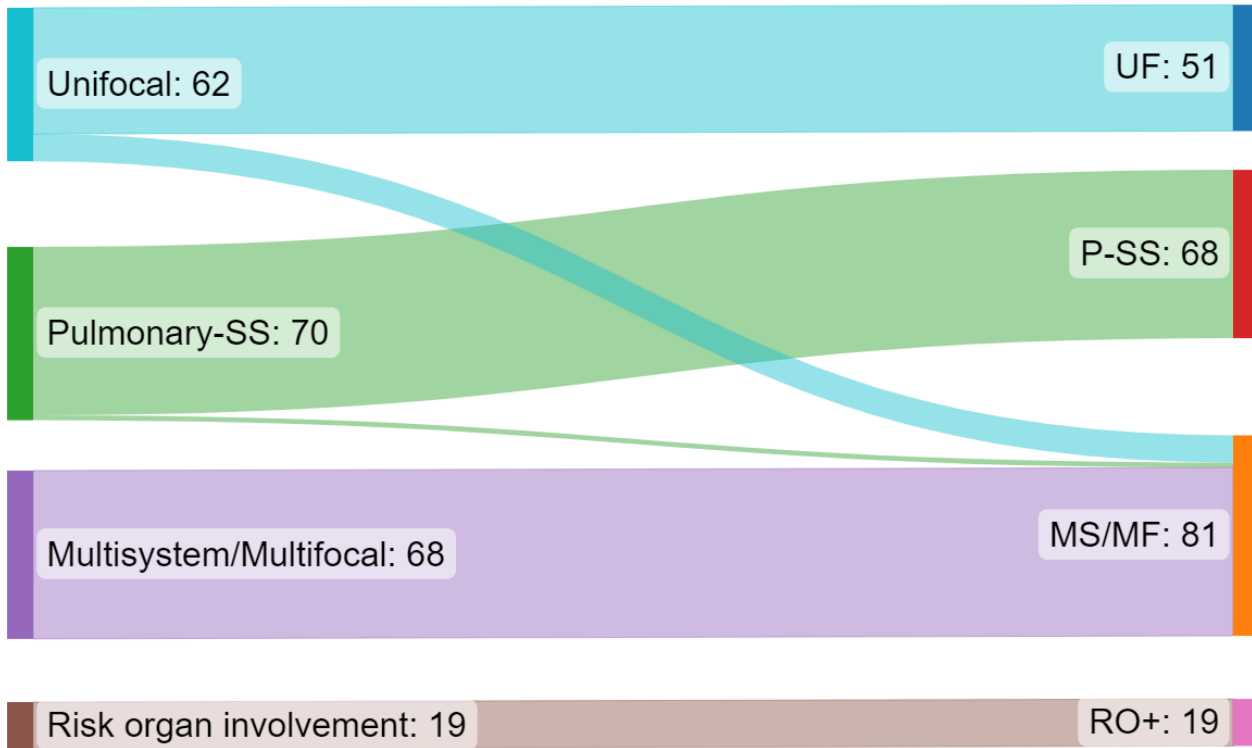


Supplementary Figure 1. Pattern of disease progression from diagnosis to last follow-up



Supplementary Table 1. Observed (O) and expected (E) number of deaths, and standardized mortality ratios (SMR) of adults with Langerhans cell histiocytosis as compared to US general population

	<i>Total study years</i>	<i>O-Deaths</i>	<i>E-Deaths</i>	<i>SMR (95%CI)</i>
Overall	1367	35	13.1726	2.66 (1.78-3.54)
Age				
<55 years	723	11	1.8507	5.94 (2.43-9.45)
≥55 years	644	24	11.3219	2.12 (1.27-2.97)
Sex				
Female	785	15	7.56887	1.98 (0.98-2.98)
Male	582	20	5.60369	3.57 (2.01-5.13)
Classification at last follow-up				
Multisystem	528	19	4.61084	4.12 (2.27-5.97)
Single-system pulmonary	473	14	2.9795	4.7 (2.24-7.16)
Single-system multifocal	9.	0	2.51443	0
Unifocal	273	2	3.06778	0.65 (-0.25-1.55)

Supplementary Table 2. Concomitant, secondary, and prior malignancies among adults with Langerhans cell histiocytosis

ID	LCH BRAF Status	Type	Additional prior malignancies & Notes	Age at SPM Dx	Classification of LCH	RO+/-	Circumstance underlying identification of malignancy	LCH treatments
<i>Second Primary Malignancies</i>								
186	NE	Non-small cell lung cancer		39	P-LCH	No	Development of chronic productive cough	Smoking cessation/ TKI inhibitor
1	NE	Non-small cell lung cancer	Serous ovarian carcinoma, Pulmonary carcinoma	67	P-LCH	No	Incidental nodule on follow up CXR after respiratory illness	Smoking cessation
10	NE	Paget disease of the breast		57	P-LCH	No	Unilateral bloody nipple discharge	Smoking reduction/ PO steroid
91	NE	Ductal carcinoma of the breast	Li Fraumeni Syndrome	29	P-LCH	No	Breast pain w/ mass	
134	NE	Ductal carcinoma of the breast		41	P-LCH	No	Breast cancer screening	Smoking reduction/ PO steroid
265	Negative BRAF ^{V600E}	Papillary thyroid carcinoma		34	P-LCH	No	Incidentally identified w/ LN bx in follow up PET-CT	Smoking cessation
11	NE	Colon adenocarcinoma		72	MS	Yes	Rectal bleeding	Resection/RT [death prior to systemic tx]
87	NE	Hepatocellular carcinoma		56	MS	No	Development of clinical course consistent w/ cirrhosis	Vinblastine/Steroid; Cladribine
3	NE	Prostate adenocarcinoma		58	SU	No	Evaluation of urinary hesitancy	Surgical resection
246	BRAF ^{V600E}	Melanoma		44	MS	No	Skin screening evaluation prior to TKI initiation	Resection; Dabrafenib
78	NE	Diffuse large B-Cell lymphoma, Melanoma		67, 74	MS	No	Follow up CT after chemotherapy w/ developing sacral lesion	Cladribine; R-CHOP [for DLBCL]
257	BRAF ^{V600E}	MGUS / Multiple myeloma	Essential thrombocythemia	57	SU	No	Development of R hip pain w/ new bx of new lesion showing plasmacytoma	Hydroxyurea
242	BRAF ^{V600E}	Myelodysplastic syndrome (EB-1)		38	SsM	No	Development of pancytopenia	RT; Vinblastine/Steroid; Cytarabine; Hydroxyurea; Vemurafenib; MUD alloSCT
209	Negative BRAF ^{V600E}	Myelodysplastic syndrome / Acute myeloid leukemia		61	MS	No	Development of pancytopenia	Cladribine
52	BRAF ^{V600E}	Chronic myelomonocytic leukemia	Endometrial carcinoma	75	SsM	No	Development of severe thrombocytopenia	RT; PO steroid; Hydroxyurea
250	BRAF ^{V600E}	Chronic myelomonocytic leukemia / Acute myeloid leukemia	Splenic marginal zone lymphoma	66	MS	Yes	Worsening monocytosis	Resection/Cladribine; RT; Vinblastine/Steroid;

227	BRAF ^{V600E}	Acute myeloid leukemia		47	P-LCH	No	Worsening cytopenias in setting of chronic kidney disease on hemodialysis	Cladribine
45	Negative BRAF ^{V600E}	Acute myeloid leukemia		70	MS	Yes	Symptom development, not specified	Cladribine

Concomitant malignancy

143	NE	Small cell lung cancer		-	P-LCH	No	-	Cytotoxic therapy for SCLC
142	NE	Ductal carcinoma of the breast		-	P-LCH	No	-	Smoking cessation
291	Negative BRAF ^{V600E}	Papillary thyroid carcinoma		-	MS	No	-	-
159	IGH/BCL2 Fusion	Follicular lymphoma		-	MS	No	-	Cladribine/RTX recommended

Prior malignancy before LCH

268	BRAF ^{V600E}	Non-small cell lung cancer	Severe cervical dysplasia*	-	P-LCH	No	-	Smoking cessation
16	NE	Ductal carcinoma of the breast		-	P-LCH	No	-	Smoking cessation
126	NE	Ductal carcinoma of the breast		-	SU	No	-	Smoking cessation; Resection
31	NE	Papillary thyroid carcinoma		-	MS	No	-	PO steroids; Cladribine
4	NE	Esophageal adenocarcinoma		-	P-LCH	No	-	Smoking reduction
289	Negative BRAF ^{V600E}	Pancreatic adenocarcinoma		-	SsM	Yes	-	Cytarabine
243	Negative BRAF ^{V600E}	Rectal adenocarcinoma		-	SU	No	-	Resection
278	Negative BRAF ^{V600E}	High-grade neuroendocrine tumor		-	P-LCH	No	-	Smoking cessation
8	BRAF ^{V600E}	Prostate adenocarcinoma		-	MS	Yes	-	Cladribine; Cytarabine; Vemurafenib
236	BRAF ^{V600E}	Prostate adenocarcinoma		-	MS	Yes	-	Cladribine; Vemurafenib
180	NE	Diffuse large B-Cell lymphoma, Melanoma		-	P-LCH	No	-	Smoking reduction
295	Negative BRAF ^{V600E}	Melanoma		-	SsM	No	-	-

56	NE	Testicular germ cell tumor	-	P-LCH	No	-	Smoking cessation recommended
151	NE	Classical Hodgkin lymphoma	-	SU	No	-	Cytotoxic therapy for HL

* Developed after diagnosis of Langerhans cell histiocytosis (LCH)

Supplementary Table 3. Molecular features of second primary cancers and LCH among those with available data

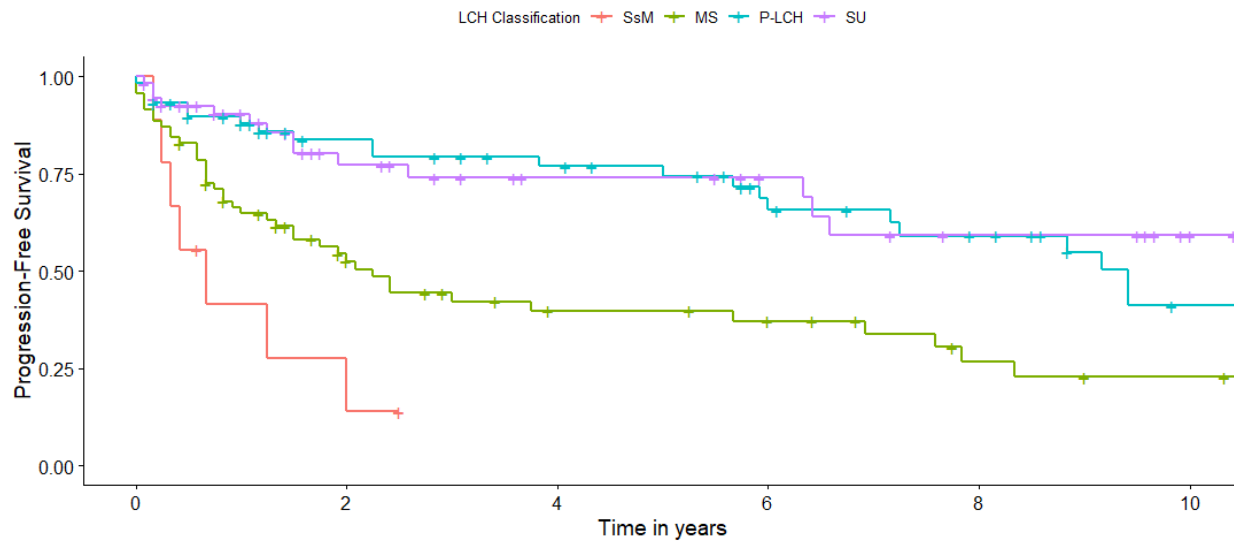
Second cancer	LCH BRAF V600E status	Second cancer BRAF V600E status	Other molecular findings in second cancer	Other molecular findings in LCH
Thyroid	Neg	Neg	-	
Malignant melanoma	Pos	Neg	-	
Breast cancer	-	-	TP53 mutated	
Multiple myeloma	Pos	Neg		
MDS	Neg	Neg	ASXL1: c.2483del; p.Gly828Alafs*10 (34%), IDH2: c.419G>A; p.Arg140Gln (49%), JAK2: c.1849G>T; p.Val617Phe (17%), SRSF2: c.284C>G; p.Pro95Arg (49%)	
AML	Neg	Neg	ASXL1: c.2483del; p.Gly828Alafs*10 (34%), IDH2: c.419G>A; p.Arg140Gln (49%), JAK2: c.1849G>T; p.Val617Phe (17%), SRSF2: c.284C>G; p.Pro95Arg (49%)	SRSF2 c.284C>G; p.Pro95Arg (26%)
CMML	Pos	Neg	TET2 c.3223_3226delGATA p.L1074fs* (44.2%), TET2 c.388G>T p.E130* (44.6%).	
CMML→AML	Pos	Not done	ASXL1 c.2060_2061del; p.Cys687Tyrf*30 (43%), IDH2 c.419G>A; p.Arg140Gln (47%), SRSF2 c.284C>A; p.Pro95His (47%)	
AML	Not done	Not available	NMP1, DMT3A, TET2 mutation by notes, report not available	

Supplementary Table 4. Cases ascribed as LCH-associated deaths.

Patient ID	Description	Cause of Death	LCH subtype at diagnosis
8	LCH due to Involvement of skin, lymph nodes, spleen, lungs, CNS and pituitary causing progressive cognitive and functional decline	LCH (transitioned to hospice)	RO+
12	Acute on chronic hypoxemic and hypercapnic respiratory failure in s/o of progressive LCH and severe pulmonary HTN	Resp failure due to progressive pulm LCH w/ pulm HTN (comfort care)	Single-system pulmonary
15	LCH-associated DIC and multi-organ failure	DIC and multi-organ failure from LCH (comfort care)	RO+
22	Hepatic and renal failure in s/o progressive LCH & secondary primary sclerosing cholangitis	Liver and kidney failure secondary to LCH with secondary PSC (hospice)	RO+
40	Severely reduced pulmonary function due to P-LCH	Progressive respiratory failure	Single-system pulmonary
61	Langerhans cell histiocytosis and secondary pulmonary artery hypertension (severe)	Progressive respiratory failure	Single-system pulmonary
69	Multisystem LCH with acute illness, died within 2 months of starting cladribine	Rapidly progressive LCH with organ failure	RO+
83	Severely reduced pulmonary function due to P-LCH	Progressive respiratory failure	Single-system pulmonary

102	LCH progression causing significant adenopathy and electrolyte disturbance (hyponatremia and hypokalemia) , bilateral pleural effusions	Progressive LCH	MS/MF
145	Progression of LCH causing pan hypopituitarism and DVT/PE	Rapidly progressive LCH with organ failure	MS/MF
159	Multi-system LCH with concomitant indolent follicular lymphoma. Died within 2 months of initiation of cladribine	Rapidly progressive LCH with organ failure	MS/MF
170	LCH of skull progressing through local therapies (surgery + radiation)	Progressive LCH to multi-system disease, multi-organ failure	Unifocal
236	Multi-system LCH progressive after systemic chemotherapy. Concomitant MDS and prostate cancer with minimal disease burden.	Progressive LCH (transitioned to hospice)	RO+

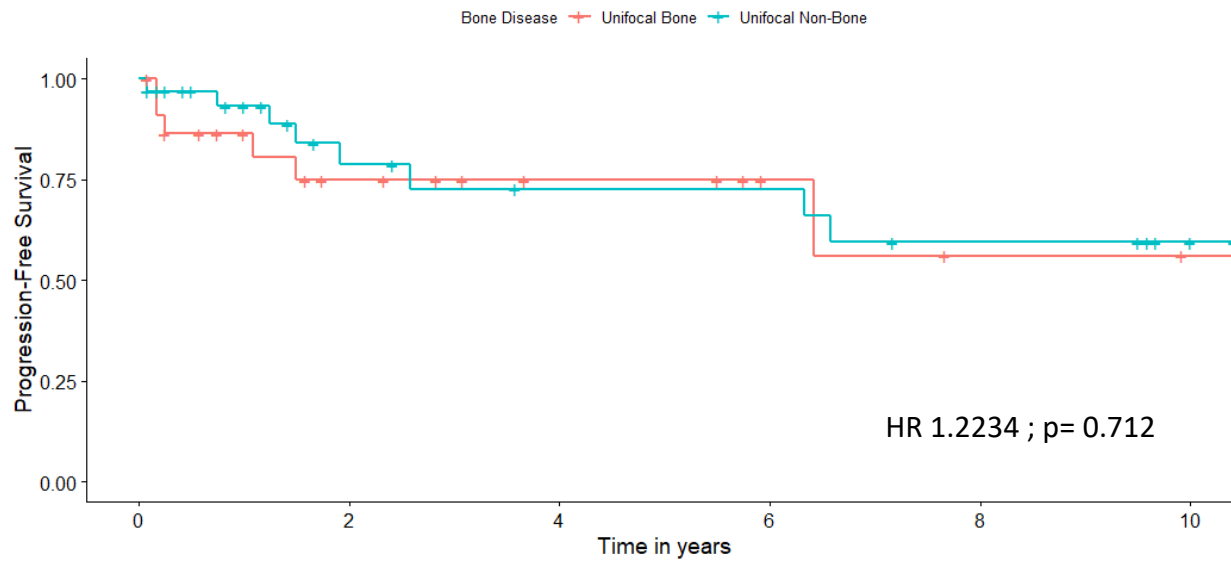
Supplementary Figure 2. Kaplan-Meier analysis of PFS by classification as proposed by the adult LCH consensus recommendations.



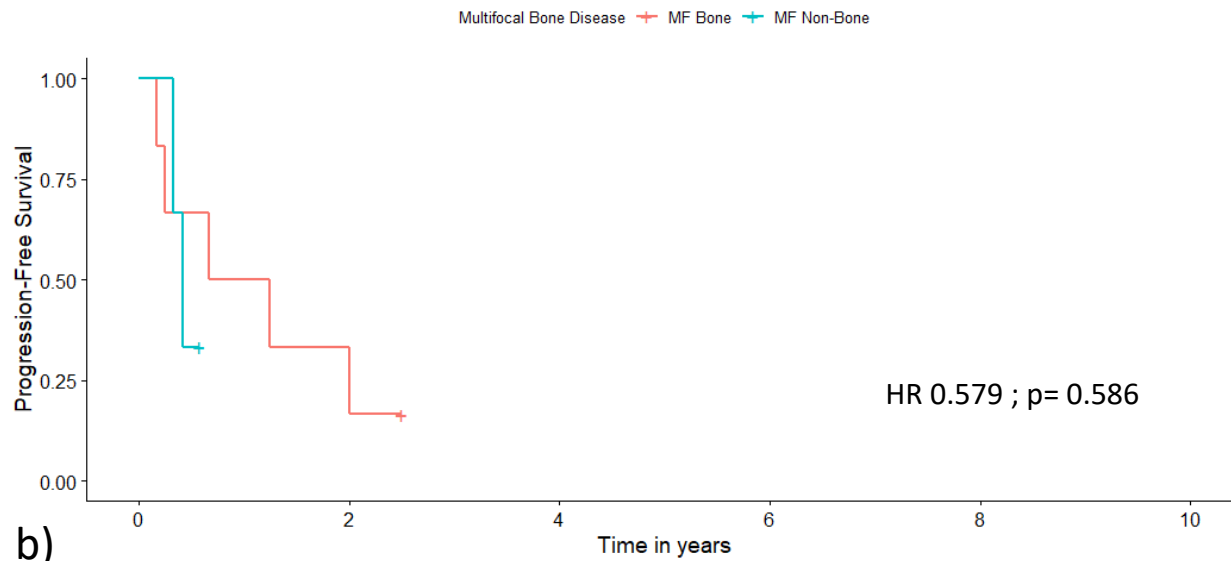
As compared to Unifocal LCH (SU):

- Multifocal (ssM) disease HR 7.1807; p=0.000031
- Single-system Pulmonary LCH HR 1.2601; p=0.495863
- Multisystem (MS) disease HR 2.9065; p=0.000576

Supplementary Figure 3. Kaplan-Meier analysis of PFS by a) Unifocal bone disease vs. unifocal non-bone LCH, and b) multifocal bone vs. multifocal non-bone LCH

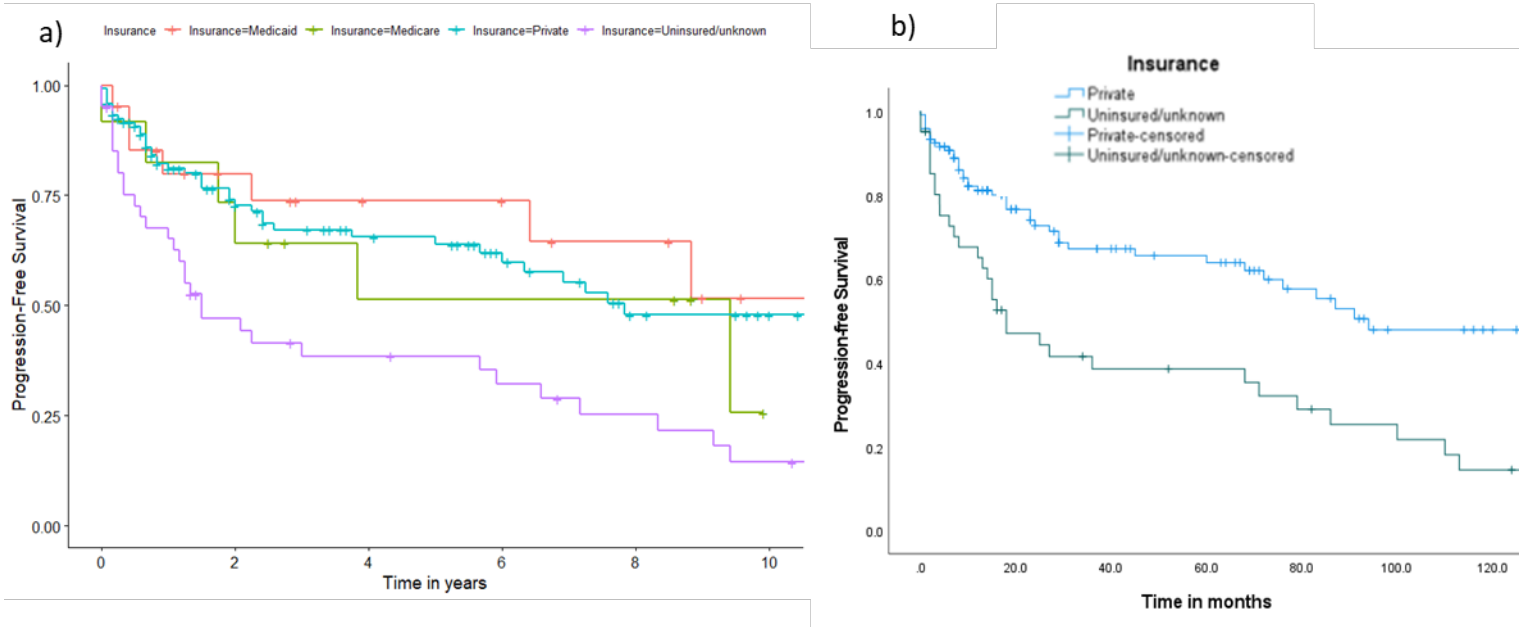


a)



b)

Supplementary Figure 4. Kaplan-Meier analysis of PFS by a) all insurance statuses (p>0.05), and b) private vs. uninsured



Supplementary Figure 5. Cumulative incidence of mortality after a 5-year landmark of diagnosis

