Supplementary Table 1: Signs and symptoms associated with KSHV-MCD and clinical benefit response criteria used to assess KSHV-MCD response.

Symptoms	**Laboratory Abnormalities**
Fever (includes chills and rigors)	Elevated C-reactive protein
Fatigue (includes lethargy)	Thrombocytopenia
Gastrointestinal (includes nausea and anorexia)	Anemia
Respiratory (includes airway hyperreactivity and cough)	Hypoalbuminemia

Response Criteria

For the purposes of response assessment, clinical symptoms attributed to MCD will be assigned an NCI-CTCAE grade equivalent, with response assessment based on changes in grade severity or symptom resolution. Increases in hemoglobin in patients who have received a transfusion do not count towards PR or CR for 3 weeks and increases in albumin or platelet count in patients who have received a transfusion do not count towards PR or CR for 7 days.

Complete Response (CR)

Full resolution of all clinical symptoms and laboratory abnormalities (whether or not these are indicator abnormalities) probably or definitely attributable to MCD, lasting at least 3 weeks.

Partial response (PR)

At least 50% of the abnormalities probably or definitely attributed to KSHV-MCD must improve by the minimum amounts specified below to attain PR.

- Only abnormalities present in a specific patient at baseline may count toward the achievement of a PR (e.g. if six of indicator abnormalities are present at baseline, at least three must meet the specified criteria to be considered a PR).
- Improvement in symptoms require at least 1 CTCAE grade equivalent improvement. For symptom groups (e.g. gastrointestinal and respiratory), where multiple symptoms within the group are present at least half of those attributable to KSHV-MCD must improve by at least 1 CTCAE grade equivalent to consider the group as a whole to be improved.
- Improvement in for each laboratory parameters requires either normalization of the lab value or else the following:
    - C-reactive protein reduction to ≤50% of baseline
    - Hemoglobin increment 2g/dL not explained by transfusion
    - Platelet increment ≥50 K/uL not explained by transfusion
    - Albumin increment ≥1g/dL not explained by transfusion
- No new indicator abnormalities probably or definitely attributed to KSHV-MCD; no indicator symptom may worsen by ≥1 CTCAE grade equivalent; and no indictor laboratory abnormality may worsen by the amount given in the criteria for progressive disease.

Stable Disease (SD)

No change in signs and symptoms of KSHV-MCD that meet criteria for any of CR, PR or PD.

Progressive Disease (PD)

PD is assessed based on the eight indicator abnormalities above. At least two indicator abnormalities must deteriorate by the minimum amounts specified below to constitute PD. The development of new indicator abnormalities not present in a specific patient at baseline is incorporated in the assessment of PD

- Deterioration in signs and symptoms require at least 1 CTCAE grade equivalent increase in severity. For symptom groups (e.g. gastrointestinal and respiratory), where multiple symptoms within the group are present at least half of those attributable to KSHV-MCD must

increase in severity by at least 1 CTCAE grade equivalent to consider the group as a whole to have deteriorated.

- Deterioration for each laboratory parameter requires an abnormal laboratory value meeting the following criteria:
    - C-reactive protein increase by ≥50% of baseline (or the upper limit of normal, whichever is greater)
    - Hemoglobin decrement 2g/dL not otherwise explained
    - Platelet decrement ≥25 K/uL not otherwise explained
    - Albumin decrement ≥0.5g/dL

Symptomatic, hematologic and biochemical response criteria for KSHV-MCD were used in the following studies:

1. Uldrick TS, Polizzotto MN, Aleman K, Wyvill KM, Marshall V, Whitby D, et al. Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-associated multicentric Castleman disease. Blood. 2014;124(24):3544.
2. Uldrick TS, Polizzotto MN, Aleman K, Mahony D, Wyvill KM, Wang V, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. Blood. 2011;117(26):6977.
3. Ramaswami R, Lurain K, Peer CJ, Serquina A, Wang V, Widell A, et al. Tocilizumab in patients with symptomatic Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. Blood. 2020;135(25):2316-9.

Supplementary Table 2: Regimens used for treatment of KSHV-MCD, all treatments apart from DA-EPOCH-R were administered until remission of symptoms.

Treatment administered	Dosage and Interval
Zidovudine (AZT) Valganciclovir (VGC)	AZT - 600 mg PO QID for 7-21 days (may titrate to response) VGC- 900 mg PO BID for 7-21 days (may titrate to response) Administered every 3 weeks until remission of symptoms and continued for 2 cycles beyond remission of symptoms. Associated publication: Uldrick TS, Polizzotto MN, Aleman K, Mahony D, Wyvill KM, Wang V, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. Blood. 2011;117(26):6977.
Rituximab	375mg/m^2 IV every week for up to 4 weeks or until remission of symptoms
Rituximab Liposomal Doxorubicin	375mg/m^2 IV every 3 weeks (may be given every week for severe flares) 20mg/m^2 IV every 3 weeks Administered until remission of symptoms and continued for 2 cycles beyond remission of symptoms.
Rituximab and Liposomal Doxorubicin with maintenance regimens • AZT/ VGC • Interferon-alpha	This option for treatment was available for participants on the study between 2006-2014. AZT - 600 mg PO QID, VGC- 900 mg PO BID x 7 days Initial: 7.5 million units SC, 3 times weekly for 2 weeks, Subsequent doses: Increase dose as tolerated each 14 days to a maximum of 45 million units subcutaneous. Three times weekly: 10 million units; 15 million units; 20 million units; 25 million units; 30 million units; 35 million units; 40 million units; 45 million units The option of maintenance therapy was provided from 4-12 months depending on clinical status. Administered until remission of symptoms and continued for 2 cycles beyond remission of symptoms. Associated publication: Uldrick TS, Polizzotto MN, Aleman K, Wyvill KM, Marshall V, Whitby D, et al. Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-associated multicentric Castleman disease. Blood. 2014;124(24):3544.
Rituximab and dose adjusted EPOCH	375mg/m^2 IV every 3 weeks CIVI – continuous IV infusion Etoposide 50 mg/m^2 /day CIVI* over 24 hours x 4 days (days 1-4) Doxorubicin 10 mg/m^2 /day CIVI over 24 hours x 4 days (days 1-4) Vincristine 0.4 mg/m^2 /day CIVI over 24 hours x 4 days (days 1-4) Prednisone 60 mg/m^2/day PO x 5 days (days 1-5) Cyclophosphamide if CD4 < 100 cells/mm^3, 187 mg/m^2 IV (Day 5)

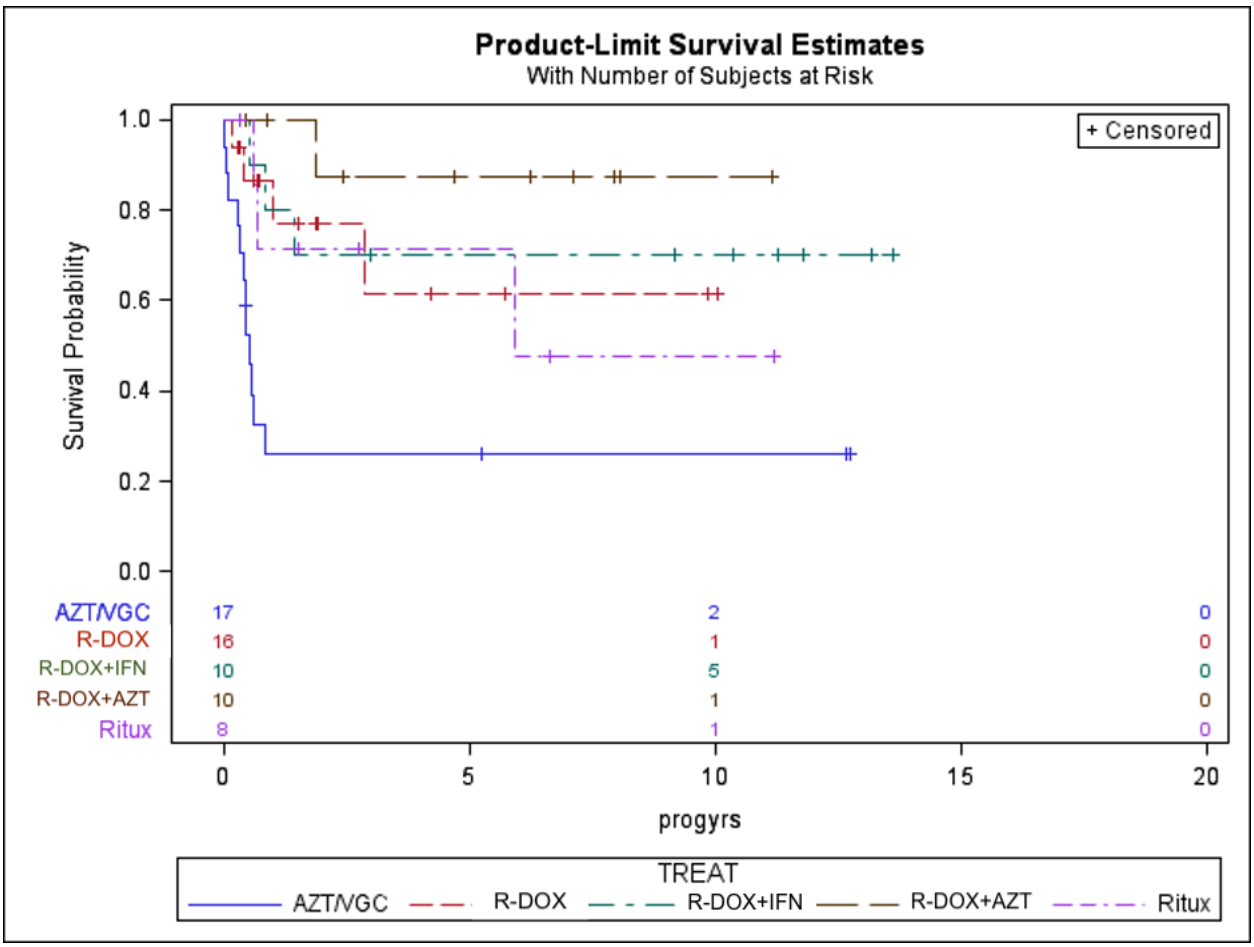
	if CD4 ≥ 100 cells/mm^3, 375 mg/m^2 IV (Day 5); follow with 500 mL or more normal saline. Filgrastim 300 µg SUBCUTANEOUS daily if <75 kg or 480 µg daily if ≥75 kg, beginning day 6 until absolute neutrophil count recovery ≥ 5000 cells/mm^3 Every 3 weeks for maximum of 6 cycles

Supplementary Table 3: Clinical characteristics by initial therapy received on study for KSHV-MCD with or without KS *Median values provided only

	AZT/VGC	Rituximab alone	Rituximab and Liposomal Doxorubicin			
			All	No maintenance	AZT/VGC maintenance	Interferon-alpha maintenance
	N=17 (%)	N=5 (%)	N=22 (%)	N=13 (%)	N=7 (%)	N=2 (%) *
Age, years (median, IQR)	41 (39, 44)	54 (53, 54)	47 (41, 54)	48 (35, 54)	47 (44, 52)	46
Sex (%)						
Cisgender Male	16 (94)	5 (100)	21 (95)	12 (92)	7 (100)	2 (100)
Cisgender Female	1 (6)	-	1 (5)	1 (8)	-	-
Race (%)						
White	9 (53)	3 (60)	8 (36)	5 (38)	1 (14)	2 (100)
Hispanic	1 (6)	-	3 (14)	1 (8)	2 (29)	-
Black	5 (29)	1 (20)	7 (32)	5 (38)	2 (29)	-
African Immigrant	2 (12)	-	2 (9)	1 (8)	1 (14)	-
Other	-	1 (20)	2 (9)	1 (8)	1 (14)	-
ECOG performance status						
0 (%)	2 (12)	-	-	-	1 (14)	-
1 (%)	7 (41)	2 (40)	8 (36)	2 (16)	5 (71)	1 (50)
2 (%)	5 (29)	2 (40)	2 (9)	-	1 (14)	1 (50)
3 (%)	3 (18)	1 (20)	6 (27)	6 (46)	-	-
4 (%)	-	-	6 (27)	5 (38)	-	-
HIV characteristics						
CD4 T-cell count, cells/µL (median, IQR)	330 (190, 571)	414 (316, 456)	142 (90, 359)	136 (84, 303)	303 (128, 427)	459
HIV viral load, copies/mL (median, IQR)	50 (50, 180)	<50 (<50, 69)	<50 (<50, 390)	<50 (<50, 458)	<50 (<50, 67)	3880
Clinical characteristics at baseline						

Hemoglobin, g/dL (median, IQR)	10.3 (9.2, 12.4)	12.3 (11.1, 12.7)	9.3 (7.9, 10.8)	8.8 (7.4, 10.1)	10.6 (9.8, 11.2)	8.9
Platelets, $10^3/\mu L$ (median, IQR)	116 (81, 200)	275 (184, 344)	92.5 (64, 220)	89 (59, 165)	141 (108, 308)	58
Albumin, g/dL (median, IQR)	2.8 (2.2, 3.3)	3.5 (3, 3.8)	2.8 (2.3, 3.3)	2.9 (2.3, 3.5)	2.9 (2.7, 3.3)	1.9
C-Reactive Protein, mg/L (median, IQR)	29.8 (10.6, 150)	57 (12, 94.4)	108 (21.8, 141)	101.2 (8.4, 152.7)	111 (56, 125)	152

Supplementary Figure 1: Progression-free survival following administration of KSHV-MCD therapies on protocol.



Supplementary Table 4: Comparisons of first flare to remission or end of treatment (patients with concurrent PEL) in all patients with KSHV-MCD cohort with or without concurrent diseases.

Cytokines	**All patients, median (IQR)**		
	Flare	**Remission/End of Treatment**	**P value**
Interferon-γ, pg/mL	32.9 (15.6, 139.6)	11.5 (5.5, 23)	<0.0001
IL-10, pg/mL	100.8 (18.6, 730)	0.8 (0.4, 3.9)	<0.0001
IL-12, pg/mL	0.2 (0.1, 0.3)	0.1 (0.1, 0.3)	0.42
IL-13, pg/mL	0.5 (0.1, 0.9)	0.2 (0.1, 0.5)	<0.0001
IL-1β, pg/mL	0.3 (0.2, 0.6)	0.2 (0.1, 0.4)	0.06
IL-2, pg/mL	0.6 (0.4, 0.9)	0.4 (0.3, 0.6)	0.04
IL-4, pg/mL	0.1 (0.06, 0.14)	0.05 (0.03, 0.07)	0.0001
IL-6, pg/mL	8 (3.8, 25.6)	2 (0.8, 4.8)	<0.0001
IL-8, pg/mL	63.1 (19.3, 107.4)	44.2 (24, 93.2)	0.87
TNF-α, pg/mL	9 (6.5, 12.6)	5 (3.5, 8.7)	<0.0001
KSHV-VL, $\log_{10}$ copies/10^6 PBMCs	3.8 (3, 5.1)	0 (0, 2)	<0.0001

Supplementary Table 5: Causes of death of patients by KSHV-MCD group

	MCD alone (4 patients)	**MCD and KS (7 patients)**	**MCD and PEL +/-KS (5 patients)**
Death due to worsening KSHV-associated process	2 (multiorgan dysfunction)	2 (pulmonary KS) 2 (multiorgan dysfunction)	4 (multiorgan dysfunction with refractory PEL) 1 (hypoxic respiratory arrest from pulmonary effusions caused by PEL)
Complications of treatment i.e. infections		1 (low CD4 count and sepsis)	
Other	1 (hyperglycemic state) 1 (unknown – autopsy not feasible)	1 (pancreatic cancer) 1 (unknown, autopsy not feasible)	