FRI0588

Interim Results of a Phase 2 Study of XmAb®5871, a Reversible B Cell Inhibitor, in IgG4-Related Disease

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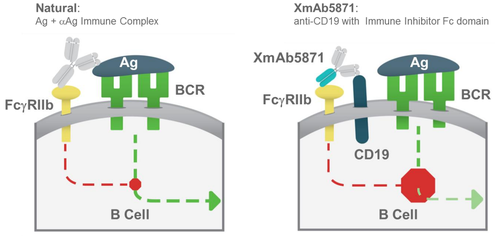
Introduction:

Antigen activated B cells are down-regulated by engagement of immune complexes with the inhibitory Fcγ receptor FcγRIIb on the B cell surface. XmAb5871, an anti-CD19 mAb, has been engineered to enhance binding to FcγRIIb. The co-ligation of the B cell receptor associated membrane protein CD19 and FcγRIIb by XmAb5871 results in inhibition of many activation pathways in both healthy and disease B cells and in potent suppression of B cell responses without destroying B cells.



Objectives:

Primary Objective: To evaluate the effect of every other week intravenous (IV) administration of XmAb5871 on the IgG4-RD Responder Index (RI) in patients with active IgG4-RD.

Secondary Objectives: To evaluate the safety and tolerability of every other week IV administration of XmAb5871 in patients with active IgG4-RD.

To evaluate the pharmacokinetics (PK) and immunogenicity of every other week IV administration of XmAb5871 in patients with active IgG4-

Exploratory Objectives: To characterize PD effects on absolute B cell count, circulating plasmablasts and serum IgG4 concentration over time.

Patient Population:

Male and female patients with histopathologically proven IgG4-RD with active disease as defined by disease activity in one or more organ systems AND an IgG4-RD RI of ≥3 were enrolled. Patients were not required to have failed prior therapy for their disease to be eligible for this study. Patients with disease in only one organ system whose primary manifestation was fibrosis were excluded.

Study Design:

Phase 2 single center, open-label, multiple-dose study

15 IgG4-RD patients were enrolled to receive 5.0 mg/kg IV infusions of XmAb5871 14 days apart for 12 doses. Dosing occurred on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, and 155. Final efficacy assessments occurred on Day 169, 2 weeks following the last dose.

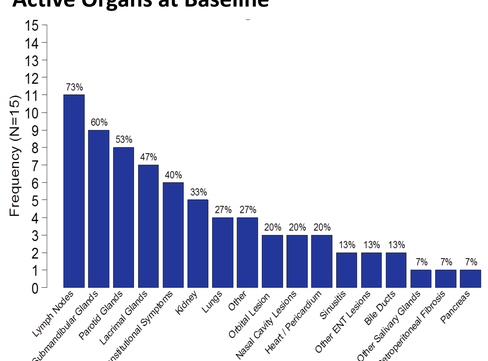
Demographics:

Age	**Years, median (range)**	**63 (43 - 77)**
Sex	**Male** **Female**	**10 (67%)** **5 (33%)**
Race	**White** **Asian** **Black**	**12 (80%)** **2 (14%)** **1 (7%)**

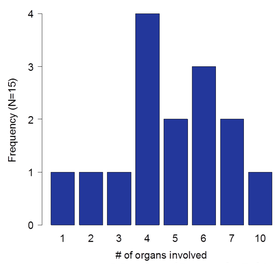
Disease Characteristics:

IgG4-RD Responder Index – median (range)	**12 (2 - 30)**
IgG4 level (normal 3.9 - 86.4 mg/dl) – median (range)	**220 (25 - 2415)**
Previously treated – n (%)	**10 (67%)**

Active Organs at Baseline

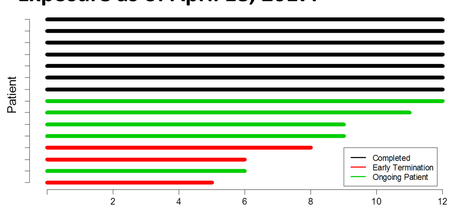


Number of Involved Organs at Baseline:



Median (Range): 5 (1-10)

Exposure as of April 18, 2017:



Median infusions (Range): 12 (5-12)

Safety:

51 TEAEs were reported in 13 patients. Of those, 35 events in 7 patients were considered to be drug-related, all mild or moderate in severity. The most common AEs thought to be XmAb5871-related were nausea, abdominal pain, chills, and headache, each reported in 2 subjects.

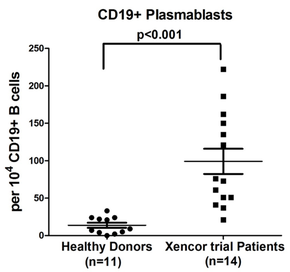
Discontinuations: 3 patients discontinued the study early. One patient never achieved a response, a second responded but then lost response and the third responded but had an infusion-related hypersensitivity reaction after her 5th infusion that was later determined to be coincident with an anti-drug antibody response.

SAEs: 1 patient had 2 unrelated SAEs, multifocal pneumonia and relapsing pneumonia due to medical non-compliance.

Immunogenicity: 5 patients have had treatment-emergent confirmed positive ADA at one or more timepoints. Two had only a single timepoint that was positive. Of the remaining 3 with positive results, 2 showed no apparent effects on PK, target coverage, safety or efficacy. The third had a hypersensitivity reaction as described above.

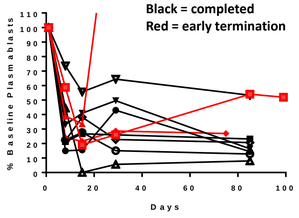
Mechanistic Studies:

Baseline Circulating Plasmablasts:



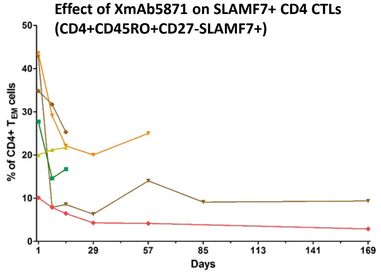
Plasmablasts at baseline are elevated in active IgG4-RD patients; XmAb5871 therapy reduces the circulating plasmablast numbers quickly.

% of Baseline Plasmablasts (CD20-CD3-)



XmAb5871 also reduced numbers of CD4+ CTLs in those subjects with measurable circulating levels.

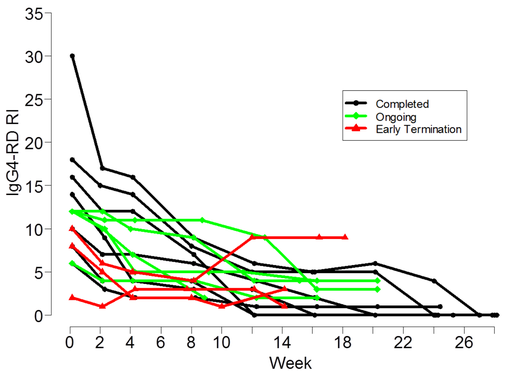
Effect of XmAb5871 on SLAMF7+ CD4 CTLs (CD4+CD45RO+CD27-SLAMF7+)



Efficacy:

The IgG4-RD Responder Index assessment was done at baseline, week 2, week 4, and then every 4 weeks thereafter.

IgG4-RD Responder Index Over Time



Conclusions:

- All 15 patients have been enrolled; 10 have completed, 5 ongoing.
- 14 of 15 patients showed a decrease of ≥2 points in the IgG4-RD RI, 12 of them within 2 weeks (i.e. after a single dose of XmAb5871).
- 5 patients were either on corticosteroids or received them at the beginning of the study. All were able to taper off within 2 months.
- 3 patients discontinued early: one no response, one flare and one AE.
- 5 patients have reached the end of the study with an IgG4-RD RI of 0 and no steroids between months 2-6 (definition of remission).
- Further studies with IgG4-RD are being planned.