

The European and French networks

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French Vasculitis Study Group

- December 1980: **L. Guillevin**



- no research, no real interest for rare diseases
- no REB, no Helsinki or Huriet
- Research funded by health social insurance

FVSG network

- Core group
- 66 millions

VS 35 millions

FVSG network

- Core group
- 66 millions in 675,000 km²



VS 35 millions in **10,000,000 km²**

FVSG network

- Core group
- 66 millions in 675,000 km²



VS 35 millions in **10,000,000 km²**

- Any center/MD in France (+ Belgium) > 60/600
- Only 1 REB

Protocoles thérapeutiques prospectifs
Cooperative prospective trials

Group
Français
d'Étude
des Vasculaires

French
Vasculitis
Study
Group

VASCULARITES SYSTÉMIQUES
SYSTEMIC VASCULITIDES
CAHIER D'OBSERVATION
REPORT FORM

Observation initiale

Ce cahier est commun à l'ensemble des protocoles
This report form is common to every trial

COORDINATION SCIENTIFIQUE
SCIENTIFIC COORDINATION

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En cas d'urgence / not for : 33 (0)6 08 95 70 31

Date de recueil des données | | | | | | | | | |

MÉDECIN RESPONSABLE
ATTENDING PHYSICIAN

Nom
Name
Prénom
First name
Service
Department
Hôpital
Hospital
Numéro de rue
Street number
Rue
Street
Ville
City
Code postal
Postal code
Pays / Country
Country
Téléphone (pays, ville, numéro)
Phone (country code, area code, phone number)
Fax (pays, ville, numéro)
Fax (country code, area code, phone number)
e-mail

MÉDECIN GÉNÉRALISTE
GENERAL PRACTITIONER

Nom
Name
Prénom
First name
Numéro de rue
Street number
Rue
Street
Ville
City
Code postal
Postal code
Pays / Country
Country
Téléphone (pays, ville, numéro)
Phone (country code, area code, phone number)
Fax (pays, ville, numéro)
Fax (country code, area code, phone number)
e-mail

Identification du patient / Identification

Trois premières lettres du nom du patient / First three letters of the patient's surname

| | |

Sexe (M ou F) / Sex (M or F) SEX

Date de naissance | | | | | | | | | | DDN

Lieu de naissance

Pays où le patient vit habituellement
Country where the patient usually lives

Ethnie / Race ETH

1 = Blanc / Caucasien - 2 = Noir / Black
3 = Asiatique / Oriental

Origine géographique GEO

Geographic origin
1 = France
2 = Europe du Nord Northern Europe
3 = Europe du sud Southern Europe
4 = Afrique du Nord North Africa
5 = Afrique Noire Sub-Saharan Africa
6 = Asie Asia
7 = Moyen-Orient Middle-East
8 = Antilles West Indies
9 = Autre Other

Néer (en clair)

Occupation

Antécédents / Medical history

ALLERGIE / ALLERGY FAMA

Familiaux allergiques
Family history of allergy

Asthme / Asthma ASTH

Si oui, durée en années
If yes, for how long ? (yr) DUAS

Corticodépendance

CORT
Corticoid dependence

Avec état de mal MAL

With status asthmaticus
Dyspnée continue DYCO
Continuous dyspnea

FVSG database

FICHIER VASC33 - Microsoft Access

Fichier Accueil Créer Données externes Outils de base de données

Formulaires

- _promoteurCHUSPAN
- _promoteurWEGENT
- CHURG BP
- CHURG MP
- CHURG_Old
- Critères PAN
- FICHIER VASC
- IGANCA
- IMPROVE
- pan
- PAN BP
- PAN_MPA_old
- WEGENT
- WEGENTpagnoux
- WEGENTpagnoux alerte M12
- WEGENTpagnoux longT

Numéro: 1144

coordonées médecin: Pr Guillevin, Dr Laroche, Avicenne, Bobigny.

Nom: [REDACTED]

Sexe HI F0: 1 Date de naissance: 16/06/1955

Vascularite: PAN ?

Remarques diagnostiques:

Protocole: 6PANMP95 CY12 EXC

coordonées patients:

N° Protocole: 6

DDNouvelles: 23/03/1995

Survie: V

Chronologie ATCD S Généraux Cut Opht ORL Pulm CardioV Digestif Rénal Neuro Scores-Rq-Evolution Biologie

Nom: [REDACTED] Signes généraux: 1

Poids: 63

Taille:

Karnofski: 60

Fièvre: 0

Amaigrissement: 1

Kilos perdus: 12

Durée amaigr: 6

Myalgies: 1

Arthralgies: 1

COLL: 0

CHURG old file

PAN MPA Old file

IMPROVE File

WEGENT

CHURP MP Suivi

BASE DE DONNEES DU SERVICE

Conception: C. Pagnoux

Enr: 8 sur 2180 Non filtré Rechercher

Mode Formulaire

FR 6:37 PM

CleanWeb - VASCULARITES - PH Christian PAGNOUX - Supervisor

Patients Monitoring Data Management Help

New patient Synchronize Print Templates Save Check data Patients list

Reference : ACC01979SIMONJ Included on : 6/30/05 Data entry Planning

To do ➔

Show : To complete

- [-] Identification
 - Identification
 - Diagnosis
 - Physicians
- [-] Initial visit
 - Medical history
 - Clinical manifestations**
 - Complementary investigation
 - Treatments
- [-] Follow-up visit

Clinical manifestations

General

Weight (kg) : 122,0

Height (cm) :

General condition (Karnofsky score) : 50

Fever : Yes No

Weights loss : Yes No

● If yes, how many kg : 12

Myalgias : Yes No

Arthralgias, arthritis : Yes No

Lymph nodes : Yes No

Specify :

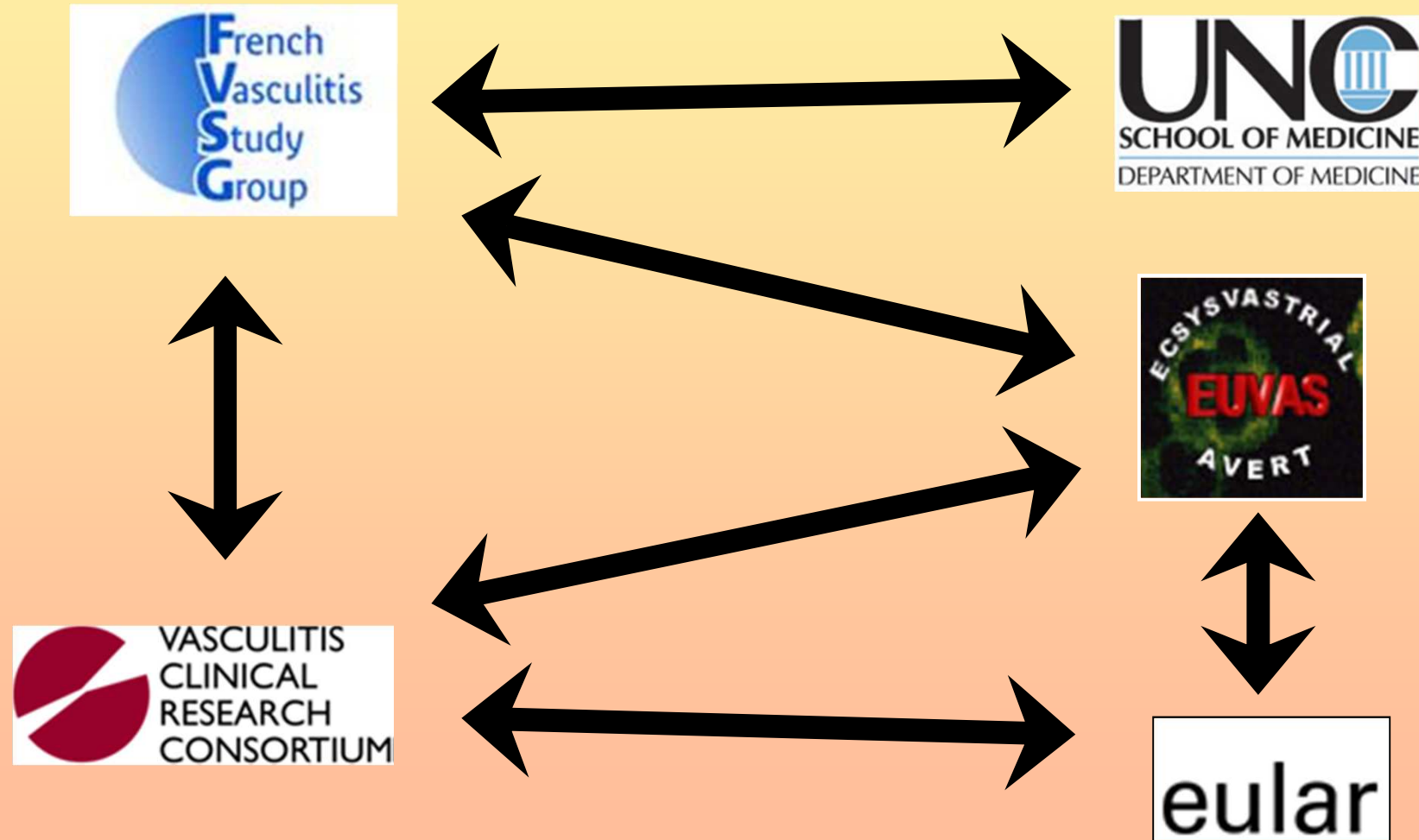
2,742 patients

16 TA	724 GPA	120 BRD
21 GCA	368 MPA	10 PACNS
	479 CSS	50 BEHC
512 PAN	92 CRYO	4 TAO
7 KD	25 HSP	315 NC

Click on a module to unfold, click on a form title to edit

Démarrer | Cacit-Notes | Boîte de réceptio... | SUEDOIS 11.06... | Microsoft PowerP... | CleanWeb - VA... | 12:05

GFEV international connections



International collaborations

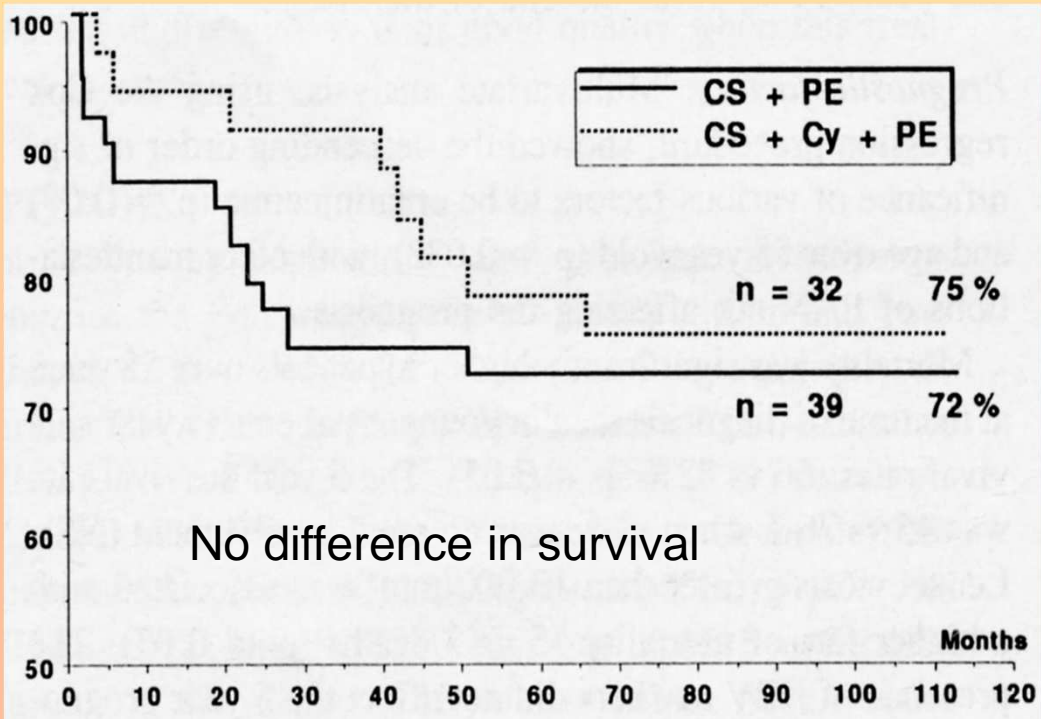
- Pagnoux C, Hogan SL, Chin H, Jennette JC, Falk RJ, Guillevin L, **Nachman PH**. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. *Arthritis Rheum* 2008;58:2908-18.
- Hauser T, Mahr A, Metzler C, Coste J, Sommerstein R, **Gross WL**, Guillevin L, Hellmich B. The leucotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: a case-crossover study. *Thorax* 2008;63:677-82.
- Lidar M, Lipschitz N, Langevitz P, Barzilai O, Ram M, Porat-Katz BS, Pagnoux C, Guilpain P, Sinico RA, Radice A, Bizzaro N, Damoiseaux J, Tervaert JW, Martin J, Guillevin L, Bombardieri S, **Shoenfeld Y**. Infectious serologies and autoantibodies in Wegener's granulomatosis and other vasculitides: novel associations disclosed using the Rad BioPlex 2200. *Ann N Y Acad Sci* 2009;1173:649-57

1980
1991
PAN MPA
CSS



Cyclophosphamide
CS + PE vs
CS + PE + oral CYC

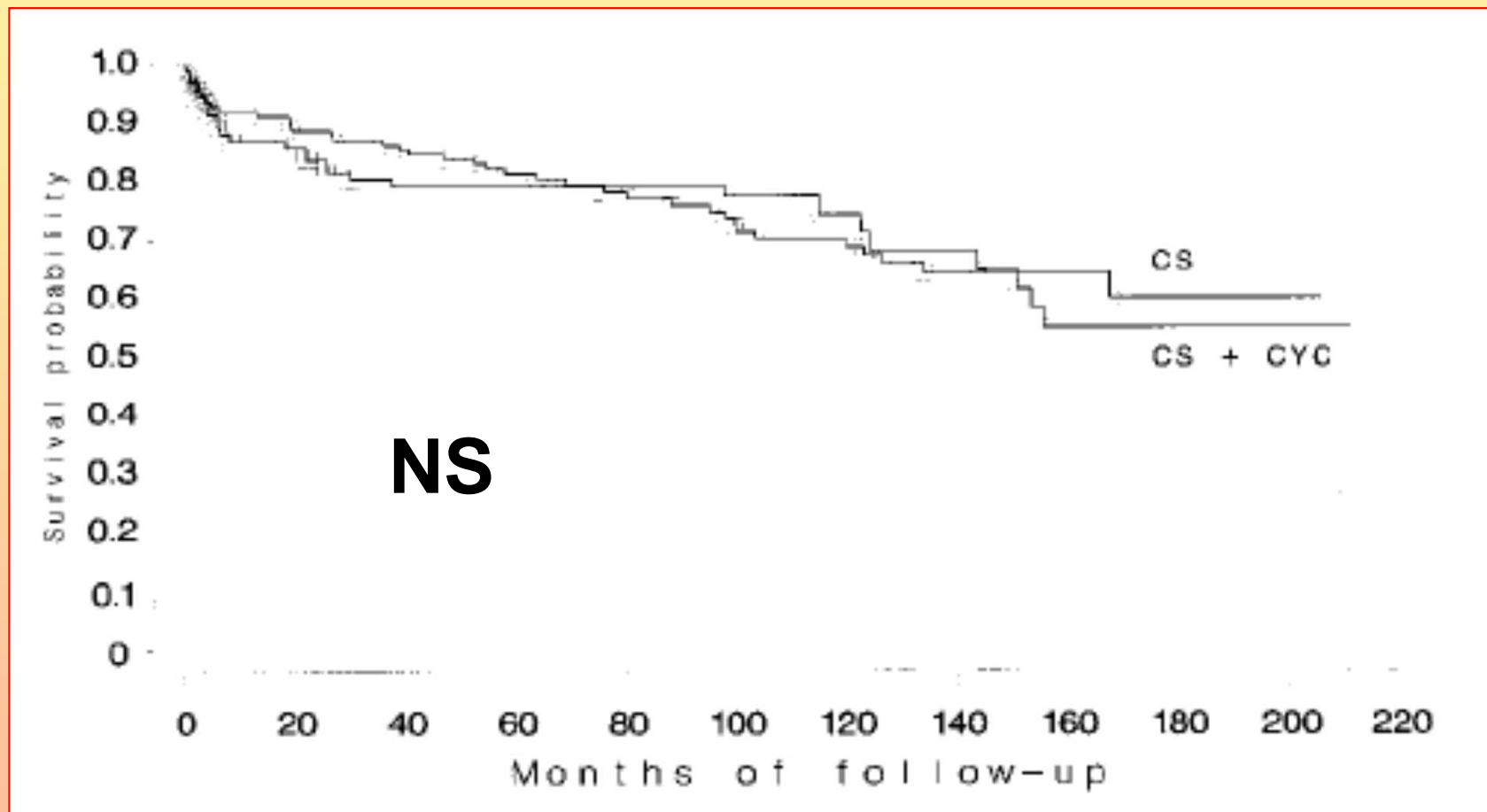
Guillevin, *J Rheumatol* 1991; 18: 567



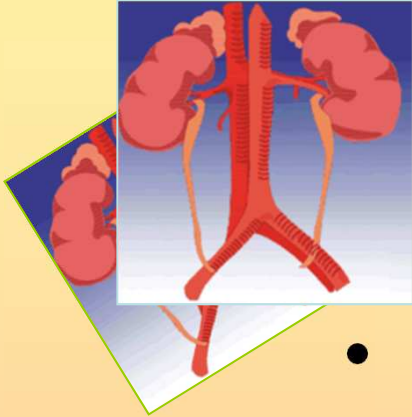
But NO stratification according to
Disease
Severity
HBV status

Relapses
9,4% without CYC
vs 38,5% with CYC
at 10 years

SURVIVAL IN 278 PAN, MPA, CSS PATIENTS



The Five Factor Score



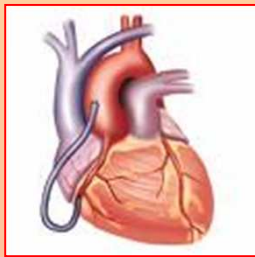
- **Proteinuria >1 g/day**

- **Creatinine level >140 $\mu\text{mol/l}$**

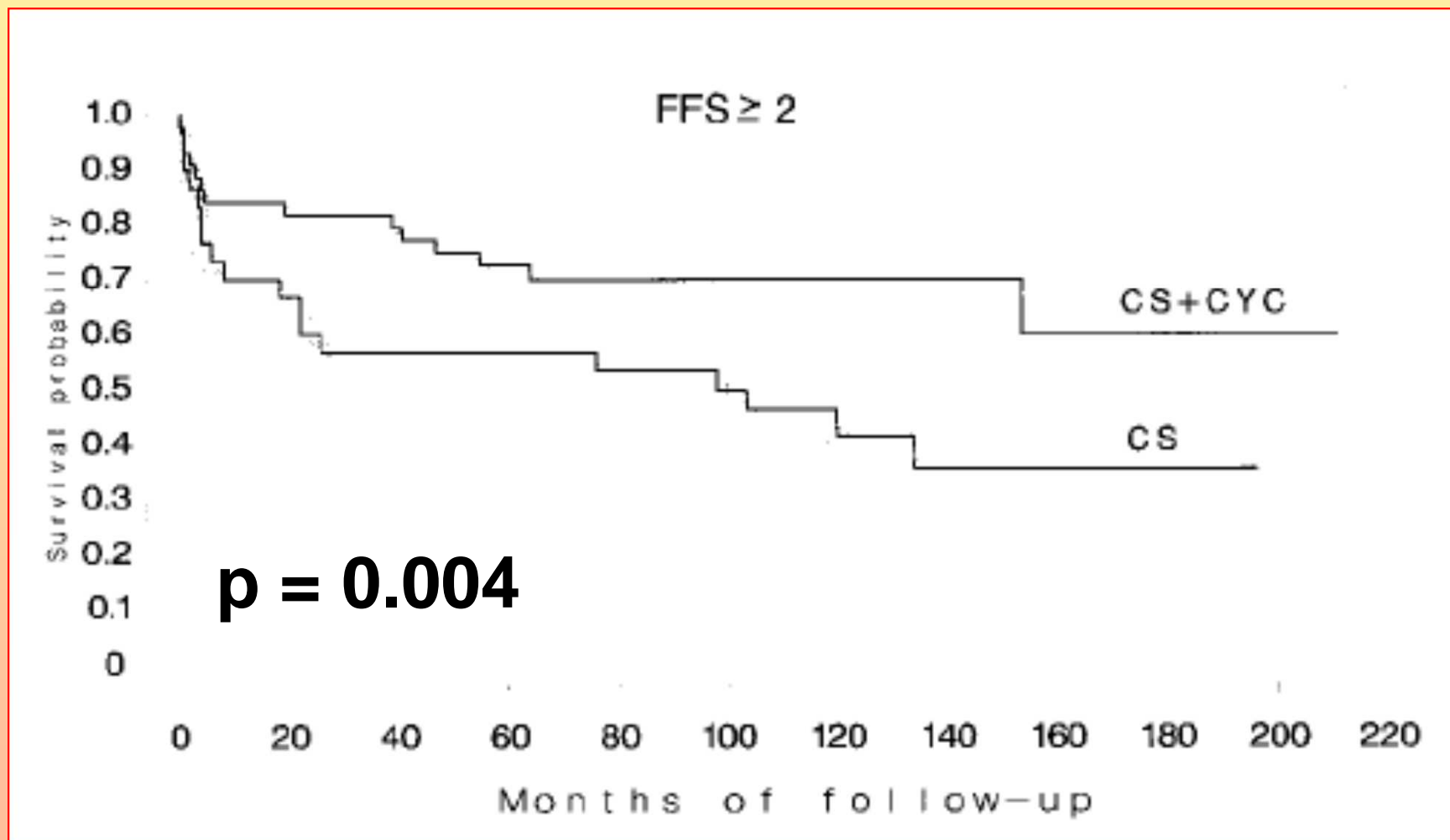
- **Specific GI involvement**

- **Specific cardiomyopathy**

- **Specific CNS involvement**



SURVIVAL IN 278 PAN, MPA, CSS PATIENTS



1994

2005



CHUSPAN

PAN or MPA & CSS – FFS=0

CS alone

(6 CYC pulse vs AZA)

2-phases open label trials

CSS #72 p. Ribi et al, *Arthritis Rheum* 2008;58:586-94

PAN-MPA #124p. Ribi et al, *Arthritis Rheum* 2010;62:1186-97

1994

2005



CHUSPAN

PAN or MPA & CSS – FFS ≥ 1

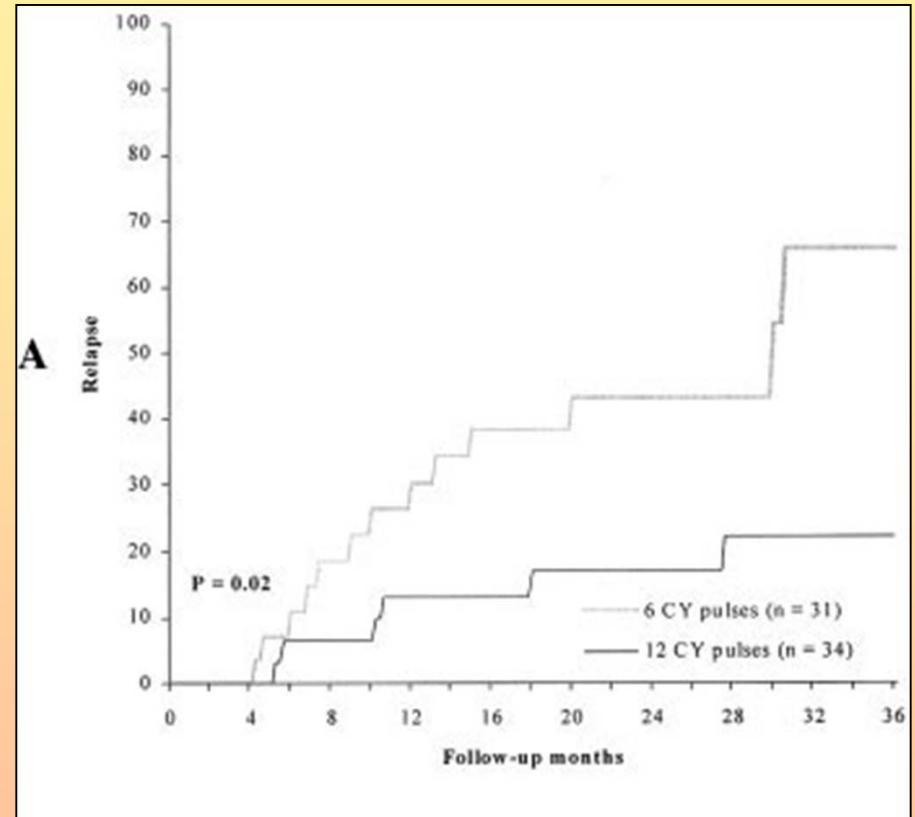
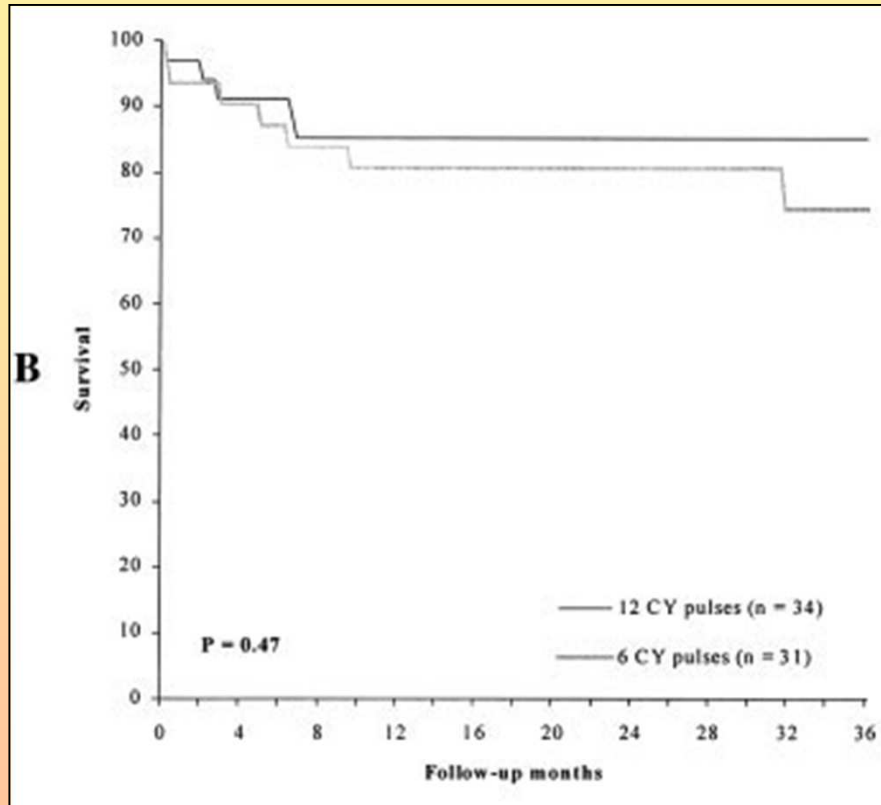
CS + 6 vs 12 CYC pulses

Open label randomized trials

PAN-MPA #65 p. Guillevin et al, *Arthritis Care Res* 2003;49:93-100

CSS #48 p. Cohen et al, *Arthritis Care Res* 2007;57:686-93

CHUSPAN PAN MP



Guillevin et al, *Arthritis Care Res* 2003;49:93-100

1989

1997



CYC routes in PAN MPA

CS + oral CYC vs

CS + IV CYC

Gayraud, *Br J Rheumatol* 1997; 36: 1290

1990

1997



Wegener's granulomatosis

CS + IV vs oral CYC

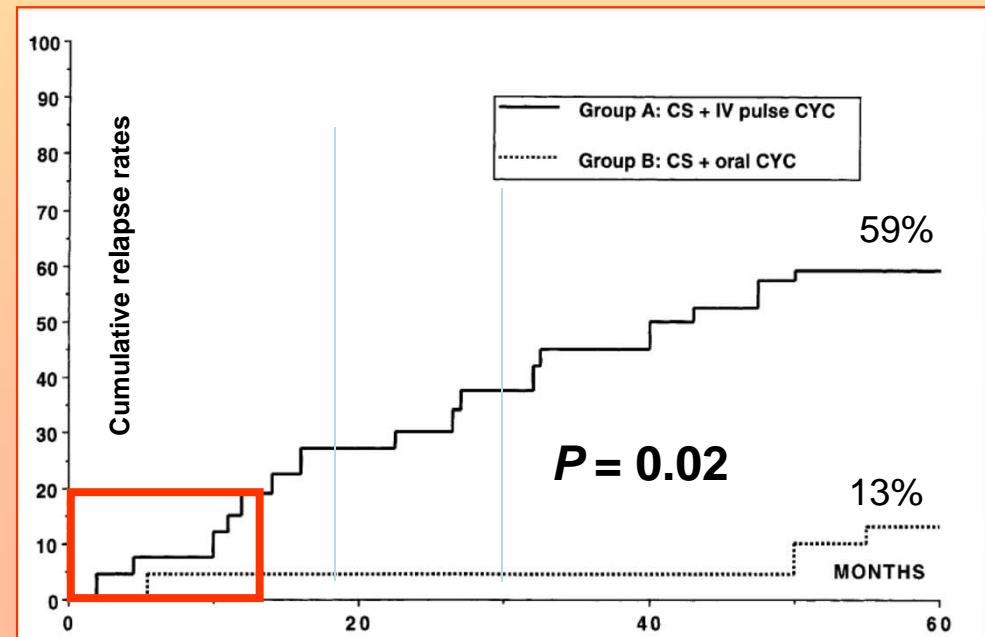
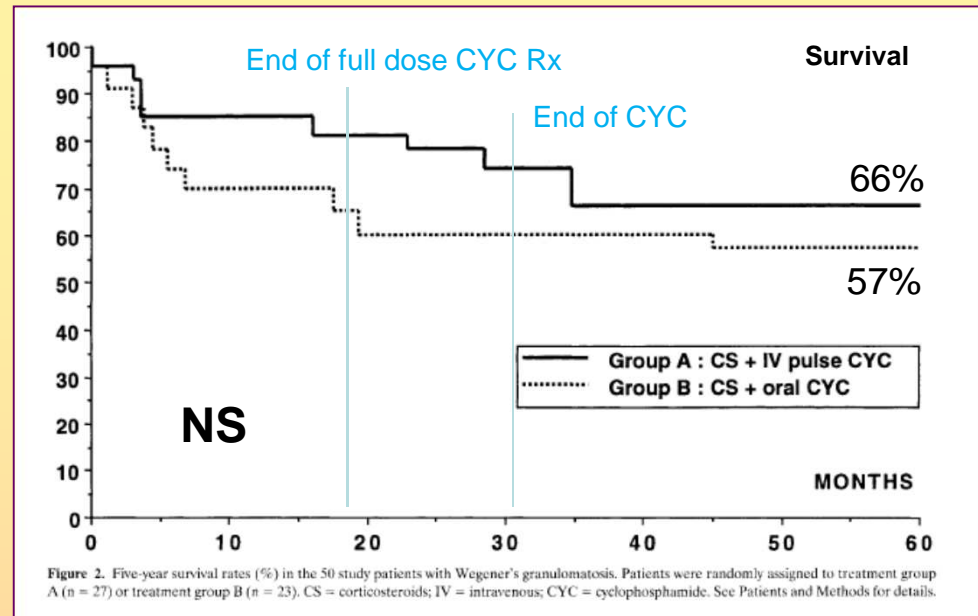
Guillevin, *Arthritis Rheum* 1997, 40: 2187

Open label RCT

- > design over 5 yrs
- 66 p/arm needed
- Interim at half-time **3 yrs**
- **50 WG enrolled**
- **Remission at M6**
IV CYC 88.9%
oral CYC 78.3% (NS)

- **Relapses (mean f/u 30 mo)**
IV CYC 59.2%
oral CYC 13% ($P = 0.02$)
- AEs
IV CYC 40.7%
oral CYC 69.6% ($P < 0.05$)
- **Cumulative CYC dose**
IV CYC 27.8 g
oral CYC 43.9 g ($P < 0.01$)

Guillevin et al, *Arthritis Rheum* 1997;62:1186-97

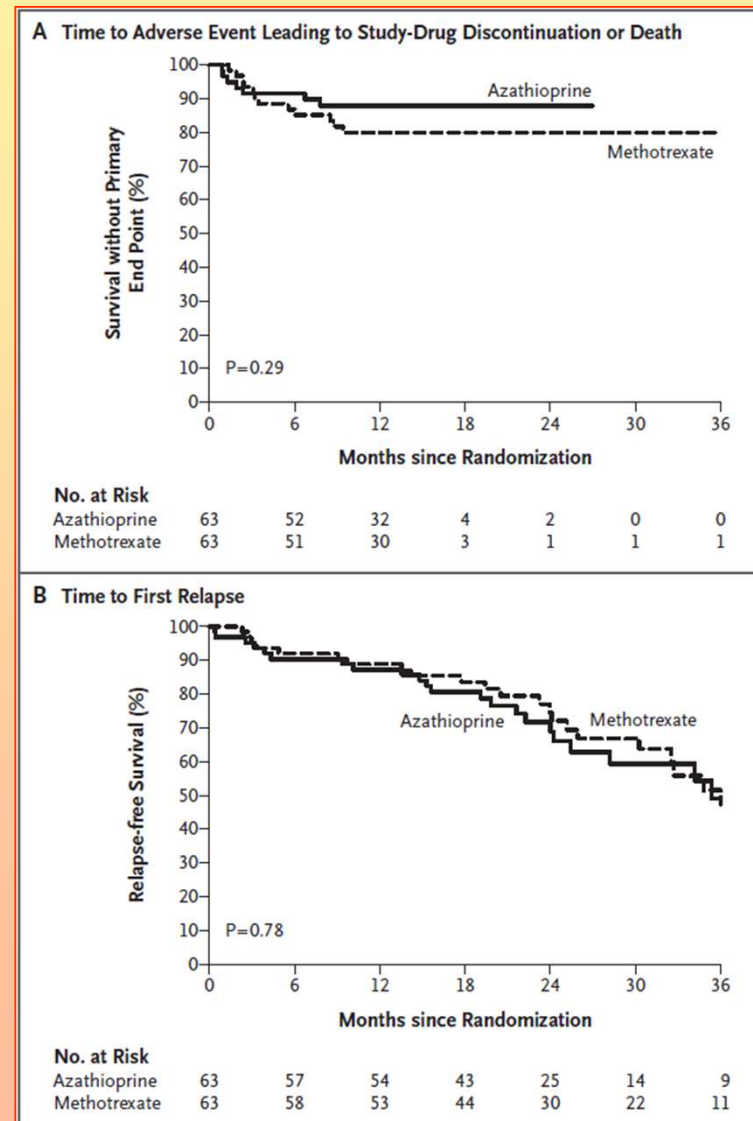


WG & MPA: MAINTENANCE

WEGENT

- > design for AE
- 159 → 126 p. (WG 75%)
- AE requiring drug withdrawal
7 AZA vs 12 MTX (P = 0.21)
- 1 death in the MTX
- Relapses
23 AZA vs 21 MTX (P = 0.71)
73% after discontinuation

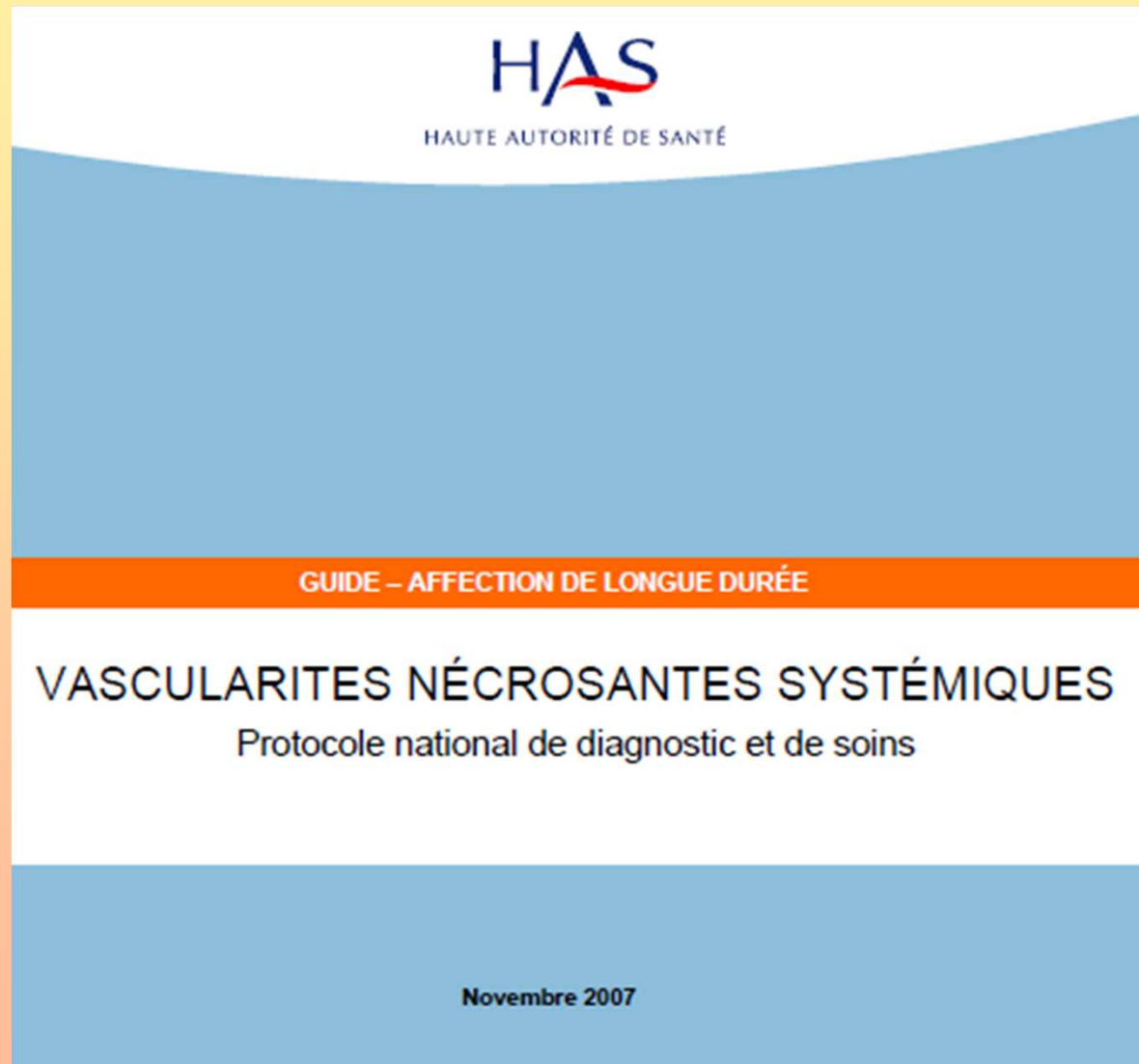
Pagnoux et al, *N Engl J Med* 2008;359:2790-803.



Ongoing FVSG trials/studies

- **CHUSPAN 2**
 - CSS, MPA or PAN with FFS = 0
 - 60/120 included
 - Double blinded study
- **MAINRITSAN**
 - RTX 500 mg/6 months vs AZA for maintenance
- **COVAC'**
 - PACNS cohort

French recommendations



Educational program and annual meetings

- Annual national meetings
 - 80 to 120 attendees since 1990
 - No way to skip 1 year...
- Website
 - vascularites.org
 - 80 to 150 visitors per day

EUVAS



EUVAS



- Unofficial group since 1985
 - Denmark + Netherlands

EUVAS



- Unofficial group since 1985
 - Denmark + Netherlands
- EC/BCR ANCA study in 1989
 - 7 → 14 centers in Europe

EUVAS



- Unofficial group since 1985
 - Denmark + Netherlands
- EC/BCR ANCA study in 1989
 - 7 → 14 centers in Europe
- BIOMED1 grant 1994 → ECSYVASTRIAL
 - 3 clinical trials: **CYCAZAREM**, NORAM, MEPEX

EUVAS



- Unofficial group since 1985
 - Denmark + Netherlands
- EC/BCR ANCA study in 1989
 - 7 → 14 centers in Europe
- BIOMED1 grant 1994 → ECSYVASTRIAL
 - 3 clinical trials: CYCAZAREM, NORAM, MEPEX
- BIOMED2 grant 1999 → AVERT
 - CYCLOPS, IMPROVE, REMAIN
- EUVAS

EUVAS



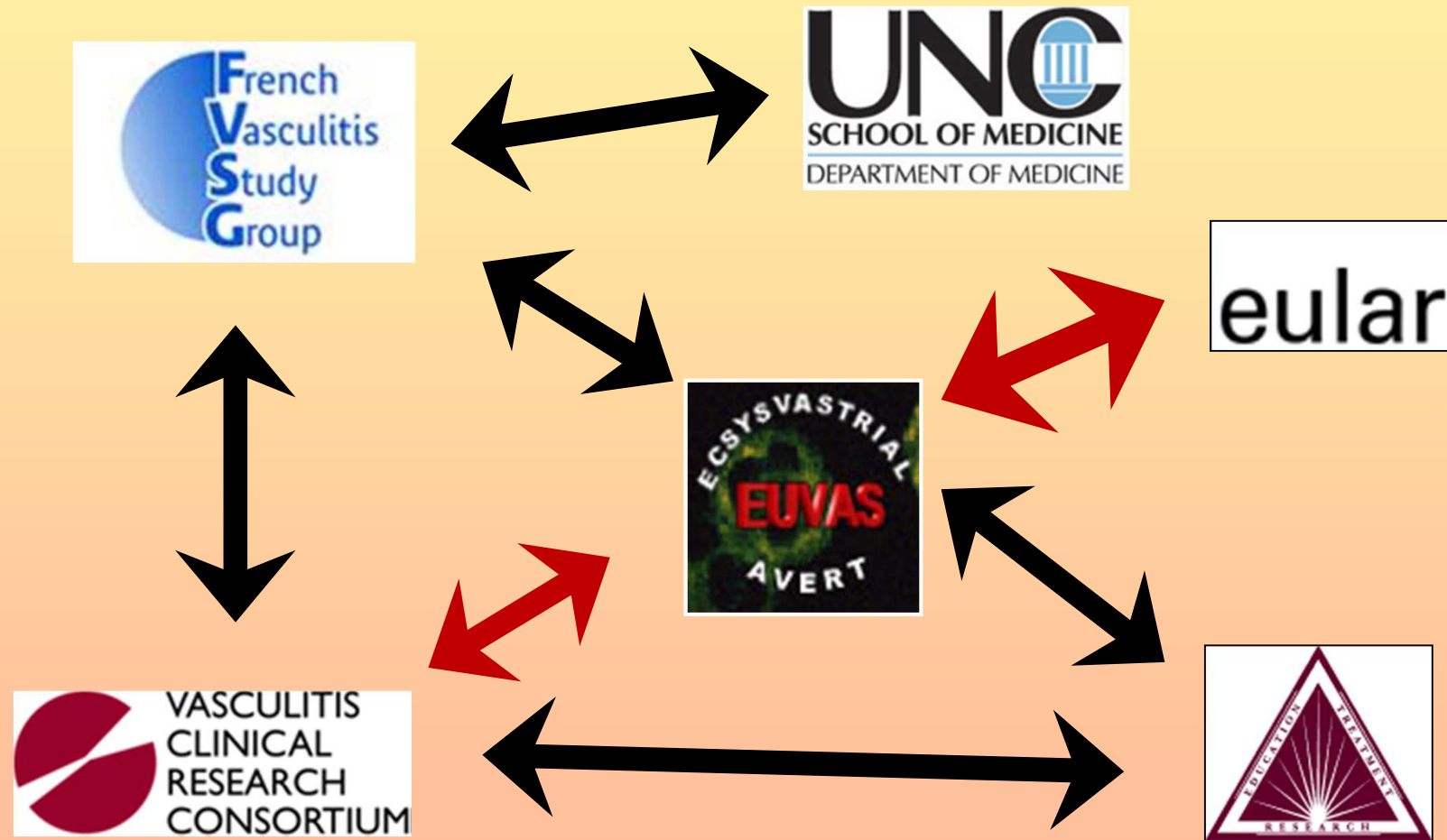
- Pharmaceutical industry funded trials
 - MYCYC, RITUXVAS, (ABAVAS)

EUVAS



- NO multicentric cohort or longitudinal database
 - UKVAS
- Long-term follow-up of trial patients

EUVAS international connections



EUVAS / EULAR

- Hellmich et al. EULAR **recommendations for conducting clinical studies and/or clinical trials** in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2007;66:605-17
- Mukhtyar et al. EULAR **recommendations for the management** of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68:310-7
- Mukhtyar et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2009;68:318-23
- Basu et al. EULAR points to consider in the development of **classification and diagnostic criteria** in systemic vasculitis. Ann Rheum Dis 2010;69:1744-50

EUVAS

- MAJOR international EU trials
- MAJOR funding
- MAJOR playerS (including « fellows »)
- MAJOR « expert » (only) meetings

- Successful network