ANCA-associated vasculitides: Rituximab and biologics

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CanVasc Annual Scientific Meeting,

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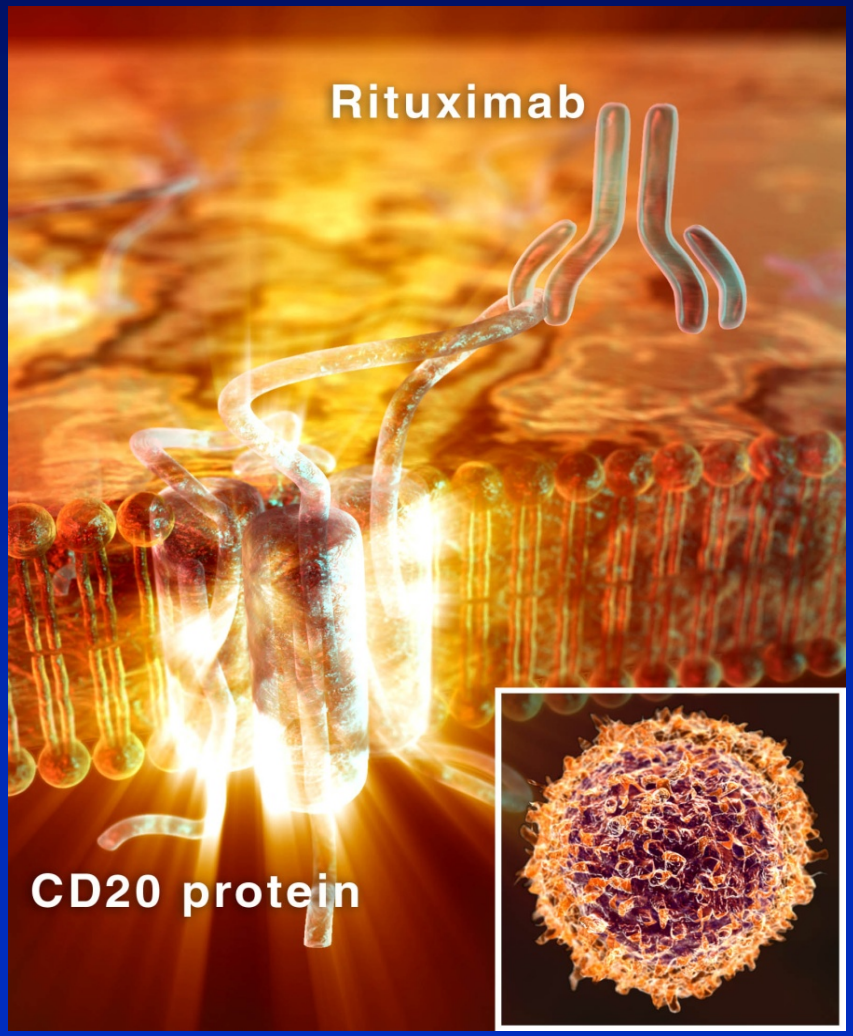
Learning objectives

- Review the current place and indications of rituximab in the treatment of ANCA-associated vasculitides (AAV)
- List some of the other biologics with a potential place and/or under investigations in AAV

Rituximab (RTX)

- Genetically engineered anti-CD20 therapeutic monoclonal antibody that *selectively* targets CD20+ B cells



Shaw et al., 2003; Silverman & Weisman, 2003

RTX selectively targets CD20+ B cells

- Composed of two fragments
  - A murine-derived region that selectively binds to the CD20 antigen on the surface of B cells
  - A human-derived region that activates cellular mechanisms to initiate B cell depletion
- CD20 is an ideal B cell target as it is not expressed on stem or plasma cells
- B cell depletion leads to a direct reduction of autoantibody production

Roitt et al., 2001; Sell & Max, 2001; Silverman & Weisman, 2003

RAVE

Rituximab Versus Cyclophosphamide for the Treatment of GPA and MPA

Stone J et al. *N Engl J Med*. 2010;363:221-232.

RAVE: Hypotheses

- Rituximab (RTX) is not inferior to conventional cyclophosphamide (CYC) therapy for the induction of remission in severe ANCA-associated vasculitis (AAV).
- RTX offers other substantial advantages over standard CYC therapy.
- B cell depletion by RTX therapy induces stable remission by re-establishing tolerance to ANCA target antigens.

Stone J et al. *N Engl J Med*. 2010;363:221-232.

RAVE: Trial Design
Non-inferiority Trial

- Assumption
  - In both treatment groups, 70% of patients would achieve disease remission and be off prednisone at 6 months.

- A non-inferiority margin of −20% was used for modeling based on a clinically acceptable efficacy difference between RTX and CYC assuming that RTX has safety advantages.

Stone J et al. *N Engl J Med*. 2010;363:221-232.

RAVE: Outcome Measures

- Primary outcome: Percentage of patients who achieved complete remission
  - Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) = 0
  - Completed steroid taper to 0 mg prednisone
- Secondary outcomes
  - Remission (BVAS/WG=0, Prednisone < 10 mg/d)
  - Disease activity, Disease flares
  - AEs, GC dose, QoL

* All patients were followed until the last patient enrolled reached month 18.

Stone J et al. *N Engl J Med*. 2010;363:221-232.

RAVE: Key Inclusion Criteria

- Active severe AAV according to Chapel Hill criteria[1]
  - BVAS/WG score ≥3
  - At least one major BVAS/WG item or deemed severe enough to require CYC[1]
  - Newly diagnosed or relapsing disease patients eligible[2]
- Positive serum assay for proteinase 3 (PR3)-ANCA or myeloperoxidase (MPO)-ANCA[2]

[1]Stone J et al. Appendix to *N Engl J Med* 2010;363:221-232.
[2]Stone J et al. *N Engl J Med*. 2010;363:221-232.

RAVE: Key Exclusion Criteria

- Disease severity
  - Limited disease not requiring CYC
  - « Too severe » disease
    - Mechanical ventilation because of alveolar hemorrhage
    - Serum creatinine > 350 mmol/L
- CYC use within 4 months prior to enrollment
- History of CYC toxicity or unresponsiveness
- Any previous RTX use

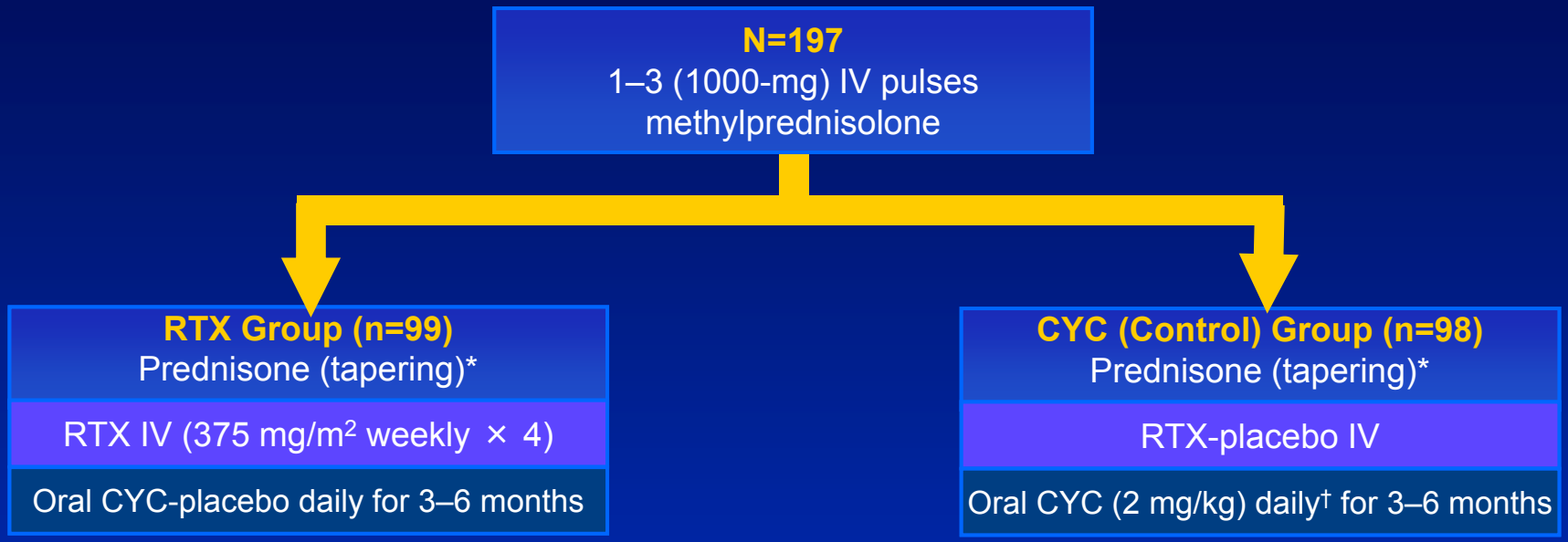
Stone J et al. Appendix to *N Engl J Med* 2010;363:221-232.

RAVE: Study Design

N=197
1–3 (1000-mg) IV pulses
methylprednisolone

Stone J et al. *N Engl J Med*. 2010;363:221-232.

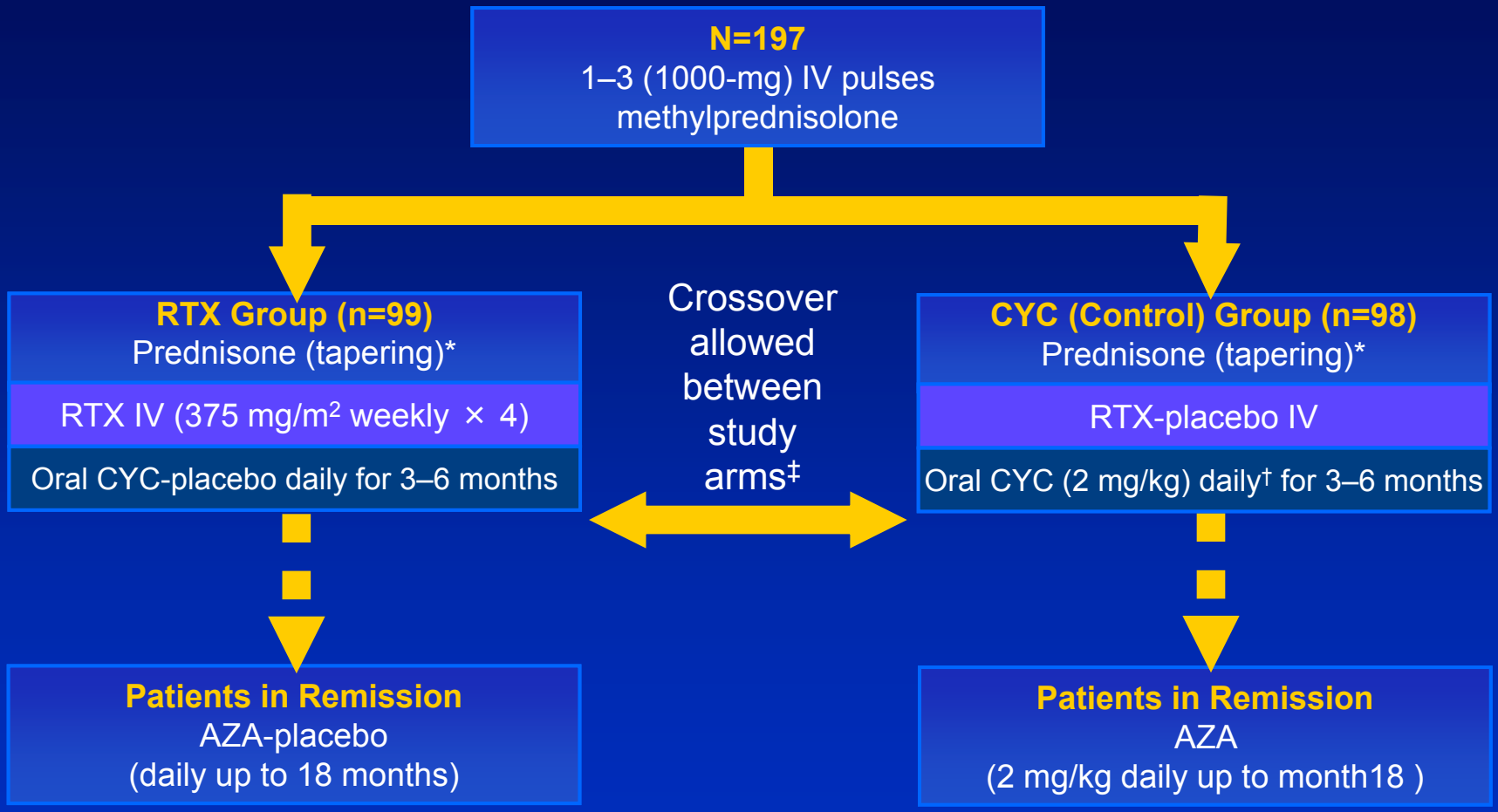
RAVE: Study Design



*Dose tapered to 0 mg/kg by 5 months for patients in remission with no flares.
†Adjusted for renal insufficiency.

Stone J et al. *N Engl J Med*. 2010;363:221-232.

RAVE: Study Design



*Dose tapered to 0 mg/kg by 5 months for patients in remission with no flares.
†Adjusted for renal insufficiency.
‡Patients with severe flares in <6 months could cross over to other study group.

Stone J et al. *N Engl J Med*. 2010;363:221-232.

RAVE: Baseline Characteristics

Demographics, ANCA Type

	RTX (n=99)	CYC (n=98)
Age, years	54.0 (16.0, 92.0)	51.5 (15.0, 80.0)
Sex (M:F)	46:54	54:46
ANCA Type[1,3]		
PR3-ANCA	67%	66%
MPO-ANCA	33%	34%

[1]Stone J et al. *N Engl J Med*. 2010;363:221-232; [2]Stone J et al. *N Engl J Med*. 2010;363:221-232;
[2]Stone J et al. Oral Presentation at ACR 2009. Philadelphia. Abstract 550.
[3]CSR ITN021AI, Oct 14, 2010: p. 71, 74, Tables, 7, 8

RAVE: Baseline Characteristics

Disease Phenotype and Baseline Measures

	RTX (n=99)	CYC (n=98)
AAV Type[1,3]		
MPA	24%	25%
WG	74%	75%
Indeterminate or missing	2%	0%
New diagnosis, relapse [1,2,3]	49%, 51%	49%, 51%
Mean BVAS/WG[1,3]	8.1	8.0

[1]Stone J et al. *N Engl J Med*. 2010;363:221-232;
[2]Stone J et al. Oral Presentation at ACR 2009. Philadelphia. Abstract 550.
[3]CSR ITN021AI, Oct 14, 2010: p. 73, Table 8

RAVE: Baseline Characteristics
Organ Involvement

	RTX (n=99)	CYC (n=98)
Constitutional signs, symptoms (%)	56	66
Cutaneous involvement (%)	20	16
Mucous membranes and eyes (%)	27	26
Ear, nose, and throat (%)	61	56
Cardiovascular (%)	0	1
Gastrointestinal (%)	2	0
Pulmonary involvement (%)	52	54
Renal involvement (%)	66	66
Neurologic involvement (%)	25	15

Stone J et al. *N Engl J Med*. 2010;363:221-232.
CSR ITN021AI, Oct 14, 2010: p. 73, Table 8

RAVE: Primary Efficacy Endpoint Analysis
Complete Remission at 6 Months: As Observed

- BVAS/WG = 0 and prednisone = 0 mg

	RTX (n=98)	CYC (n=95)	Difference	*p superiority*
Number (%)	63 (64.3%)	52 (54.7%)	9.5%	0.177*
95% CI	54.8%, 73.8%	44.7%, 64.8%	−4.3%, 23.4%	

As observed: patients with non-missing results at 6 months
**P* value pertains to superiority of RTX versus CYC treatment

CI, confidence interval.

CSR ITN021AI, Oct 14, 2010: p. 75, 77, Table 10

RAVE: Primary Efficacy Endpoint Analysis

Complete Remission at 6 Months: ITT

- BVAS/WG = 0 and prednisone = 0 mg

	RTX (n=99)	CYC (n=98)	Difference	*P*
Number (%)[1]	63 (63.6%)	52 (53.1%)	10.6%	0.09*
95% CI	54.1%, 73.2%[2]	43.1%, 63.0%[2]	−3.2%, 24.3%[1]	

Primary analyses performed by the intent-to-treat (ITT) method, worst case imputation
**P* value pertains to superiority of RTX versus CYC treatment

CI, confidence interval.

[1]Stone J et al. *N Engl J Med*. 2010;363:221-232
[2]Stone J et al. Oral Presentation at ACR 2009. Philadelphia. Abstract 550.

RAVE: Secondary Efficacy Endpoint
Remission at 6 Months

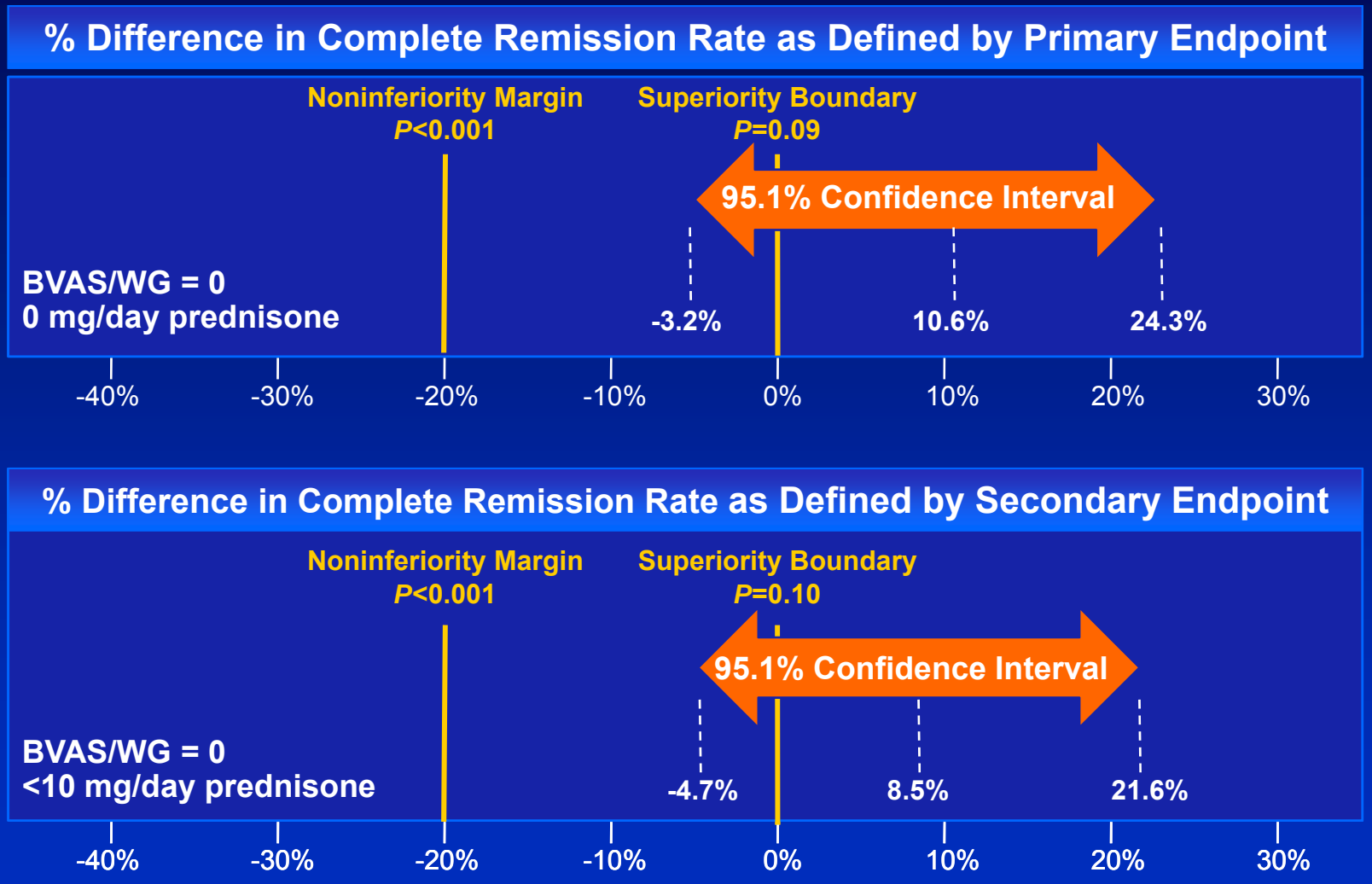
- BVAS/WG = 0 and prednisone <10 mg

	RTX (n=99)	CYC (n=98)	Difference	*P*
Number (%)[1]	70 (70.7%)	61 (62.2%)	8.5%	0.208[3]
95% CI	61.8%, 79.7%[2]	52.6%, 71.8%[2]	−4.7%, 21.6%[1,3]	

ITT analysis, worst case imputation

[1]Stone J et al. *N Engl J Med*. 2010;363:221-232.
[2]Stone J et al. Oral Presentation at ACR 2009. Philadelphia. Abstract 550.
[3]CSR ITN021AI, Oct 14, 2010: p. 78, Table 13

RAVE: Analysis of Efficacy Endpoints*

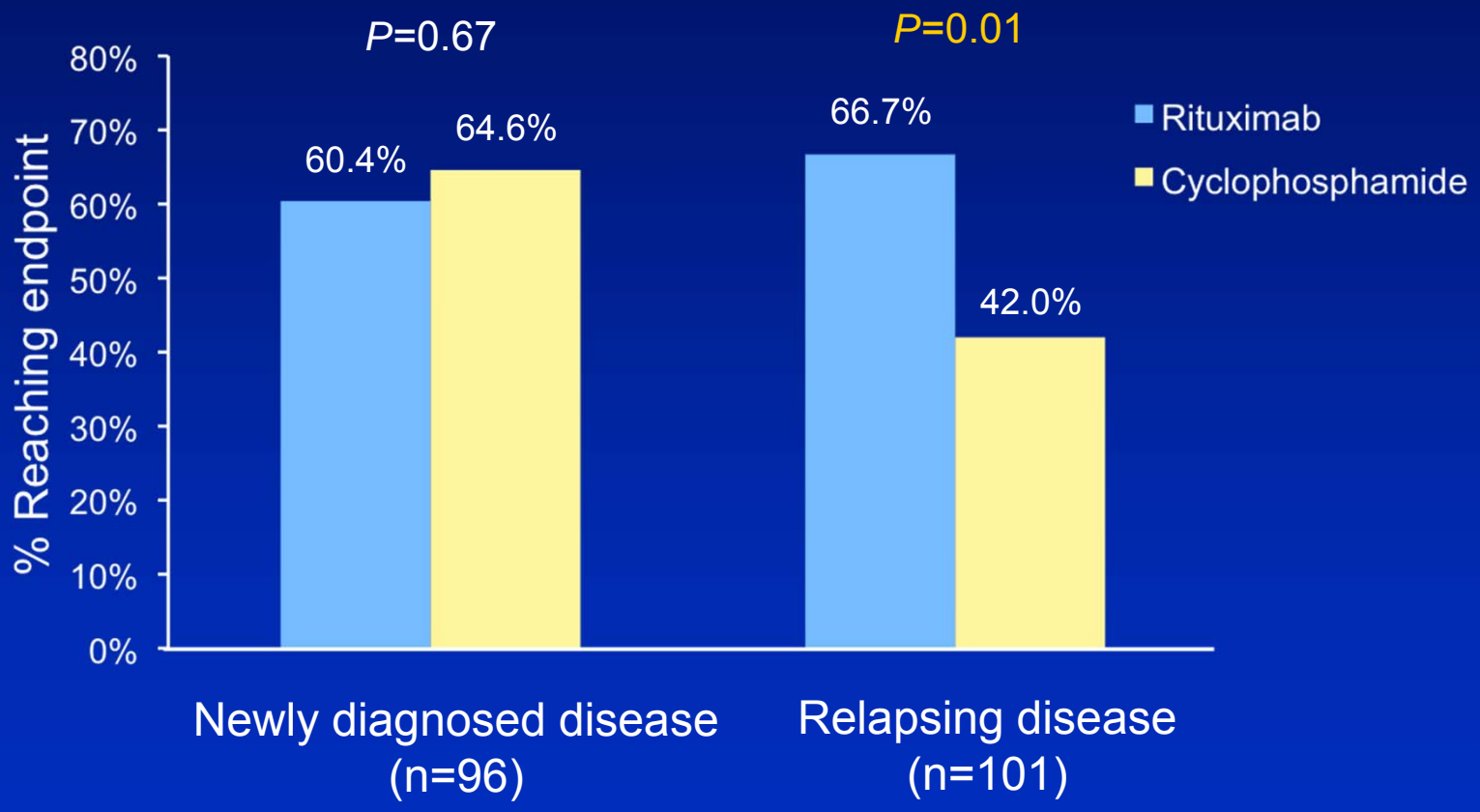


*ITT analysis, worst case imputation

Stone J et al. *N Engl J Med*. 2010;363:221-232.

RAVE: Rituximab vs. Cyclophosphamide in Patients with Relapsing Disease at Baseline

Pre-specified Exploratory Endpoint



[1]Stone J et al. Oral Presentation at ACR 2009. Philadelphia. Abstract 550.
[2]Stone J et al. *N Engl J Med*. 2010;363:221-232.
[3]CSR ITN021AI, Oct 14, 2010: p. 82, Table 18

RAVE: Flares by 6 Months

	RTX (n=99)	CYC (n=98)	*P*
No. of patients with at least one limited flare (%)	12 (12.1%)	14 (14.3%)	
Rate of limited flares	0.026	0.026	0.98*
No. of patients with at least one severe flare (%)	5 (5.1%)	10 (10.2%)	
Rates of severe flares (per patient-month)	0.011	0.019	0.29*

**P* value pertains to superiority of RTX versus CYC treatment

CSR ITN021AI, Oct 14, 2010: p. 79, Table 14

RAVE: AEs and Serious AEs at 6 months

	RTX (n=99)	CYC (n=98)
Total number of adverse events	997	978
No. (%) of patients with ≥1 adverse event	94 (95%)	97 (99%)
Total number of serious adverse events	46	54
No. (%) of patients with ≥1 serious adverse event	33 (33%)	33 (34%)

CSR ITN021AI, Oct 14, 2010: p. 96, 99: Tables 26, 31

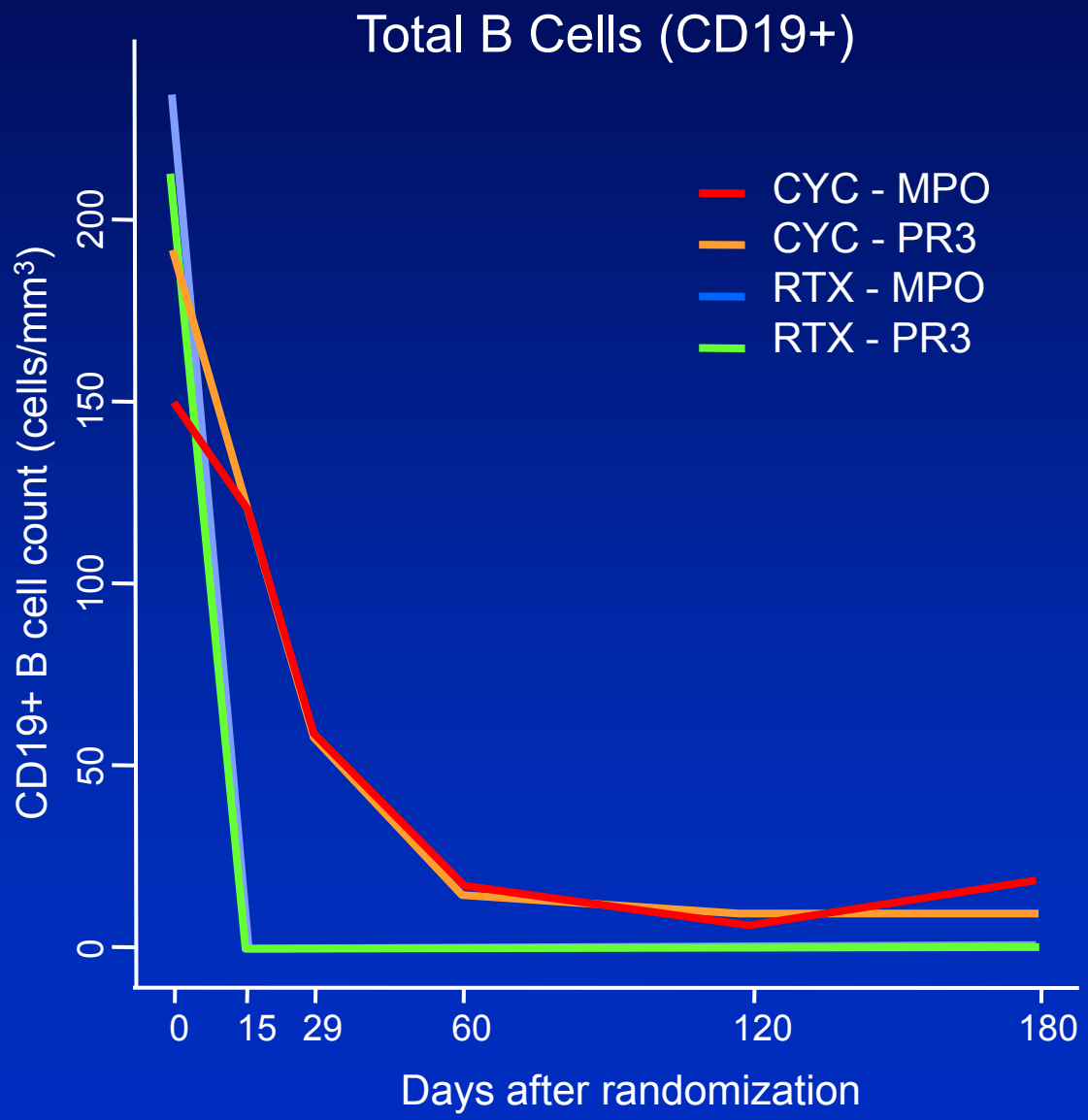
RAVE: Number of Selected AEs at 6 Months

	RTX (n=99)	CYC (n=98)
Death (all causes)	1	2
Leukopenia (≥ grade 2)	5	17
Thrombocytopenia (≥ grade 3)	3	1
Infections (≥ grade 3)	10	10
Hemorrhagic cystitis	1	1
Malignancy	1	2
Venous thromboembolic events	5	8
Hospitalization due to disease or treatment	10	4
Infusion reaction preventing further infusions of investigational medication	1	0

CSR ITN021AI, Oct 14, 2010: p. 99, Table 28

RAVE: Median B Cell Counts

- B cells undetectable after two RTX infusions (<10 CD19+ cells/mm^3)
- B cells decline but remain detectable in CYC arm
- No difference in B cell response between PR3-ANCA and MPO-ANCA patients



Stone J et al. *N Engl J Med*. 2010;363:221-232.

RAVE: Summary

- Rituximab is not inferior to cyclophosphamide for remission induction in patients with severe AAV
- No difference in treatment response to RTX or CYC in patients with major renal disease or alveolar hemorrhage.
- No difference in disease flares by 6 months.
- No difference in severe adverse events rate by 6 months.

[1]Stone J et al. *N Engl J Med*. 2010;363:221-232.
[2]Stone J et al. Oral Presentation at ACR 2009. Philadelphia. Abstract 550.

MAINRITSAN

MAINtenance of remission using RITuximab for Systemic ANCA-associated vasculitides

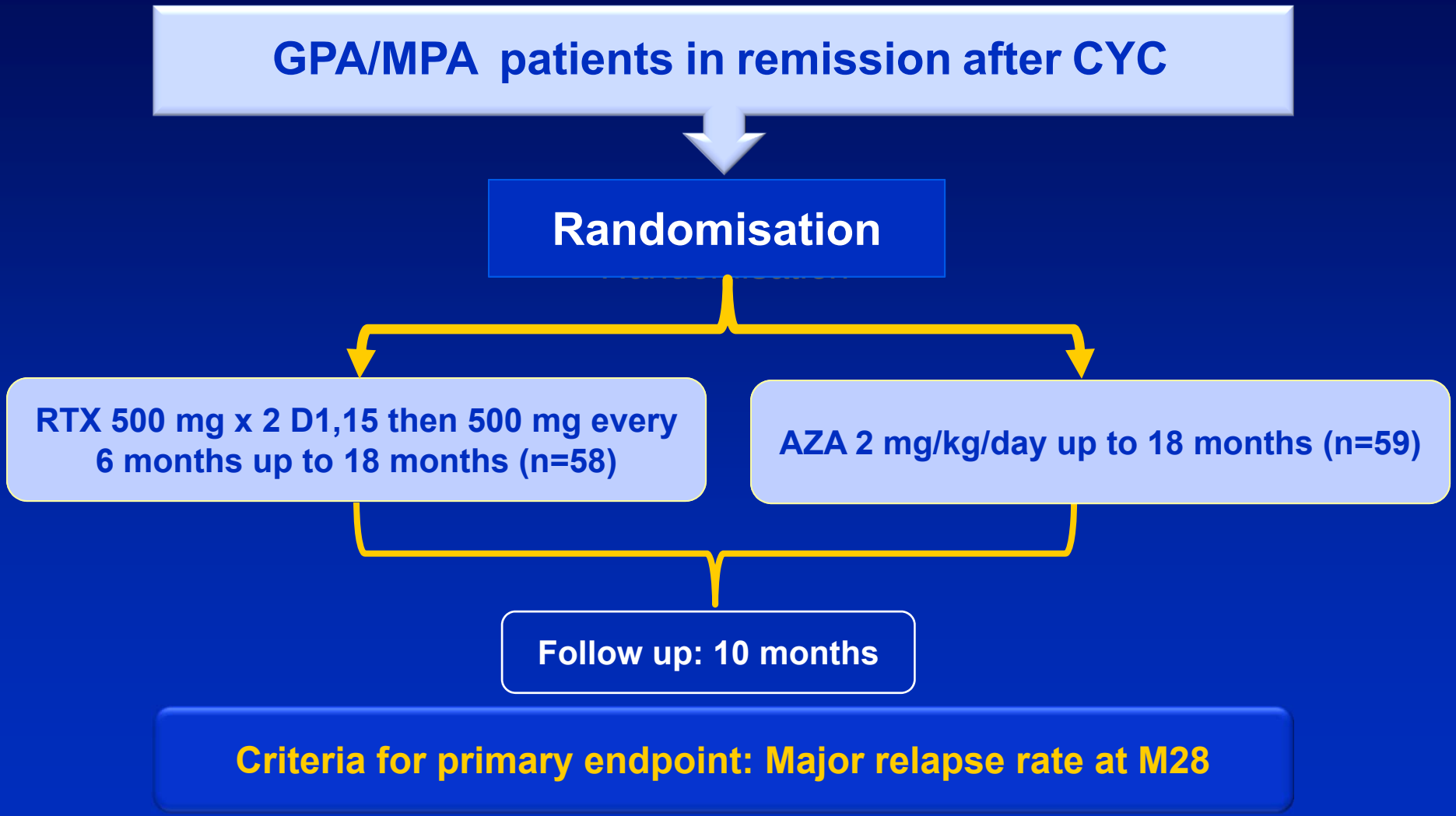
L. Guillevin, C. Pagnoux, A. Karras, C. Khoutra, O. Aumaitre, P. Cohen, F. Maurier, O. Decaux, H. Desmurs-Clavel, P. Gobert, T. Quemeneur, C. Blanchard-Delaunay, P. Godmer, X. Puechal, P. L. Carron, P. Y. Hatron, N. Limal, M. Hamidou, M. Ducret, F. Vende, E. Pasqualoni, B. Bonnotte, P. Ravaud, L. Mouthon Sr and French Vasculitis Study Group (FVSG)

ACR Oral presentation 1652
Monday 12 November 2:30 pm: 146 C

MAINRITSAN: Objective and methods

- Objective
  - To assess the efficacy of Rituximab (RTX) vs. Azathioprine (AZA) to maintain ANCA-associated vasculitis (AAV) remission
- Methods
  - Randomised, open-label Phase III study
  - Primary endpoint: Major relapse rate at 28 months
  - Other outcome measures were the serious adverse event rate associated with each maintenance regimen
- Hypothese
  - The RTX arm will have a 50% lower relapse rate than that of AZA and a similar safety profil

MAINRITSAN: Study design



MAINRITSAN: Patient characteristics

Baseline characteristics	
Total patients, n = 117	
Female, Male, n	66, 51
Mean age, years	55 ± 13
Newly diagnosed, n (%)	93 (79.5)
Relapsers, n (%)	24 (20.5)
Type AAV	
Granulomatosis with polyangiitis, n (%)	86 (75)
Microscopic polyangiitis, n	23
Kidney-limited disease, n	5
Main clinical manifestations at dx or relapse, n (%)	
ENT involvement	88 (77.2)
Lung	69 (60.5)
Kidney	82 (71.9)

MAINRITSAN: Preliminary results

- 73.7% of patients have completed their 28 months of follow-up
  Last patient visit and trial closure scheduled in Oct 2012

	RTX (n=58)	AZA (n=59)
Major relapses, n (%)	3 (5.2)	15 (25.4)
Drop-outs, n (%)	6 (10.3)	21 (35.6)
Deaths, n		3
Sepsis	–	1
Pancreatic cancer	–	1
Mesenteric ischemia	–	1
SAEs, n (%)	32 (50)	37 (50.8)
Infections	9	9*
Death	0	3

* 1 death

MAINRITSAN: Conclusions

- Rituximab is superior to Azathoprine to maintain remission in ANCA-associated vasculitides
- A 500 mg dose every 6 months seems to be sufficient. Relapses are rare.
- Treatment tolerance was good, with a limited number of side effects, mainly transient

ABATACEPT

A multi-Center, Open-label Pilot Study of Abatacept in the treatment of mild relapsing GPA

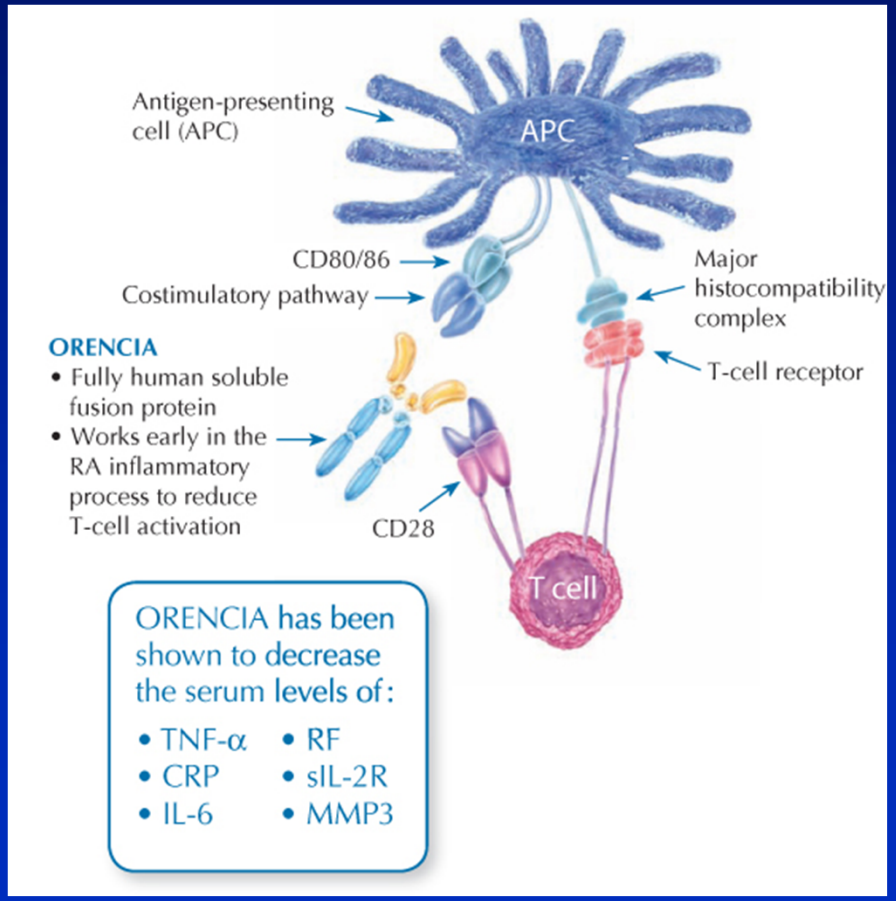
Langford CA, Cuthbertson D, Hoffman GS, Krischer JP, McAlear CA, Monach PA, Seo P, Ytterberg SR and Merkel PA

For the Vasculitis Clinical Research Consortium

ACR Oral presentation
November 2012

Abatacept (Orencia)

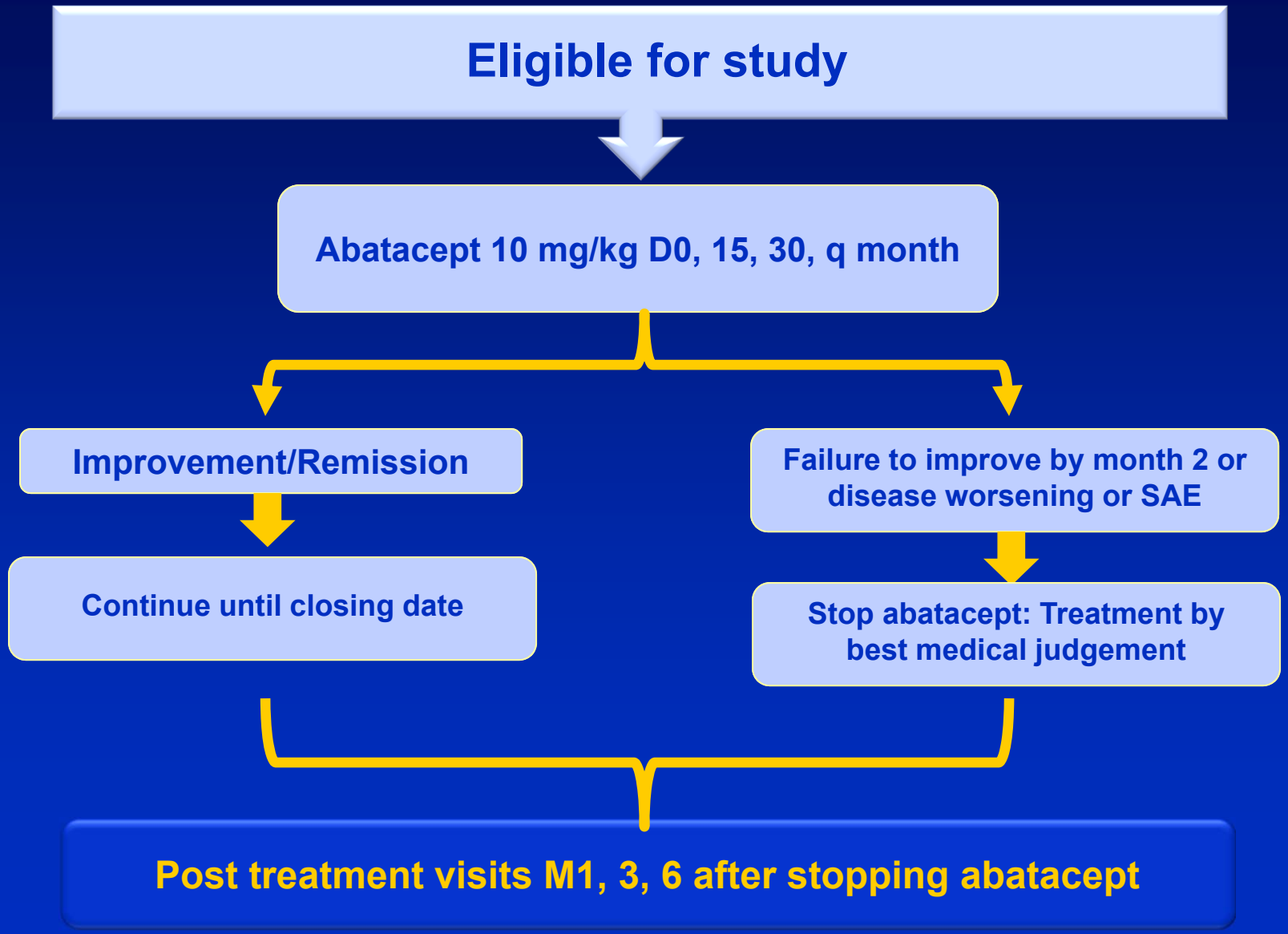
- IgG1-CTLA-4
- Genetically engineered selective costimulation modulator that inhibits T-cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28



Abatacept: Study overview

- Objectives
  - To examine the safety of abatacept in GPA
  - To gather preliminary data on the efficacy of abatacept in GPA
- Methods
  - Open-label, multi-center, pilot study
  - Patients with a mild relapse < 28 days
- Primary outcome: disease worsening
  - Development of any major BVAS/WG criteria
  - Increase BVAS/WG ≥ 2
  - SSx requiring prednisone > 30 mg/d within the first 2 months

Abatacept: Study design



Abatacept: Patient characteristics

Patient characteristics	
Total patients, n = 20	
Female, Male, n	9, 11
Mean age, years	45 ± 27
Mean disease duration, months	100
ANCA type, %	
PR3	80
MPO	10
Negative	10
BVAS/WG at entry, mean	3.1 (1-6)
Main clinical manifestations at relapse, %	
ENT involvement	90
Lung	30
Kidney	0
MSK	50
Skin	40
Treatment during trial, %	
AZA	15
MTX	35
MMF	20
None	30

Abatacept: Efficacy endpoints

	n (%)	Mean
Disease worsening	2 (10%)	
Disease improvement	18 (90%)	
Remission	16 (80%)	
Time to remission, mo (range)		3.75 (1-19)
Relapse	3 (19%)	
Time to relapse, mo (range)		8.33 (6-10)
Reached common closing, n	14 (70%)	
Did not reach common closing, n	6 (30%)	
Minor relapse	6	
Major relapse	0	
Off prednisone at common closing, n	7 (50%)	

Abatacept: AEs and SAEs

- AEs
  - 92 events in 17 patients
  - 35 infections (37% upper airway)
- SAEs
  - 9 events in 7 patients
  - 7 infections, 2 SGS dilation

Abatacept: Conclusions

- In this population of mild relapsing GPA, Abatacept was well tolerated and brought about disease remission and prednisone discontinuation in a high percentage of patients
- These findings suggest that abatacept warrants further study as a possible treatment option for patients with non-severe relapsing GPA

New targets to watch

- Anti-CD52: Alemtuzumab (NCT01405807)
  - Alemtuzumab for ANCA Associated Refractory Vasculitis - a Study of Safety and Efficacy
  - Recruiting
  - Principal Investigator: David Jayne
  - Estimated Study Completion Date: March 2014
- Anti-C5: Eculizumab (NCT01275287)
  - Eculizumab as an addition to conventional therapy in patients with active ANCA vasculitis that need a a more rapid decrease in disease activity
  - Recruiting
  - Principal Investigator: Patrick Nachman
  - Estimated Study Completion Date: May 2014

New targets to watch

- Anti-BLyS
  - Belimumab: NCT01663623
    - BREVAS
    - A Phase 3, Multi-Center, Multinational, Randomized, Double-Blind, Study to Evaluate the Efficacy and Safety of Belimumab in Combination With Azathioprine for the Maintenance of Remission in Wegener's Granulomatosis and Microscopic Polyangiitis
    - Not yet recruiting
    - Estimated Study Completion Date: August 2016
  - Blisibimod: NCT01598857
    - BIANCA-SC
    - A Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Blisibimod in Addition to Methotrexate During Induction of Remission in Subjects With ANCA-Associated Small Vessel Vasculitis
    - Not yet recruiting
    - Estimated Primary Completion Date: April 2014

Rituximab and biologics: Conclusions

- Rituximab:
  - Approved in Canada for the induction of remission in patients with severely active GPA or MPA who have a severe intolerance or other contraindication to cyclophosphamide, or who have failed an adequate trial of cyclophosphamide.
  - Data on maintenance treatment is promising
- Abatacept:
  - Warrants further study as a possible treatment option for patients with non-severe relapsing GPA
- Many new therapeutic targets being studied

Aknowledgements

- Mr Jacques Marier
- Dr Yves Troyanov
- Dr Christian Pagnoux