

Prolonged remission with pembrolizumab and radiation therapy in a patient with multisystem Langerhans cell sarcoma

Langerhans cell sarcoma (LCS) is an exceedingly rare hematologic cancer with approximately ten to 12 new cases reported in the United States each year.¹ LCS is a malignant histiocytic neoplasm that frequently involves the reticuloendothelial system (lymph nodes, liver, spleen) and may spread to the skin, lung, bone, or other soft tissues.² Patients with localized or single-system disease are generally treated with surgical resection or radiation therapy and tend to do better than those with multi-system involvement. In patients with multi-system disease, outcomes have been dismal with a 5-year overall survival of only 15%.³ The rarity of this diagnosis has limited our understanding of the disease biology and development of effective treatment. A variety of systemic treatment strategies have been used in LCS, most of them adopted from treatment of aggressive lymphomas, such as anthracycline- and platinum-based regimens.^{3,4} However, the treatment outcomes published in case reports and case series have been disappointing. The identification of mutations in the mitogen-activated protein kinase (MAPK) pathway in other histiocytic neoplasms, especially Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD) have led to the utilization of targeted therapies. Data on the efficacy of kinase inhibitors and immunotherapy in LCS and other malignant histiocytosis are limited. In this report, we present a case of LCS with exquisite response to the immune checkpoint inhibitor (ICI) pembrolizumab and radiation therapy after disease progression on the MEK inhibitor cobimetinib.

A 33-year-old Caucasian female with no comorbidities presented with a sensation of fullness in her abdomen without any associated pain, nausea, vomiting, or other systemic symptoms. CT scan of the abdomen revealed a lobulated soft tissue mass centered within the mesentery measuring 8.6 cm with additional para-aortic adenopathy. F18-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) revealed a large right mesenteric mass with a maximum standardized uptake value (SUV_{max}) of 16.4 along with additional FDG-avid left mesenteric, retroperitoneal, and left supraclavicular lymph nodes. The spleen size was normal but showed mild, diffuse FDG uptake, possibly suggestive of involvement by LCS. Detailed laboratory evaluation at baseline was unremarkable. CT-guided core biopsy of the mesenteric mass showed a diffuse infiltrate of large pleomorphic cells with occasional multinucleation, conspicuous

nucleoli, and abundant pale eosinophilic cytoplasm, intermixed with eosinophils. By immunohistochemistry, the malignant cells were positive for CD68, CD163 (partial), S100, CD1a (partial), and langerin. They did not express BRAF^{V600E} (VE1), B-cell (CD19, CD20, CD79a, PAX5), or T-cell (CD2, CD3, CD43) markers. The morphology and immunophenotypic features were diagnostic of LCS. Additionally, a PD-L1 immunostain (clone 22C3, Dako North America Inc., Carpinteria, CA) showed strong membranous staining in 95% of tumor cells (Figure 1). Multigene next-generation sequencing demonstrated several mutations: *SETD2* p.Q2362* stop gain-loss of function (LOF), variant allele frequency (VAF) 22.4%; *SETD2* c.4715+1G>C splice region variant-LOF, VAF 5.5%; *NRAS* p.Q61L missense variant (exon 3)-gain of function, VAF 14.6%; *TP53* p.R280T missense variant-LOF, VAF 8.5%; *SMARCB1* c.629-1G>c splice region variant-LOF, VAF 5.7%; and *PTPN11* p.E76K missense variant-LOF, VAF 10.6%. Tumor mutational burden (TMB) was 3.3 m/MB. Bone marrow biopsy showed no LCS. Given the presence of the activating *NRAS* mutation, single-agent therapy with a MEK inhibitor (trametinib) was initiated at a dose of 2 mg orally (p.o.) daily. Unfortunately, restaging studies in 2 months demonstrated radiographic progression with new FDG avid lymph nodes in bilateral cervical region along with progression in the dominant right mesenteric mass and a new omental nodule (Figure 2A). Because of the high PD-L1 expression on the tumor specimen, pembrolizumab monotherapy at a dose of 200 mg intravenously (i.v.) every 3 weeks was initiated. Two months after initiation of pembrolizumab therapy, PET-CT demonstrated stable disease in the large right-sided mesenteric mass with normalization of the FDG uptake in the bilateral cervical adenopathy and improvement in the FDG avid omental nodule (Figure 2B). After this initial response, imaging 4 months post pembrolizumab revealed slight increase in size of the right mesenteric mass from 7.5 cm x 5.8 cm x 8.6 cm to 9 cm x 8.7 cm x 10.5 cm, along with increase in the size of the left sided mesenteric nodule with SUV_{max} increasing from 4.8 to 10.5 (Figure 2C). Due to the anatomic and metabolic progression, external beam radiation therapy to the sites of progressive disease (right mesenteric mass and left mesenteric nodule) was completed utilizing four-dimensional CT planning and delivered via intensity modulated radiation therapy with daily cone-beam CT localization for total dose of 3,600 cGy over 18 fractions. She continued pembrolizumab mono-

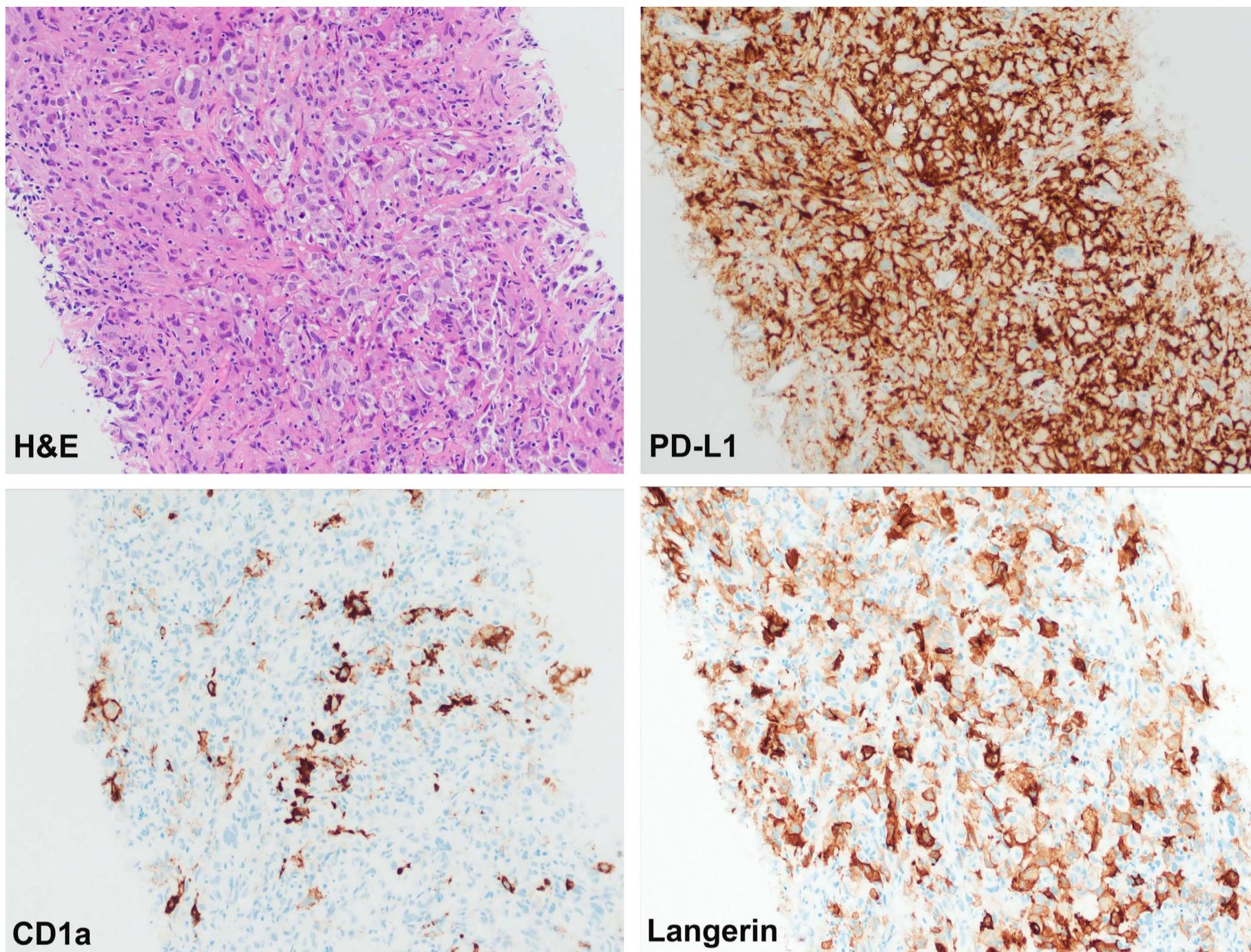


Figure 1. Core biopsy of mesenteric mass involved by Langerhans cell sarcoma characterized by large pleomorphic cells (arrows) with expression of CD1a (partial) and Langerin. PD-L1 immunostain demonstrates membranous positivity in 95% of the tumor cells. H&E: hematoxylin and eosin; magnification x200.

therapy and demonstrated an ongoing reduction in the size and FDG avidity of the of the dominant mesenteric mass (Figure 2D). At 1-year follow-up, her PET-CT demonstrated a significant reduction in size of the mesenteric mass from 9.0 cm x 8.6 cm (SUV_{max} 18.0) to 2.7 cm x 2.4 cm (SUV_{max} 3.2) and resolution of FDG uptake all other sites of disease (Figure 2E). Approximately 18 months into the pembrolizumab therapy, the patient developed grade 2 diarrhea and grade 1 transaminitis that prompted symptomatic treatment and dose reduction to 300 mg i.v. every 6 weeks. At the time of last follow-up, after 36 months of initiation of pembrolizumab, she continued to be in a sustained near complete remission.

Treatment options for multisystem LCS are not well-defined and the use of lymphoma-based chemotherapy regimens have limited success. Therefore, novel approaches are needed in the treatment of these aggressive malignancies. Malignant histiocytic neoplasms demon-

strate occasional presence of mutations in MAPK pathway (like the presence of a *NRAS* mutation in our patient), but limited data currently exist on the role of targeted therapy in these patients. A recent report demonstrated a durable (>2 year) complete response with trametinib in a patient with histiocytic sarcoma (HS) that was noted to have an activating *MAP2K1*^{F53L} mutation.⁵ Similarly, an excellent initial response with vemurafenib was noted in a *BRAF*^{V600E} primary central nervous system HS, but the disease progressed quickly after only 4 months of treatment.⁶

PD-L1 immunohistochemistry and TMB have been used as predictive markers in selecting patients for treatment with ICI in various malignancies (e.g., lung cancer, esophageal cancer, triple negative breast cancer among others).^{7,8} However, limited information exists for PD-L1 staining and TMB in histiocytic neoplasms. A prior study of histiocytic and dendritic cell neoplasms included 14 patients with HS, of which seven were noted to be PD-L1 positive, but

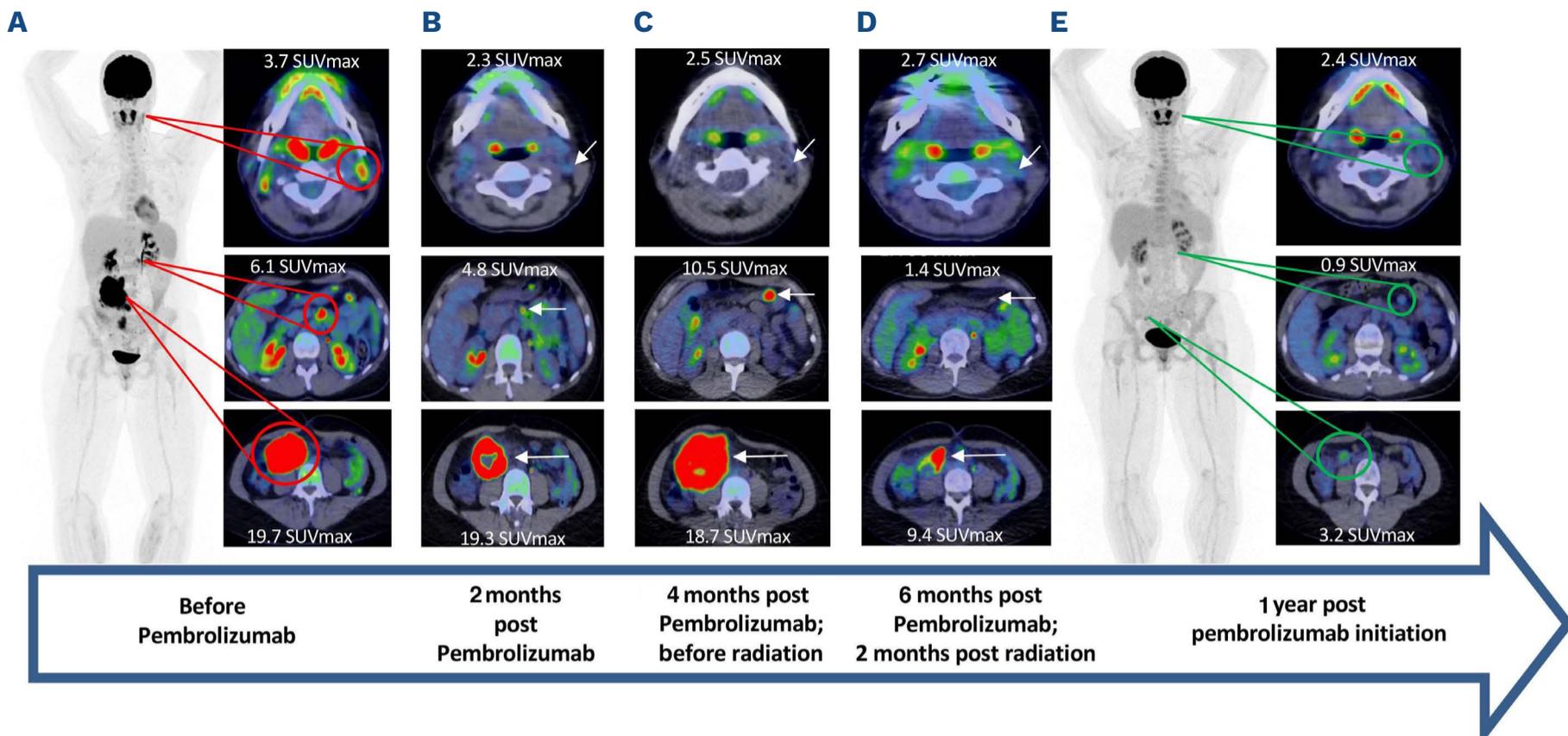


Figure 2. Clinical course of the patient Langerhans cell sarcoma of the mesentery (non-*BRAF*^{V600E} mutated) previously failed treatment with trametinib. A 34 year-old female with biopsy proven Langerhans cell sarcoma (LCS) of the mesentery (non-*BRAF*^{V600E} mutated) previously failed treatment with trametinib. Maximum intensity projection and axial fused F-18 fluorodeoxyglucose positron emission tomography – computed tomography (FDG PET-CT) images demonstrate two intensely FDG avid abdominal masses before (A) and after completion of pembrolizumab with external beam radiation therapy (3,600 centigray) to the abdomen (E). The intervening axial fused FDG PET-CT images reveal response in the cervical adenopathy post initiation of pembrolizumab (B), but subsequent progression in the abdominal masses (C). Post radiation therapy and continuation of pembrolizumab demonstrate eventual near complete response from all sites of LCS (D and E).

there were no patients with LCS in the study population. In this study, staining for PD-L1 was scored as positive if at least 5% of the malignant tumor cells stained positive in a membranous pattern with an intensity of 2+ or 3+.⁹ Another study from our group including 16 patients with histiocytic neoplasms did not have any LCS patients, but the one patient with HS had 5% PD-L1 expression and TMB of 4.27 m/MB.¹⁰ It is important to note that the patient in the current report has a stable/low TMB and a durable response is still demonstrated.

To the best of our knowledge, this represents the first report of prolonged remission using anti-PD1 agent pembrolizumab in combination with radiation therapy in a patient with multisystem LCS. Pembrolizumab or other ICI can be an important therapeutic strategy for these patients who otherwise have a guarded prognosis with limited efficacious options available. A previous report for a patient with HS (PD-L1 expression unknown, TMB intermediate) treated with ipilimumab/nivolumab demonstrated a transient minor response before progression at the 4 month mark,¹¹ somewhat similar to what occurred in our case. Our patient had a focal disease progression approximately 4-months into pembrolizumab, which responded to radiation therapy and continued to demonstrate ongoing systemic remission with maintenance pembrolizumab. In malignant histiocytosis with systemic involvement such as our case, achieving a sustained sys-

temic remission with focal radiation therapy would be unusual. An abscopal effect from the use of radiation therapy could have potentially augmented the response to pembrolizumab, which has been demonstrated in various solid tumors.¹² Utilizing adjunct treatment strategies like focused radiation or surgical resection in appropriate clinical scenarios while continuing ICI may have therapeutic potential. Limited information is available regarding PD-L1 expression in LCS and its implication on response to ICI and these need to be studied further.

Our case highlights that the combination of systemic anti-PD1 agent and focal radiation can be an efficacious treatment option with the potential to provide sustained remissions in LCS. With the lack of treatment options for patients with LCS, further exploration of the role of immune-checkpoint inhibitors in combination with other modalities like radiation therapy is warranted, including correlative biomarker analysis.

Authors

Saurabh Zanwar,¹ Aishwarya Ravindran,² Jithma P. Abeykoon,¹ Jason R. Young,³ Timothy F. Kozelsky,⁴ Karen L. Rech,² Gaurav Goyal^{1,5} and Ronald S. Go¹ on behalf of the Mayo Clinic–University of Alabama at Birmingham Histiocytosis Working Group.

¹Division of Hematology, Mayo Clinic, Rochester, MN; ²Division of Hematopathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; ³Department of Radiology, Mayo Clinic, Jacksonville, FL; ⁴Division of Radiation Oncology, Mayo Clinic Health System, Albert Lea, MN and ⁵Division of Hematology-Oncology, University of Alabama at Birmingham, Birmingham, AL, USA

Correspondence:

R. S. Go - go.ronald@mayo.edu

<https://doi.org/10.3324/haematol.2022.280948>

Received: February 27, 2022.

Accepted: May 13, 2022.

Prepublished: May 26, 2022.

©2022 Ferrata Storti Foundation

Published under a CC BY-NC license



Disclosures

No conflicts of interest to disclose.

Contributions

SZ, AR, GG and RSG conceived, wrote the first draft and modified the final draft; JPA, JRY, TK, KLR critically appraised the manuscript and approved the final draft of the manuscript.

Funding

The study was supported in part by the University of Iowa/Mayo Clinic Lymphoma SPORE CA97274 and the Walter B. Frommeyer, Jr., Fellowship Award in Investigative Medicine, University of Alabama at Birmingham (to GG).

Data-sharing statement

There is no relevant data to disclose.

References

1. Tella SH, Kommalapati A, Rech KL, Go RS, Goyal G. Incidence, clinical features, and outcomes of Langerhans cell sarcoma in the United States. *Clin Lymphoma Myeloma Leuk.* 2019;19(7):441-446.
2. Yi W, Chen W-y, Yang T-x, Lan J-p, Liang W-n. Langerhans cell sarcoma arising from antecedent langerhans cell histiocytosis: A case report. *Medicine.* 2019;98(10):e14531.
3. Howard JE, Dwivedi RC, Masterson L, Jani P. Langerhans cell sarcoma: a systematic review. *Cancer Treat Rev.* 2015;41(4):320-331.
4. Alhaj Moustafa M, Jiang L, Tun HW. Langerhans cell sarcoma: the Mayo Clinic experience with an extremely rare disease. *J Clin Oncol.* 2020;38(15_suppl):e19543.
5. Gounder MM, Solit DB, Tap WD. Trametinib in histiocytic sarcoma with an activating MAP2K1 (MEK1) mutation. *N Engl J Med.* 2018;378(20):1945-1947.
6. Idbaih A, Mokhtari K, Emile JF, et al. Dramatic response of a BRAF V600E-mutated primary CNS histiocytic sarcoma to vemurafenib. *Neurology.* 2014;83(16):1478-1480.
7. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet.* 2020;396(10265):1817-1828.
8. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med.* 2018;378(22):2078-2092.
9. Xu J, Sun HH, Fletcher CD, et al. Expression of programmed cell death 1 ligands (PD-L1 and PD-L2) in histiocytic and dendritic cell disorders. *Am J Surg Pathol.* 2016;40(4):443-453.
10. Goyal G, Lau D, Nagle AM, et al. Tumor mutational burden and other predictive immunotherapy markers in histiocytic neoplasms. *Blood.* 2019;133(14):1607-1610.
11. Lee M-y, Bernabe Ramirez C, Ramirez DC, Maki RG. Utility of immune checkpoint inhibitors (ICI) in 3 patients (pts) with sarcomas of antigen presenting cells (follicular dendritic cell sarcoma [FDCS], histiocytic sarcoma [HS]). *J Clin Oncol.* 2020;38(Suppl 15):Se23574.
12. Dagoglu N, Karaman S, Caglar HB, Oral EN. Abscopal effect of radiotherapy in the immunotherapy era: systematic review of reported cases. *Cureus.* 2019;11(2):e4103.