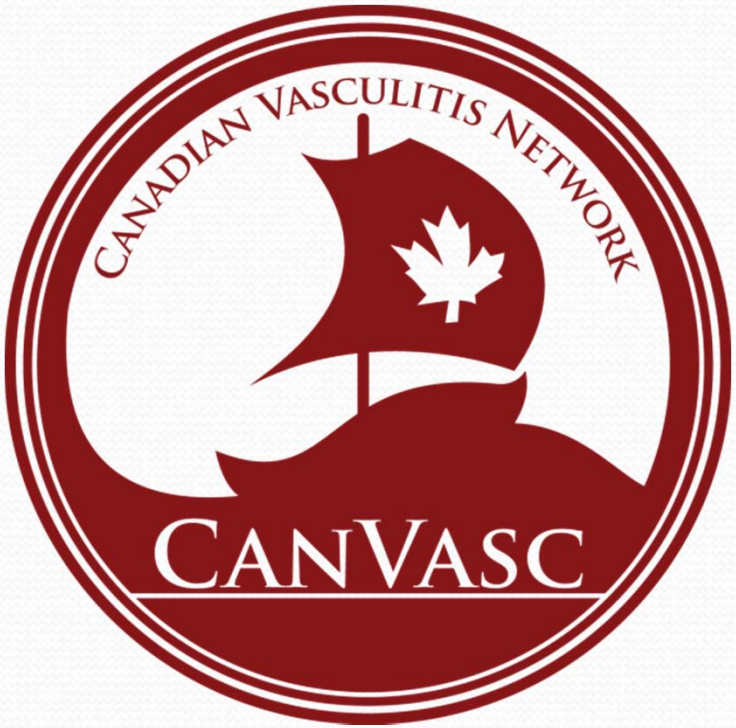
Vasculitis STUDIES in Canada and CanVasc projects



Ongoing CanVasc activities and studies

- Why CanVasc?
- What is it?
- What are its objectives?
- Identify some ongoing and future projects

CanVasc creation

- Drs. Pagnoux, Carette, Khalidi
- CanVasc = created on November 1st, 2010

Objectives

- **organize a dedicated health and research network across Canada** for patients with vasculitis with identification of referral (multidisciplinary) centers.

The network


Yukon
Northwest Territories
Nunavut
British Columbia
Alberta
Saskatchewan
Manitoba
Ontario
Québec
NFLD
PEI
Nova Scotia
New Brunswck

CanVasc core member meetings

- 1st core member meeting 12 Feb. 2011 (CRA)
- 2nd core member meeting, 9 June 2011
- 3rd core member meeting,

  29 March 2012 (CRA)

June 2011

- **4th core member meeting,**

  14 or 15 February 2013 (CRA, Ottawa)

Objectives

- **organize a dedicated health and research network across Canada**
- **Develop educational and awareness programs for health care providers**

Recent Evidence in VasculitIs SclIence and Treatment

Management of AAV in the clinical setting

The CanVasc website

Creator and webmaster: Dr. Christian Pagnoux

2nd annual CanVasc meeting

Montréal, QC

November 22nd, 2012

Registration and information on

http://www.canvasc.ca

Objectives

- **organize a dedicated health and research network across Canada**
- **Develop educational and awareness programs for health care providers**
- **Initiate, conduct, and promote studies** on vasculitis across Canada using an existing, efficient and rapidly mobilisable network

Studies

- **Creation of a Canadian database** for all Canadian centers (ongoing process) for adult vasculitis patients (Drs. Barra, Pagnoux – Twilt, Benseler, Cabral)

- Extension of pediatric **CNS vasculitis database** to Canadian adults (Dr. Twilt, Milman, Benseler, Pagnoux → Dr. Lanthier)

« Support » for core members' initiatives

- Dr. Yacyshyn, Edmonton: PD Survey, Takayasu systematic review
- Dr. Liang, Sherbrooke: Management of AASV / influence of guidelines
- Dr. Pagnoux, Nair, Khalidi, Carette: Cytokine profile in EGPA

Other potential collaborations / studies « affiliated » with CanVasc

- Dr. Ma Donglai (Toronto) and Marvin Fritzler (Calgary)
- Dr. Siminovitch: Genetic study on GPA/MPA
- Dr. Siminovitch: Cytoflux study on GPA/MPA

Two Biomarker Discovery Strategies

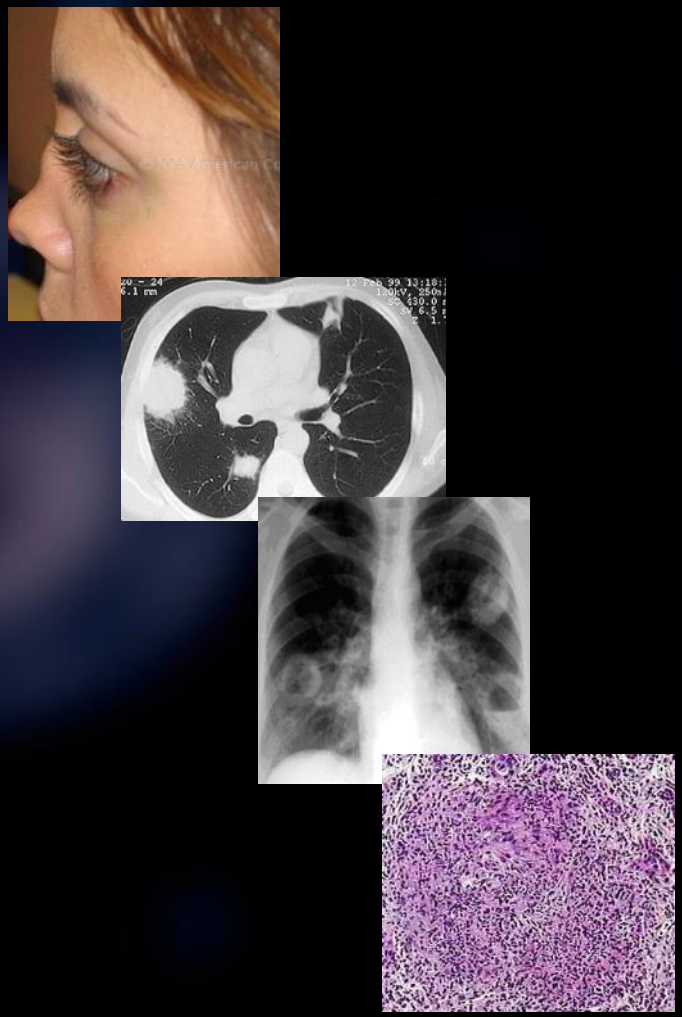
A) Genotype Profiling

Use genome-wide association and whole exome sequencing to identify clinically-relevant genetic profiles.

B) Immunophenotyping

Use multiparameter flow cytometry to classify and monitor disease.

Canada-initiated study of GPA genetics



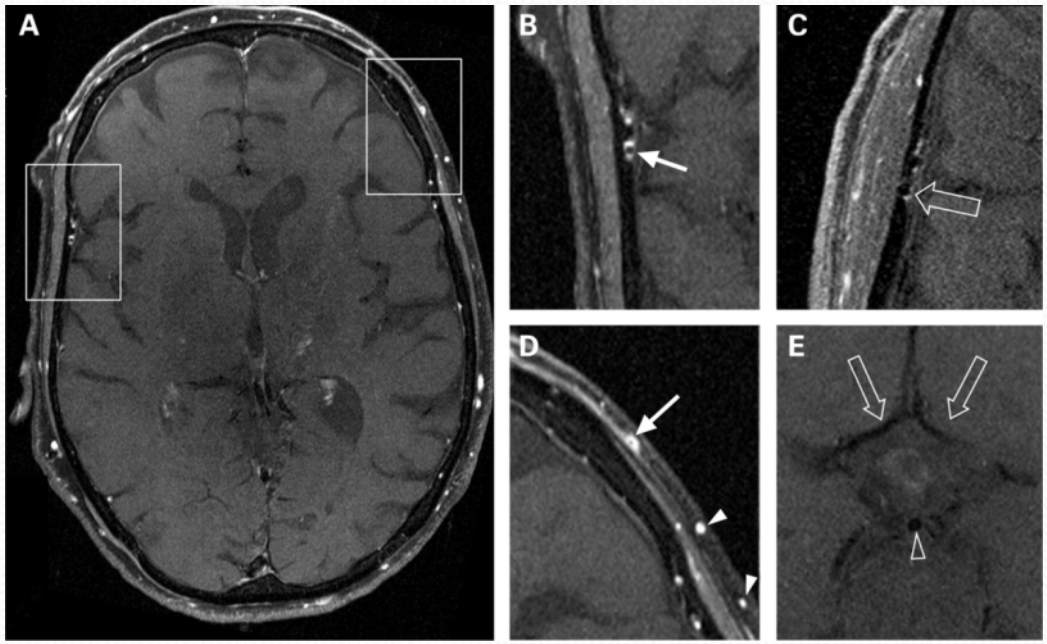
- Genotype 459 cases/1503 controls (Canadian)
- GWAS 700,000 markers
- Replicate 578 cases/1228 controls (WGGER, VCRC)

GENE	Proposed Function	P-value
HLA-DPB1	Immunoregulation	1.9×10^{-50}
HLA-DPA1	Immunoregulation	2.1×10^{-39}
SEMA6A	Immunoregulation	2.0×10^{-8}

Data from K. Siminovitch et al.

McMaster's GCA / MRI study

- Dr. Khalidi
- Dr. Clements-Baker
- Dr. Rebello
- Dr. Ioannidis



Bley et al. Ann Rheum Dis 2009;68:1369-1370

Other potential collaborations / studies from « affiliated » CanVasc

- Dr. Licht: complement
- Dr. Swartz, Mikulis, Mandell: CNS vessel imaging
- Dr. Milman: International Classification of Function in vasculitis

…others

Talk low, talk slow
and don't say too much

Objectives

- **organize a dedicated health and research network across Canada**
- **Develop educational and awareness programs for health care providers**
- Establish and regularly update **Canadian recommendations for the diagnostic and therapeutic management** of patients with vasculitis

Management of SNV patients

- Canadian consensus for the management of ANCA vasculitides
  - Ongoing process
  - under the aegis of CRA therapeutic committee
  - Led by Drs. Pagnoux and Liang (CanVasc)
  - By Fellows: **Dr. Famorca** (adult) and Twilt (pediatrics)

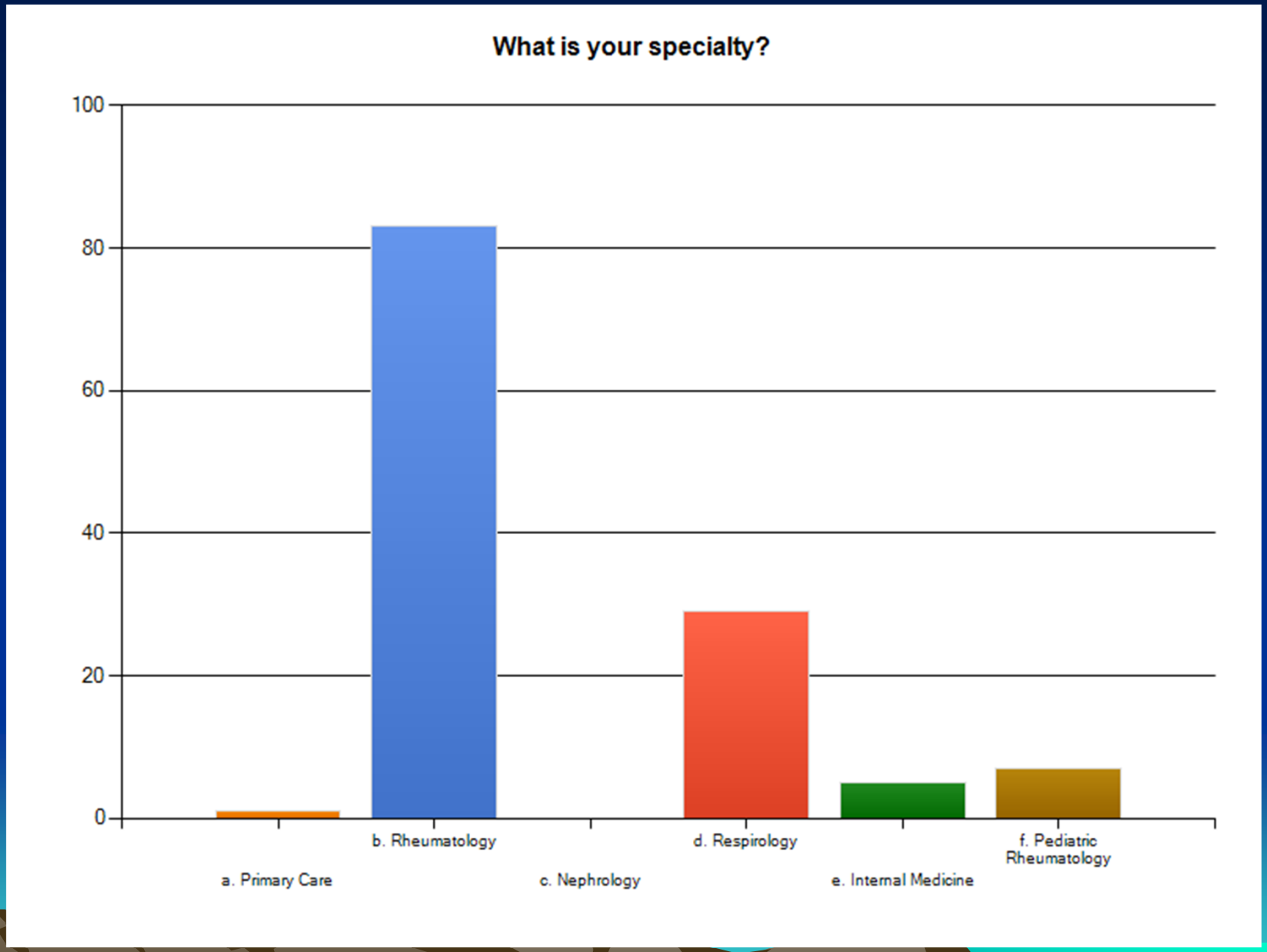
VASCULITIS NEEDS ASSESSMENT QUESTIONAIRE

Results

136 physicians

English - 121

French -15


What is your specialty?
100
80
60
40
20
0
a. Primary Care
b. Rheumatology
c. Nephrology
d. Respirology
e. Internal Medicine
f. Pediatric Rheumatology

Indicate which of the following 5 topics, would you like to see included in the upcoming Canadian ANCA-associated vasculitis recommendations ?

- 1. Remission InductionTreatment
- 2. Treatment of refractory cases
- 3. Treatment of relapsing patients
- 4. Indication of the use of Biologics
- 5. Remission maintenance treatment

Canadian consensus for the management of ANCA vasculitides

- Needs assessment questionnaire

- Review of literature on the ~25 identified points to cover
- Writing of draft with grading of evidence (GRADE)

  → Dr. Lucy McGeoch

- Reviewing by CanVasc core members (Spring 2013)
- Revised draft → subgroups (CSN, CRA, CSN committees)
- Revised draft V2 → Final version (Fall 2013)

Objectives

- **organize a dedicated health and research network across Canada**
- **Develop educational and awareness programs for health care providers**
- **Canadian Recommendations for the diagnostic and therapeutic management**
- **Initiate, conduct, and promote studies** on vasculitis across Canada using an existing, efficient and rapidly mobilisable network
- **Stand as the Canadian advisory group in vasculitis**

REIMBURSEMENT CRITERIA

For the induction of remission of severely active Granulomatosis with Polyangiitis (GPA) OR microscopic polyangiitis (MPA) as combination treatment with glucocorticoids, in patients who meet all of the following criteria:

1. The patient must have severe active disease that is life- or organ-threatening. At least one supporting laboratory and/or imaging report must be provided. The organ(s) and how the organ(s) is(are) threatened must be specified.
2. There is a positive serum assays for either proteinase 3-ANCA (anti-neutrophil cytoplasmic autoantibodies) or myeloperoxidase-ANCA. A copy of the laboratory report must be provided.
3. Cyclophosphamide cannot be used for the patient for at least ONE of the following reasons:

a) The patient has failed a minimum of six IV pulses of cyclophosphamide; OR
b) The patient has failed three months of oral cyclophosphamide therapy; OR
c) The patient has a severe intolerance or an allergy to cyclophosphamide; OR
d) Cyclophosphamide is contraindicated; OR
e) The patient has received a cumulative lifetime dose of at least 25 g of cyclophosphamide; OR
f) The patient wishes to preserve ovarian/testicular function for fertility.

The initial treatment would be a once weekly infusion dosed at 375 mg/m^2 x 4 weeks.

The physician must confirm that the treatment would not be a maintenance infusion as maintenance infusions will not be funded.

Renewals will be considered provided that, the patient meets the same criteria for initial approval and the request for retreatment is made no less than 6 months after the last does of the patient's last treatment cycle with Rituxan.

Ongoing NON-CanVasc studies in Canada

VCRC studies: Hamilton + Toronto

International studies : several co-investigator sites

- Institutional/research group studies: PEXIVAS, DCVAS
- Pharmaceutical companies: (to start soon)

VCRC longitudinal studies

- GCA, TA, PAN, MPA/GPA, EGPA
- Visits every
  - 3 months for 2 years then yearly
  - Every year

Current Accruals - Participants Registered (as of 20/Nov/2012 03:06 PM)

	Boston University School of Medicine (VCRC)		Cleveland Clinic Foundation (VCRC)		Johns Hopkins University (VCRC)		Mayo Clinic (VCRC)		Mount Sinai Hospital, Toronto (VCRC)		St. Joseph's Healthcare Hamilton (VCRC)		University of South Florida (VCRC)		Total	
	Cumulative	Current Year*	Cumulative	Current Year*	Cumulative	Current Year*	Cumulative	Current Year*	Cumulative	Current Year*	Cumulative	Current Year*	Cumulative	Current Year*	Cumulative	Current Year*
5502	20	0	16	3	19	0	51	2	16	2	100	7	0	0	**240**	**20**
5503	37	0	27	0	15	0	26	1	24	1	9	1	0	0	**150**	**4**
5504	16	0	8	1	8	0	9	1	13	0	19	0	0	0	**79**	**3**
5505	72	0	105	6	81	0	91	7	109	15	69	4	0	0	**569**	**41**
5506	29	0	19	2	26	0	18	1	41	4	16	0	0	0	**161**	**10**
5510	83	1	62	16	1	0	37	6	16	3	18	3	0	0	**313**	**49**
5515	8	0	4	0	0	0	1	0	9	2	2	1	0	0	**24**	**3**
5522	9	0	0	0	4	0	7	0	0	0	0	0	0	0	**20**	**0**
5523	8	0	7	0	8	0	16	2	4	2	9	1	0	0	**71**	**8**
5531	467	0	0	0	0	0	0	0	0	0	0	0	0	0	**467**	**0**
5533	0	0	0	0	0	0	0	0	0	0	0	0	707	0	**707**	**0**
5534	0	0	0	0	0	0	0	0	0	0	0	0	386	0	**386**	**0**
5599	0	0	0	0	0	0	0	0	0	0	0	0	510	510	**510**	**510**

* Current year begins August 1st and ends July 31st

Protocol Management Tools

5502	VCRC Longitudinal Protocol for Giant Cell Arteritis
5503	VCRC Longitudinal Protocol for Takayasu's Arteritis
5504	VCRC Longitudinal Protocol for Polyarteritis Nodosa
5505	VCRC Longitudinal Protocol for Granulomatosis with Polyangiitis (...
5506	VCRC Longitudinal Protocol for Churg-Strauss Syndrome
5510	VCRC Genetic Repository One-Time DNA Protocol
5515	VCRC Imaging Protocol for Magnetic Resonance and Positron Emissio...
5522	A Multi-Center, Open-label Pilot Study of Abatacept (CTLA4-Ig) in...
5523	Concurrent Pilot Studies in Giant Cell Arteritis and Takayasu's A...
5531	Reproductive Health in Men and Women with Vasculitis

VASCULITIS CLINICAL RESEARCH CONSORTIUM

ACR 2012 #1655 (oral) - Monday

An Open-Label Trial of Abatacept in Mild Relapsing GPA

Mild relapsing: confined to ≥1 sites, with Rx being the reinstitution or increase in CS to <30mg OD and/or an increase or addition of a 2nd immunosuppressant but not CYC (no AH, no renal)

CTLA4-Ig, abatacept
10 mg/kg IV D1, 14, 28 then monthly
On top of ongoing Rx with CS (15), AZA (3), MTX (7), MMF (4)

→ 20 patients

Variable	Value at Study Entry	
Age (range)	45 years (17-73)	
Female/Male	9/11	
PR3-cANCA	80%	
MPO-pANCA	10%	
GPA duration mean (range)	100 months (5-326)	
BVAS/WG mean (range)	3.1 (1-6)	
VDI mean (range)	2.5 (0-7)	
Organ Involvement	**Before Study Entry (Ever)**	**Active Disease at Study Entry**
Constitutional	85%	30%
ENT	100%	90%
Musculoskeletal	75%	50%
Cutaneous	60%	40%
Mucous membranes	25%	5%
Lung	70%	30%
Kidney	40%	-
Eye	30%	-
Nerve	20%	-

Langford C et al – Cleveland Clinic Foundation / VCRC

ACR 2012 #1655 (oral) - Monday

An Open-Label Trial of Abatacept in Mild Relapsing GPA

- 18 (90%) had disease improvement
- 16 (80%) achieved remission with BVAS/WG=0 (median duration of remission before study closure was 12 months [4-21])
- 11/15 on PDN were able to stop PDN

- 3 relapses (19% of those who achieved remission), at a median of 8.3 months
- 6 (30%) dropped out because active disease, not severe (3 relapsers + 3 failures)

- 9 SAEs in 7 patients, including 7 infections, none severe

Langford C et al – Cleveland Clinic Foundation / VCRC

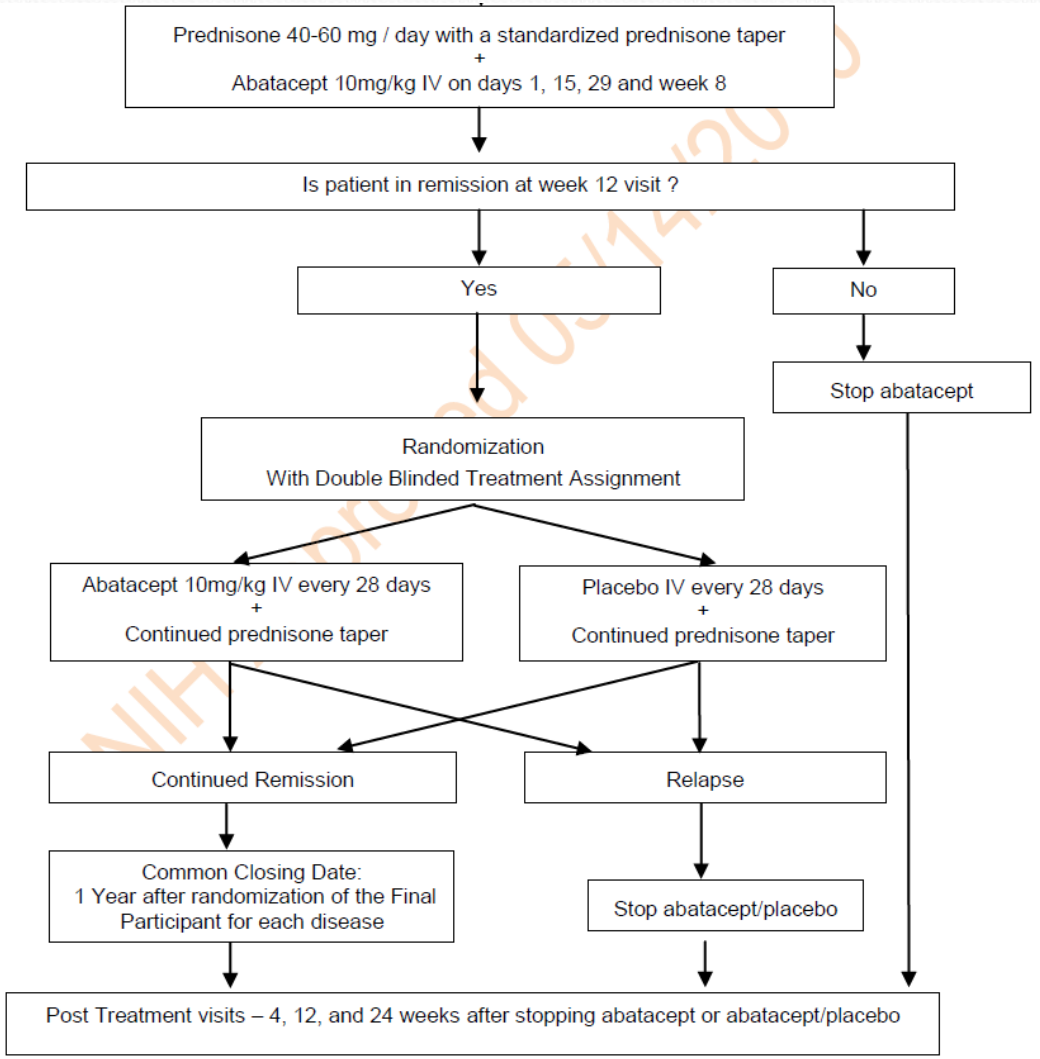
Phase III STUDY IN MILD GPA RELAPSE ???

AGATA LVV

- VCRC 5523
- CTLA4-Ig

- 2 Hamilton
- 1 Toronto

- 33+33 Needed
- Total 71 initial phase
  but only ~50 rdm



VCRC patient registry

http://rarediseasesnetwork.epi.usf.edu/vcrc/index.htm

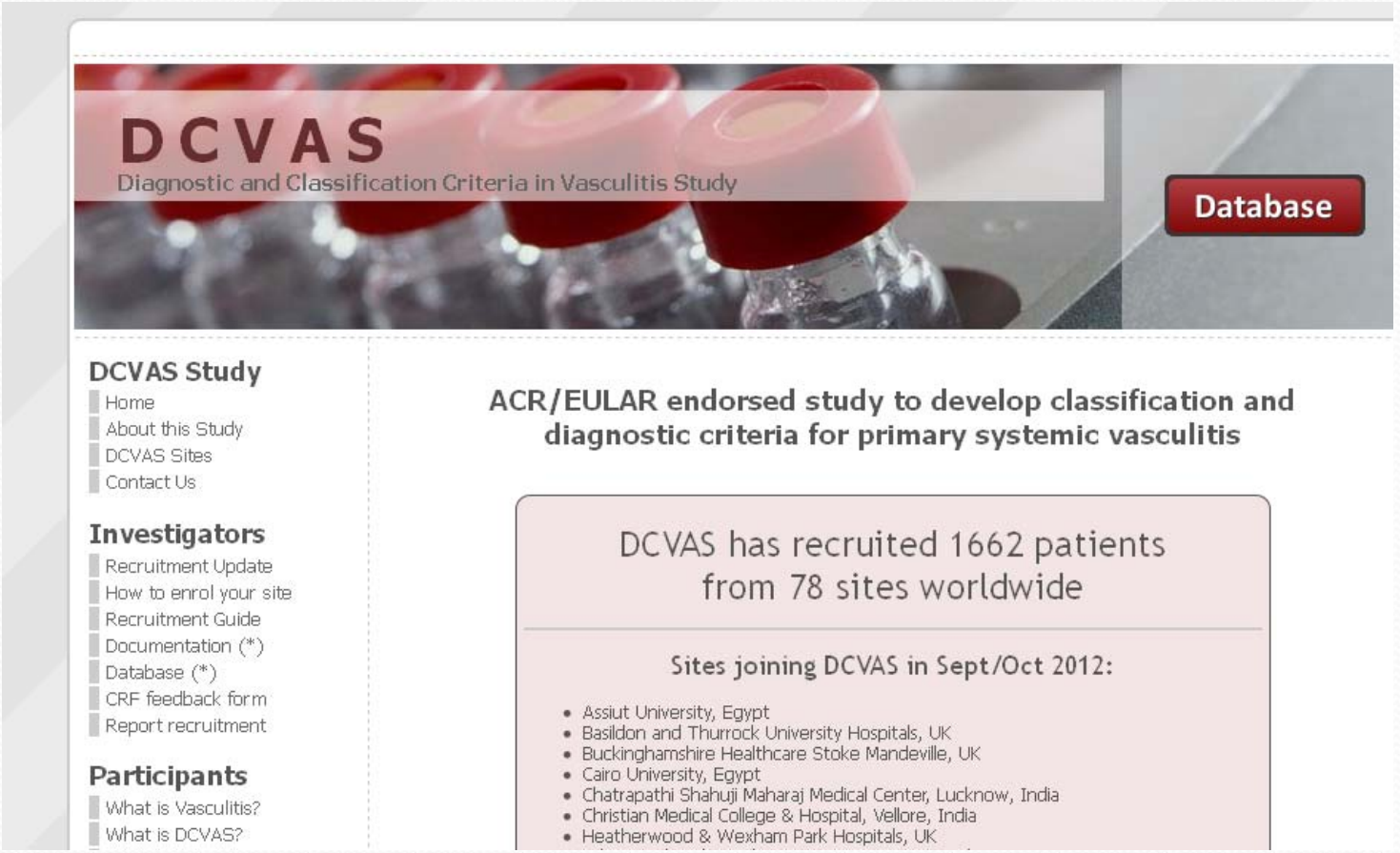
> 3,000

International studies with Canada!

- PEXIVAS
- DCVAS

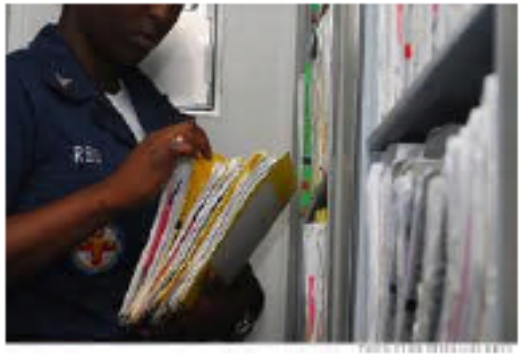
International studies with Canada!

- PEXIVAS
- DCVAS



Identifying participants

DCVAS



Patients over 18 years with

- A new diagnosis of vasculitis
- An established diagnosis

  Date of diagnosis must not be more than two years before the date of enrolment
  Patients can have had symptoms for longer

- A potential diagnosis of vasculitis

CA	St Joseph's Healthcare London, Ontario	40
CA	University of Ottawa	10
CA	St Joseph's Healthcare Hamilton, Ontario	23
CA	Mount Sinai Hospital, Toronto	7
CA	University of Manitoba, Winnipeg	9

Mid-Sept. 2012

+ Calgary?

DCVAS Study
- Home
- About this Study
- DCVAS Sites
- Contact Us

Investigators
- Recruitment Update
- How to enrol your site
- Recruitment Guide
- Documentation (*)
- Database (*)
- CRF feedback form
- Report recruitment

Participants
- What is Vasculitis?
- What is DCVAS?
- Vasculitis Foundation
- Vasculitis UK
- ClinicalTrials.gov
- UKCRN Portfolio

Publications
- Articles
- Newsletters

Funders
- EULAR
- American College of Rheumatology
- Vasculitis Foundation

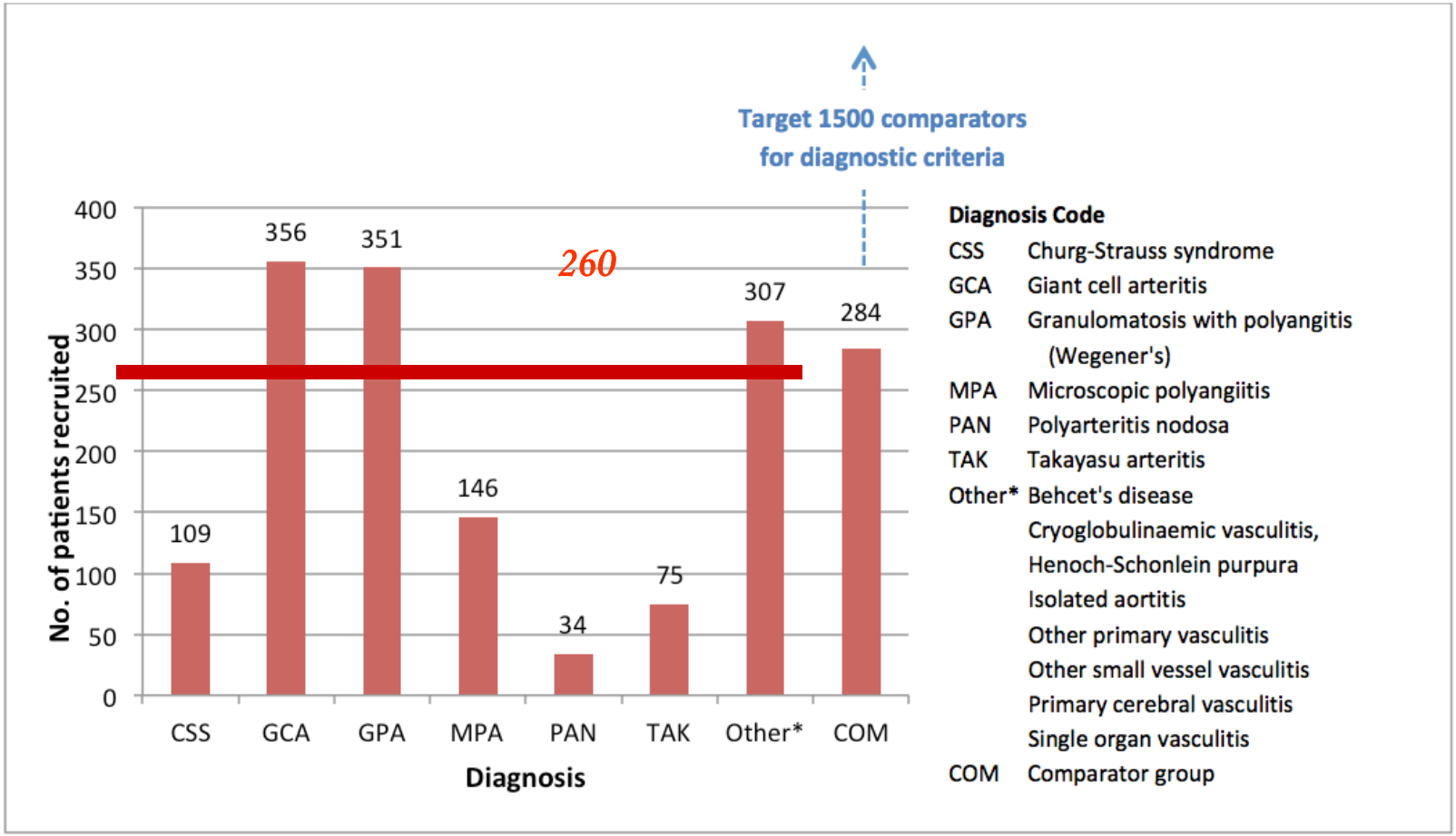
Sponsor
- University of Oxford

Recruitment and Site Update

Top 20 Recruiting Sites

Region	Country Code	Site Code	Site Name	Total patients
UK	GB	NO	Nuffield Orthopaedic Centre Oxford	136
NA	US	BU	Boston University Medical Campus	114
EU	SI	JJ	University Medical Centre Ljubljana	83
EU	IT	SS	Santa Maria Nuova Hospital, Reggio Emilia	80
EU	DE	SH	Klinikum Bad Bramstedt	68
UK	GB	NU	Nottingham University Hospitals NHS Trust	66
EU	DE	JE	Universitätsklinikum Jena	63
EU	CZ	PR	General University Hospital, Prague	59
UK	GB	IP	Ipswich Hospital NHS Trust	53
EU	DE	ES	Kreiskliniken Esslingen	50
EU	DK	UC	University Hospital, Copenhagen (Rigshospitalet)	47
EU	TR	IS	Istanbul University, Istanbul Medical School	45
EU	PL	JA	University of Jagiellonian	41
NA	CA	ON	St Joseph's Healthcare London, Ontario	40
UK	GB	NN	Norfolk and Norwich University Hospitals NHS Foundation Trust	39
EU	CH	UB	University Hospital Basel	37
UK	GB	SE	Southend University Hospital NHS Trust	33
EU	IT	PA	University of Parma	27
EU	DE	TU	Universitätsklinikum Tübingen	27
OR	NZ	AK	Auckland DHB	25

Sites recruiting highest number of patients per month (recruiting 6 months or more)


Target 1500 comparators
for diagnostic criteria
400
350
300
250
200
150
100
50
0
No. of patients recruited
356
351
260
307
284
146
109
75
34
CSS
GCA
GPA
MPA
PAN
TAK
Other*
COM
Diagnosis
Diagnosis Code
CSS Churg-Strauss syndrome
GCA Giant cell arteritis
GPA Granulomatosis with polyangitis (Wegener's)
MPA Microscopic polyangiitis
PAN Polyarteritis nodosa
TAK Takayasu arteritis
Other* Behcet's disease
Cryoglobulinaemic vasculitis,
Henoch-Schonlein purpura
Isolated aortitis
Other primary vasculitis
Other small vessel vasculitis
Primary cerebral vasculitis
Single organ vasculitis
COM Comparator group

DCVAS SCREENING

Screening Date	D D / M M M / Y Y Y Y
Screening ID	☐☐☐☐☐☐☐☐
Gender	☐ Male ☐ Female
Date of birth:	D D / M M M / Y Y Y Y

Inclusion criteria

		Yes	No
1.	Is the patient over the age of 18 years?	☐	☐
2.	Does the patient have a diagnosis of vasculitis? **OR** Is vasculitis a potential diagnosis for their current illness?	☐	☐
3.	Has the patient given informed consent? **OR** The patient does not have capacity to provide informed consent but a 'consultee' ("surrogate") has declared that the patient would want to participate in the study?	☐	☐

If "No" is ticked for any of the inclusion criteria, then patient is NOT eligible for the study.

I confirm that the patient:

Meets ALL the inclusion criteria for the study: ☐

Or

Does not meet the inclusion criteria for the study ☐

Signature of Investigator :_____ Print name: _____

UNIVERSITY OF OXFORD

Diagnostic and classification criteria in vasculitis study | DCVAS

Home | Edit | Review | Complete

Patient ID: C A T O C P 0 0 0 1

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33

Clinical Features - 3 Skin

Present at any time since the onset of the current illness = Tick the relevant box if symptoms or signs were present during the current illness. The current ilness includes the whole period from when you think the vasculitis or mimic disease started until the date of diagnosis. This includes items that may have occured and disappeared in the course of this illness.

Skin

Not involved ☐

Please tick if present at any time since th

SYMPTOMS

- ☑ Pruritus
- ☐ Painful skin lesion of any type
- ☐ Other Symptom (please specify)

10-15 min

DCVAS

- Each center willing to participate to contact R. Luqmani

dcvas@ndorms.ox.ac.uk

- Each center will need local REB approval

- US $15 per patients with full set of data
  (US $10 if paper sheet)

International PHARMA-sponsored or -supported studies with Canada

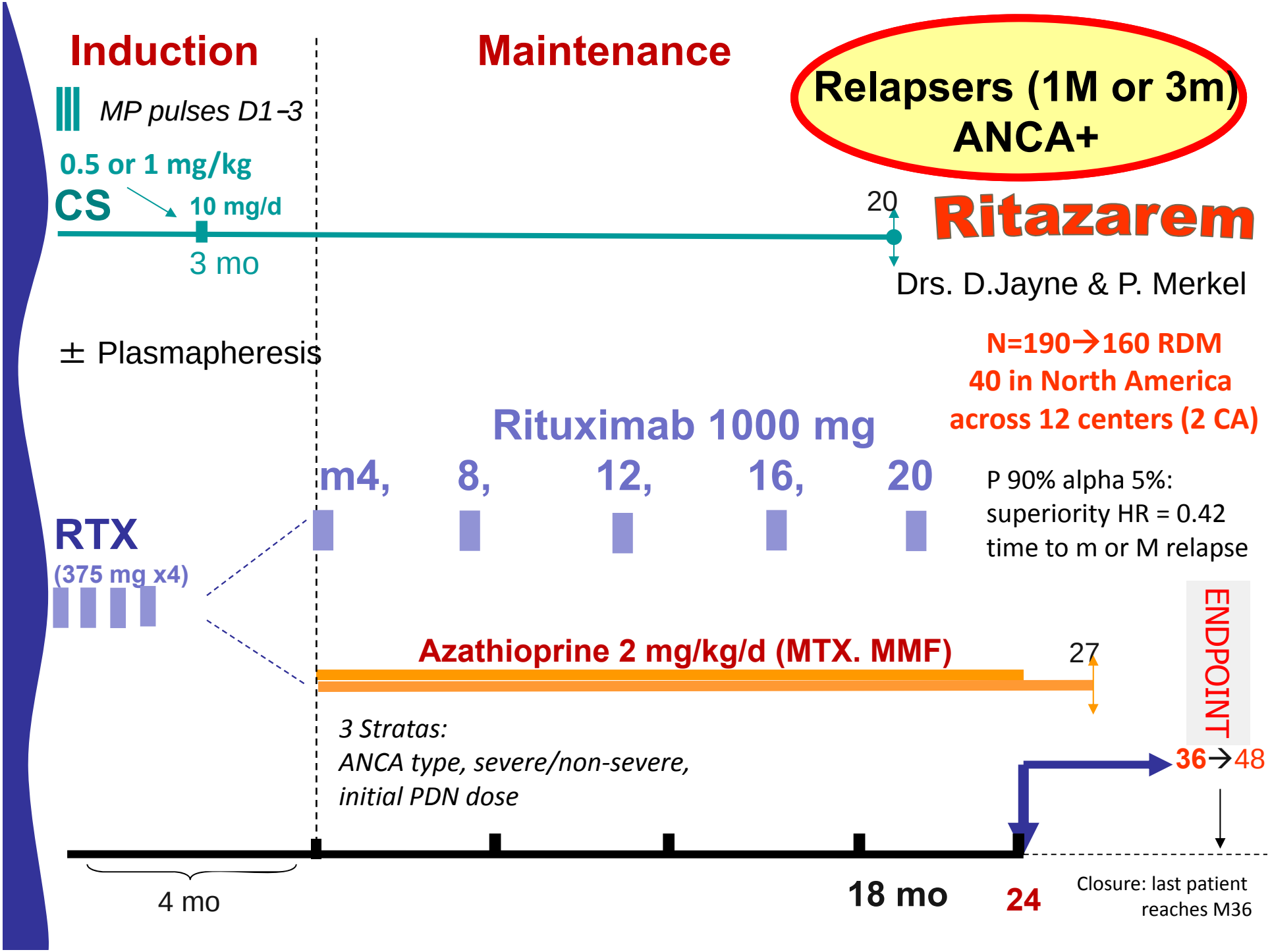
- RITUXIMAB for maintenance

  (Investigator-driven; pharma-supported)

- TOCILIZUMAB for LVV

- MEPOLIZUMAB for EGPA

- Belimimab for AASV?


Induction
Maintenance
MP pulses D1-3
0.5 or 1 mg/kg
CS
10 mg/d
3 mo
20
Relapsers (1M or 3m)
ANCA+
Ritazarem
Drs. D.Jayne & P. Merkel
± Plasmapheresis
N=190→160 RDM
40 in North America
across 12 centers (2 CA)
Rituximab 1000 mg
m4, 8, 12, 16, 20
P 90% alpha 5%:
superiority HR = 0.42
time to m or M relapse
RTX
(375 mg x4)
Azathioprine 2 mg/kg/d (MTX. MMF)
27
ENDPOINT
3 Stratas:
ANCA type, severe/non-severe,
initial PDN dose
36→48
4 mo
18 mo
24
Closure: last patient
reaches M36

GCA Protocol

A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF TOCILIZUMAB IN SUBJECTS WITH GIANT CELL ARTERITIS

PPD®

Number of Patients about 250

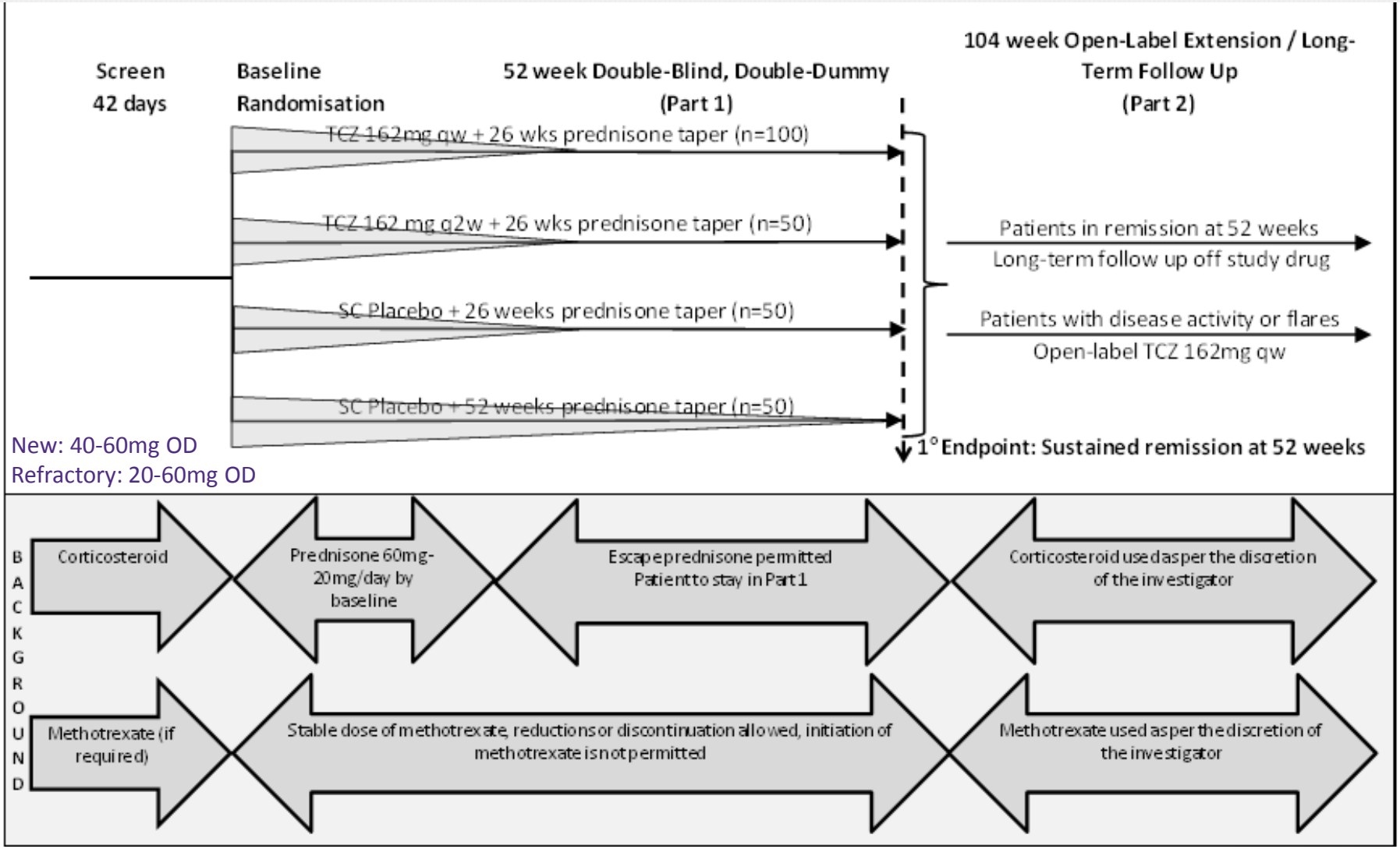
- 100 sites: US (20) / Canada (6 to 7: Hamilton, Newmarket, Kitchener, Toronto, Trois-Rivieres, St Catherine)
- 1 to 5 patients per sites maxi.
- New or refractory (relapsing or non-relapsing) GCA active within 6 wk
  - Age ≥ 50 years
  - ESR > 30 mm/hr and CRP ≥ 1 mg/dL *OR* ESR > 50 mm/hr

  AND ≥1 of the following:
  - Unequivocal *cranial symptoms* of GCA (new-onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss, otherwise unexplained mouth or jaw claudication)
  - Symptoms of PMR

  AND ≥1 of the following:
  - Temporal artery biopsy revealing features of GCA
  - Evidence of LVV by angiography or cross-sectional imaging study such as MRA, CTA, or PET-CTA

PPD

Design of Protocol



IºEP = proportion of CS-free at M6 in sustained remission at 52 wk

MEPOLIZUMAB IN CSS