Immunothérapie et myélome

Journées de la SFGM-TC
Le 19 novembre 2021

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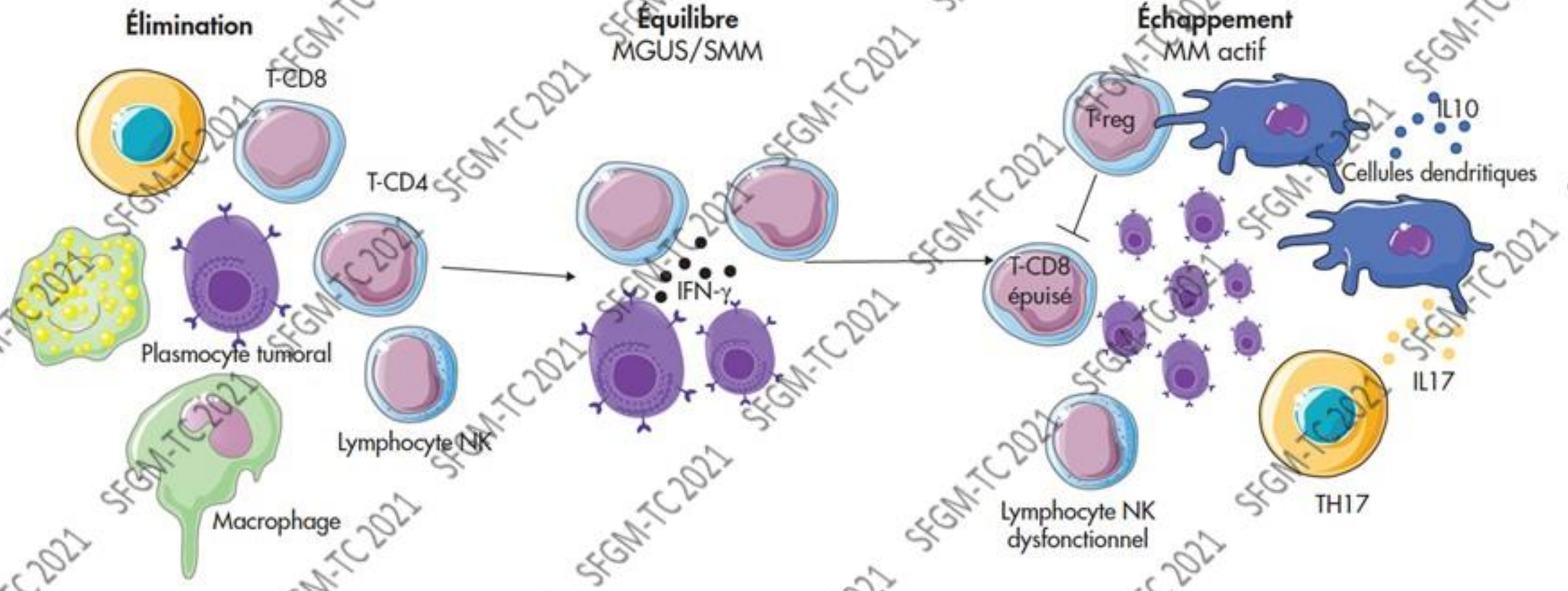
ifm

Qu'est-ce que l'immunothérapie ?

Immunothérapie anti-tumorale

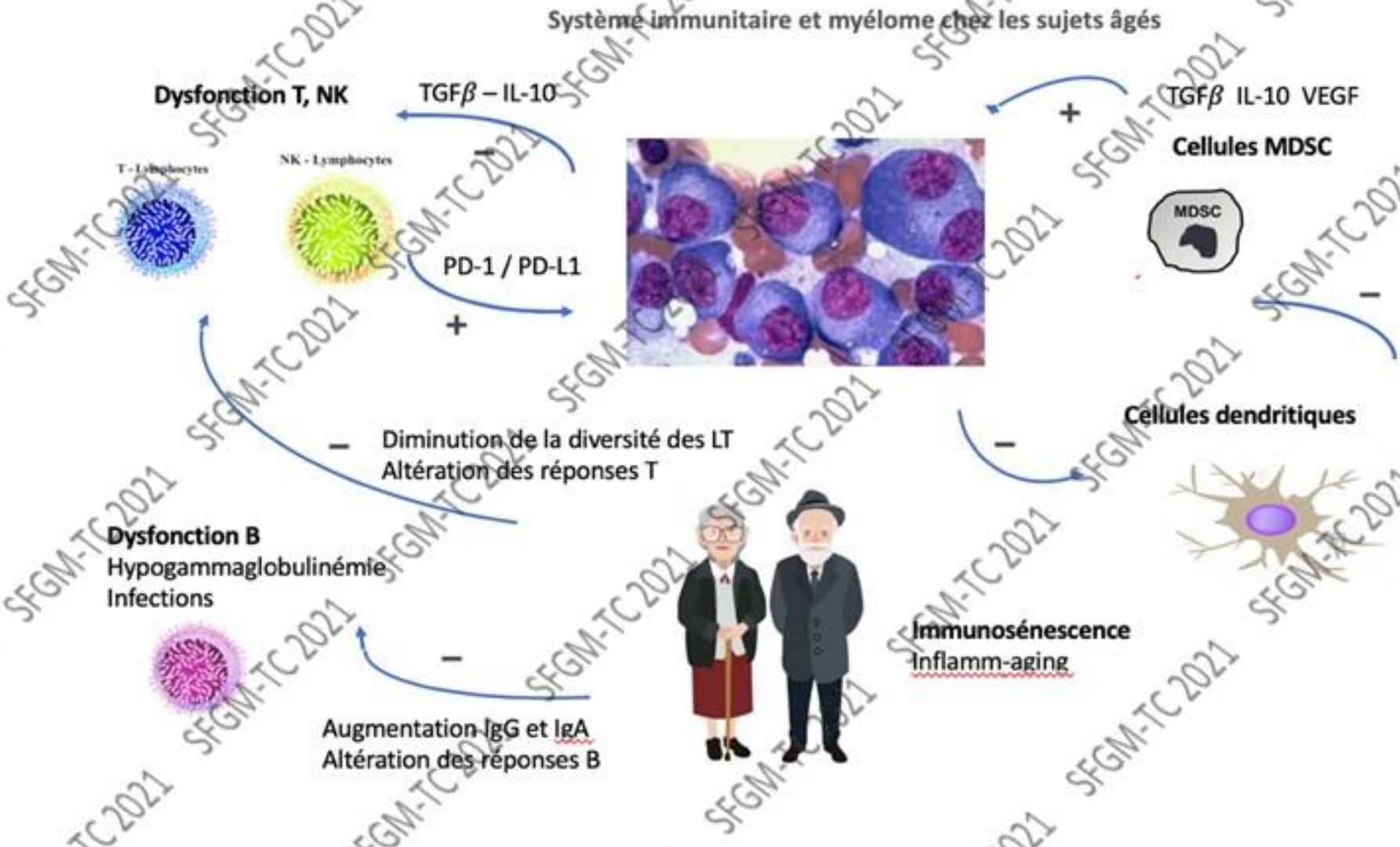
« Approche thérapeutique qui agit sur le système immunitaire, ayant pour objectif d'éduquer et d'activer les défenses immunitaires d'un patient afin qu'elles éliminent elles-mêmes les cellules cancéreuses »

Système immunitaire et myélome



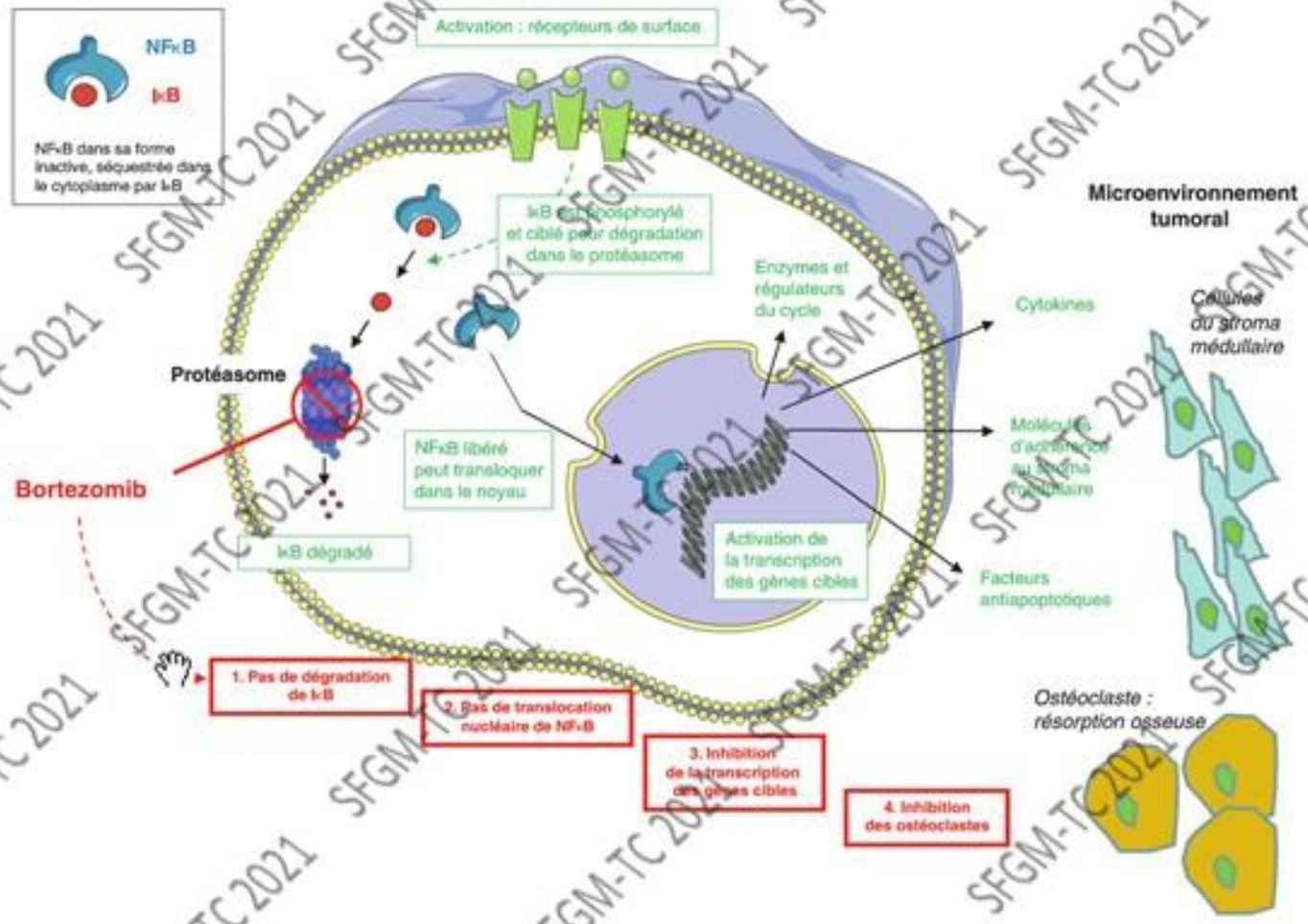
S Le Grand & A Perrot, Hématologie 2021

Système immunitaire, vieillissement et myélome



Immunothérapie et « anciennes molécules » ?

- **Inhibiteurs du protéasome**

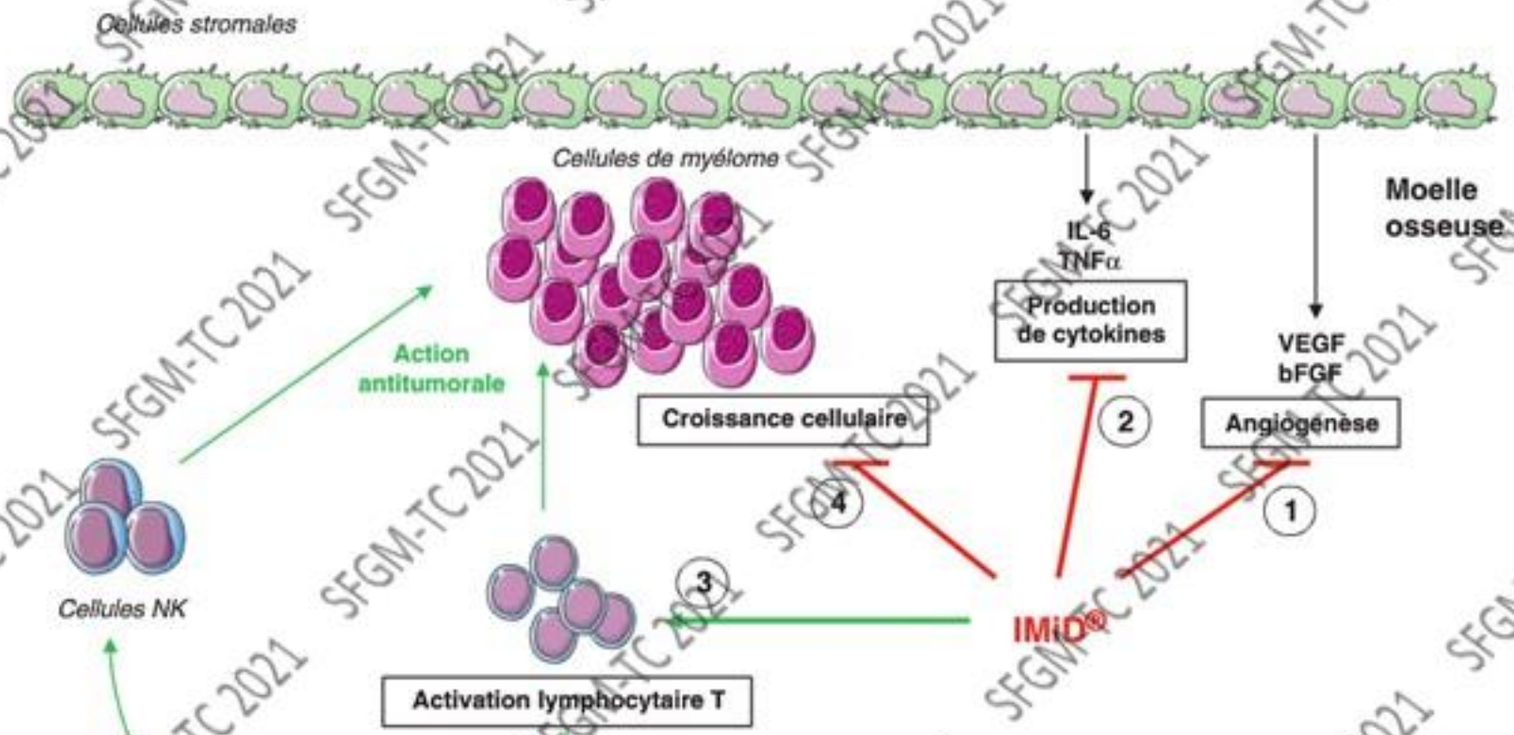


- Inhibition NFkB dans les cellules dendritiques
- Inhibition d'autres enzymes protéasomales qui augmenterait l'activation T et la cytotoxicité NK

Mais augmentation de l'apoptose des cellules B normales

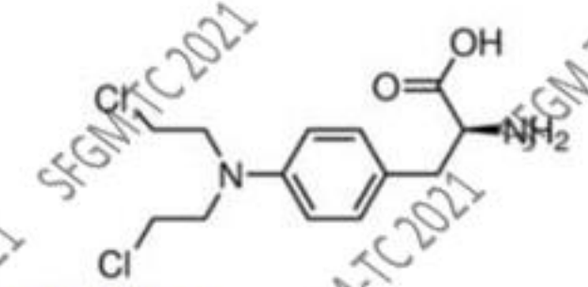
Immunothérapie et « anciennes molécules » ?

- **Immunomodulateurs**



Immunothérapie et « anciennes molécules » ?

- **Alkylants**



Melphalan

L-Phenylalanine mustard, 4-[Bis(2-chloroethyl)amino]-L-phenylalanine, L-PAM

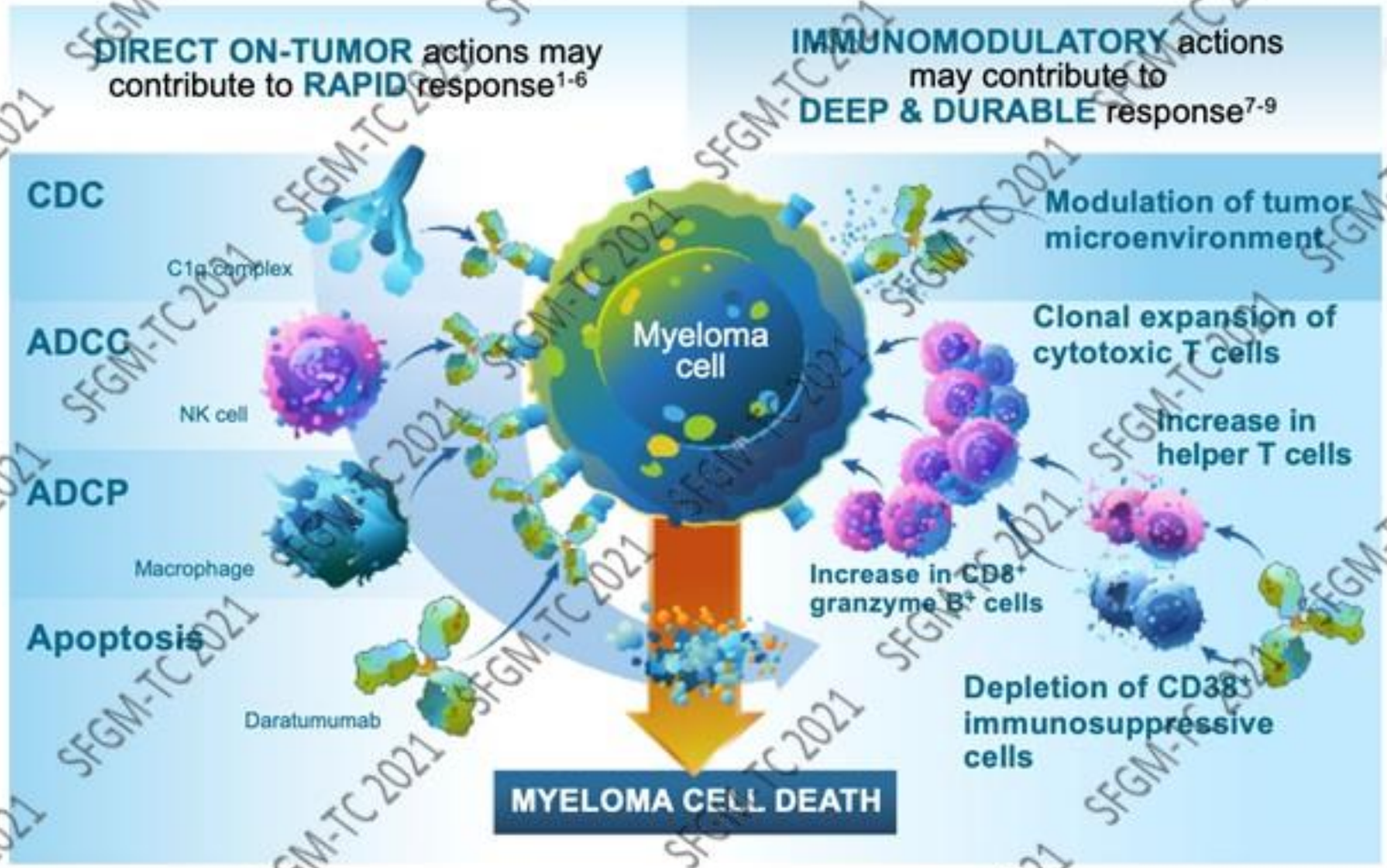
- « Burst » transitoire de cytokines pro-inflammatoires
- Induction de mort cellulaire immunogénique
- Priming de cellules T CD8 effecteurs mémoires
- Prolifération de T CD4

Mais déplétion des monocytes, des cellules dendritiques

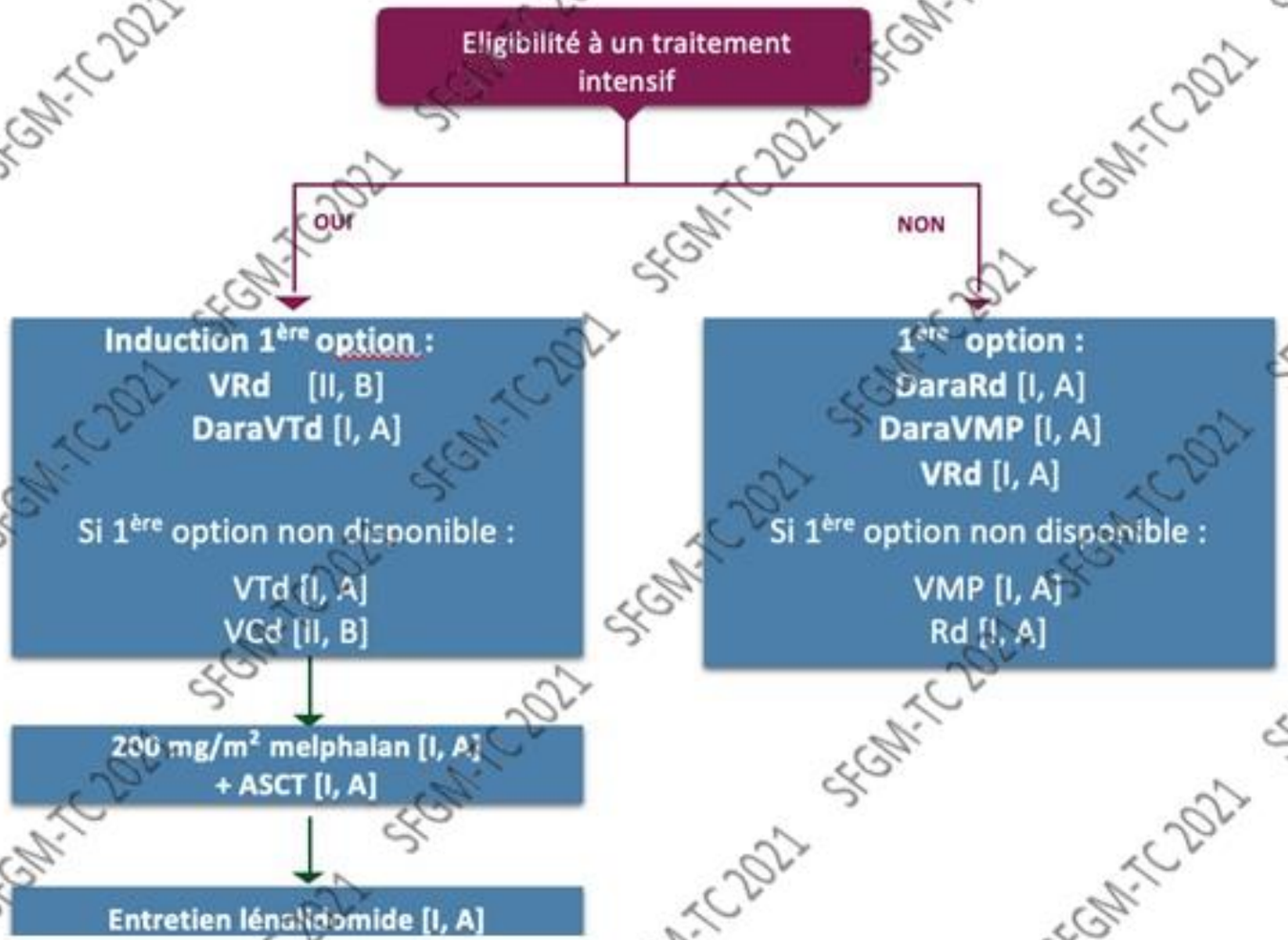
M A Firer et al, Cancers 2021

L'immunothérapie d'aujourd'hui

- **Anticorps monoclonaux anti-CD38**



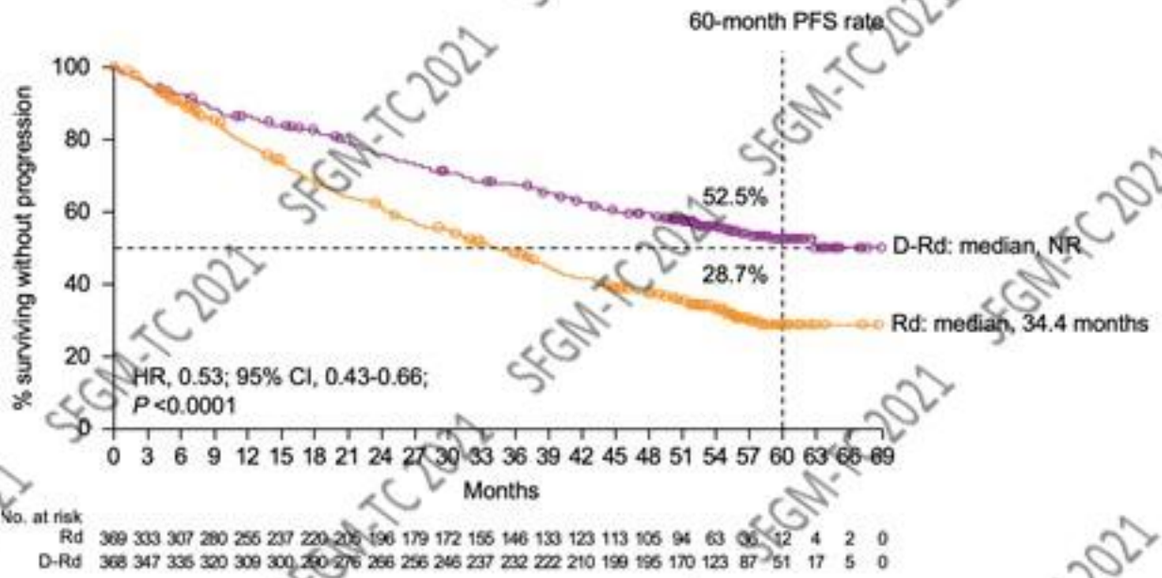
Recommandations EHA / ESMO

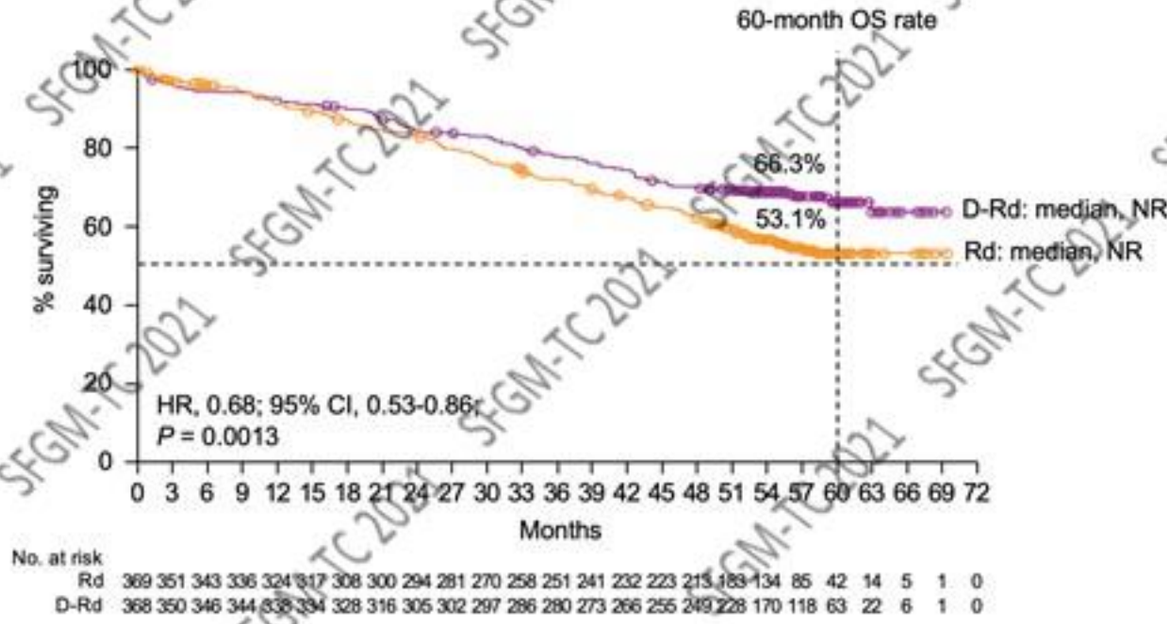


M Dimopoulos et al, Ann Oncol 2021

Approbation et remboursement D-Rd

Réduction de 57 % du risque de progression et décès par rapport à Rd
Réduction de 32 % du risque de décès par rapport à Rd





T Facon et al, N Engl J Med 2019
T Facon et al, EHA LBA 2021

D-Rd ou VRd ?

Comparaison indirecte MAIA / base de données Flatiron Health

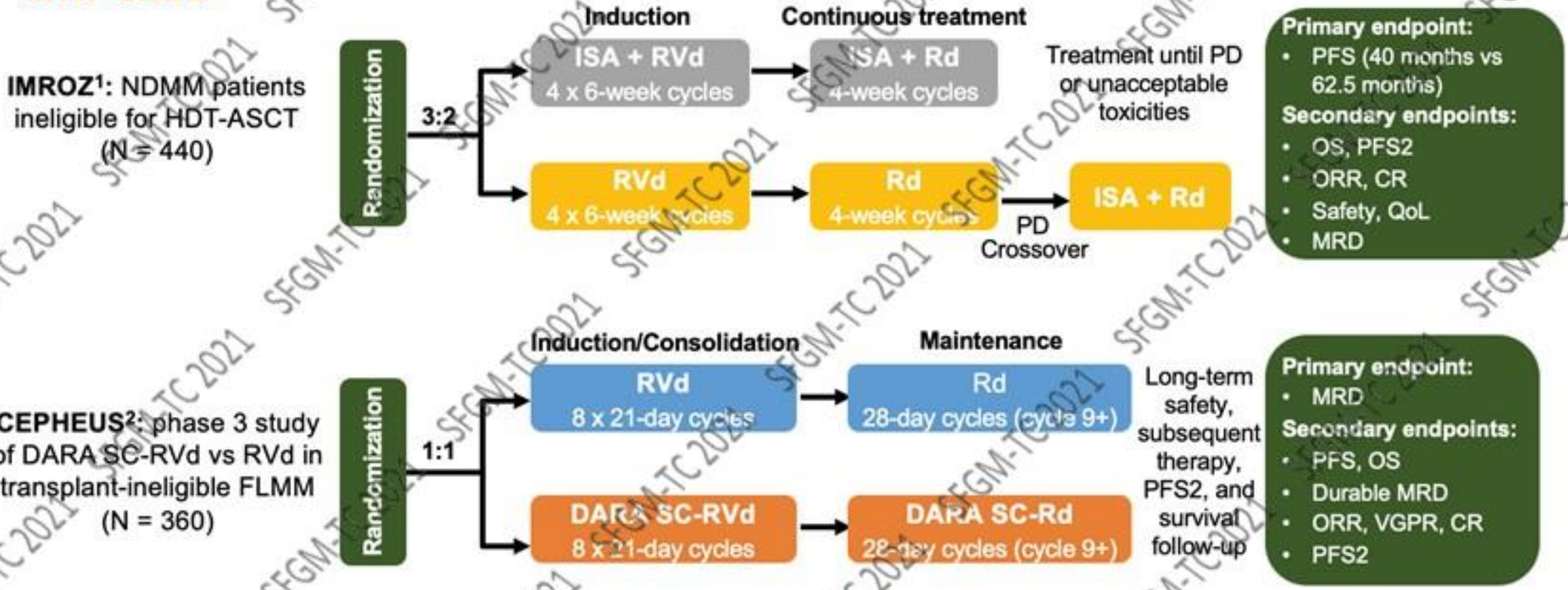
	Comparaison directe (HR)		Comparaison indirecte (HR)
	MAIA D-Rd vs MAIA Rd	**FH VRd vs FH Rd**	**MAIA D-Rd vs FH VRd**
Analyse primaire: PFS des traitements	0.54 (0.42, 0.71), P < .001	0.80 (0.62, 1.02), P = .08	0.68 (0.48, 0.98), P = .04
Analyses de sensibilité			
Ajustement pour les données démographiques uniquement	0.54 (0.42, 0.71), P < .001	0.82 (0.64, 1.05), P = .11	0.66 (0.46, 0.95), P = .02
Estimation doublement robuste de l'association entre le traitement et la PFS	0.54 (0.42, 0.71), P < .001	0.79 (0.61, 1.01), P = .06	0.69 (0.48, 0.99), P = .045
Restreindre aux cliniques FH avec un suivi moyen pendant le traitement ≥ 12 mois	0.54 (0.42, 0.71), P < .001	0.81 (0.51, 1.28), P = .36	0.67 (0.23, 0.85), P = .14
Restreint aux patients avec ≥12 mois de suivi sous traitement	0.50 (0.35, 0.71), P < .001	0.73 (0.49, 1.10), P = .14	0.69 (0.40, 1.17), P = .17
Analyse de l'intention de traitement	0.53 (0.42, 0.67), P < .001	1.02 (0.84, 1.25), P = .83	0.52 (0.38, 0.70), P < .001
Analyses de sous-groupes			
<75	0.55 (0.40, 0.79), P = .001	0.69 (0.49, 0.97), P = .03	0.80 (0.51, 1.26), P = .33
≥75	0.55 (0.39, 0.78), P = .001	0.94 (0.67, 1.32), P = .72	0.58 (0.37, 0.91), P = .02

HR: Hazard ratio
FH: Base de données de santé américaine Flatiron Health

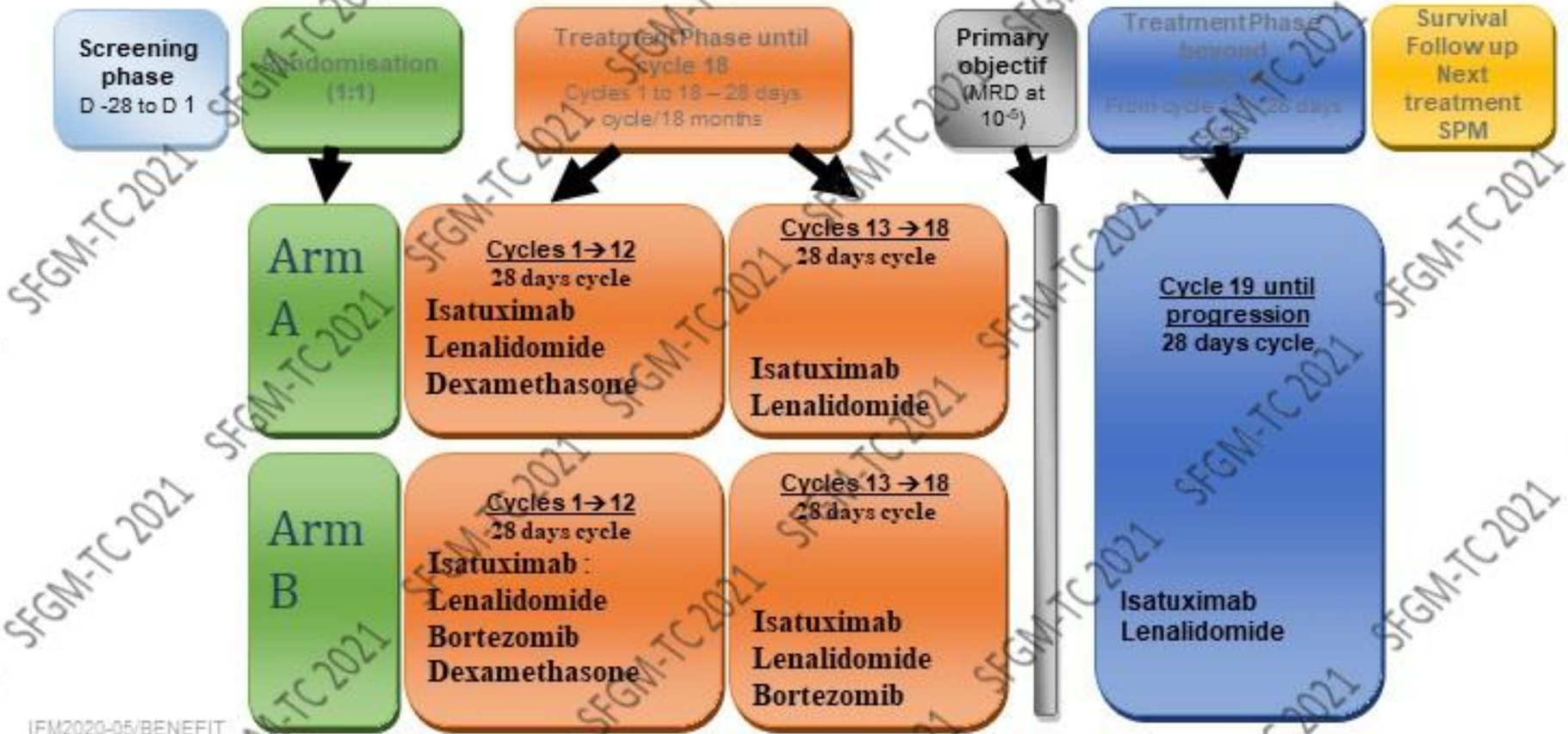
B Durie et al, Am J Hematol 2020

Peut-on faire mieux que DaraRd ?

Essais IMROZ et CEPHEUS fermés aux inclusions : VRD + anti-CD38



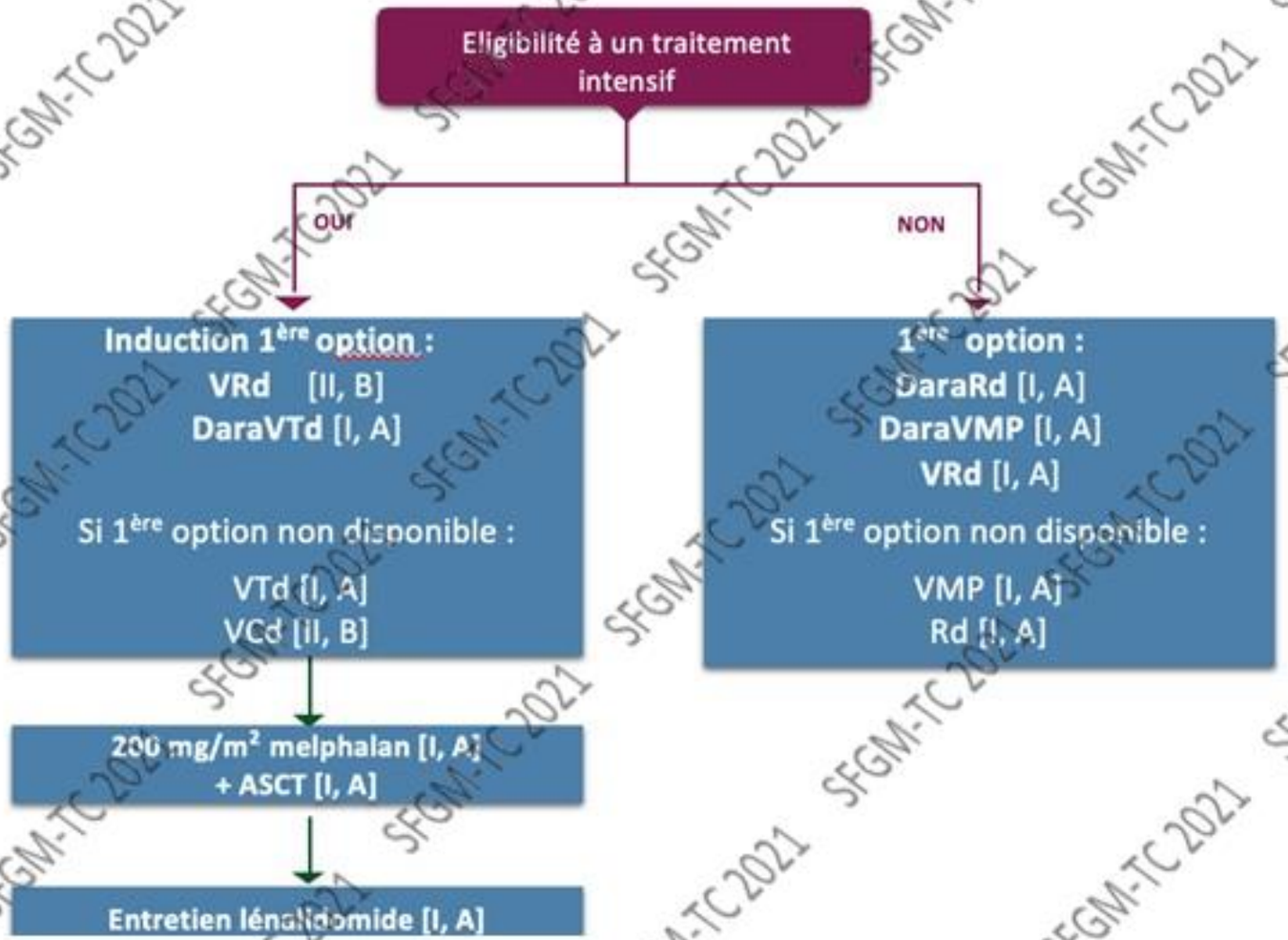
Essai de phase III chez les patients non fragiles



IFM2020-05/BENEFIT

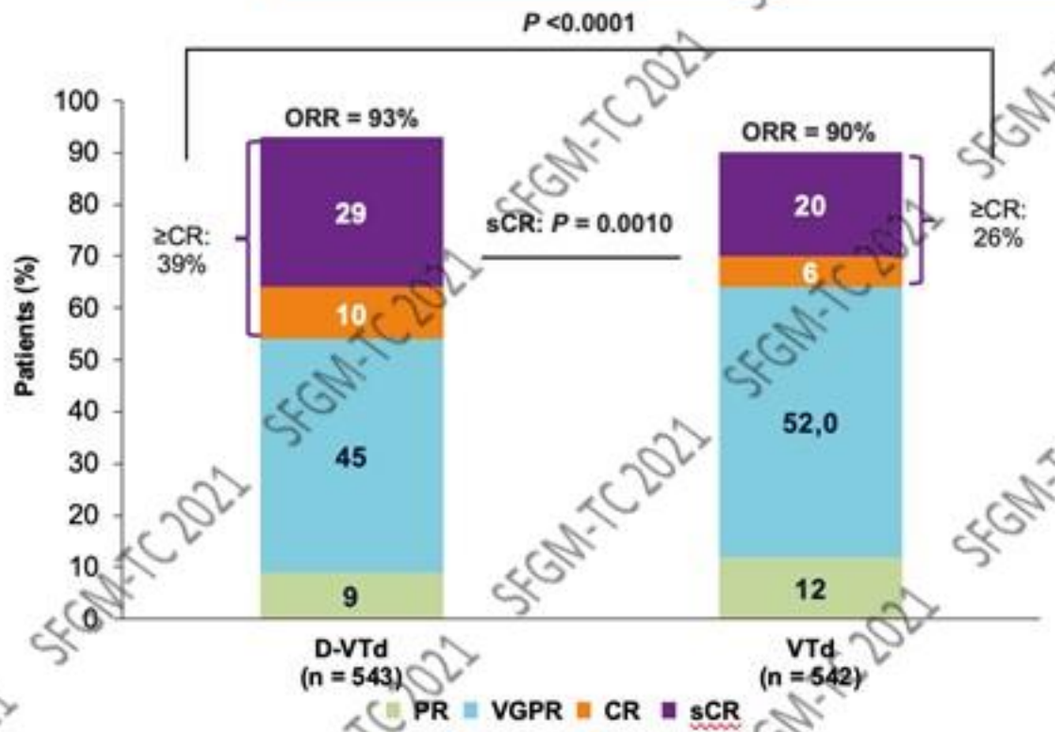
Pr Leleu - CHU Poitiers

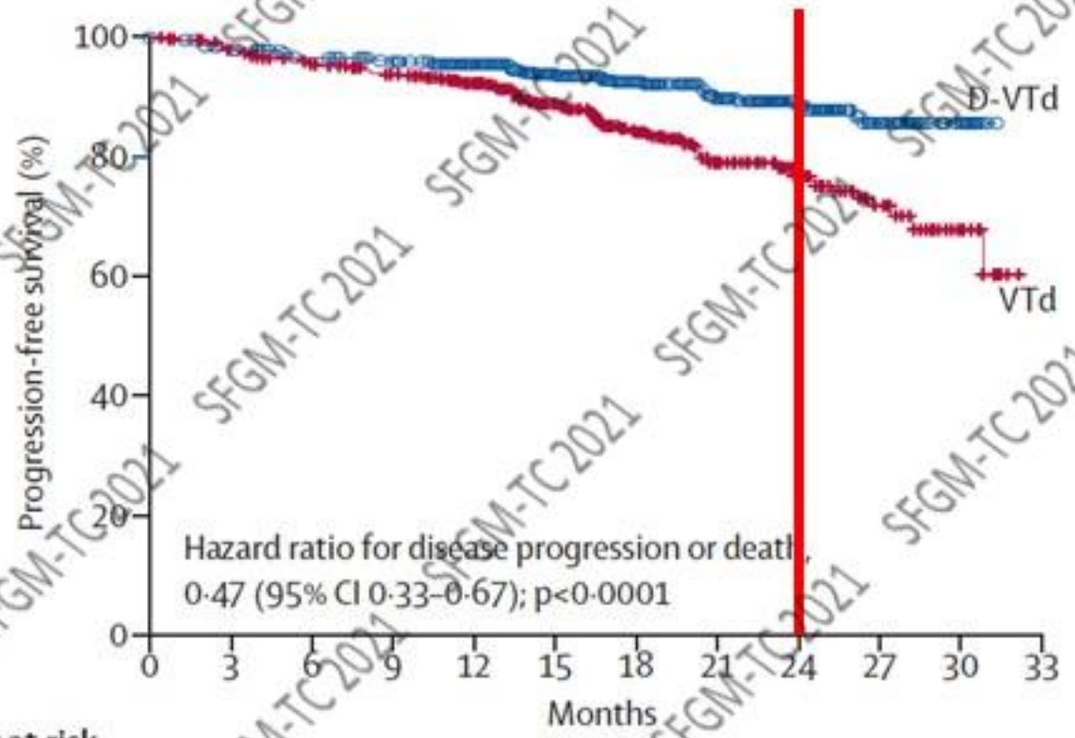
Recommandations EHA / ESMO



M Dimopoulos et al, Ann Oncol 2021

Approbation et remboursement D-VTD





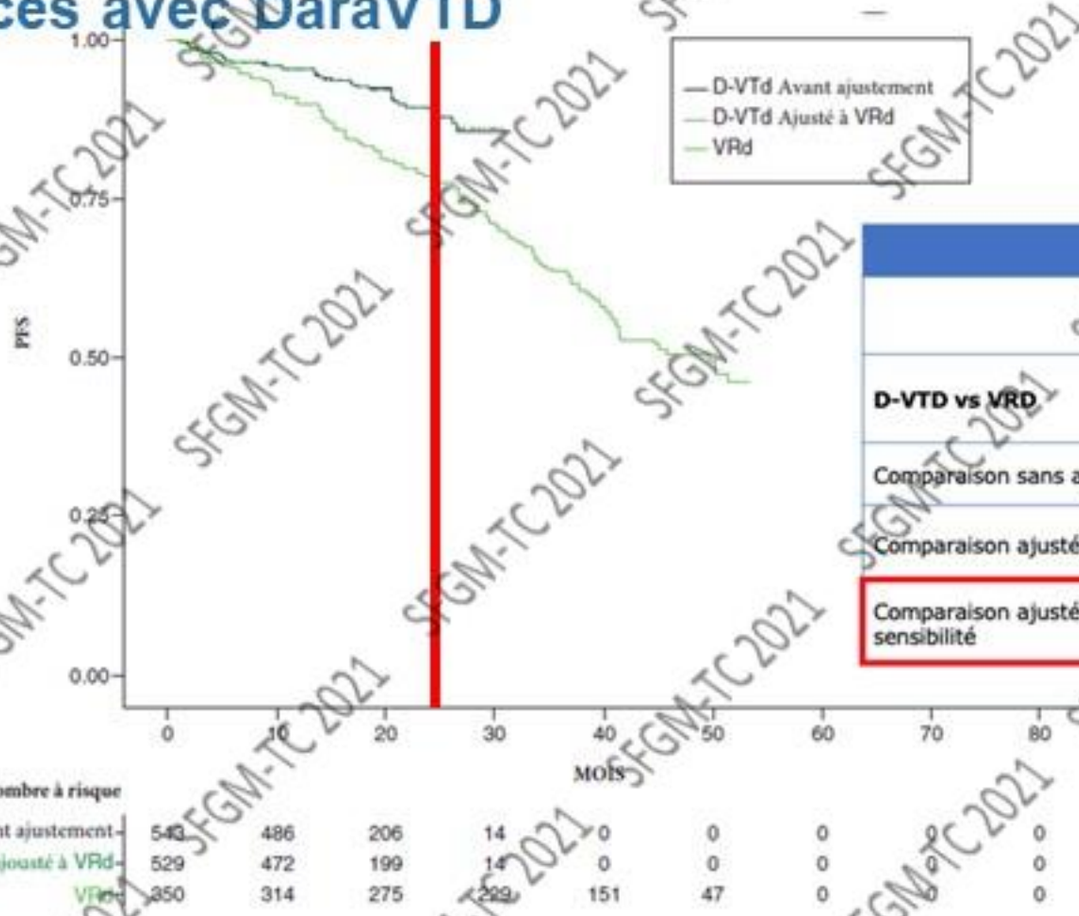
Number at risk

D-VTd	543	520	501	492	442	346	261	185	122	61	14	0
VTd	542	519	497	475	413	319	233	163	104	50	14	0

P Moreau et al, Lancet 2019

Dara VTD ou VRD ?

Réduction de 53 % du risque de progression et décès avec DaraVTD

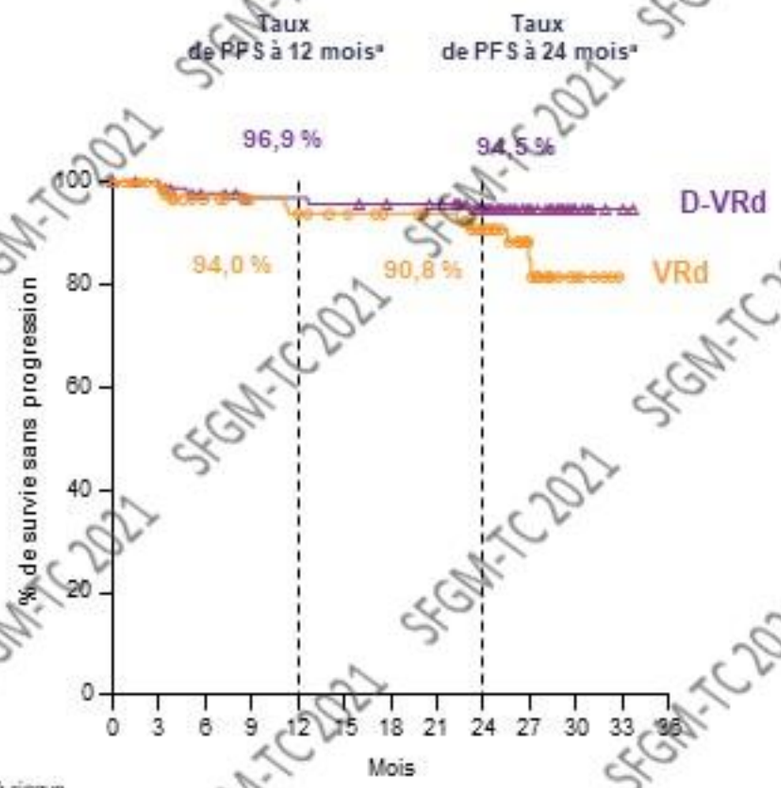


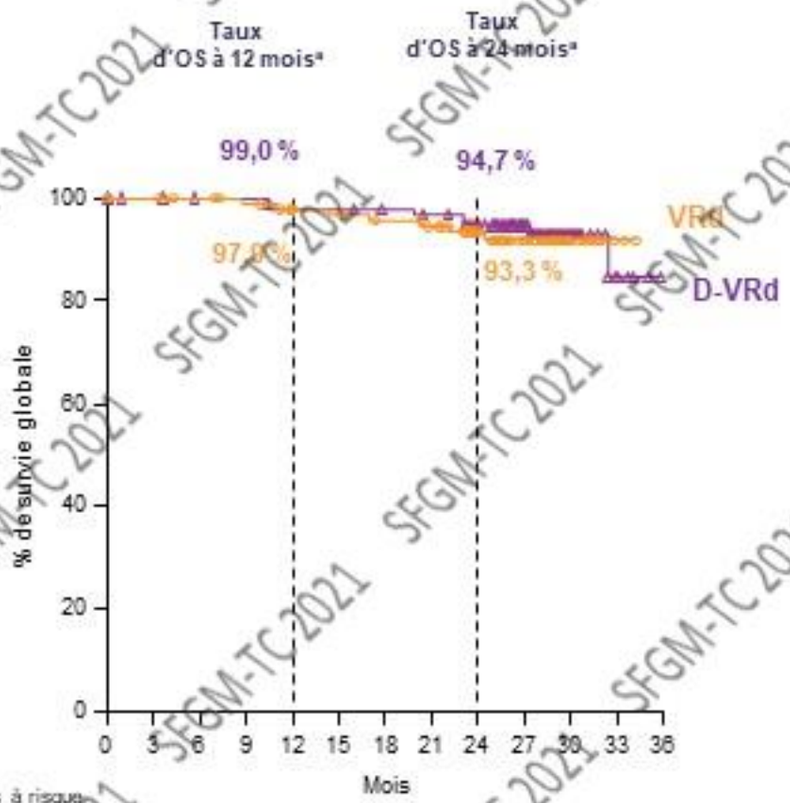
	Survie sans progression (PFS)		
	Taille effective échantillon	HR (95% IC)	p
D-VTD vs VRD			
Comparaison sans ajustement	543	0.48 (0.33–0.69)	< 0.001
Comparaison ajustée	529	0.47 (0.33–0.69)	< 0.001
Comparaison ajustée avec analyse de sensibilité	525	**0.47 (0.33–0.68)**	< 0.001

P Moreau et al, Immunotherapy 2021

Dara VRD ou VRD ?

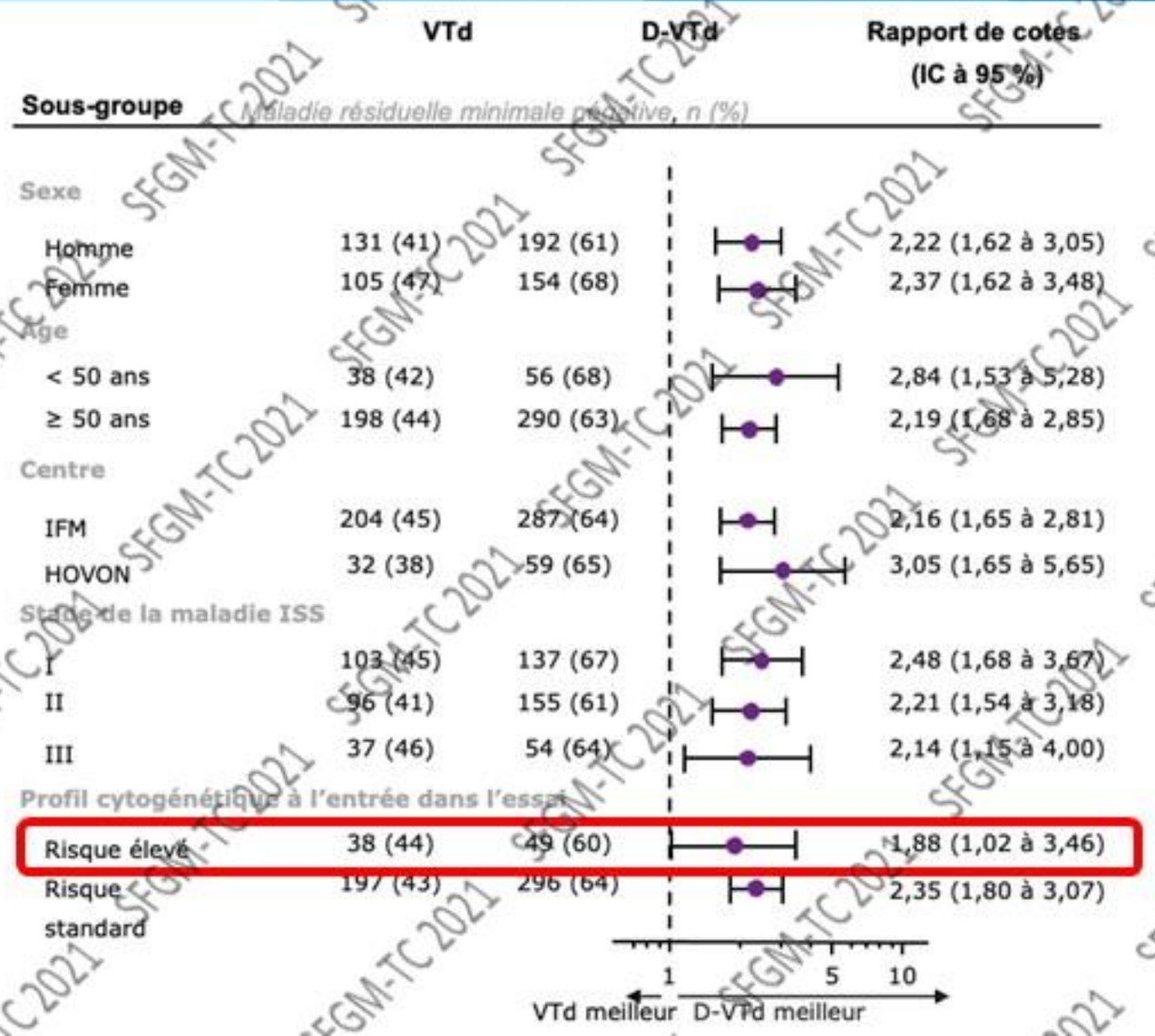
Phase 2 GRIFFIN





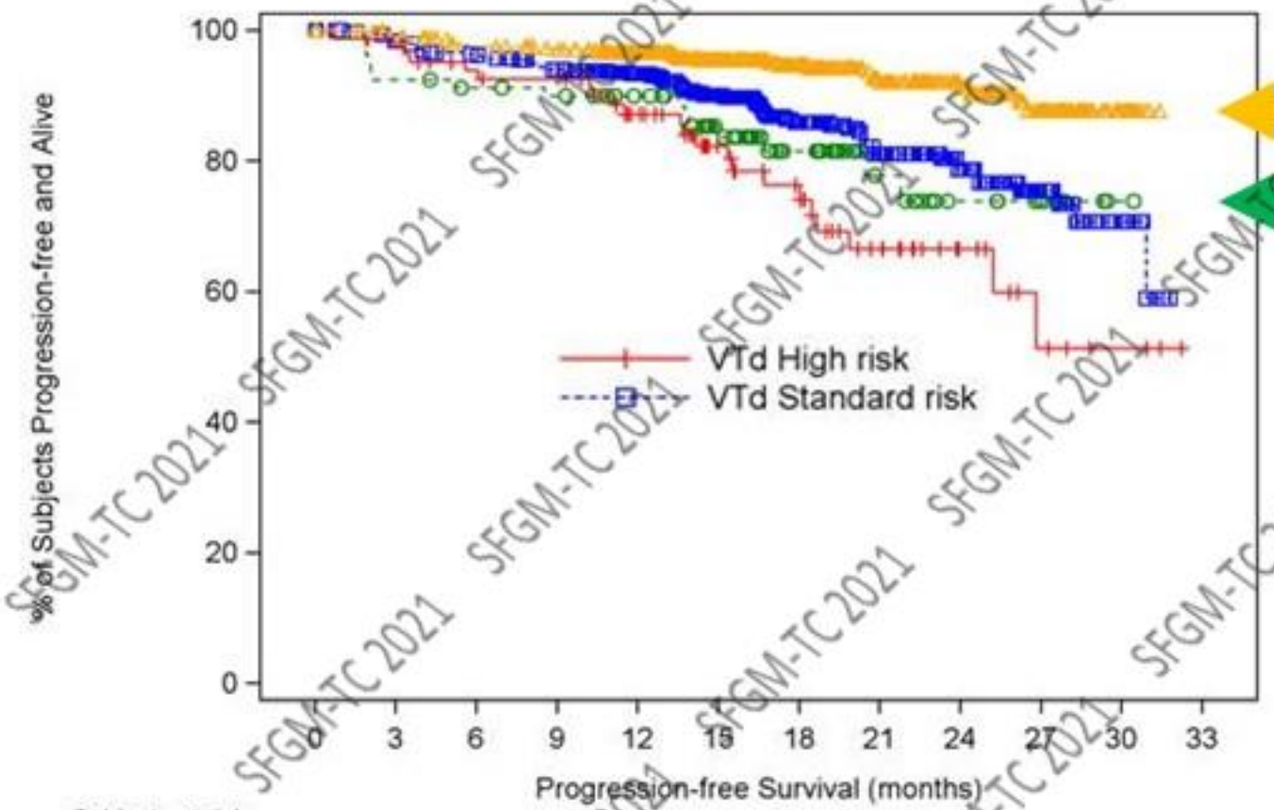
P Vorrhees et al, Blood 2020

D-VTD + ASCT(s?) chez les patients de haut risque ?



P Moreau et al, Lancet 2019

D-VTD chez les patients de haut risque

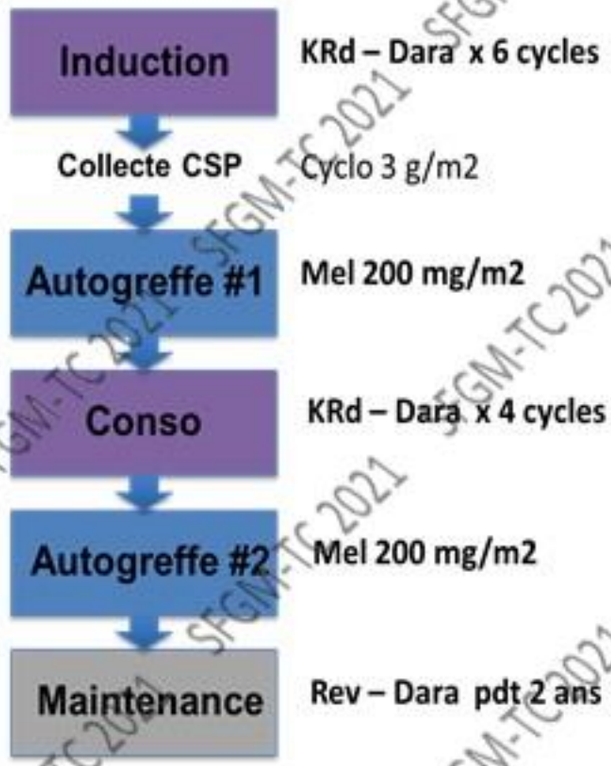


Subjects at risk												
VTd High risk	86	80	74	72	59	43	35	22	12	6	3	0
DVTd High risk	82	74	71	69	63	49	33	20	11	7	1	0
VTd Standard risk	454	437	421	401	352	274	196	139	91	44	11	0
DVTd Standard risk	460	445	429	422	378	296	227	164	111	54	13	0

P Moreau et al, Lancet 2019

Dédier des essais aux patients de haut risque?

Essai IFM 2018-04

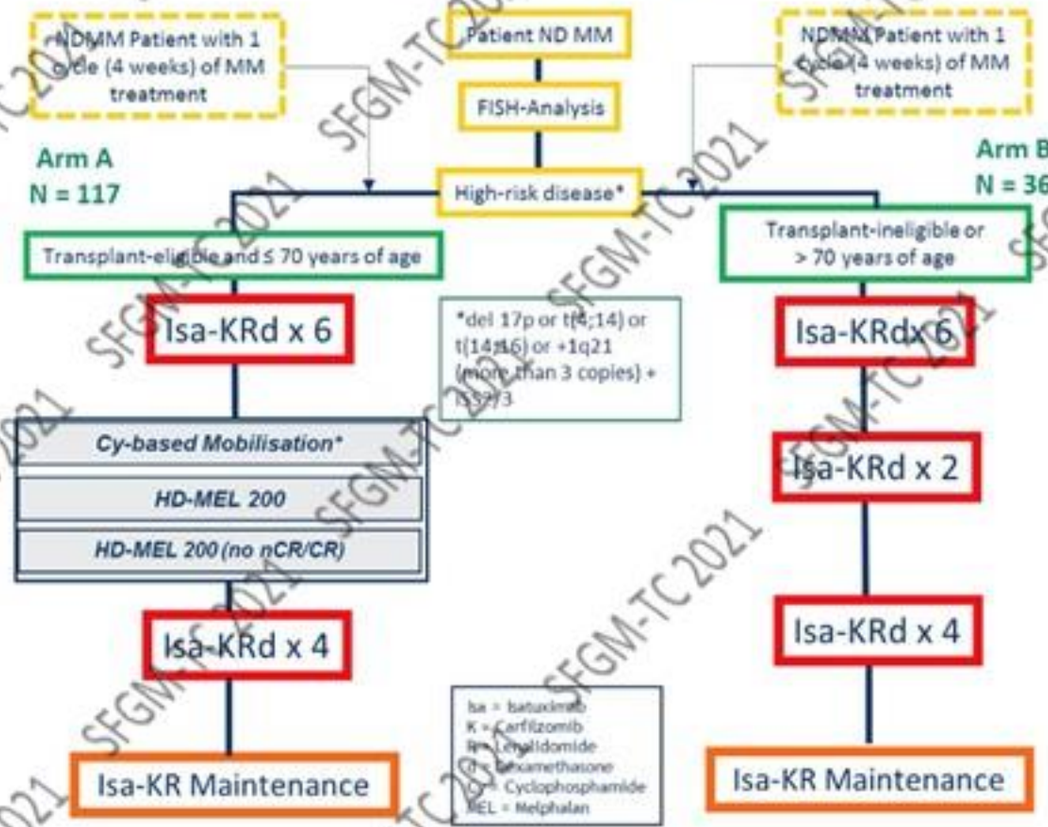


K: 20/36 mg/m2 J1-2, 8-9, 15-16
R: 25 mg J1-21
D: 40 mg hebdo
Dara IV : 16 mg/kg

R: 10 mg J1-21
Dara IV : 16 mg/kg tous les 2 mois

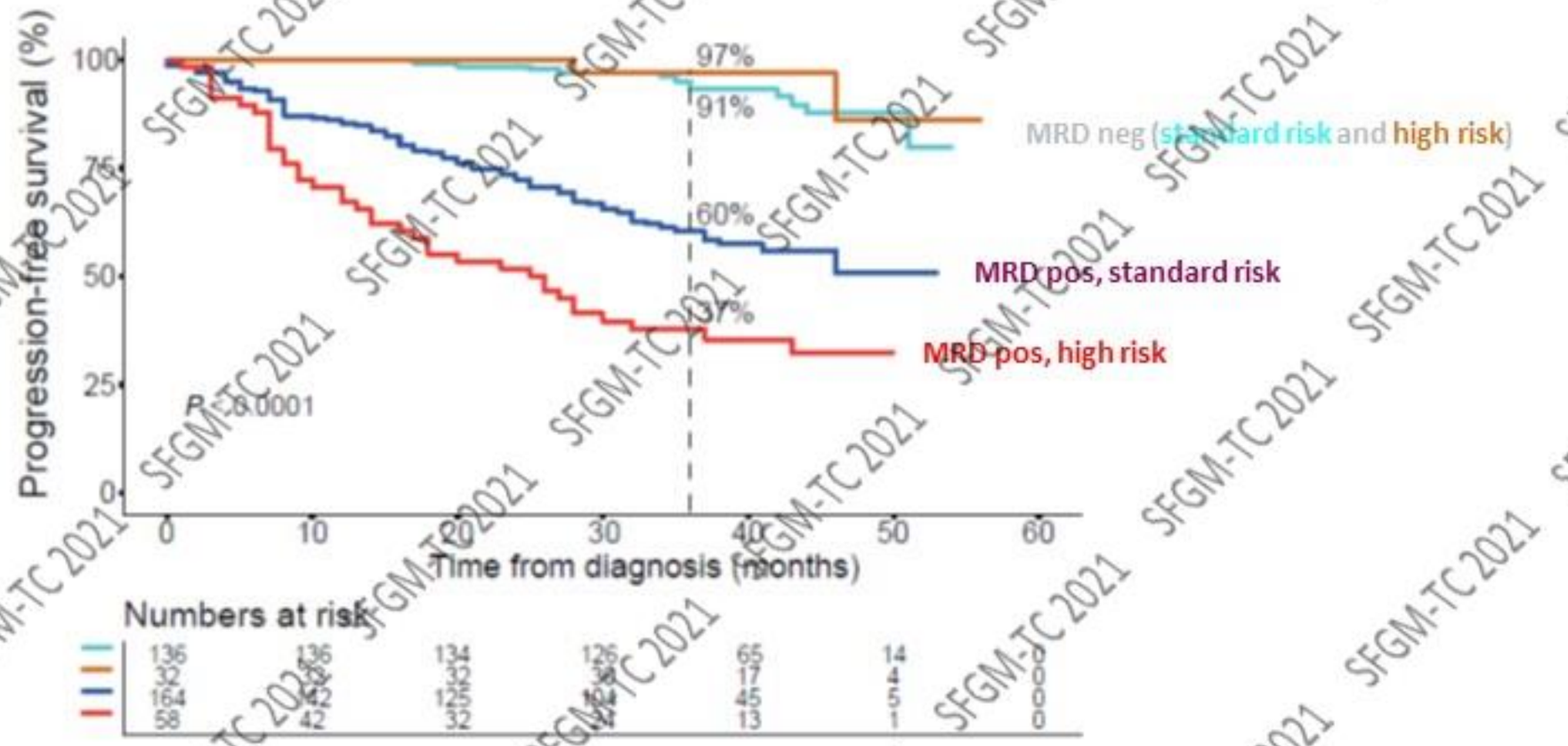
C Touzeau – P Moreau

Essai CONCEPT



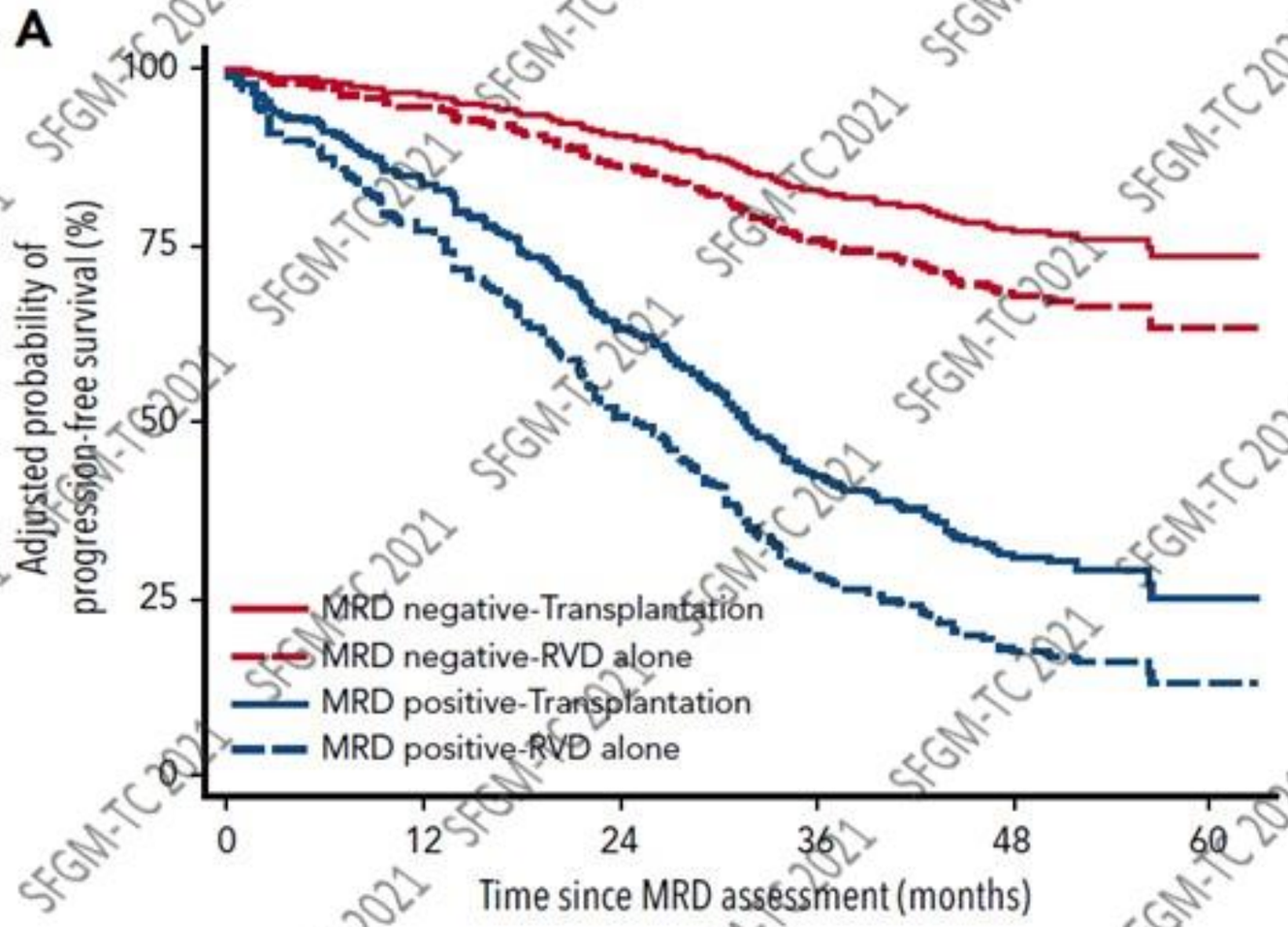
LB Leypold .. K Weisel, EHA 2021

Quand on confronte MRD et cytogénétique



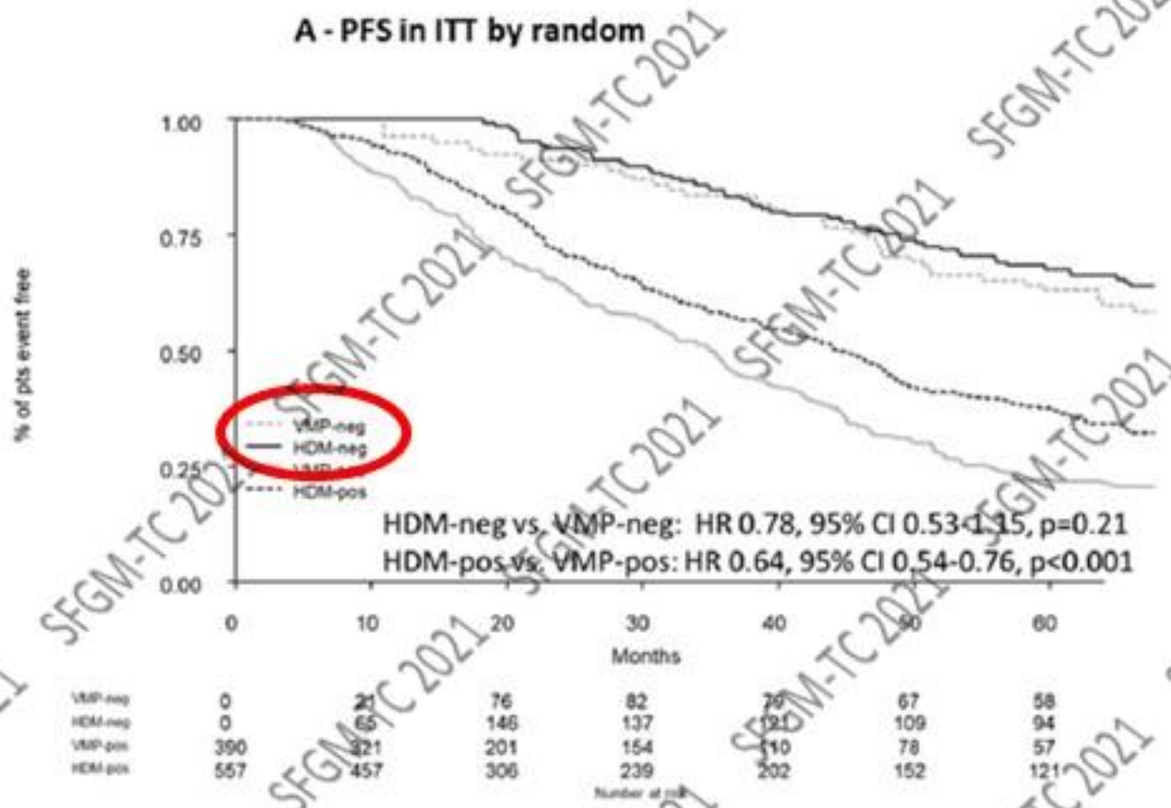
Goicoechea et al, Blood 2021

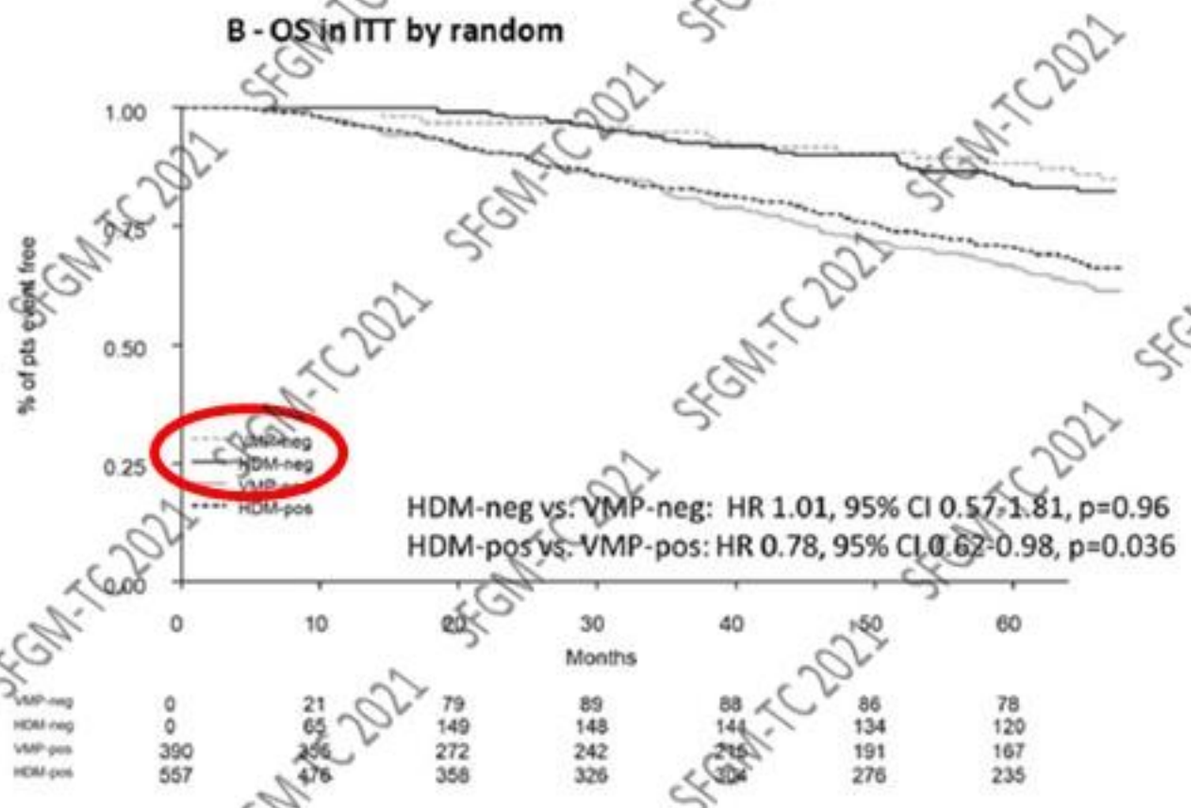
Rationnel pour rediscuter la greffe selon la MRD



Perrot A et al, Blood 2018

Autogreffe si MRD négative ?

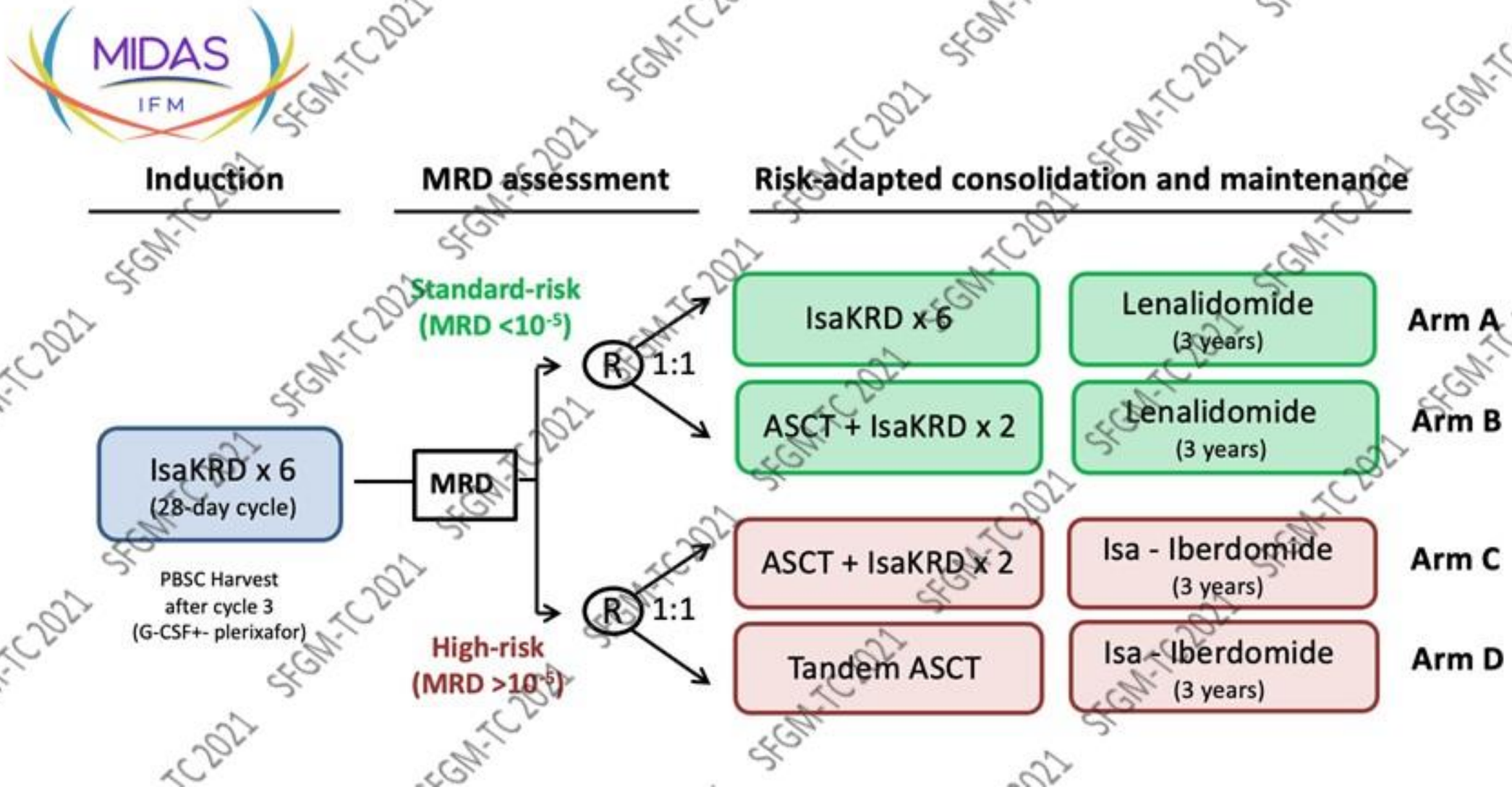




Pas de différence de PFS ni OS pour les patients MRD (-) dans les bra

Perrot A et al, Blood 2018

Etude de phase III chez les patients éligibles à la greffe



L'arrivée de l'immunothérapie en rechute : et demain ?

Anticorps monoclonaux

CD38 :
Daratumumab
Isatuximab

SLAMF7 :
Elotuzumab

PD-1/L1 :
Pembrolizumab
Nivolumab

Anticorps monoclonaux conjugués

BCMA :
Belantamab mafodotin

Anticorps monoclonaux bispécifiques

BCMA :
AMG 420
CC93269
Teclistamab
Elranatamab

GPRC5D :
Talquetamab

CAR-T cells

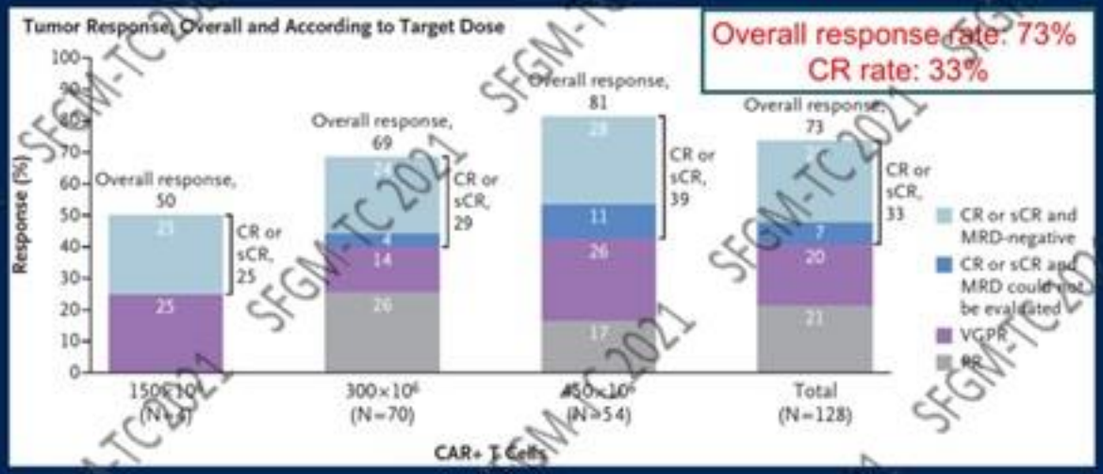
BCMA :
bb2121 : ide-cel
Cilta-cel

GPRC5D

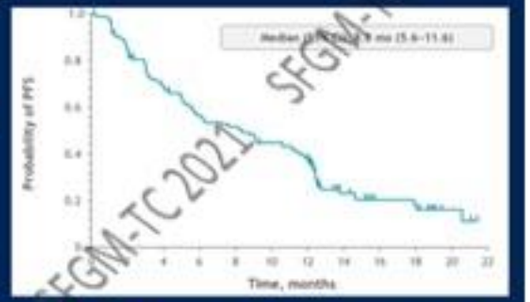
CAR T cells : ide-cel

Baseline Characteristics	N=128
Median age	61 years
Median Prior Lines	6
Triple Class Refractory	84%
Penta Refractory	26%
Bridging Therapy	88%

Adverse Events	
CRS (all; grade 3 or 4)	84% (5%)
ICANS (all; grade 3 or 4)	18% (3%)
Infections (all; grade 3 or 4)	69% (22%)
Grade 3 or 4 neutropenia > 1 month	41%
Grade 3 or 4 thrombocytopenia > 1 month	48%



Survival Outcomes	
Median PFS	8.8 months
Median PFS in CR	20.2 months
Median OS	19.4 months



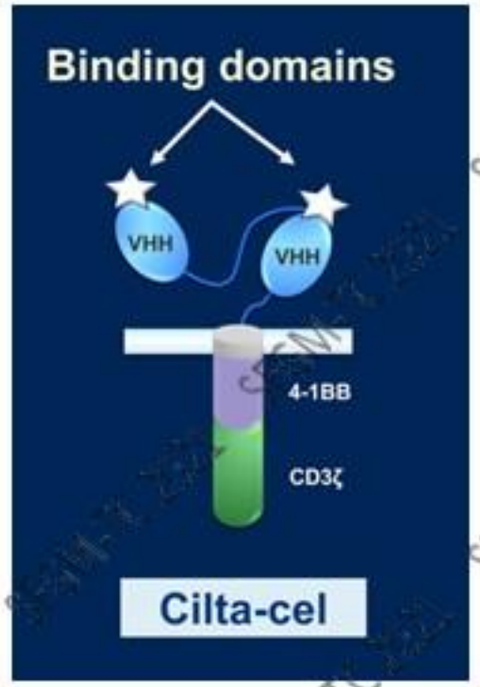
Excellent response rates (including MRD negative) and PFS, but no plateau in PFS

The bar in triple class refractory MM has been set high

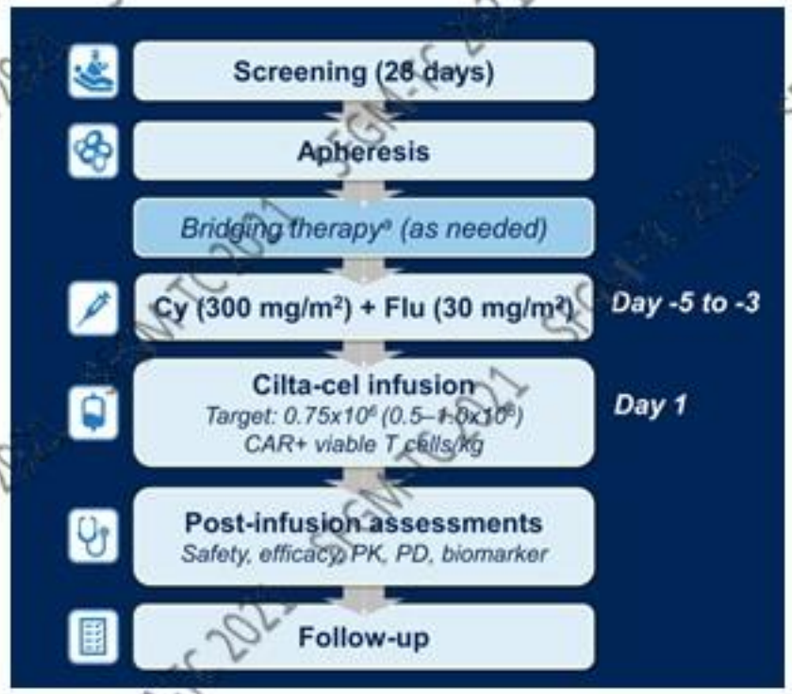
N Munshi et al, N Engl J Med 2021

CAR T cells : cilta-cel

CARTITUDE-1 (patients triple-réfractaires)

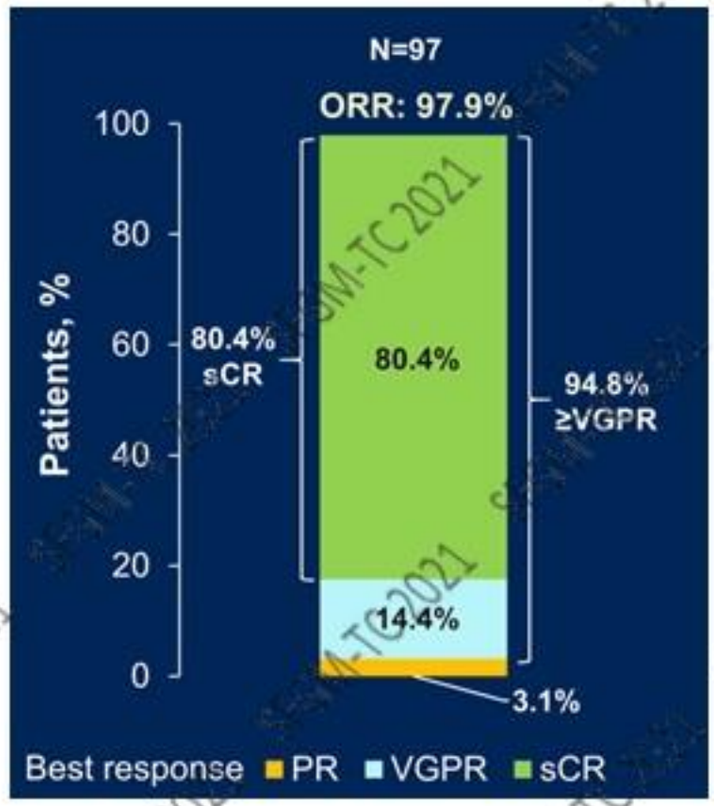


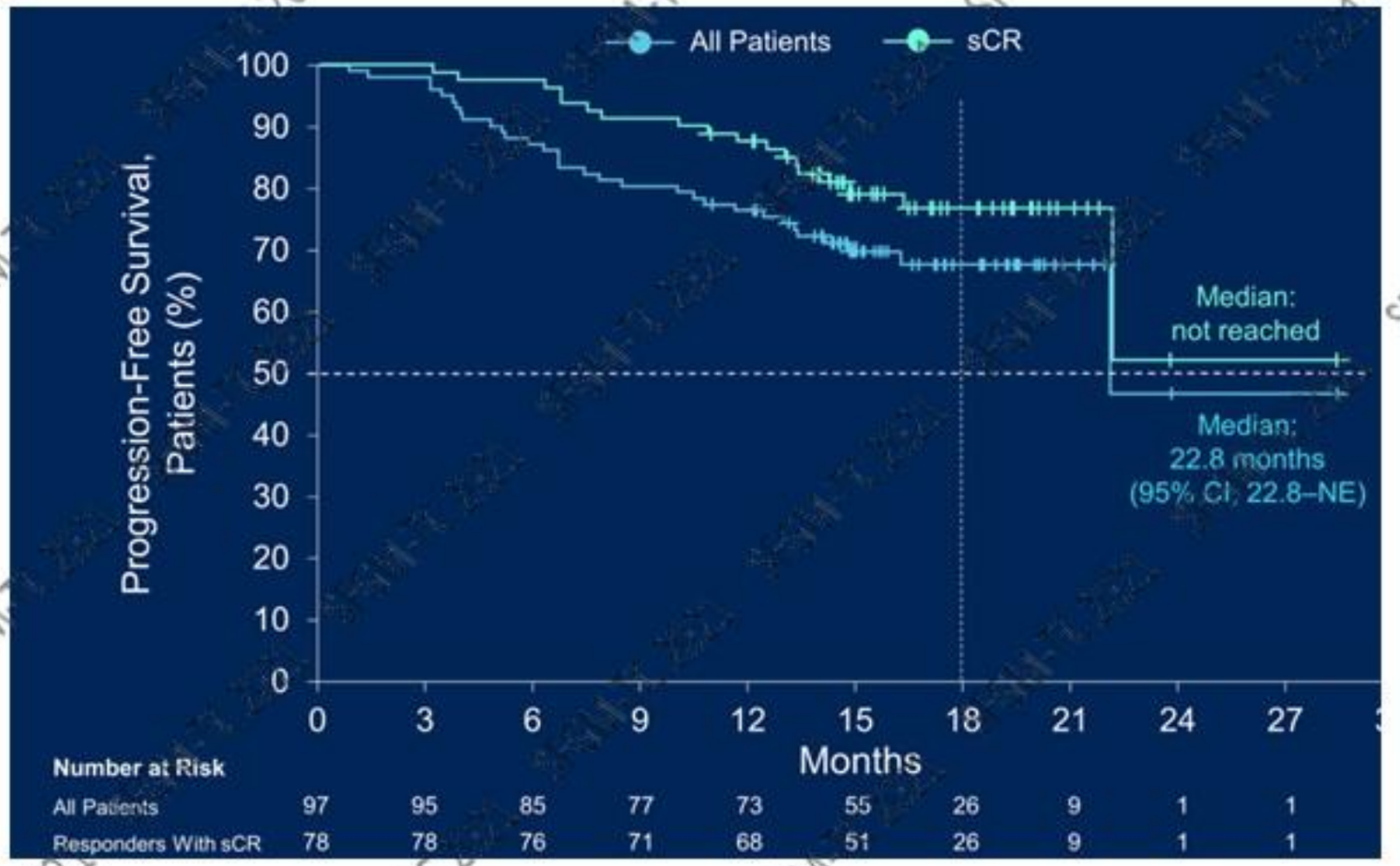
Characteristic	
Prior lines of therapy, median (range)	6.0 (3–18)
Prior lines of therapy, n (%)	
3	17 (17.5)
4	16 (16.5)
≥5	64 (66.0)
Previous stem-cell transplantation, n (%)	
Autologous	87 (89.7)
Allogeneic	8 (8.2)
Triple-class exposed,[c] n (%)	97 (100)
Penta-drug exposed,[d] n (%)	81 (83.5)
Triple-class refractory[c]	85 (87.6)
Penta-drug refractory[d]	41 (42.3)
Refractory status, n (%)	
Carfilzomib	63 (64.9)
Pomalidomide	81 (83.5)
Anti-CD38 antibody	96 (99.0)
Refractory to last line of therapy, n (%)	96 (99.0)



S Usmani et al, ASCO 2021

CAR T cells : cilta-cel

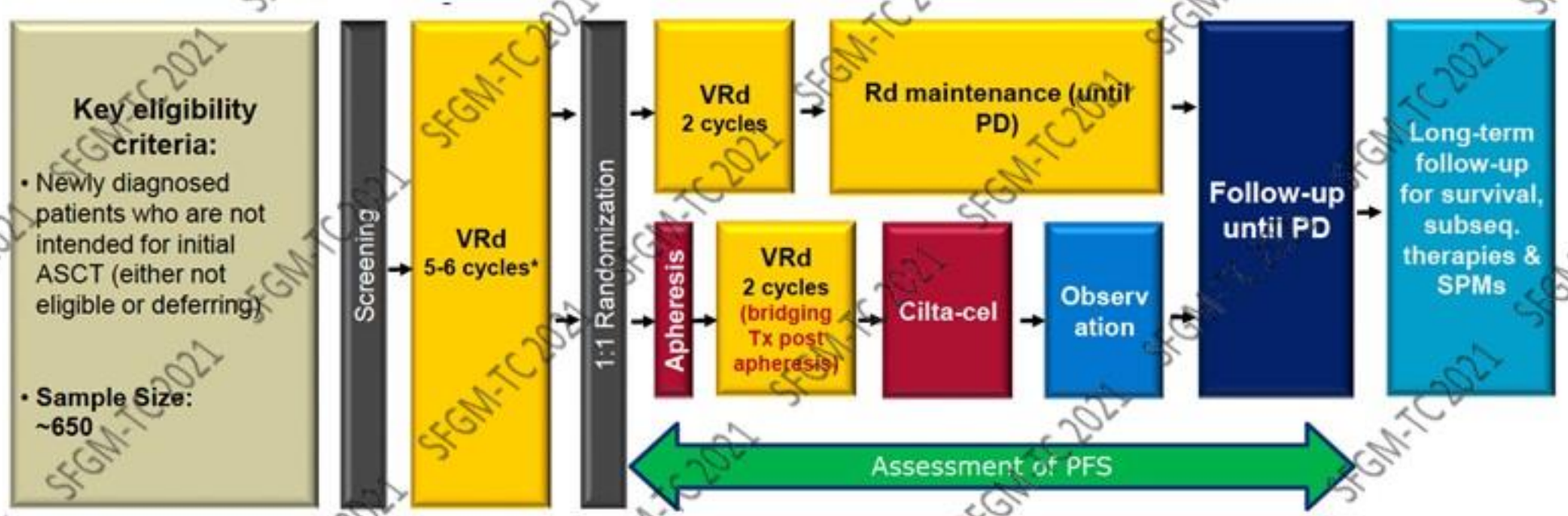




S Usmani et al, ASCO 2021

Vers la première ligne…

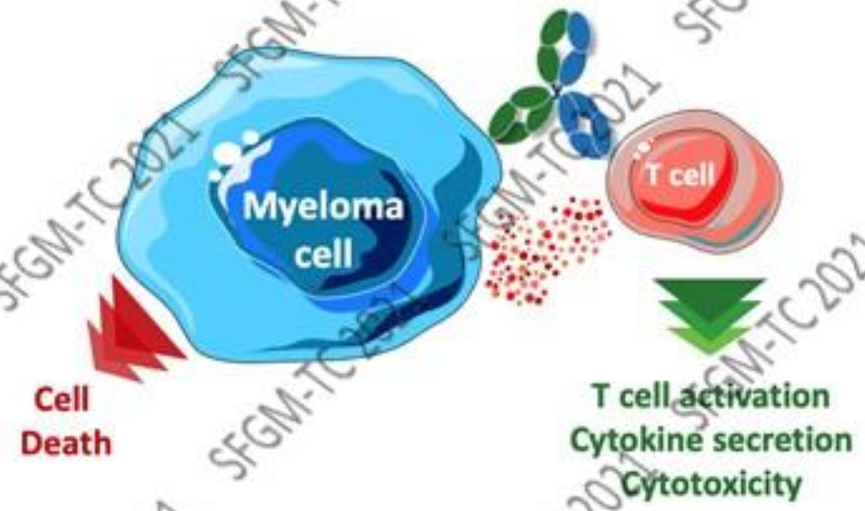
- CARTITUDE 5



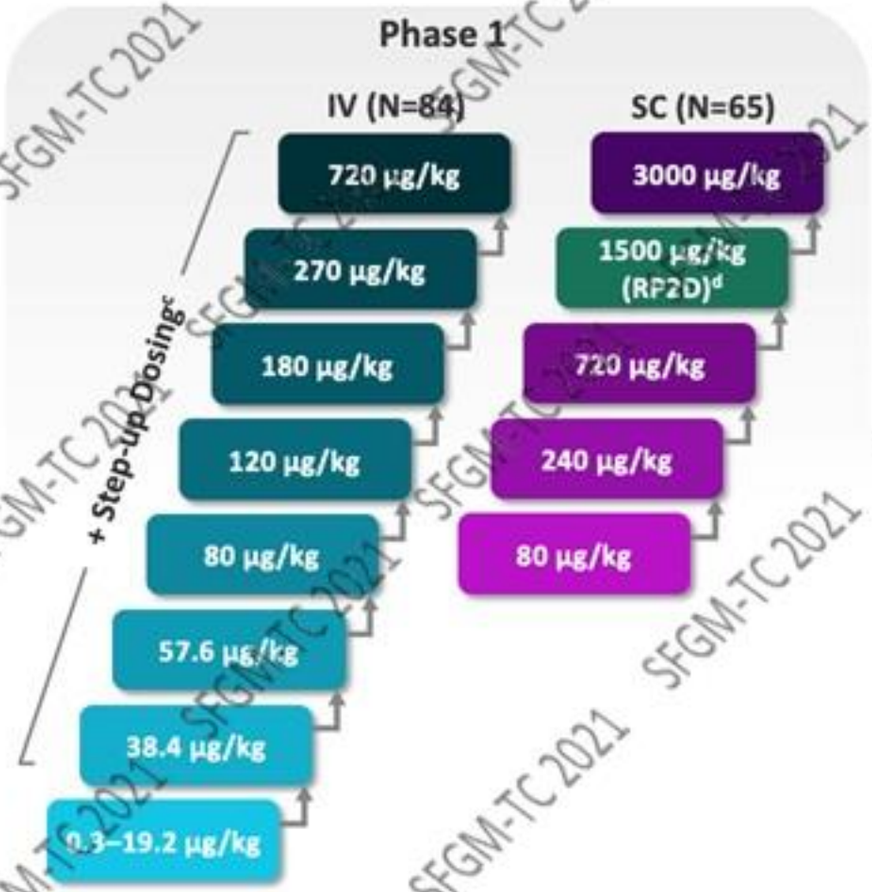
Anti-BCMA: la concurrence des bispécifiques

	CAR-T	Bispecific Antibodies
Lead time	~ 4 weeks*	None
Need for ongoing dosing	No	Yes
Hospitalization	Yes	Yes, for initial cycle(s)
CRS	++++ (~ 85-95%)	+++ (~ 65-75%)
ICANS	++ (~20%)	+ (~<5%)
Cytopenias	++++	+++
Infections	+++	++
Response rates	++++ (~ 73-95%)	+++ (~ 65-80%)
PFS	8.8 m; 66% @18m	Too early
Less fit patients	Challenging	May be doable
Renal dysfunction	Not evaluated in trials; Hurdle: lymphodepletion	Not evaluated in trials, but no known limitation

First in class: Teclistamab



Etude MAJESTEC-1



Garfall et al, ASH 2020

MajesTEC-1: patients characteristics

Characteristic, n (%)	Total N=149	1500 µg/kg SC (RP2D) n=33
Median age (range), years	63 (24–84)	61 (39–84)
≥70 years	33 (22)	8 (24)
Male	81 (54)	22 (67)
Bone marrow plasma cells ≥60%[a]	34 (25)	3 (10)
Extramedullary plasmacytomas ≥1	18 (12)	6 (18)
Median years since diagnosis (range)	7 (1–26)	6 (1–12)
High-risk cytogenetics[b]	36 (32)	8 (38)
Prior transplantation	127 (85)	28 (85)

Characteristic, n (%)	Total N=149	1500 µg/kg SC (RP2D) n=33
Median prior lines of therapy (range)	6 (2–14)	5 (2–11)
Triple-class[c] exposed	143 (96)	33 (100)
Penta-drug[d] exposed	102 (69)	21 (64)
Refractory status		
Carfilzomib	99 (66)	22 (67)
Pomalidomide	115 (77)	24 (73)
Anti-CD38[e]	138 (93)	32 (97)
Triple-class[c] refractory	121 (81)	28 (85)
Penta-drug[d] refractory	58 (39)	12 (36)
Refractory to last line of therapy[f]	136 (91)	29 (88)

Garfall et al, ASH 2020

MajesTEC-1: AE

AEs (≥20% of Total) n (%)	Total N=149		1500 µg/kg SC (RP2D) n=33	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic				
Neutropenia	85 (57)	69 (46)	17 (52)	11 (33)
Anemia	82 (55)	47 (32)	13 (39)	7 (21)
Thrombocytopenia	59 (40)	32 (22)	11 (33)	4 (12)
Leukopenia	41 (28)	21 (14)	11 (33)	6 (18)
Nonhematologic				
CRS	82 (55)	0	21 (64)	0
Pyrexia	45 (30)	0	6 (18)	0
Diarrhea	34 (23)	1 (1)	4 (12)	0
Nausea	33 (22)	1 (1)	6 (18)	0
Fatigue	33 (22)	2 (1)	8 (24)	1 (3)
Headache	32 (22)	0	4 (12)	0
Cough	31 (21)	3 (2)	1 (3)	0

- **2 DLTs across all doses; no DLT at RP2D**
  - Gr 4 delirium (20 µg/kg IV step-up dose)
  - Gr 4 thrombocytopenia (180 µg/kg IV)
- **Maximum tolerated dose not reached**
- **Infections in 52% of patients; 27% at RP2D**
  - 15% had gr ≥3 infections across all doses
  - 6% had gr ≥3 infections at RP2D
- **Neurotoxicity in 7 patients (5%); 1 (3%) at RP2D**
  - 2 gr ≥3 events with IV dosing; none with SC
- **Injection-site reactions in 32% of patients; 36% at RP2D (all gr 1–2)**
- **1 TRAE leading to death; none at RP2D**
  - Gr 5 pneumonia at 80 µg/kg IV

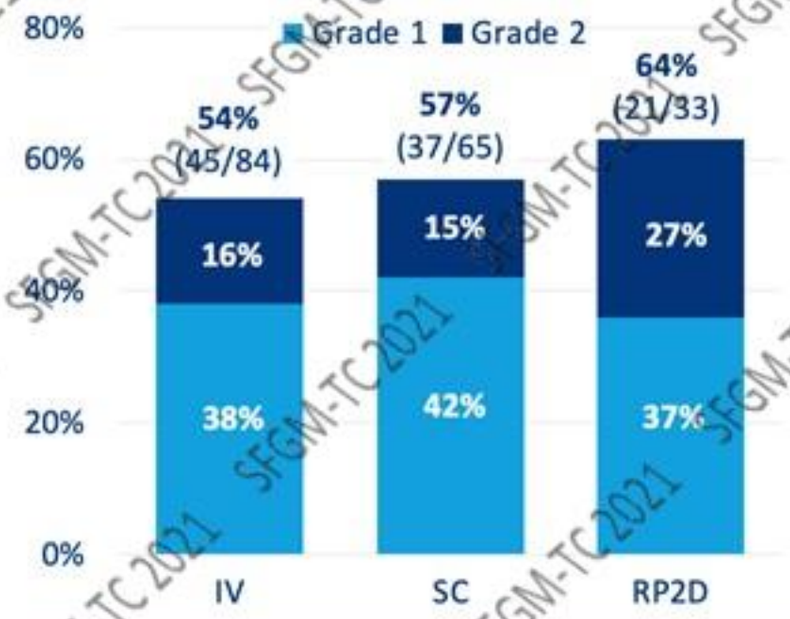
Garfall et al, ASH 2020

MajesTEC-1: CRS

Parameter, n (%)	Total (N=149)	IV (n=84)	SC (n=65)
Patients with CRS	82 (55)	45 (54)	37 (57)
Median time to CRS onset[a] (range), days	2 (1–5)	1 (1–3)	2 (1–5)
Median duration of CRS (range), days	2 (1–8)	1 (1–7)	2 (1–8)
Patients with supportive measures to treat CRS[b]	76 (51)	43 (51)	33 (51)
Tocilizumab	35 (23)	22 (26)	13 (20)
Steroids	19 (13)	15 (18)	4 (6)
Low flow oxygen	9 (6)	6 (7)	3 (5)
Single low-dose vasopressor	1 (1)	1 (1)	0

- No treatment discontinuations due to CRS
- CRS was generally confined to step-up and first full doses

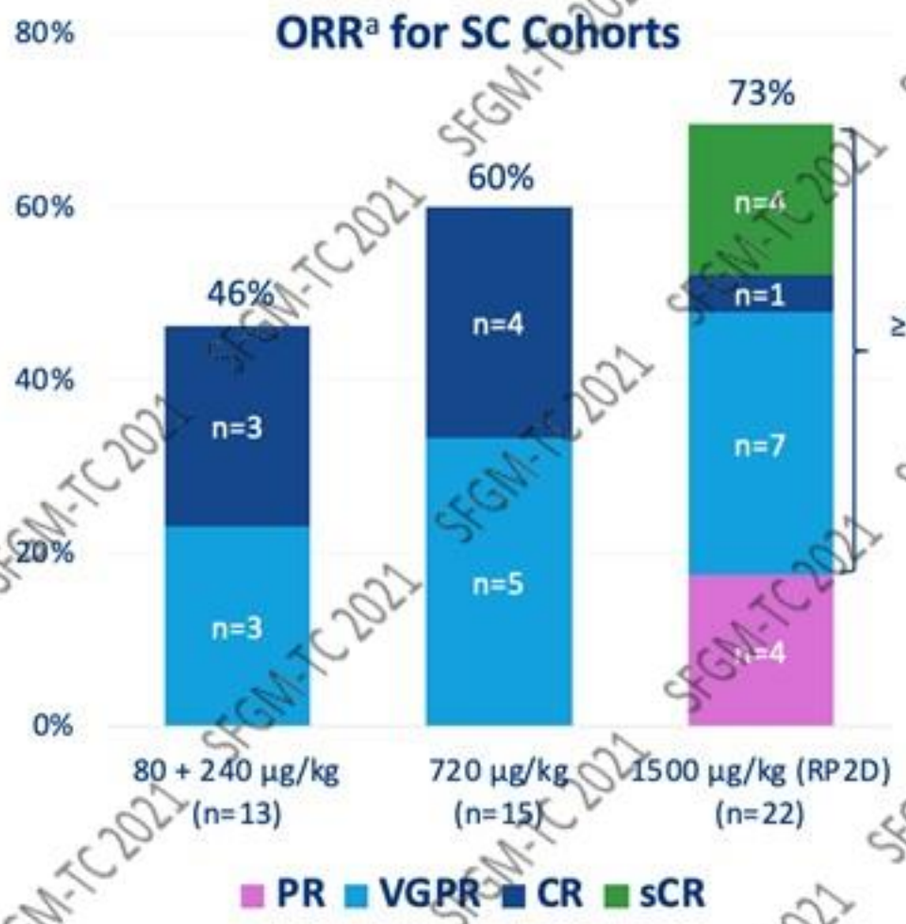
Maximum CRS Grade by Dose Groups[c]



- Step-up dosing to mitigate risk of severe CRS
- No grade ≥3 CRS events

Garfall et al, ASH 2020

MajesTEC-1: ORR

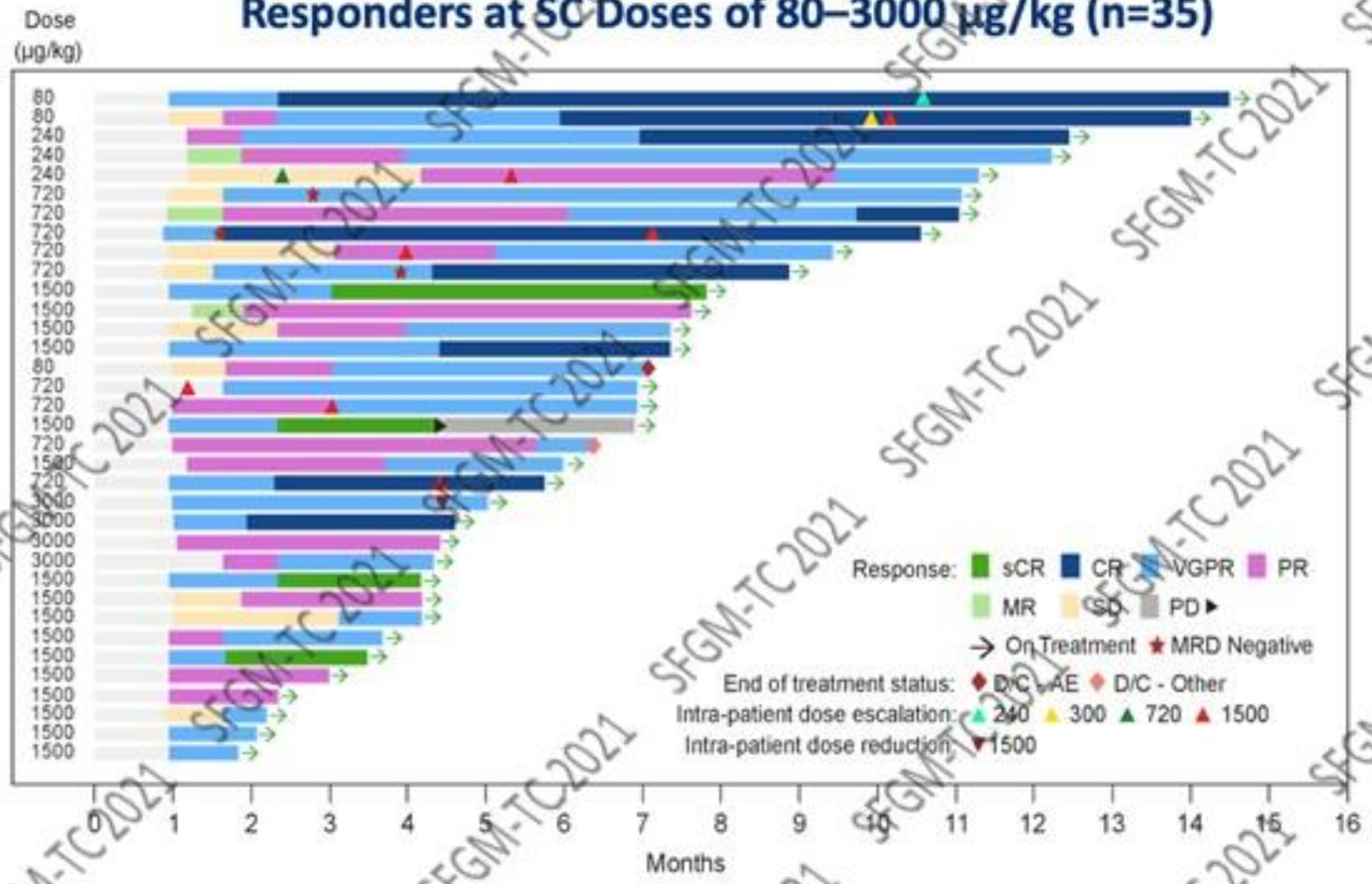


- At the RP2D of 1500 µg/kg SC:
  - Median time to first confirmed response was 1 month (0.3–3)
  - 14/20 (70%) triple-class refractory patients responded
  - 6/8 (75%) penta-drug refractory patients responded
- Most active doses were 270–720 µg/kg IV and 720–3000[b] µg/kg SC
  - ORR[a] at these doses was 69% (47/68)
  - ≥VGPR was 59%; ≥CR was 26%
  - 67% (18/27) ORR in IV cohorts and 71% (29/41) ORR in SC cohorts
- Of 11 evaluable patients across all IV and SC doses so far, 8 had MRD-neg CR at 10^{-6} and 1 at 10^{-5} sensitivity

Garfall et al, ASH 2020

MajesTEC-1: duration of response

Responders at SC Doses of 80–3000 µg/kg (n=35)

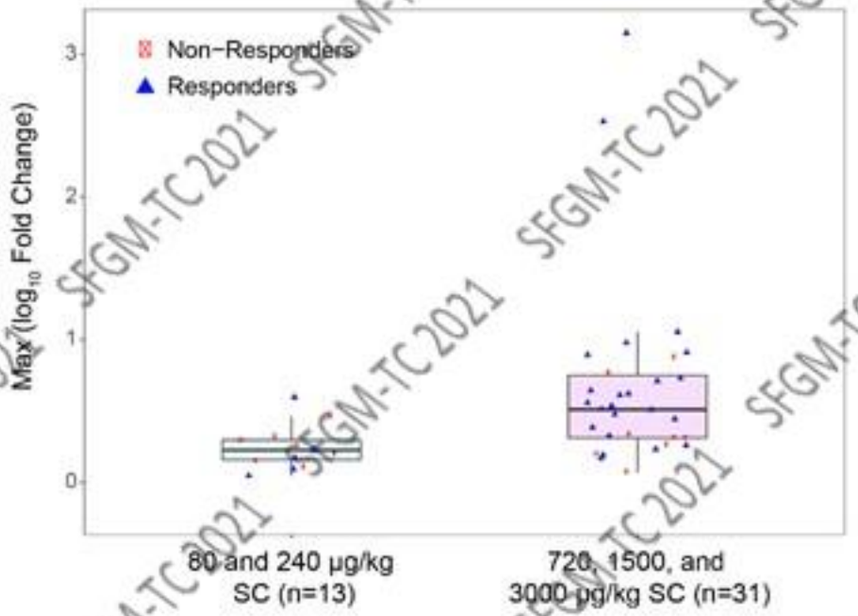


- Responses were durable and deepened over time
- Among responders treated at the RP2D, 15/16 (94%) are alive and progression-free after mF/U of 3.9 months (1.7–7.4)
- Among responders in SC cohorts, 32/35 (91%) remain on treatment with ongoing responses after mF/U of 6.5 months (1.7–14)
- Among responders treated at the most active IV and SC doses, 44/47 (94%) remain on treatment with ongoing responses after mF/U of 6.5 months (1.7–14)
- 5/5 evaluable patients across IV and SC cohorts showed sustained MRD negativity

Garfall et al, ASH 2020

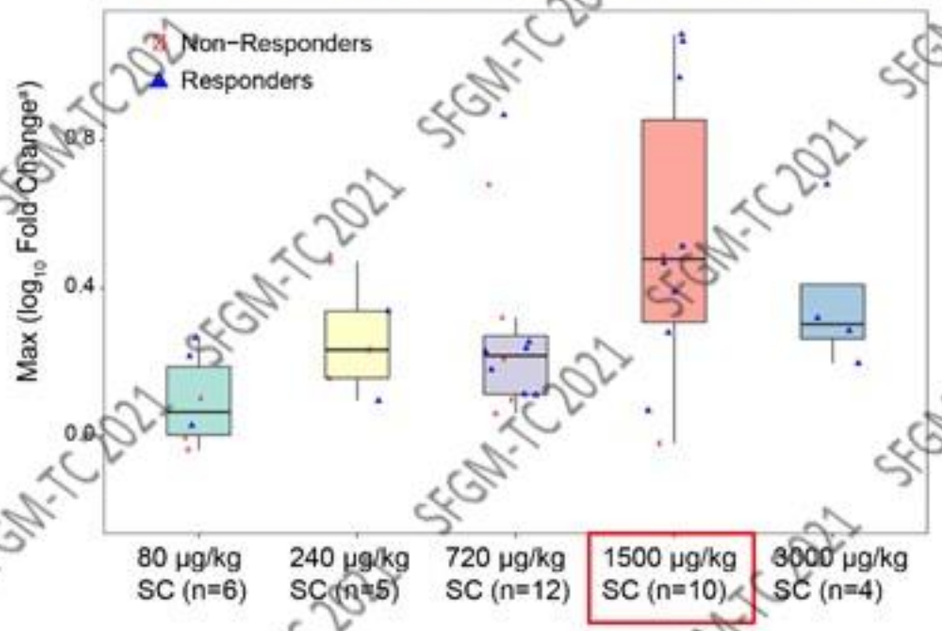
MajesTEC-1: pharmacodynamics

Induction of IL2Rα in SC Cohorts



- Highest induction of cytokines (IL-10, IL2Rα, IL-6) at doses ≥720 µg/kg SC

Induction of PD-1⁺ T Cells in SC Cohorts

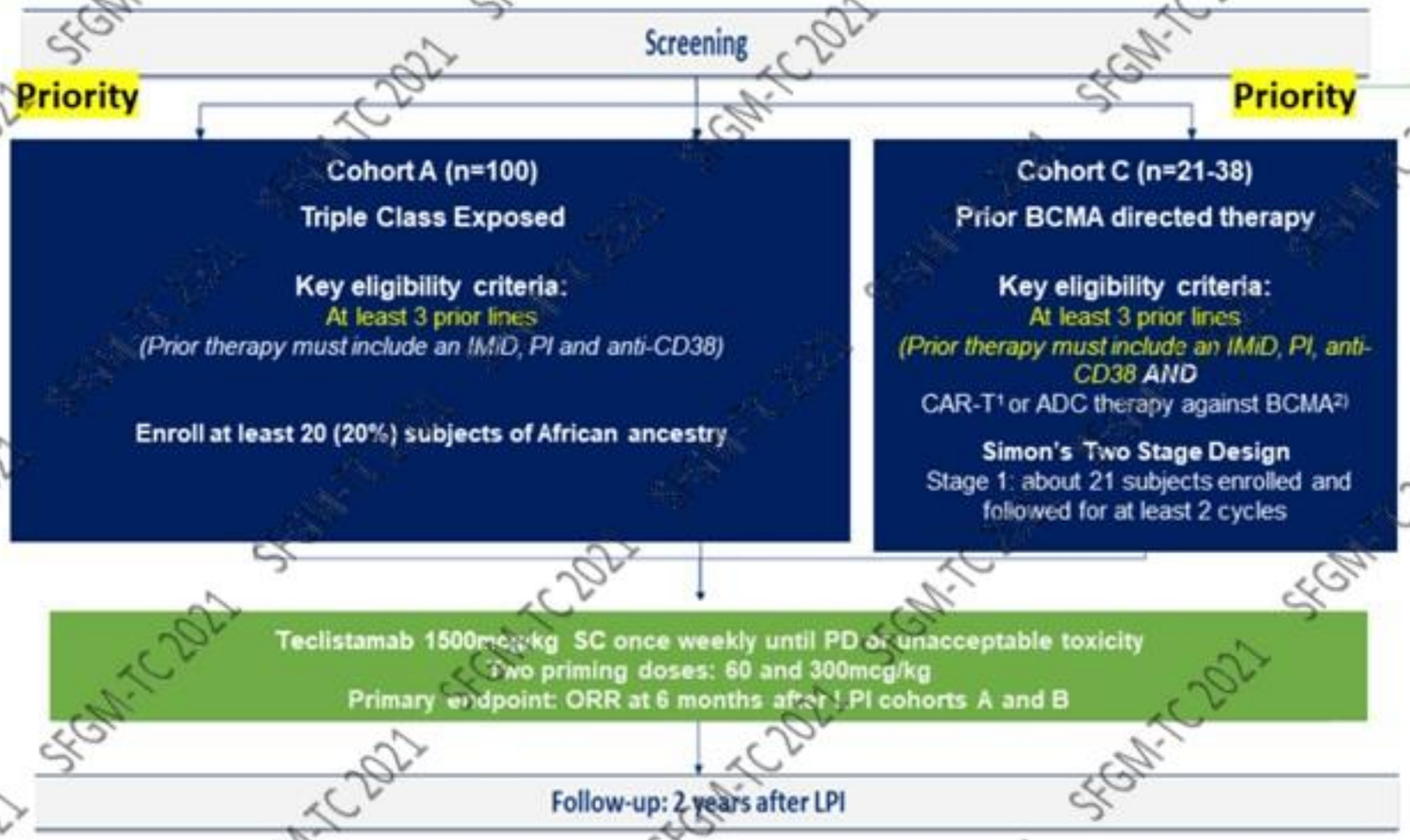


- PD-1⁺ T cells were induced in the periphery, indicating T cell activation
- Consistent T cell activation observed at RP2D (1500 µg/kg SC)

Garfall et al, ASH 2020

Phase 2 in RRMM (> 3 previous lines)

64007957MMY1001: Phase 2 Study Design



Exemple d'un patient

-62 years-old man
- Medical history : bipolarity

- IgA lambda MGUS since 2014 (pic 14 g/L)

- IgA lambda MM diagnosed in may 2016
CRAB criteria: bone, hypercalcemia, renal insufficiency

1) VTD, HD Melphalan with ASCT and consolidation
Relapse en 2017

2) Rev/Dex (novembre 2017 - novembre 2018)

3) Dara/Pom/Dex (janvier 2019 - décembre 2019)
PD

4) Carfilzomib-Dexamethasone (december 2019 – december 2020)
Baseline 19 g/L - nadir 1,5 g/L
Progression 08 Dec 2020

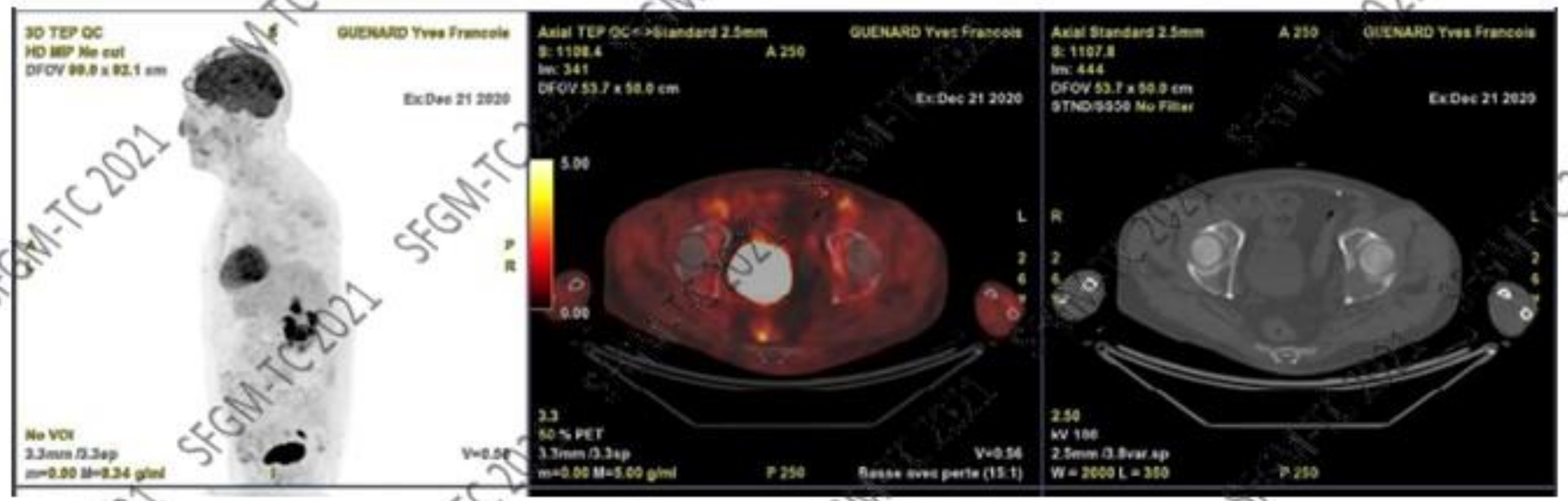
Exemple d'un patient

Inclusion in MMY1001p3 in december 2020_M-spike: 20.4 g/L

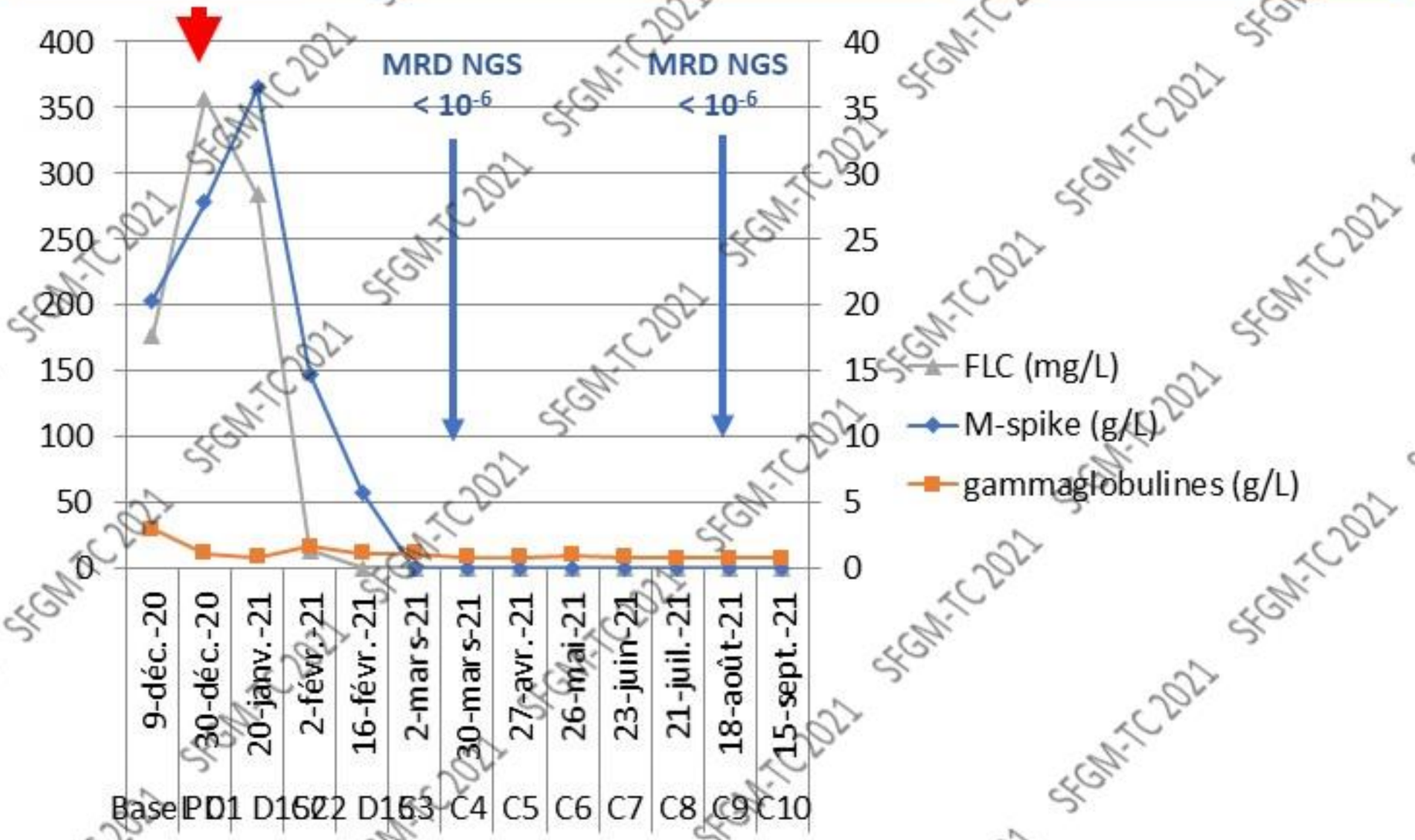
Cytogenetics: intermediate (LP=0,9)

Caryotype moléculaire NGS hypodiploïde à 44 chromosomes, avec monosomie 13, nullisomie Y, gain 1q, gains partiels 22q et Xq, et délétions partielles 1p (non 1p32), 7p, 11q, 14q et 18q. Présence d'une t(4;14). Absence de del(17p). Absence de t(11;14). Présence dune mutation ATM clonale et d'une mutation KRAS sous-clonale.

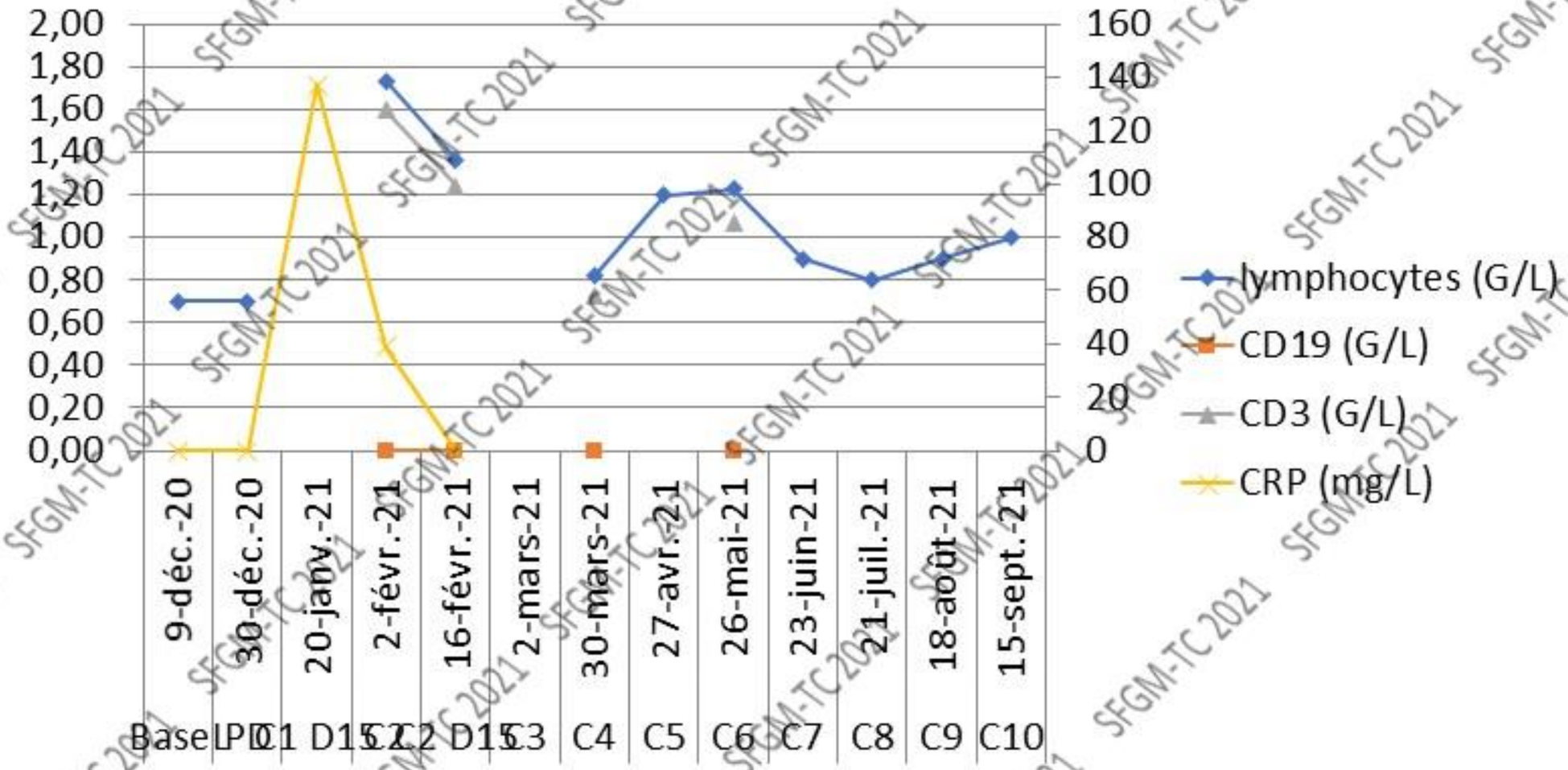
Bone lesions



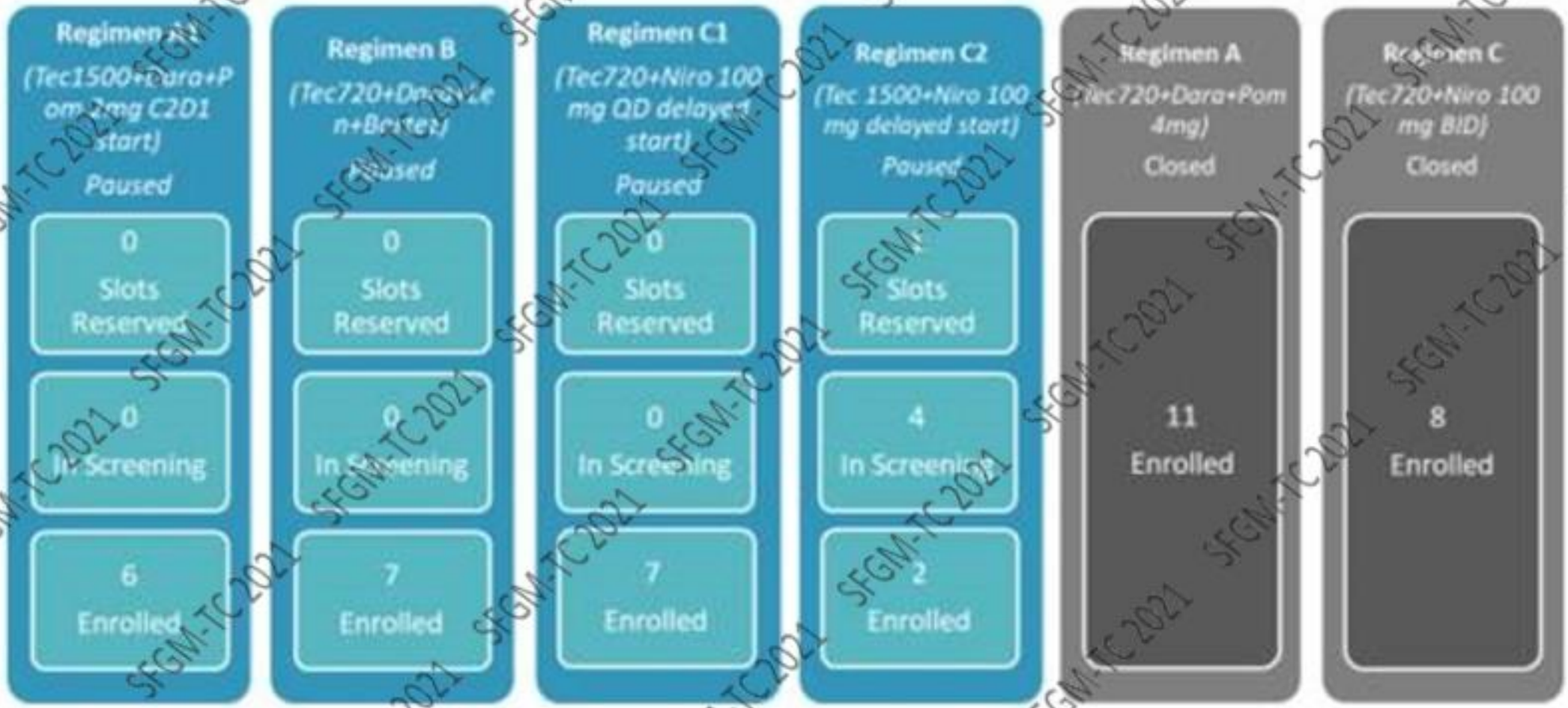
Exemple d'un patient



Exemple d'un patient

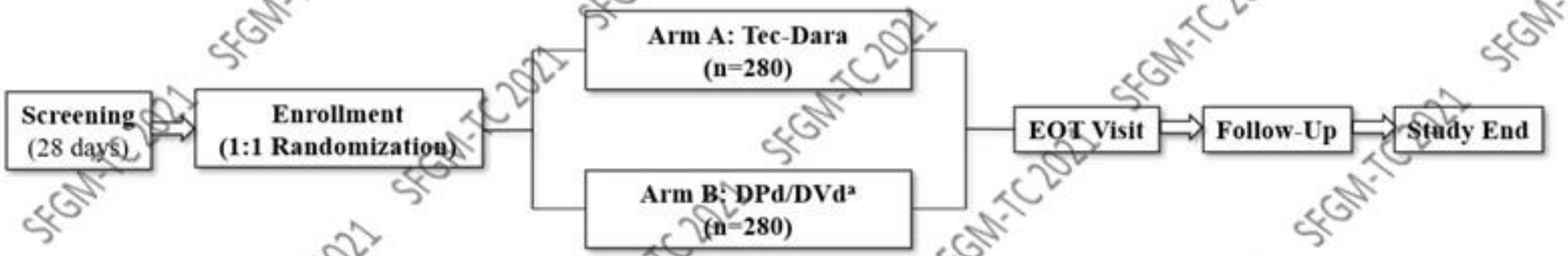


Phase 1-2 in combination in RRMM (> 1 previous line)



Phase 3 in RRMM (1-3 previous lines)

Cooming soon…



Arm A :

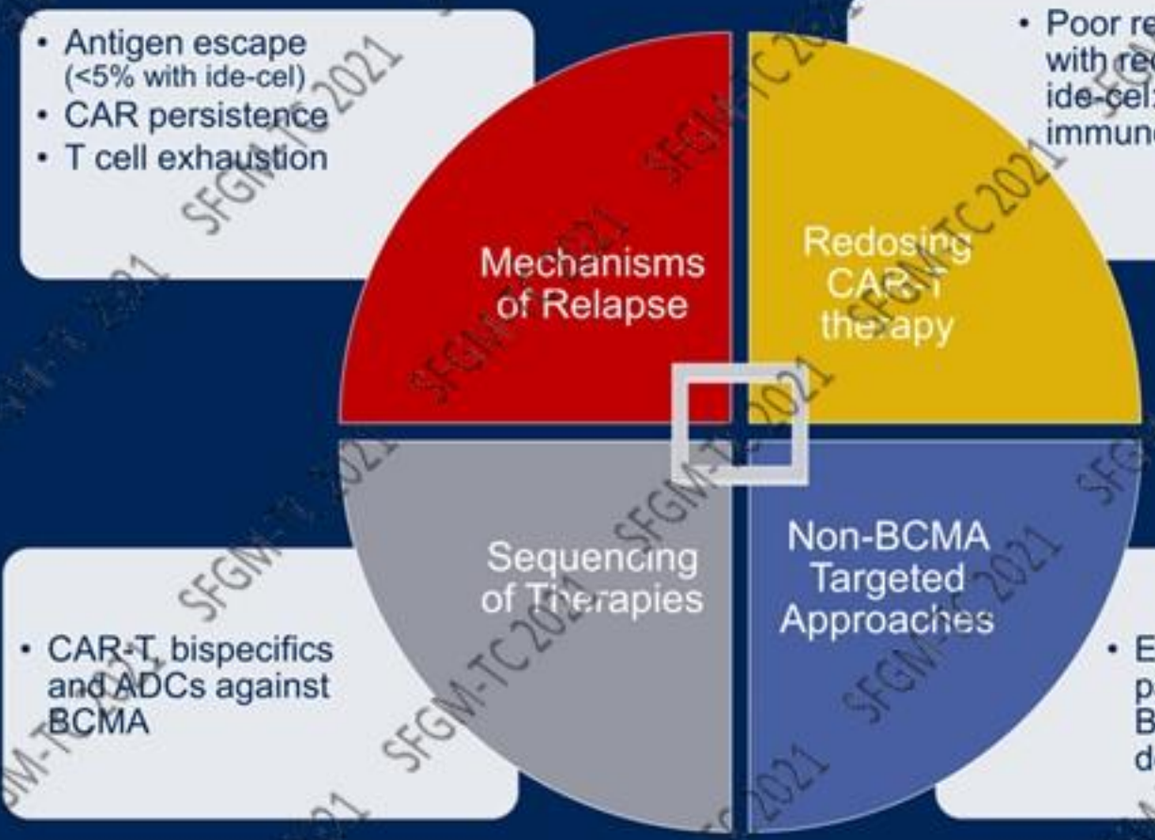
- Tec: Flat-dose with 3 step-up doses
- Dex premedication until 1st treatment dose of Tec

Arm B :

- Treatment per investigator choice
- ≤60% participants will receive either 1 of the 2 regimens.
- At screening, investigator must declare the treatment regimen the participant is to receive should they be randomized to Arm B

Hexa-refractory patients: new unmet need?

Approaches to mitigate relapse
- **Dual Targeting**
- **Increasing BCMA expression**
- **Fully Human CAR-T cells**
- **Earlier use**



- Antigen escape (<5% with ide-cel)
- CAR persistence
- T cell exhaustion

- Poor responses with redosing of ide-cel: Anti-CAR immune response?

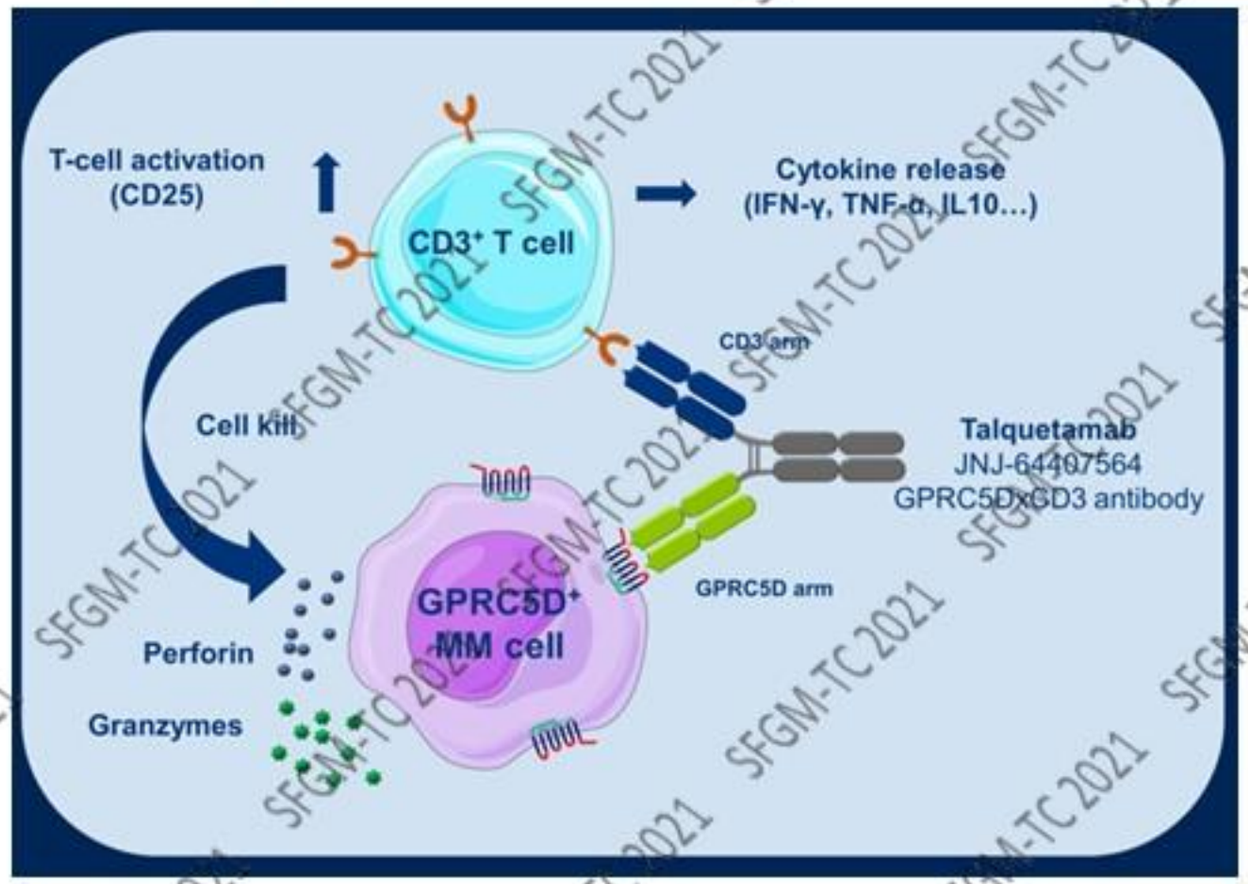
Fully Human CAR-T cells

- CAR-T, bispecifics and ADCs against BCMA

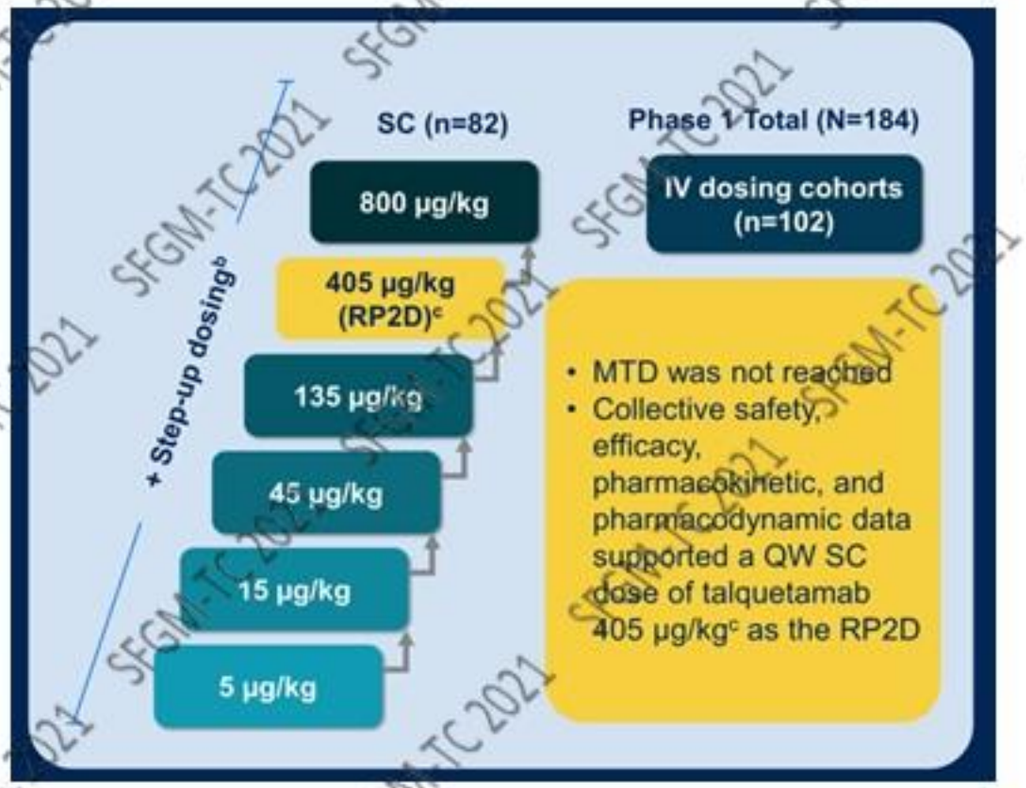
- Especially in patients with BCMA loss or down-regulation

GPRC5D, FCRH5 and others

Autres cibles sur le plasmocyte

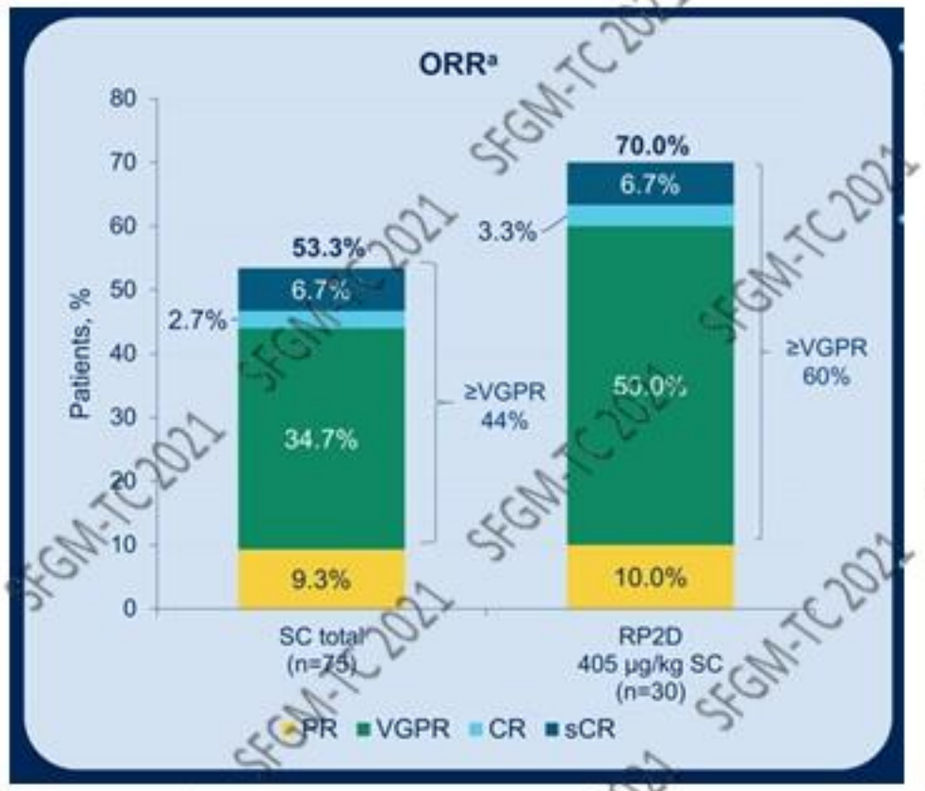


Etude MonumenTAL-1

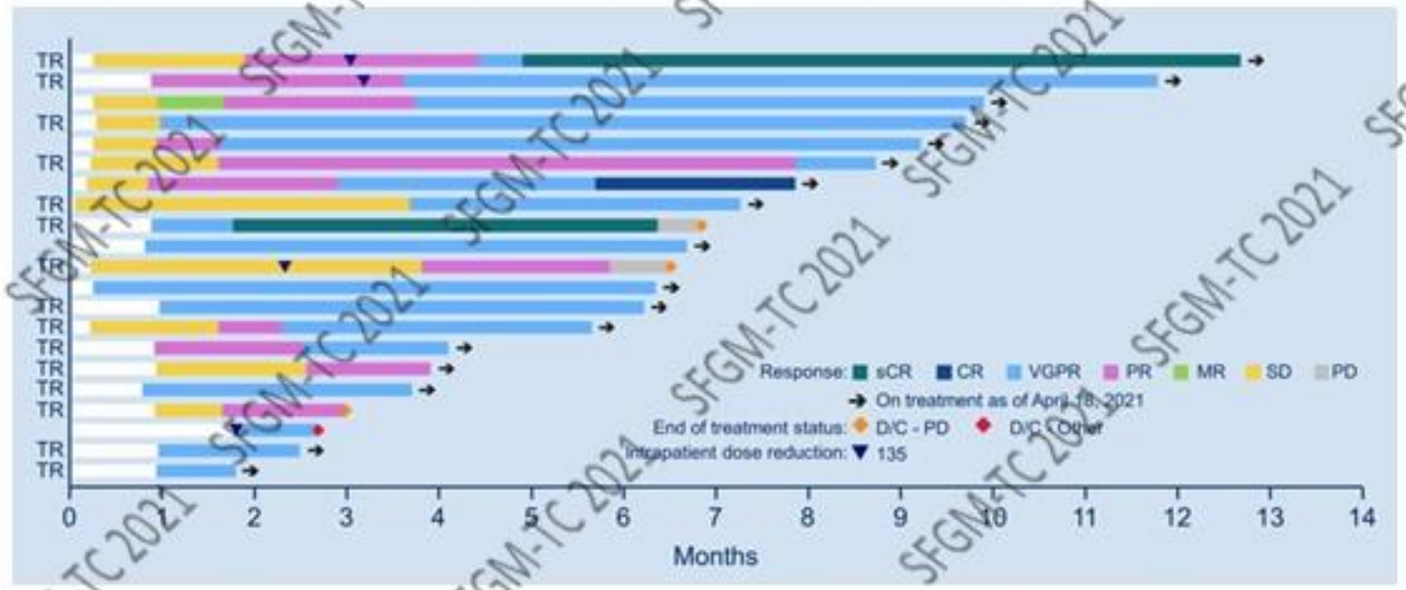


JG Berdeja et al, ASCO 2021

Talquetamab : anti-GPRC5D x CD3



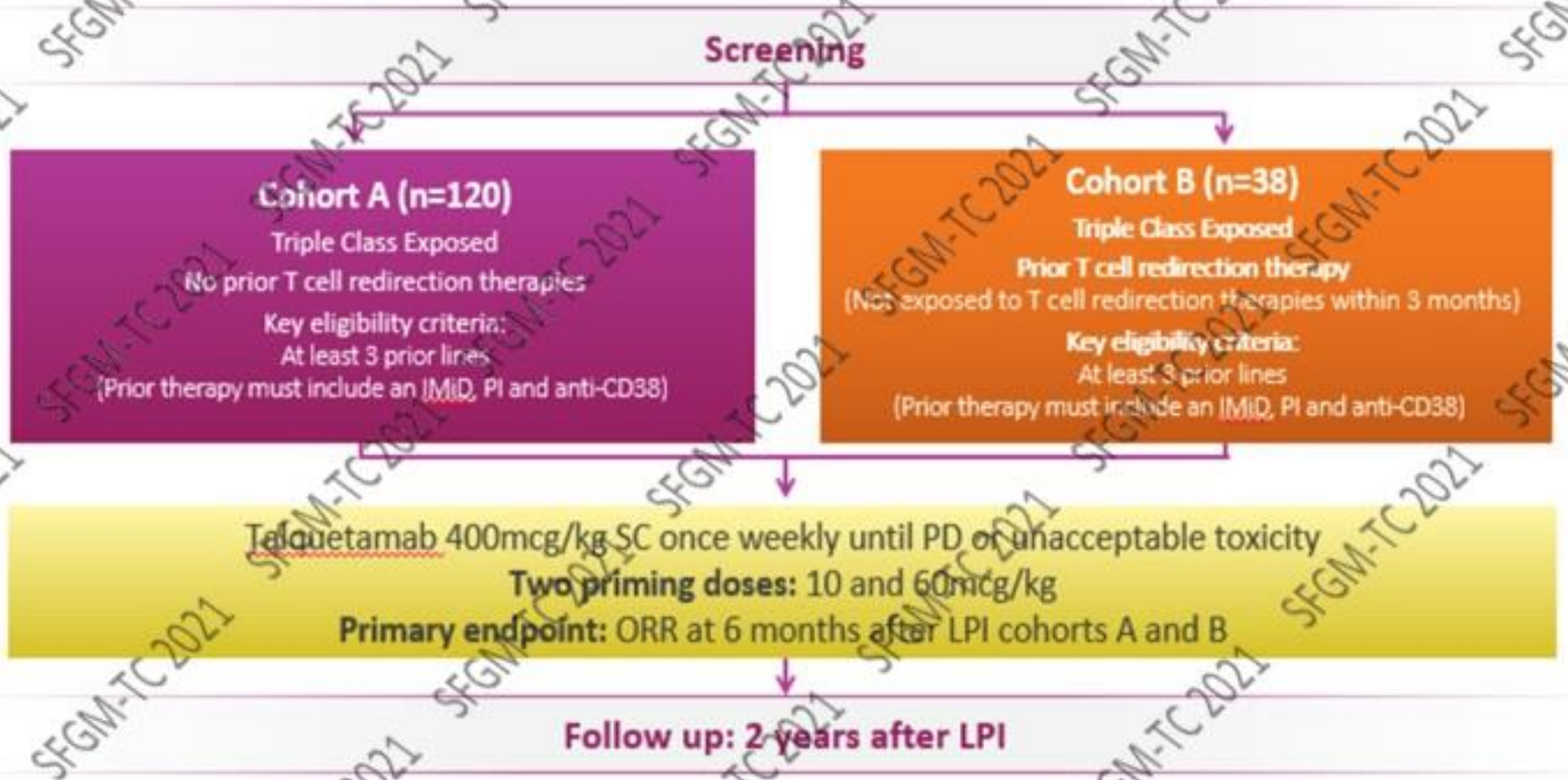
81 % des patients toujours sous traitement à 6,3 mois



JG Berdeja et al, ASCO 2021

Phase 2 in RRMM (> 3 previous lines)

64407564MMY1001: Phase 2 Study Design



Autres cibles sur le système immunitaire

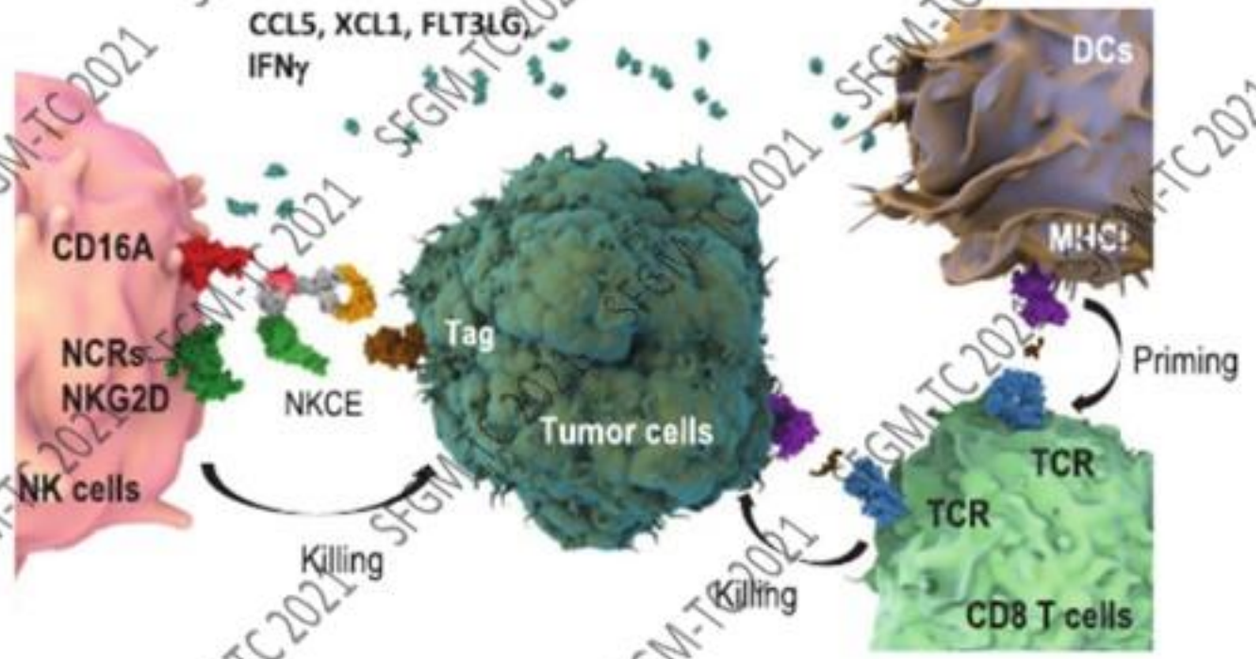
European Journal of Immunology

HIGHLIGHTS

REVIEW

Natural killer cell engagers in cancer immunotherapy: Next generation of immuno-oncology treatments

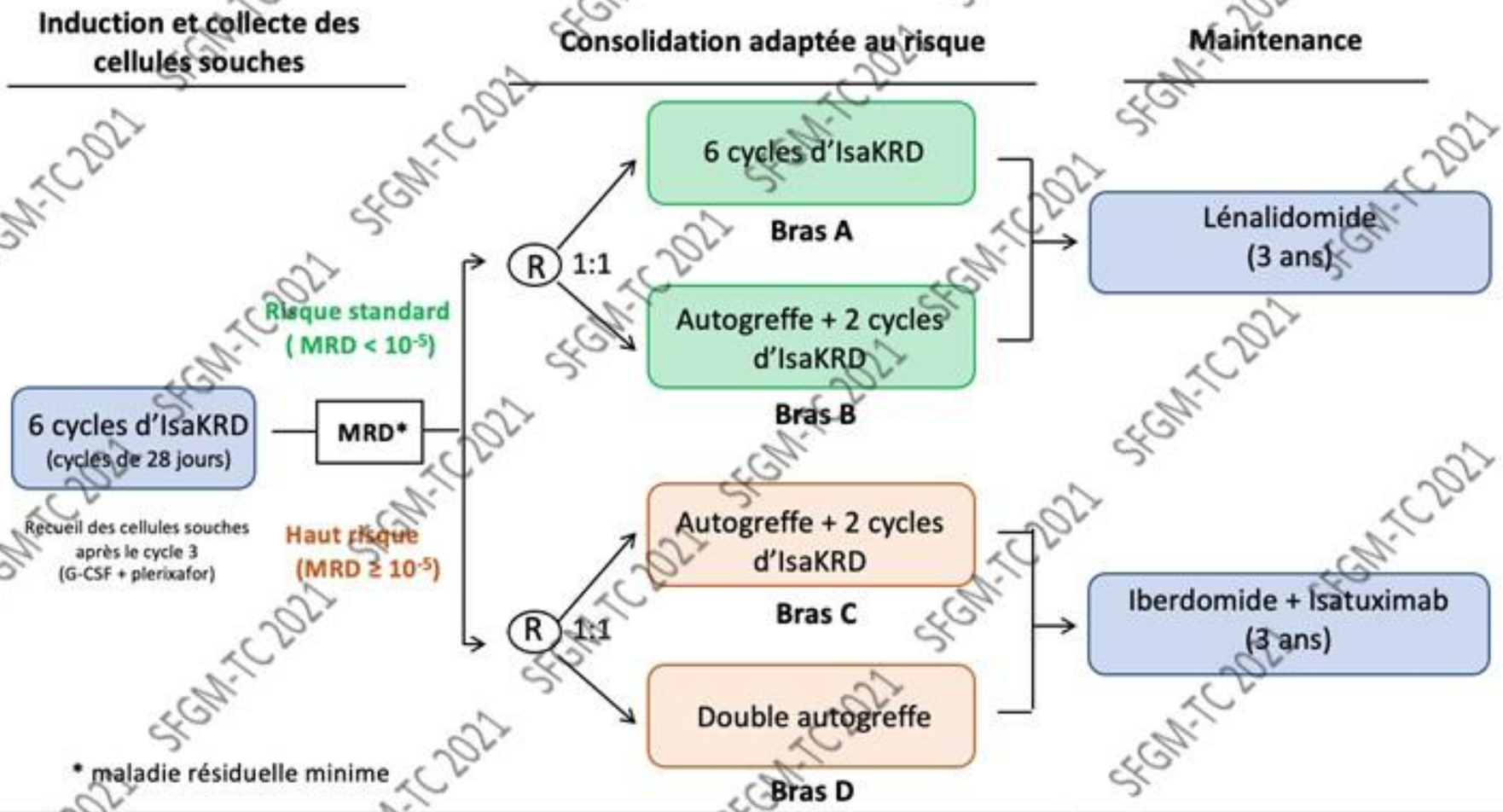
Olivier Demaria[1], *Laurent Gauthier*[1], *Guilhaume Debroas*[1] *and Eric Vivier*[1,2,3]



O Demaria et al, Eur J Immunol 2021

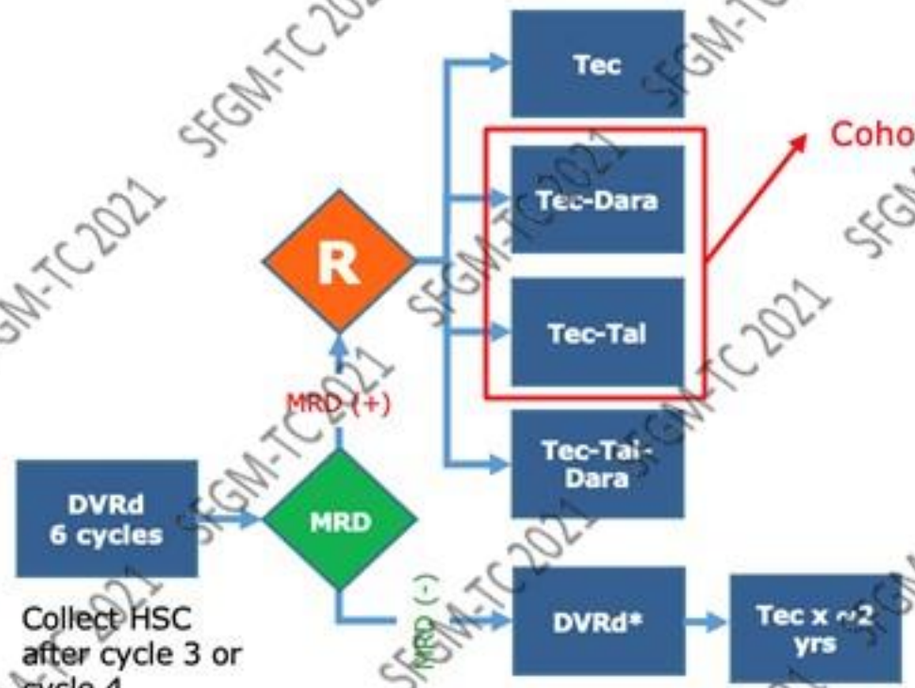
Aujourd'hui : adapter le traitement au risque du patient

Stratégie adaptée sur la réponse : protocole IFM 2020-02 MIDAS



Et demain… en y intégrant l'immunothérapie

Projet d'étude de phase 2



Patients
TE NDMM
transplant deferred

Phase 2
N: 120-200

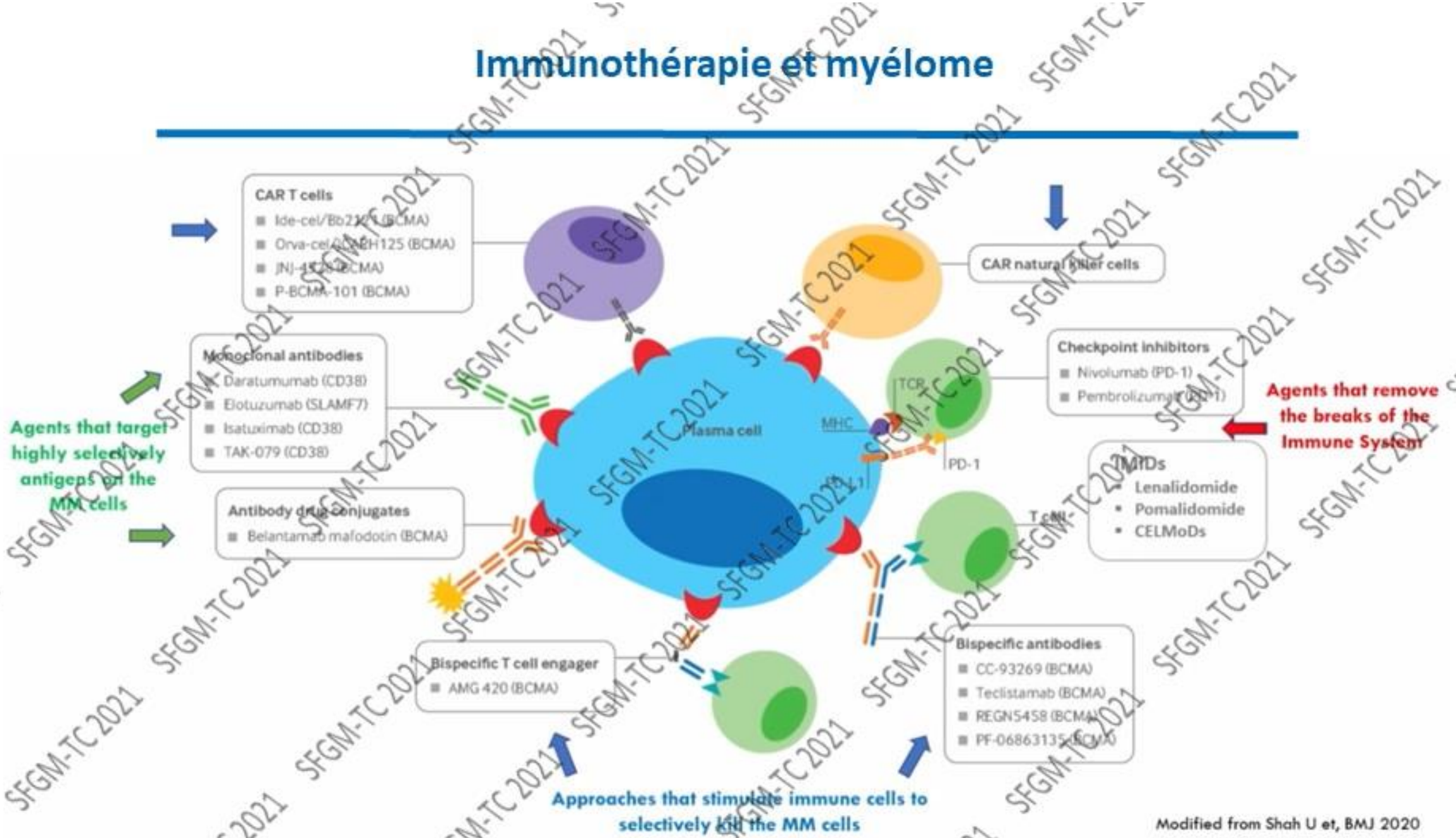
Collect HSC
after cycle 3 or
cycle 4

Endpoints

Primary
- 50% conversion to MRD-negative at 1 year

Exploratory
- MRD conversion to MRD-negative at 6 months
- Mass spectrometry
- NGS
- Flow cytometry
- Imaging

Immunothérapie et myélome



Modified from Shah U et, BMJ 2020

Immunothérapie et myélome

Concept +++

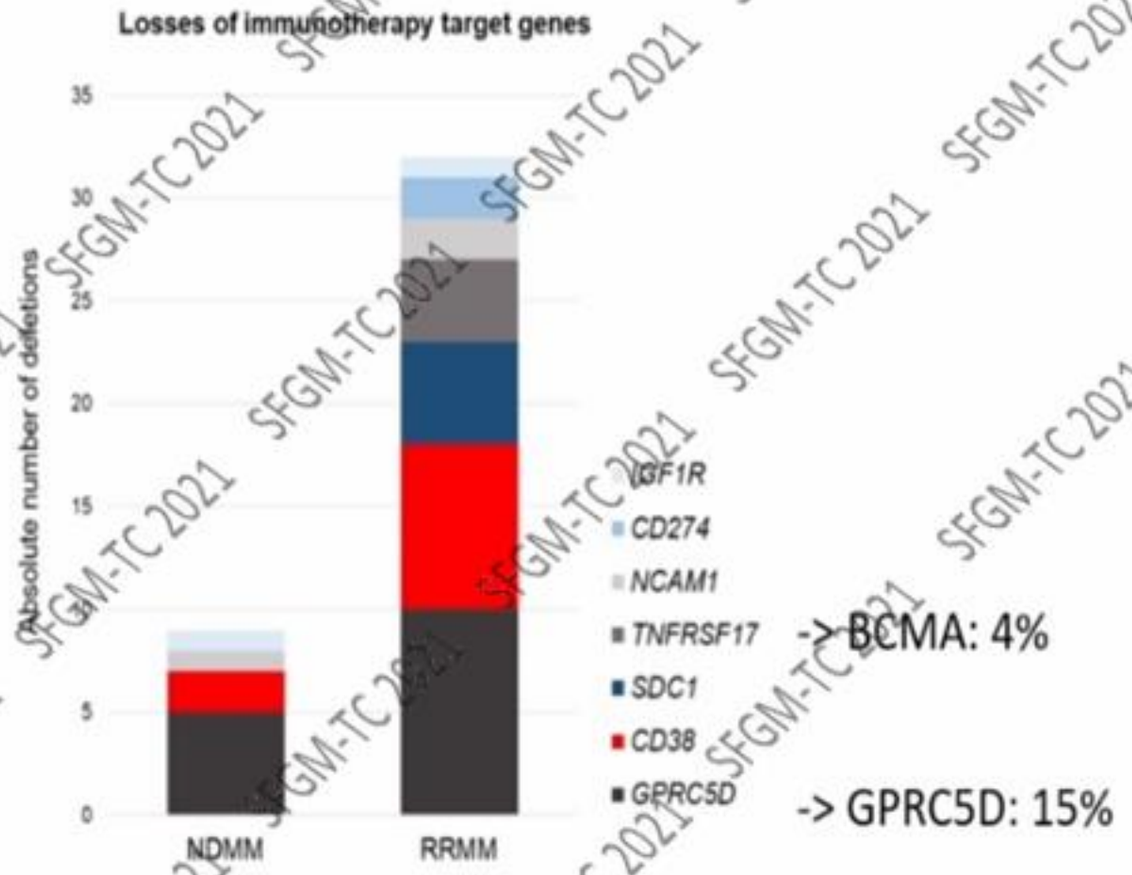
Développement clinique très rapide

Mais…

--> Pour qui ? Comment ?
--> Quelles combinaisons ?
--> Efficacité identique chez les patients de haut risque ?
--> Efficacité en induction ? Consolidation ? Maintenance ?
--> Restauration durable de l'immunité anti-tumorale ? Autres facteurs ?

Expression des cibles d'intérêt de l'immunothérapie

- Délétions hétérozygotes pour *GPRC5D* (15%), *CD38* (10%) et BCMA (4%)
- + de délétions chez les patients en rechute
- Analyse en RNAseq : délétions hétérozygotes → pas de différence significative d'expression des cibles

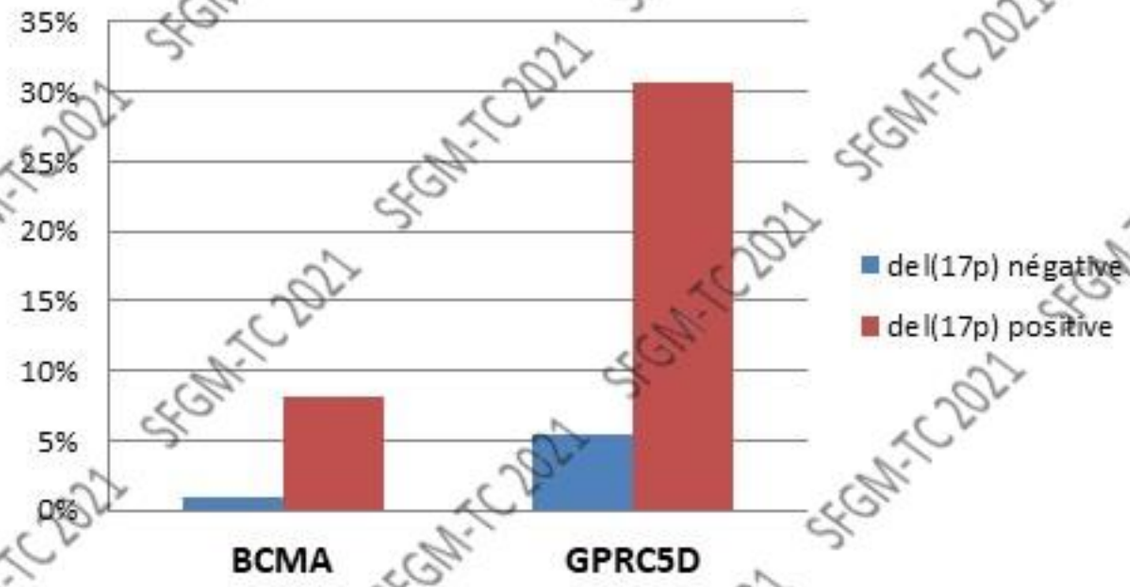


Truger et al, EHA 2021

Et chez les patients de haut risque ?

Patients avec del17p

Pourcentages de délétions hétérozygotes

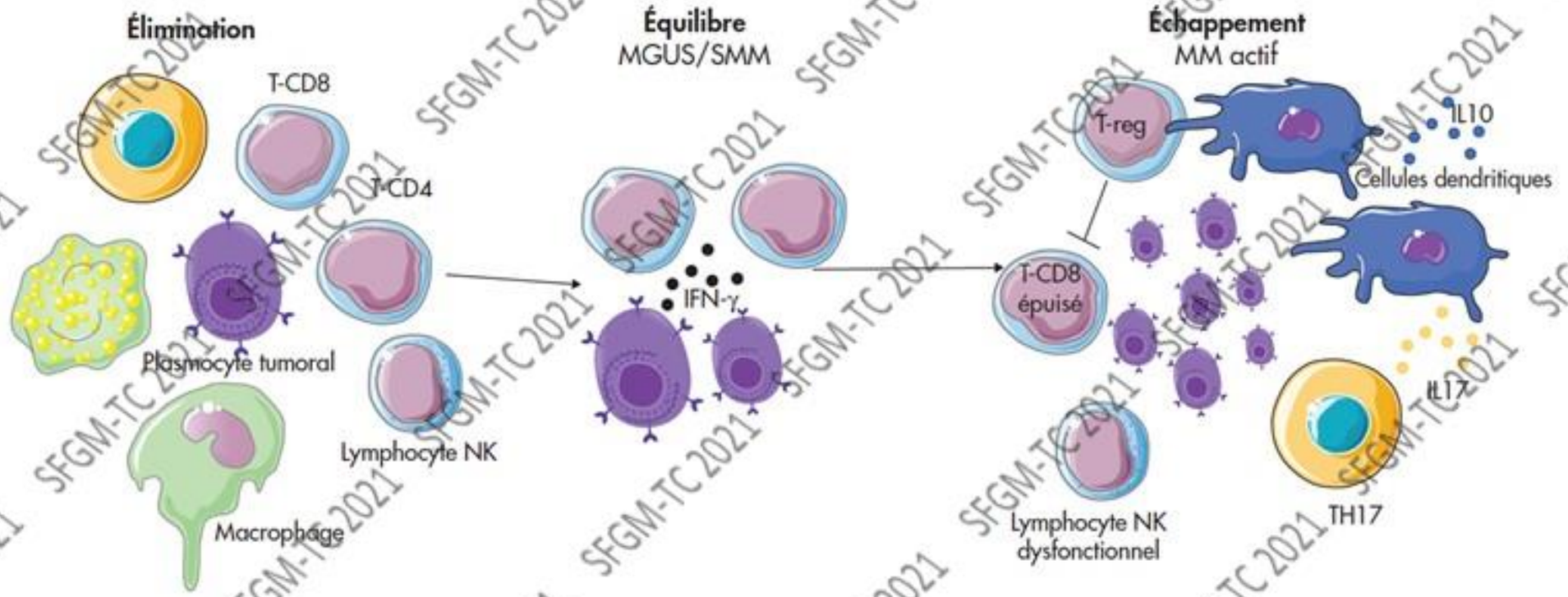


Délétions hétérozygotes	Del(17p) négative (n=111)	Del(17p) positive (n=111)	p-value
% BCMA	0.9%	8.1%	**0,01**
% GPRC5D	5.4%	30.6%	**1,01E-06**

Données non publiées

Questions en suspens : profils MGUS-like

Patients en réponse partielle ou MRD + sans progression

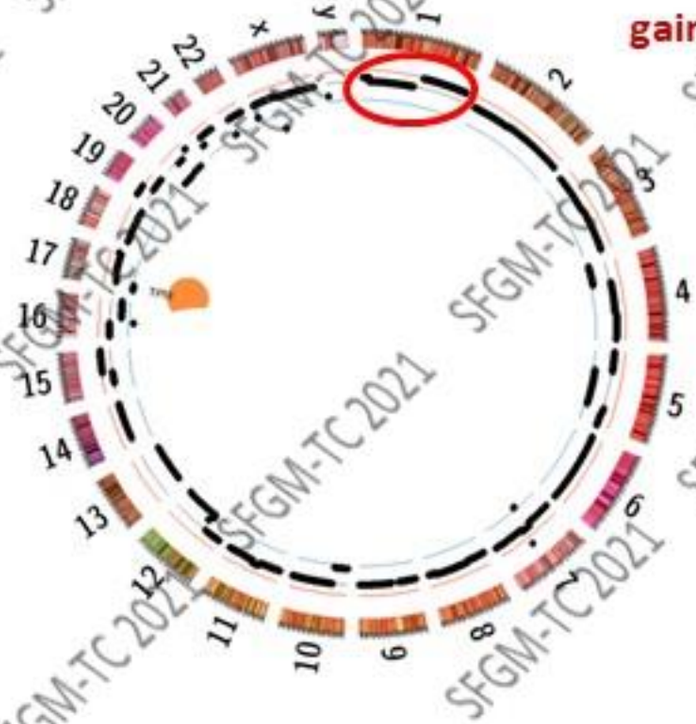


S Le Grand & A Perrot, Hématologie 2021

Questions en suspens : rôle du micro-environnement dans la sélection clonale

Diagnostic (Avril 2019)
BULK TUMORAL

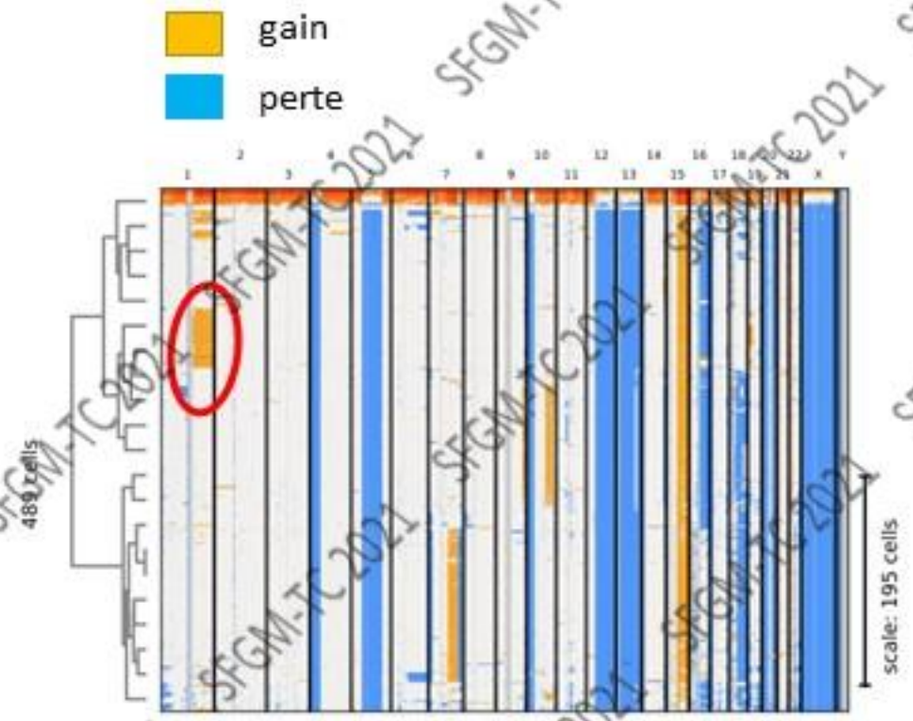
Traitement intensif



Rechute (Octobre 2020)
BULK TUMORAL

Données non publiées

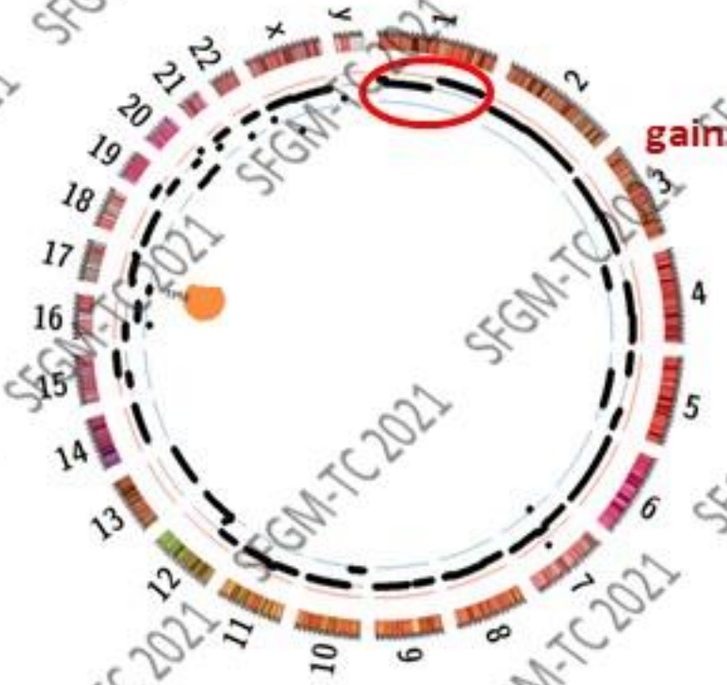
Peut-on prédire la sélection clonale ?
Pourra-t-on l'éviter avec l'immunothérapie ?



Diagnostic (Avril 2019)

SINGLE CELL

Traitement intensif

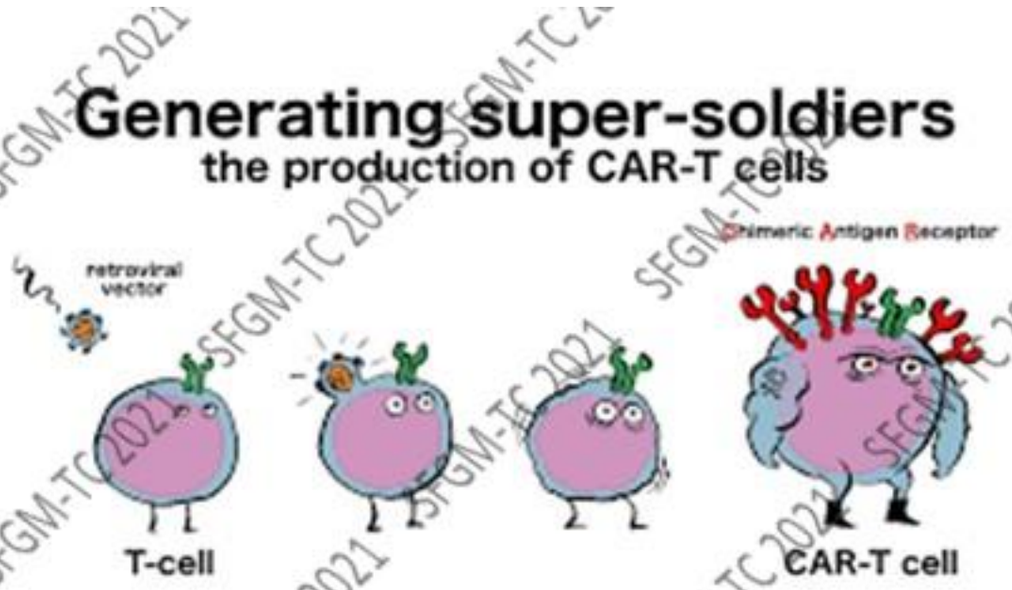


Rechute (Octobre 2020)

BULK TUMORAL

Données non publiées


IMMUNOTHERAPIE
Utiliser le Corps Pour Vaincre le Cancer


Generating super-soldiers
the production of CAR-T cells
Chimeric Antigen Receptor
retroviral vector
T-cell
CAR-T cell


OMG! CLARK! WHERE'VE YOU BEEN! YOU MISSED IT! CAR-T CELL WAS FIGHTING CANCER AND HE WON!
BROOMS
THE SECRET LIFE OF WHITE BLOOD CELLS