Photophérèse extra-corporelle dans le traitement de la GVH aigue

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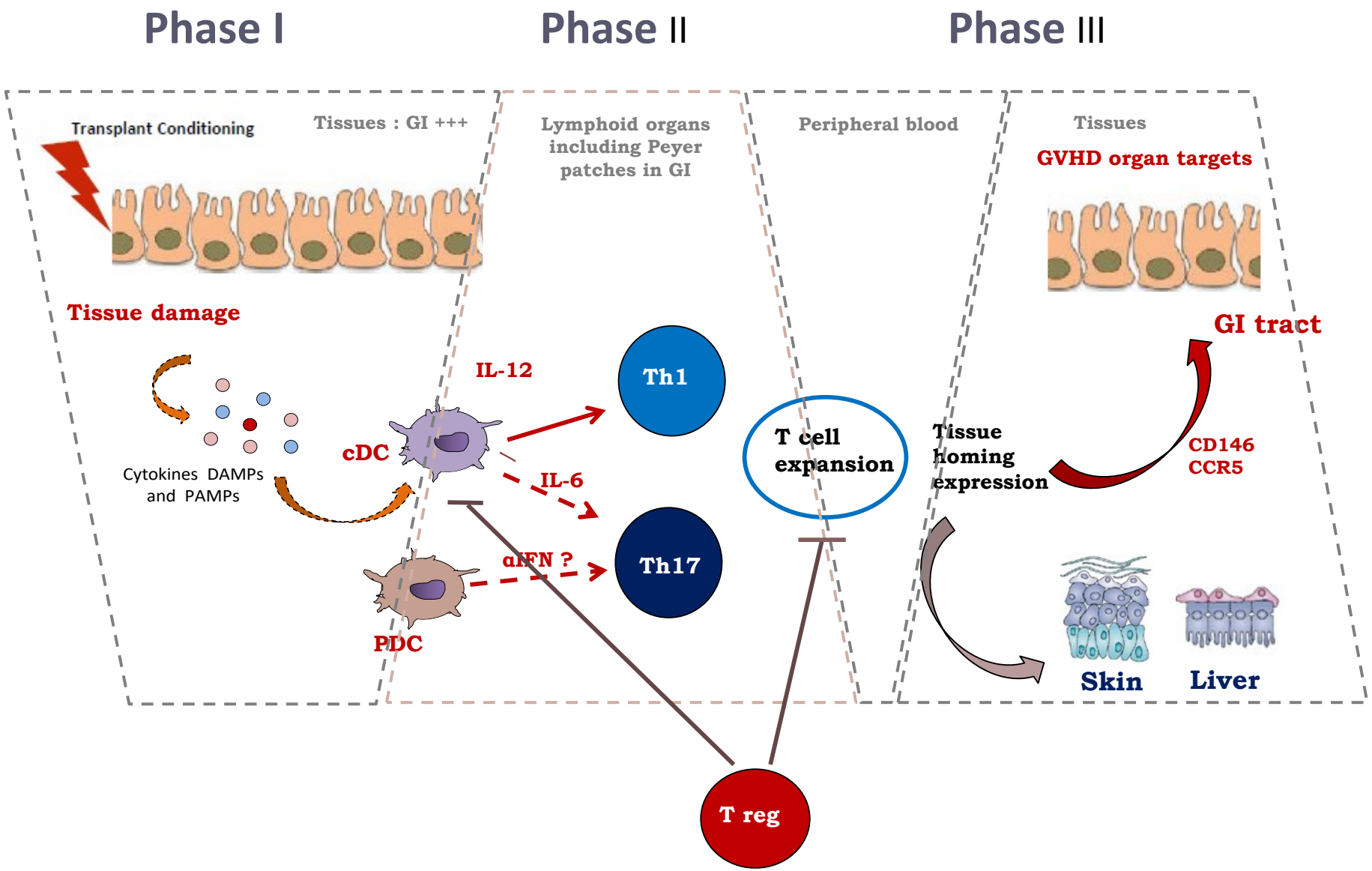
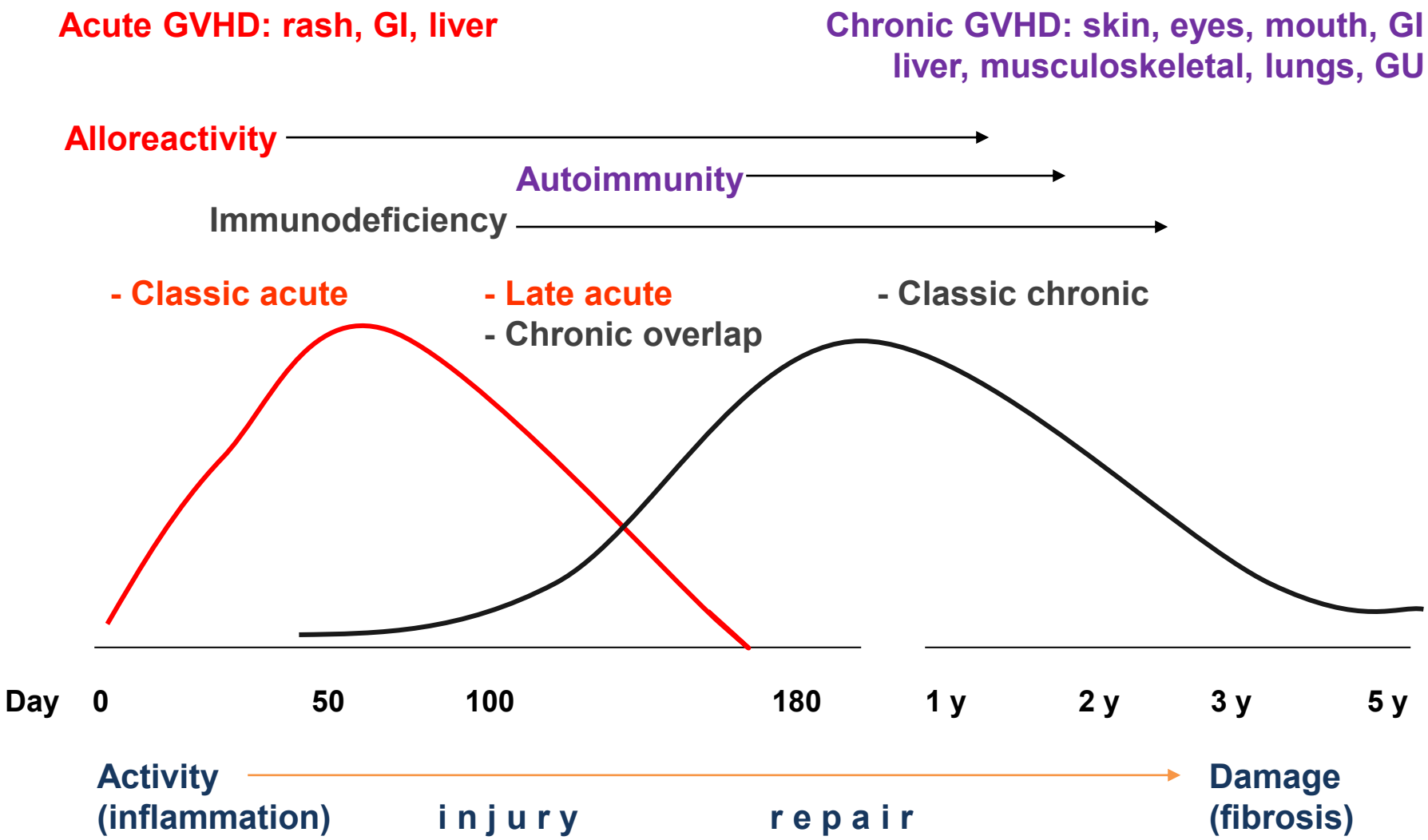
54511 Vandoeuvre les Nancy

Schéma simplifié de la physiopathologie de la GVH aigue



Alloréactivité: de la GVH aigue à la GVH chronique



Première ligne de traitement de la GvH aigue

- Cortidoides (2 mg/kg/jour) demeurent le traitement de reference de la GVH aigue de grade II-IV GvHD
- Aucune étude d'association à un autre traitement immunosupresseur n'a montré de supériorité aux corticoides (MMF, anti-R-IL2, JAK inhibiteur …)

- Taux de réponse aux cortidoides à J28 variables:meilleurs taux de réponse(CR+PR) chez :
  - **grade II (60-80%) que grade III/IV (<50%)**
  - patients avec un organe attaint versus 2 ou 3
  - Donneur HLA compatible
  - Prophylaxie de la GVH: ATG et Endoxan post-greffe

- 50 à 60% des patients GVH aigue grade II-IV sont cortico-résistants ou dépendants

- 40 to 50% des GVH aigue grade II-IV aGVHD sont toujours sous immunosupresseurs à 1 an post-greffe

MacMillan et al., BBMT 2015; 21:761-767
Mielcarek et al. Haematologica 2015; 100(6): 842-848

Quel serait le traitement ideal en première ligne de traitement de la GVH aigue

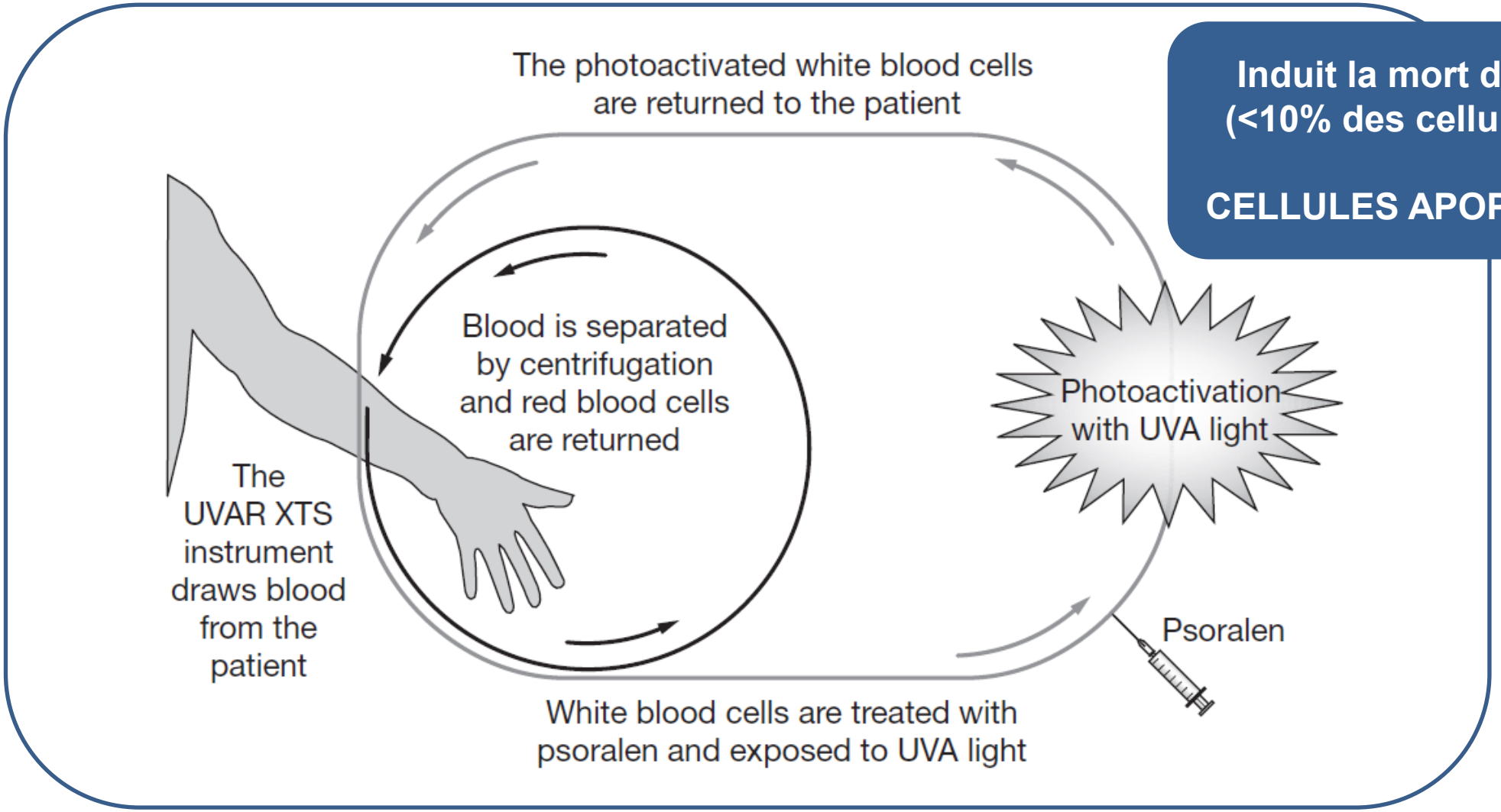
- Mieux controller l'alloréactivité :
  - Améliorer la durée de réponse aux corticoides
  - limiter le development de GVH chronique

- Limiter l'exposition aux corticoides et leurs effets secondaires:
  - Infections
  - Diabète
  - Dysmetabolisme and maladies cardiovasculaires
  - Complications osseuses (osteoporose, osteonecrose)

- Préserver la reconstitution immunitaire lymphoide et l'effet GVL

⇨ Stratégies immunomodulatrices plutôt que immunosuppressives/déplétion lymphocytaire

Photopherese extra-corporelle: PCEC

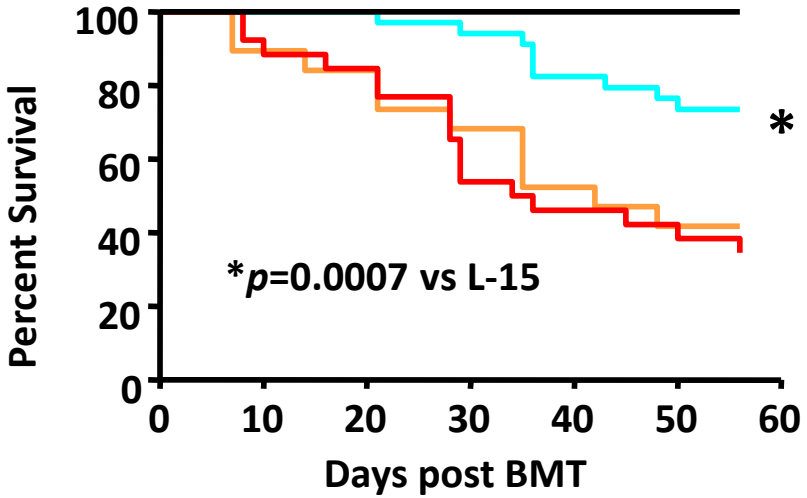


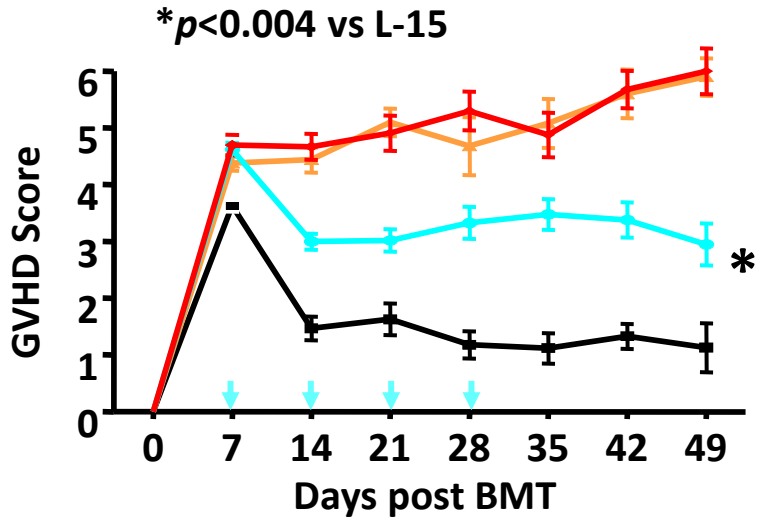
Induit la mort des LT et CPAs (<10% des cellules sanguines)

CELLULES APOPTOTIQUES +++

Marshall, Nature Clinical Practice Oncology 2006; 3(6):302-314

Modèles murins: réduction de la GVH par administration de cellules du donneur ou receveur traitées par PCEC





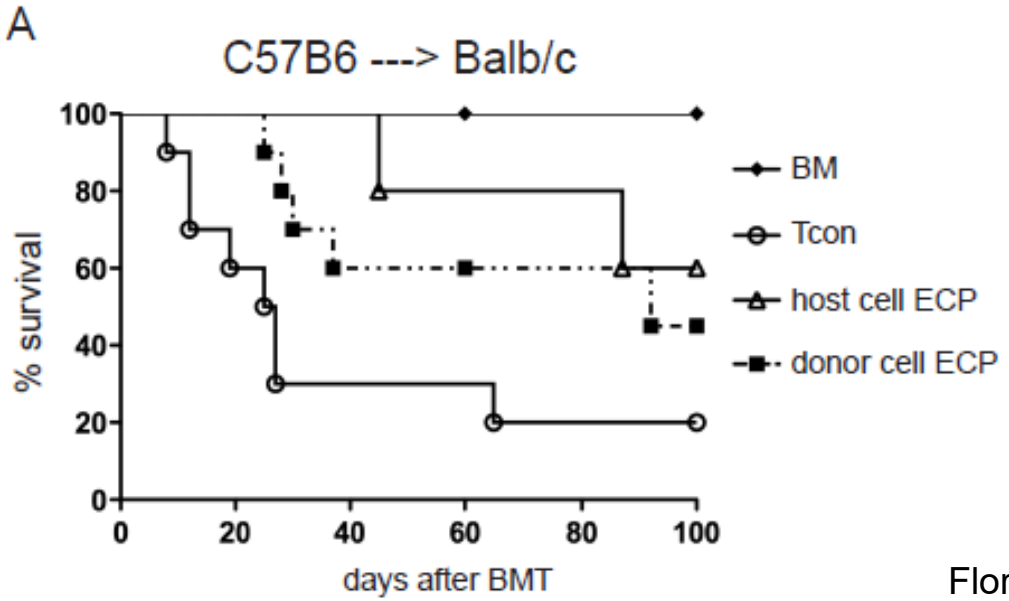
ALLO + Diluent (n=26)

SYN +/- ECP (n=15)

ALLO ECP treated SPC (n=34)

ALLO non ECP treated SPC (n=19)

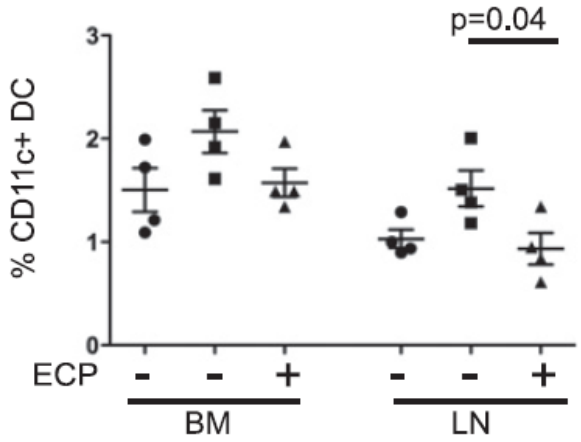
Gatza et al., Blood 2008



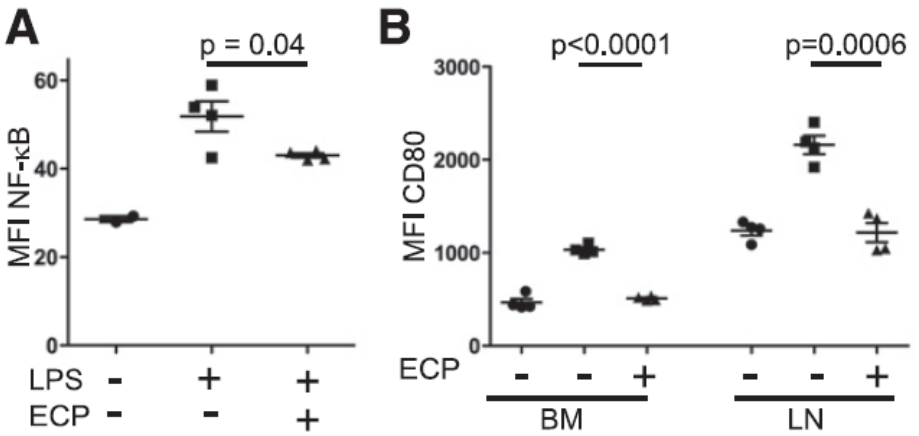
Florek et al., Blood 2014, 124(11): 1832-42

Mecanismes d'action de la PCEC dans les modèles murins

↘ CPAs

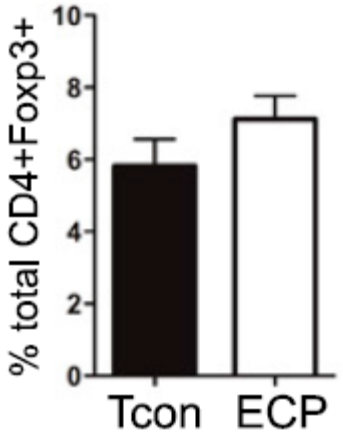


↘ Activation des CPAs

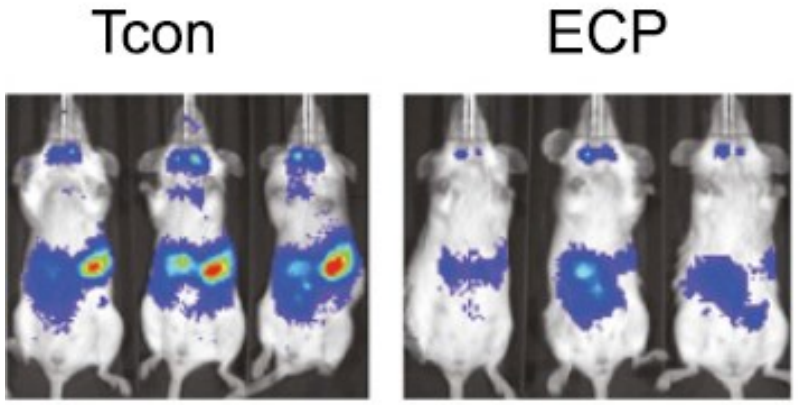


↗ Tregs

IL-10 dependant

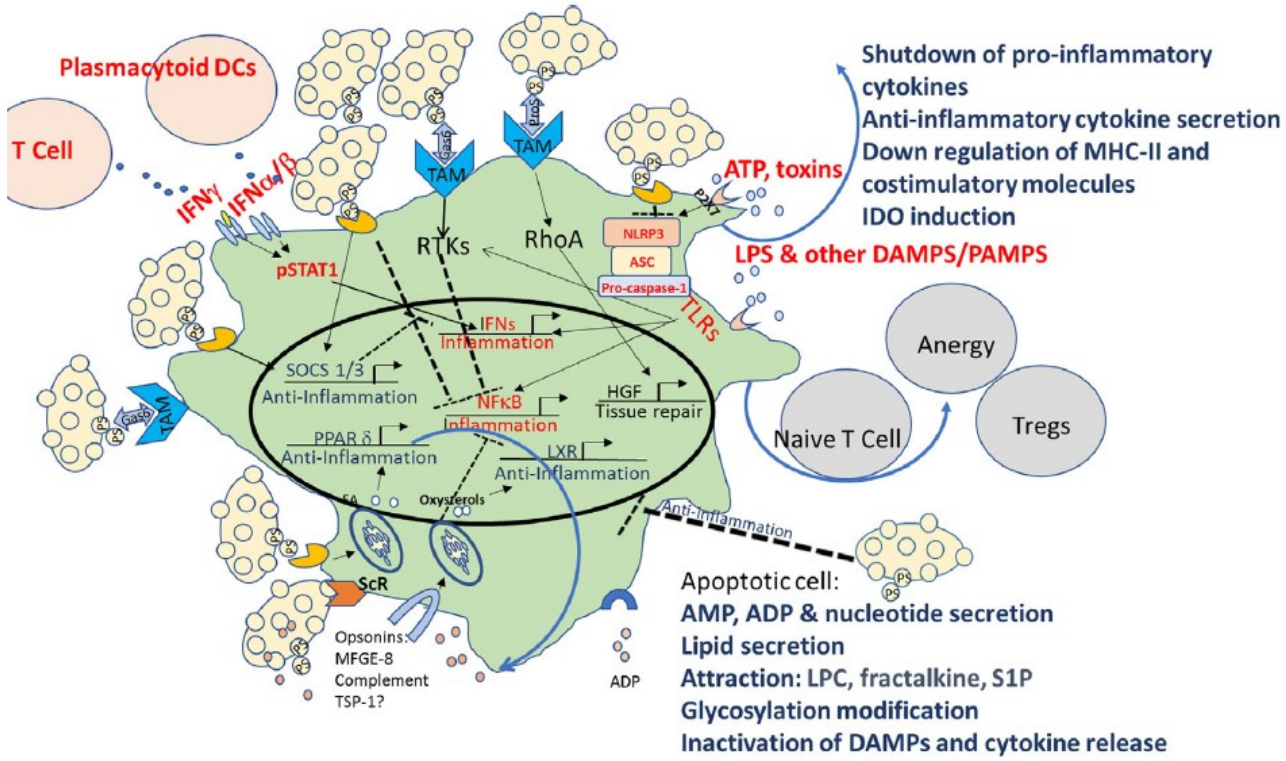


↘ Proliferation/expansion des LT du donneur (Thymus, rate, foie, TD)

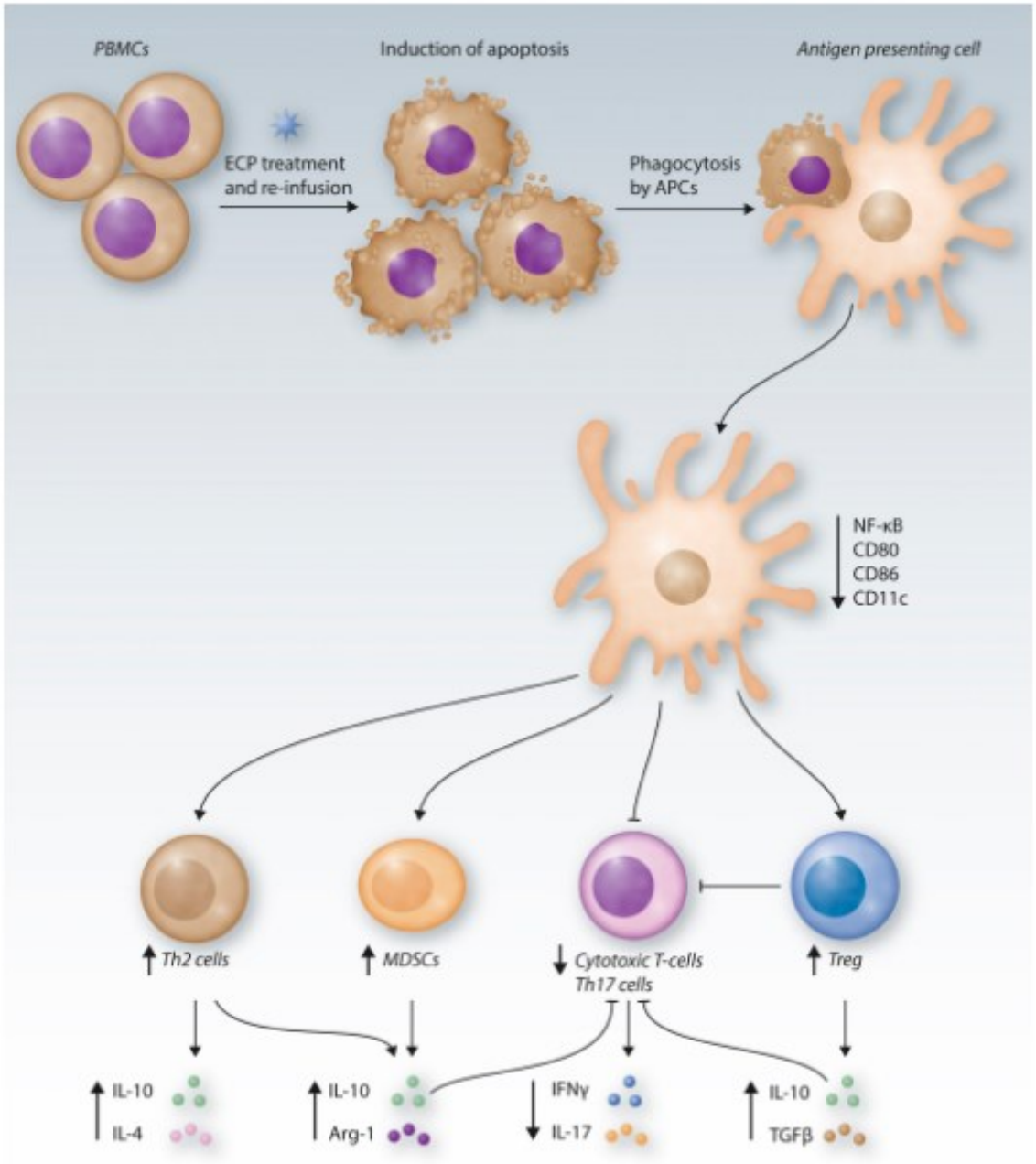


Florek et al., Blood 2014, 124(11): 1832-42

Mecanismes d'action de la PCEC



Trahtemberg et al., Frontiers in immunology 2017; 8: 1356

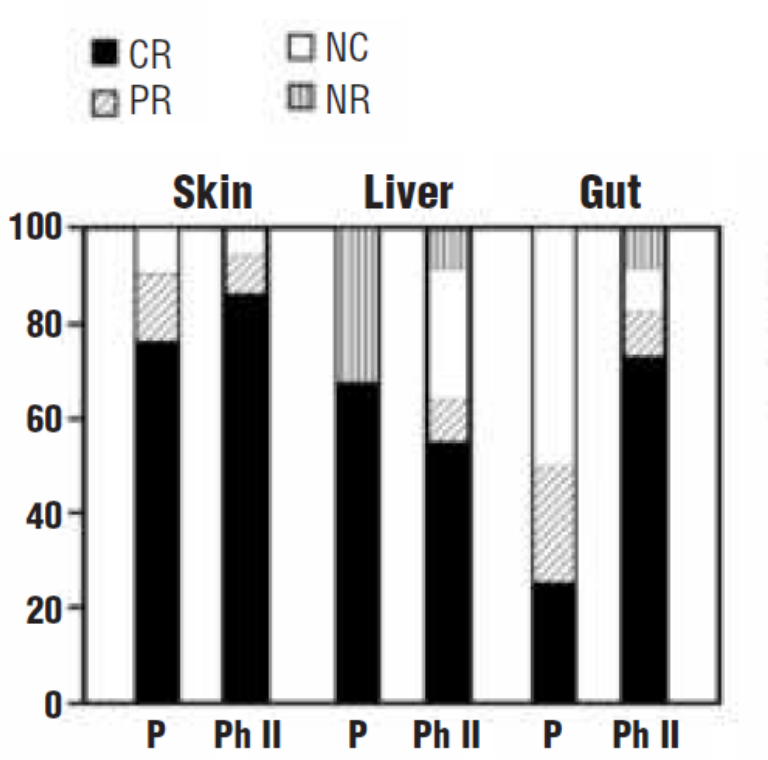


Braun et al., Hemasphere 2021

PCEC en 2eme ligne de traitement de la GVH aigue

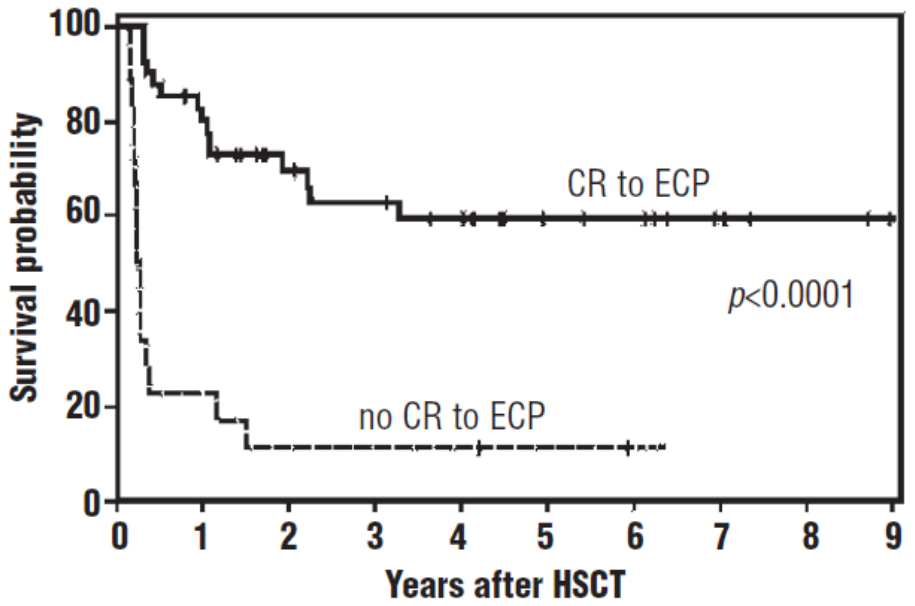
Première étude de PCEC dans la GVH aigue cortico-R

- **PCEC :**
  - 2 à 3 séances par semaine pendant 4 à 6 semaines
  - Puis toutes les deux semaines
- **Schémas d'arrêt PCEC**
  - après avoir atteint une réponse maximale dans 2 centres (Vienne, Nottingham)
  - ou progressivement réduit dans 1 centre (Nashville)



	All	*Steroid-Refractory**	*Steroid-Dependent°*
Best response after month (median)	1.3	1.4	1.4
Range	0.5-6	0.5-6	0.5-4.5
Med.days to discontinuation of steroids after the start of ECP	55	51	65
Range	17-284	17-284	18-156

Overall survival

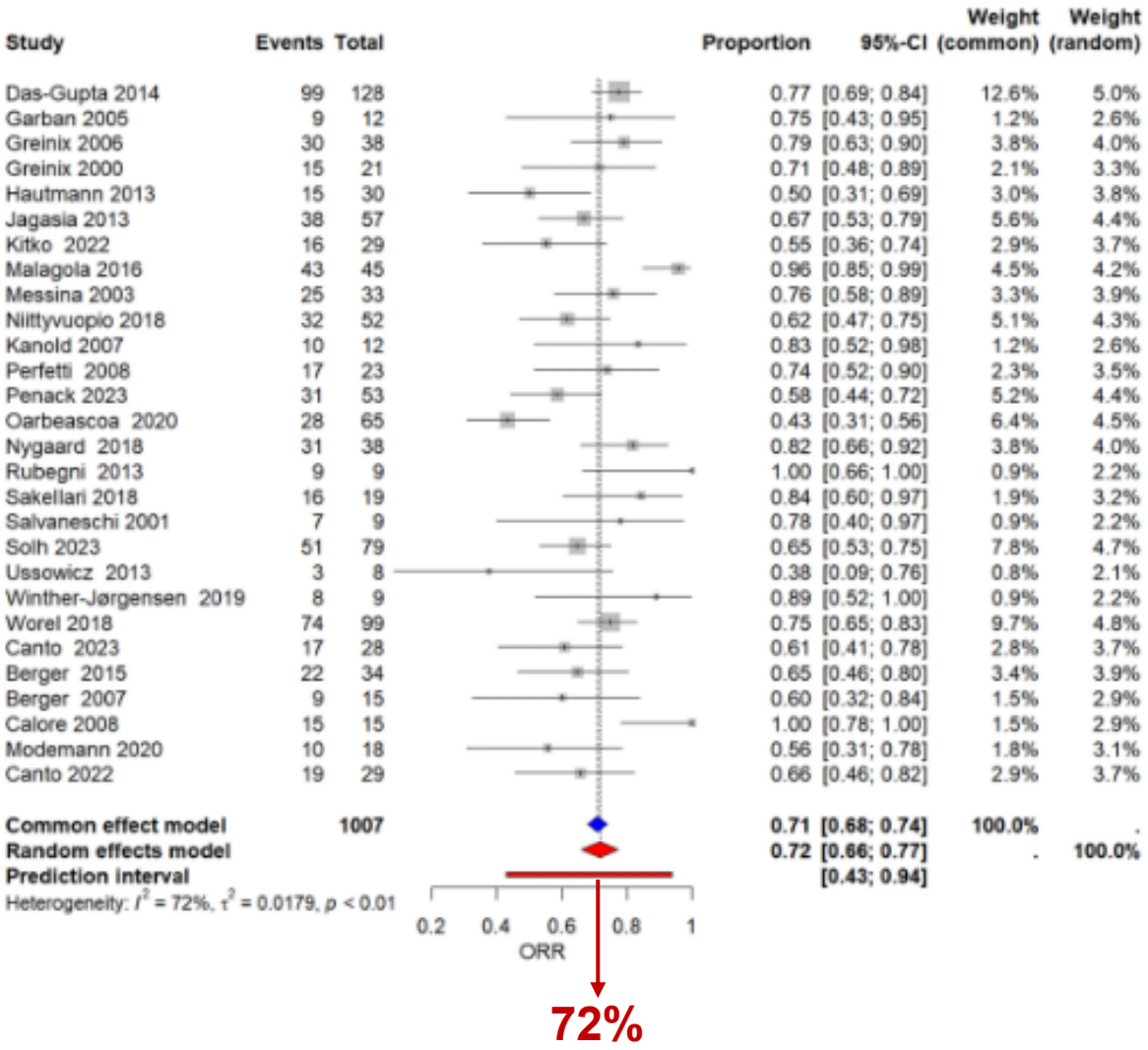


Greinix et al., Haematologica 2006; 91:405-408

Dernière métanalyse PCEC dans la GVH aigue cortico-R/D

29 études, 1249 patients

Taux de réponse : CR+PR

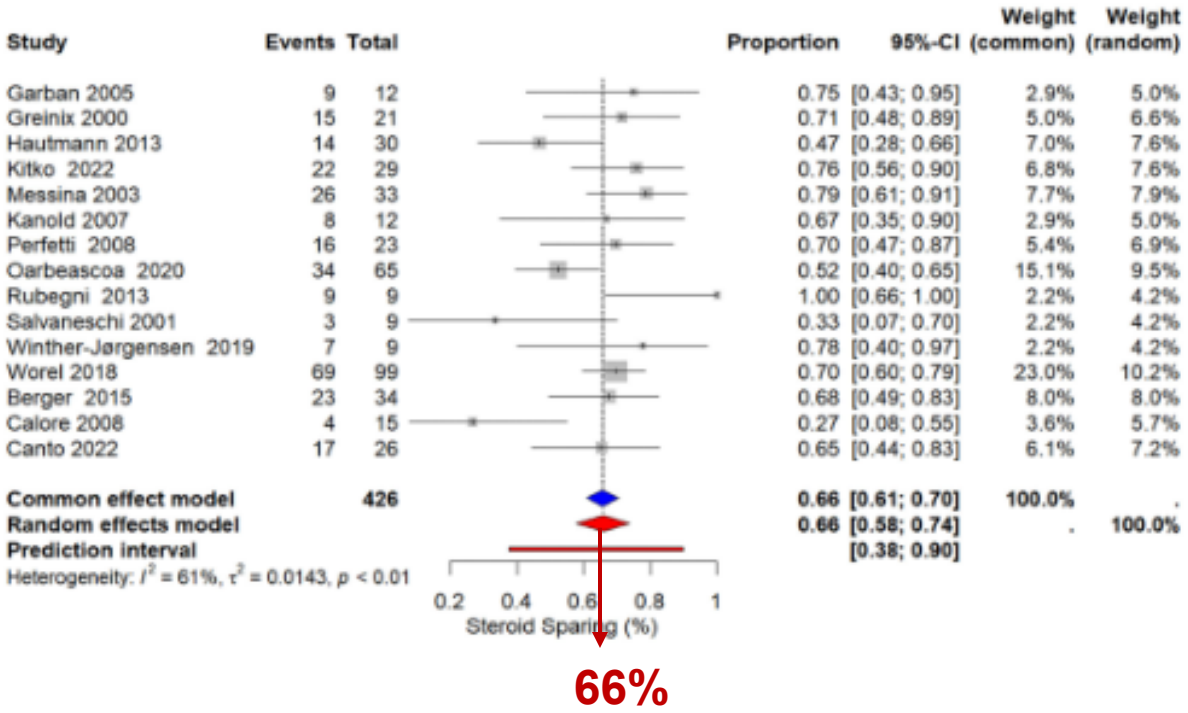


Study	Events	Total	Proportion	95%-CI	Weight (common)	Weight (random)
Das-Gupta 2014	99	128	0.77	[0.69; 0.84]	12.6%	5.0%
Garban 2005	9	12	0.75	[0.43; 0.95]	1.2%	2.6%
Greinix 2006	30	38	0.79	[0.63; 0.90]	3.8%	4.0%
Greinix 2000	15	21	0.71	[0.48; 0.89]	2.1%	3.3%
Hautmann 2013	15	30	0.50	[0.31; 0.69]	3.0%	3.8%
Jagasia 2013	38	57	0.67	[0.53; 0.79]	5.6%	4.4%
Kitko 2022	16	29	0.55	[0.36; 0.74]	2.9%	3.7%
Malagola 2016	43	45	0.96	[0.85; 0.99]	4.5%	4.2%
Messina 2003	25	33	0.76	[0.58; 0.89]	3.3%	3.9%
Niittyvuopio 2018	32	52	0.62	[0.47; 0.75]	5.1%	4.3%
Kanold 2007	10	12	0.83	[0.52; 0.98]	1.2%	2.6%
Perfetti 2008	17	23	0.74	[0.52; 0.90]	2.3%	3.5%
Penack 2023	31	53	0.58	[0.44; 0.72]	5.2%	4.4%
Oarbeascoa 2020	28	65	0.43	[0.31; 0.56]	6.4%	4.5%
Nygaard 2018	31	38	0.82	[0.66; 0.92]	3.8%	4.0%
Rubegni 2013	9	9	1.00	[0.66; 1.00]	0.9%	2.2%
Sakellari 2018	16	19	0.84	[0.60; 0.97]	1.9%	3.2%
Salvaneschi 2001	7	9	0.78	[0.40; 0.97]	0.9%	2.2%
Solh 2023	51	79	0.65	[0.53; 0.75]	7.8%	4.7%
Ussowicz 2013	3	8	0.38	[0.09; 0.76]	0.8%	2.1%
Winther-Jørgensen 2019	8	9	0.89	[0.52; 1.00]	0.9%	2.2%
Worel 2018	74	99	0.75	[0.65; 0.83]	9.7%	4.8%
Canto 2023	17	28	0.61	[0.41; 0.78]	2.8%	3.7%
Berger 2015	22	34	0.65	[0.46; 0.80]	3.4%	3.9%
Berger 2007	9	15	0.60	[0.32; 0.84]	1.5%	2.9%
Calore 2008	15	15	1.00	[0.78; 1.00]	1.5%	2.9%
Modemann 2020	10	18	0.56	[0.31; 0.78]	1.8%	3.1%
Canto 2022	19	29	0.66	[0.46; 0.82]	2.9%	3.7%
Common effect model		**1007**	**0.71**	**[0.68; 0.74]**	**100.0%**	.
Random effects model			**0.72**	**[0.66; 0.77]**	.	**100.0%**
Prediction interval				**[0.43; 0.94]**		

Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.0179$, $p < 0.01$

72%

Taux d'épargne cortisonique



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Greinix 2000	15	21	0.71	[0.48; 0.89]	5.0%	6.6%
Hautmann 2013	14	30	0.47	[0.28; 0.66]	7.0%	7.6%
Kitko 2022	22	29	0.76	[0.56; 0.90]	6.8%	7.6%
Messina 2003	26	33	0.79	[0.61; 0.91]	7.7%	7.9%
Kanold 2007	8	12	0.67	[0.35; 0.90]	2.9%	5.0%
Perfetti 2008	16	23	0.70	[0.47; 0.87]	5.4%	6.9%
Oarbeascoa 2020	34	65	0.52	[0.40; 0.65]	15.1%	9.5%
Rubegni 2013	9	9	1.00	[0.66; 1.00]	2.2%	4.2%
Salvaneschi 2001	3	9	0.33	[0.07; 0.70]	2.2%	4.2%
Winther-Jørgensen 2019	7	9	0.78	[0.40; 0.97]	2.2%	4.2%
Worel 2018	69	99	0.70	[0.60; 0.79]	23.0%	10.2%
Berger 2015	23	34	0.68	[0.49; 0.83]	8.0%	8.0%
Calore 2008	4	15	0.27	[0.08; 0.55]	3.6%	5.7%
Canto 2022	17	26	0.65	[0.44; 0.83]	6.1%	7.2%
Common effect model		**426**	**0.66**	**[0.61; 0.70]**	**100.0%**	.
Random effects model			**0.66**	**[0.58; 0.74]**	.	**100.0%**
Prediction interval				**[0.38; 0.90]**		

Heterogeneity: $I^2 = 61\%$, $\tau^2 = 0.0143$, $p < 0.01$

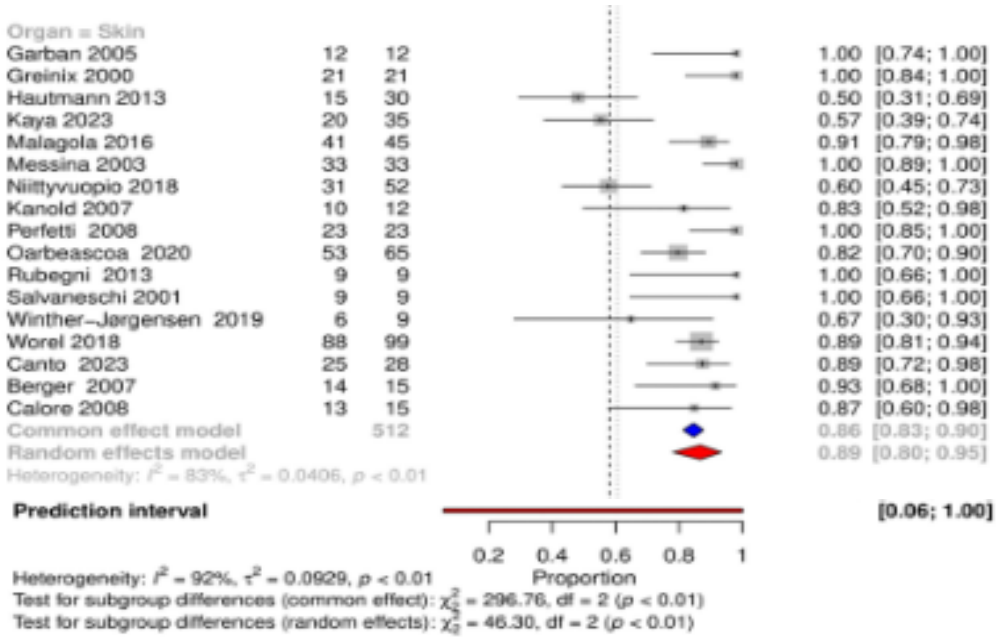
66%

Muhanna et al; Frontiers Immunol 2025

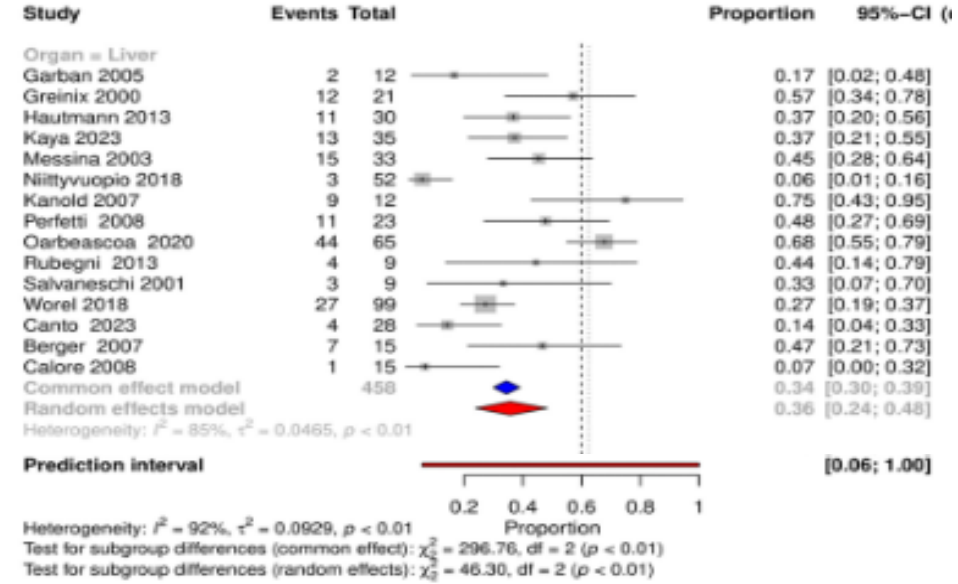
PCEC : Taux de réponse par organe de GVH aigue

29 études, 1249 patients

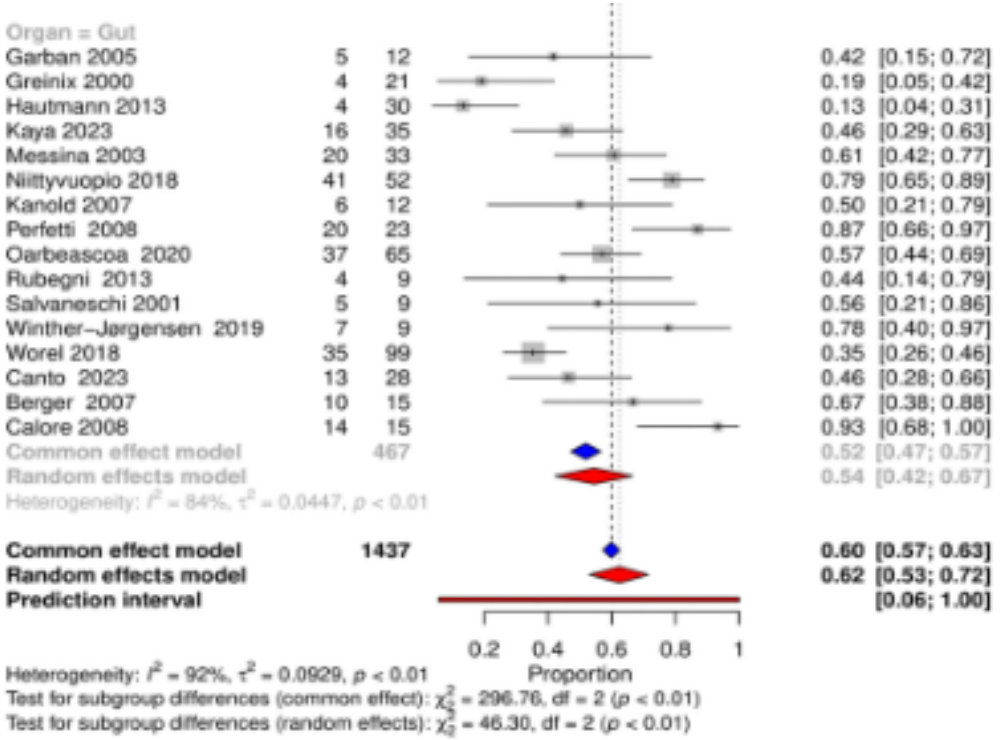
PEAU



FOIE



TUBE DIGESTIF



Meilleure efficacité dans grade II que III-IV dans toutes les études (HR<0.5)

Muhanna et al; Frontiers Immunol 2025

Comparaison PCEC vs JAKAVI dans la GVH aigue cortico-R/D

Variable	Level	ECP (n=53)	Ruxo (n=40)
Type of steroid	Prednisone	25 (47.1%)	13 (32.5%)
	Methylprednisone	28 (42.9%)	29 (67.5%)
Steroid initial dose (mg/kg/day)	median (min-max) [IQR]	2 (0.5-2.5) [1-2]	1 (0.3-2) [1-2]
	missing	1	0
Time between start and end of steroids (days)	median (min-max) [IQR]	88 (3-1213) [50.2-171.8]	49.5 (3-293) [18-109.5]
	missing	9	2
Other systemic drugs or strategies used to treat aGvHD (other than steroids)	No other drugs/strategies	23 (43.4%)	17 (42.5%)
	CNI	22 (41.5%)	15 (37.5%)
	MMF	5 (9.4%)	4 (10%)
	Sirolimus	5 (9.4%)	5 (12,5%)
	Others #	5 (9.4%)	5 (12,5%)
Acute GvHD overall grade (at start of SR treatment)	Grade II	20 (37.7%)	9 (22.5%)
	Grade III	19 (35.8%)	13 (32.5%)
	Grade IV	14 (26.4%)	18 (45%)
Skin aGvHD grade (at start of SR treatment)	0	19 (36.5%)	12 (31.6%)
	1	4 (7.7%)	3 (7.9%)
	2	10 (19.2%)	6 (15.8%)
	3	19 (36.5%)	12 (31.6%)
	4	0 (0%)	5 (13.2%)
	missing	1	2

Variable	Level	ECP (n=53)	Ruxo (n=40)
Liver aGvHD grade (at start of SR treatment)	0	34 (66.7%)	23 (59%)
	1	7 (13.7%)	2 (5.1%)
	2	4 (7.8%)	4 (10.3%)
	3	5 (9.8%)	6 (15.4%)
	4	1 (2%)	4 (10.3%)
	missing	2	1
Lower GI aGvHD grade (at start of SR treatment)	0	22 (43.1%)	8 (21.1%)
	1	4 (7.8%)	3 (7.9%)
	2	4 (7.8%)	3 (7.9%)
	3	8 (15.7%)	10 (26.3%)
	4	13 (25.5%)	14 (36.8%)
	missing	2	2
Upper GI aGvHD grade (at start of SR treatment)	0	29 (58%)	27 (73%)
	1	21 (42%)	10 (27%)
	missing	3	3

Penack et al; Frontiers Immunol 2023

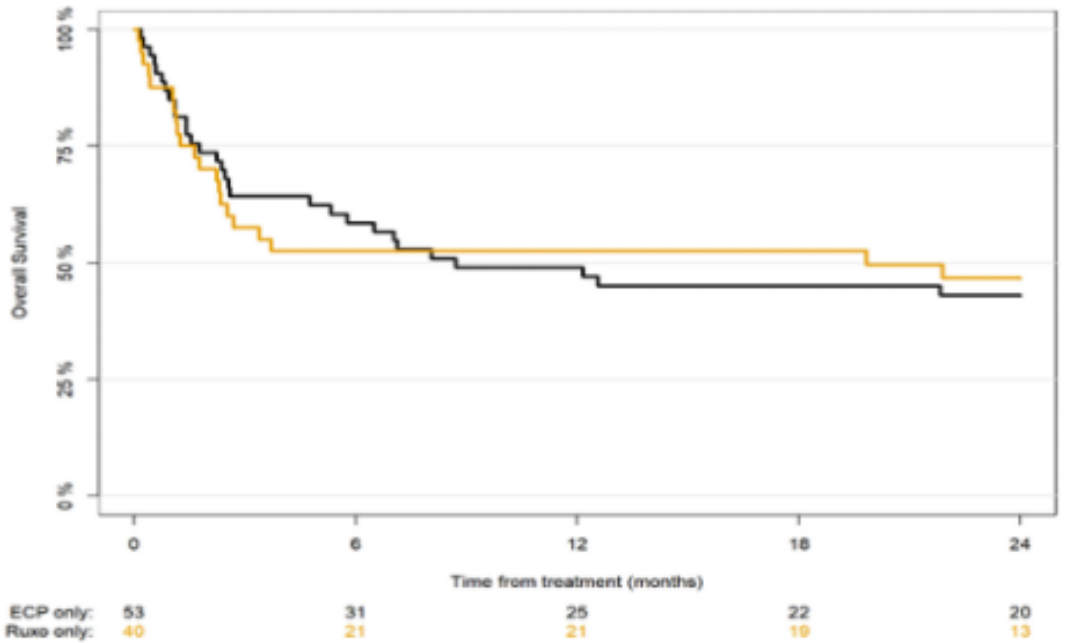
Comparaison PCEC vs JAKAVI dans la GVH aigue cortico-R/D

TABLE 3 Multivarate analyses.

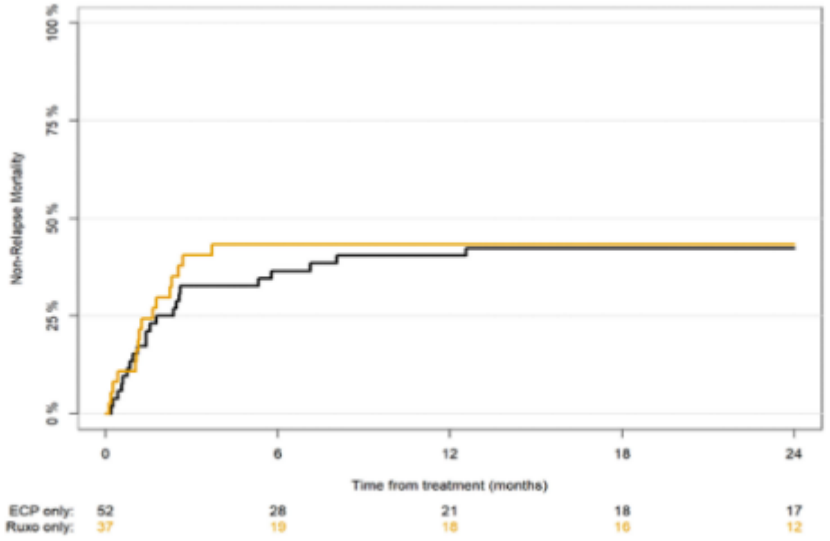
Variable	Hazard ratio/Odd ratio [95% CI]	P
Overall response rate at day +90	1.13 [0.41;3.22]	0.81
Overall survival	0.73 [0.42-1.29]	0.28
Progression-free survival	0.76 [0.43-1.35]	0.35
Relapse incidence	0.95 [0.33-2.77]	0.93
Non-relapse mortality	0.72 [0.36-1.42]	0.34

Results are given for the Ruxolitinib group with the ECP group being the reference.

Survie globale



Mortalité non liée à la rechute (NRM)

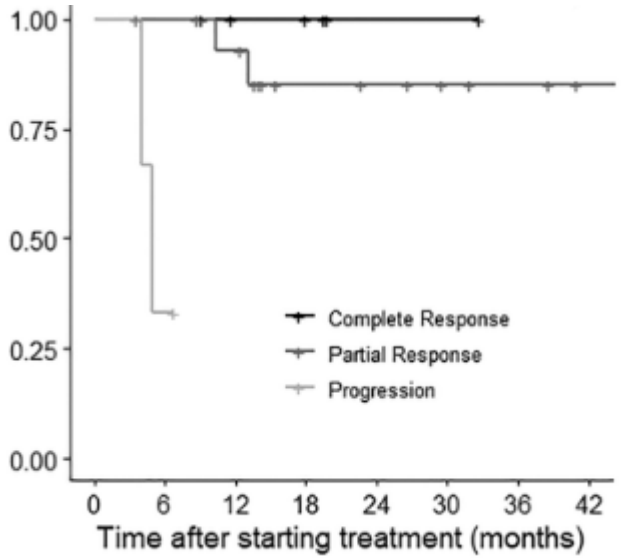


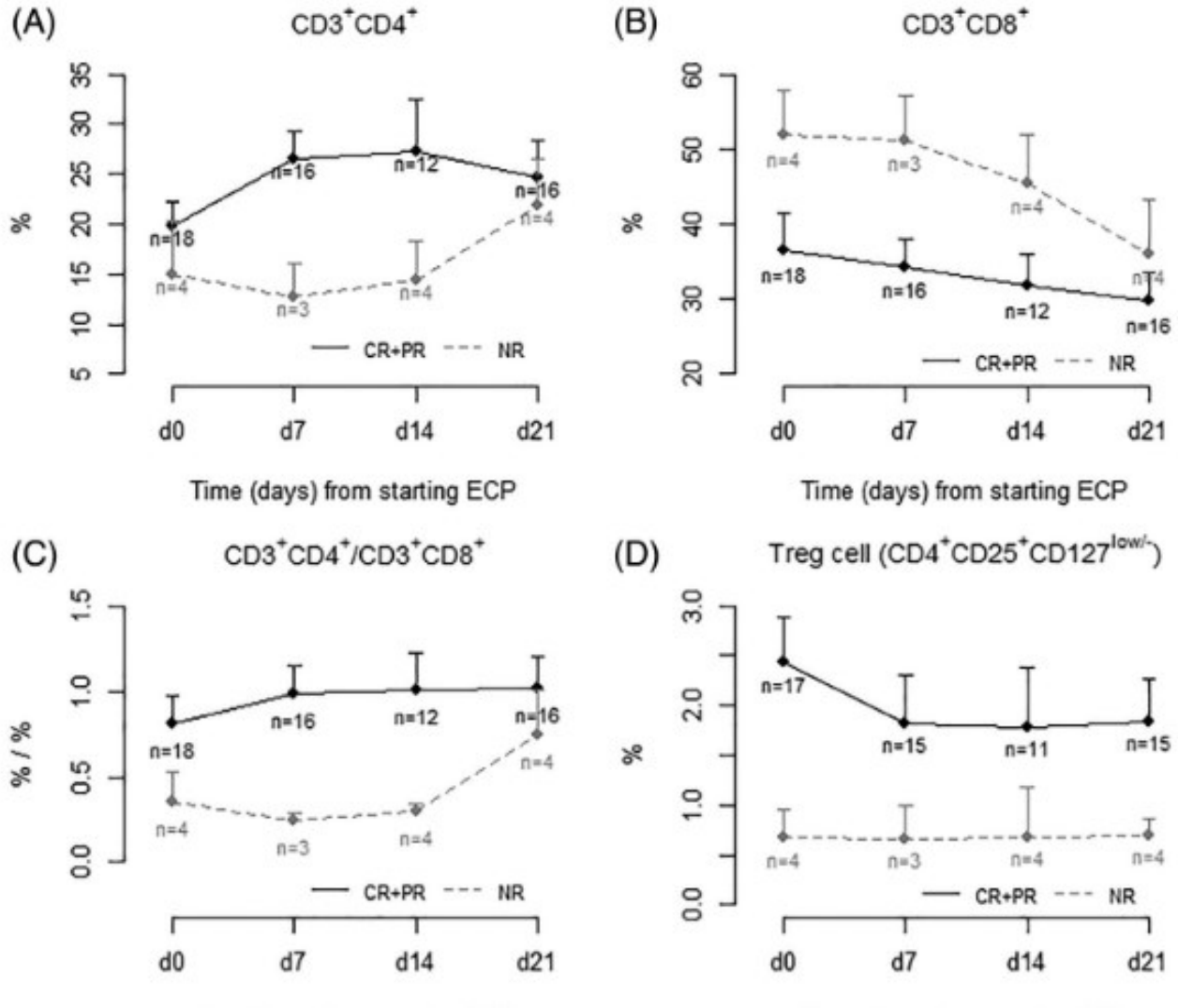
Penack et al; Frontiers Immunol 2023

Effets de la PCEC sur la reconstitution immunitaire

- ✓ GVH aigue 2eme ligne
- ✓ 37 patients adultes

Survie globale



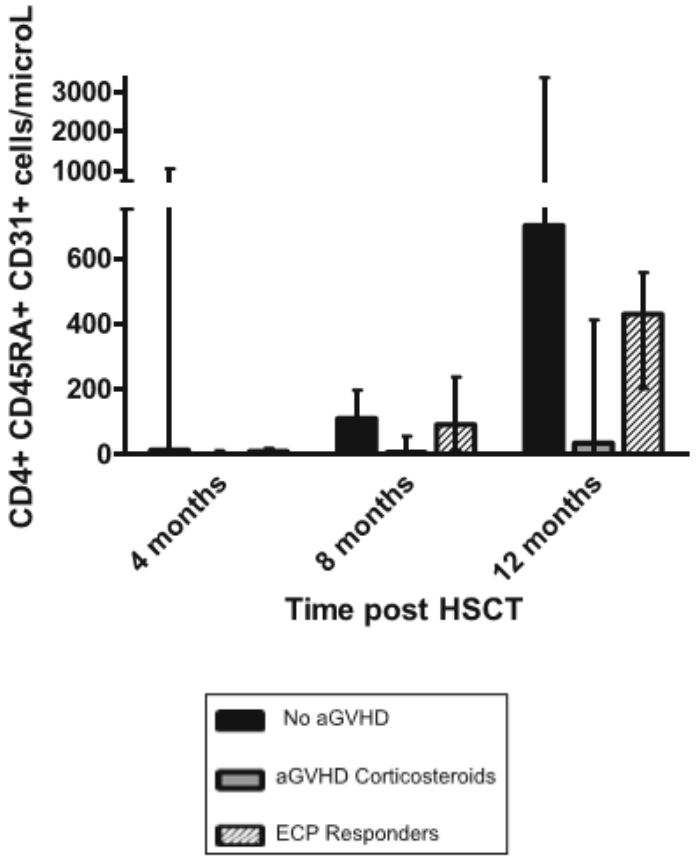


Amat et al; Journal of Clinical apheresis 2020

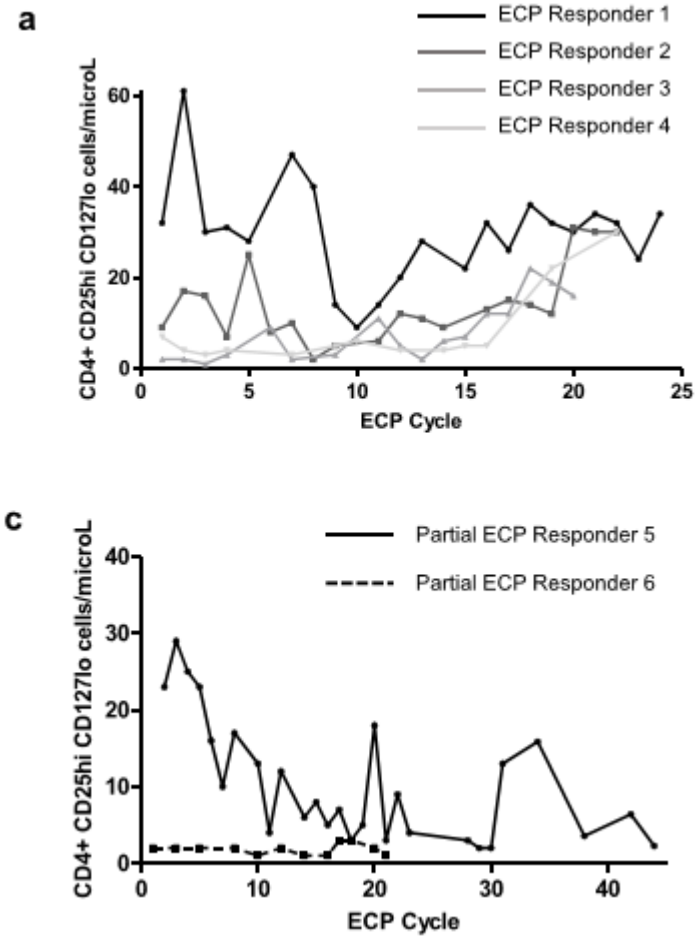
Effets de la PCEC sur la reconstitution immunitaire

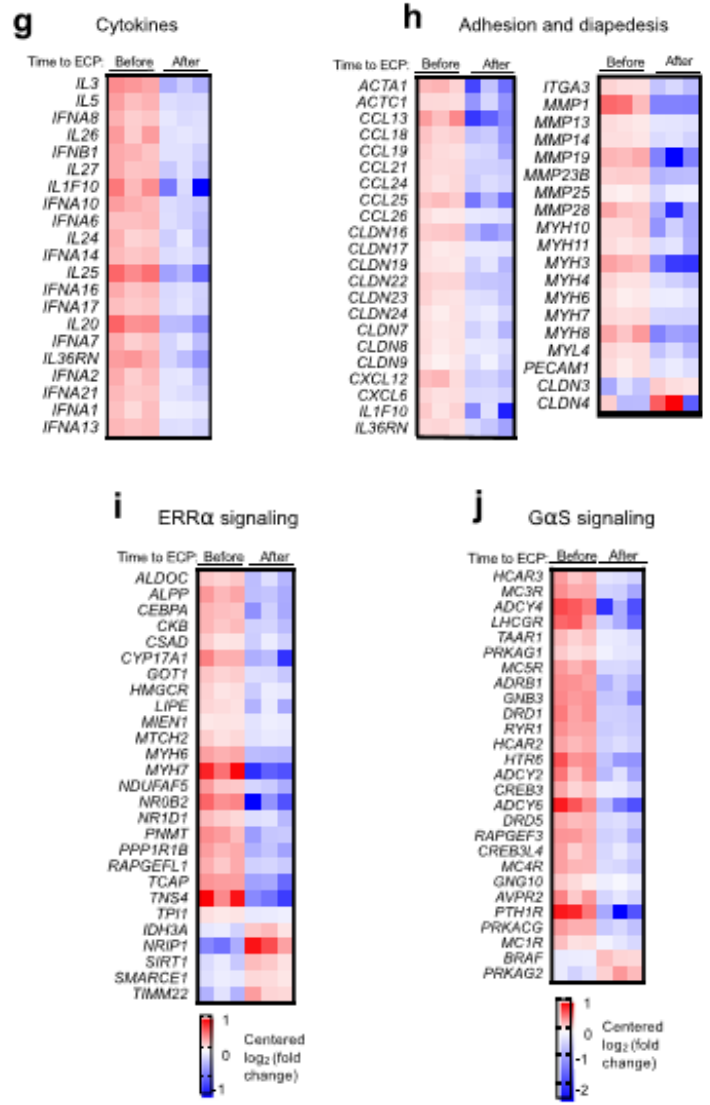
✓ **Etude pédiatrique**

T émigrants thymiques



T régulateurs





Flinn et al; Journal of Clinical Immunol 2021

Indication de la PCEC dans la GVH aigue cortico-R/D ?

- **ASBMT**
  - ECP= one possible second line treatment in steroid refractory aGVHD
  - 3 ECP /week (week 1), 2/week (week 2-12) and then 2 ECP/month

Martin et al. *Biol Blood Marrow Transplant. 2012 ; 18(8): 1150–1163*

- **Italian GITMO**
  - Recommendation of ECP in aGVHD not responding to steroids and calcineurin inhibitor
  - In particular in skin GVHD

Pierelli et al. Transfusion 2013, 5340–235, 232

- **European Dermatology Forum (EDF)**
  - ECP is recommended in aGVHD refractory to steroids (2 mg/kg)
  - 2 to 3 ECP /week until CR

Knobler et al. J Eur Acad Dermatol Venereol 2014, 28, 1–37

- **UK and Scandinavian Photopheresis Expert group (consensus statement)**
  - ECP is recommended in steroid refractory, or dependant or intolerant patients
  - 2 ECP/week for at least 8 weeks in grade II (stop at CR + steroids < 20 mg)
  - 3 ECP/week for at least 4 weeks in grade III-IV before reduction of dose (at least 2-3 months in total)

Alfred et al. Br J Haematol 2017, 177, 287–310

JAKAVI à depuis obtenu l'AMM en 2eme ligne de traitement de la GVH aigue
PCEC : option thérapeutique en cas d'intolérance au JAKAVI, GVH aigue cutanée +++
Association JAKAVI + PCEC ?

PCEC en 1ere ligne de traitement de la GVH aigue ?

Randomized Phase II Trial of Extracorporeal Phototherapy and Steroids vs. Steroids-Alone For Newly Diagnosed Acute GVHD

Bone Marrow Transplant. 2021 June ; 56(6): 1316–1324.

- Patients with aGVHD and who received <72 hours of steroids were randomized to receive:
  - **2 mg/kg methylprednisolone (MP) alone (n=30)**
  - **Or 2 mg/kg methylprednisolone (MP) with ECP (n=51)**

- ECP schedule was:
  - days 1-14 : 8 sessions (4/week)
  - days 15-28 : 6 sessions (3/week)
  - days 29-56 : 8 sessions (2/week)

- Primary endpoint = **treatment success at day 56** post-randomization:
  - alive in remission +
  - achieving aGVHD response without additional therapy +
  - < 1 mg/kg of MP at day 28 and < 0.5 mg/kg on day 56

Randomized Phase II Trial of Extracorporeal Phototherapy and Steroids vs. Steroids-Alone For Newly Diagnosed Acute GVHD

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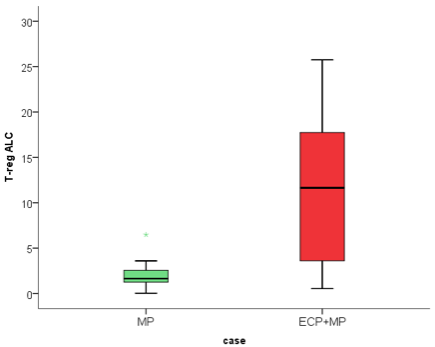
Characteristic	Treatment Arm		p-value
	ECP + Steroids	Steroids-Alone	
	N=51	N=30	
Acute GVHD Grade at Enrollment, N (%)			0.37
Grade II	44 (86)	29 (97)	
Grade III	5 (10)	1 (3)	
Grade IV	2 (4)	0	
Organ and Stage at Enrollment, N (%)			
Skin			0.89
Stage 0	7 (14)	4 (13)	
Stage 1–2	5 (10)	3 (10)	
Stage 3	37 (73)	23 (77)	
Stage 4	2 (4)	0	
Upper GI Tract			0.79
Stage 0	39 (77)	24 (80)	
Stage 1	12 (23)	6 (20)	
Lower GI Tract			0.57
Stage 0	38 (74)	25 (84)	
Stage 1–2	11 (22)	4 (13)	
Stage 3–4	2 (4)	1 (3)	
Liver			0.46
Stage 0	47 (92)	26 (87)	
Stage 1	4 (8)	4 (13)	

Day 56 Treatment Success*

Treatment Arm	Risk Group	Success	Failure	Total
Steroids- Alone	**All Patients**	**16 (53%)**	**14 (47%)**	**30**
	Visceral	3 (43%)	4 (57%)	7
	Skin-only	13 (57%)	10 (43%)	23
ECP + Steroids	**All Patients**	**33 (65%)**	**18 (35%)**	**51**
	Visceral	7 (47%)	8 (53%)	15
	Skin-only	26 (72%)	10 (28%)	36

- Significantly higher **treatment success** by adding ECP to steroids on day 56 **in SKIN GVHD only** :
  - **72%** in the ECP + steroid arm
  - Vs **57%** in the steroid arm (p=0.027)
- ECP+MP was associated with:
  - more robust recovery of CD4+ and CD8+ cells
  - significantly higher absolute number of regulatory T-cells (p=0.043)



Protocole **COPAVEHDI**

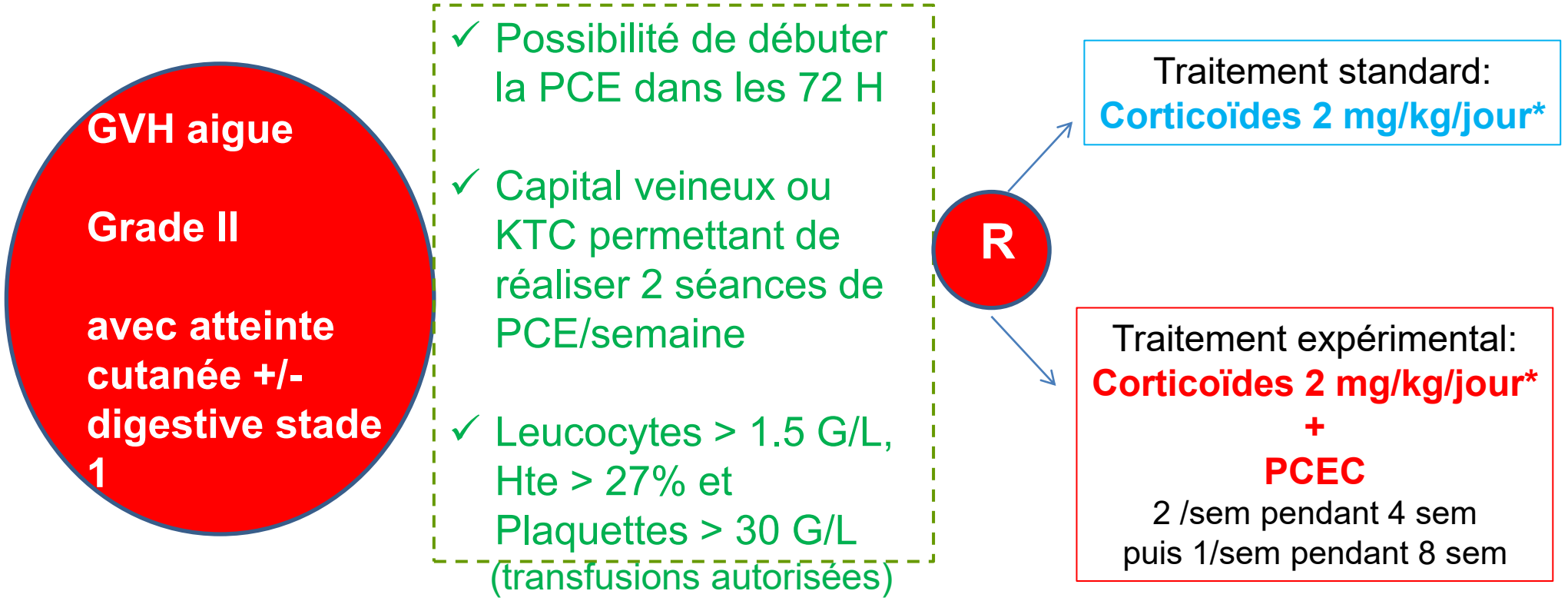
Etude de phase II muticentrique randomisée comparant un traitement standard par corticoides seuls à une association de corticoides et de photochimiothérapie extracorporelle en première ligne thérapeutique en cas de GVH aigue de grade II cutanée survenant après allogreffe de cellules souches hématopoiétiques

Promoteur : CHRU de NANCY

Investigateur coordonnateur : Pr Marie-Thérèse RUBIO – Hématologie

Financement : MALLINCKRODT US

Protocole COPAVEHDI: Etude multicentrique de phase II randomisée



***Décroissance de la corticothérapie rapide protocolisée dans les 2 bras**

COPAVEHDI: primary end point

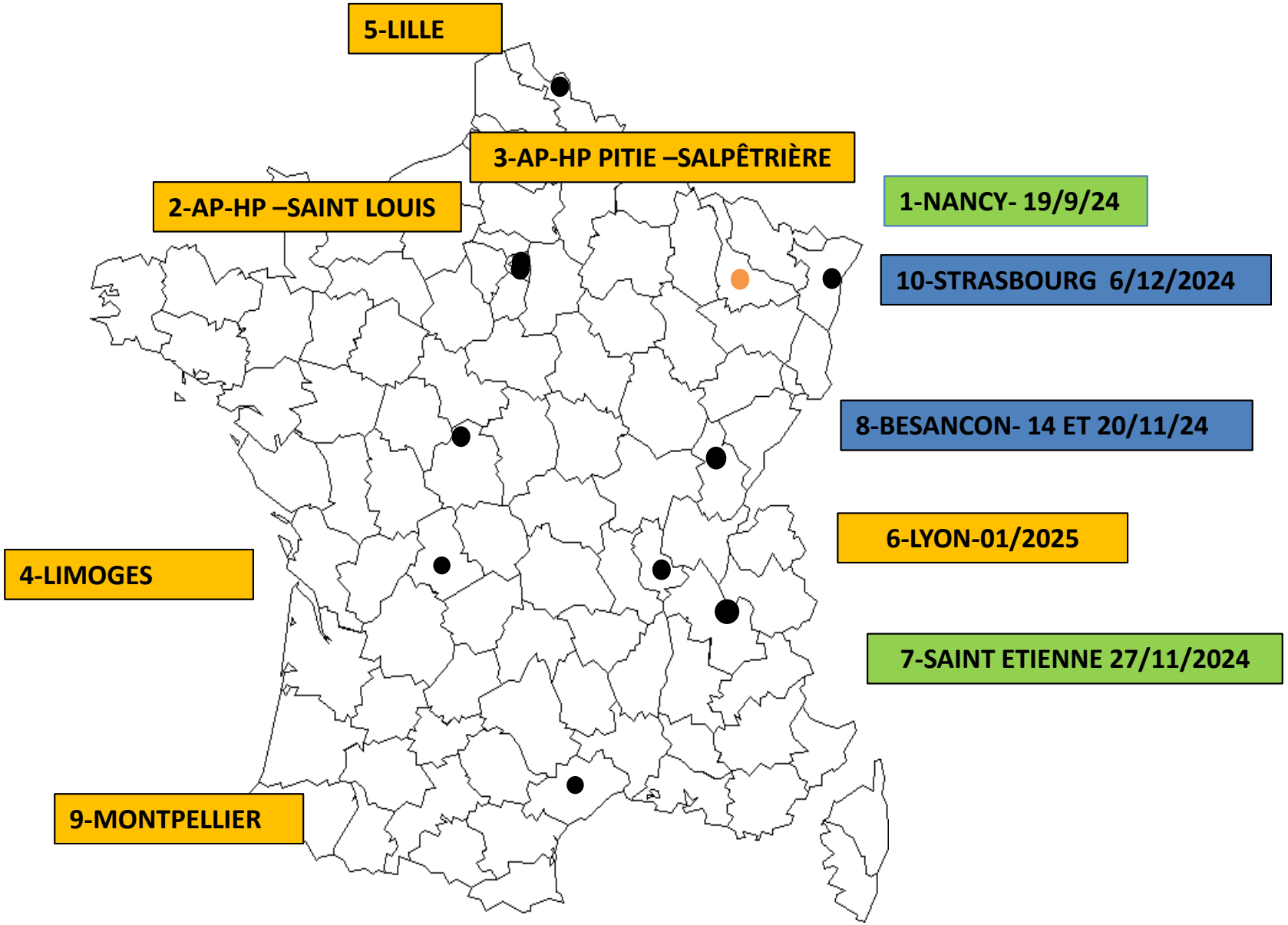
- **Primary end point:**

Estimate and compare the probability of being **free of treatment failure at 6 months** between the experimental group (steroids + ECP) and the control group (steroids alone)

- **Free of treatment failure =**
  - alive +
  - without relapse +
  - without additional line of treatment for aGVHD +
  - without systemic therapy for chronic GVHD

- **Hypothesis:**
  - Addition of ECP will increase FFTF at 6 months of 20% compared to steroids alone *(40-50% to 60-70%)*
  - **120 patients** required (60/arm) with an **intermediate decisional analysis** at **42 patients (21/arm)**.

Etude multicentrique nationale (10 centres)



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- **Hypothesis:**
  - Addition of ECP will increase FFTF at 6 months of 20% compared to steroids alone *(40-50% to 60-70%)*
  - **78 patients** required (39/arm) with an **intermediate decisional analysis** at **40 patients (20/arm)**.

CONCLUSIONS

- ECP seems to be efficient in the treatment of aGVHD
- Better responses in grade I-II in comparison to grade III-IV aGVHD: start as soon as possible
- Better results in skin GVHD
- Seems to be a good candidate to improve the results of aGVHD:
  - allows fast tapering of steroids in steroid refractory/dependant aGVHD
  - good tolerance profile (no increase of infections)
  - low risk of relapse
- The interest of ECP in first line treatment in grade II skin GVHD is currently explored in a prospective randomized study

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