CMV CHEZ LE PATIENT TRANSPLANTÉ D'ORGANE SOLIDE, QUOI DE NEUF EN 2025

DES MALADIES INFECTIEUSES 2025

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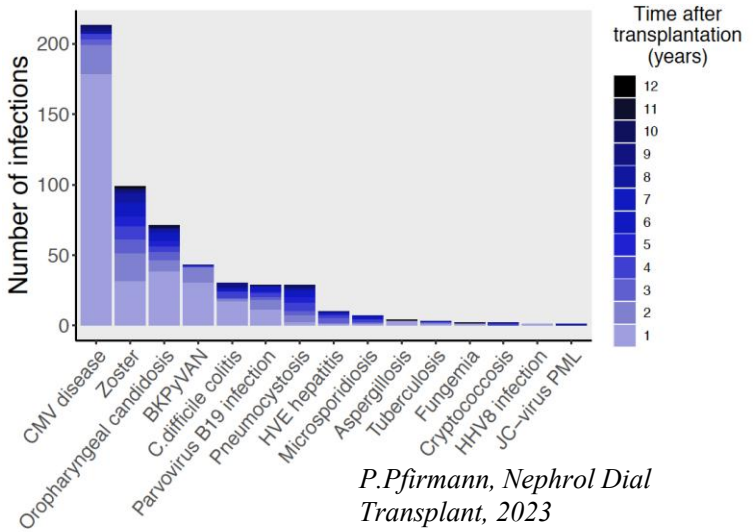
université de BORDEAUX

ImmunoConcEpT
Immunology from Concept and Experiments to Translation

Current epidemiology of CMV disease in kidney transplantation



P.Pfirmann, Nephrol Dial Transplant, 2023

Curative treatment 17.5%

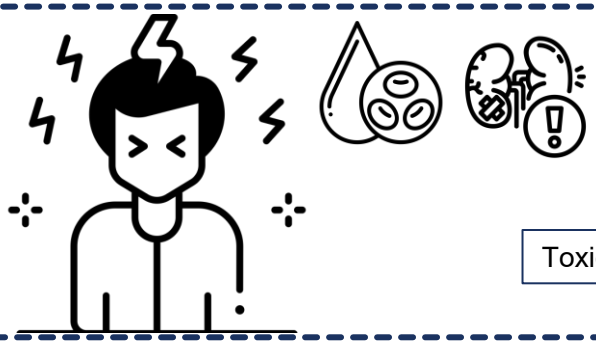
Persistence 28.5%

Clinical relapse: 20.7%

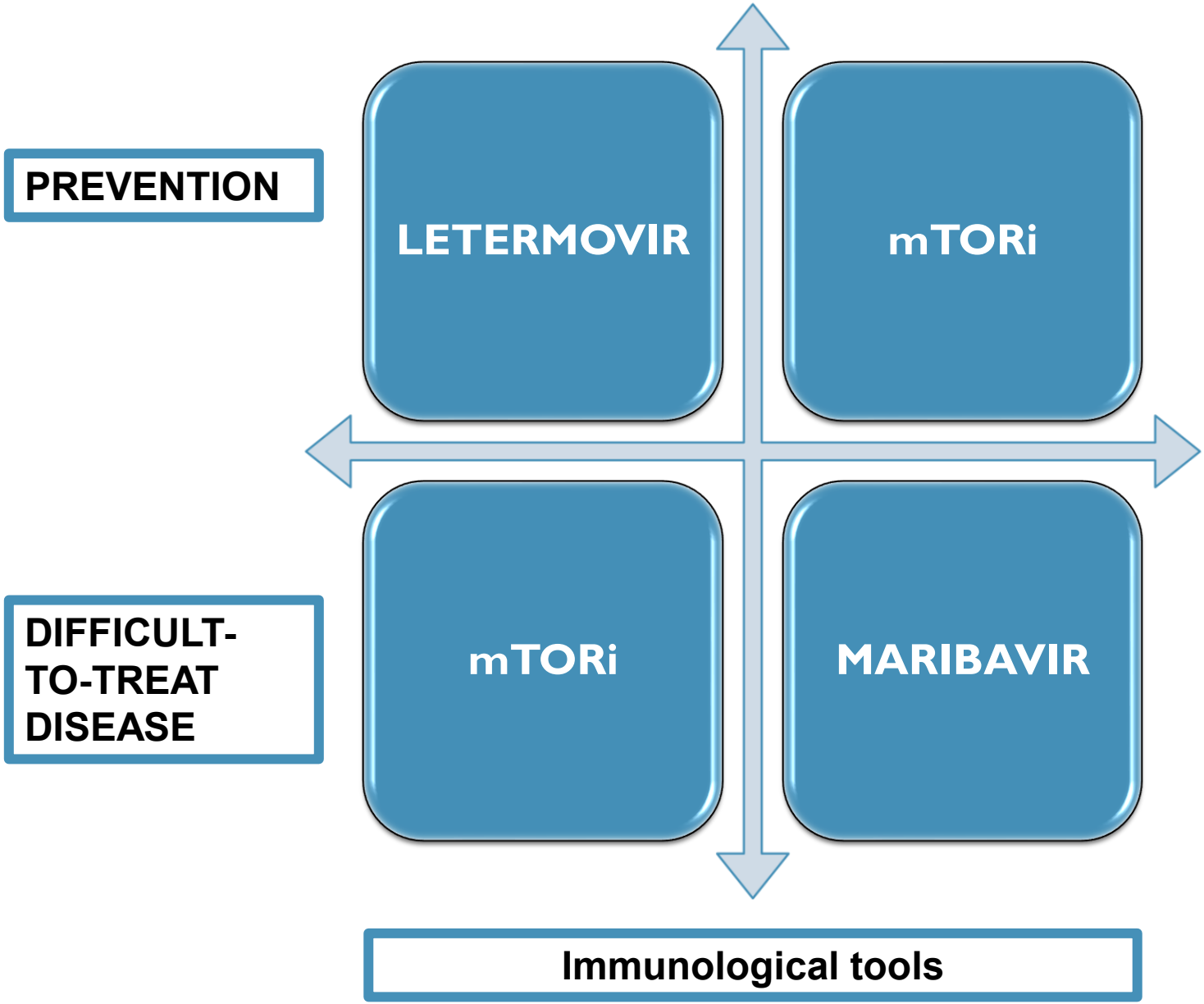
Mutation: 6%

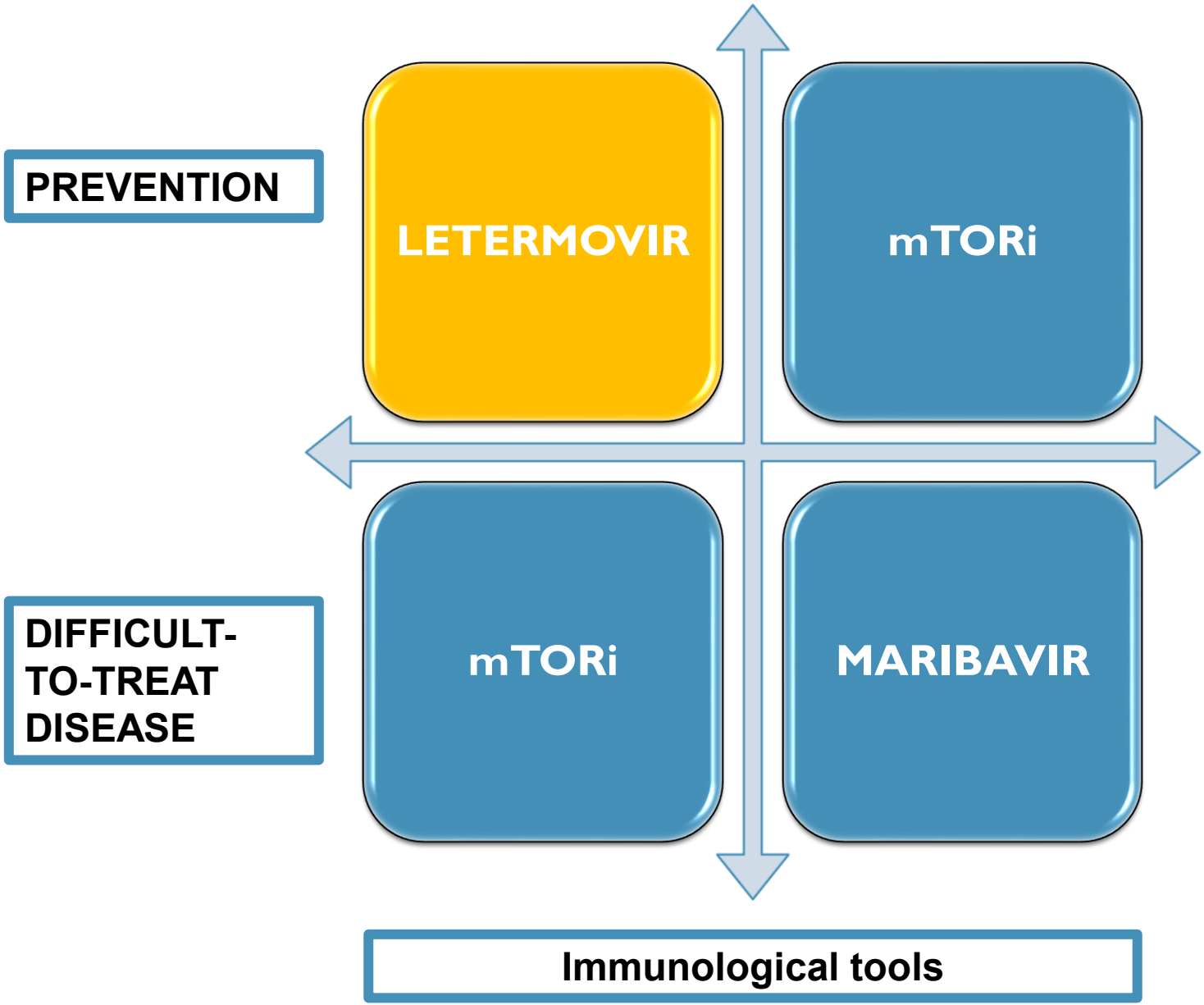
M.Acquier Open Forum Infect Dis 2023

1st opportunistic infection
Difficult to treat events



Toxicity of antiviral drus


PREVENTION
DIFFICULT-TO-TREAT DISEASE
LETERMOVIR
mTORi
mTORi
MARIBAVIR
Immunological tools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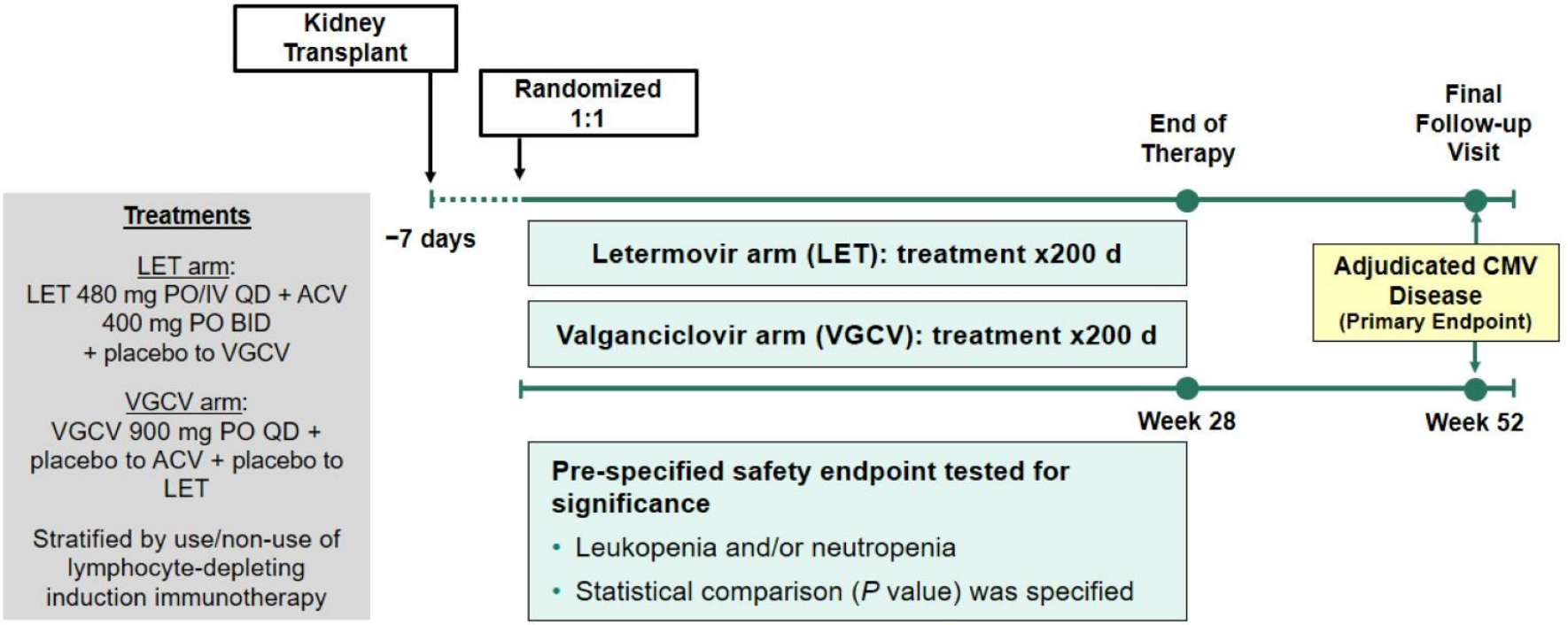
UNIVERSAL PROPHYLXIS WITH LETERMOVIR IN D+R- PATIENTS

Safety and Efficacy of Letermovir Versus Valganciclovir for Prevention of Cytomegalovirus Disease in CMV High-risk D+/R− Kidney Transplant Recipients: A Phase 3 Randomized Study

Limaye JAMA 2023

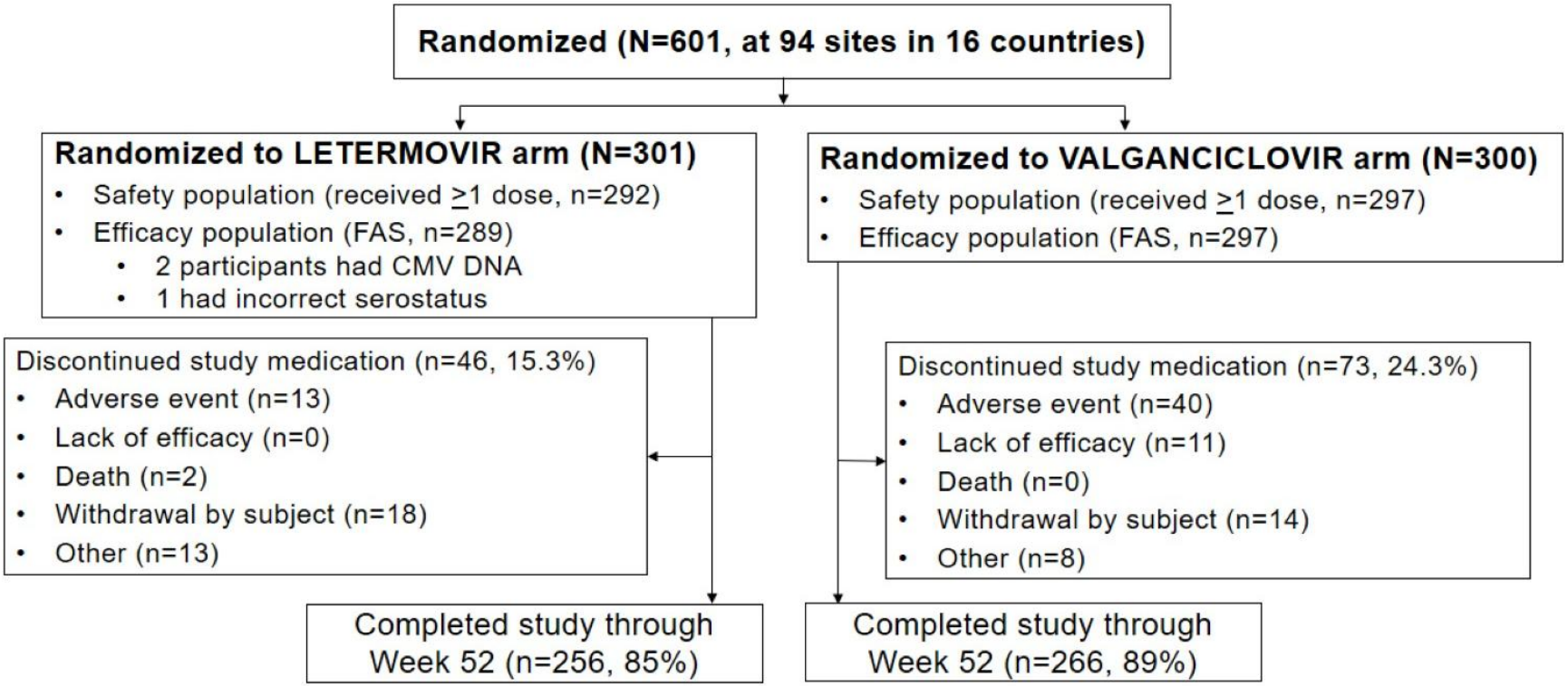
STUDY DESIGN



ACV, VGCV, and GCV doses modified based on CrCl; LET dose adjusted to 240 mg QD if receiving CsA;
Participants unable to tolerate swallowing tablets after randomization received IV formulations with doses adjusted accordingly
ACV, acyclovir; AE, adverse event; ANC, absolute neutrophil count; CrCl, creatinine clearance; CsA, cyclosporin A; GCV, ganciclovir; WBC, white blood cell

Limaye JAMA 2023

FLOW CHART



Safety population (APaT): All participants who took at least one dose of study drug;
Efficacy population (FAS): All participants who took at least one dose of study drug and were the correct serostatus and CMV DNA negative on Day 1.

Limaye JAMA 2023

CMV DISEASE INCIDENCE

	LET Arm (N=289)	VGCV Arm (N=297)
CMV Disease (syndrome or end-organ disease),[a] n (%)	30 (10.4)	35 (11.8)
Difference LET − VGCV (95% CI)[b]	**−1.4% (–6.5%, 3.8%)**	
	Non-inferior[c]	

Approach to handling missing values: Observed failure (OF) approach. With OF, participants who discontinue prematurely from the study for any reason are not considered failures.

[a]CMV disease case

[b]The 95% CIs for th … armonic mean of sample size per arm for ea …

[c]LET is concluded … VGCV) is no higher than 10%. LET is concl … CV) is less than 0.

Investigator-Reported CMV Disease	LET Arm (N=289)	VGCV Arm (N=297)
CMV Disease Through Week 52	**50 (17.3)**	**51 (17.2)**
Difference LET − VGCV (95% CI)	0.1 (−6.1, 6.3)	

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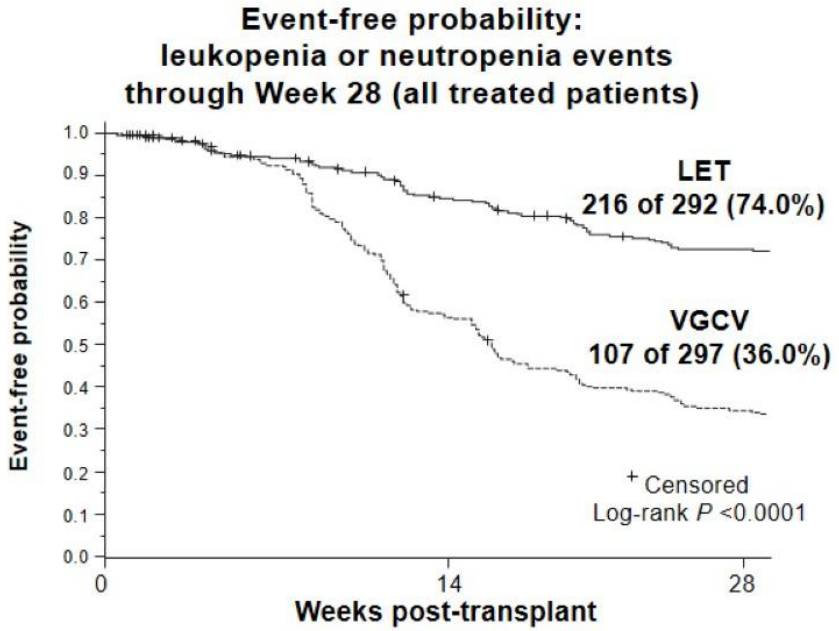
LEUCO/NEUTROPENIA DURING PROPHYLAXIS



G-CSF, granulocyte colony-stimulating factor in FAS

	Difference in % vs VGCV	
	Estimate (95% CI)[a]	*P*-value[a]
With one or more leukopenia or neutropenia events (reported as AE or by lab criteria)	**−37.9 (−45.1, −30.3)**	**<0.0001**
Leukopenia		
Reported as an AE	−25.7 (−32.3, −19.1)	
WBC <3500 cells/μL	−35.3 (−42.5, −27.7)	
Neutropenia		
Reported as an AE	−13.8 (−18.7, −9.3)	
ANC <1000 cells/μL	−15.4 (−20.7, −10.5)	

[a]Based on Miettinen & Nurminen method.

	LET Arm (N=289)	VGCV Arm (N=297)
≥1 use of any G-CSF during treatment period, n (%); 95% CI	5 (1.7) 0.6, 4.0	21 (7.1) 4.4, 10.6

Letermovir presents a better tolerance

Limaye JAMA 2023

MEDICATIONS WITH LETERMOVIR

CICLOSPORINE+LETERMOVIR= LETERMOVIR 240mg (demie-dose)

CICLOSPORINE+LETERMOVIR= CONTRE-INDICATION STATINES

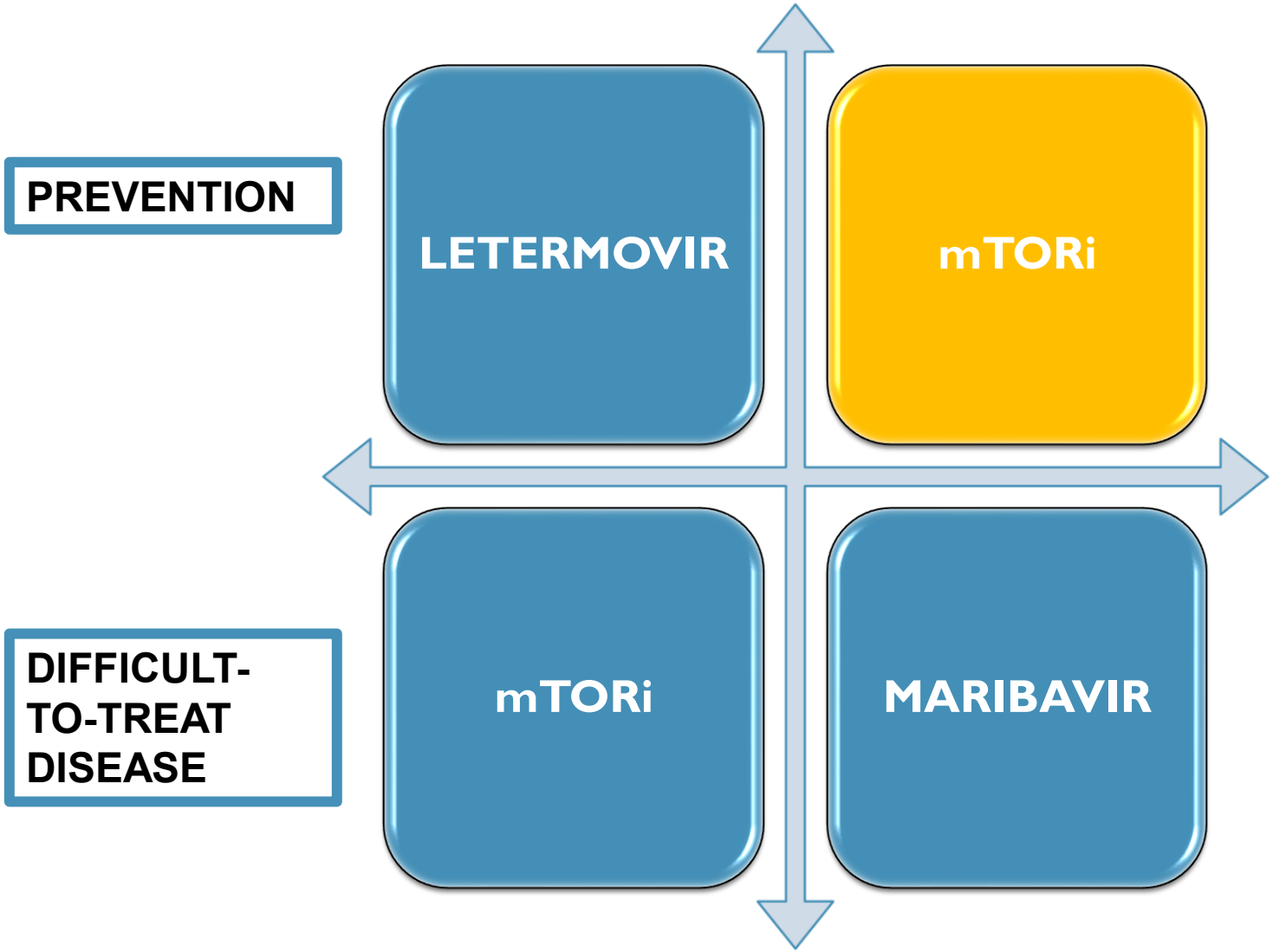
TACROLIMUS+LETERMOVIR= baisse de 30%-50% du tacrolimus

CICLOSPORINE+LETERMOVIR= CONTRE-INDICATION DABIGATRAN

RECOMMENDATION

•We recommend that either (val)ganciclovir or letermovir can be used for primary prophylaxis in D+/R- kidney transplant recipients (strong, high)

•For D+/R- or R+ lung, heart, liver, kidney transplants where prophylaxis is used, if there is intolerance to (val)ganciclovir, we suggest switching to PET or to letermovir prophylaxis (weak, low).


PREVENTION
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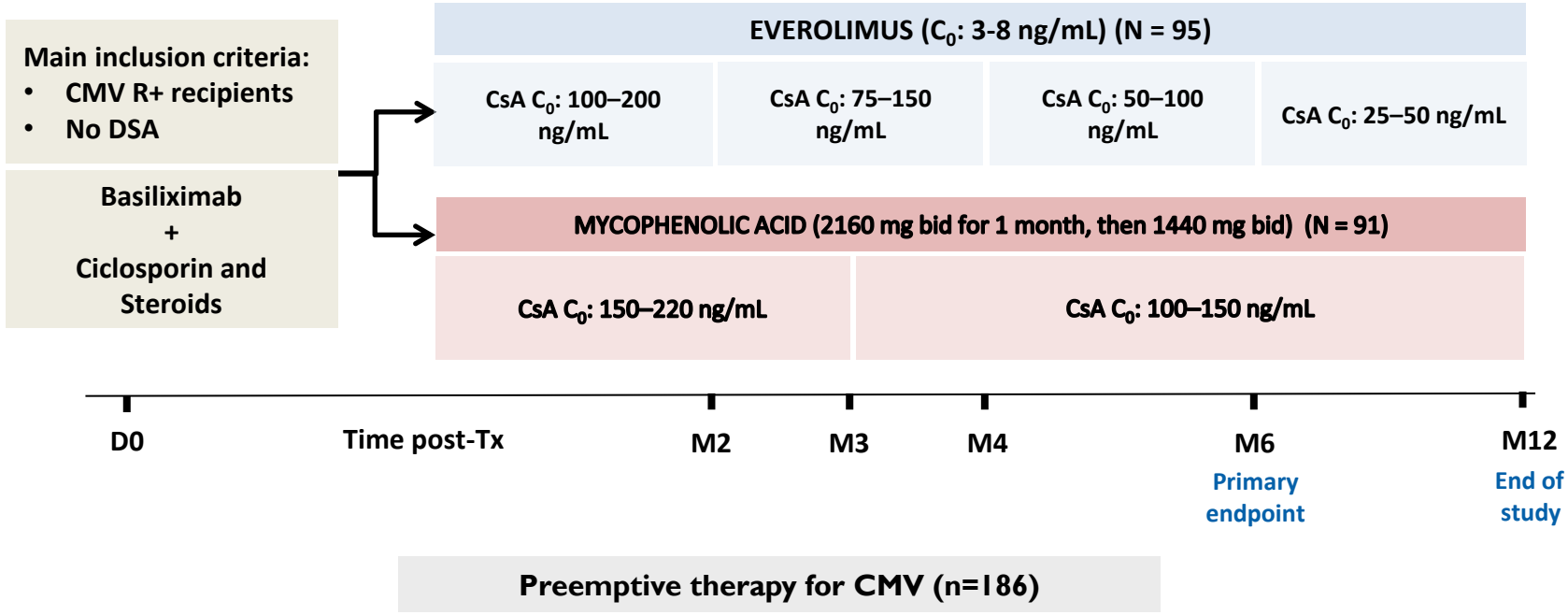
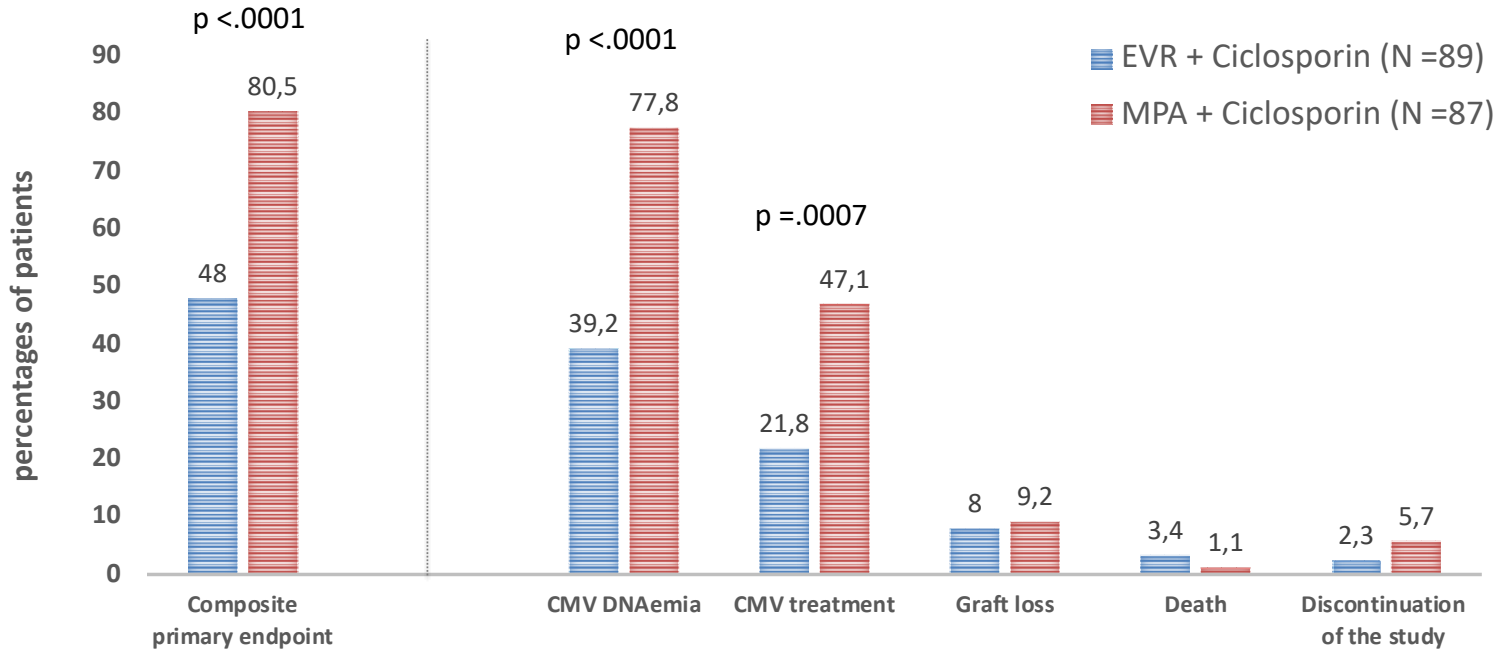
STUDY DESIGN



Inclusion: Mai 2014 – Octobre 2017

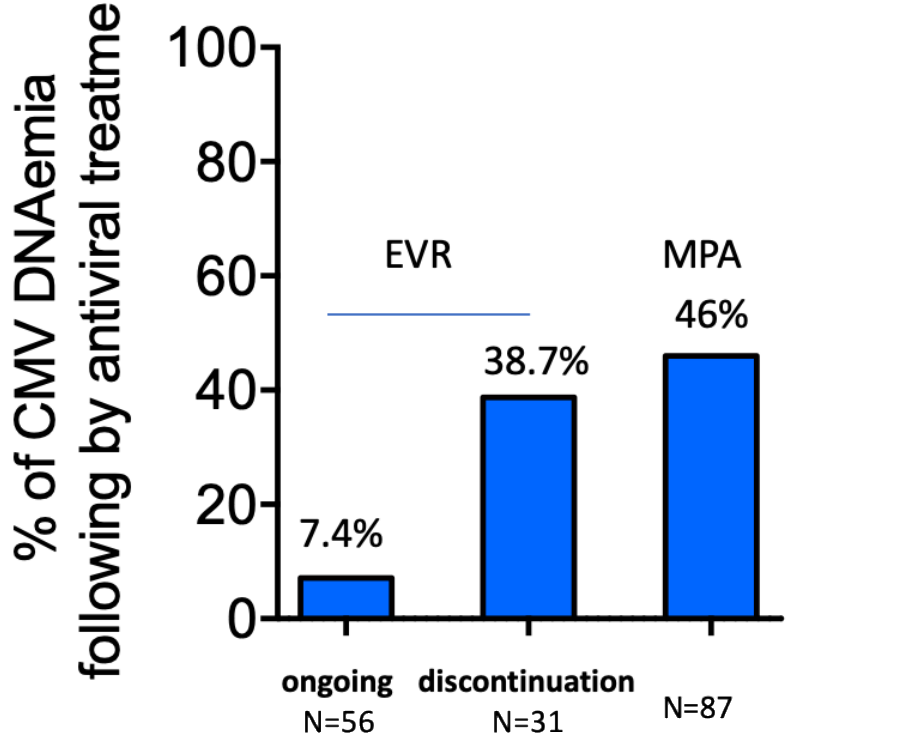
PI Lionel Couzi, *Kaminski H et al Am Journal of Transplant 2022*

PRIMARY ENDPOINT AT 6 MONTHS POST-TRANSPLANTATION



PI Lionel Couzi, *Kaminski H et al Am Journal of Transplant 2022*

ONGOING TREATMENT ANALYSIS

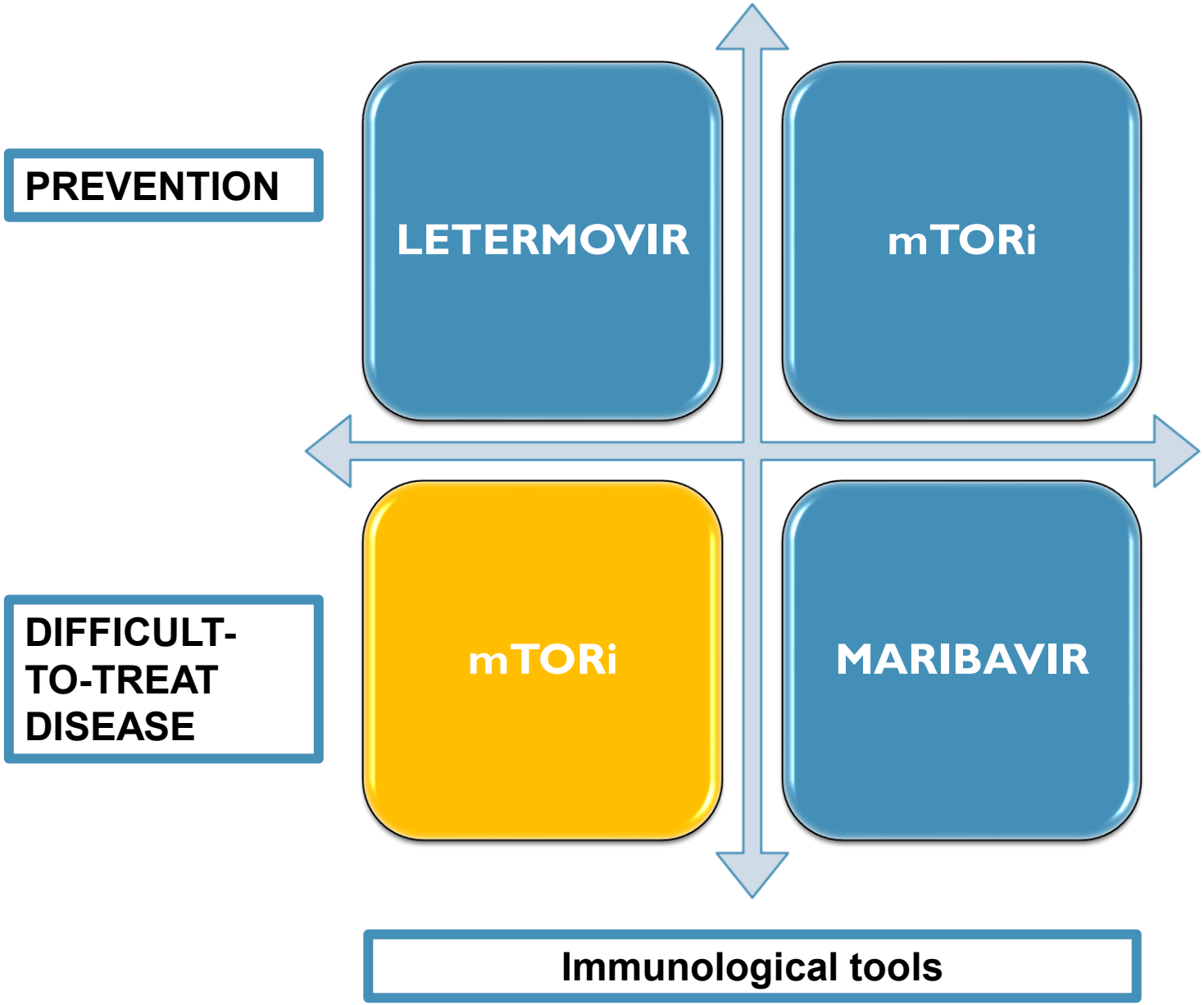


7.4% of patients with ONGOING EVR undergo CMV DNAemia requiring treatment

PI Lionel Couzi, *Kaminski H et al Am Journal of Transplant 2022*

RECOMMENDATIONS

- In R+ kidney transplant patients given de novo mTOR-based immunosuppression, we recommend either a pre-emptive strategy or close clinical monitoring (strong, high).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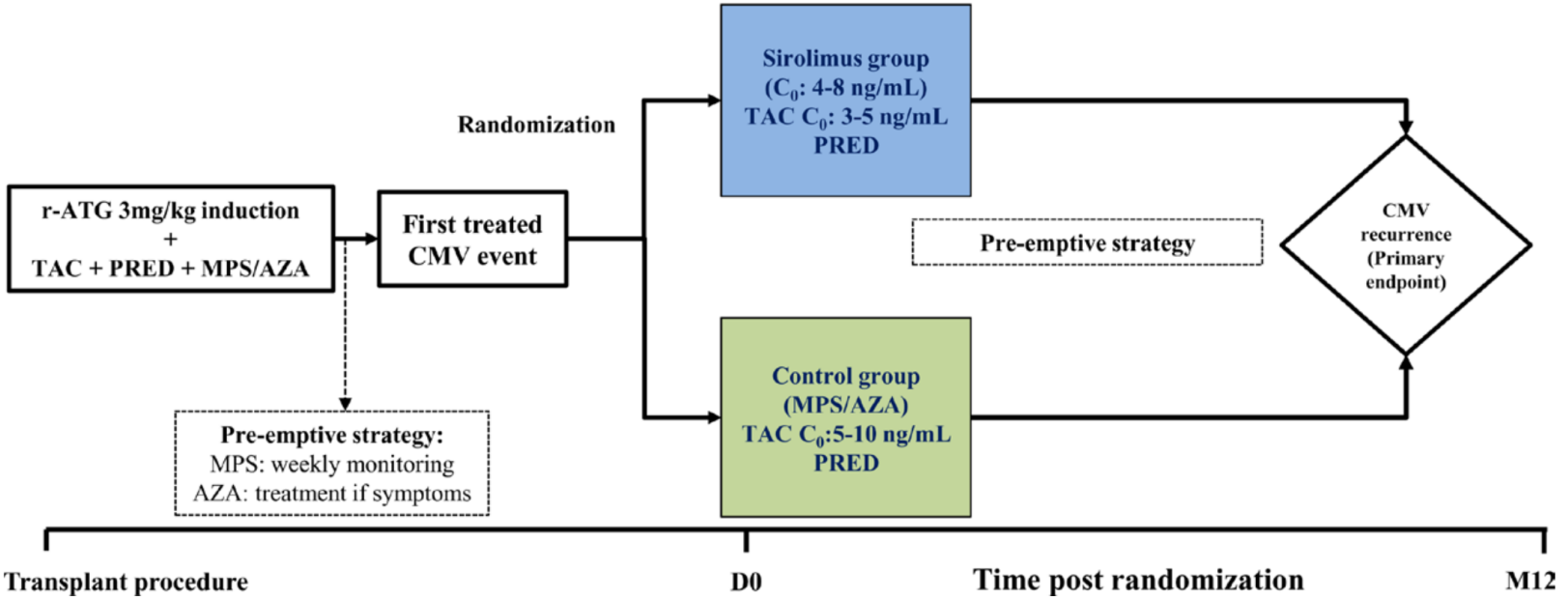
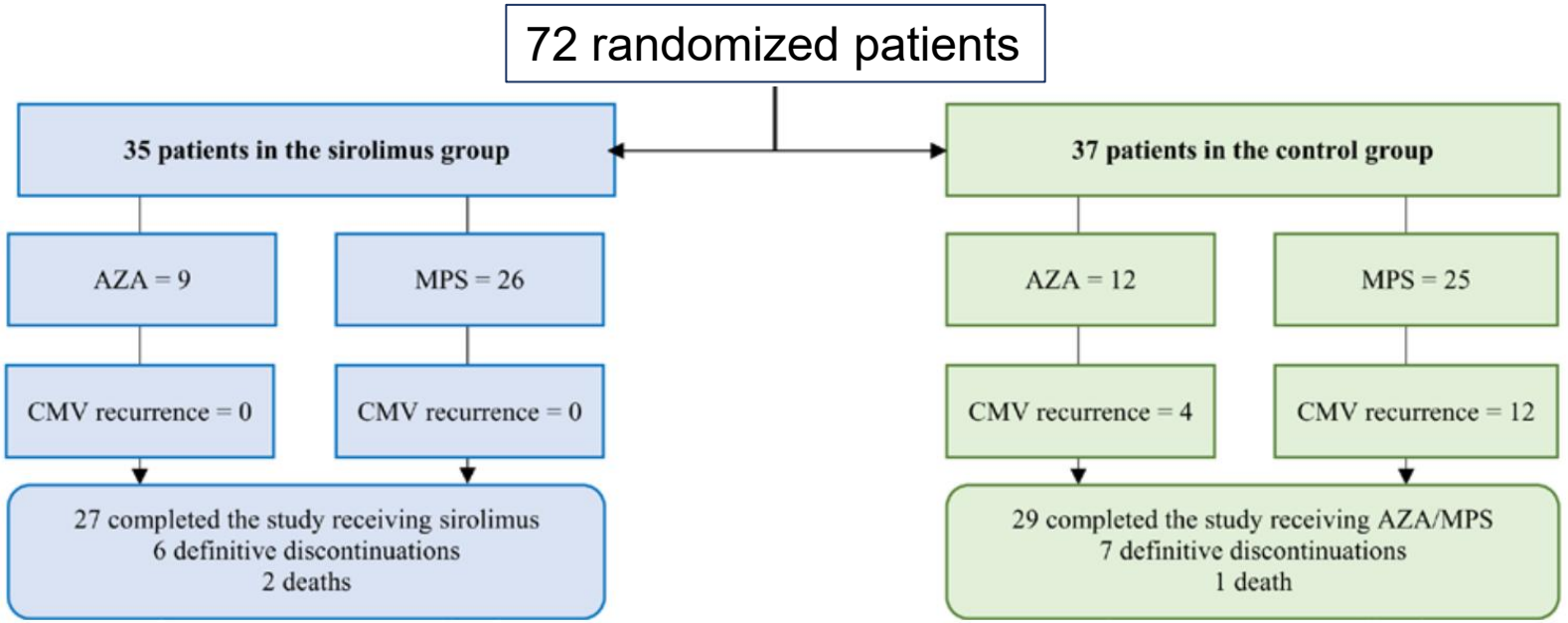
Conversion to mTOR Inhibitor to Reduce the Incidence of Cytomegalovirus Recurrence in Kidney Transplant Recipients Receiving Preemptive Treatment: A Prospective, Randomized Trial

Laila Almeida Viana, Transplantation 2023



MTORI TO REDUCE CMV RECURRENCES IN R+



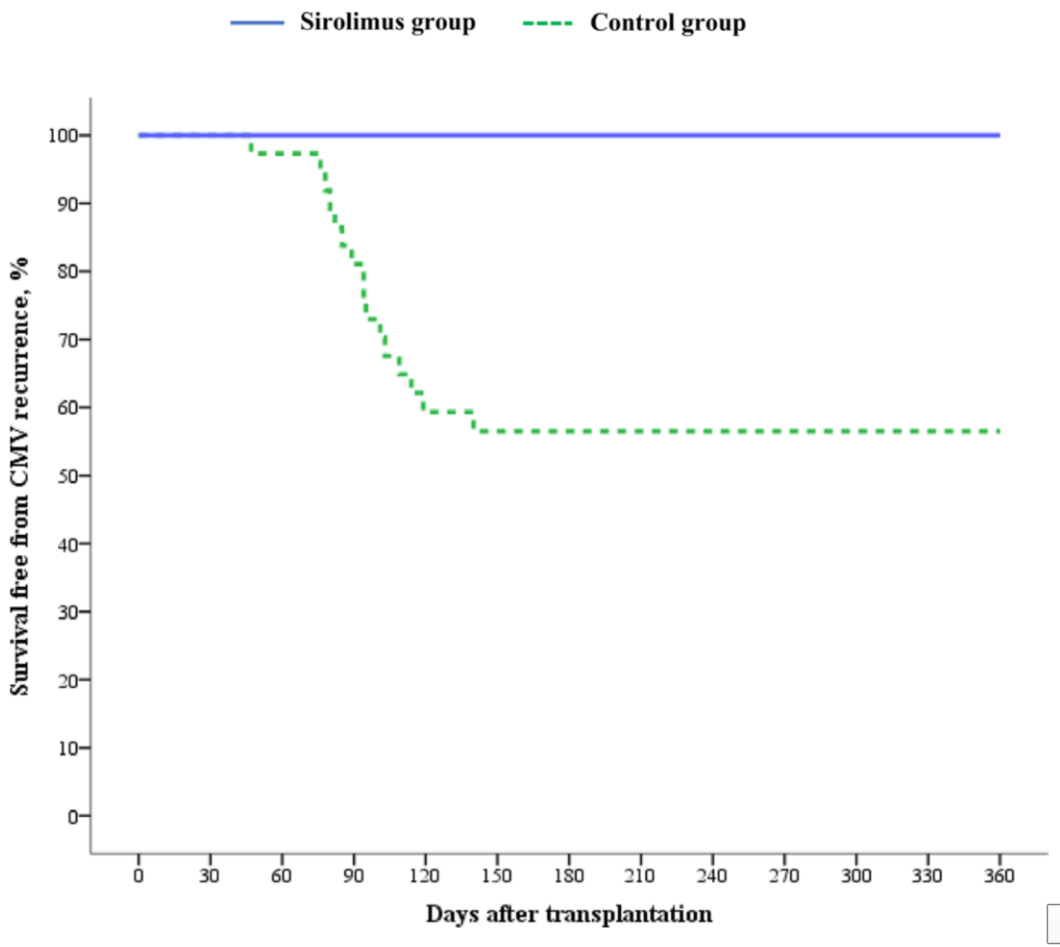
Laila Almeida Viana, Transplantation 2023

MTORI TO REDUCE CMV RECURRENCES IN R+

low-immunological-risk

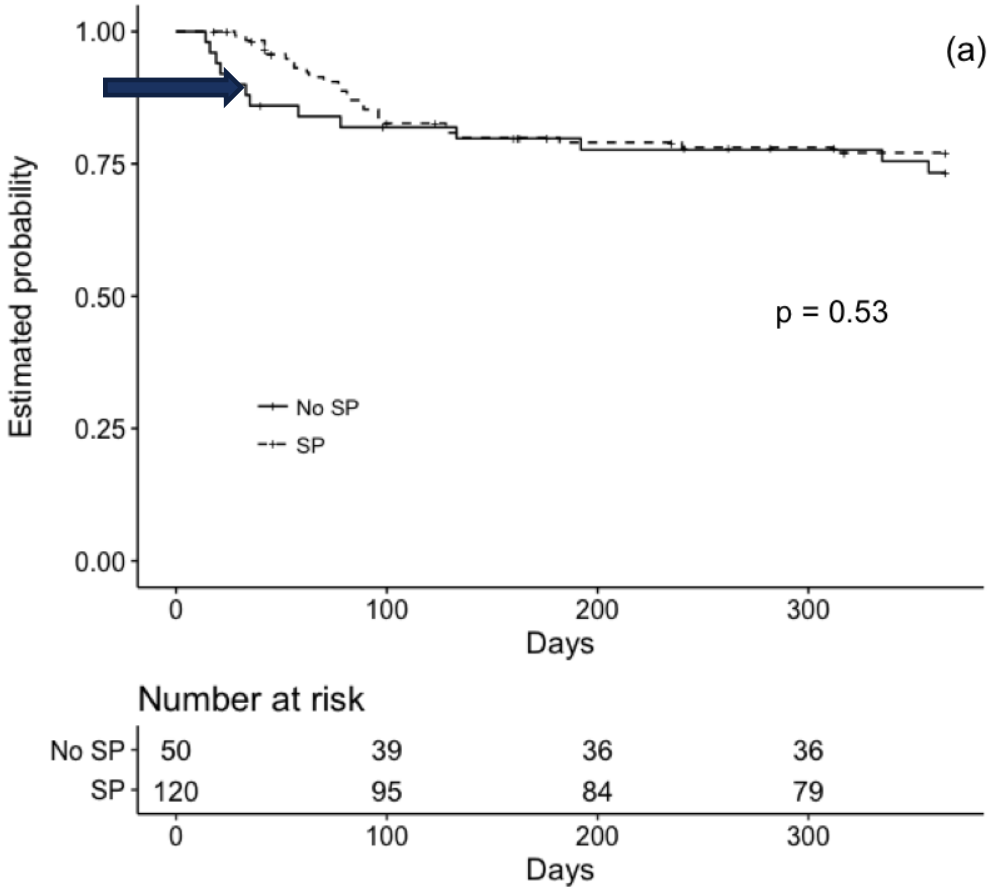
R+ transplant recipients

Preemptive therapy
0% in SRL versus 43%in MPA/AZA; *P*<0.0001



Laila Almeida Viana, Transplantation 2023

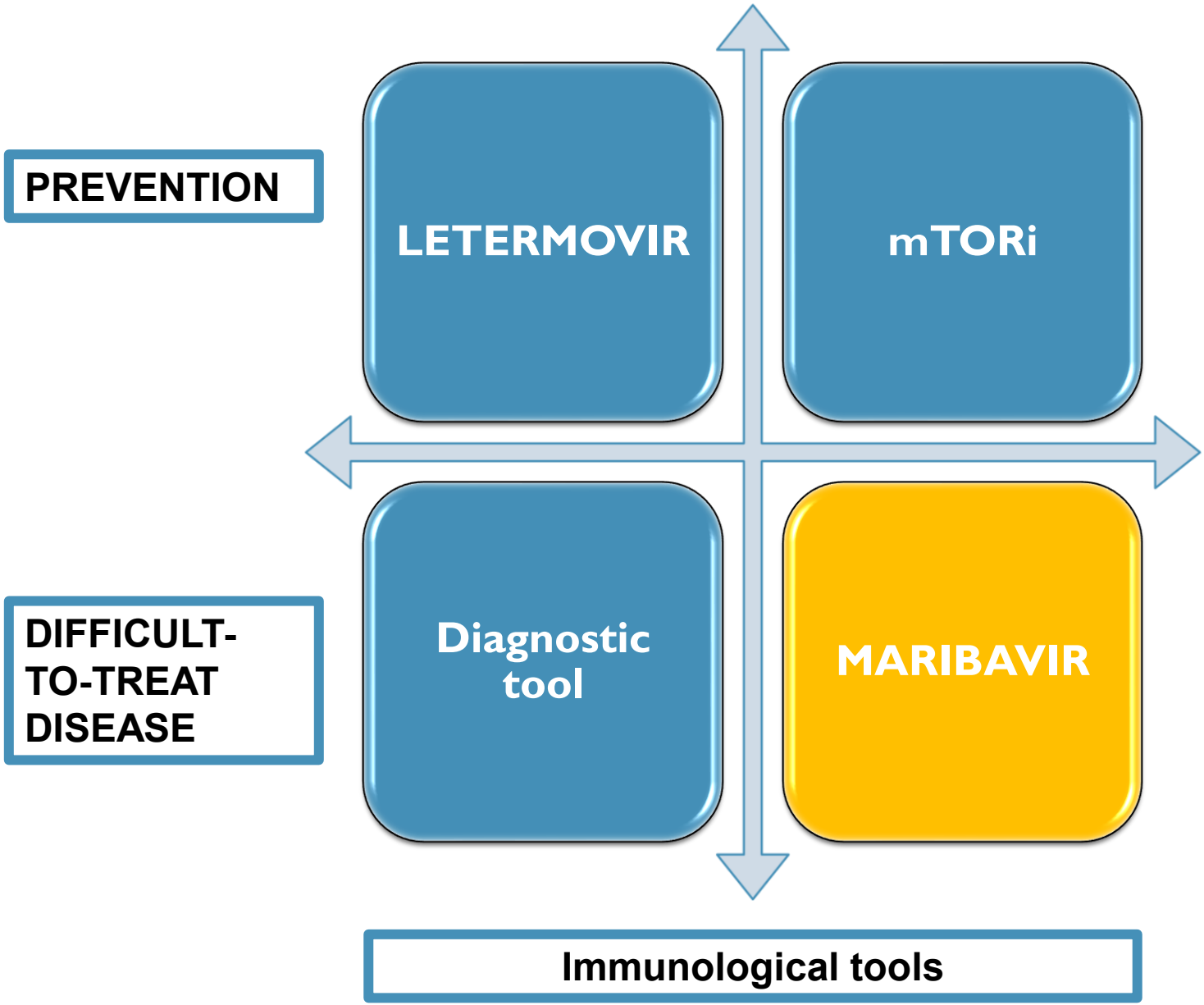
SECONDARY PROPHYLAXIS ONLY DELAYS THE RISK OF RECURRENCE



Gardiner, Clin Infect Dis. 2017 Nov 29;65(12):2000-2007

RECOMMENDATION

- We suggest secondary prophylaxis to delay and/or prevent recurrent CMV infection in high-risk situations such as increased immunosuppression, low absolute lymphocyte count, low CMV-specific cell-mediated immunity, repeated recurrences, inability to monitor patients for CMV replication (weak, low).
- The choice of agents for secondary prophylaxis and duration of secondary prophylaxis can be individualized (expert opinion). Typical duration for secondary prophylaxis is 1-3 months. Further discrimination can be based on evaluation of immune status.
- After a first episode of CMV infection/disease, we suggest considering switching to mTOR inhibitor from an antiproliferative agent in low immunological risk R+ kidney transplant recipients to reduce the rate of recurrent CMV infection (weak, moderate).


PREVENTION
DIFFICULT-TO-TREAT DISEASE
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Diagnostic tool
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MARIBAVIR
FOR REFRACTORY/RESISTANT CMV INFECTION

Définition:

- Refractory: No CMV DNAemia decrease (>1 log10) after 2 weeks of curative treatment
- Resistant: refractory CMV infection with identified mutation inducing GCV or FCV resistance

Clinical Infectious Diseases

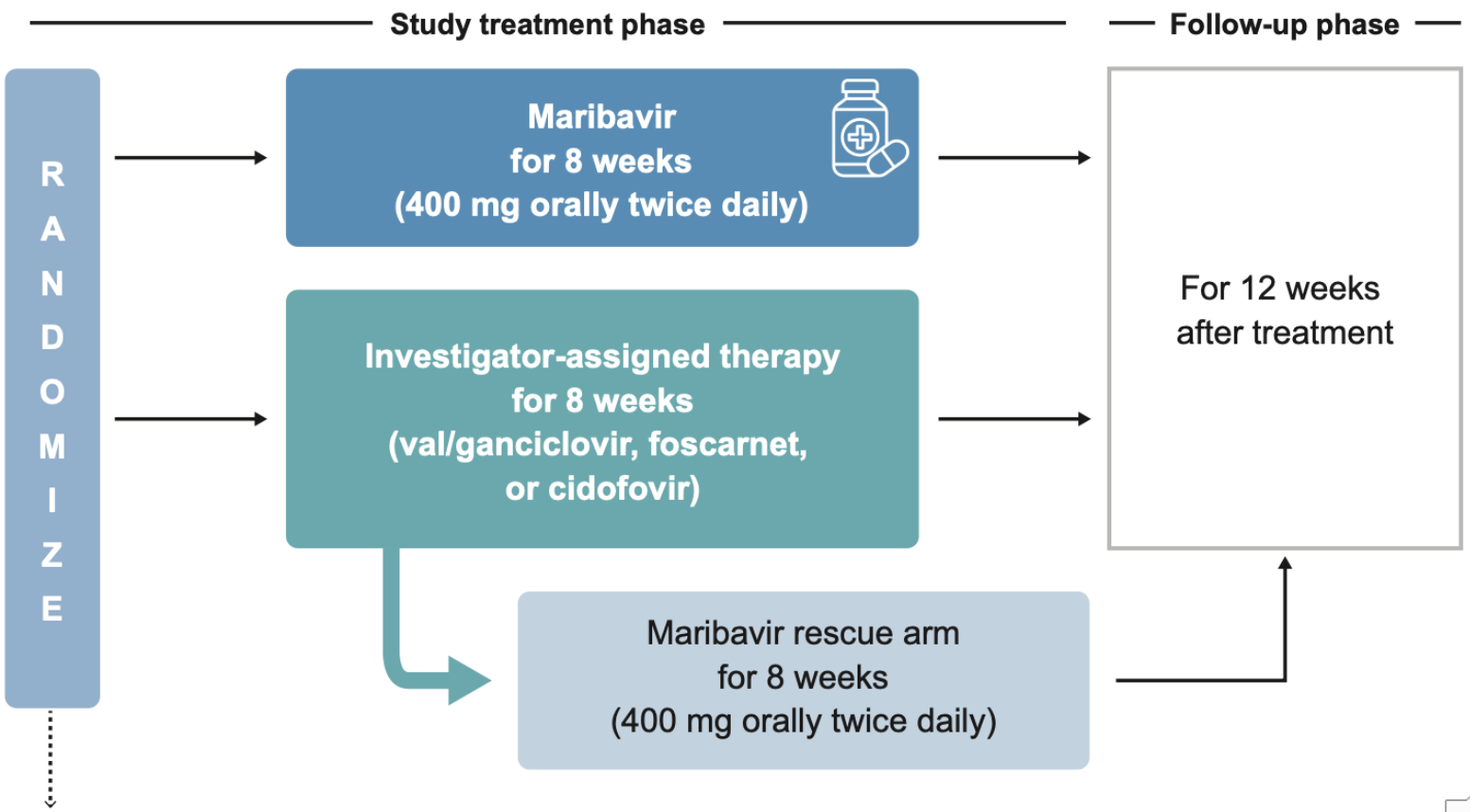
MAJOR ARTICLE

Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial

Robin K. Avery,[1] Sophie Alain,[2] Barbara D. Alexander,[3] Emily A. Blumberg,[4] Roy F. Chemaly,[5] Catherine Cordonnier,[6] Rafael F. Duarte,[7] Diana F. Florescu,[8] Nassim Kamar,[9] Deepali Kumar,[10] Johan Maertens,[11] Francisco M. Marty,[12,a] Genovefa A. Papanicolaou,[13,14] Fernanda P. Silveira,[15] Oliver Witzke,[16] Jingyang Wu,[17] Aimee K. Sundberg,[18] and Martha Fournier[18]; for the SOLSTICE Trial Investigators[b]

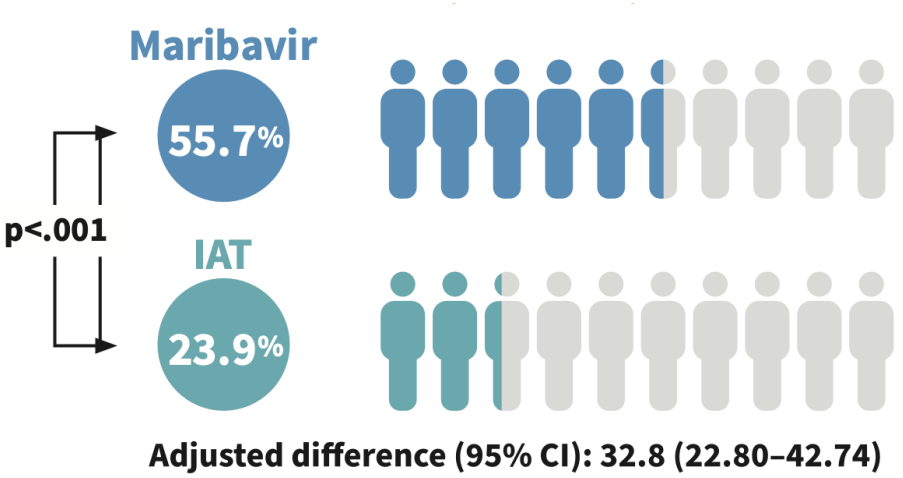
Early access in France (April 2023)

STUDY DESIGN



Randomization 2:1 (maribavir:IAT) stratified by **transplant type** (SOT or HCT) and **screening plasma CMV DNA level** (high: ≥91,000 IU/mL; intermediate: ≥9,100 and <91,000 IU/mL; low: ≥910 and <9,100 IU/mL)

MARIBAVIR FOR RESISTANT/REFRACTORY CMV INFECTION



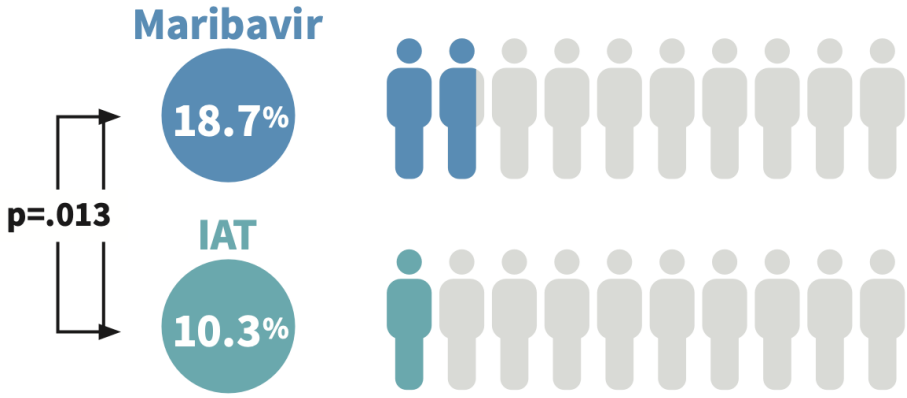
n/N

131/235

28/117

- Higher viral clearance at 8 weeks of treatment

- Higher rate of symptom-free and clearance at week 8 and maintenance at week 16



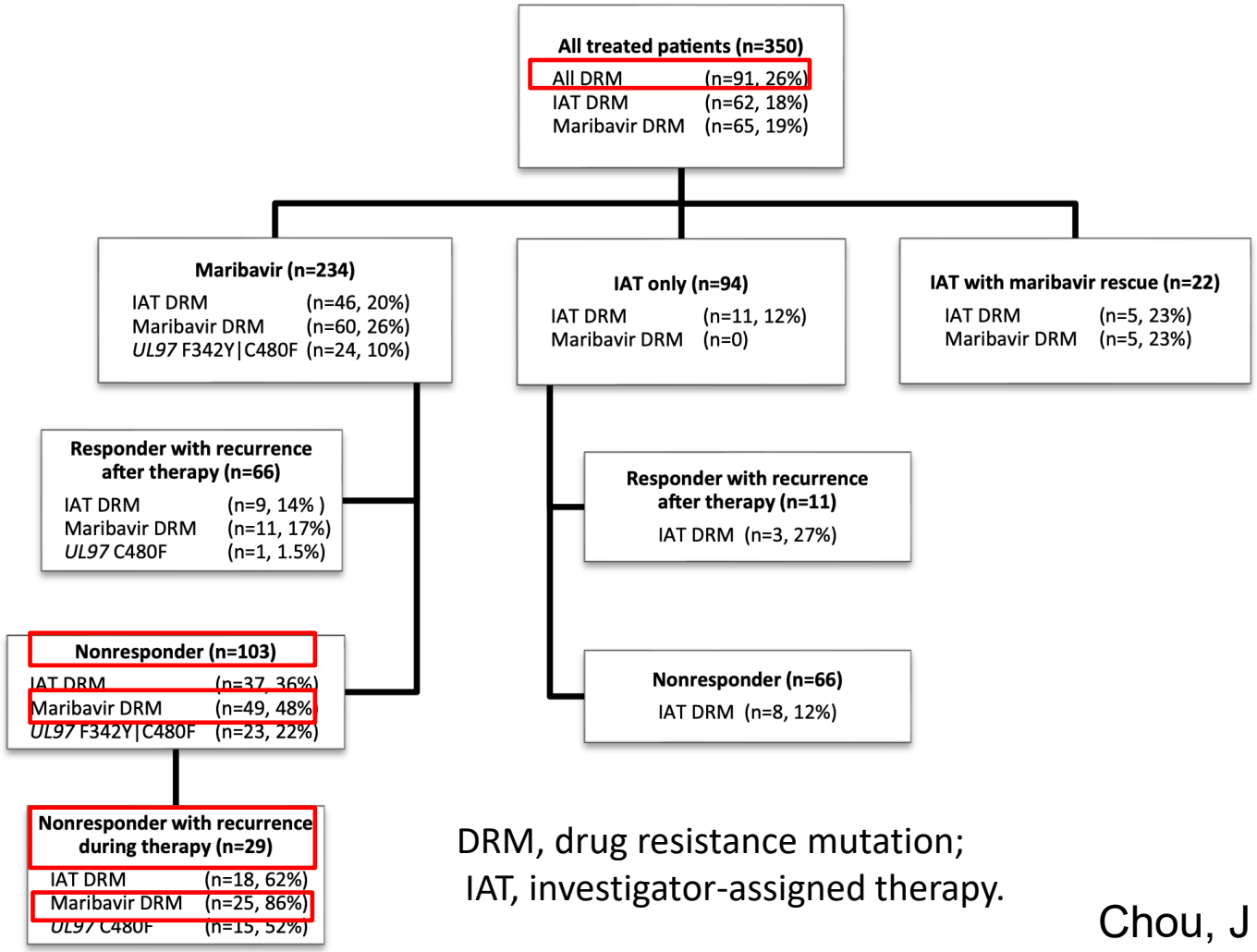
n/N

44/235

12/117

- Few patients with symptoms at inclusion, weak DNAemia
- **Statistical différence only in the group with identified mutation : 63 vs 20%** (44 vs 32% for refractory patients)

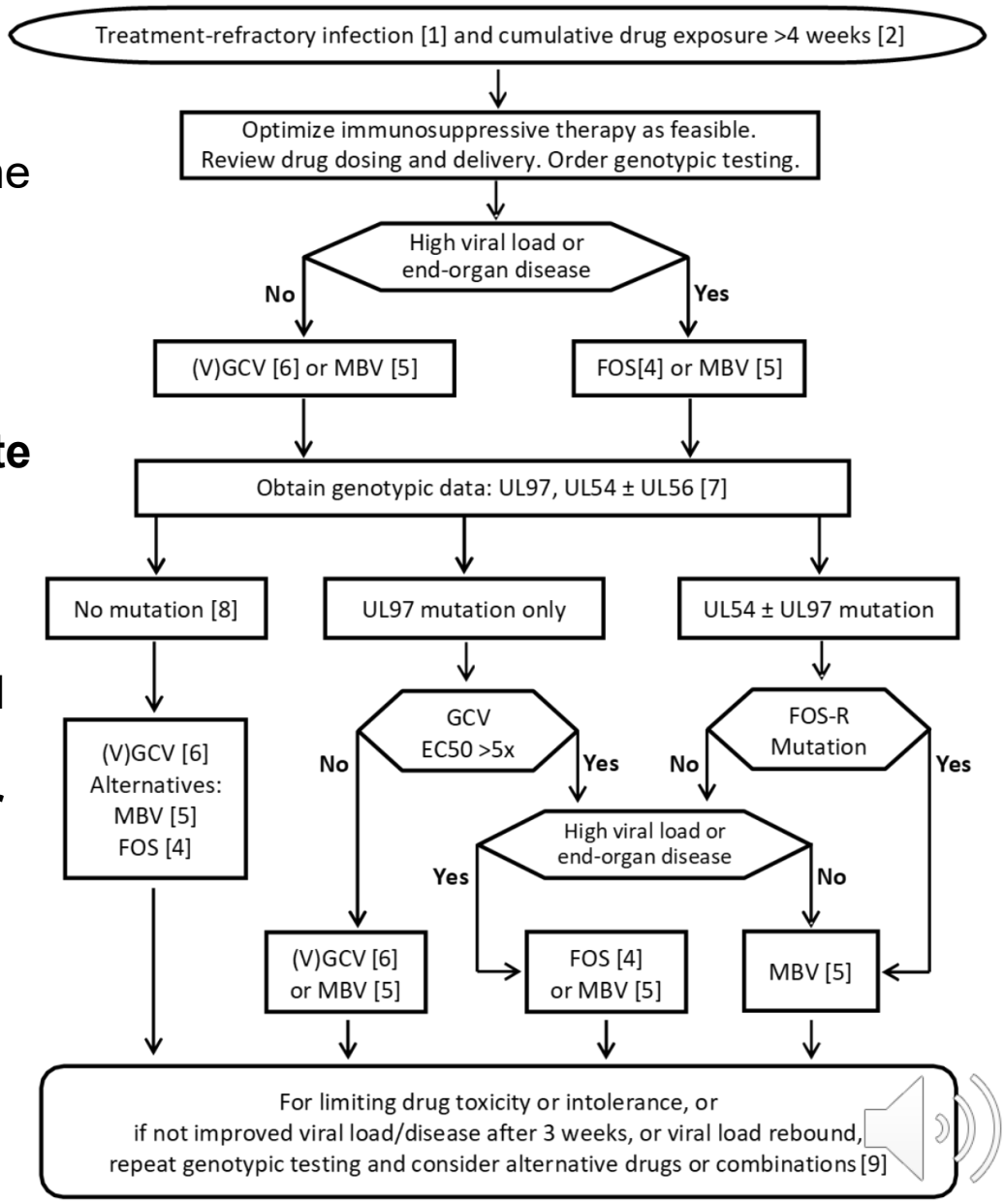
MUTATION OCCURRENCE AFTER THE USE OF MARIBAVIR?

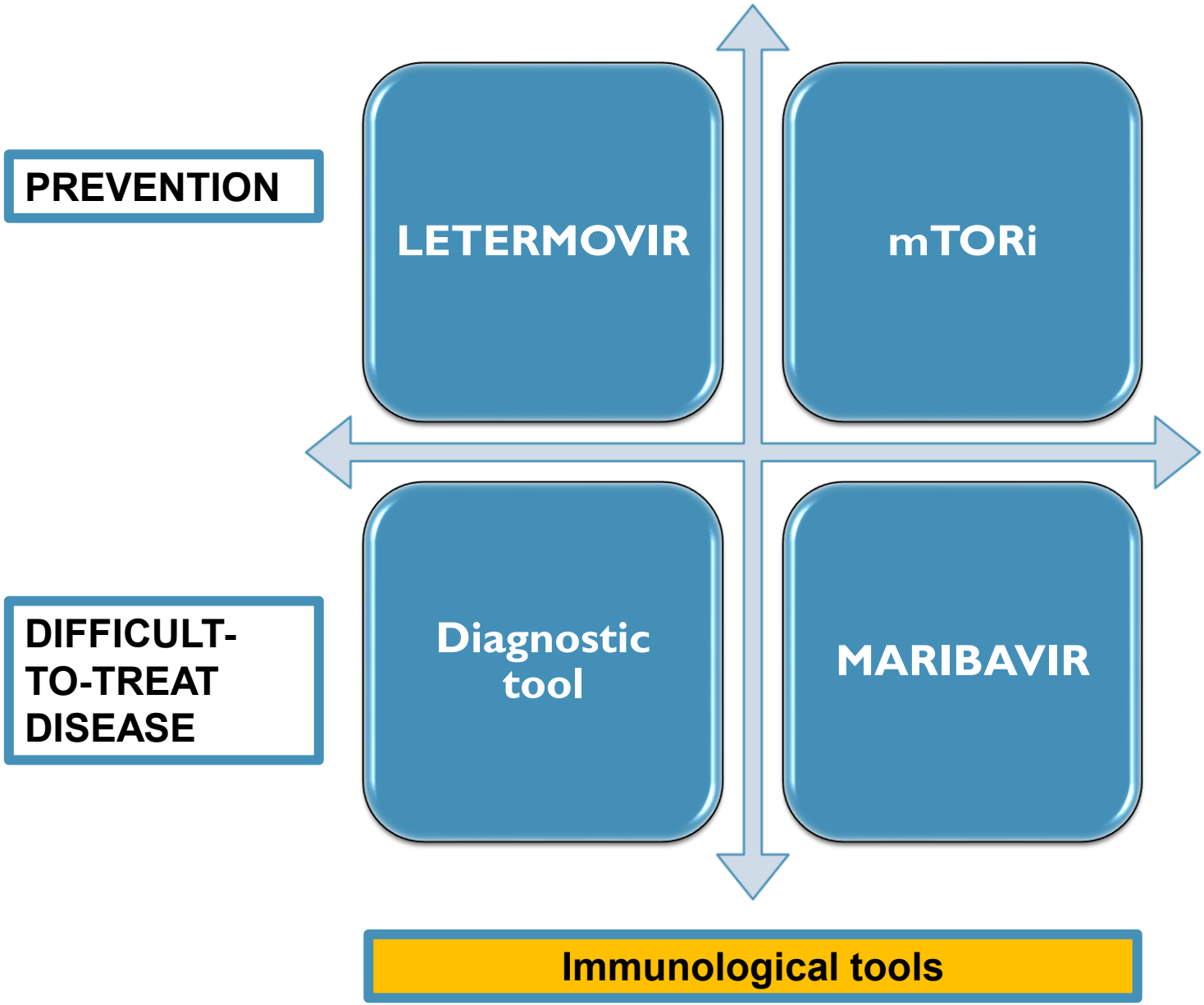


DRM, drug resistance mutation;
IAT, investigator-assigned therapy.

Chou, J of Inf Dis, 2023

1. We **recommend maribavir** as the principal alternative therapy in cases of resistance to either ganciclovir or foscarnet (strong, high), **especially with clinically well cases with low or moderate viral loads (for example, < 4.7 log10 IU/mL (50,000 IU/mL) on plasma)** (weak, low).
2. **We suggest foscarnet as initial therapy in clinically unwell cases with high viral loads (for example, ≥ 4.7 log10 IU/mL** (50,000 IU/mL) on plasma), and suspected or proven ganciclovir resistance (weak, low).

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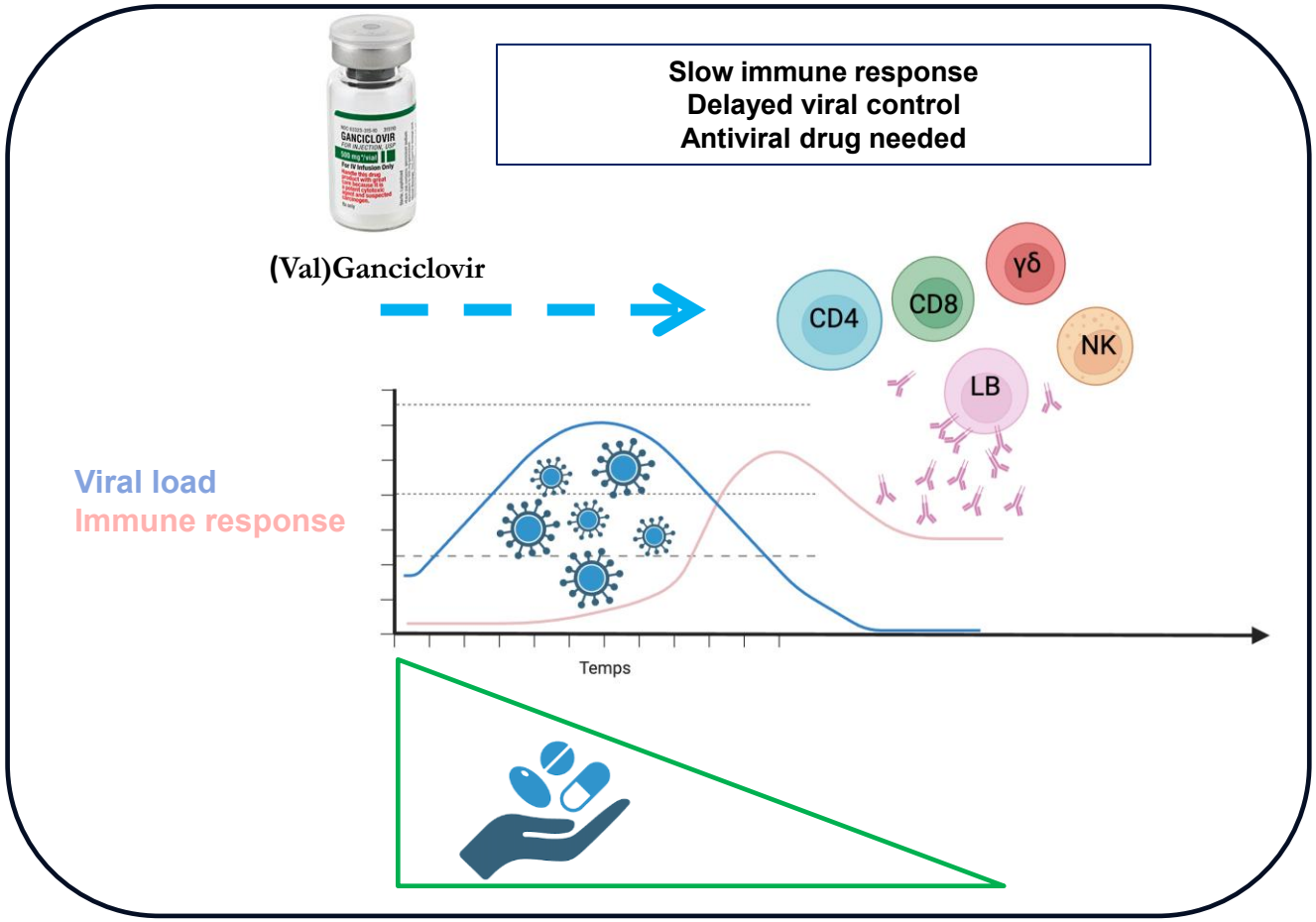
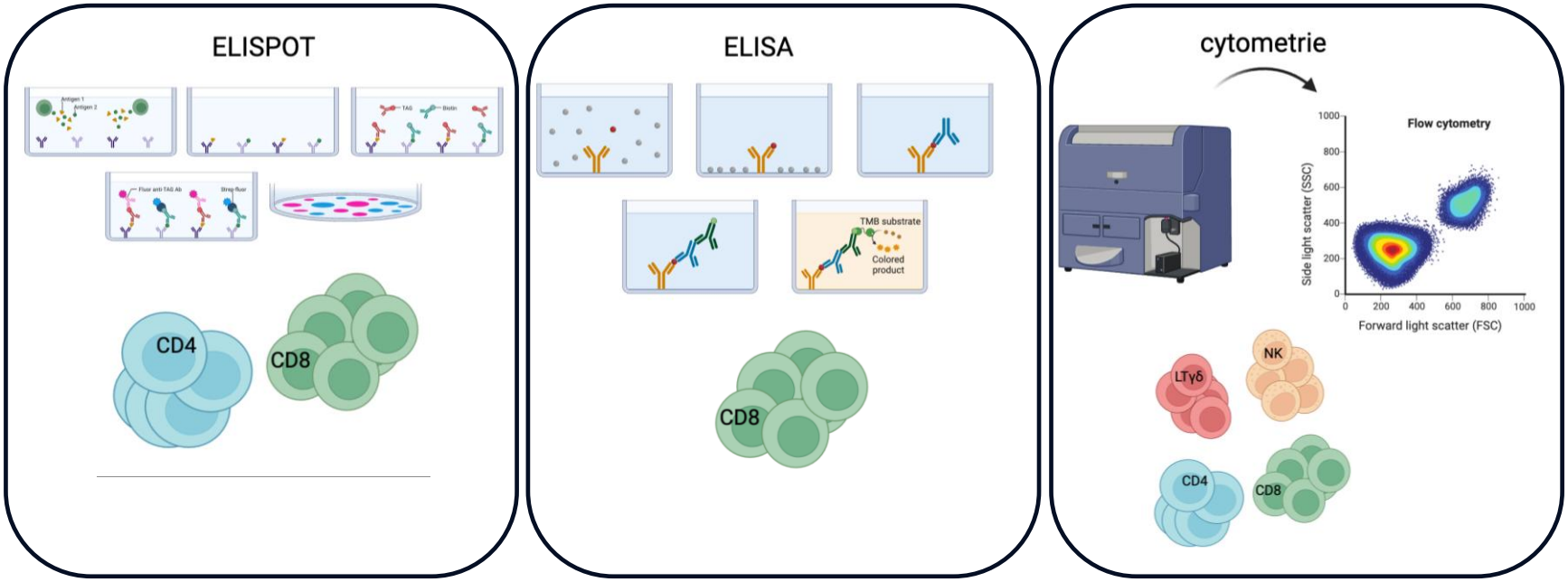
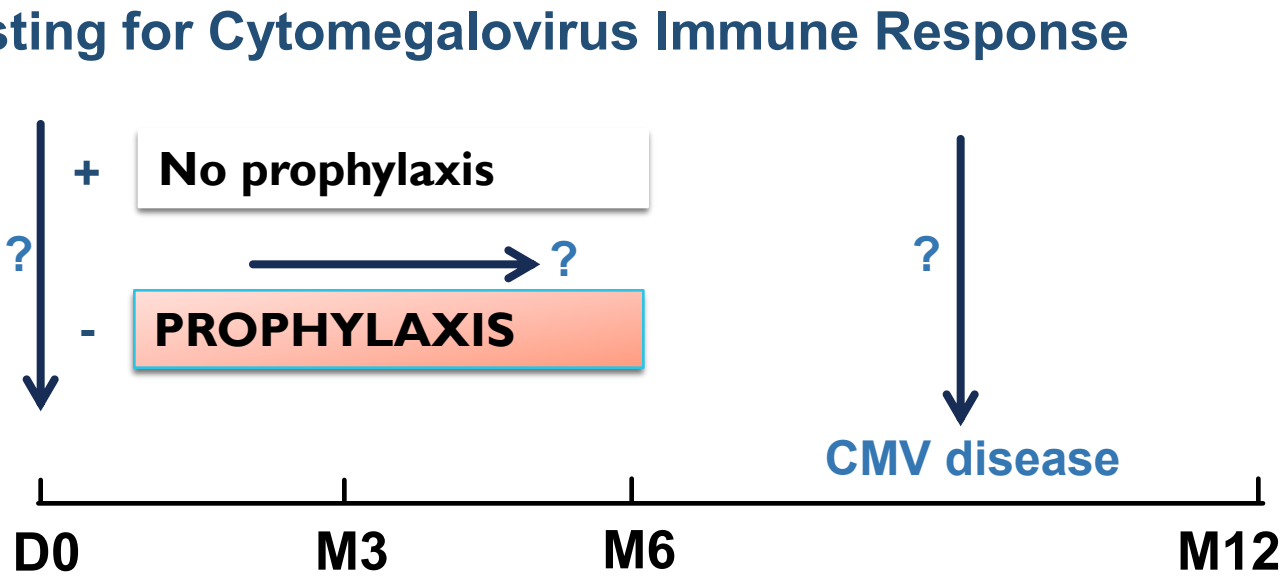
Management of CMV infection in kidney transplantation



Measurement of CMV specific cellular actors



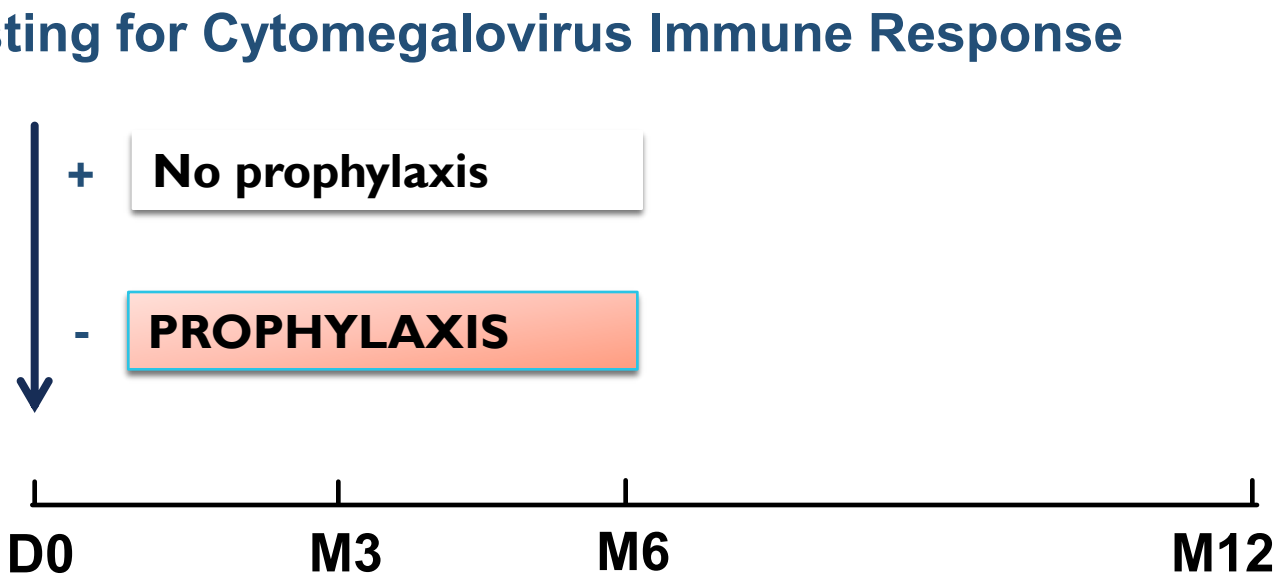
HOW TO PERSONALIZE CMV TREATMENT BASED ON IMMUNE MONITORING?



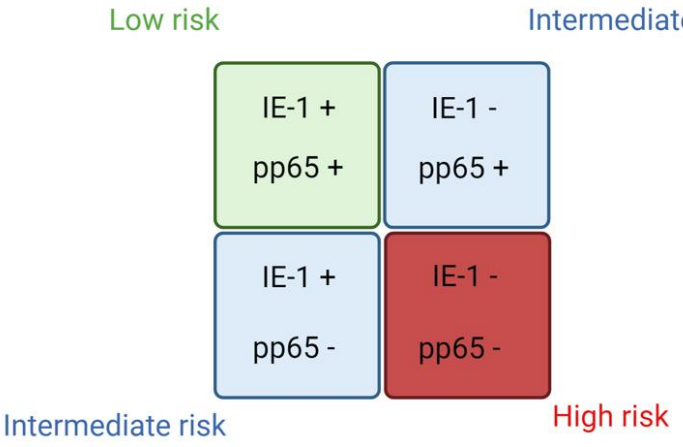
1. In R+ patients: could preventive treatment be avoided?
2. In R+ patients with rATG, could we adjust the duration of prophylaxis?
3. In R+ and D+R- patients during CMV disease, could we predict CMV relapse?

AIM N°1 :

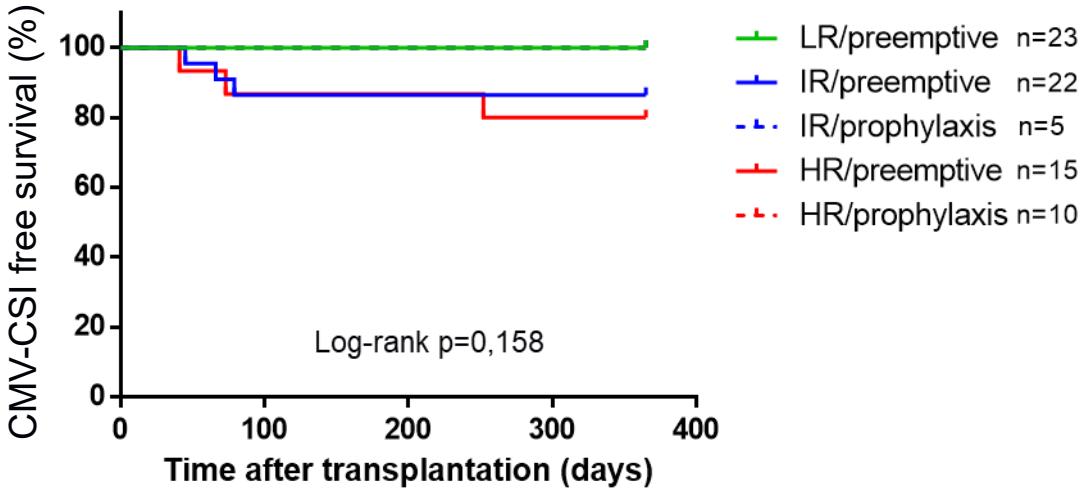
IN R+ PATIENTS: COULD PREVENTIVE TREATMENT BE AVOIDED?



IMMUNOGUIDED PREVENTION WITHDRAWAL IN R+ ANTIIL2R PATIENTS



NPV 98.13 %



Vall d'Hebron Institut de Recerca

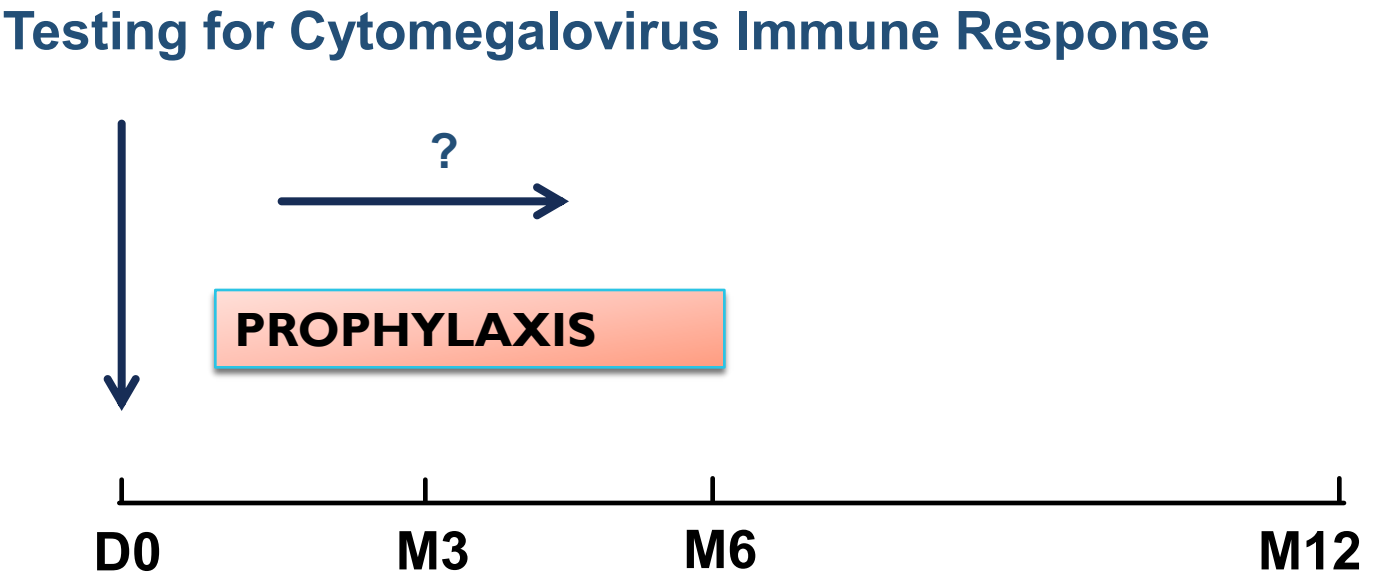
Vall d'Hebron

yes in R+antiIL2RA if ELISPOT is + at day 15

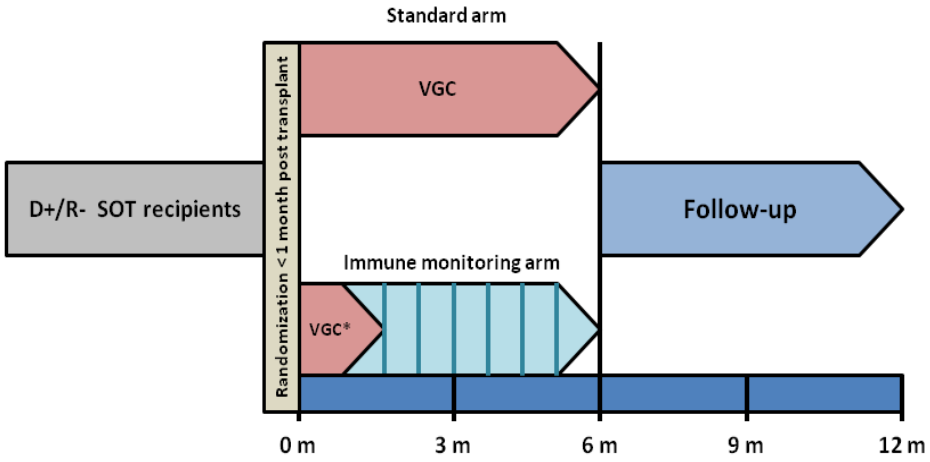
Kervella D and Bestard O, BRIEF ORAL ESOT 2023 BOS7_2
9/18/2023 Complications and infections after kidney transplant

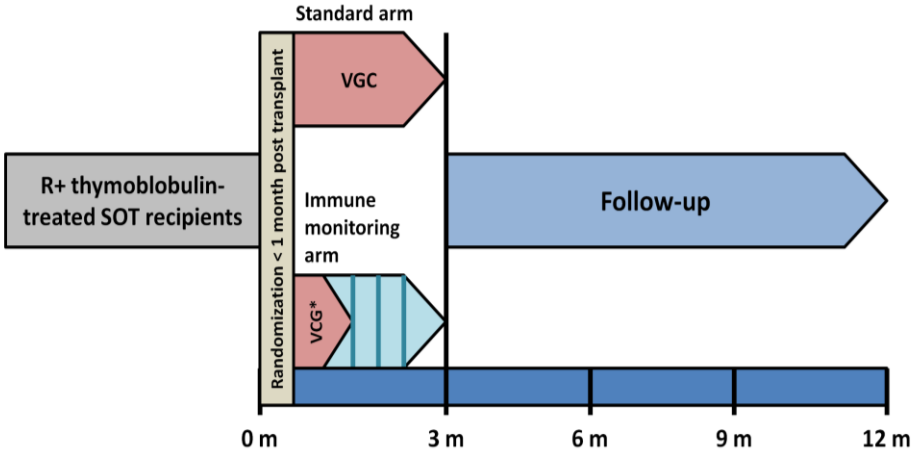
AIM N°2 :

IN R+ PATIENTS WITH ATG, COULD WE ADJUST THE DURATION OF PROPHYLAXIS?
→ DECREASE USELESS PREVENTIVE TREATMENT



Immunoguided Discontinuation of Prophylaxix in D+R- and R+ ATG patients



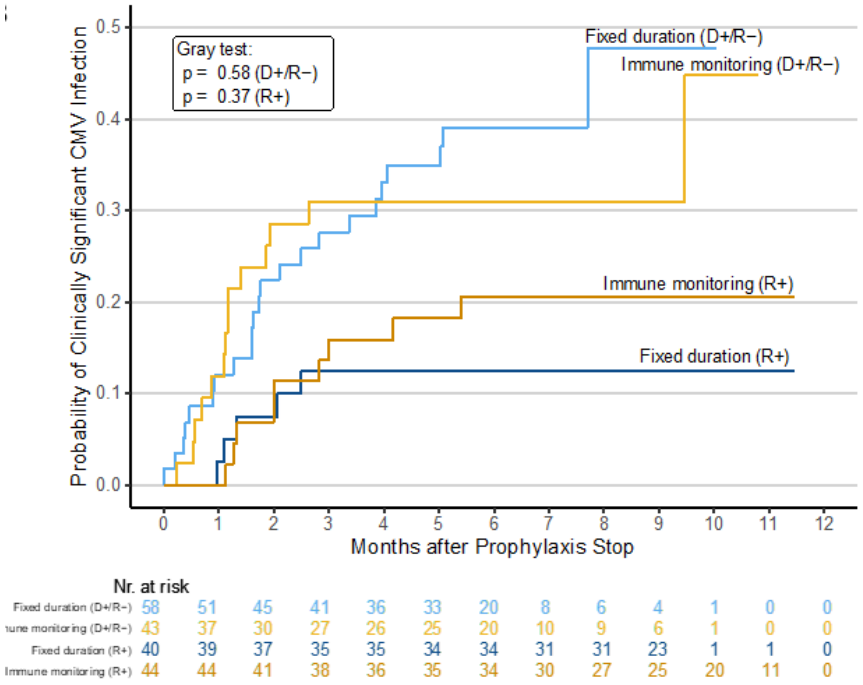


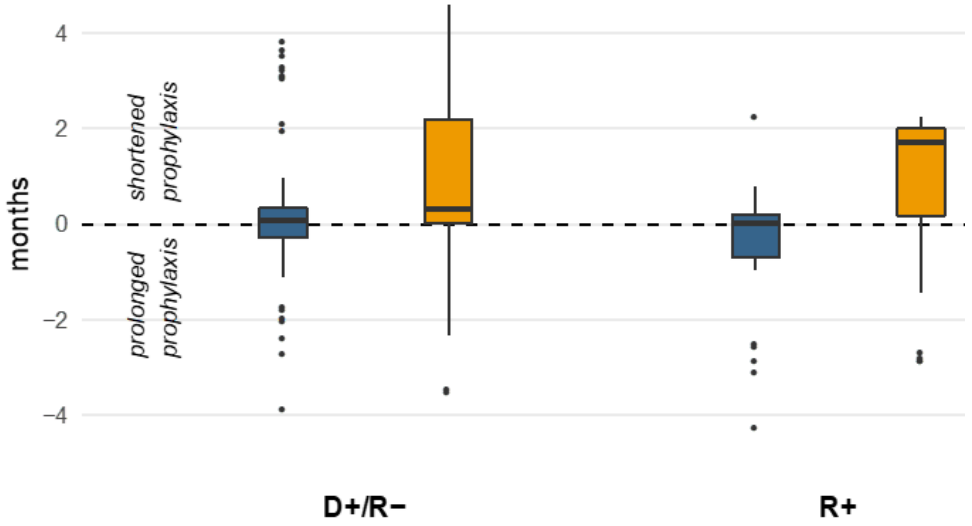
* Stop prophylaxis when assay positive

ELISPOT
D+R-
R+ ATG

O.Manuel, Clin Inf Dis, 2023

Immunoguided Discontinuation of Prophylaxix in D+R- and R+ ATG patients





ELISPOT
D+R-
R+ ATG

1) Not useful for D+R-
2) For R+ ATG: there is still clinically CMV infection occuring with immunomonitoring

O.Manuel, Clin Inf Dis, 2023

Immunoguided Discontinuation of Prophylaxix in R+ ATG patients

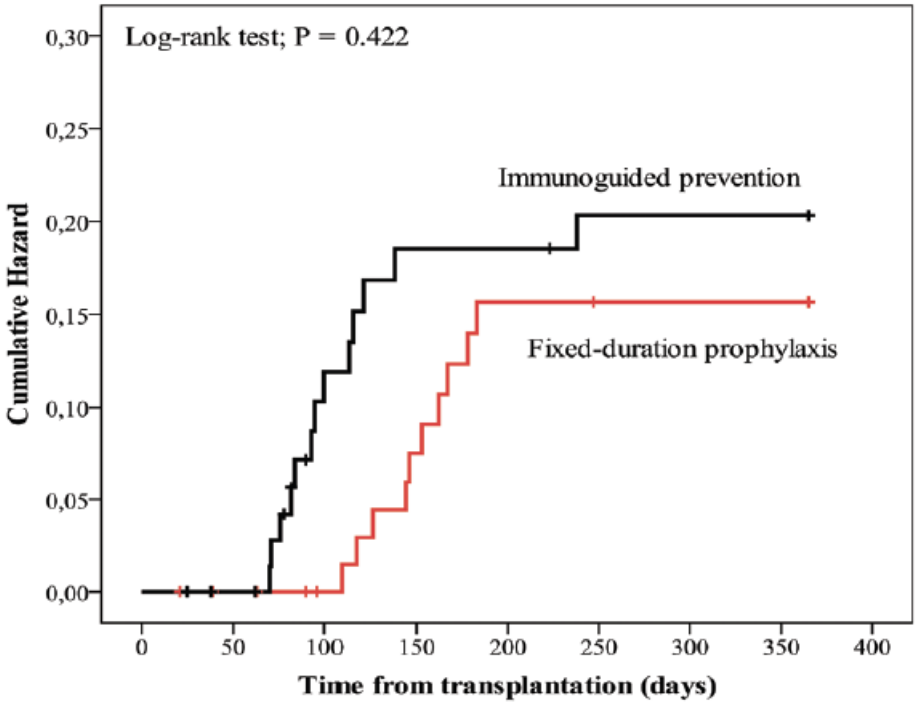
	Immunoguided prevention (n=76)	Fixed-duration Prophylaxis (n=74)	p-value
Primary outcome Incidence of CMV disease	**0 (0.0)**	**2 (2.7)**	**0.243**
Secondary outcome Incidence of DNAemia	**13 (17.1)**	**10 (13.5)**	**0.542**
Neutropenia at month 12	7 (9.2)	28 (37.8)	<0.001

Quantiferon
R+
ATG induction

Paez-Vega, Clinical Infectious Disease 2021

Immunoguided Discontinuation of Prophylaxix in R+ ATG patients

Discontinuation of prophylaxis was followed by tight preemptive strategy and all CMV replication were curatively treated



Quantiferon R+ ATG induction

Paez-Vega, Clinical Infectious Disease 2021

Conventional CMV-specific T cell measurement

Recommendations

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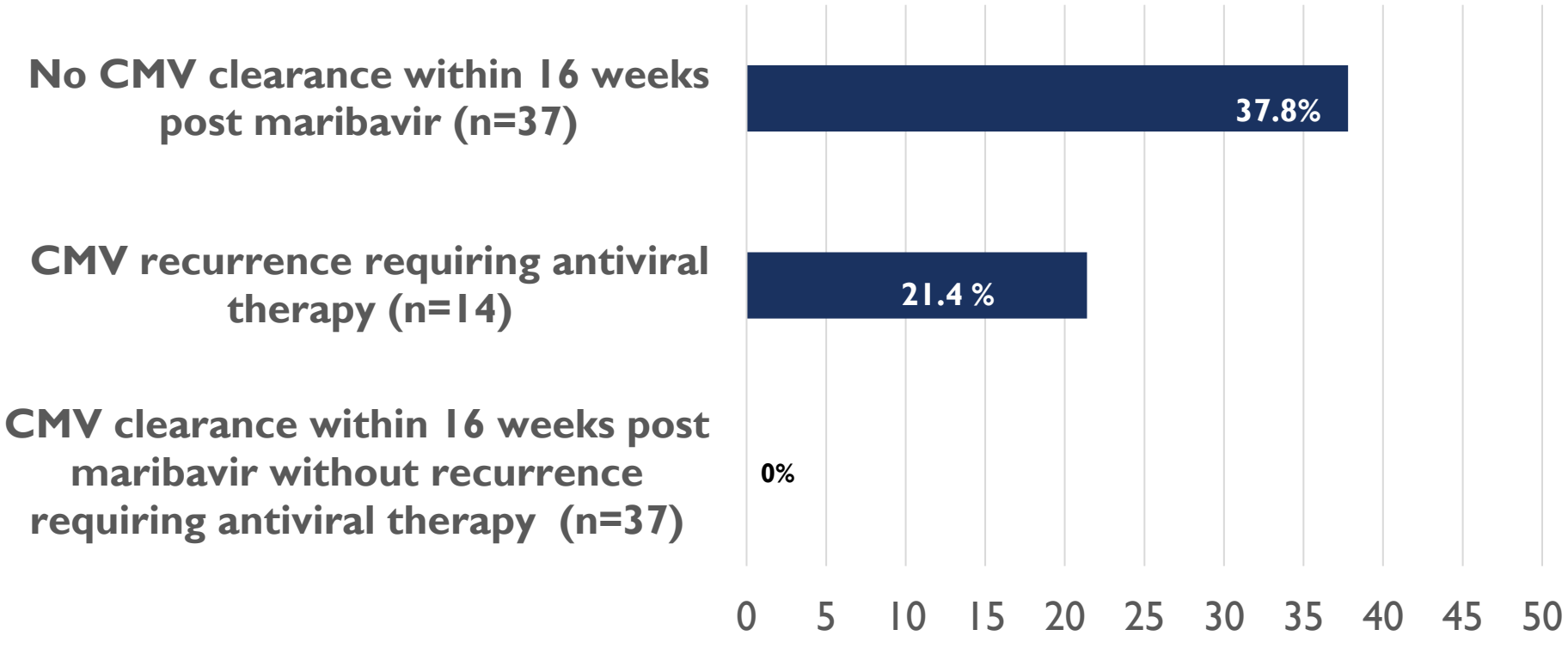
ImmunoConcEpT
Immunology from Concept and Experime to Transition

Multivariate analysis of variables associated with sustained clearance

covariables	HR	CI95%	p-value
Acute rejection before maribavir treatment	6.568	1.521-37.345	0.018
CMV DNA levels <10 000 IU/mL at the time of maribavir introduction	3.535	1.356-9.671	0.011
Asymptomatic CMV infection	3.484	1.303-9.920	0.015

MUTANT CMV STRAINS ASSOCIATED WITH MARIBAVIR RESISTANCE (%)

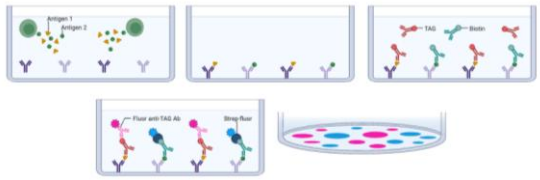


Multivariate analysis of variables associated with mutant strain emergence

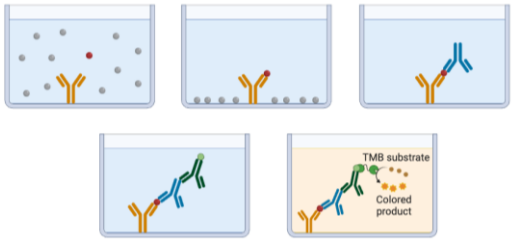
covariables	HR	CI95%	p-value
CMV DNA levels >10 000 IU/mL at the time of maribavir introduction	4.95	1.45-23.25	0.0187

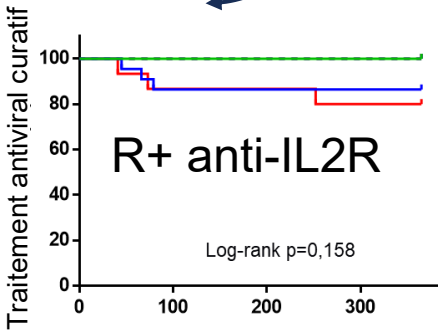
Conventional CMV-specific T cell measurement

ELISPOT

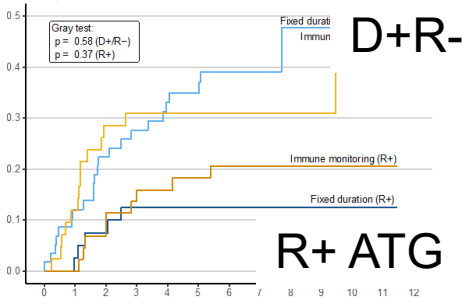


ELISA

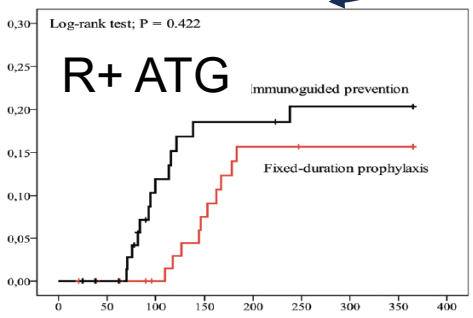


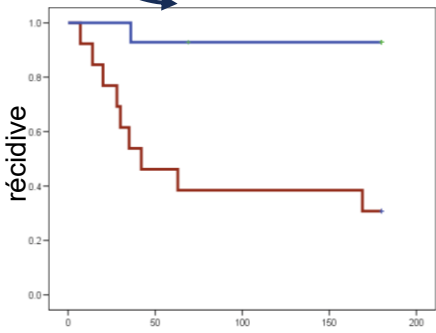


When can we avoid useless prophylaxis?



When can we decrease prophylaxus duration?





How can we adapt curative treatment?

Limits

1. No predictive when NEGATIVE
Control with other unconventional cellular actors?

2. 15% of CMV-CMI positive patients do undergo CMV need antiviral drug . **Dysfunctional CMV-specific immunity?**

O.Manuel, Clin Inf Dis, 2023- Paez-Vega, Clin Inf Dis 2021- Kumar, Am J Transplant. 2017

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Thank you for LISTENING!

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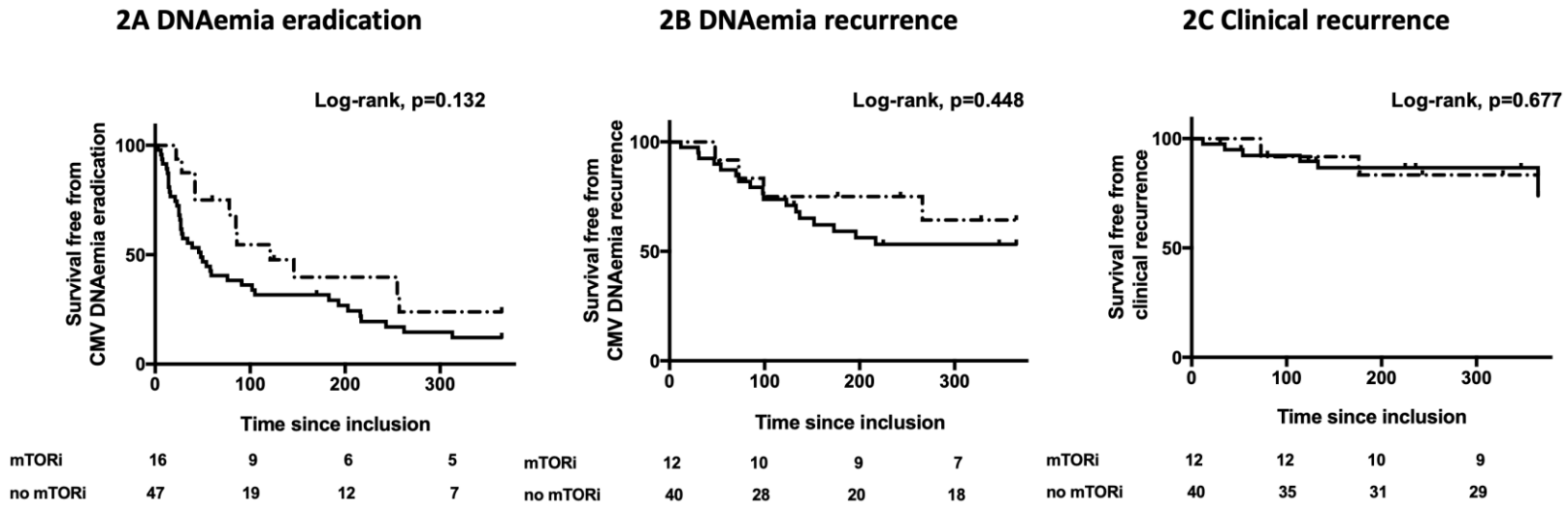
MTORI TO REDUCE CMV RECURRENCES IN D+R-



80% D+R-
Retrospective study
Not only after a first episode of CMV infection

Kaminski, microbiology and immunology, 2020