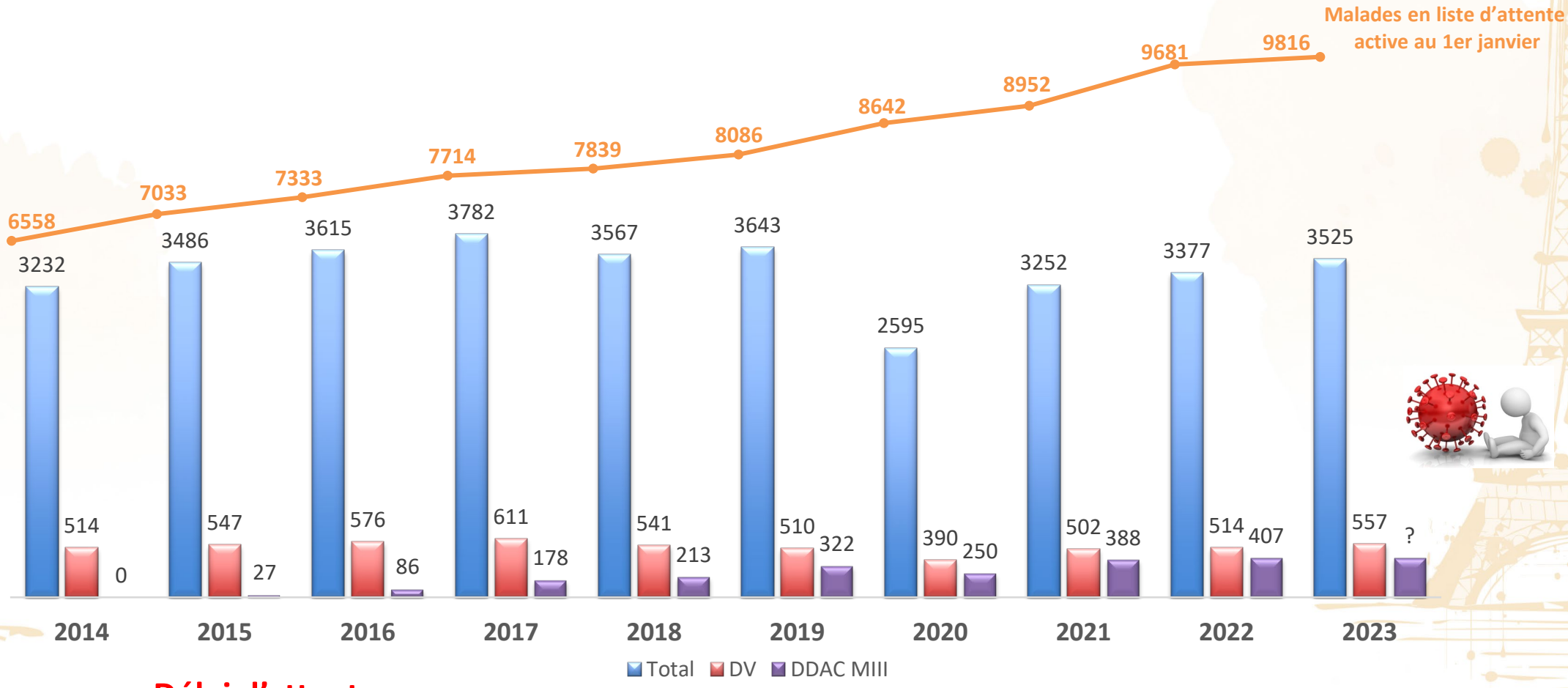


Espérance de vie



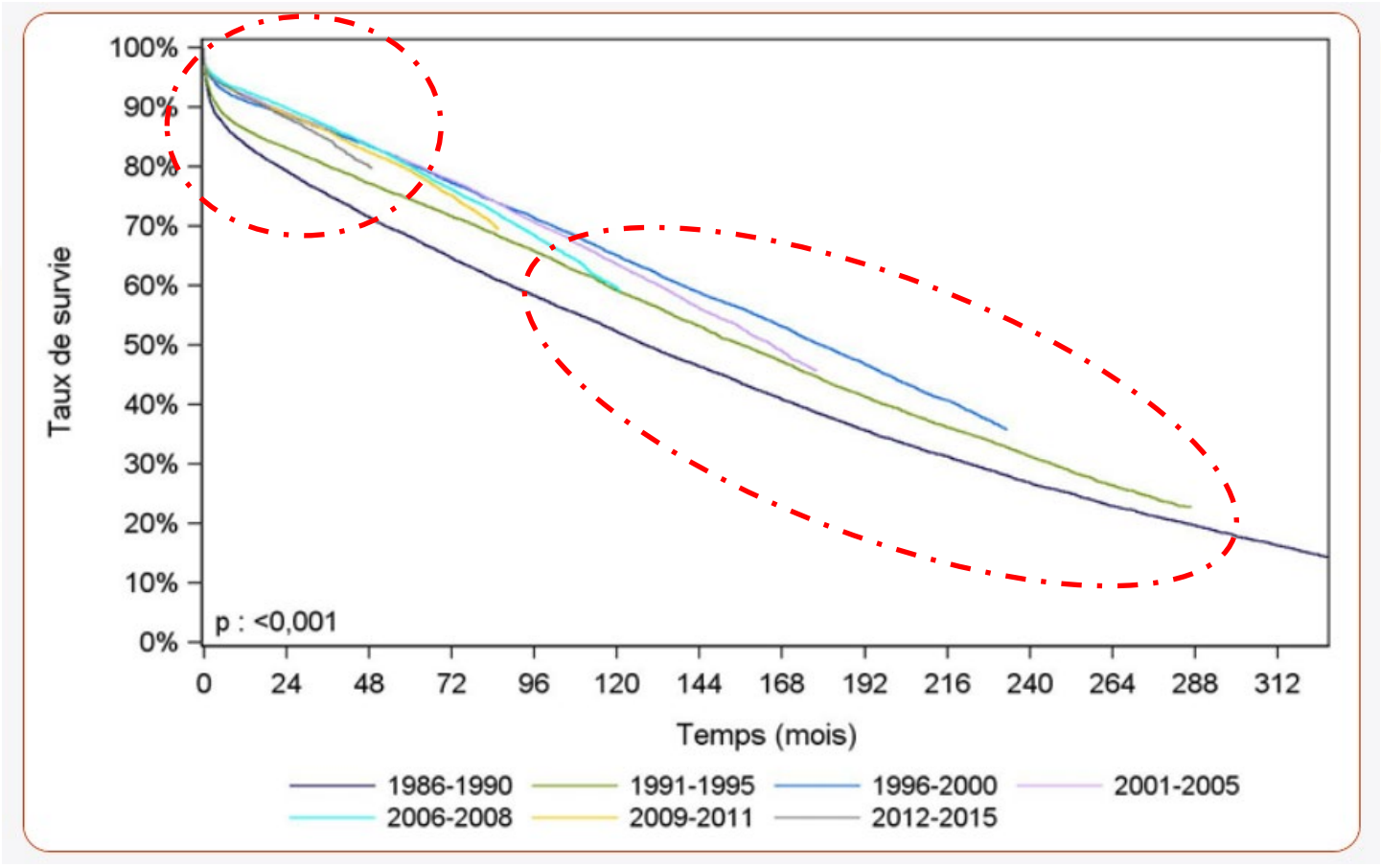
Rapport REIN, 2016

Activité de greffe rénale en France



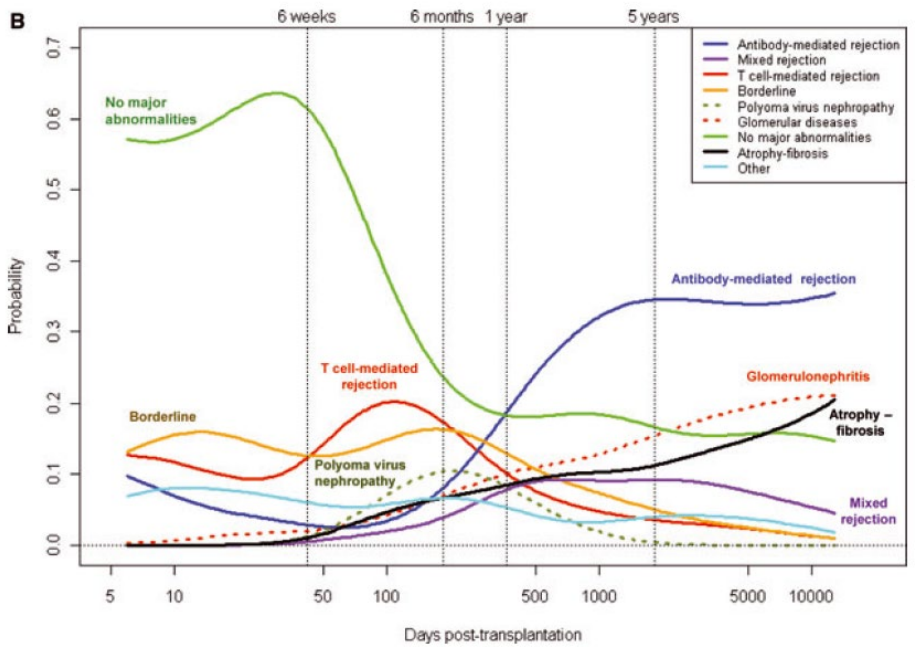
Pénurie d'organes… Délai d'attente …

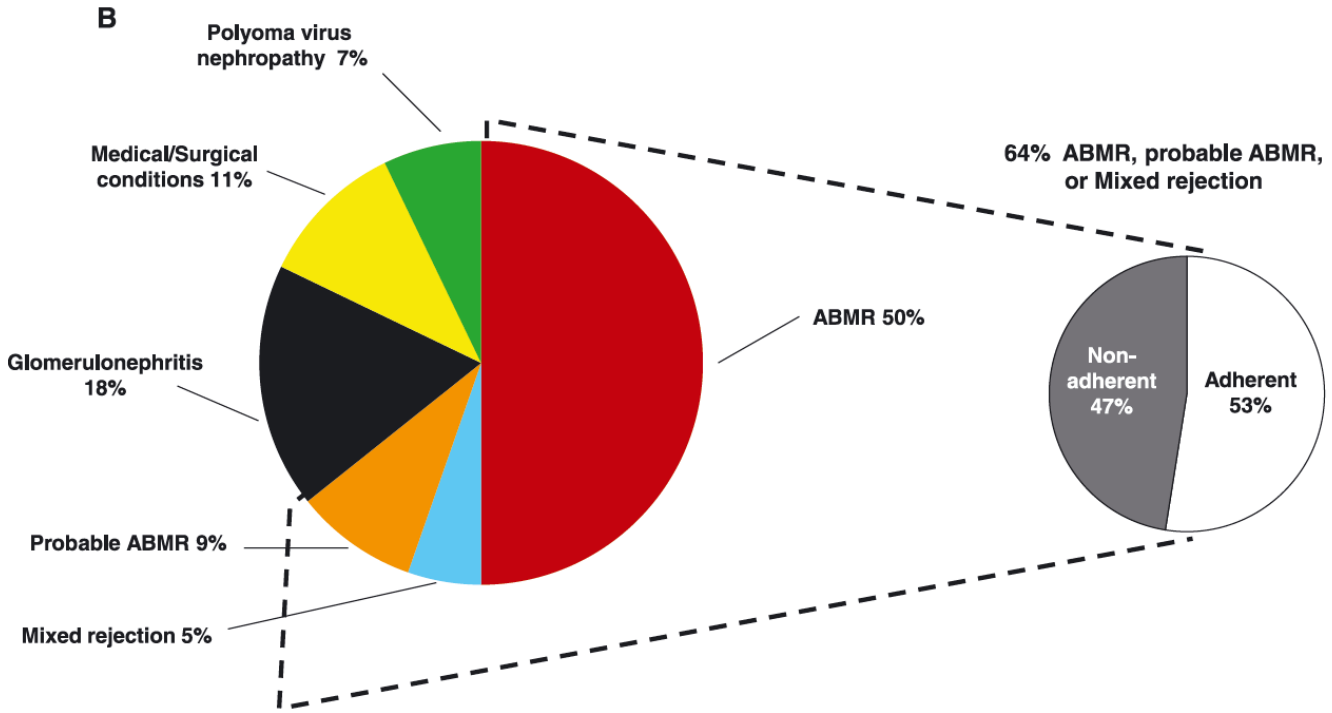
Durée de vie du greffon limitée, malgré une amélioration à court terme…



Rapport Agence de la Biomédecine - France - 2016

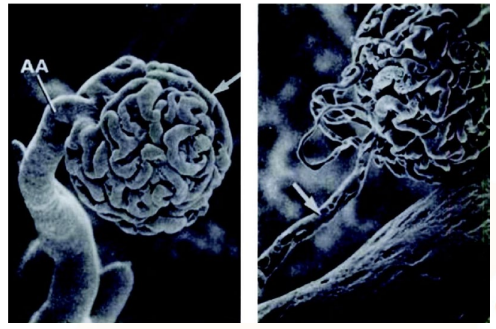
En grande partie liée au rejet humoral?





Sellares, AJT, 2011

Et aux anticalcineurines??? ;)



Gold standard = Tacrolimus + MMF + Stéroïdes

Symphony Study, Ekberg, NEJM, 2007

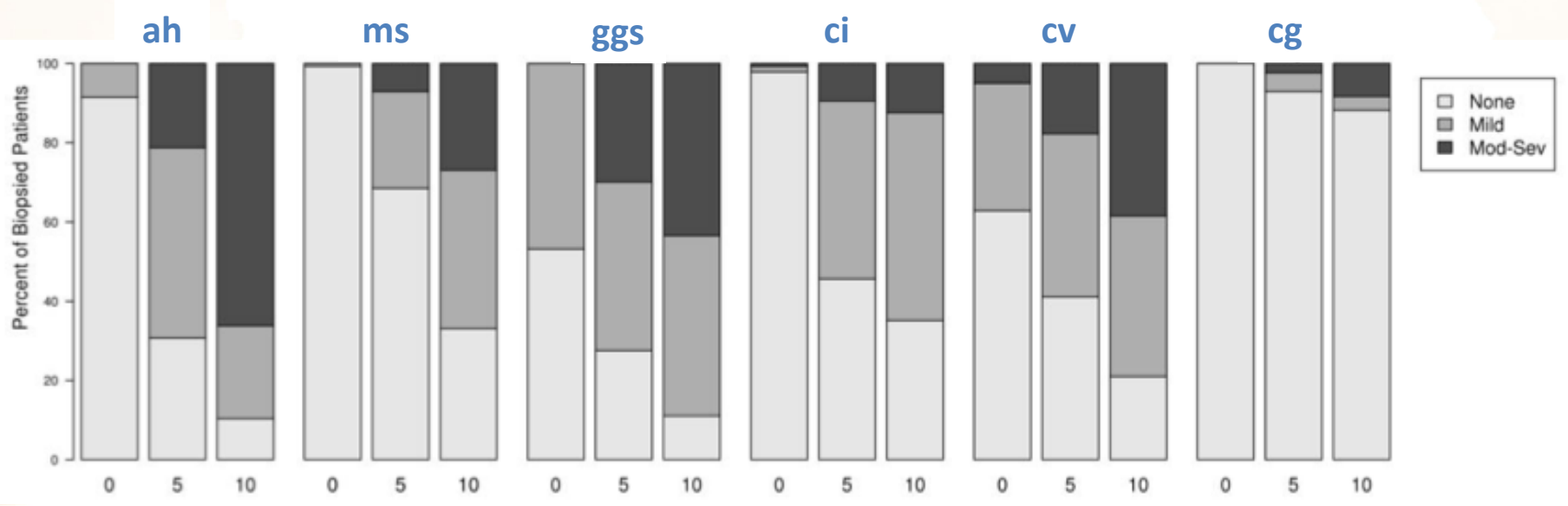
Anomalies histologiques majeures:
cg > 0
Autres scores de Banff > 2
ggs > 2
Sclérose mésangiale > 2

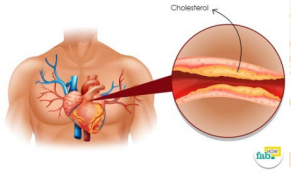
Pré implantatoire
5 %

à 5 ans
64 %

à 10 ans
82 %

Baisse du DFG et majoration de la protéinurie à 5 et 10 ans

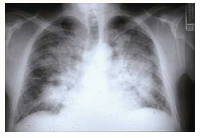


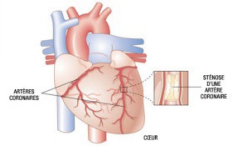


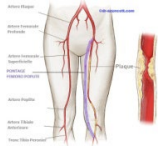
Fibrose sévère et glomérulopathie d'allogreffe 12%

Stegall, AJT, 2017

Notre quotidien …





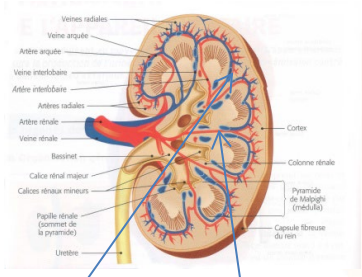


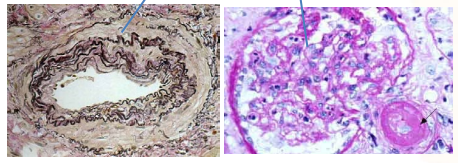
Augmentation du risque de DGF

Décompensation cardiaque

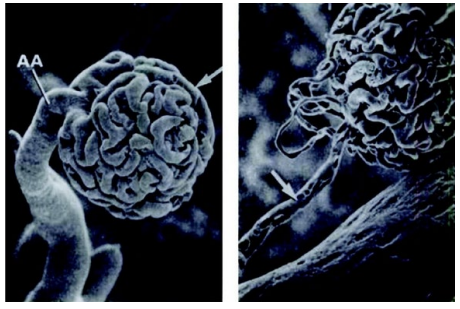
Prolongation hospitalisation

Augmentation du risque d'infection



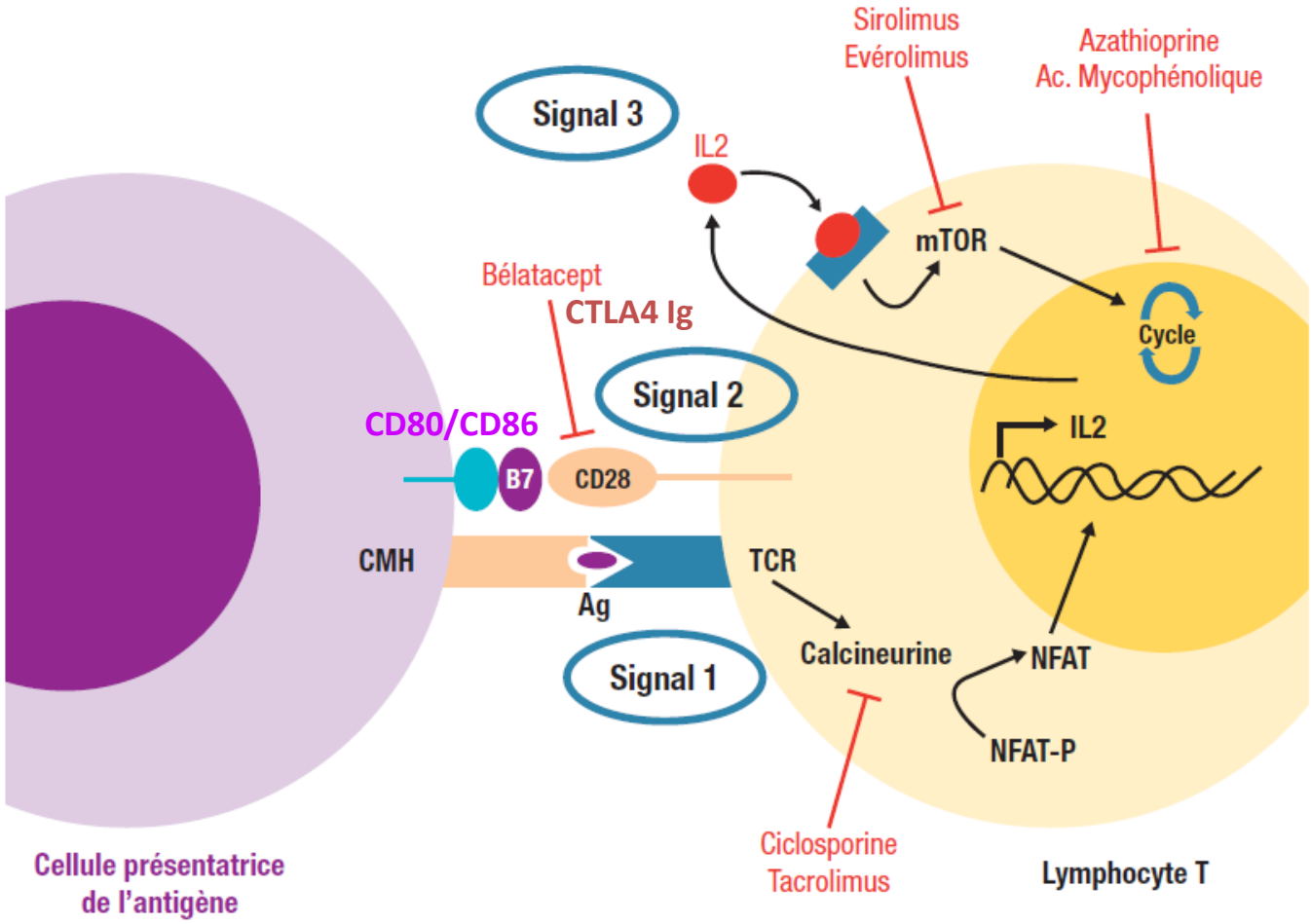


Risque de DGF et ECD

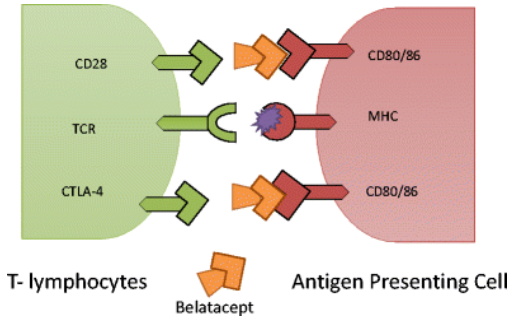


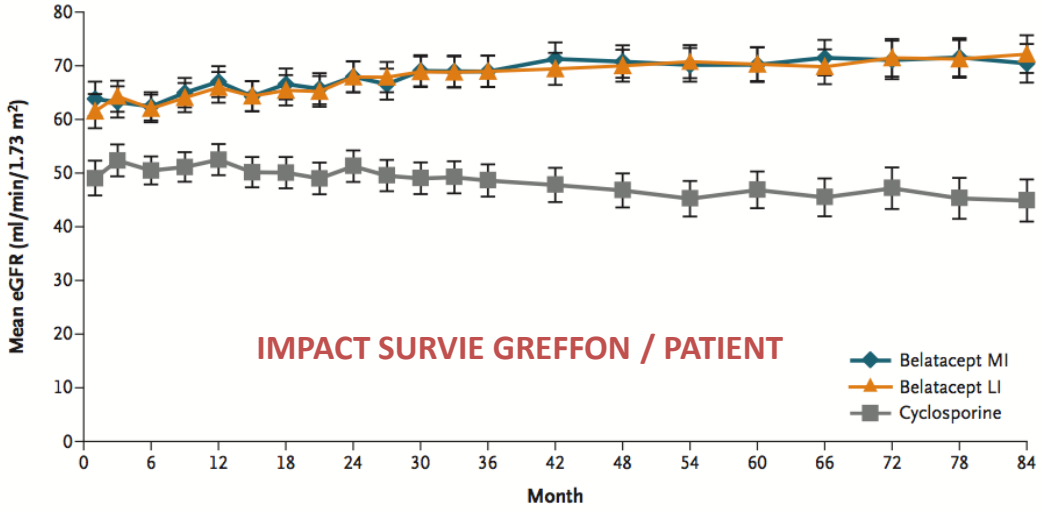
Anticalcineurines…

La solution le belatacept?

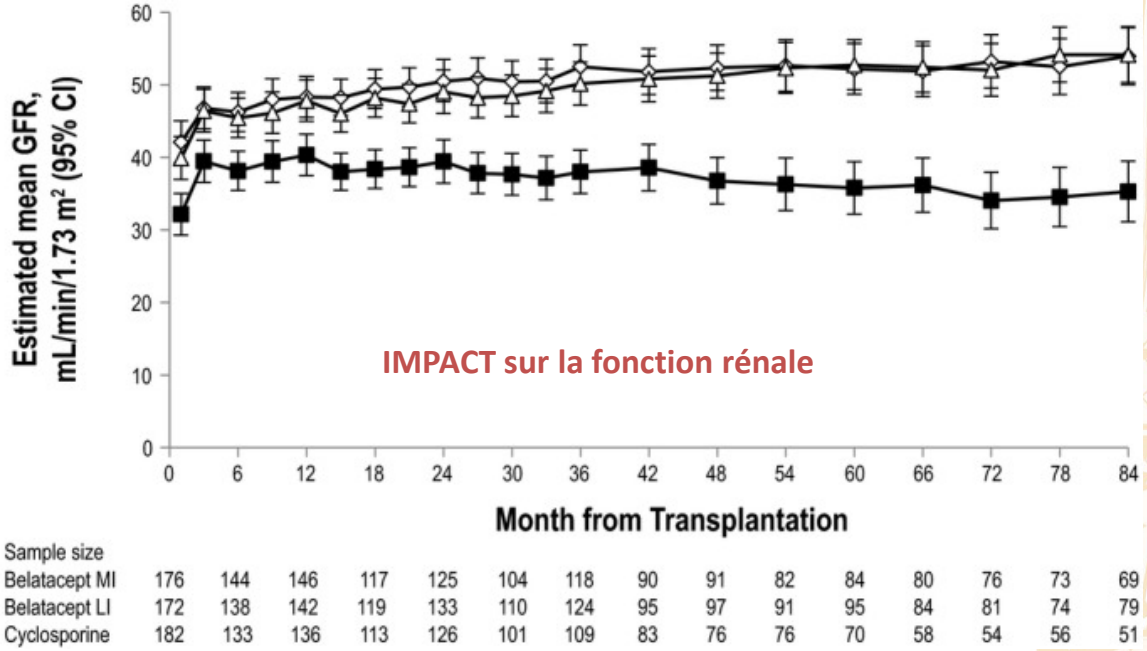


Belatacept de novo





IMPACT SURVIE GREFFON / PATIENT



IMPACT sur la fonction rénale

Sample size															
Belatacept MI	176	144	146	117	125	104	118	90	91	82	84	80	76	73	69
Belatacept LI	172	138	142	119	133	110	124	95	97	91	95	84	81	74	79
Cyclosporine	182	133	136	113	126	101	109	83	76	76	70	58	54	56	51

- **Problème du comparateur**
- **Rejet cellulaire sévère, parfois CTC-R**

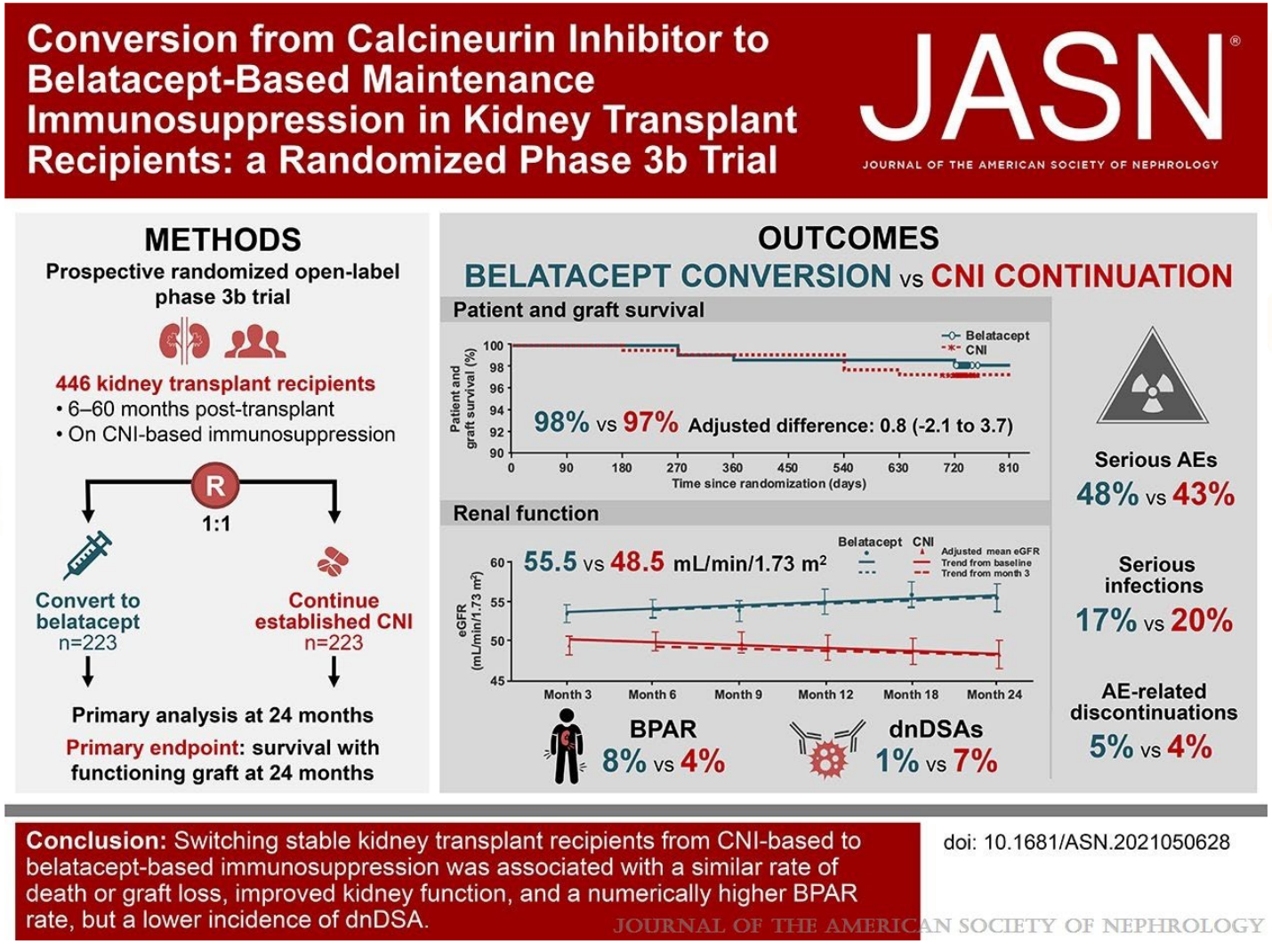
- Voie IV
- Hôpital
- Coût
- PTLD?

Tacro 0% !!

Vincenti, NEJM, 2016
Durrbach, AJT,2016

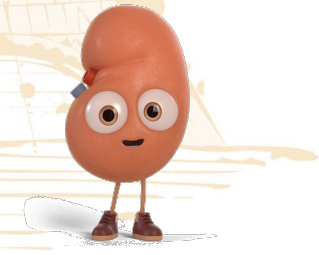
BELATACEPT switch: patient stable

Tacro
90% !!



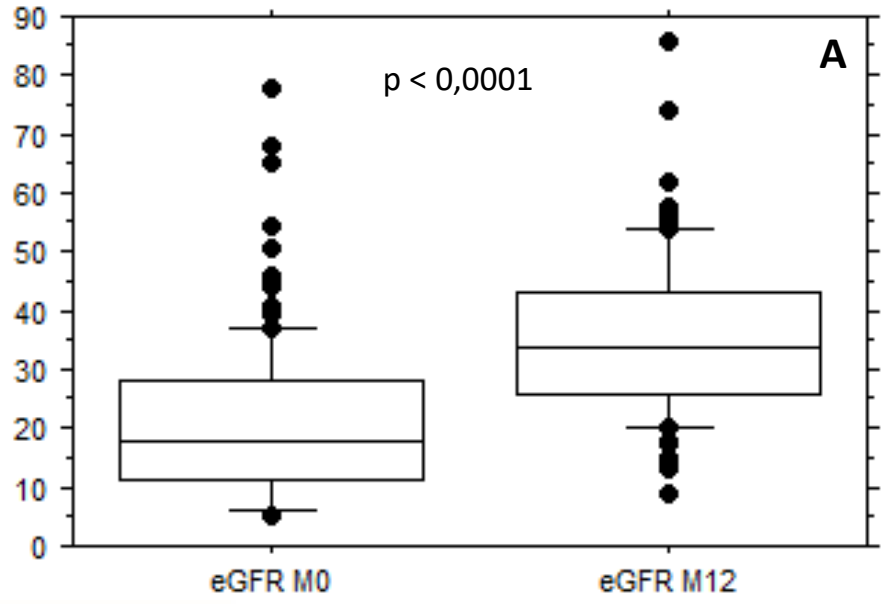
Budde, JASN, 2021

Bénéfices attendus d'un switch au belatacept



Améliorer la fonction rénale

N=280 patients
Switch précoce: 108
Switch tardif: 172

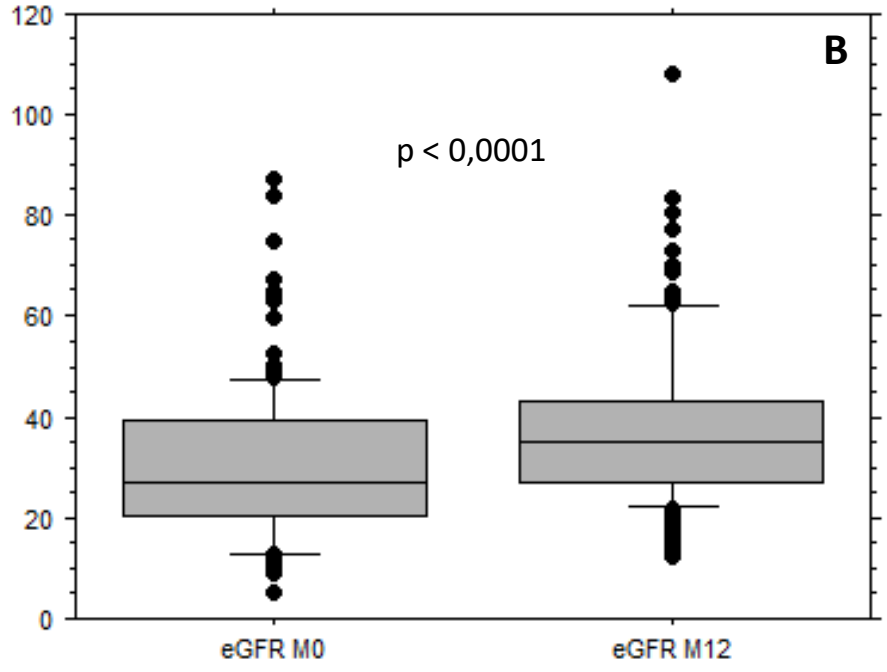


21,3 ± 14,0 35,7 ± 14,0

+ 12,7 ± 15,4 mL/min/1,73 m²

Conversion précoce (< 6 mois post KT)

p = 0,009



30,0 ± 15.0 38,1 ± 16,1

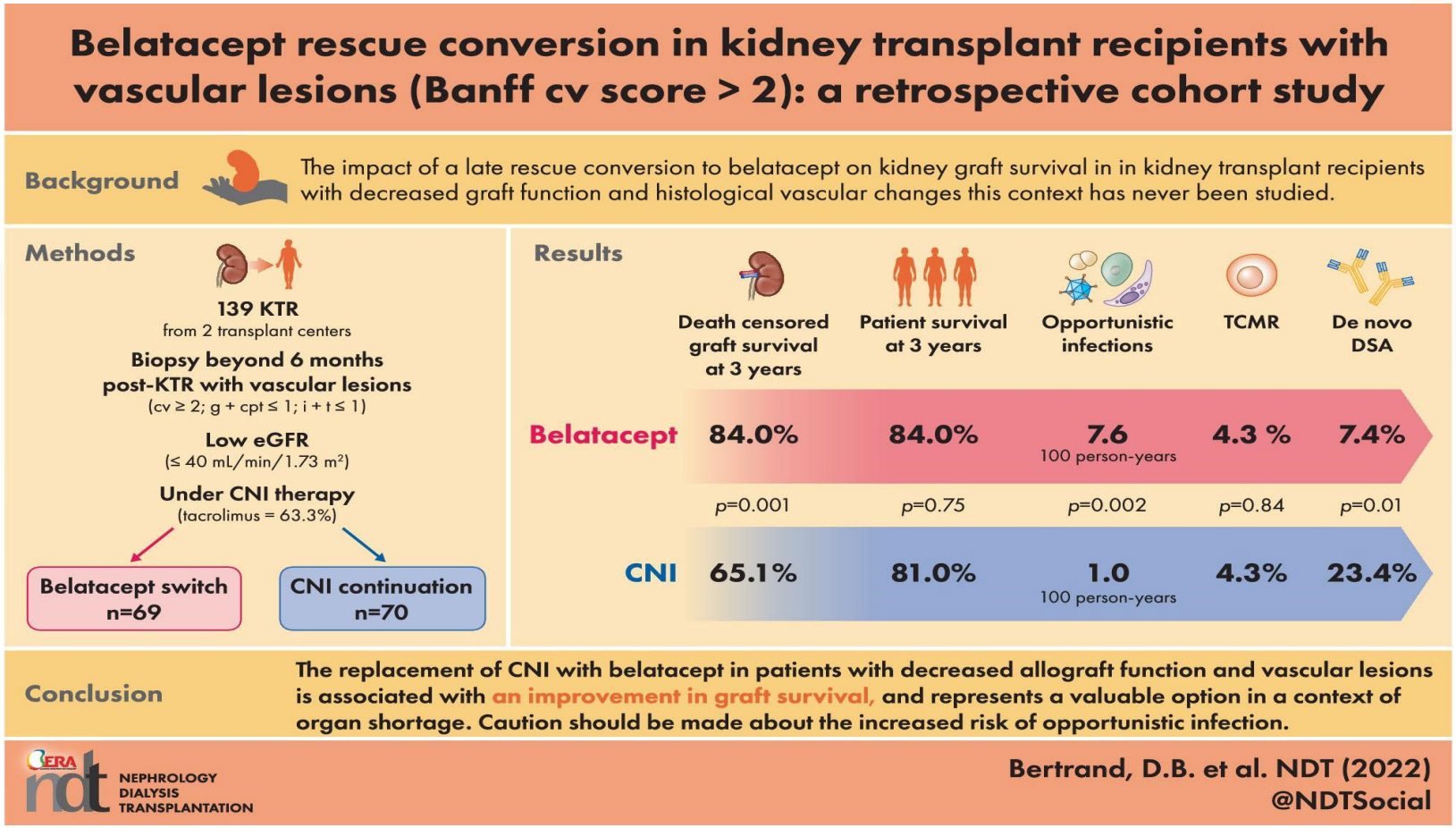
+ 6,4 ± 11,9 mL/min/1,73 m²

Conversion tardive (> 6 mois post KT)

Bertrand, NDT, 2020

Amélioration survie rénale?

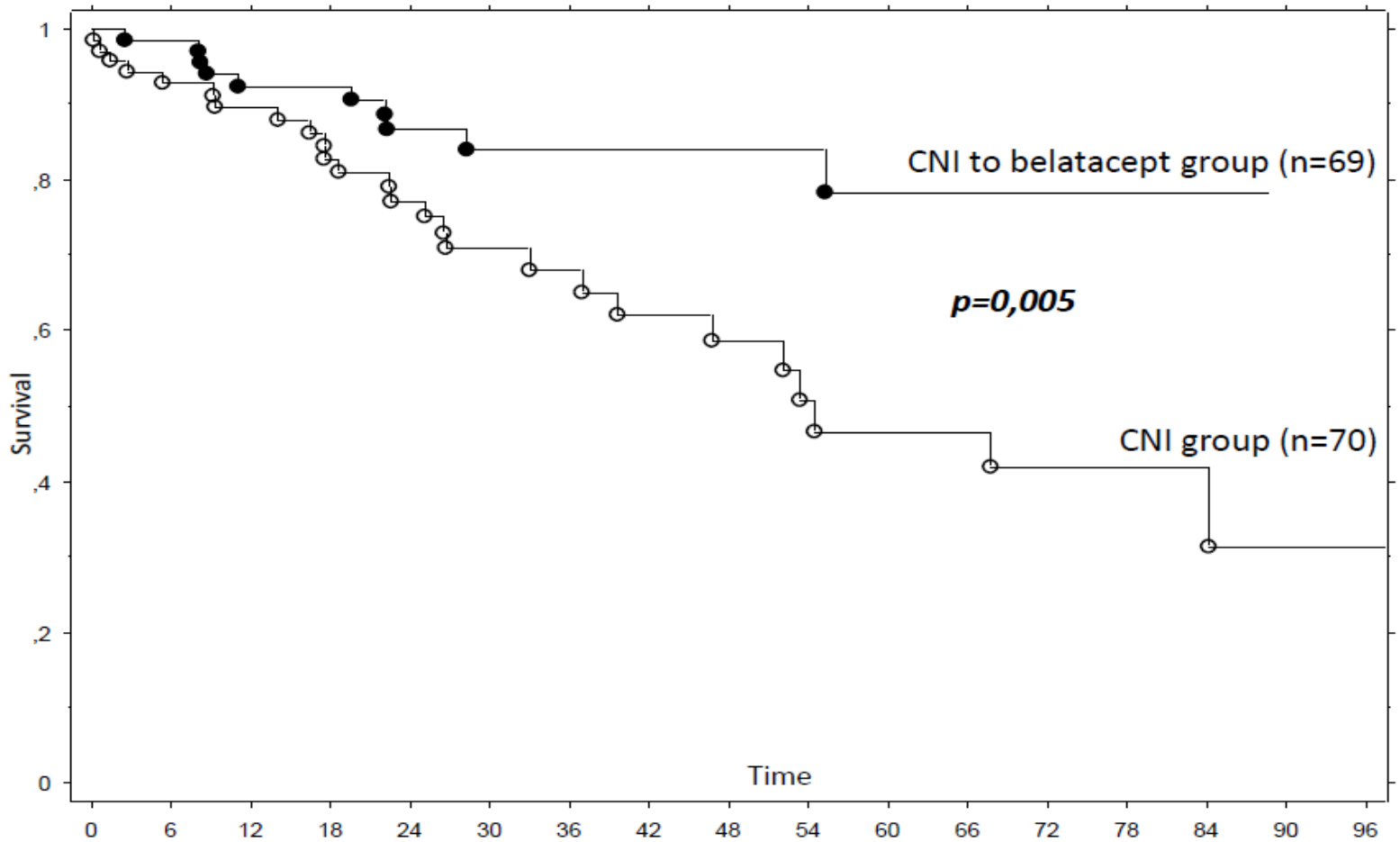
Tacro
63% !!



Bertrand, NDT, 2023

Amélioration de la survie rénale?

Tacro 63% !!



Bertrand, NDT, 2023

Amélioration de la survie rénale?

Population:
Patients transplantés
à Necker et Saint-Louis à Paris

NIH U.S. National Library of Medicine
ClinicalTrials.gov
NCT04733131

Belatacept cohort:
311 patients converted to belatacept with a kidney allograft evaluation under CNI

CNI control cohort:
2,904 patients with a kidney allograft evaluation under CNI

1:1 optimal propensity score matching using 11 parameters

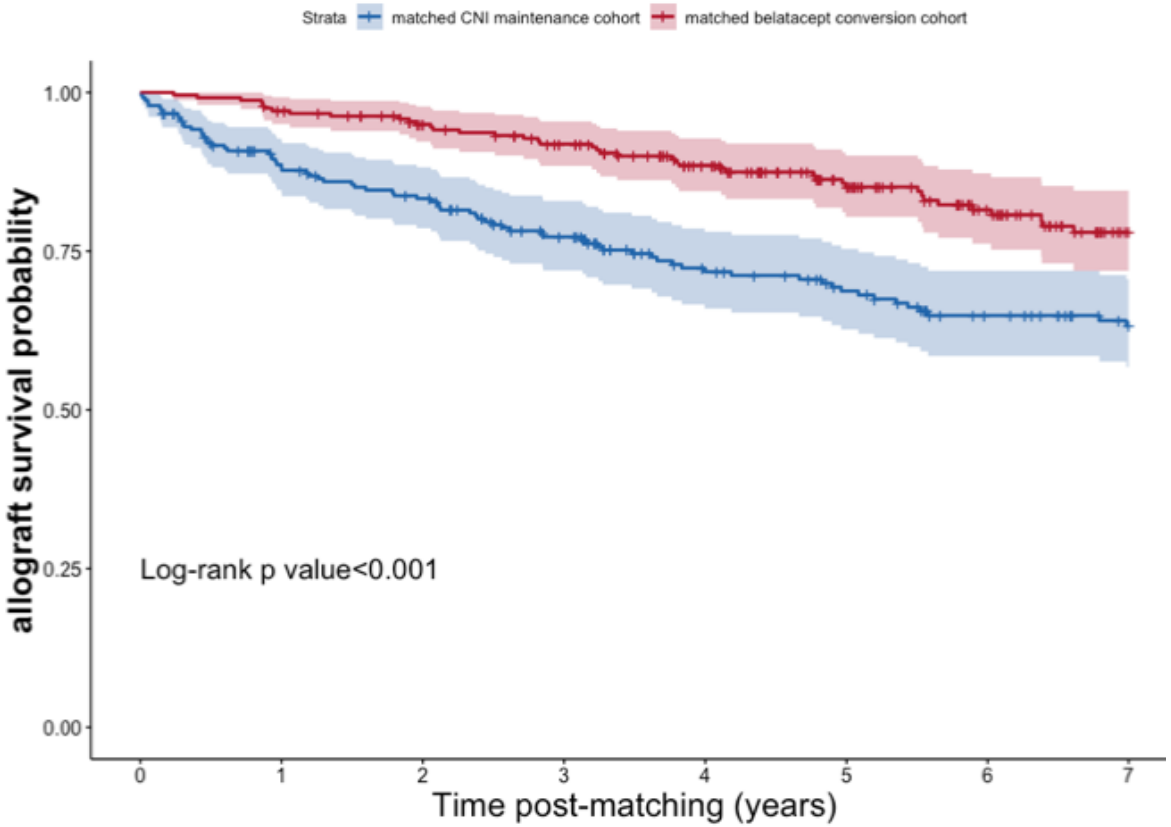
- Recipient age
- Prior transplant
- DGF
- Donor type
- Time from transplant and the kidney allograft evaluation
- eGFR*
- Proteinuria*
- DSA*
- cv Banff scores*
- ah Banff scores*
- IFTA Banff scores*

CJASN
Clinical Journal of the American Society of Nephrology

*Au moment de l'évaluation du greffon

Divard et al., cJASN, 2024

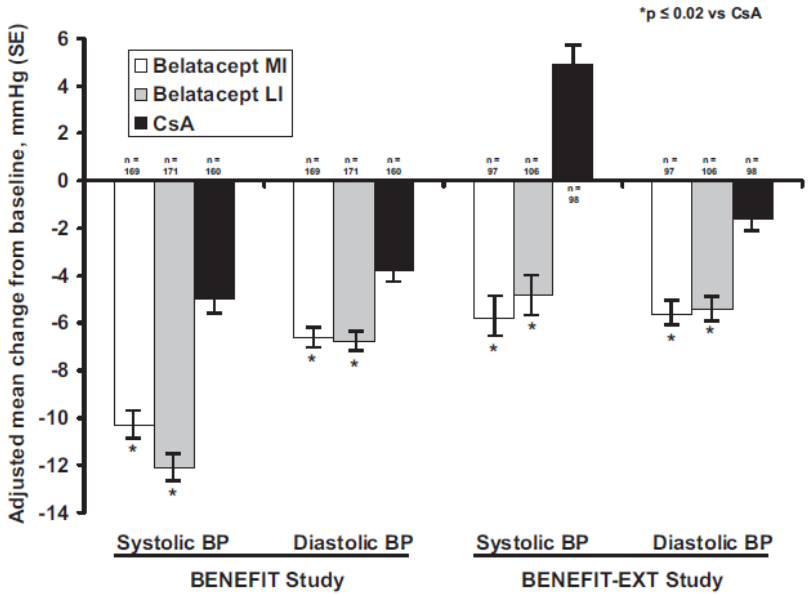
Amélioration de la survie rénale?

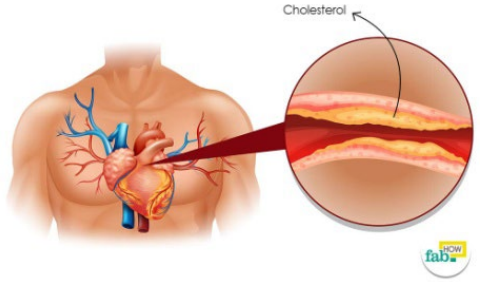


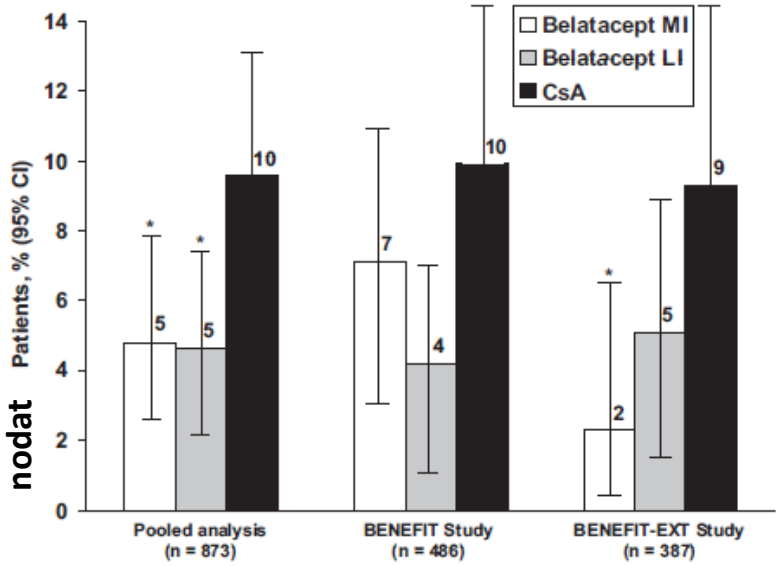
CJASN®
Clinical Journal of the American Society of Nephrology

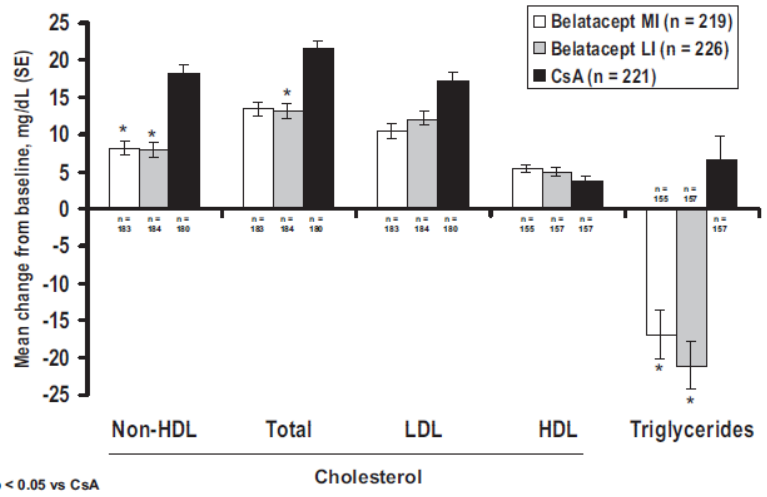
Divard et al. accepted

Profil cardiovasculaire et diabète



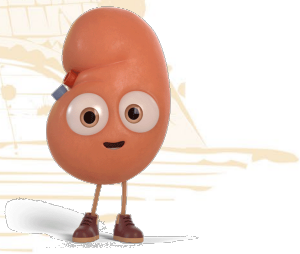






Vanrenterghem, Transplantation, 2011

Quels sont les risques d'un switch au belatacept?



Risque de rejet (cellulaire!)

BENEFIT
17% vs 7%

Month 12 endpoints	Belatacept MI (n = 219)	Belatacept LI (n = 226)	Cyclosporine (n = 221)
Acute rejection			
Acute rejection, n (%)	49 (22)	39 (17)	16 (7)
95% CI	16.9–27.9	12.3–22.2	3.8–10.7
Difference from CsA (97.3% CI)	15.1 (7.9, 22.7)	10.0 (3.3, 17.1)	–
Banff grade, n (%)			
Mild acute (IA)	7 (3)	4 (2)	3 (1)
Mild acute (IB)	3 (1)	8 (4)	5 (2)
Moderate acute (IIA)	17 (8)	16 (7)	6 (3)
Moderate acute (IIB)	20 (9)	10 (4)	2 (1)
Severe acute (III)	2 (1)	1 (<1)	0

BENEFIT EXT
17,7% vs 14,1%

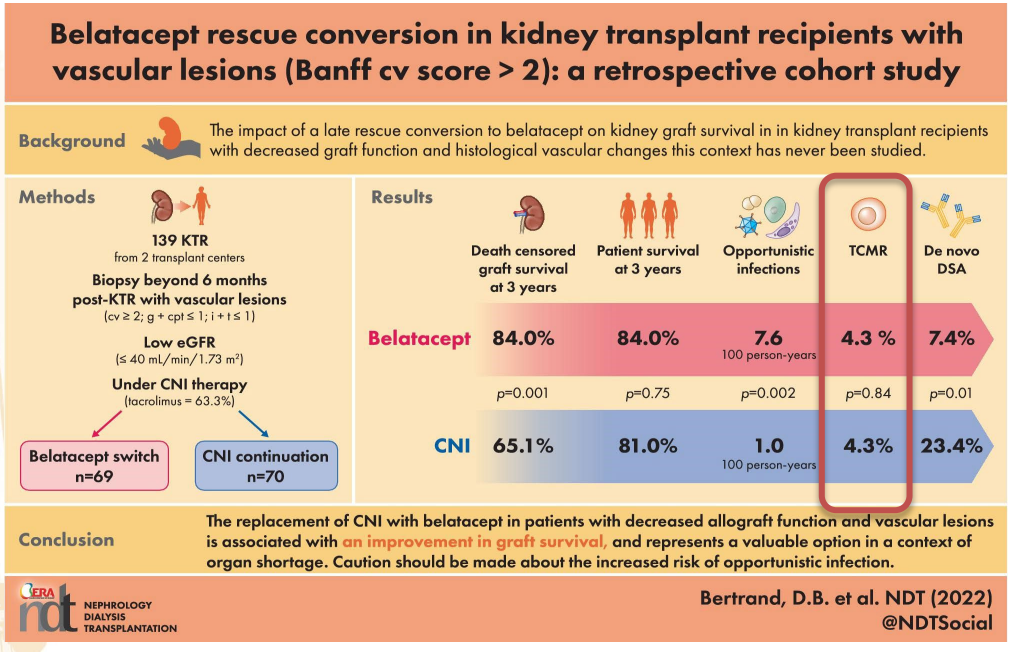
Month 12 endpoints	Belatacept MI (n = 184)	Belatacept LI (n = 175)	Cyclosporine (n = 184)
Acute rejection			
Acute rejection, n (%)	33 (17.9)	31 (17.7)	26 (14.1)
95% CI	12.4–23.5	12.1–23.4	9.1–19.2
Difference from cyclosporine (97.3% CI)	3.8 (–4.7, 12.4)	3.6 (–5.0, 12.3)	–
Banff grade, n (%)			
Mild acute (1A)	–	4 (2)	2 (1)
Mild acute (1B)	7 (4)	2 (1)	2 (1)
Moderate acute (IIA)	10 (5)	17 (10)	17 (9)
Moderate acute (IIB)	16 (9)	8 (5)	5 (3)
Severe acute (III)	–	–	–

	Bertrand et al (n=453)	Bertrand et al (n = 280)	Darres et al (n=219)	Brakemeier et al (n = 79)	Grinyo et al (n = 84)	Budde et al (n=446)
Rejection post conversion n(%)	24 (5,3%)	18 (6,4%)	18 (8,2%)	9 (11,4%)	7 (8,3%)	8%

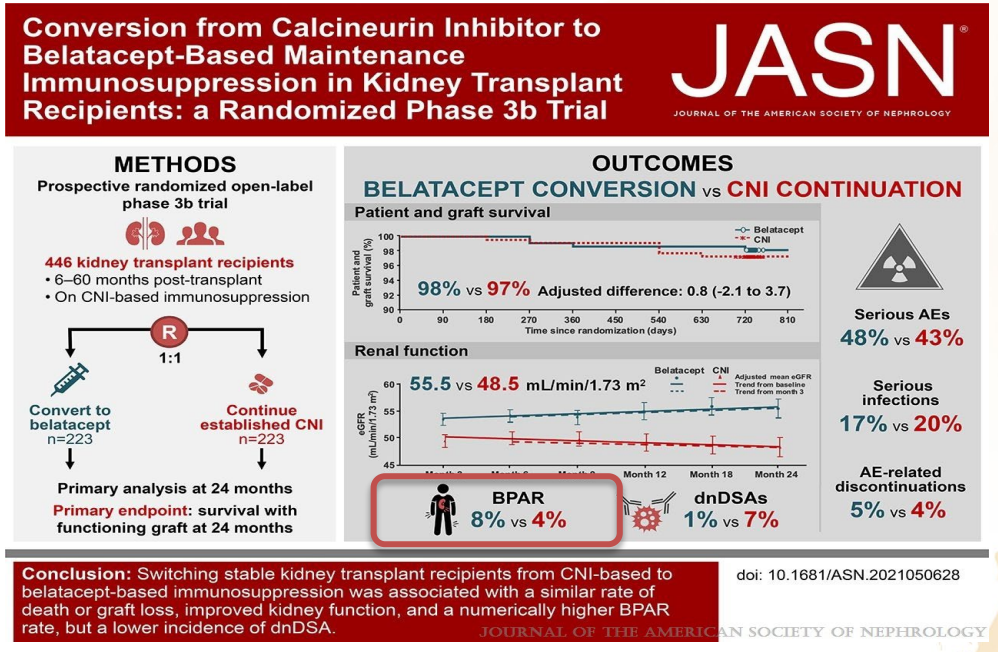
Darres et al, Transplantation, 2018
Bertrand, NDT, 2020. Bertrand, Terrec et al JCM, 2020

Brakemeier et al, Transp Int, 2016. Grinyo et al, AJKD, 2017
Budde, JASN, 2021

Risque de rejet (cellulaire!)



Bertrand, NDT, 2023



Budde, JASN, 2021

Centres SPIESSER ASTRE

Infections opportunistes

Mean time of exposure:17,6 ± 15,5 months. Cumulative exposure : 5128 months

280 KT

34 patients (12,1%)

42 episodes of OPI

After a mean time of 10,8 ± 11,3 months post conversion

0,008 OPI per month of exposure
9,8 OPI per 100 person-years

Hospitalization in all cases
Mean duration:
20,5 ± 28,5 days

Death: 9/34 (26,5%)

Graft loss: 4/34 (11,8%)

Bertrand, NDT, 2020

Infections opportunistes

CMV Disease

18 patients (18/42: 42,9%)

Mean time of occurrence after the switch: 10,8 ± 10,1 months

D+/R-: 9/18
D+/R+ D-/R+: 7/18
D-/R-: 2/18

Multi organ involvement in 8 patients (2 chorio-retinitis)

Death: 4/18 (22,2%)

Pneumocystis pneumonia

12 patients (12/42: 28,6%)

Mean time of occurrence after the switch: 13,9 ± 11 months

+ another OPI (7/12)
mainly CMV disease (6/7)

Death: 4/12 (33,3%)

Others

VZV (zoster): 3 patients

EBV (PTLD): 2 patients

Jc Virus (PML): 2 patients

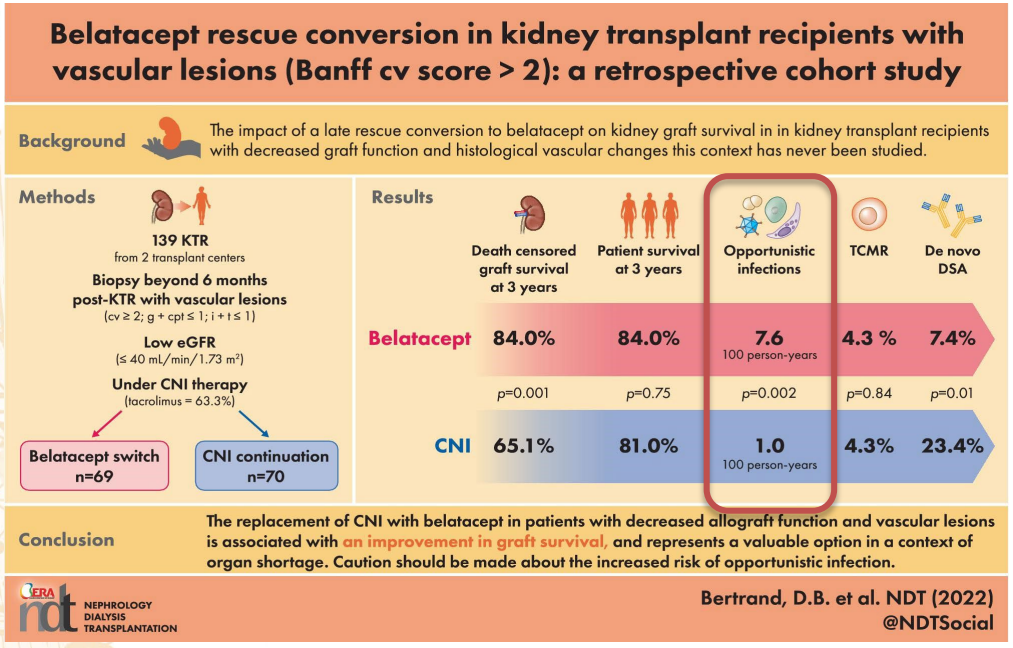
Mycobacteria: 2 patients

Aspergilosis (invasive):1 patient

Toxoplasmosis: 1 patient

Bertrand, NDT, 2020

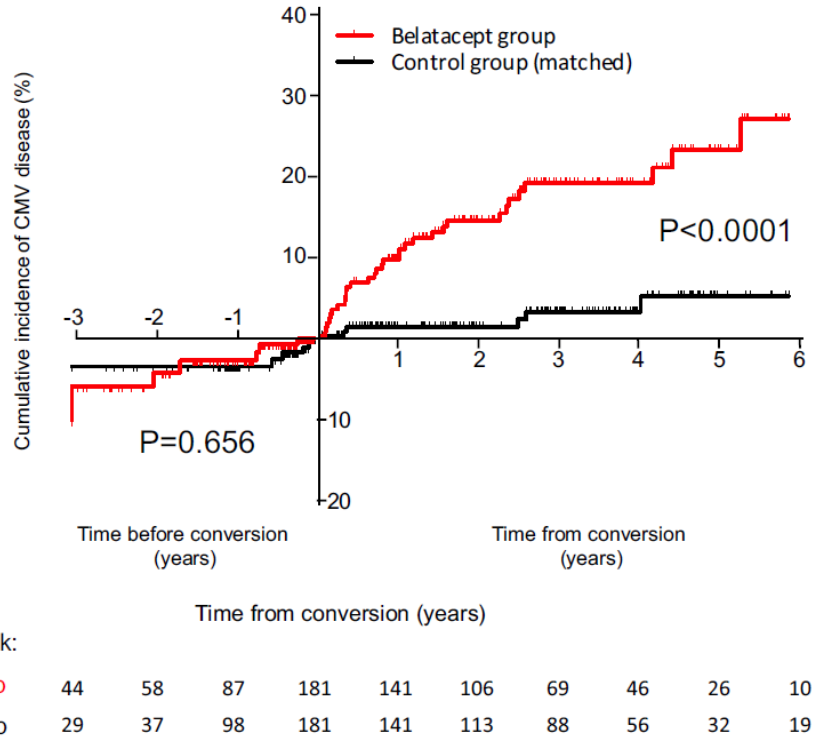
Infections opportunistes et bela

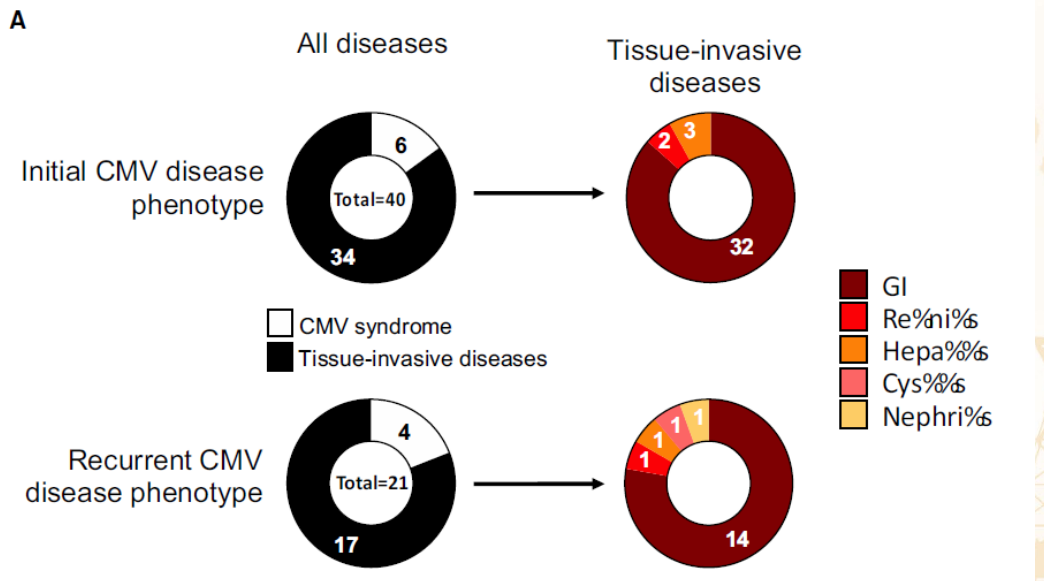


	CNI group (n=70)	Belatacept group (n=69)	p
Cumulative months of treatment exposure	2343	2200	
Pneumocystis pneumonia n (%)	0 (0)	4 (5,8)	0,04
Cryptococcus neoformans infection n (%)	0 (0)	1 (1,4)	0,31
Aspergillosis n (%)	0 (0)	1 (1,4)	0,31
Varicella or zoster (%)	1 (1,4)	5 (7,2)	0,07
EBV positive PTLD n (%)	1 (1,4)	0	0,43
CMV disease n (%)	0 (0)	3 (4,3)	0,08
Total OPI n (%)	**2 (2,9)**	**14 (20,3)**	**0,002**
OPI/month of exposure	0,001	0,006	
OPI/100 person-years	**1,0**	**7,6**	
OPI related death n(%)	1 (1,4)	3 (4,3)	0,10

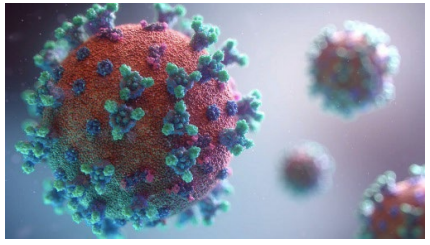
Bertrand, NDT, 2022

OPI: CMV et bela

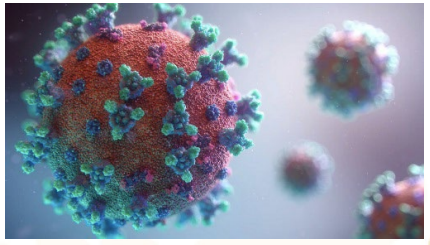


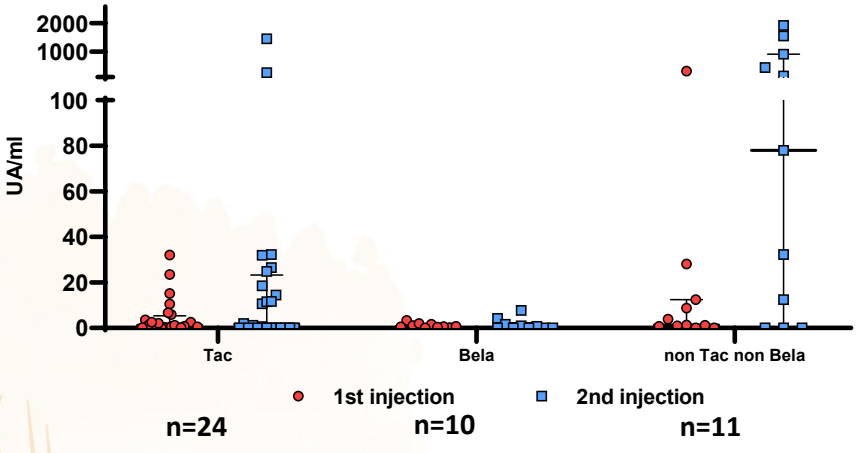


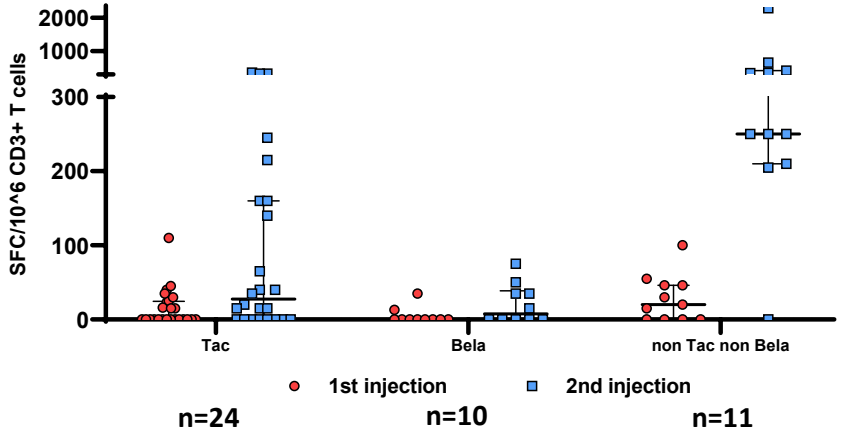
Chavarot, AJT, 2021

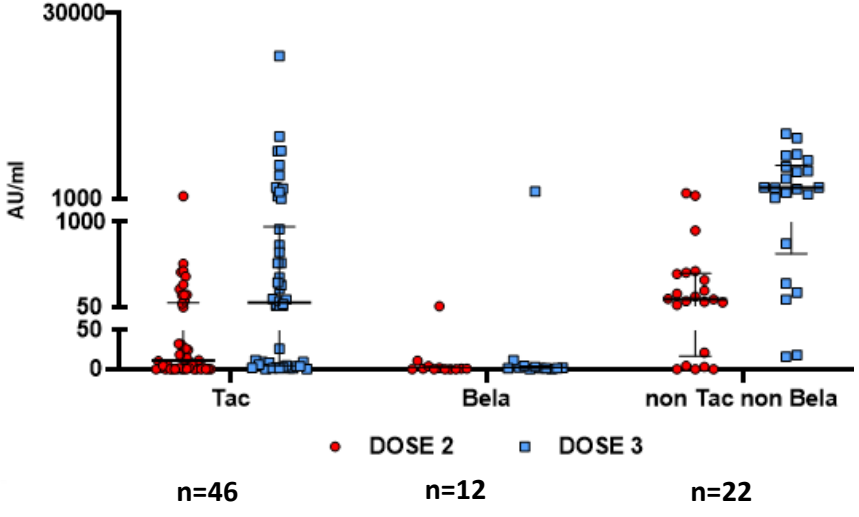


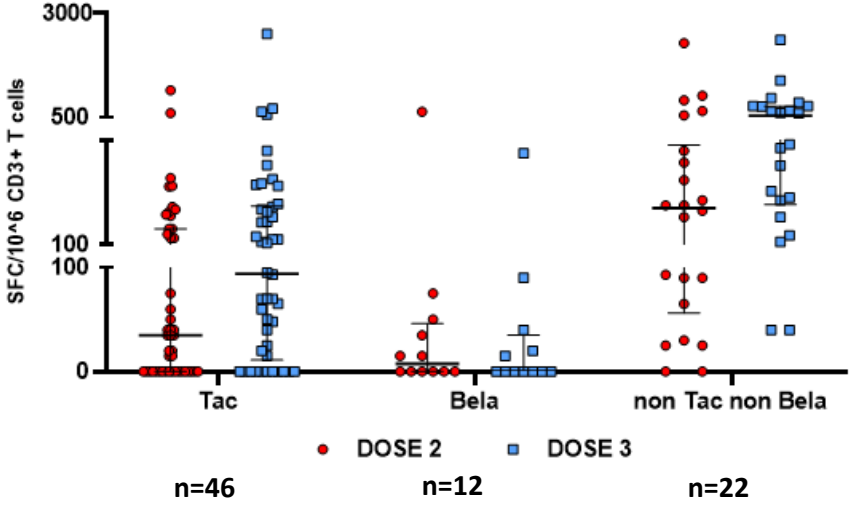
Vaccination et belatacept







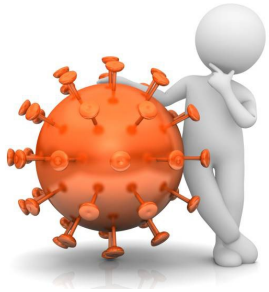




Bertrand, JASN, 2021
Bertrand, KI, 2021
Chavarot, AJT, 2021

En conclusion

- Gain de fonction
- Gain de Survie greffon
- Gain de Survie patient?
- Profil métabolique



- Risque de TCMR
- Plus d'infections opportunistes
- Mauvaise efficacité vaccinale
- Voie IV

Observance!

Un équilibre difficile à atteindre…

Risque de TCMR

Plus d'infections opportunistes

Monitoring et suivi thérapeutique du belatacept???

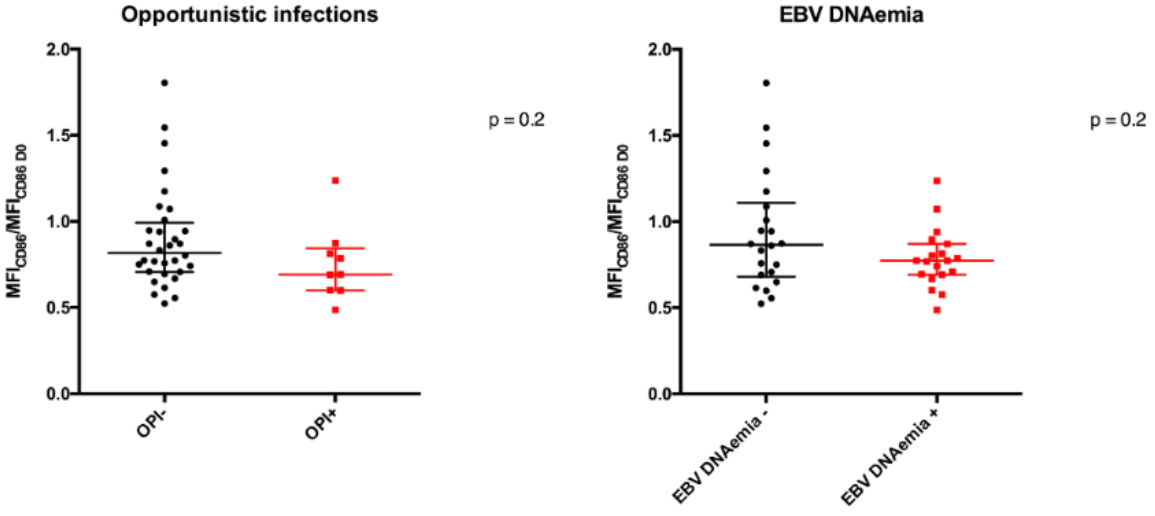
Comment monitorer le belatacept?

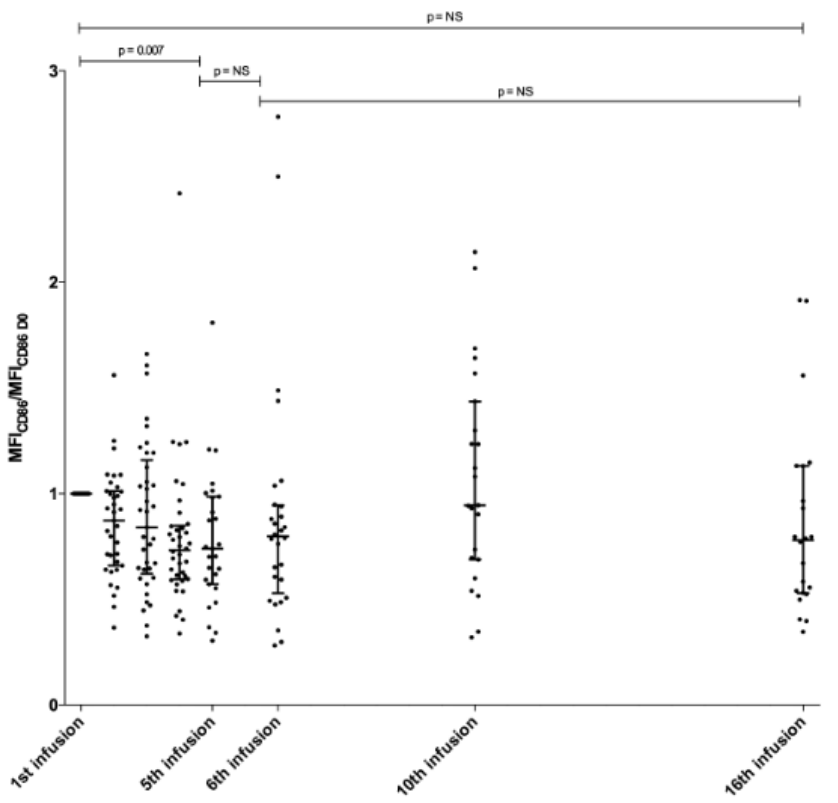
BRIEF COMMUNICATION

AJT

CD86 occupancy in belatacept-treated kidney transplant patients is not associated with clinical and infectious outcomes

Tristan de Nattes[1,2] | Ludivine Lebourg[1] | Isabelle Etienne[1] | Charlotte Laurent[1] | Mathilde Lemoine[1] | Audrey Dumont[1] | Dominique Guerrot[1] | Serge Jacquot[2] | Sophie Candon[2] | Dominique Bertrand[1]





variabilité intra-individuelle élevée: 31.58% durant la première année suivant la conversion

Comment monitorer le belatacept?

biomedicines

MDPI

Article

A Validated LC-MS/MS Method for Performing Belatacept Drug Monitoring in Renal Transplantation

Stéphanie Chhun [1,2,*], Mathieu Trauchessec [3], Sophie Melicine [1], Frédéric Nicolas [4], Agathe Miele [3], Srboljub Lukic [1], Estelle Vilain [4], Lucile Amrouche [4], Dorothée Lebert [3], Dany Anglicheau [2,4], Eric Tartour [1,2] and Julien Zuber [2,4]

N=108

Concentrations résiduelles 1.4 à 24.8 µg/ml avec variabilité inter-individuelle de 46% et variabilité intra-individuelle était de 17%

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Short Communication

Quantification of belatacept by liquid chromatography-tandem mass spectrometry in human plasma: Application to a pharmacokinetic study in renal transplant recipients

Aurélie Truffot [a,*], Jean-François Jourdil [b,d], Elodie Veyret-Gautier [b,d], Johan Noble [c], Thomas Jouve [c], Paolo Malvezzi [c], Lionel Rostaing [c], Françoise Stanke-Labesque [b,d]

[a] Laboratoire de Virologie, Centre Hospitalier Universitaire Grenoble-Alpes, 38000 Grenoble, France
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[d] Univ. Grenoble Alpes, INSERM, CHU Grenoble Alpes, HP2, 38000 Grenoble, France

N=17

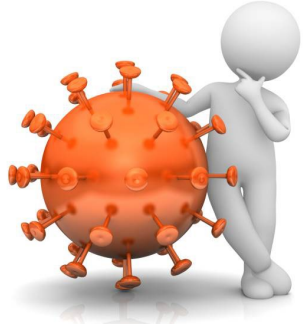
Concentrations résiduelles 5.1 et 15 µg/ml avec une variabilité inter-individuelle de 33%

Pas d'étude de dosage résiduelle en fonction des évènements cliniques en vrai vie

Projet Biosynex i-Tracker Bélatacept

Dosage « résiduelle belatacept » + ac anti belatacept (sérothèque)

En situation stable
Pas de complication



Complications infectieuses opportunistes

Rejets

Merci pour votre attention!

@dommibertrand

CHU ROUEN NORMANDIE