

Supplementary Table 1. Adverse Events by Category

	Rituximab	Siltuximab	Tocilizumab
Occurrences of any adverse event	83	90	26
Event Categorization			
Blood and lymphatic system disorders	1 (1.2)	3 (3.3)	0
Cardiac disorders	7 (8.4)	1 (1.1)	1 (3.8)
Ear and labyrinth disorders	0	2 (2.2)	0
Eye disorders	1 (1.2)	1 (1.1)	0
Gastrointestinal disorders	8 (9.6)	16 (17.8)	6 (23.1)
General disorders and administration site conditions	12 (14.5)	9 (10.0)	2 (7.7)
Immune system disorders	2 (2.4)	2 (2.2)	4 (15.4)
Investigations	0	6 (6.7)	0
Musculoskeletal and connective tissue disorders	20 (24.1)	9 (10.0)	0
Nervous system disorders	7 (8.4)	10 (11.1)	2 (7.7)
Respiratory, thoracic and mediastinal disorders	11 (13.3)	5 (5.6)	4 (15.4)
Skin and subcutaneous tissue disorders	10 (12.0)	18 (20.0)	5 (19.2)
Vascular disorders	4 (4.8)	8 (8.9)	2 (7.7)

Supplementary Table 2. Adverse Event Listing

	Rituximab	Siltuximab	Tocilizumab
N Patients Treated	62	66	34
Total Events	83	90	26
Event Category, N			
<i>Event, N (% of category)</i>			
Blood and lymphatic system disorders	1	3	0
Anaemia	1 (100)	0	0
Adenopathy	0	1 (33.3)	0
Cytopenia	0	1 (33.3)	0
Thrombocytopenia	0	1 (33.3)	0
Cardiac disorders	7	1	1
Atrial fibrillation	1 (14.3)	0	0
Chest pain	3 (42.9)	1 (100)	0
Chest tightness	1 (14.3)	0	0
Tachycardia	2 (28.6)	0	1 (100)
Ear and labyrinth disorders	0	2	0
Ear ringing	0	1 (50)	0
Tinnitus	0	1 (50)	0
Eye disorders	1	1	0
Vision blurred	1 (100)	0	0
Eye irritation	0	1 (100)	0
Gastrointestinal disorders	8	16	6
Abdominal distension	0	0	1 (16.7)
Abdominal pain	1 (12.5)	2 (12.5)	0
Bad taste	1 (12.5)	1 (6.3)	0
Constipation	0	0	1 (16.7)
Diarrhea	2 (25)	5 (31.3)	2 (33.3)
Nausea	2 (25)	6 (37.5)	0
Nausea and vomiting	1 (12.5)	1 (6.3)	1 (16.7)
Swallowing difficult	1 (12.5)	0	0
Vomiting	0	1 (6.3)	1 (16.7)
General disorders and administration site conditions	12	9	2
Edema	2 (16.7)	2 (22.2)	0
Fatigue	4 (33.3)	5 (55.6)	1 (50)
Fever	2 (16.7)	0	1 (50)
Infusion related reaction	3 (33.3)	1 (11.1)	0
Pain	1 (8.3)	0	0
Swelling	0	1 (11.1)	0
Immune system disorders	2	2	4
Anaphylactic reaction	0	0	4 (100)
DRESS syndrome	0	1 (50)	0
Hypogammaglobulinemia	1 (50)	0	0
Pemphigus	1 (50)	0	0
Stevens Johnson type reaction	0	1 (50)	0
Investigations	0	6	0
Bilirubin elevated	0	1 (16.7)	0
Human anti-mouse antibody positive	0	1 (16.7)	0

Weight increased	0	4 (66.7)	0
Musculoskeletal and connective tissue disorders	20	9	0
Arthralgia	1 (5)	2 (22.2)	0
Back pain	2 (10)	1 (11.1)	0
Bone pain	1 (5)	1 (11.1)	0
Chills	6 (30)	0	0
Myalgia	0	2 (22.2)	0
Pain in extremity	1 (5)	3 (33.3)	0
Restless legs	1 (5)	0	0
Rigors	8 (40)	0	0
Nervous system disorders	7	10	2
Headache	4 (57.1)	6 (60)	2 (100)
Neuropathy	1 (14.3)	2 (20)	0
Numbness	0	1 (10)	0
Shakiness	1 (14.3)	0	0
Slurred speech	0	1 (10)	0
Tingling	1 (14.3)	0	0
Respiratory, thoracic and mediastinal disorders	11	5	4
Chest heaviness		1 (20)	0
Constriction throat	1 (9.1)	0	1 (25)
Cough	2 (18.2)	0	0
Difficulty breathing	1 (9.1)	0	0
Hypoxemia	0	0	1 (25)
Itchy throat	2 (18.2)	0	1 (25)
Restrictive pulmonary disease	1 (9.1)	0	0
Shortness of breath	2 (18.2)	2 (40)	0
Sinus pain	0	1 (20)	0
Sore throat	0	1 (20)	0
Stridor	1 (9.1)	0	0
Tachypnea	1 (9.1)	0	1 (25)
Skin and subcutaneous tissue disorders	10	18	5
Dermatitis	0	0	1 (20)
Diaphoresis	0	1 (5.6)	0
Facial swelling	2 (20)	0	1 (20)
Hidradenitis	0	1 (5.6)	0
Itching	2 (20)	1 (5.6)	0
Pruritus generalized	0	0	1 (20)
Rash	3 (30)	9 (50)	2 (40)
Rash generalized	1 (10)	0	0
Rash maculo-papular	0	1 (5.6)	0
Rash pruritic	1 (10)	2 (11.1)	0
Skin hyperpigmentation	0	1 (5.6)	0
Sunburn	0	1 (5.6)	0
Urticaria	1 (10)	1 (5.6)	0
Vascular disorders	4	8	2
Dizziness	1 (25)	0	0
Flash hot	0	2 (25)	0
Flushing	2 (50)	2 (25)	0
Hypertension	1 (25)	2 (25)	0
Hypotension	0	1 (12.5)	2 (100)
Lightheadedness	0	1 (12.5)	0

Supplementary Table 3. Listing of All unique combinations of treatments (regimens)

Unique combination	N times administered	Regimen Category
Corticosteroid	51	Corticosteroids
Corticosteroid+Siltuximab	40	Siltuximab +/- Corticosteroids
Siltuximab	21	Siltuximab +/- Corticosteroids
Corticosteroid+Tocilizumab	17	Tocilizumab +/- Corticosteroids
Tocilizumab	7	Tocilizumab +/- Corticosteroids
Corticosteroid+Rituximab	22	Rituximab +/- Corticosteroids
Rituximab	11	Rituximab +/- Corticosteroids
Corticosteroid+Cyclophosphamide+Doxorubicin+Rituximab+Vincristine	3	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Doxorubicin+Vincristine	2	Chemotherapy +/- Other treatments
Corticosteroid+Etoposide+Immunoglobulin human normal+Rituximab	2	Chemotherapy +/- Other treatments
Anakinra+Ciclosporin+Corticosteroid+Cyclophosphamide+Immunoglobulin human normal+Rituximab+Siltuximab+Sirolimus+Tocilizumab	1	Chemotherapy +/- Other treatments
Anakinra+Corticosteroid+Eculizumab+Etoposide+Immunoglobulin human normal+Methotrexate	1	Chemotherapy +/- Other treatments
Anakinra+Corticosteroid+Etoposide	1	Chemotherapy +/- Other treatments
Baricitinib+Bortezomib+Ciclosporin+Corticosteroid+Cyclophosphamide+Immunoglobulin human normal+Rituximab+Siltuximab+Sirolimus	1	Chemotherapy +/- Other treatments
Bendamustine+Corticosteroid+Rituximab	1	Chemotherapy +/- Other treatments
Bleomycin+Corticosteroid+Dacarbazine+Doxorubicin+Vinblastine	1	Chemotherapy +/- Other treatments
Bortezomib+Celecoxib+Corticosteroid+Siltuximab+Thalidomide	1	Chemotherapy +/- Other treatments
Bortezomib+Ciclosporin+Corticosteroid+Cyclophosphamide+Doxorubicin+Etoposide+Immunoglobulin human normal+Rituximab+Thalidomide	1	Chemotherapy +/- Other treatments
Bortezomib+Ciclosporin+Corticosteroid+Immunoglobulin human normal+Siltuximab+Thalidomide	1	Chemotherapy +/- Other treatments
Bortezomib+Ciprofloxacin+Corticosteroid+Pentoxifylline+Siltuximab+Thalidomide+Tocilizumab	1	Chemotherapy +/- Other treatments
Bortezomib+Cisplatin+Corticosteroid+Cyclophosphamide+Daratumumab+Doxorubicin+Etoposide+Rituximab+Sirolimus+Thalidomide	1	Chemotherapy +/- Other treatments
Bortezomib+Cisplatin+Corticosteroid+Cyclophosphamide+Doxorubicin+Etoposide+Rituximab+Thalidomide+Tocilizumab	1	Chemotherapy +/- Other treatments

Bortezomib+Corticosteroid+Cyclophosphamide+Doxorubicin+Etoposide+Immunoglobulin human normal+Rituximab+Siltuximab+Thalidomide	1	Chemotherapy +/- Other treatments
Bortezomib+Corticosteroid+Cyclophosphamide+Doxorubicin+Etoposide+Rituximab+Siltuximab+Thalidomide+Tocilizumab	1	Chemotherapy +/- Other treatments
Bortezomib+Corticosteroid+Cyclophosphamide+Doxorubicin+Etoposide+Rituximab+Sirolimus	1	Chemotherapy +/- Other treatments
Bortezomib+Corticosteroid+Cyclophosphamide+Doxorubicin+Etoposide+Rituximab+Thalidomide	1	Chemotherapy +/- Other treatments
Bortezomib+Corticosteroid+Cyclophosphamide+Rituximab+Tocilizumab	1	Chemotherapy +/- Other treatments
Bortezomib+Corticosteroid+Rituximab	1	Chemotherapy +/- Other treatments
Bortezomib+Corticosteroid+Thalidomide+Tocilizumab	1	Chemotherapy +/- Other treatments
Ciclosporin+Corticosteroid+Cyclophosphamide+Doxorubicin+Immunoglobulin human normal+Plasmapheresis/plasma exchange+Rituximab+Sirolimus+Tocilizumab+Vincristine	1	Chemotherapy +/- Other treatments
Ciclosporin+Corticosteroid+Cyclophosphamide+Etoposide+Rituximab+Tocilizumab	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Doxorubicin+Etoposide+Immunoglobulin human normal+Rituximab+Vincristine	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Doxorubicin+Etoposide+Rituximab+Tocilizumab+Vincristine	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Doxorubicin+Hydroxychloroquine phosphate+Vincristine	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Doxorubicin+Immunoglobulin human normal+Rituximab+Vincristine	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Doxorubicin+Rituximab+Siltuximab+Vincristine	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Doxorubicin+Rituximab+Sirolimus+Tocilizumab+Vincristine	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Eculizumab+Immunoglobulin human normal+Rituximab+Siltuximab	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Etoposide+Rituximab	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Etoposide+Rituximab+Tocilizumab	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Etoposide+Rituximab+Vincristine	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Lenalidomide+Thalidomide	1	Chemotherapy +/- Other treatments
Corticosteroid+Cyclophosphamide+Rituximab	1	Chemotherapy +/- Other treatments
Corticosteroid+Decitabine+Siltuximab	1	Chemotherapy +/- Other treatments

Corticosteroid+Etoposide	1	Chemotherapy +/- Other treatments
Corticosteroid+Etoposide+Immunoglobulin human normal+Sirolimus+Tocilizumab	1	Chemotherapy +/- Other treatments
Corticosteroid+Etoposide+Rituximab	1	Chemotherapy +/- Other treatments
Cyclophosphamide+Etoposide+Immunoglobulin human normal+Rituximab+Ruxolitinib	1	Chemotherapy +/- Other treatments
Cyclophosphamide+Etoposide+Rituximab+Sirolimus	1	Chemotherapy +/- Other treatments
Decitabine+Rituximab	1	Chemotherapy +/- Other treatments
Decitabine+Siltuximab	1	Chemotherapy +/- Other treatments
Sirolimus	6	Immunomodulator(s) +/- Corticosteroids
Ciclosporin+Corticosteroid	3	Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Immunoglobulin human normal	3	Immunomodulator(s) +/- Corticosteroids
Azathioprine+Corticosteroid	2	Immunomodulator(s) +/- Corticosteroids
Anakinra+Corticosteroid	1	Immunomodulator(s) +/- Corticosteroids
Anakinra+Corticosteroid+Sirolimus	1	Immunomodulator(s) +/- Corticosteroids
Ciclosporin+Corticosteroid+Mycophenolate mofetil	1	Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Hydroxychloroquine phosphate	1	Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Immunoglobulin human normal+Mycophenolate mofetil	1	Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Immunoglobulin human normal+Sirolimus	1	Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Immunoglobulin human normal+Thalidomide	1	Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Lenalidomide	1	Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Mycophenolate mofetil	1	Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Sirolimus	1	Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Thalidomide	1	Immunomodulator(s) +/- Corticosteroids
Eculizumab	1	Immunomodulator(s) +/- Corticosteroids
Hydroxychloroquine phosphate	1	Immunomodulator(s) +/- Corticosteroids
Immunoglobulin human normal	1	Immunomodulator(s) +/- Corticosteroids
Immunoglobulin human normal+Sirolimus	1	Immunomodulator(s) +/- Corticosteroids
Lisafoclox	1	Immunomodulator(s) +/- Corticosteroids

Thalidomide	1	Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Rituximab+Siltuximab	7	Anti-IL6 + Rituximab +/- Other
Corticosteroid+Rituximab+Tocilizumab	3	Anti-IL6 + Rituximab +/- Other
Corticosteroid+Rituximab+Sirolimus+Tocilizumab	2	Anti-IL6 + Rituximab +/- Other
Corticosteroid+Immunoglobulin human normal+Rituximab+Siltuximab	1	Anti-IL6 + Rituximab +/- Other
Corticosteroid+Immunoglobulin human normal+Rituximab+Tocilizumab	1	Anti-IL6 + Rituximab +/- Other
Rituximab+Siltuximab	1	Anti-IL6 + Rituximab +/- Other
Rituximab+Siltuximab+Sirolimus	1	Anti-IL6 + Rituximab +/- Other
Corticosteroid+Immunoglobulin human normal+Tocilizumab	2	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Siltuximab+Sirolimus	2	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Siltuximab+Sirolimus	2	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Adalimumab+Siltuximab	1	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Anakinra+Ciclosporin+Corticosteroid+ Immunoglobulin human normal+Lenalidomide+Siltuximab+Upadacitinib	1	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Ciclosporin+Corticosteroid+Immunoglobulin human normal+Tocilizumab	1	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Eculizumab+Immunoglobulin human normal+Rituximab+Siltuximab+Sirolimus	1	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Eculizumab+Immunoglobulin human normal+Siltuximab	1	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Eculizumab+Siltuximab	1	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Hydroxychloroquine phosphate+Siltuximab	1	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Hydroxychloroquine phosphate+Tocilizumab	1	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Immunoglobulin human normal+Siltuximab	1	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Ravulizumab+Siltuximab	1	Anti-IL6 + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Excision of thymus+Siltuximab	1	Anti-IL6 + Procedure +/- Corticosteroids
Radiation therapy+Siltuximab	1	Anti-IL6 + Procedure +/- Corticosteroids
Siltuximab+Splenectomy	1	Anti-IL6 + Procedure +/- Corticosteroids
Corticosteroid+Immunoglobulin human normal+Rituximab	4	Rituximab + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Hydroxychloroquine phosphate+Rituximab	2	Rituximab + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Rituximab+Sirolimus	2	Rituximab + Immunomodulator(s) +/- Corticosteroids

Celecoxib+Corticosteroid+Rituximab	1	Rituximab + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Methotrexate+Rituximab	1	Rituximab + Immunomodulator(s) +/- Corticosteroids
Corticosteroid+Plasmapheresis/plasma exchange	2	Other procedure +/- drug therapy
Celecoxib+Corticosteroid+Plasmapheresis/ plasma exchange+Rituximab+Splenectomy	1	Other procedure +/- drug therapy
Corticosteroid+Immunoglobulin human normal+Plasmapheresis/plasma exchange	1	Other procedure +/- drug therapy
Radiation therapy+Rituximab	1	Other procedure +/- drug therapy
Plasmapheresis/plasma exchange	4	Other procedure
Excision of thymus	1	Other procedure
Radiation therapy	1	Other procedure
Splenectomy	1	Other procedure
No medical treatment	2	No medical treatment

Supplementary Table 4. Regimens administered to 102 iMCD patients

	Patients ever received, N (%)	Frequency of administration, N (%)
Corticosteroids	45 (44.1)	51 (16.8)
Siltuximab ± Corticosteroids	51 (50.0)	58 (19.1)
Tocilizumab ± Corticosteroids	20 (19.6)	23 (7.6)
Rituximab ± Corticosteroids	29 (28.4)	33 (10.9)
Chemotherapy-based regimen	31 (30.4)	49 (16.2)
Immunomodulator ± Corticosteroids	23 (22.5)	31 (10.2)
Anti-IL6 + Rituximab ± Other	13 (12.7)	16 (5.3)
Anti-IL6 + Immunomodulator(s) ± Steroids	13 (12.7)	16 (5.3)
Anti-IL6 + Procedure ± Corticosteroids	2 (2.0)	3 (1.0)
Rituximab + Immunomodulator(s) ± Corticosteroids	9 (8.8)	10 (3.3)
Procedure + drug therapy	4 (3.9)	5 (1.7)
Procedure	6 (5.9)	7 (2.3)
No medical treatment*	2 (2.0)	2 (0.7)
	Total patients: 102	Total regimens administered: 304

*No medical treatment beyond diagnostic lymph node excision

Supplementary Table 5. Chemotherapy regimens listed by patient and response status

Patient ID	Response ever achieved by patient	Regimen	Regimen response
R1	Yes	Bortezomib + Corticosteroid + Thalidomide + Tocilizumab	R
R1	Yes	Bendamustine + Corticosteroid + Rituximab	NR
R2	Yes	Ciclosporin + Corticosteroid + Cyclophosphamide + Etoposide + Rituximab + Tocilizumab	R
R3	Yes	Bortezomib + Corticosteroid + Cyclophosphamide + Doxorubicin + Etoposide + Immunoglobulin human normal + Rituximab + Siltuximab + Thalidomide	R
R3	Yes	Bortezomib + Corticosteroid + Cyclophosphamide + Doxorubicin + Etoposide + Rituximab + Siltuximab + Thalidomide + Tocilizumab	NR
R3	Yes	Bortezomib + Celecoxib + Corticosteroid + Siltuximab + Thalidomide	NR
R3	Yes	Bortezomib + Ciclosporin + Corticosteroid + Immunoglobulin human normal + Siltuximab + Thalidomide	NR
R3	Yes	Bortezomib + Ciclosporin + Corticosteroid + Cyclophosphamide + Doxorubicin + Etoposide + Immunoglobulin human normal + Rituximab + Thalidomide	NR
R4	Yes	Corticosteroid + Cyclophosphamide + Etoposide + Rituximab + Tocilizumab	R
R5	Yes	Corticosteroid + Cyclophosphamide + Etoposide + Rituximab + Vincristine	R
R6	Yes	Corticosteroid + Cyclophosphamide + Etoposide + Rituximab	R
R6	Yes	Corticosteroid + Cyclophosphamide + Rituximab	R
R7	Yes	Bortezomib + Cisplatin + Corticosteroid + Cyclophosphamide + Doxorubicin + Etoposide + Rituximab + Thalidomide + Tocilizumab	R
R8	Yes	Corticosteroid + Cyclophosphamide + Doxorubicin + Immunoglobulin human normal + Rituximab + Vincristine	R
R9	Yes	Corticosteroid + Etoposide + Immunoglobulin human normal + Rituximab	R
R9	Yes	Corticosteroid + Etoposide + Immunoglobulin human normal + Rituximab	R
R10	Yes	Corticosteroid + Cyclophosphamide + Doxorubicin + Hydroxychloroquine phosphate + Vincristine	R
R11	Yes	Corticosteroid + Cyclophosphamide + Eculizumab + Immunoglobulin human normal + Rituximab + Siltuximab	R
R11	Yes	Anakinra + Corticosteroid + Etoposide	NR
R11	Yes	Anakinra + Corticosteroid + Eculizumab + Etoposide + Immunoglobulin human normal + Methotrexate	NR
R12	Yes	Cyclophosphamide + Etoposide + Immunoglobulin human normal + Rituximab + Ruxolitinib	R
R12	Yes	Cyclophosphamide + Etoposide + Rituximab + Sirolimus	NR
R12	Yes	Corticosteroid + Cyclophosphamide + Doxorubicin + Etoposide + Immunoglobulin human normal + Rituximab + Vincristine	NR
R13	Yes	Bortezomib + Corticosteroid + Rituximab	R

NR1	No	Corticosteroid + Etoposide + Rituximab	NR
NR2	No	Corticosteroid + Cyclophosphamide + Doxorubicin + Rituximab + Vincristine	NR
NR3	No	Bleomycin + Corticosteroid + Dacarbazine + Doxorubicin + Vinblastine	NR
NR4	No	Ciclosporin + Corticosteroid + Cyclophosphamide + Doxorubicin + Immunoglobulin human normal + Plasmapheresis/plasma exchange + Rituximab + Sirolimus + Tocilizumab + Vincristine	NR
NR5	No	Bortezomib + Cisplatin + Corticosteroid + Cyclophosphamide + Daratumumab + Doxorubicin + Etoposide + Rituximab + Sirolimus + Thalidomide	NR
NR6	No	Corticosteroid + Cyclophosphamide + Doxorubicin + Rituximab + Vincristine	NR
NR7	No	Corticosteroid + Decitabine + Siltuximab	NR
NR7	No	Decitabine + Rituximab	NR
NR8	No	Corticosteroid + Etoposide	NR
NR8	No	Corticosteroid + Cyclophosphamide + Doxorubicin + Rituximab + Vincristine	NR
NR9	No	Corticosteroid + Cyclophosphamide + Doxorubicin + Rituximab + Sirolimus + Tocilizumab + Vincristine	NR
NR9	No	Bortezomib + Corticosteroid + Cyclophosphamide + Doxorubicin + Etoposide + Rituximab + Sirolimus	NR
NR10	No	Bortezomib + Corticosteroid + Cyclophosphamide + Rituximab + Tocilizumab	NR
NR11	No	Corticosteroid + Etoposide + Immunoglobulin human normal + Sirolimus + Tocilizumab	NR
NR11	No	Baricitinib + Bortezomib + Ciclosporin + Corticosteroid + Cyclophosphamide + Immunoglobulin human normal + Rituximab + Siltuximab + Sirolimus	NR
NR12	No	Corticosteroid + Cyclophosphamide + Doxorubicin + Rituximab + Siltuximab + Vincristine	NR

Supplementary Table 6. Chemotherapy agents stratified by inclusion in response-achieving regimens

Contains	Regimens achieved response	Regimens did not achieve response
Bortezomib	4/15 (27)	8/25 (32)
Cyclophosphamide	11/15 (73)	14/25 (56)
Etoposide	9/15 (60)	11/25 (44)
Doxorubicin	4/15 (27)	12/25 (48)
Vincristine	3/15 (20)	7/25 (28)
Cisplatin	1/15 (7)	1/25 (4)
Bendamustine	0	1/25 (4)
Bleomycin	0	1/25 (4)
Dacarbazine	0	1/25 (4)
Vinblastine	0	1/25 (4)
Decitabine	0	2/25 (8)
Methotrexate	0	1/25 (4)

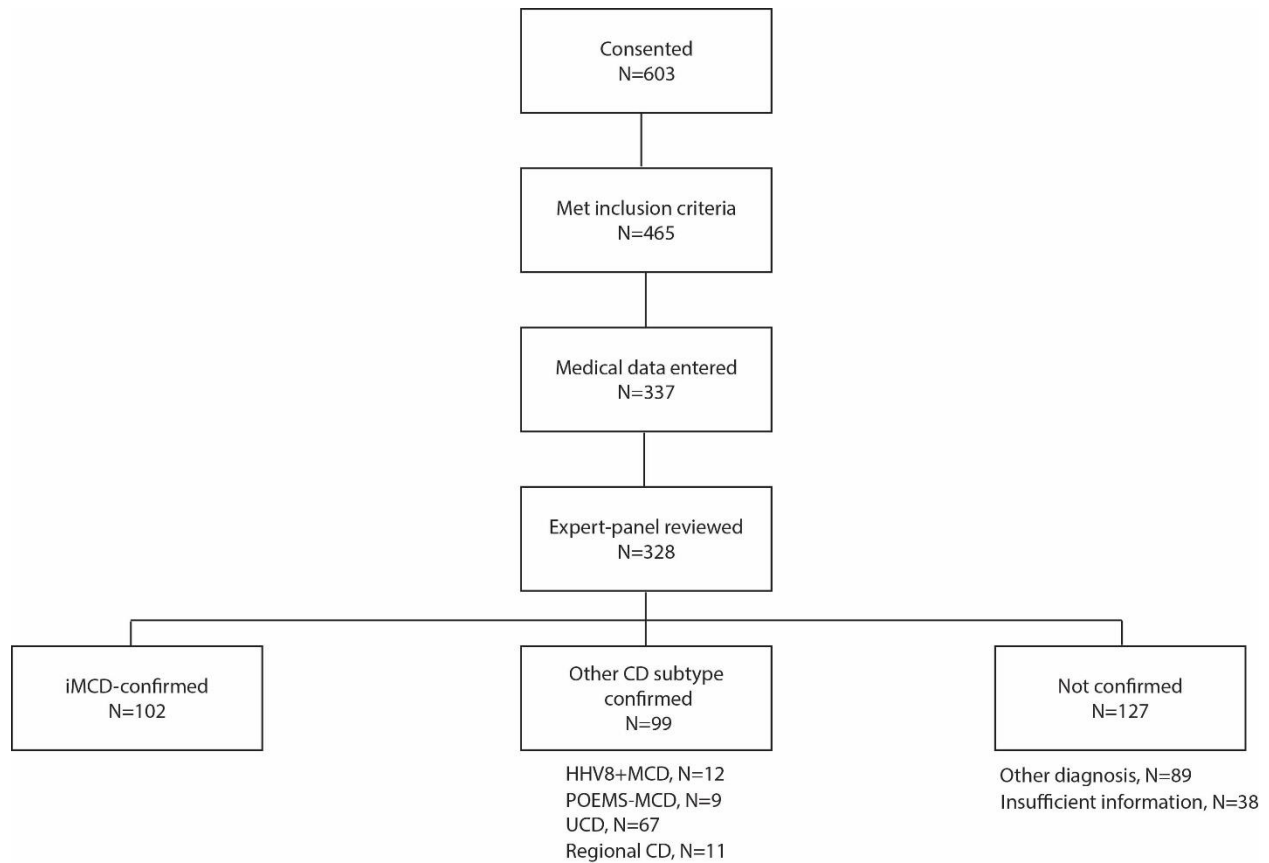
Supplementary Table 7. Lymph node and symptomatic response

	Patients ever achieved a response*		N patients with evaluable regimen
	Yes, N (%)	No, N (%)	
Anti-IL6 ± Corticosteroids†	25 (52.1)	23 (47.9)	48
Siltuximab ± Corticosteroids	19 (52.8)	17 (47.2)	36
Tocilizumab ± Corticosteroids	7 (46.7)	8 (53.3)	15
Rituximab ± Corticosteroids	8 (36.4)	14 (63.6)	22
Chemotherapy-based regimen	13 (52.0)	12 (48.0)	25
Immunomodulator ± Corticosteroids	4 (26.7)	11 (73.3)	15
Anti-IL6 + Rituximab ± Other	3 (60.0)	2 (40.0)	5
Anti-IL6 + Immunomodulator(s) ± Steroids	1 (20.0)	4 (80.0)	5
Anti-IL6 + Procedure ± Corticosteroids	0	0	0
Rituximab + Immunomodulator(s) ± Corticosteroids	0	5 (100)	5
Corticosteroids	1 (4.5)	21 (95.5)	22
Procedure + drug therapy	1 (33.3)	2 (66.7)	3
Procedure	0	1 (100)	1
No Medical Treatment	0	2 (100)	2

*For patients who >1 instance of the same regimen category, they are considered to have achieved response if response was achieved at least one time.

†Includes patients ever treated with either Siltuximab ± Corticosteroids and/or Tocilizumab ± Corticosteroids. Best response among those regimens is included; therefore, the N evaluable for each Siltuximab ± Corticosteroids and Tocilizumab ± Corticosteroids may not sum to the N evaluable for Anti-IL6 ± Corticosteroids

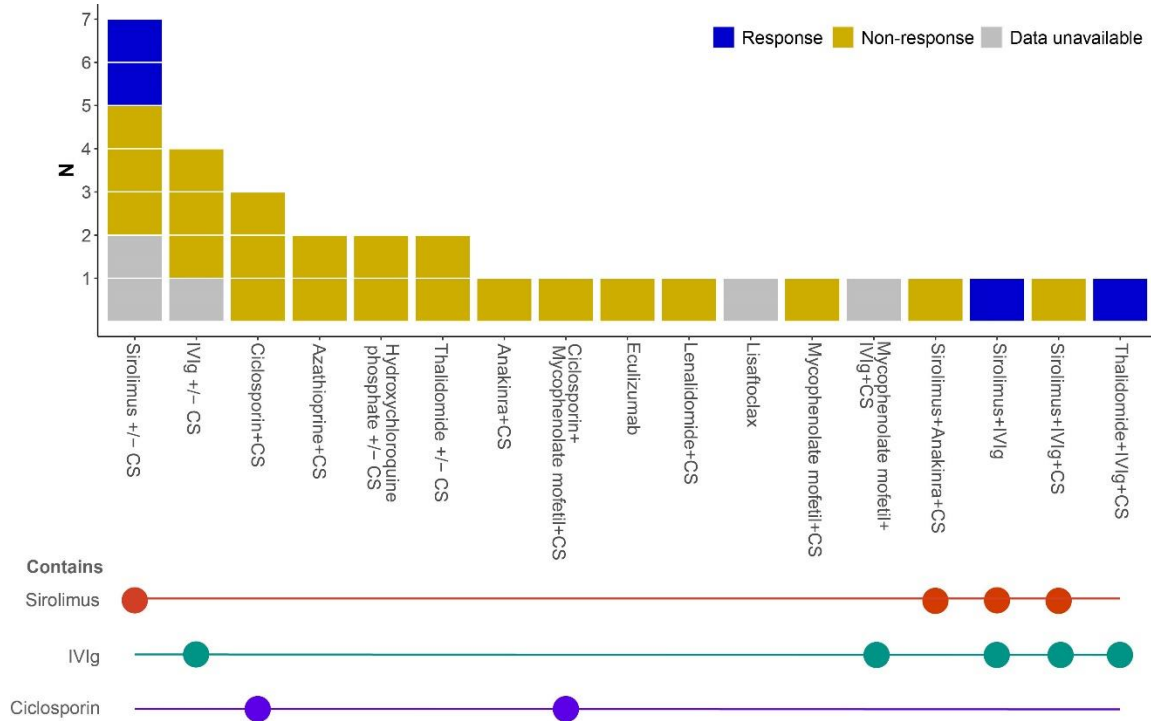
Supplementary Figure 1. Study consort diagram



Study flow diagram demonstrating the number of patients who enrolled through the study and were eligible for analysis. There were 102 iMCD patients who enrolled, met inclusion criteria, underwent expert panel review, and met criteria for iMCD. Of the other 328 patients reviewed by the expert panel, 99 were determined to be another Castleman disease (CD) subtype, and 127 were not confirmed to have CD due to insufficient information or information that suggested another disease process. Of these 127 patients, 37 (29.1%) were excluded due to insufficient information. This may include patients for whom a hematoxylin and eosin stained lymph node slide could not be obtained or for whom clinical diagnostic data could not be obtained (i.e., records and/or lymph node tissue were past retention dates). The remaining 89 (70.1%) patients were determined to be inconsistent with a CD diagnosis either because of an inconsistent pathologic diagnosis, an inconsistent clinical and pathologic diagnosis, or for whom

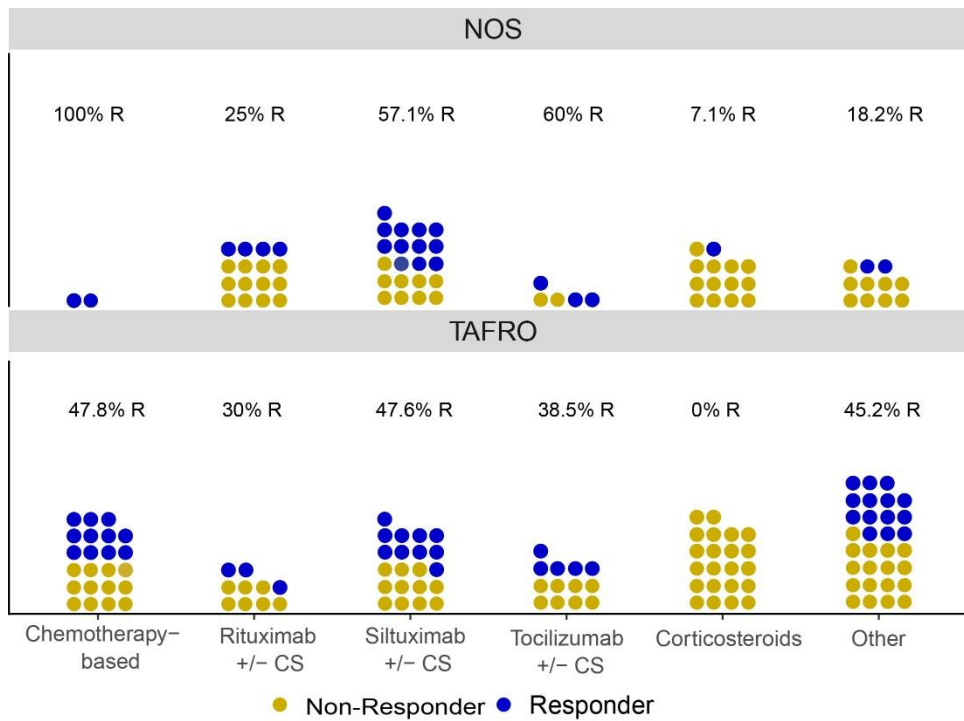
another autoimmune, infectious, or neoplastic disorder was strongly suspected. Of note, these 127 patients that were not confirmed represent patients who were suspected to have all subtypes of CD and are not limited to patients suspected to have iMCD. Abbreviations: HHV8+MCD: human herpes virus 8-associated multicentric CD; POEMS-MCD: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes multicentric CD; UCD: unicentric CD.

Supplementary Figure 2. Regimen administration and response assessment among regimens identified as immunomodulator(s) ± corticosteroids



Visual depiction of regimens identified as immunomodulator(s) ± corticosteroids. Among the immunomodulator regimens, we found 17 unique combinations, the most frequent of which was sirolimus ± corticosteroids (n=7). Across all immunomodulator ± corticosteroid regimens, we observed a relatively low response. Four (19%) patients with an evaluable regimen achieved at least one response. Shaded circles indicate if a regimen contains the three most frequently found immunomodulators: sirolimus (red), intravenous immunoglobulins (IVIg) (teal), or cyclosporin (purple). Abbreviations: CS: corticosteroids

Supplementary Figure 3. Best response stratified by clinical subtype



Response proportions by NOS and TAFRO subtype were similar to those observed in mild/moderate and severe disease. Of note, the majority of chemotherapy-based regimens were administered to TAFRO patients which resulted in a 47.8% response. Abbreviations: CS: corticosteroids