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Emapalumab as salvage therapy for adults with malignancy-associated hemophagocytic lymphohistiocytosis

*William T. Johnson[1,2], *Zachary D. Epstein-Peterson[1,2], Nivetha Ganesan[1], Timothy Pak[3], Tiffany Chang[1], Phuong Dao[4], Alison J. Moskowitz[1,2], Robert N. Stuver[1,2], Paola Ghione[1,2], Natasha Galasso[1], Niloufer Khan[5], M. Lia Palomba[1,2], Philip C. Caron[1,2], Anita Kumar[1,2], Roni Tamari[2,6], Jennifer K. Lue[1,2], Ariela Noy[1,2], Lorenzo Falchi[1,2], Andrew M. Intlekofer[1,2,7], Boglarka Gyurkocza[2,6], Miguel-Angel Perales[2,6], Michael Scordo[2,6], A. Zara Herskovits[8], Gilles Salles[1,2], Santosha A. Vardhana[1,2,7], Steven M. Horwitz[1,2]

Author affiliations:

[1]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
[2]Department of Medicine, Weill Cornell Medical College, Cornell University, New York, NY, USA.
[3]Department of Medicine, New York Presbyterian Brooklyn Methodist Hospital-Weill Cornell Medical College, New York, NY, USA.
[4]Department of Pharmacy, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
[5]Department of Hematology and Hematopoietic Cell Transplant, Lymphoma Division, City of Hope Comprehensive Cancer, Duarte, CA, USA.
[6]Department of Medicine, Adult Bone Marrow Transplant and Cellular Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
[7]Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
[8]Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

Authorship contributions:

Denotes authors contributed equally. WTJ and ZDEP* conceived the study, interpreted the data, and wrote the manuscript with input from other authors. N. Ganesan performed statistical analyses and constructed the figure. TP assisted with data extraction and writing of the manuscript. TC assisted with data extraction. N. Galasso organized the project, assisted in data extraction, and execution of the IRB approval. PD, AJM, RNS, PG, MLP, PCC, AK, RT, JKL, AN, LF, AMI, BG, MAP, MS, GS made substantial contributions through critical revisions of the manuscript, table, and figures. SMH provided oversight to the research study design and critically revised the manuscript. All authors gave their approval for the final manuscript submission.

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Running head:

Emapalumab for malignancy-associated HLH

Corresponding author:

William T. Johnson, DO
530 East 74th Street New
York, NY 10021
Johnsow3@mskcc.org

Data-sharing agreement:

Requests for deidentified data that are not included in this article should be directed to the corresponding author, William T. Johnson, DO (johnsow3@mskcc.org).

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Malignancy-associated HLH (M-HLH) is a rare, life-threatening, and poorly understood cancer complication characterized by profound immune dysregulation, the sequelae of which include fevers, pancytopenia, coagulopathy, and multiorgan failure.[1-5] M-HLH carries a grim prognosis and frontline management is geared towards addressing both the underlying malignancy as well as the inflammatory milieu, and frequently incorporates agents commonly used for treating both primary and secondary HLH such as etoposide and high-dose steroids.[2-5] Other immunosuppressive agents, such as ruxolitinib and anakinra, have been described for treating M-HLH, but robust single-agent efficacy data remain limited.[6, 7]

Emapalumab is a fully human IgG1 monoclonal antibody that binds to and neutralizes interferon-gamma (IFNγ).[8] It is approved by the U.S. Food and Drug Administration for adults and pediatrics with relapsed or refractory primary HLH, and the growing body of evidence supporting the clinical benefit of emapalumab for treating various other etiologies of secondary HLH and hyperinflammatory states is encouraging.[9-14]

It is often problematic to differentiate between M-HLH responses from responses to the underlying malignancy itself as collectively these patients have diverse presenting features and clinical characteristics. Additionally, responses are frequently confounded by multiple M-HLH treatments utilized in combination or quick succession.[3, 4] Furthermore, determining the immediate cause of death, whether M-HLH-related, malignancy-related, infection-related, or other, poses numerous challenges. Here, we report the initial Memorial Sloan Kettering Cancer Center (MSKCC) experience with emapalumab for treating adults with refractory M-HLH.

We first queried the MSKCC pharmacy database to identify adults treated with emapalumab from January 2019 through December 2022. We performed manual chart reviews to confirm an active malignancy diagnosis, and extracted data required for diagnosing HLH according to the HLH-2004 criteria, and for investigating other relevant M-HLH biomarkers.[1, 3, 15]

The primary objectives were to determine M-HLH-specific overall survival (OS) and emapalumab-specific OS, defined from the start of frontline M-HLH-directed treatment (steroids and/or etoposide), and from the first emapalumab dose until death or last follow-up, respectively. Secondary objectives included describing patient baseline clinical characteristics and M-HLH biomarker responses to emapalumab. M-HLH biomarkers—ferritin, soluble interleukin-2 receptor alpha (sIL2r), lactate dehydrogenase (LDH), complete blood cell counts, and liver function tests (LFTs)—were considered assessable only if abnormal at the time of emapalumab initiation. M-HLH biomarker responses were assessed according to the definitions in the pivotal primary HLH registry trial, and measured at the time of best ferritin response.[8] Best ferritin response was defined as the maximum reduction in ferritin assessed $\geq$72 hours after the first emapalumab dose. This definition was selected based on the dosing frequency of emapalumab in the registry trial.[8] Because cytokine measurements were ordered at the discretion of the treating physician, best response for sIL2r was assessed independently at the closest time point to best ferritin response. This retrospective study was approved by the MSKCC institutional review board. Informed consent was not required.

In total, 15 adult patients were treated with emapalumab for M-HLH. The median age was 65 years (range, 19-73). All but one patient presented with M-HLH in the setting of relapsed malignancy, and most were heavily pretreated (Supp table 1). At the start of emapalumab treatment, all patients had a markedly elevated ferritin (median 48,204 ng/mL; range, 6,007-372,503) and abnormal LFTs, while most had pancytopenia. All patients assessed for sIL2r (n=13) had elevated levels, including above the upper limit reported (>20,000 pg/mL; n=7). Six patients had abnormal hepatic uptake on their positron emission tomography/computed tomography scan, 2 of whom underwent a biopsy that confirmed hepatic involvement of malignancy. All but 3 patients met the HLH-2004 diagnostic criteria despite none

undergoing natural killer cell activity testing, and 5 patients not having a bone marrow biopsy performed to determine evidence of hemophagocytosis (Supp table 1).[15]

Patients received a median of 2 doses of emapalumab (range, 1-7), and all were hospitalized during treatment. All patients received high-dose steroids before and concurrently with emapalumab. Before their first emapalumab dose, 9 (60%) patients received etoposide, and another 2 patients started etoposide concurrently with emapalumab (Supp table 1, Figure 1). Three patients progressed on additional M-HLH-directed therapy prior to emapalumab (patient 5, tocilizumab x6 doses; patient 10, high-dose intravenous immunoglobulin; patient 11, alemtuzumab x8 doses). The median time from last malignancy-directed treatment (excluding steroids and/or etoposide alone) to first emapalumab dose was 8 days (range, NA-248).

The median M-HLH-specific and emapalumab-specific OS rates were 18 days (range, 4-292) and 4 days (range, 1-257), respectively (Figure 1). Seven patients died or initiated hospice care within 72 hours of their first emapalumab dose, 7 patients lived longer than 7 days, and 4 patients lived longer than 14 days. One patient (patient 13) was discharged and remained alive at the time of data cutoff (257 days from the first emapalumab dose). The immediate precipitating cause of death was deemed secondary to M-HLH-associated organ failure complications in 8 (53%) patients, directly related to organ failure complications from sepsis in 3 (20%) patients, and directly related to the progression of malignancy in 3 (20%) patients (Supp table 1).

The 8 patients who survived ≥72 hours after their first emapalumab dose were assessed for M-HLH biomarker responses (Figure 2). Seven (88%) showed a best ferritin response, at a median of 10 days (range, 5-17) and 3 doses (range, 2-5), with a 64% median reduction in ferritin (range, 29-91%). Among these responders, those assessable for sIL2r (n=4), total bilirubin (n=5), aspartate aminotransferase (n=5), and alanine aminotransferase (n=3) had median reductions in these biomarkers of 35% (range, 32-62%), 26% (range, 17-46%), 86% (range, 15-93%), and 87% (range, 34-91%), respectively. Lymphocyte counts, neutrophil counts, hemoglobin concentrations, and platelet counts improved in only 1 patient (patient 13, Figure 3). Her hemoglobin concentration and platelet count before emapalumab were 9.3 g/dL and 15 K/µL, stabilized post-emapalumab, and she remained persistently transfusion-independent at the time of last follow-up (257 days from the first emapalumab dose). No patients achieved a best ferritin response of <2000 ng/mL, which defined a complete response.[8] Figure 3 depicts 3 patients who demonstrated sustained improvements in M-HLH biomarkers with emapalumab monotherapy after progression on etoposide and steroids. All 3 demonstrated both a >50% reduction as their best ferritin response, and a sustained improvement in sIL2r.[8] Notably, none of these 3 patients were treated with concurrent malignancy-directed therapy after starting emapalumab.

Before receiving emapalumab, 7 patients displayed Epstein-Barr virus (EBV) reactivation, while 8 had an undetectable EBV viral load (VL). Among the former group, post-emapalumab EBV VL decreased (n=2), remained above the upper limit clinically reported (>800,000 IU/mL; n=1), or was not reassessed (n=1), and 3 died <72 hours post-emapalumab. Among the latter group, EBV VL remained undetectable for 9-21 days (n=3) or reactivated (7,313 IU/mL; n=1, day 7), and 4 died <72 hours post-emapalumab. Five patients displayed cytomegalovirus (CMV) reactivation before receiving emapalumab, while 9 had an undetectable CMV VL. Among the former group, post-emapalumab CMV VL decreased (n=1) or was not reassessed (n=1), and 3 died <72 hours post-emapalumab. Among the latter group, CMV VL remained undetectable (n=4), or was not reassessed (n=2), and 3 died <72 hours post-emapalumab. One patient was never assessed for a CMV VL. In total, 9 (60%) patients were treated for other infections before or concurrently with emapalumab.

Limitations to this study include the variabilities in emapalumab dosing strategies as well as the variabilities in the patient's underlying clinical characteristics, prior malignancy-directed treatments, and pre-emapalumab M-HLH-directed therapies. These differences contributed to the marked heterogeneity of our population of study. Additionally, this cohort was enriched in patients with particularly aggressive malignancies as the majority were heavily pretreated for their cancer, had M-HLH refractory to etoposide, and received prolonged high doses of steroids before starting emapalumab, compounding the generally high mortality rate of M-HLH. [1, 3]

The absence of monitoring serum C-X-C motif chemokine ligand 9 (CXCL9) levels is a potential limitation of this study. CXCL9 is a specific and reliable surrogate of localized IFNγ activity, and reductions in serum CXCL9 levels are associated with responses to emapalumab when treating primary HLH and macrophage activation syndrome.[8, 12] Uniform assessments of serum CXCL9 levels in these patients may have identified those who had M-HLH that was primarily driven by IFNγ, and may have guided emapalumab dosing strategies relative to improvements or progressions in other M-HLH biomarkers and clinical parameters. Nonetheless, further research in this context is needed before definitive assumptions can be made.

In conclusion, these data suggest that salvage emapalumab administered in random fashion to refractory M-HLH patients with multiply relapsed hematological malignancies absent of effective concurrent malignancy-directed therapy is not highly beneficial. Nevertheless, 7 out of the 8 patients surviving ≥72 hours post-emapalumab initiation demonstrated notable improvements in M-HLH biomarkers including patients who had progressed on etoposide and steroids, and were not treated with any further malignancy-directed therapy. This suggests that IFNγ may represent a therapeutic target to mitigate the hyperinflammatory state of M-HLH. A prospective study is warranted to determine if utilizing emapalumab earlier in the M-HLH course, in synergy with malignancy-directed treatment and with dosing strategies guided by serum CXCL9 levels, can improve the outcomes for M-HLH patients.

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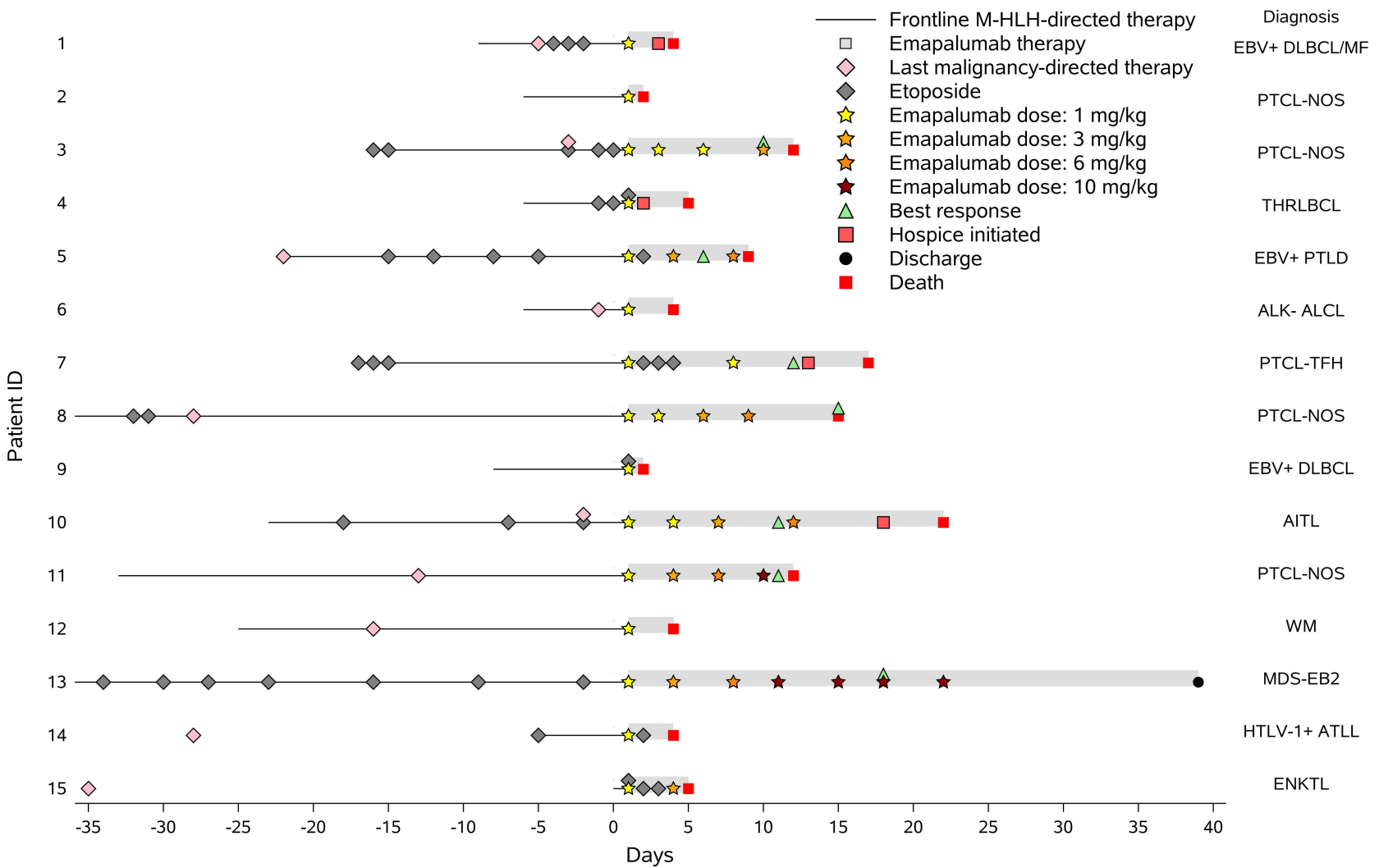
Figure legends:

Figure 1. Swimmer plot summarizing the malignancy-associated hemophagocytic lymphohistiocytosis (M-HLH) treatment course from day -35 prior to first emapalumab dose. All patients received steroids from the start of M-HLH treatment and concurrently with emapalumab. The start of frontline M-HLH-directed therapy included initiation of steroids and/or etoposide. Last malignancy-directed therapy included any treatment other than steroids and/or etoposide alone. Last malignancy-directed therapies prior to day -35 are not shown. *EBV, Epstein-Barr virus; DLBCL, diffuse large B-cell lymphoma; MF, mycosis fungoides; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; THRLBCL, T-cell/histiocyte-rich large B-cell lymphoma; PTLD, post-transplant (allogeneic stem cell transplant) lymphoproliferative disorder; ALK, anaplastic lymphoma kinase; ALCL, anaplastic large cell lymphoma; PTCL-TFH, peripheral T-cell lymphoma with a follicular T-helper cell phenotype; AITL, angioimmunoblastic T-cell lymphoma; WM, Waldenstrom macroglobulinemia; MDS-EB2, myelodysplastic syndrome with excess blasts 2; HTLV-1, human T-lymphotropic virus type 1; ATLL, adult T-cell leukemia/lymphoma; ENKTL, extranodal NK/T-cell lymphoma*.

Figure 2. Percent change in malignancy-associated hemophagocytic lymphohistiocytosis (M-HLH) biomarkers for patients surviving ≥72 hours after their first emapalumab dose as determined at the time of best ferritin response. M-HLH biomarker responses were not calculated if their corresponding values were not abnormal at the time of first emapalumab dose or if they were never evaluated and these represent the missing values. Patients 5 and 11 did not demonstrate a change in sIL2r level below the upper limit that is clinically reported (20,000 pg/mL) at any time point. *sIL2r, soluble interleukin-2 receptor alpha; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Tbili, total bilirubin.*

Figure 3. Longitudinal improvements in malignancy-associated hemophagocytic lymphohistiocytosis biomarkers in 3 patients who demonstrated both a >50% reduction as their best ferritin response, and a sustained improvement in soluble interleukin-2 receptor alpha (sIL2r) with emapalumab monotherapy after progression on etoposide and steroids. Percent change at each timepoint was calculated from day -6 post-emapalumab for patients 3 and 8, and day -7 post-emapalumab for patient 13. *sIL2r, soluble interleukin-2 receptor alpha; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Tbili, total bilirubin; ANC, absolute neutrophil count; ALC, absolute lymphocyte count.*


Frontline M-HLH-directed therapy
Emapalumab therapy
Last malignancy-directed therapy
Etoposide
Emapalumab dose: 1 mg/kg
Emapalumab dose: 3 mg/kg
Emapalumab dose: 6 mg/kg
Emapalumab dose: 10 mg/kg
Best response
Hospice initiated
Discharge
Death
Diagnosis
1
EBV+ DLBCL/MF
2
PTCL-NOS
3
PTCL-NOS
4
THRLBCL
5
EBV+ PTLD
6
ALK- ALCL
7
PTCL-TFH
8
PTCL-NOS
9
EBV+ DLBCL
10
AITL
11
PTCL-NOS
12
WM
13
MDS-EB2
14
HTLV-1+ ATLL
15
ENKTL
Patient ID
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-5
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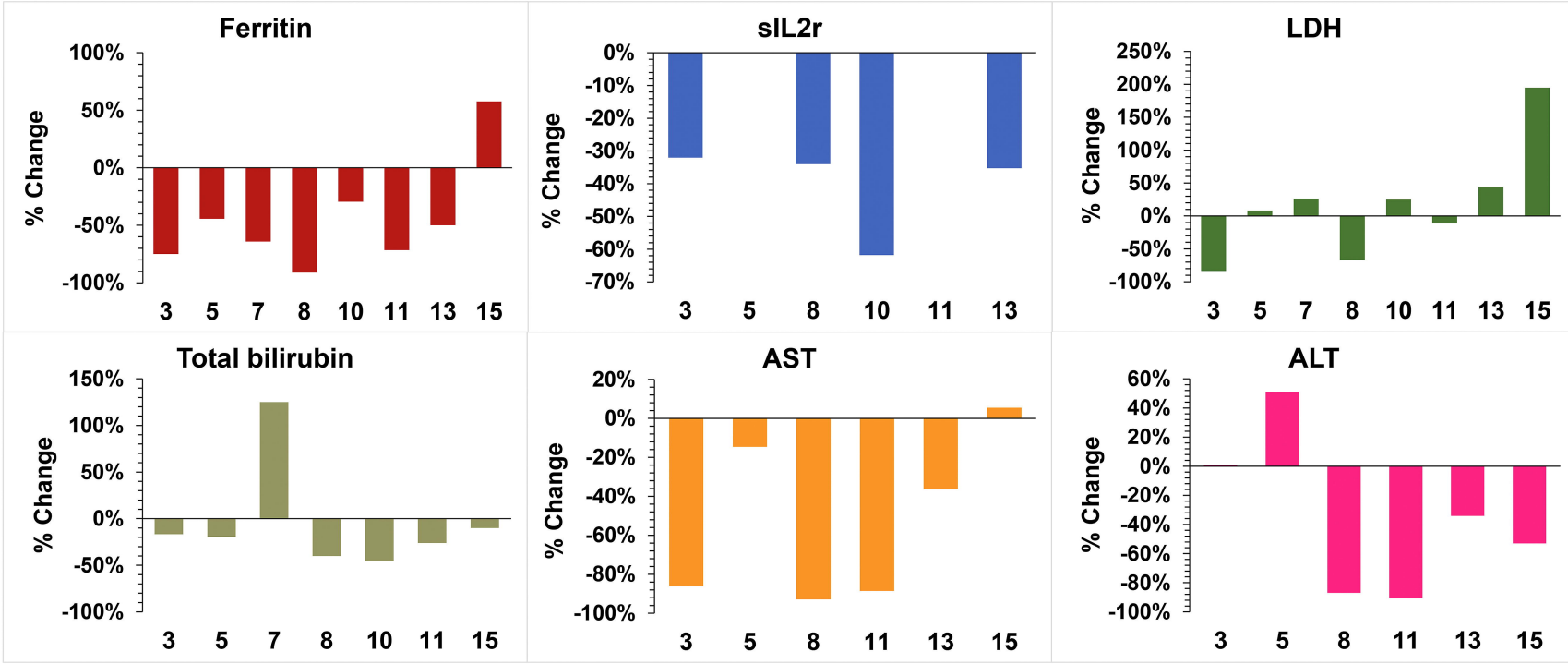
30
35
40
Days


Ferritin
% Change
100%
50%
0%
-50%
-100%
3 5 7 8 10 11 13 15
sIL2r
% Change
0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
3 5 8 10 11 13
LDH
% Change
250%
200%
150%
100%
50%
0%
-50%
-100%
3 5 7 8 10 11 13 15
Total bilirubin
% Change
150%
100%
50%
0%
-50%
-100%
3 5 7 8 10 11 15
AST
% Change
20%
0%
-20%
-40%
-60%
-80%
-100%
3 5 8 11 13 15
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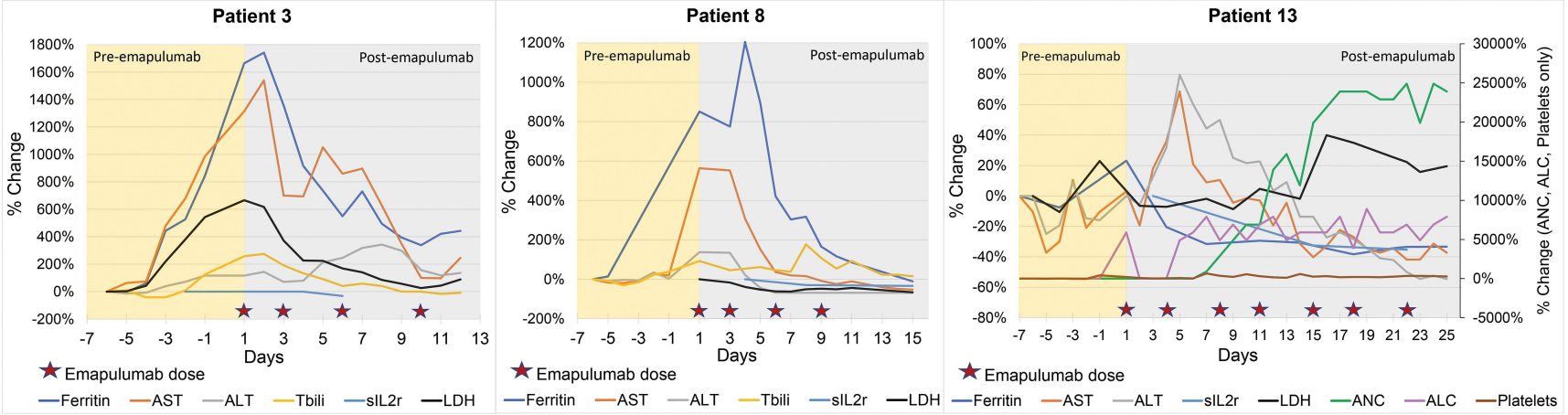
-80%
-100%
3 5 8 11 13 15


Patient 3
Pre-emapulumab
Post-emapulumab
% Change
1800%
1600%
1400%
1200%
1000%
800%
600%
400%
200%
0%
-200%
-7 -5 -3 -1 1 3 5 7 9 11 13
Days
Emapulumab dose
Ferritin AST ALT Tbili sIL2r LDH
Patient 8
Pre-emapulumab
Post-emapulumab
% Change
1200%
1000%
800%
600%
400%
200%
0%
-200%
-7 -5 -3 -1 1 3 5 7 9 11 13 15
Days
Emapulumab dose
Ferritin AST ALT Tbili sIL2r LDH
Patient 13
Pre-emapulumab
Post-emapulumab
% Change
100%
80%
60%
40%
20%
0%
-20%
-40%
-60%
-80%
30000%
25000%
20000%
15000%
10000%
5000%
0%
-5000%
% Change (ANC, ALC, Platelets only)
-7 -5 -3 -1 1 3 5 7 9 11 13 15 17 19 21 23 25
Days
Emapulumab dose
Ferritin AST ALT sIL2r LDH ANC ALC Platelets

Supplemental table 1: Clinical characteristics prior to emapalumab and best ferritin responses with emapalumab treatment

ID	Malignancy	Age (y)	No. of prior malignancy therapies	Last malignancy-directed therapy	Total dose (in mg) of etoposide received prior to emapalumab initiation	Ferritin (ng/mL)	sIL2r (pg/mL)	Phagocytosis on BMB	WBC (K/μL)	Platelet count (K/μL)	Tbili (mg/dL)	AST (u/L) / ALT (u/L)	No. of HLH-2004 criteria*	Splenomegaly	Hepatomegaly	PET/CT details of liver	Other infection†	Precipitating cause of death or indication for hospice/comfort measures	Best ferritin response (ng/mL)
1	EBV+ DLBCL / stage IVB MF	58	9	CEP	200	12,283	NE	Y	0.4	5	5.4	103 / 67	5‡	Y	Y	Heterogenous uptake (SUV 2.8)	Y	MODS from sepsis	NE
2	PTCL-NOS	73	0	NA	0	7,683	>20,000	Y	281,000[§]	115	2.2	547 / 61	5	N	N	Heterogenous uptake (SUV 4.4)	N	Cardiac arrest with M-HLH	NE
3	PTCL-NOS	69	3	GemE	502	372,503[§]	>20,000	NE	0.1	17	4.3	495 / 288	4‡	Y	N	No abnormal uptake	Y	Toxic metabolic encephalopathy with M-HLH	92,611
4	THRLBCL	54	4	Tafa + Len	300	17,798	>20,000	NE	5.5	29	15.6	263 / 801	4	Y	N	Diffuse uptake, hypodense lesions (SUV 8.5)[‖]	N	POM	NE
5	EBV+ PTLD	46	1	Rituximab	375	42,594	>20,000	Y	0.1	10	23.3	226 / 178	6	Y	Y	Diffuse uptake (SUV 5.7)	Y	MODS with M-HLH and DAH	23,717
6	ALK- ALCL	54	5	BV	0	20,735	19,205	Y	8.7	6	2.3	68 / 35	6	Y	Y	No abnormal uptake	N	MODS with M-HLH and ARDS	NE
7	PTCL-TFH	69	2	Romi + Duve	234	8,536	NE	Y	1.1	5	2	23 / 13	5‡	Y	N	No abnormal uptake	Y	MODS with M-HLH	3,031
8	PTCL-NOS	61	4	HD-MTX	172	10,797	6,699[¶]	NE	1.4	15	2.5	544 / 76	6‡	Y	N	No abnormal uptake	Y	POM in CNS	9,649
9	EBV+ DLBCL	67	1	R-CHOP	0	28,640	>20,000	NE	3.6	10	21.7	2118 / 971	5‡	Y	N	Hepatic lesions (SUV 12.8)	N	POM	NE
10	AITL	69	4	GemE	662	6,007	11,176	Y	<0.1	13	4.6	17 / 39	5	Y	N	No abnormal uptake	Y	GI hemorrhage with M-HLH	4,237
11	PTCL-NOS	65	3	Alemtuzumab	0	19,521	>20,000	Y	24.2	25	51.7	105 / 381	6	Y	Y	No abnormal uptake	Y	Ischemic colitis with M-HLH	5,545
12	WM	71	5	Benda + Ibr	0	7,216	15,363	Y	<0.1	11	46.5	22 / 35	5	Y	Y	No abnormal uptake[‖]	Y	MODS from sepsis	NE
13	MDS-EB2	69	2	Allo-SCT	966	22,790	3,273[¶]	Y	0.3	15	0.5	67 / 88	5	N	Y	Heterogenous uptake (SUV 4)	N	NA	14,168
14	HTLV-1+ ATLL	53	4	Clinical trial	283	10,132	>20,000	N	4.9	9	2	292 / 350	4	N	Y	No abnormal uptake	Y	MODS from sepsis	NE
15	ENKTL	19	2	SMILE	0	86,048	10,997	NE	40.3	51	8	4869 / 1890	6‡	N	N	No abnormal uptake	N	MODS with M-HLH	135,680

*No patients were evaluated for NK-cell activity which is a datum in the HLH-2004 diagnostic criteria. †Infection other than Epstein-Barr virus or cytomegalovirus. ‡Indicates patients missing ≥1 additional datapoint used in the HLH-2004 diagnostic criteria (excluding NK-cell activity). §83% of the WBC were secondary to malignant disease. ‖Biopsy-proven hepatic involvement of malignancy. ¶First sIL2r level was measured after the start of emapalumab. EBV, Epstein-Barr virus; DLBCL, diffuse large B-cell lymphoma; MF, mycosis fungoides; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; THRLBCL, T-cell/histiocyte-rich large B-cell lymphoma; PTLD, post-transplant (allogeneic stem cell transplant) lymphoproliferative disorder; ALK, anaplastic lymphoma kinase; ALCL, anaplastic large cell

lymphoma; PTCL-TFH, peripheral T-cell lymphoma with a follicular T-helper cell phenotype; AITL, angioimmunoblastic T-cell lymphoma; WM, Waldenstrom macroglobulinemia; MDS-EB2, myelodysplastic syndrome with excess blasts 2; HTLV-1, human T-lymphotropic virus type 1; ATLL, adult T-cell leukemia/lymphoma; ENKTL, extranodal NK/T-cell lymphoma; CEP, cyclophosphamide, etoposide, and prednisone; GemE; gemcitabine and etoposide; Tafa + Len, tafasitimab and lenalidomide; BV, brentuximab vedotin; Romi + Duve, romidepsin and duvelisib; HD-MTX, high-dose methotrexate; R-CHOP, rituximab, cyclophosphamide, vincristine, and prednisone; Benda + Ibr, bendamustine and ibrutinib; Allo-SCT, allogeneic stem cell transplant; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide; sIL2r, soluble interleukin-2 receptor alpha; BMB, bone marrow biopsy; WBC, white blood cell; Tbili, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; OHI, optimized HLH inflammatory index; PET/CT, positron emission tomography/computed tomography scan; SUV, standard uptake value; MODS, multiple organ dysfunction syndrome; POM, progression of malignancy; CNS, central nervous system; DAH, diffuse alveolar hemorrhage; ARDS, acute respiratory distress syndrome; NE, not evaluated; NA, not applicable. Best ferritin response was considered NE in patient living ≤72 hours after first emapalumab dose.