

**UNE INJECTION UNIQUE DE CELLULES STROMALES MESENCHYMATEUSES (CSM)
AU JOUR 3 APRES GREFFE HEPATIQUE EST INSUFFISANTE
POUR INDUIRE UNE TOLERANCE OPERATIONNELLE**

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Contexte : CSM

- Effet immunosuppresseur et immuno-régulateur
- Effet anti-inflammatoire
- Effet sur la régénération des tissus/organes
- Effet protecteur dans l'I/R

- Rôle of CSM en transplantation d'organe?

Objectifs

- Primary endpoint: Feasibility & safety for LT recipients
 - tolerability of infusion
 - infections (bacterial, viral, fungi)
 - cancers (PTLD, others)
 - patient and graft survivals
- Phase 2: IS weaning

M&M

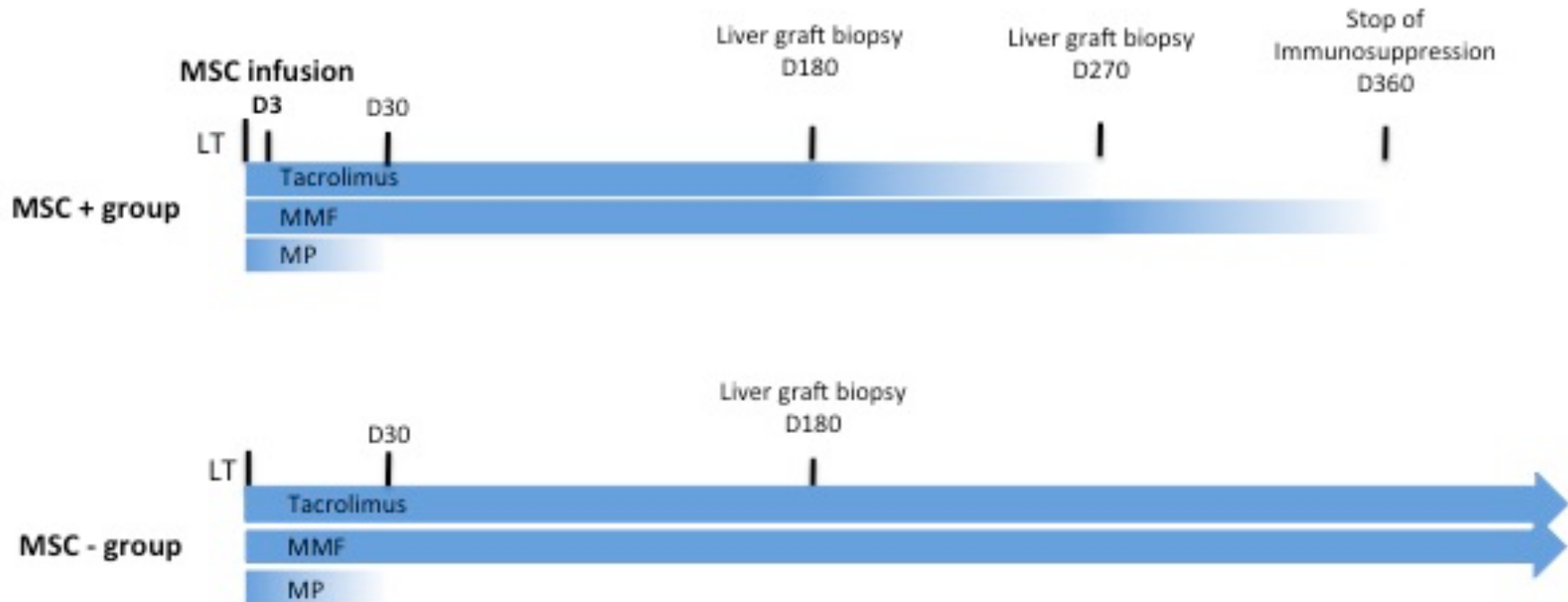
- Receveurs hépatiques cadavériques (DBD & DCD)
- IS classique
- Allo CSM

- Dose: 1.5 to 3 .10⁶ CSM/kg
- Injection iv (voie centrale) au jour 3 (+/-2)

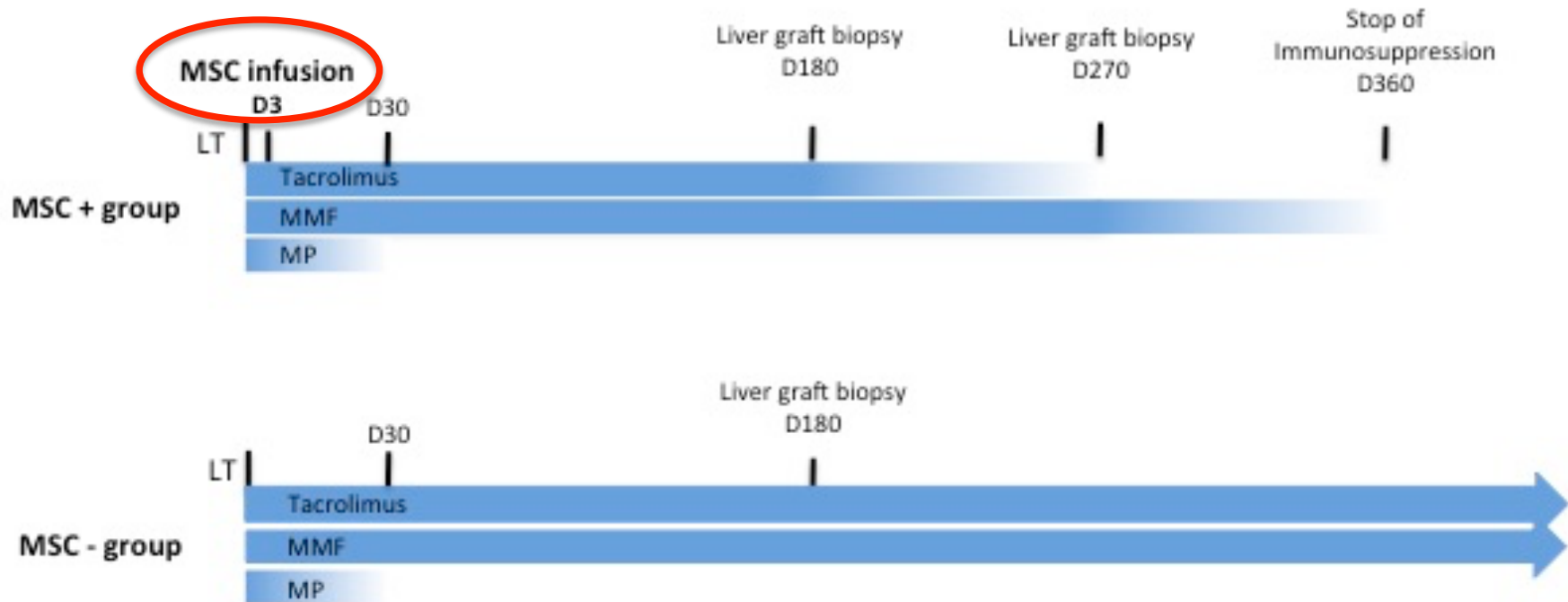
M&M: liver 1

- Liver transplantation
 - 2 groups: -10 MSC +: MSC group
 - 10 MSC -: Control group
 - prospective, no randomisation, unblinded
 - regular immunosuppression (TAC-MMF)
 - protocol biopsy at month 6 in both groups
 - follow-up of one year completed for all patients
- MSC group:
 - tapering of TAC from month 6 to 9, then biopsy
 - tapering MMF from month 9 to 12

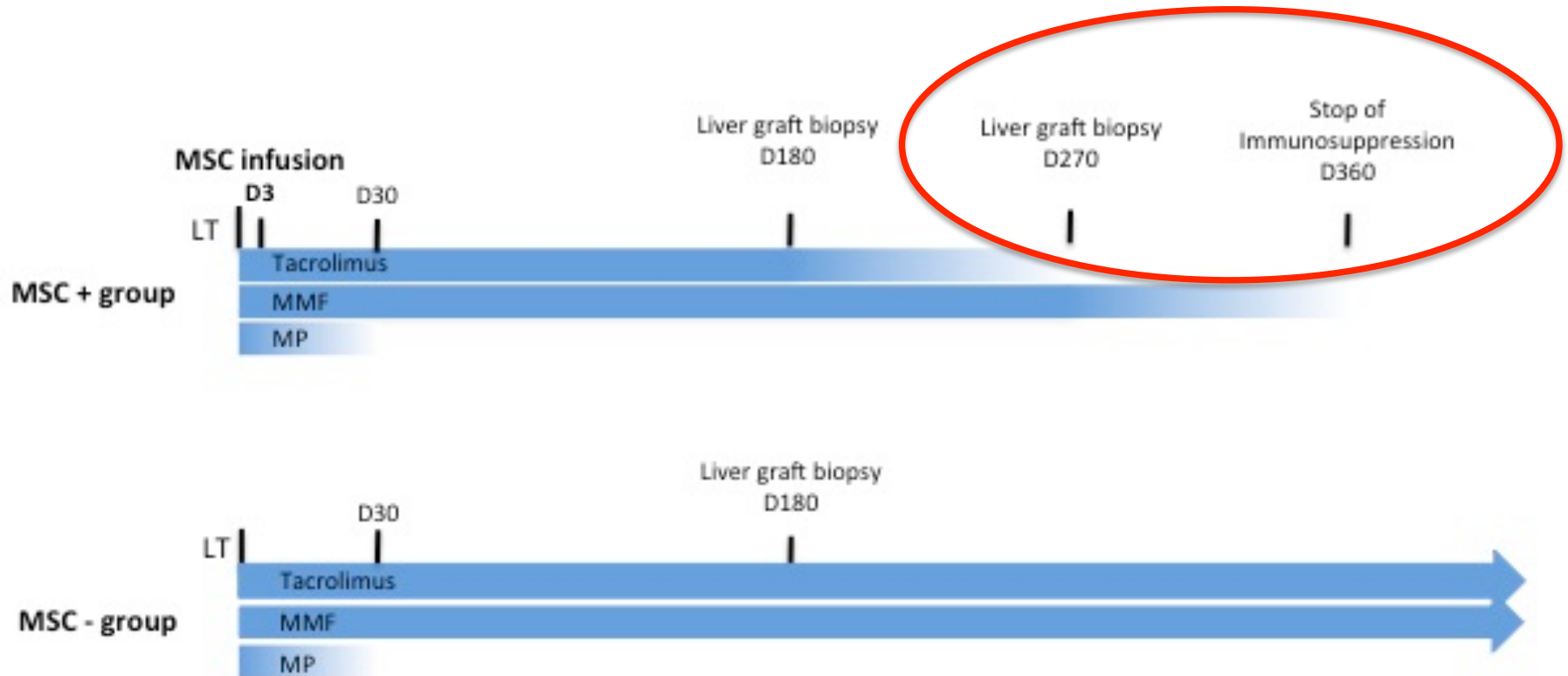
M&M



M&M



M&M



MSC injection in LT recipients

	Per protocol	Study (Median) (IQR; Ranges)
MSC Injection day	day 3 +/- 2	3 (3-3.25; 2-5)
Dose MSC (10^6 /kg)	1.5-3	2.1 (2.0-2.4; 1.9-2.7)
Injection volume (ml)		342 (322-469; 306-614)
Injection duration (min)		25 (16.2-40; 11-60)

Median (IQR; Ranges)

Infusional toxicity

	Pre Infusion	15 min	End of infusion	<i>P</i>
Body temperature (°C)	36.0 (35.4-37.7)	36.3 (35-36.9)	36.2 (35.5-37)	0.87
Mean PA (mmHg)	103.3 (87-124)	107 (84-119.5)	106 (94-115)	0.83
Heart rate (per min)	81 (65-102)	82.5 (65-102)	80.5 (68-101)	0.17
NI O2 saturation	99 (93-100)	100 (92-100)	97.5 (93-100)	0.67

Median (Ranges) (Friedman test & ANOVA)

- No hepatic artery or portal vein thrombosis
- No sign of pulmonary embolism or post infusional intubation
- No anaphylactic reaction, no skin reaction

Infectious complications

		MSC group (n=10)	Control group (n = 9)	P
Overall		2	6	0.06
Fungal		0	0	
Viral	CMV disease	0	0	
	HSV	2	0	
	VZV	0	1	
Bacterial	Wound	0	1	
	Urinary	0	2	
	Sinusitis	0	1	
	Pulmonary	0	1	

n (Chi square)

Infectious complications

		MSC group (n=10)	Control group (n = 9)	P
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Fungal		0	0	
Viral	CMV disease	0	0	
	HSV	2	0	
	VZV	0	1	
Bacterial	Wound	0	1	
	Urinary	0	2	
	Sinusitis	0	1	
	Pulmonary	0	1	

n (Chi square)

Cancer (6-month follow-up)

	MSC group (n=10)	Control group (n = 9)	P
Overall	1	0	>0.99
de novo	0	0	
HCC recurrence	1	0	

n (Chi square)

Follow-up at 6 months

- No rejection in either groups
- One death in the control group (hepatic artery fistula)

Month-6 graft biopsies

	MSC group (n=10)	Control group (n = 9)	P
Banff	3 (0-6)	4 (0-7)	0.21
Fibrosis	1 (0-2)	1 (0-3)	0.48

median (Ranges)

Month-6 graft biopsies

	MSC group (n=10)	Control group (n = 9)	P
CD3	196 (95-334)	162 (93-590)	0.86
CD4	101 (54-212)	103 (17-496)	> 0.99
CD8	69 (15-196)	85 (12-300)	0.49
CD68	28.5 (12-75)	40 (15-104)	0.58
CD1a	1 (0-3)	1 (0-3)	0.83
CD138	7.5 (4-38)	6 (2-44)	0.50
CD20	27 (3-95)	28 (10-163)	0.66
FoxP3	2 (0-16)	4 (0-33)	0.49

median (Ranges)

Follow-up at 1 year

- Patient and graft survivals at 90% in both groups

Cancer

	MSC group (n=10)	Control group (n = 9)	P
Overall	1	1	>0.99
de novo	0	0	
HCC recurrence	1	1	

Peripheral Blood Lymphocyte count

Month 1	MSC group (n=10)	Control (n=9)	P
White blood cells (/μL)	6,630 (3,280-9,700)	5,190 (4,150-10,030)	0.67
Lymphocytes (/μL)	855 (380-1,690)	940 (300-1,550)	0.92
CD3 (/μL)	687 (288-1,406)	620 (200-1,336)	0.48
CD45RA (/μL)	119 (50-557)	147 (48-234)	0.70
CD45RO (/μL)	373 (179-516)	201 (79 -609)	0.23
CD3+CD4+ (/μL)	535 (230-978)	349 (128-786)	0.30
CD3+CD56+ (/μL)	27 (1-87)	42 (4-154)	0.35
CD3+CD8+ (/μL)	115 (49-418)	142 (57-336)	0.76
CD19 (/μL)	144 (30-286)	99 (38-369)	0.70
CD56 (/μL)	109 (45-365)	188 (58-618)	0.27

Peripheral Blood Lymphocyte count

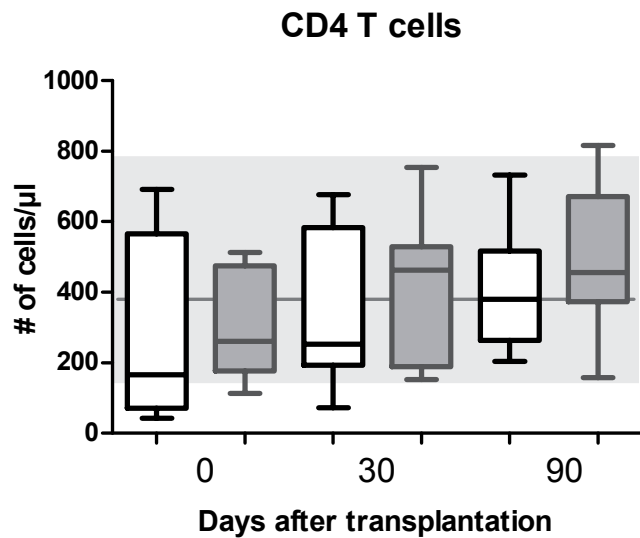
Month 3	MSC group (n=10)	Control (n=9)	P
White blood cells (/μL)	5,265 (970-8,160)	5,200 (2,470-7,030)	0.39
Lymphocytes (/μL)	875 (420-1,880)	760 (490-1,760)	0.82
CD3 (/μL)	767 (352-1,225)	553 (274-1,419)	0.30
CD45RA (/μL)	123 (51-389)	82 (54-259)	0.58
CD45RO (/μL)	381 (171-680)	179 (135-765)	0.23
CD3+CD4+ (/μL)	516 (292-923)	285 (202-976)	0.27
CD3+CD56+ (/μL)	21 (1-99)	34 (2-197)	0.76
CD3+CD8+ (/μL)	202 (41-496)	228 (56-362)	0.94
CD19 (/μL)	93 (34-354)	100 (21-321)	0.76
CD56 (/μL)	154 (66-331)	119 (59-550)	0.82

Peripheral Blood Lymphocyte count

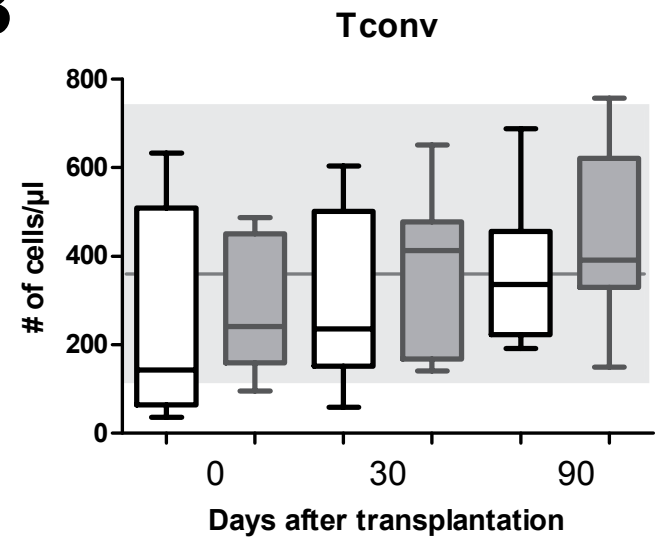
Month 6	MSC group (n=10)	Control (n=9)	P
White blood cells (/μL)	4,815 (4,200-8,150)	5,440 (2,680-11,430)	0.99
Lymphocytes (/μL)	1,250 (660-2,260)	1,000 (540-1,340)	0.23
CD3 (/μL)	880 (395-2,098)	592 (342-1,366)	0.27
CD45RA (/μL)	127 (76-364)	108 (61-298)	0.58
CD45RO (/μL)	396 (214-615)	267 (156-864)	0.20
CD3+CD4+ (/μL)	623 (348-728)	359 (224-1,163)	0.20
CD3+CD56+ (/μL)	31 (1-91)	36 (3-117)	0.54
CD3+CD8+ (/μL)	238 (38-1,471)	210 (73-345)	0.70
CD19 (/μL)	99 (25-256)	192 (52-258)	0.27
CD56 (/μL)	191 (66-386)	210 (55-490)	>0.99

Peripheral blood CD4+ T cells

A

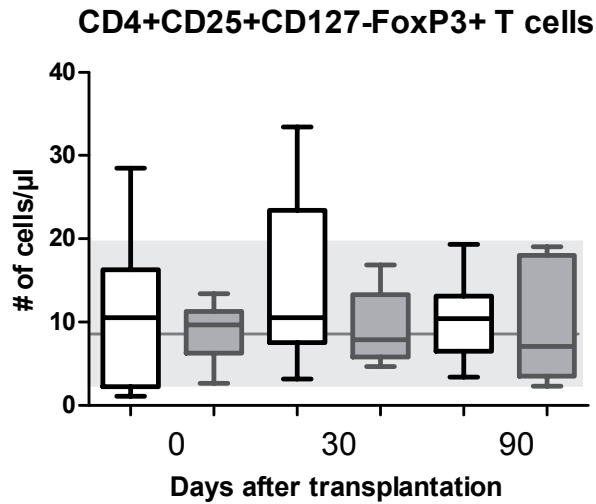


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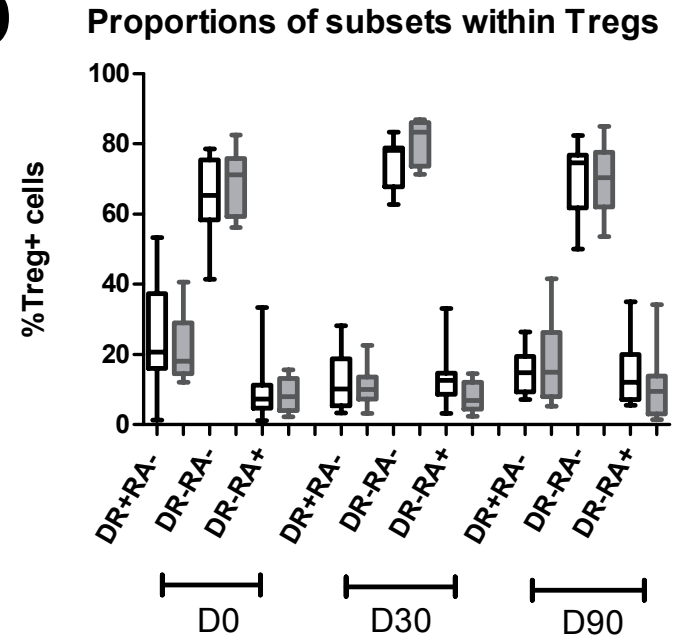


Peripheral blood CD4+ T cells

C



D



Phase 2 : IS weaning

- 9 MSC + patients underwent MSC weaning attempt (first TACRO, then MMF)
- 1 patient was successfully weaned
- 2 patients were on MMF monotherapy at month 9, but did not “tolerate” MMF weaning
- 6 patients had increasing liver tests during TACRO weaning

Conclusions

- L'injection de CSM au J3 après greffe hépatique est faisable et semble bien tolérée
- L'injection de CSM au J3 après greffe hépatique n'est pas suffisante pour induire une tolérance
- Timing? dose? nombre? source? IS?

Merci à:

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Sponsors



Present & Future

- MSC Lab (Dr François Jouret)
- GMP accreditation of the MSC
- Complete results of the kidney – MSC trial

- Phase 2 trial
- Repeated allo MSC infusion in 10 liver transplants with tolerogenic IS protocol (basilixumab – everolimus – MMF – low dose steroids and progressive IS weaning)