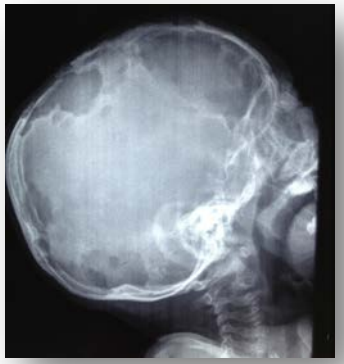
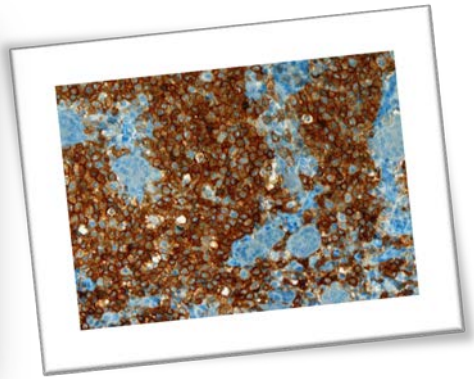
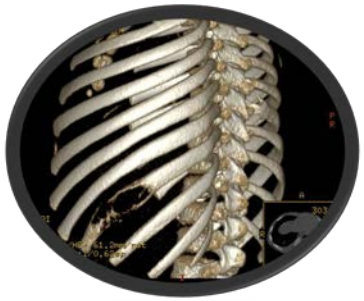
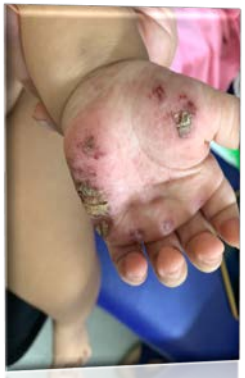
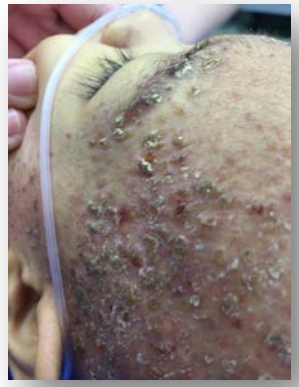






How I Treat Difficult Langerhans Cell Histiocytosis

Intensive Review in Pediatric Hematology/Oncology"
28-29 November, 2020

Chalinee Monsereenusorn, MD

Assistant Professor
Division of Hematology-Oncology, Department of Pediatrics,
Phramongkutklao Hospital and College of Medicine

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Outlines

- Biology
- Classification of histiocytosis
- Clinical presentations
- Investigations
- Classification of LCH
- Difficult LCH
  - RO+MS-LCH
  - Liver compromised LCH
  - Refractory or relapse MFB
  - Refractory RO+ MS-LCH
  - Role of stem cell transplantation in LCH
  - Pulmonary LCH
  - Adult LCH

Biology

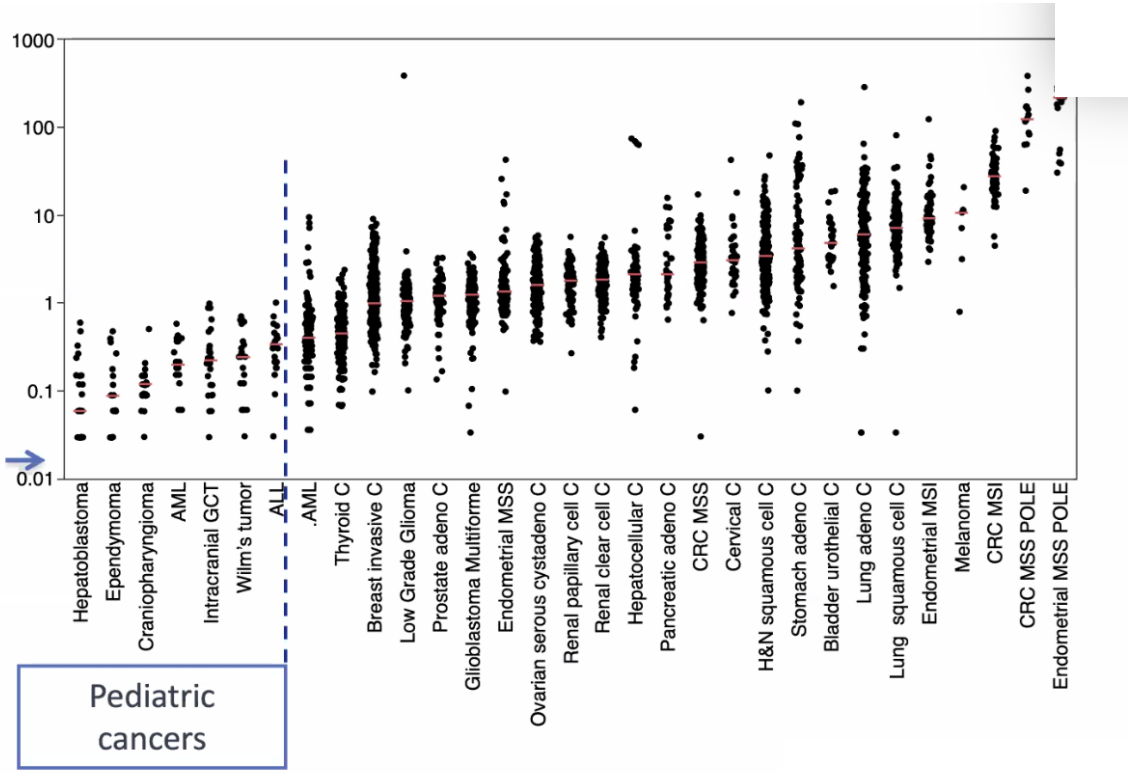
- Inflammatory response *vs.* Oncogenic event ???
- Originate from a myeloid-derived precursor to a dendritic lineage and Langerin
  - Langerin (CD 207) is NOT limited to epidermal LC
  - LCH CD 207+ cells express several genes associated with immature myeloid dendritic cells
  - LCH lesions do not arise from epidermal LCs but from accumulation of BM-derived immature myeloid dendritic cells
- Uncontrolled clonal periforation of CD1a+/CD207+ cells

Badalian-Very et al., Annu Rev Pathol 2013; 8: 1-20
Badalian-Very et al., Blood 2010; 116: 1919-23
Chakraborty et al., Blood 2014; 124: 3007-15
Allen et al. Journal Immunol 2010

Very Low Mutation Frequency in LCH

Median of ONE somatic mutation per LCH sample

0.03 muts/MB



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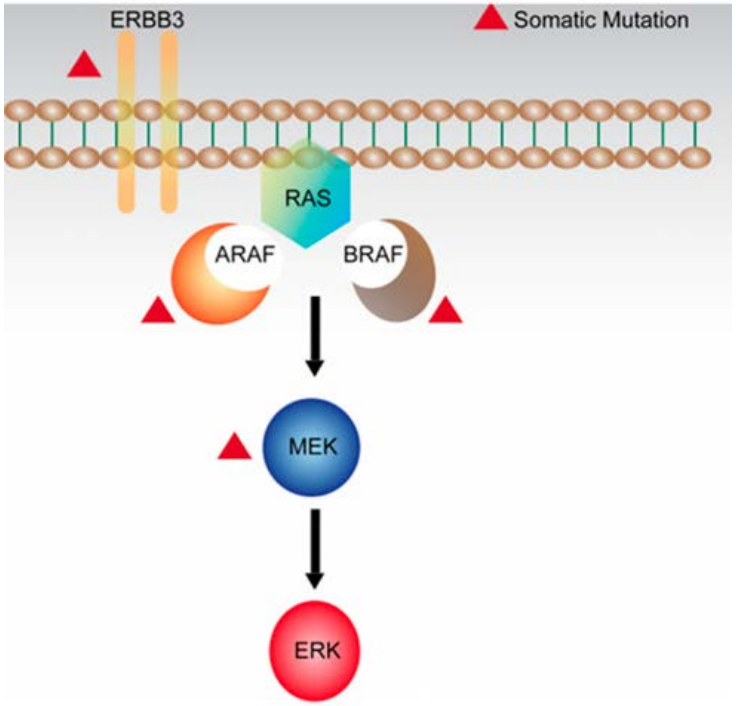
Chakraborty et al., Blood 2014; 124: 3007-15
Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)

Biology

- Activation of the MAPK/ERK signaling pathway
  - 60-70% somatic mutation in BRAF (*BRAF*^{V600E})
  - 10-25% Others
    - Mutation in MAP2K1
    - Mutation in ARAF
  - ¼ Unknown



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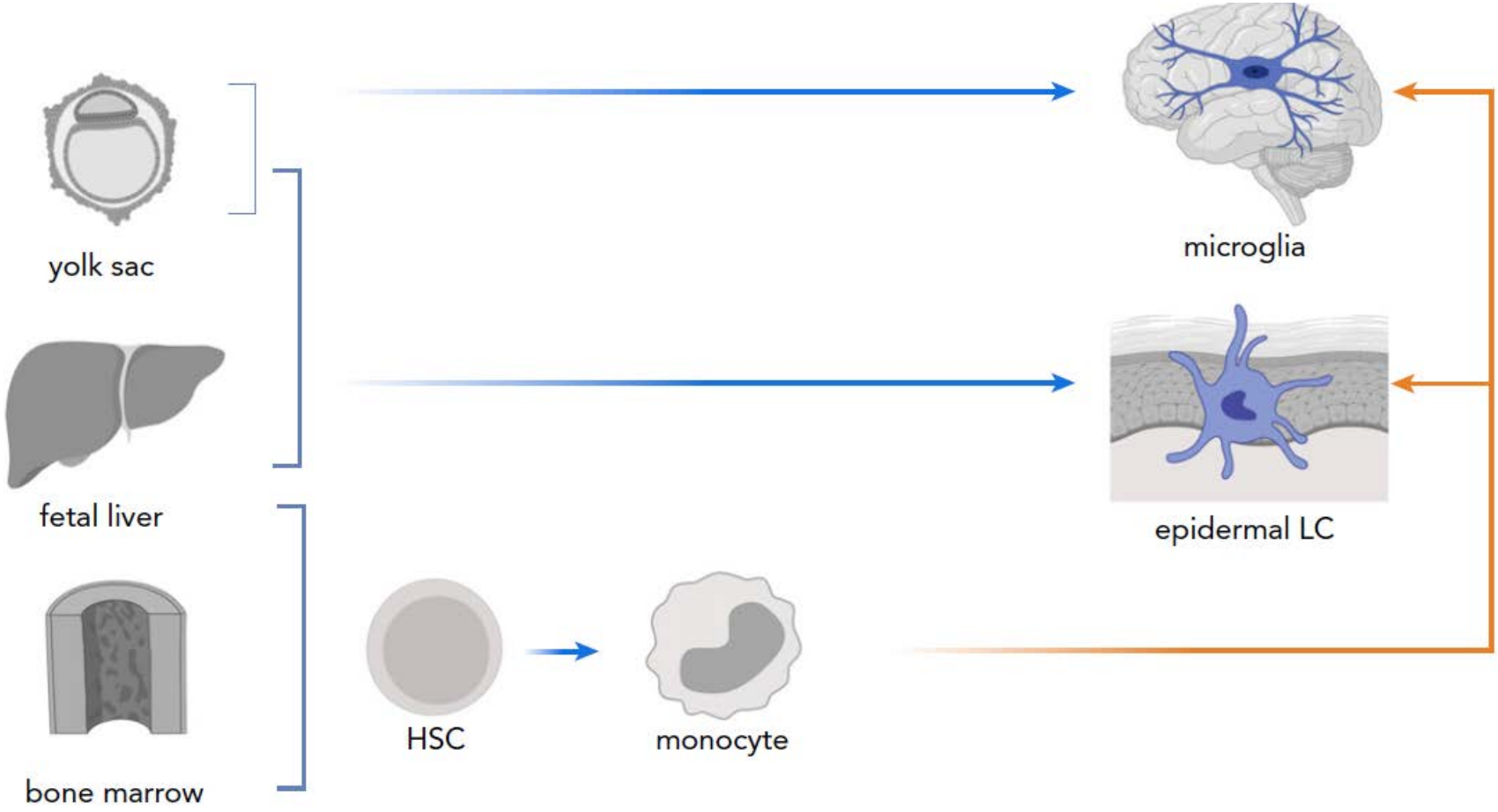
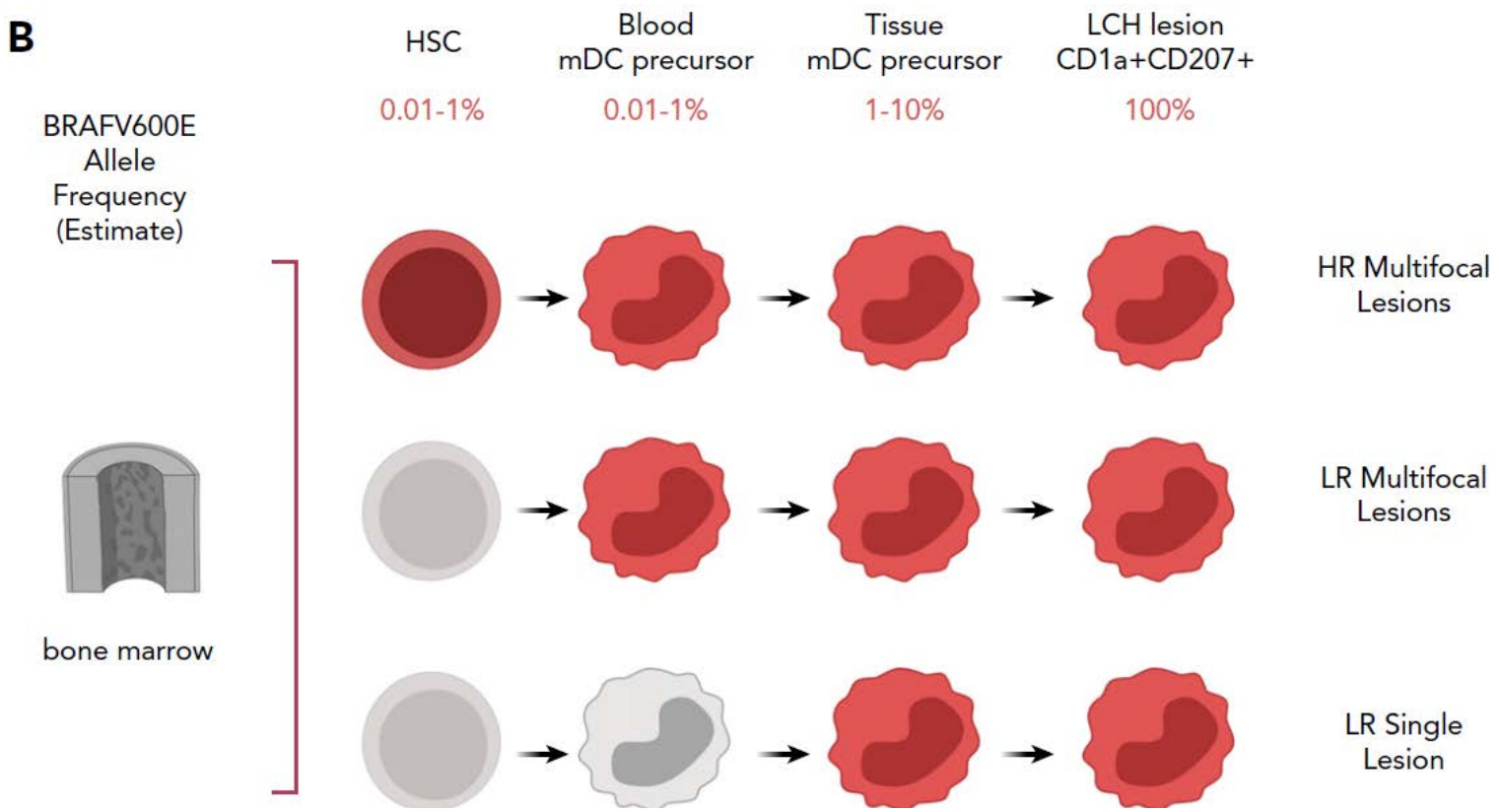


Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. Blood. 2020;135(16):1319-1331



Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. Blood. 2020;135(16):1319-1331

Classification of histiocytosis (LCRMH)

Group	Disease
L Group LCH	• LCH • Indeterminate-cell histiocytosis (ICH) • Erdheim-Chester Disease (ECD) • Mixed LCH/ECD

C Group
Cutaneous non-LCH
	• Cutaneous non-LCH
	  • Xanthomatous granuloma (XG) family: JXG
	  • Non-XG family: cutaneous RDD, NXG, other
	• Cutaneous non-LCH with a major systemic component
	  • XG family: XD
	  • Non-XG family: MRH

R Group RDD	• Familial RDD • Sporadic RDD
M Group Malignant histiocytoses	• Primary Malignant Histiocytoses • Secondary Malignant Histiocytoses
H Group HLH	• Primary HLH • Secondary HLH (non-Mendelian HLH) • HLH of unknown/uncertain origin

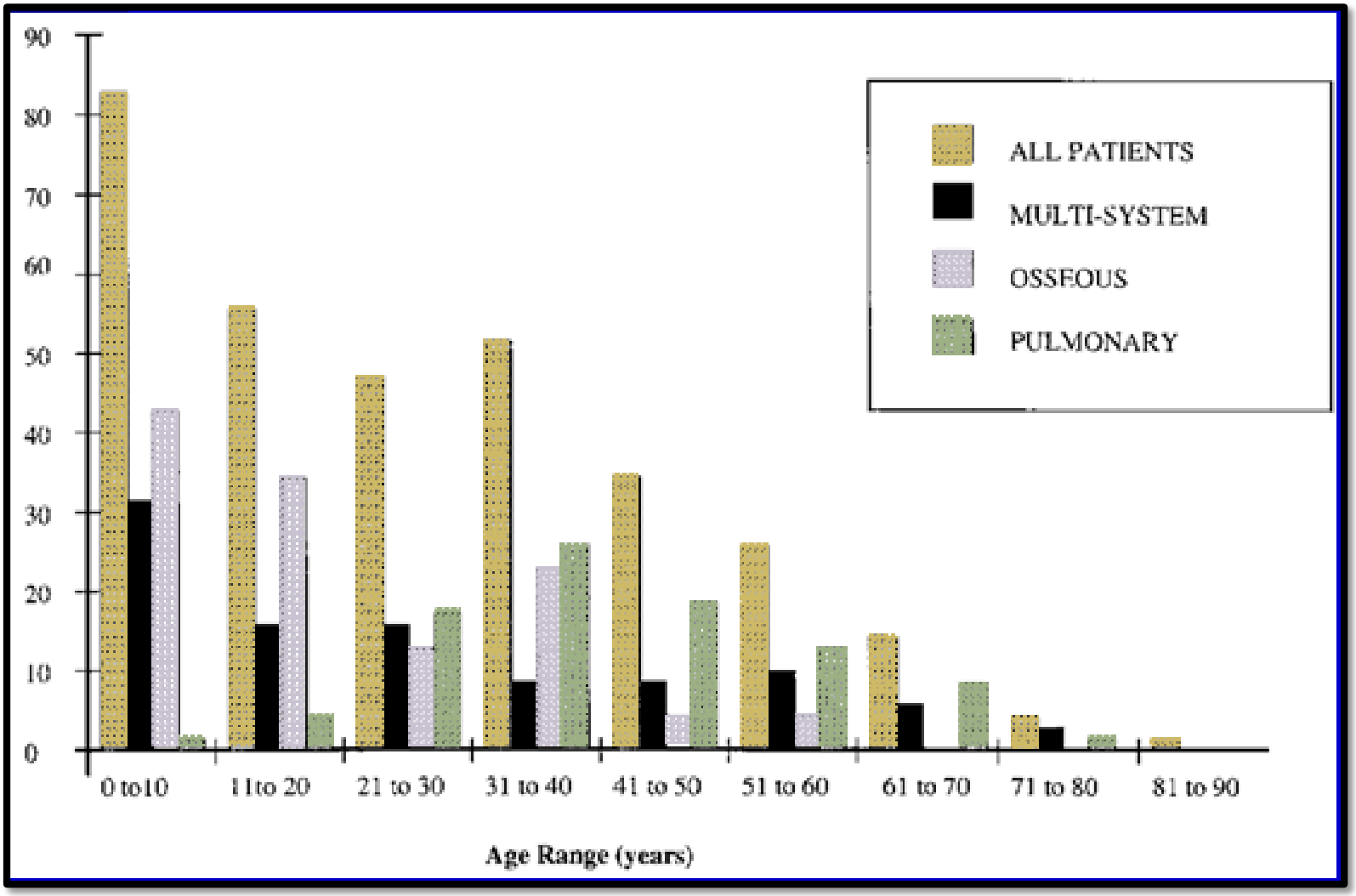
Emile JF, Abla O, Fraitag S, et al. *Blood*. 2016;127(22):2672-2681.

Langerhans Cell Histiocytosis

- Clonal proliferation of "Langerhans Cells"
- Multiple organs and systems can be involved
- Clinical presentation and outcome very variable

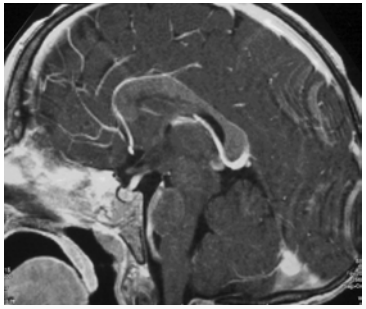
Eosinophilic Granuloma
Skin Disease
Poliostotic Bone Disease
Hand-Schuler-Christian
Multi-systemic Disease
Letterer-Siwe

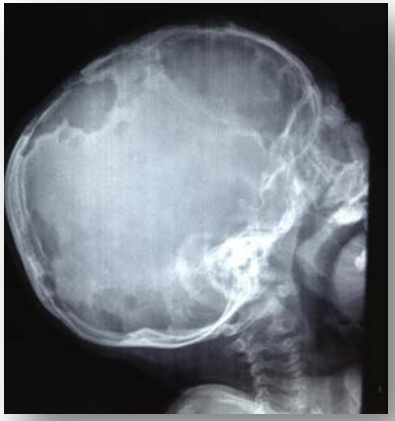
Age distribution of LCH patients

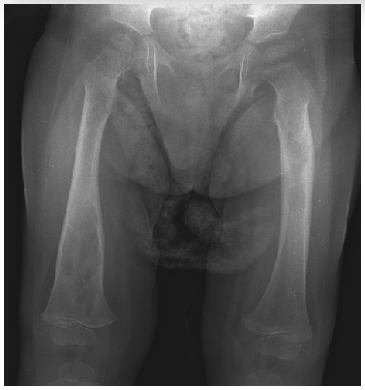


Howarth et al., Cancer 1999; 85: 2278-90

Organ system involvement in LCH







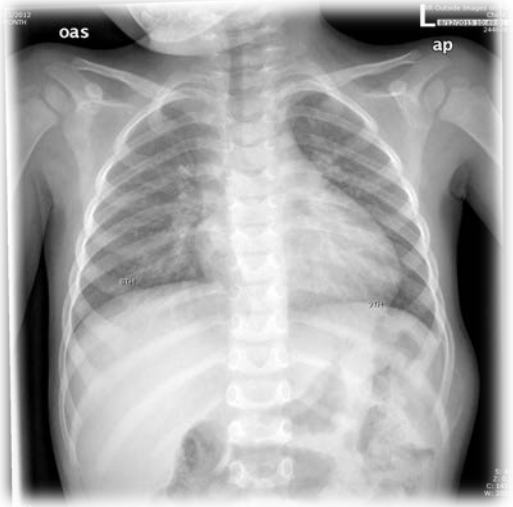
Brain	Neuroendocrine deficits Neurodegeneration
Skull and craniofacial bones	
Chest	Lung disease (infants, smokers) Thymus
Abdomen	Liver Spleen GI tract
Skeleton	Bones
Skin	Cradle cap, seborrhea
Hematopoietic system	pancytopenia, hypersplenism
Lymph nodes	

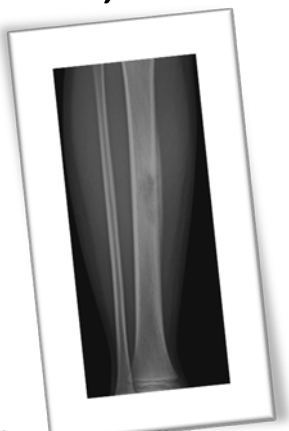
Organ system involvement in LCH

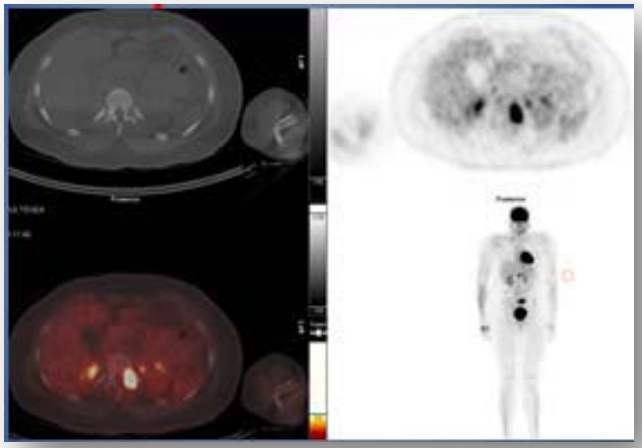
Site	% of cases involved
Bone	80
Skin	60
Liver, spleen, LN	33
Bone marrow	30
Lungs	25
Orbit	25
Orodental	20
Otological	20
DI	15
GI tract	<5

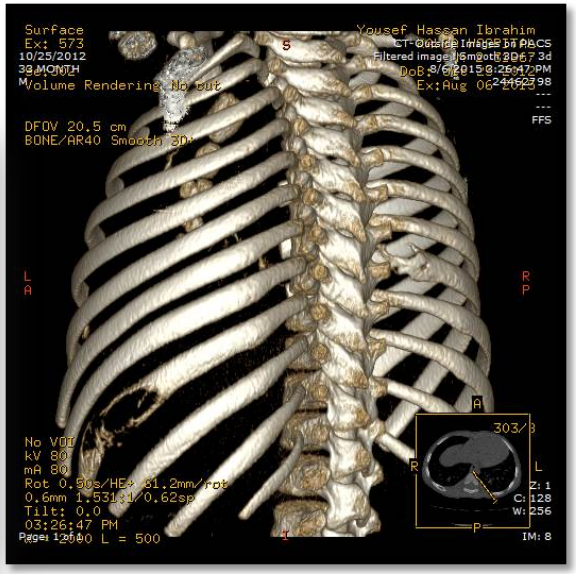
Investigations

- Plain film skull
- Plain x-ray of primary lesion
- Bone survey
- CT/MRI primary lesion
- Abdominal ultrasound
- MRI pituitary
- PET scan : almost always positive in LCH*
- CBC, blood chem

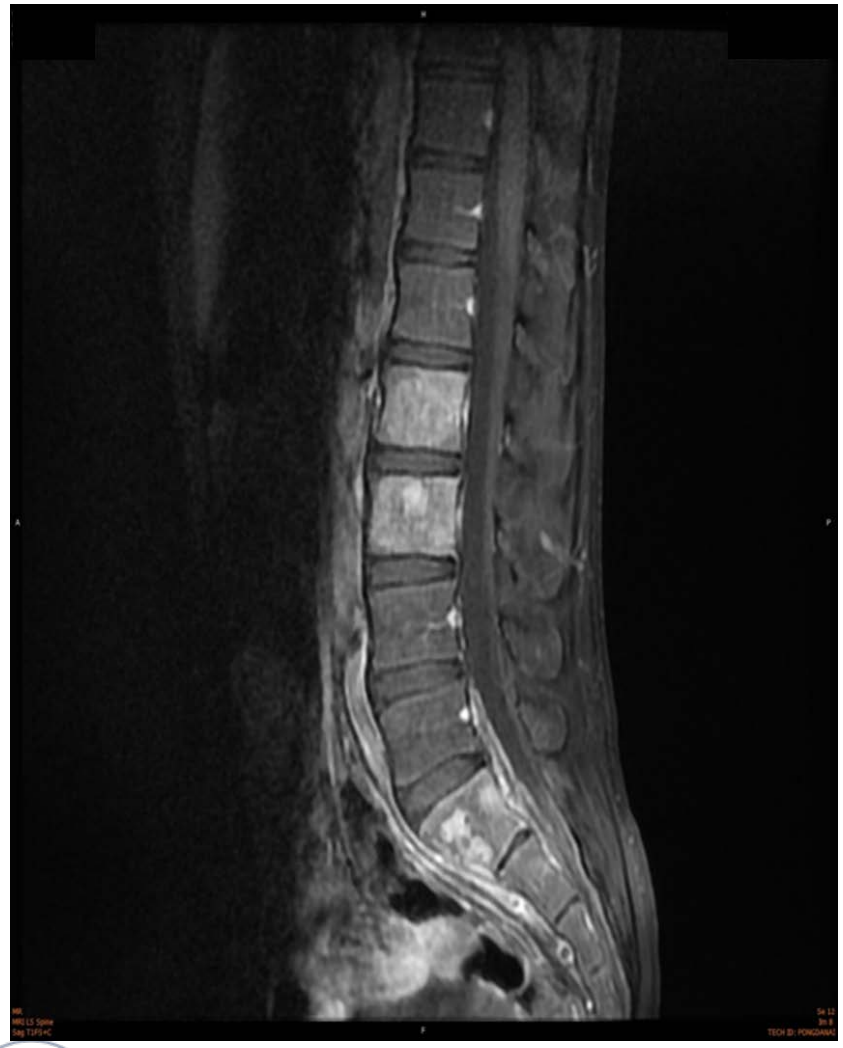


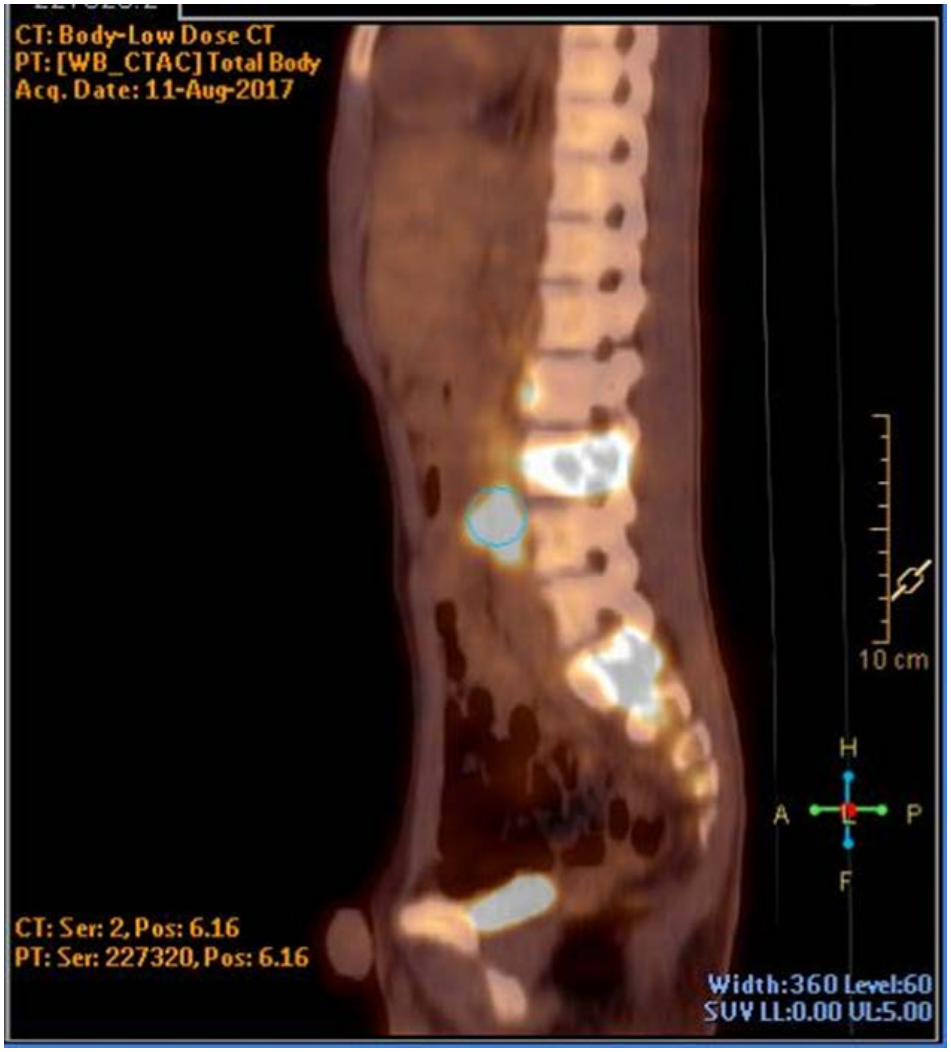






*Agarwal et al., Jpn J Radiol; 2016, 34:267–76

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PT: [WB_CTAC] Total Body
Acq. Date: 11-Aug-2017
10 cm
H
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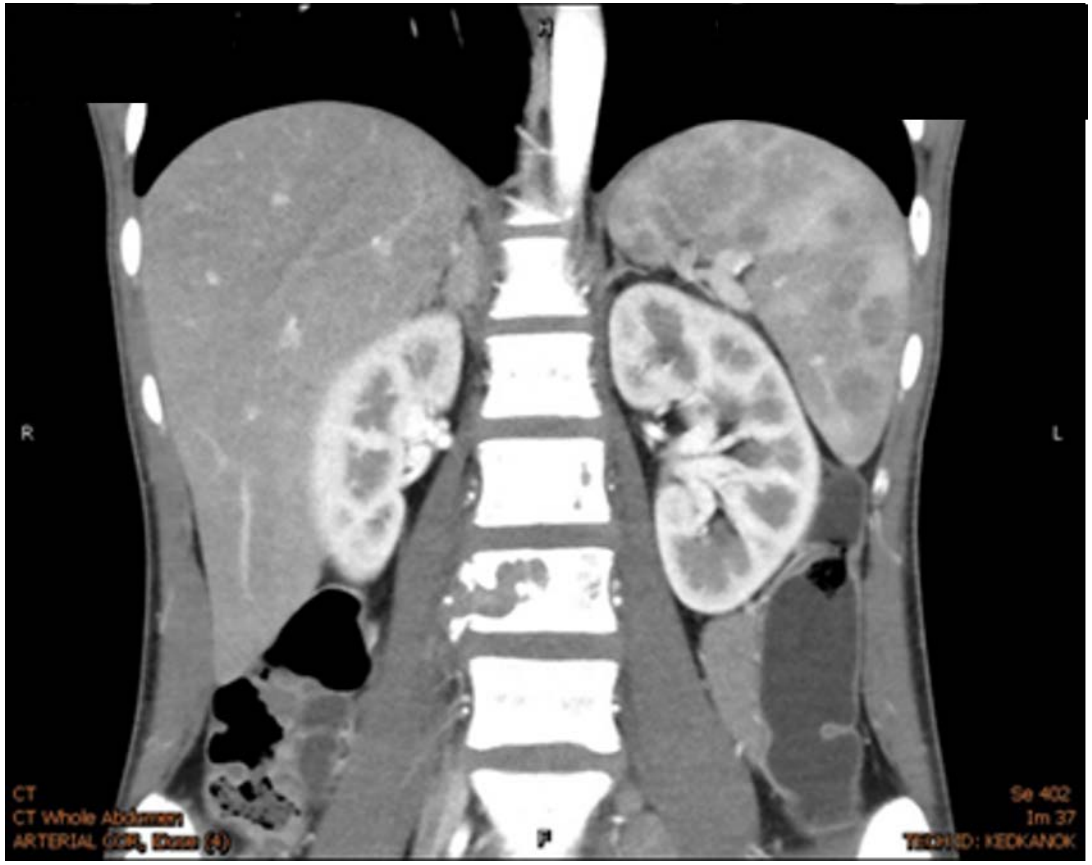
CT: Ser: 2, Pos: 6.16
PT: Ser: 227320, Pos: 6.16
Width:360 Level:60
SUV LL:0.00 UL:5.00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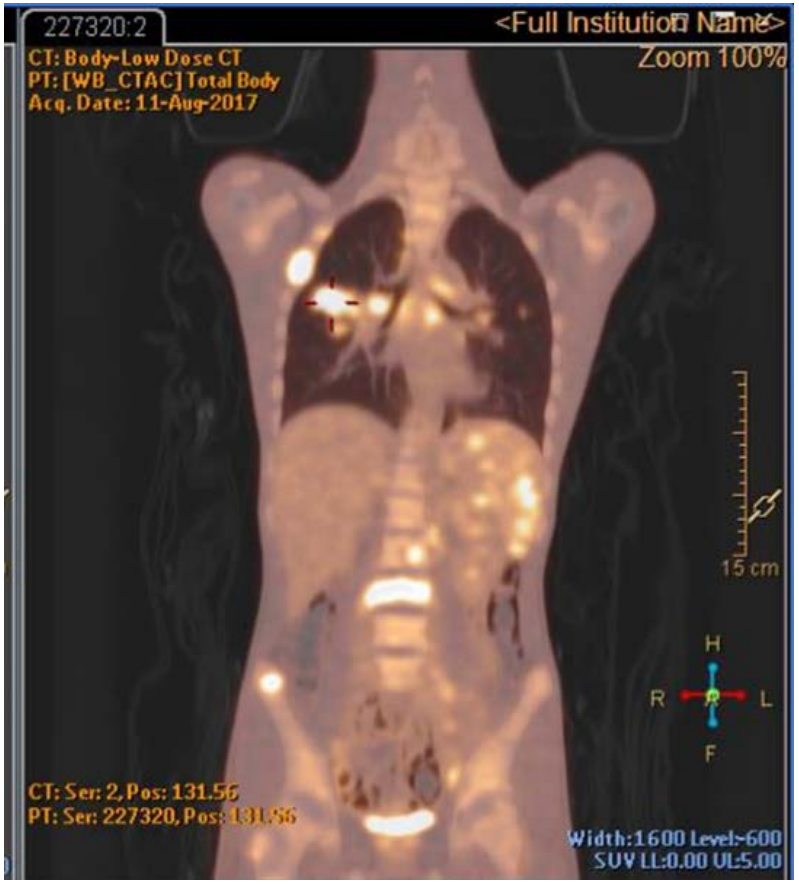
Se 402
1m 37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PT: [WB_CTAC] Total Body
Acq. Date: 11-Aug-2017
Zoom 100%
15 cm
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CT: Ser: 2, Pos: 131.56
PT: Ser: 227320, Pos: 131.56
Width:1600 Level:600
SUV LL:0.00 UL:5.00

FDG PET-CT in LCH

At diagnosis

		Per-patient presence of LCH lesions		
		Positive	Negative	Total
Per-patient FDG PET-CT findings	Positive	20[a]	1[b]	21
	Negative	0	5[c]	5
	Total	20	6	26
		Sensitivity = 100% (20/20)	Specificity = 83% (5/6)	

At follow-up

Per-scan presence of recurrent or progressive disease		
Positive	Negative	Total
6	2[a]	8
0	75	75
6	77	83
Sensitivity = 100% (6/6)	Specificity = 97% (75/77)	

Jessop S, et. al. Pediatric Blood & Cancer. 2020 Jan;67(1):e28034.

Clinical Classification of LCH patients

Clinical Classification	Involved Organs
Multisystem LCH **RO+/-**	≥ 2 systems +/- Bone marrow, liver, and/or spleen
Single System LCH • **Single site (unifocal)** • **Multiple sites (multifocal)** • **Special site**	1 system • Skin, bone, lymph node, other (thyroid, thymus) • Multifocal bone • Skull-base lesion with intracranial extension or vertebral lesion with intraspinal soft tissue extension
Pulmonary LCH	Isolated lung disease
CNS LCH	• Tumorous lesion • Neurodegenerative LCH

Adapted from Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. Blood. 2020;135(16):1319-1331

Prognosis

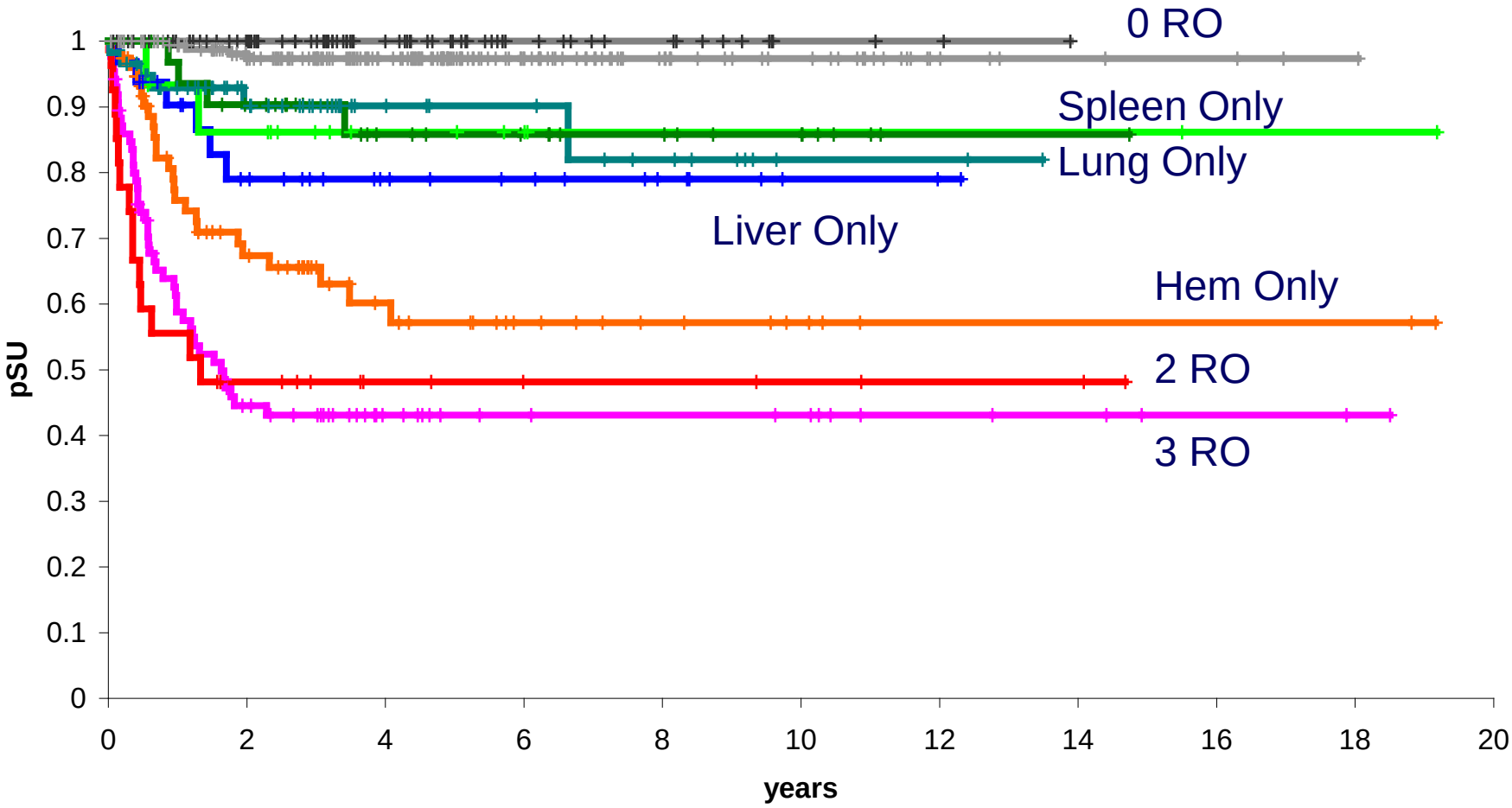
- Rapid response to initial treatment within 6 weeks
- Involvement of “Risk organs”; hematopoietic system, liver, spleen and lungs
- Age at diagnosis: diagnosed before 2 years of age, mortality rate 66% (but not include in “Risk”)
- Number of organ involvement : mortality rate is increasing follow by numbers of organ involvement
- Bone involvement associated with favorable prognosis
- Organ dysfunction presented at diagnosis or during the course of disease
- Patients with MFB have excellent prognosis but high tendency for disease reactivation (30-50%) and permanent consequences

Gadner et al., J Pediatr 2001; 138: 728-34
Gadner et al., Blood 2008; 111: 2556-62
Gadner et al., Klin Padiatr 1987; 199: 173-82
Gadner et al., Blood 2013; 121: 5006-14

Risk organs involvement definition

- Hematopoietic involvement: (+/- BM involvement~CD1a +)
  - At least 2 of the following:
  1. **Anemia:**
     - Hemoglobin <10 g/dl
     - Infants <9.0 g/dl
  2. **Leukocytopenia:** WBC <4,000/µL
  3. **Thrombocytopenia:** platelets <100,000/µL
- Spleen involvement: enlargement >2 cm BCM in the MCL by PE
- Liver involvement: ≥ 1 of the following
  1. **Enlargement** >3 cm BCM in the MCL by PE
  2. **Dysfunction** i.e. hypoproteinemia <55 g/L, hypoalbuminemia <25 g/L, not due to other causes
  3. **Histopathological findings** of active disease

Outcome by Risk Organ Involvement



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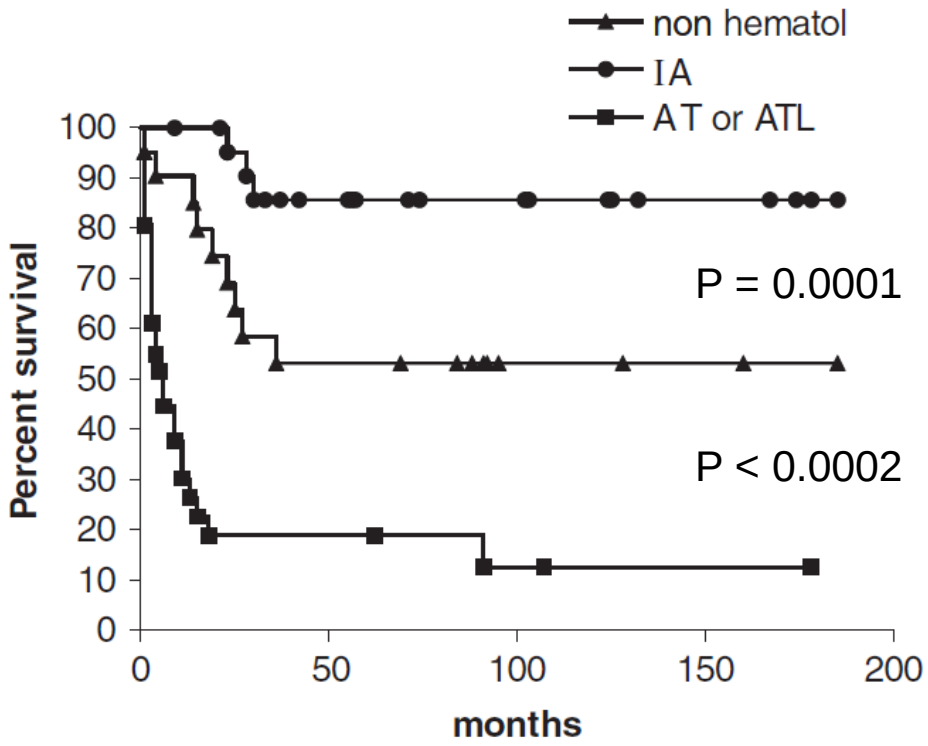
Data from LCH Studies
Provided by Vienna Data Center

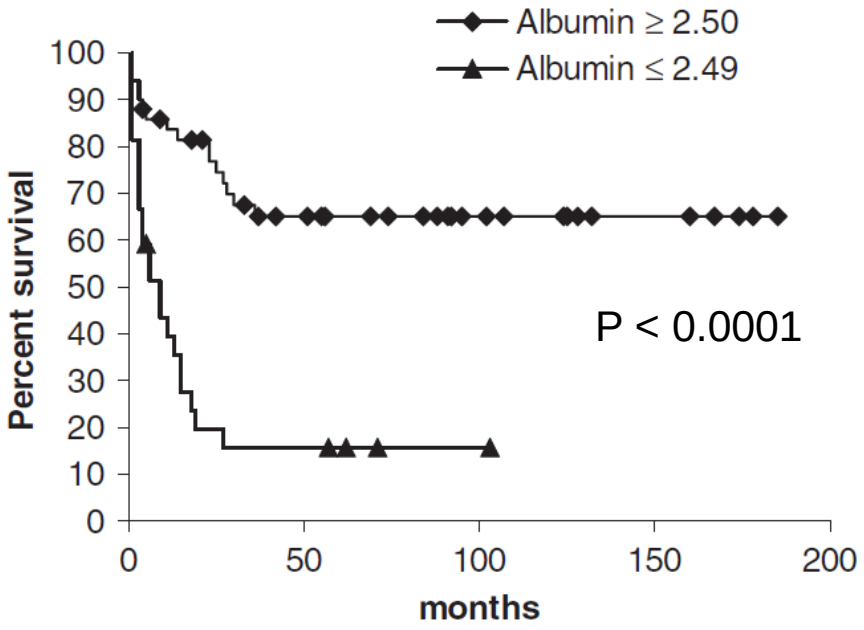
PMK RO+ MS-LCH patients' characteristic

No	Age at diagnosis (months)	Abnormal LFT	Risk organs involvement	Other organ involvement	Chemotherapy regimens	Disease status	Status at last follow-up	Follow-up time	BRAF^{V600E} mutation
1	20	TP 4.8 alb 2.4 TB 13.7 DB 12.9 AST 56 ALT 47 ALP 451	Liver, spleen, hematopoietic	Skin, bone	Ara-C, prednisolone	Progressive	DWD	12 months	Not done
2	3	TP 8 alb 4.8 TB 14 DB 0.5 AST 30 ALT 16 ALP 254	Liver, spleen, hematopoietic	Lung, bone	DAL-Hx83: VBL, VP-16, 6-MP, MTX, prednisolone	Remission	Alive, NED	16 years	Not done
3	14	-	Liver, spleen	Bone, lymph nodes	LCH-III (High risk): MTX, VBL, Prednisolone, 6-MP	Reactivation MFB	AWD	8 years 7 months	Not done
4	15 years 7 months	-	Liver, spleen	Lung, bone (special site)	TPOG 2018: (High risk): VBL, Prednisolone, 6-MP	Reactivation	AWD	32 months	Negative
5	16	TP 6.27 alb 2.73 TB 0.65 DB 0.28 AST 29.8 ALT 19.2 ALP 80	Liver, spleen, hematopoietic	Skin, bone	TPOG 2018: (High risk): VBL, Prednisolone, 6-MP	Progressive	DWD	7 months	Positive

Mosereenusorn et.al. under review

Hematologic involvement and hypoalbuminemia related with MS-LCH outcome





Pediatric Cancer & Hematologic Disorder
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Braier JL, Rosso D, Latella A, et al. J Pediatr Hematol Oncol. 2010;32(4):e122-e125.

BRAF^{V600E} Clinical Correlation

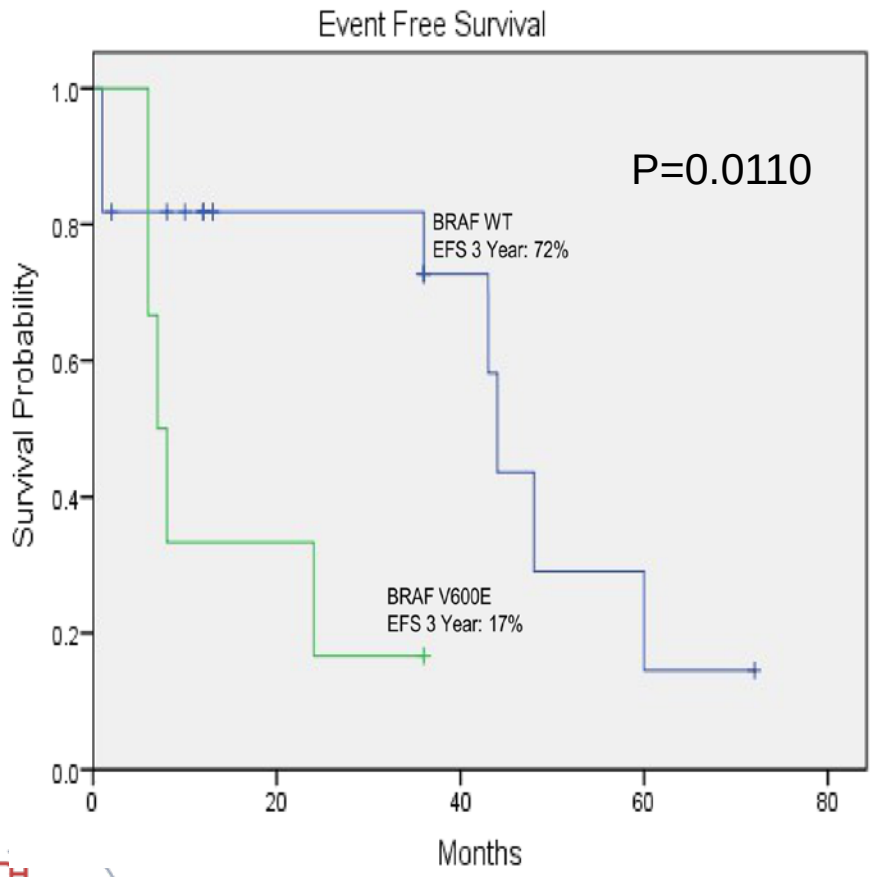
- 63% of patients with *BRAF*^{V600E}
- No significant correlation:
  - High risk vs. Low risk
  - Age (<2 vs. 2-8 vs. >8 years)
  - Gender
  - Single vs. multifocal
  - Overall survival

Berres et al., JEM 2014

BRAF^{V600E} mutation correlated with survival

- *BRAF*^{V600E} positive 6/31 (19%)
- All cases of *BRAF*^{V600E} were MS-LCH (100% vs. 41%, p=0.0348)

A



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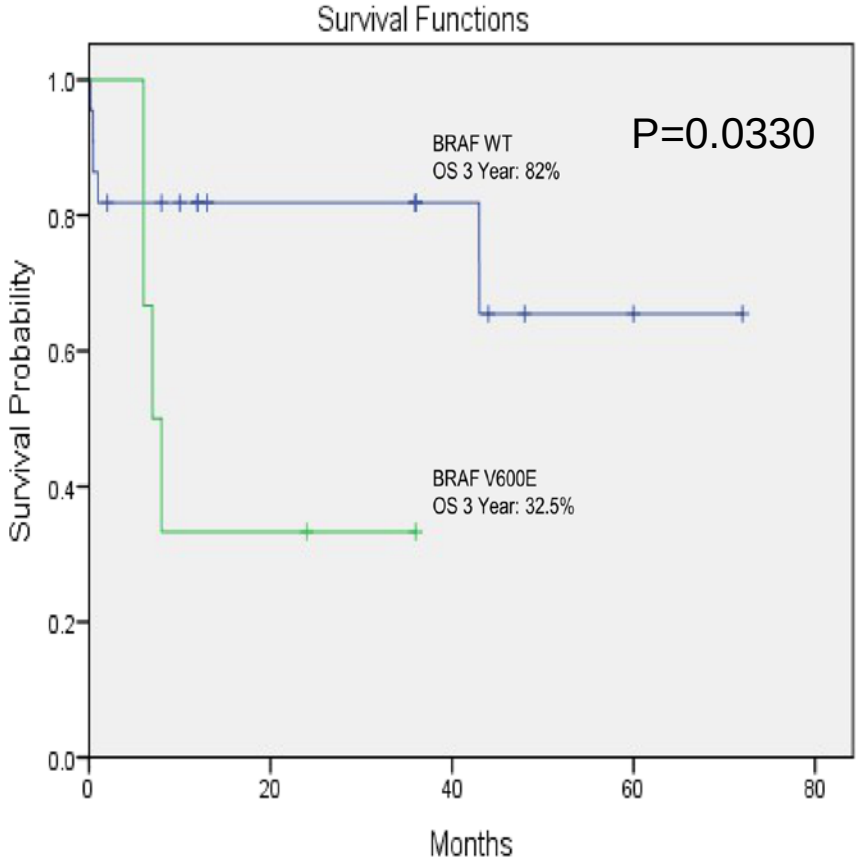
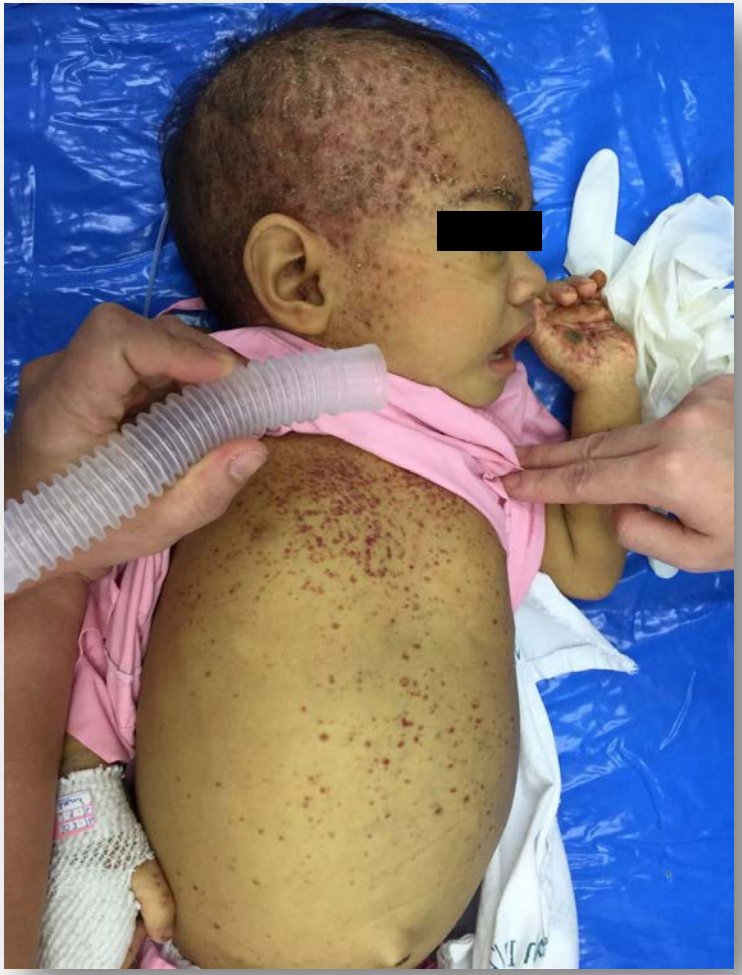
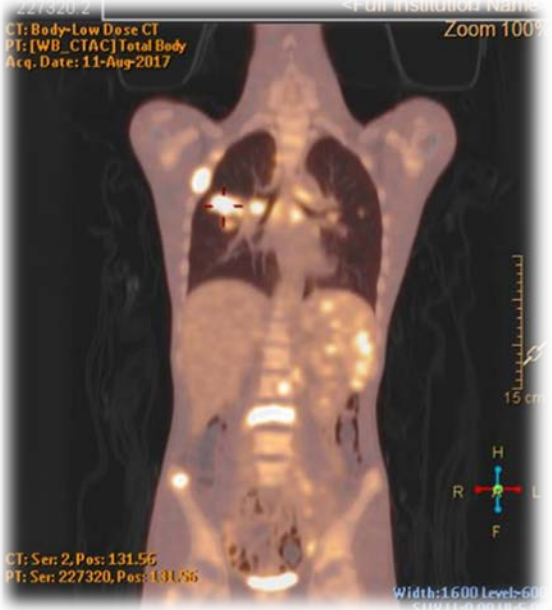


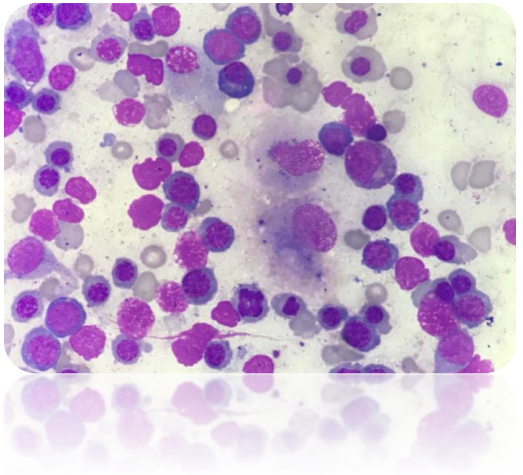
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Bhatia P, Singh M, Sharma M, et al. Blood Cells Mol Dis. 2020;82:102356.

RO+ MS-LCH







Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Parental permission for educational propose only

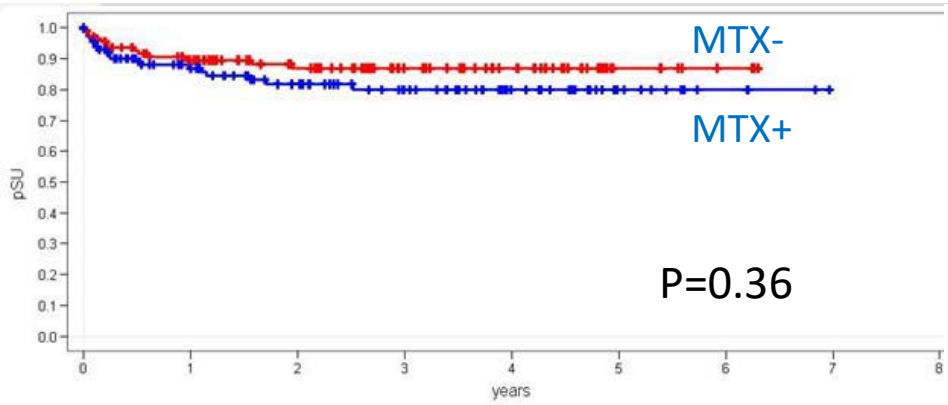
LCH protocols

Protocol	Chemotherapy	Duration
DAL-HX-90	VBL, PRED, VP-16, 6-MP, MTX	12 mo
JLSG-96	Ara-C, VCR, PRED, Dox, CTX, MTX	12 mo
LCH-I	VBL, methylpred, VP-16	6 mo
LCH-II	VBL, PRED, VP-16, 6-MP	6 mo
LCH-III	VBL, PRED, 6-MP, MTX	6/12 mo

Monsereenusorn et al., Hematol Oncol Clin North Am 2015; 29: 853-73

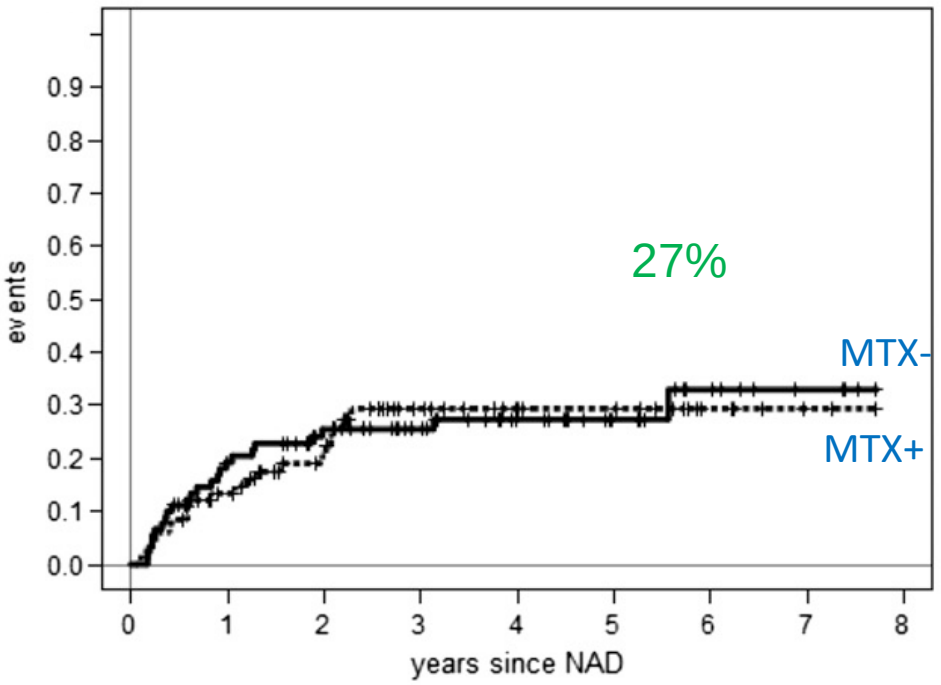
Addition MTX in RO+MS LCH

- Survival



	Patients	Deaths	5-yr OS
MTX	115	19	0.82 ±0.04
No MTX	112	14	0.87 ±0.03

- Reactivations

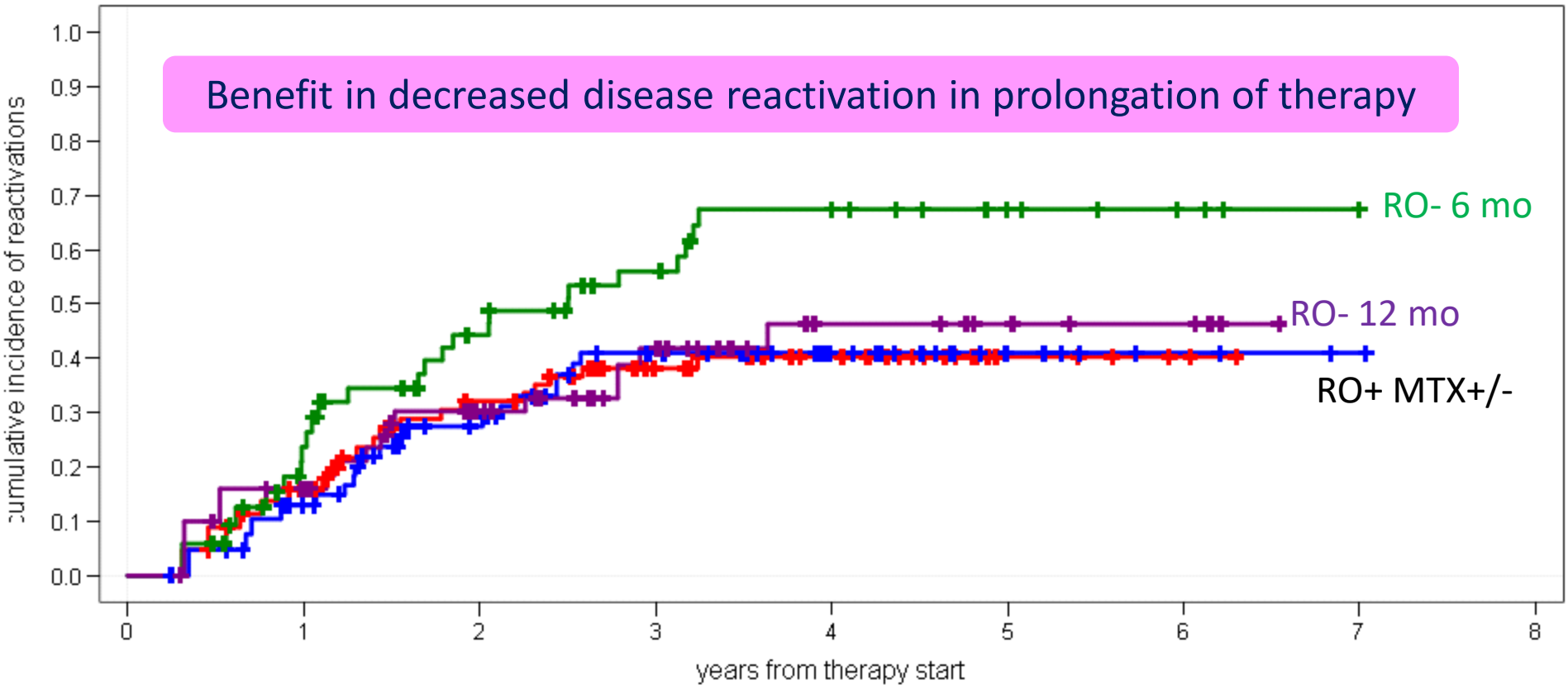


No advantage with added MTX

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Gadner et al., Blood 2013; 121: 5006-14

Therapy prolongation improves outcome in MS LCH



The probability of reactivation in the "Risk Group" (both treatment arms total 12 months) was similar to the 12-month treatment arm of the "Low risk" trial

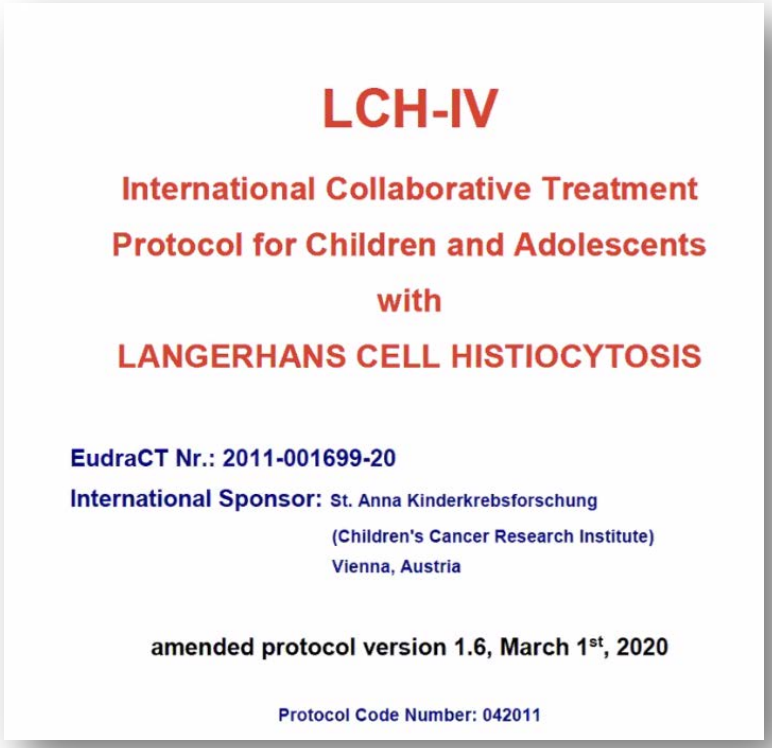
Gadner et al., Blood 2013; 121: 5006-14

Outcomes among different LCH protocols

	Multifocal SS-LCH			MS-LCH						
									LCH-III	
Variable	DAL-HX	JLSG-96	JLSG-02	DAL-HX	JLSG-96	JLSG-02	LCH-I	LCH-II	RO −	RO +
N	34	32	67	63	59	97	143	193	269	285
Duration (mo)	12	7.5	12	12	7.5	12	6	6	6/12	12
Response rate (%)	94.1	96.9	85.1	79	76.3	84.5	53	67	86	70–72
Reactivation rate (%)	17.6	28.1	22	30	45.3	25	58	46	54/37	25–29
Survival rate (%)	—	100	100	94	94.4	97.6	79	76.5	99	84
Incidence of DI (%)	2.9	3.2	1.5	11.9	8.9	18.6	22.5	21.8	12	8–9

Monsereenusorn et al., Hematol Oncol Clin North Am 2015; 29: 853-73

LCH IV Study Aims



LCH-IV

International Collaborative Treatment Protocol for Children and Adolescents with LANGERHANS CELL HISTIOCYTOSIS

EudraCT Nr.: 2011-001699-20

International Sponsor: St. Anna Kinderkrebsforschung (Children's Cancer Research Institute) Vienna, Austria

amended protocol version 1.6, March 1st, 2020

Protocol Code Number: 042011

1. Decrease the frequency of reactivations and improve survival by
   - Prolongation of therapy
   - Additional 6-MP
2. Investigate salvage regimen for low risk disease
3. Decrease mortality by
   - Early switch to salvage regimen
   - Identification of patient at risk
4. Investigate LCH CNS disease

Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)

Current study: LCH IV for LCH

- **STRATUM I**: 1st line therapy for MS-LCH (Group 1) and SS-LCH (isolated "CNS-risk" or multifocal bone lesions) (Group 2)
- **STRATUM II**: 2nd line treatment for *non risk* LCH
- **STRATUM III**: Salvage treatment for *risk* LCH
- **STRATUM IV**: HSCT for *risk* LCH
- **STRATUM V**: Monitoring and Treatment of CNS-LCH
- **STRATUM VI**: Natural history and management of "other" SS-LCH not eligible for stratum I group 2
- **STRATUM VII**: Long-term follow-up

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

HISTIOCYTE SOCIETY

ClinicalTrials.gov identifier (NCT number): NCT02205762

LCH patients with hyperbilirubinemia

- Contraindication for vinblastine and vincristine
- Prednisolone will be the KEY for induction
- Cytarabine substitution may be considered.
- Escalation dose of cytarabine monthly will be recommended, rely on hematological toxicity.

Recurrent LCH

20-50% of patients

- Low risk: SS-MFB, MS RO-
  - Disease reactivation 1/3 of patients
  - Response well to 2nd line therapy
  - 6-MP and MTX, indomethacin, bisphosphanate, *BRAF* inhibitor, cladribine
- High risk: RO+
  - Poor response to standard therapy

MS-LCH without risk organ involvement	MS-LCH with risk organ involvement
1. Cladribine 2. 6-MP with methotrexate 3. Prednisolone with methotrexate 4. Bisphosphonate (local skin and bone) 5. Clofarabine 6. Imatinib mesylate	1. Cytarabine with cladribine 2. Clofarabine 3. BRAF inhibitor 4. Hematopoietic stem cell transplantation (HSCT)

Monsereenusorn et al., Hematol Oncol Clin North Am 2015; 29: 853-73
Monsereenusorn et al., Expert Opinion on Orphan Drugs. 2016; 4(10): 1057-68

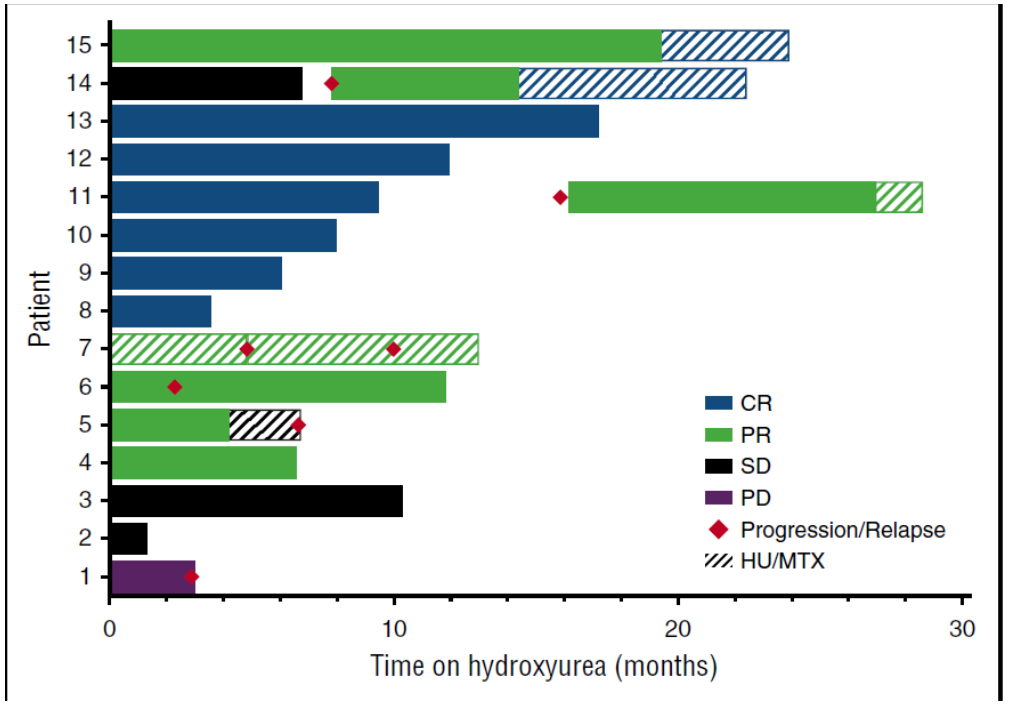
blood

To the editor:

Hydroxyurea: a new old therapy for Langerhans cell histiocytosis

Daniel J. Zinn,* Amanda B. Grimes,* Howard Lin, Olive Eckstein, Carl E. Allen, and Kenneth L. McClain

Texas Children's Cancer and Hematology Centers, Baylor College of Medicine, Houston, TX



Hydroxyurea 20 mg/kg/day
N=15 relapse LCH
8/15 (53%) CR
4/15 (27%) PR
3/15 (20%) SD

Zinn DJ, et al. Blood. 2016 Nov 17;128(20):2462-5.

Bisphosphonates

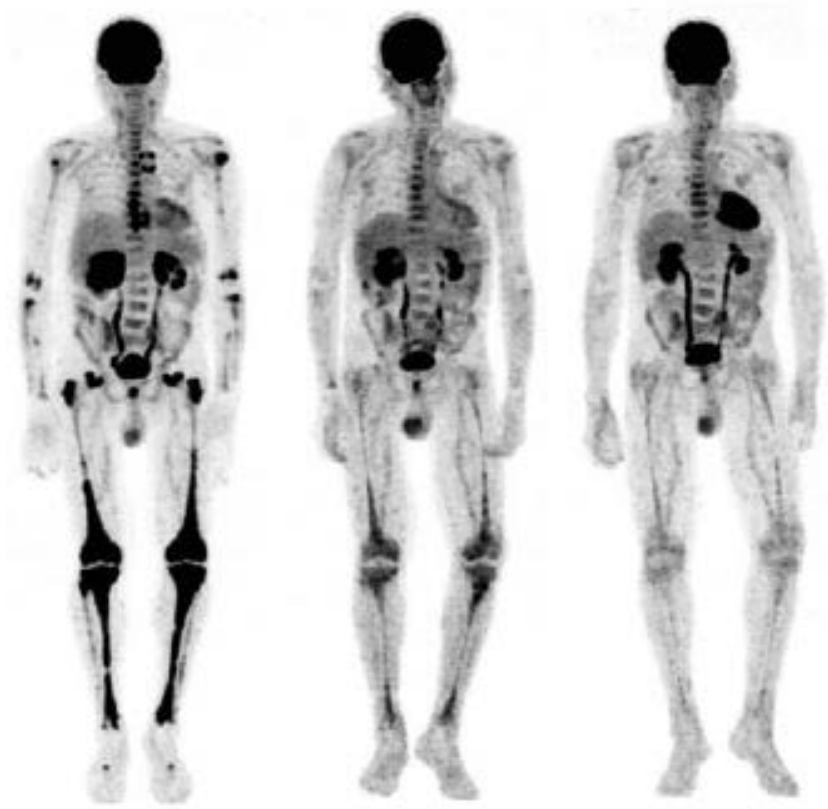
- Osteoclast inhibitors
  - Improve bone structure
  - Decrease inflammatory substance

- Dose
  - Pamidronate 90 mg IV x 3 days q 3 mo
  - Pamidronate 90 mg IV q mo
  - Etidronate 200 mg/m2/day x 14 days oral q 3 mo

Targeted therapy for LCH with BRAF mutation

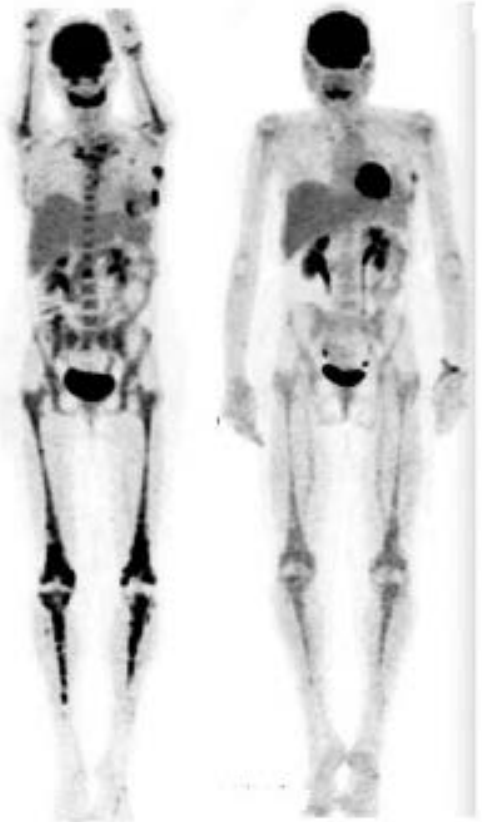
HAROCHE et al

BLOOD, 28 FEBRUARY 2013 • VOLUME 121, NUMBER 9



Before Vemurafenib | Vemurafenib 1 month | Vemurafenib 4 months

Patient #1

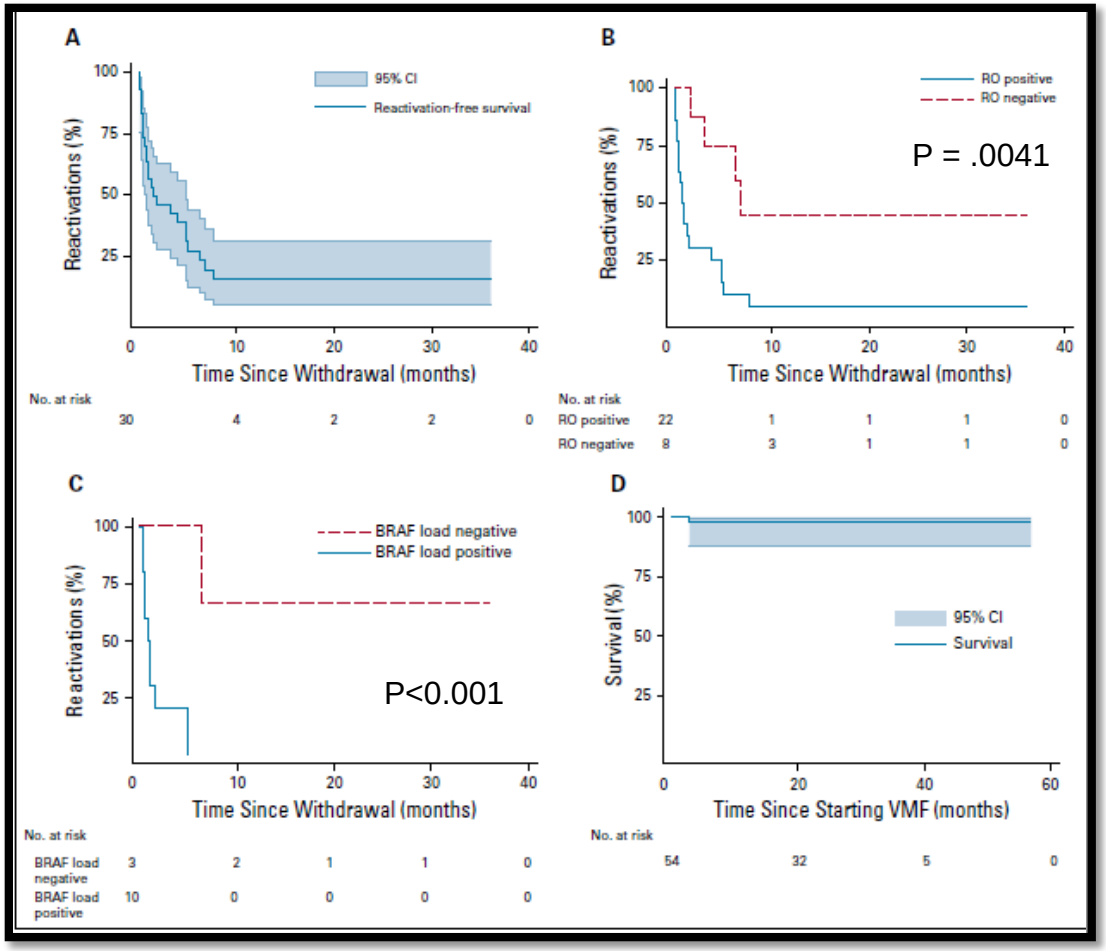


Before Vemurafenib | Vemurafenib 1 month

Patient #2

Vemurafenib for Refractory MS-LCH in Children

- N=54 from 12 countries
- VMF 20 mg/kg/day



Donadieu J, Larabi IA, Tardieu M, et al. J Clin Oncol. 2019;37(31):2857-2865

HSCT in refractory pediatric LCH

- N=30
- 11 MAC, 19 RIC
- 23/26 RO+ MS-LCH
- Disease status at HSCT:
  - 4 no AD
  - 2 AD-regression, 4 AD-stable, 16 AD-progressive
- 5-year OS 59.6%, FFS 56.3%
- 5-year OS of no AD/AD-regression 100% vs. 54.5% of AD-stable and progressive (p = 0.040)
- Disease state at the time of HSCT was the most important prognostic factor.

Kudo K, Maeda M, Suzuki N, et al. *Int J Hematol*. 2020;111(1):137-148.

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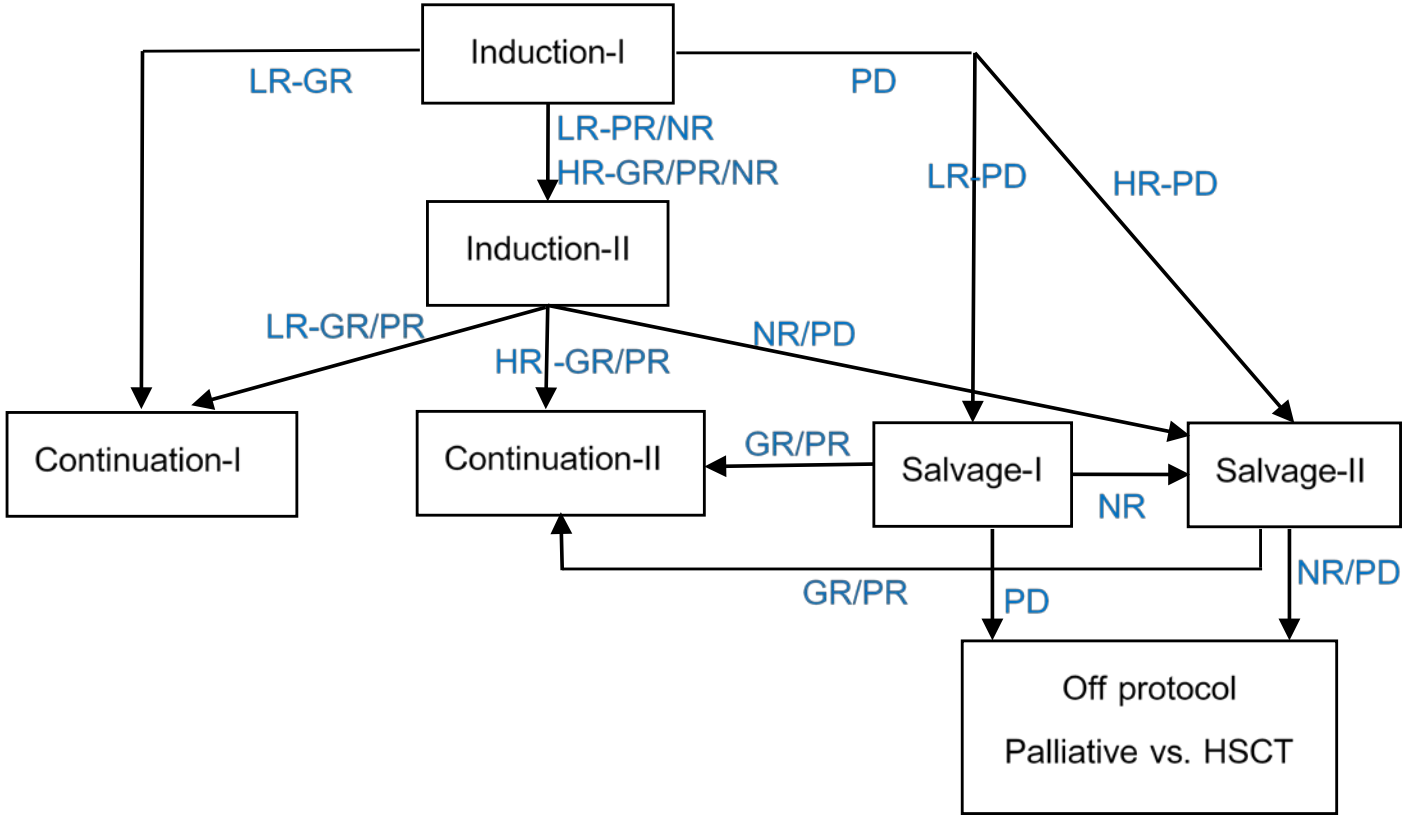
LCH 2018 treatment Guideline



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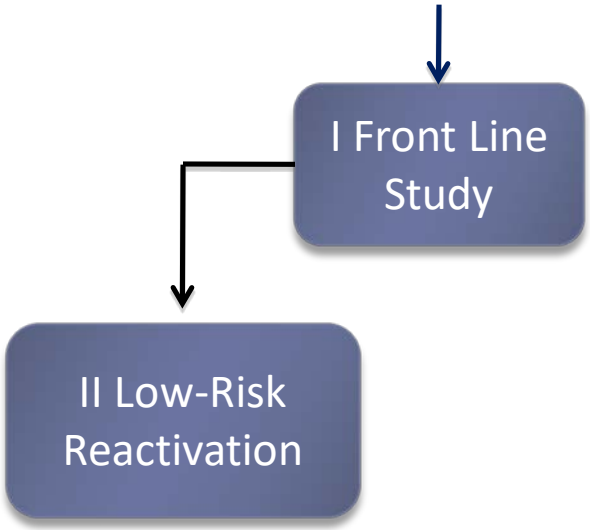
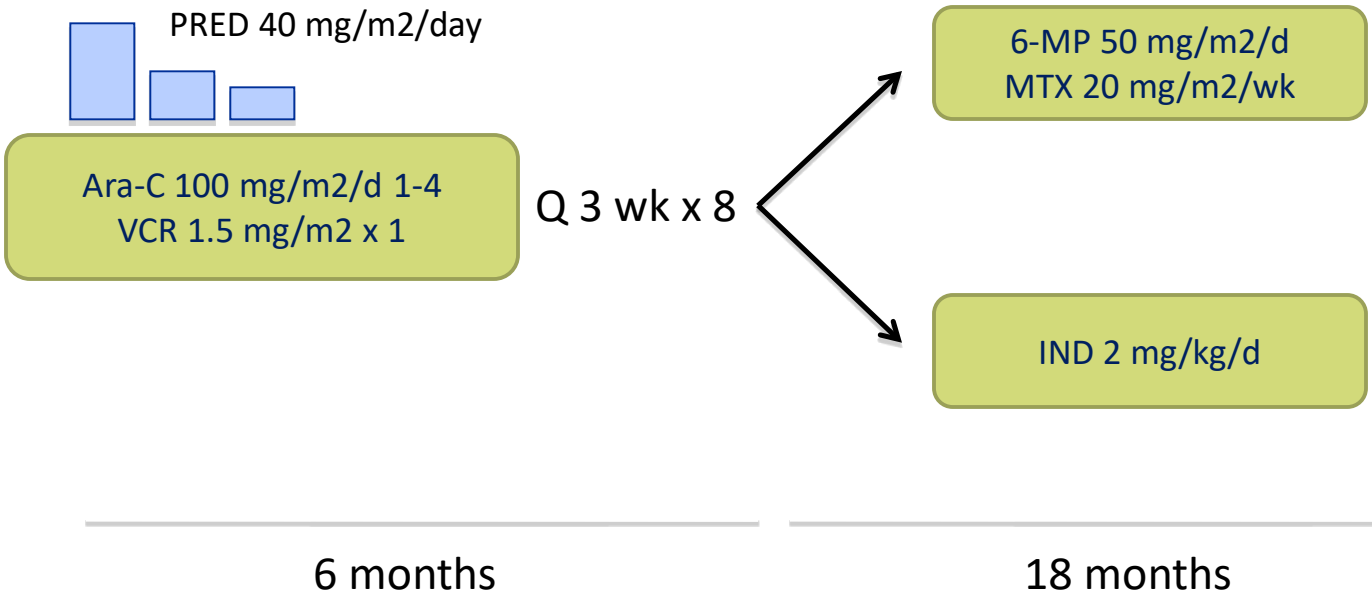
GR; good response, PR; partial response, NR; not response, PD; progressive disease

LCH-IV Study



LCH-IV – Stratum II Second line therapy

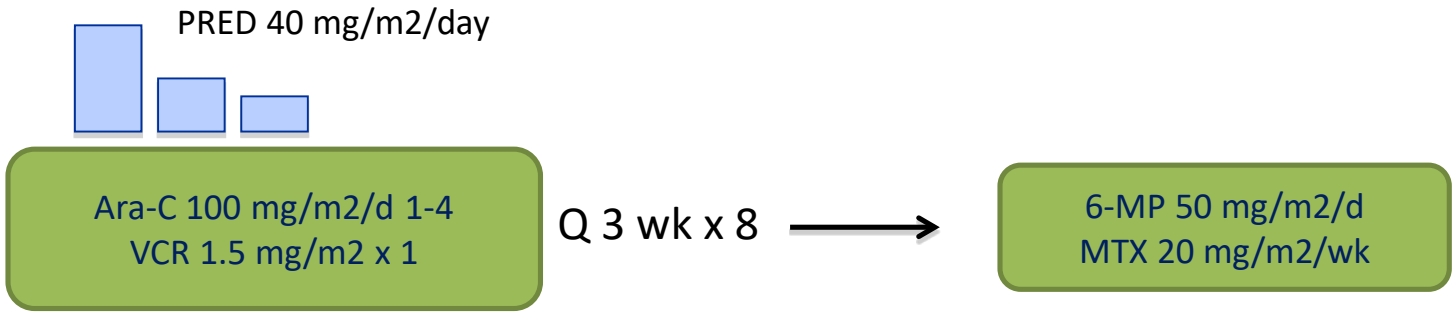
RO- LCH Reactivation



LCH treatment Guideline

Salvage I regimen

For LR with progressive disease



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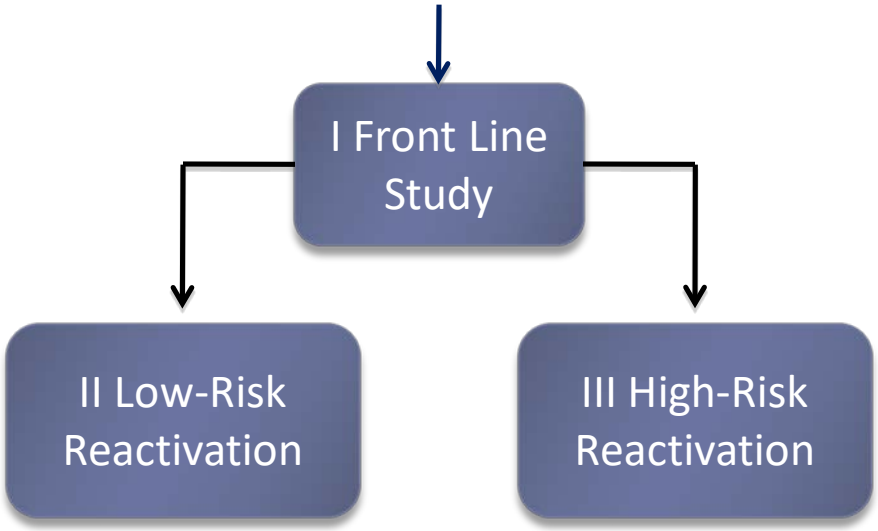
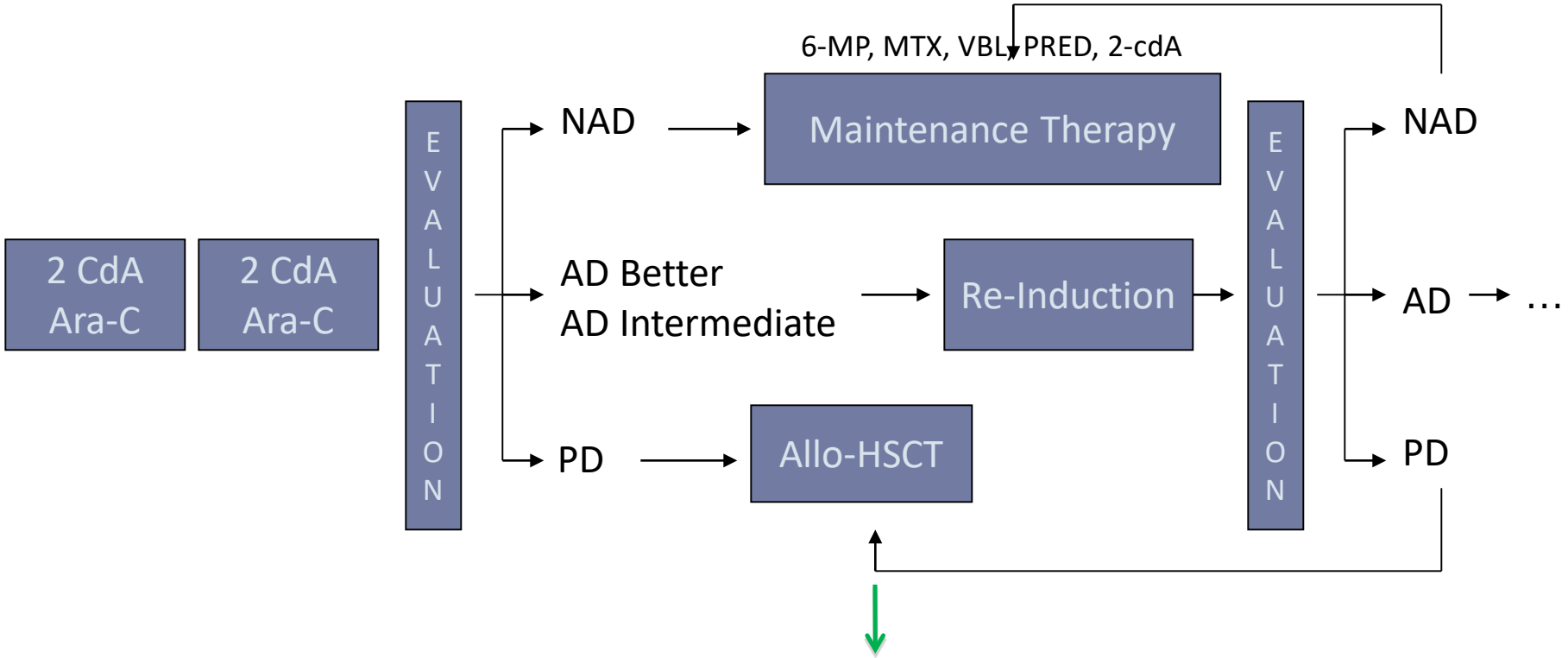
LCH-IV – Stratum II Second line therapy
RO- LCH Reactivation

LCH-IV Study


I Front Line Study
II Low-Risk Reactivation
III High-Risk Reactivation

LCH-IV – Stratum III Salvage therapy

RO+ LCH Reactivation



LCH-IV – Stratum IV

High-Risk HSCT

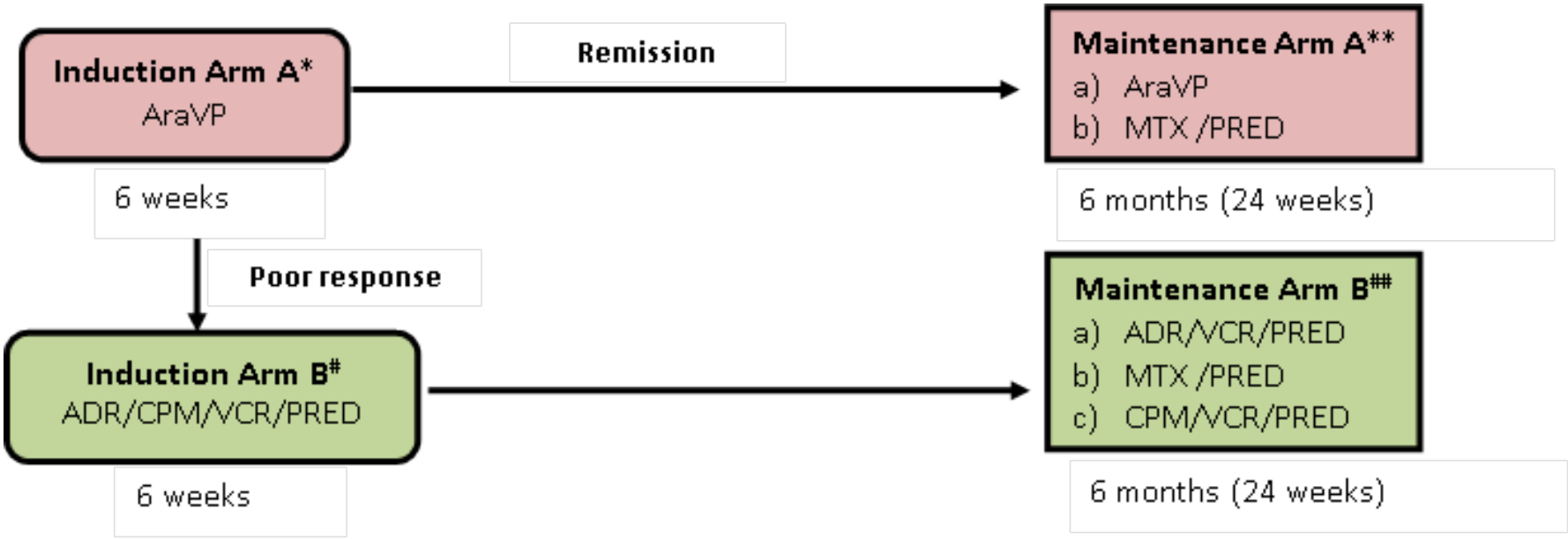
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

HISTIOCYTE SOCIETY

LCH treatment Guideline

Salvage II regimen

For HR with progressive disease*



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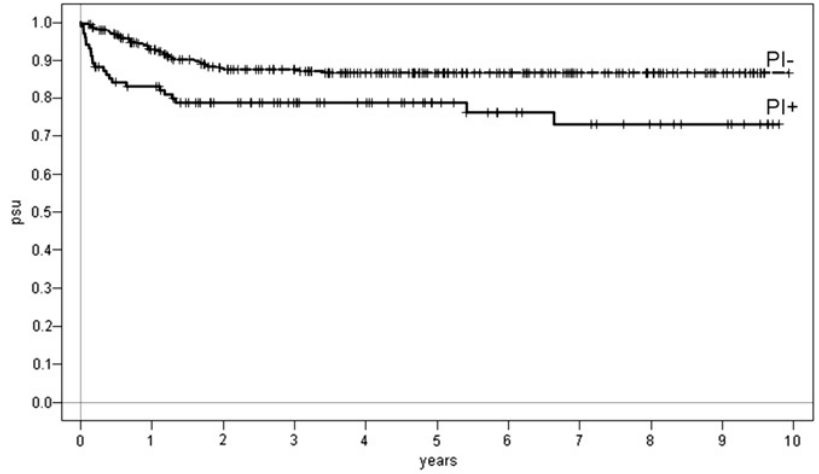
*or NR/PD for Induction-II or NR for Salvage-I protocol

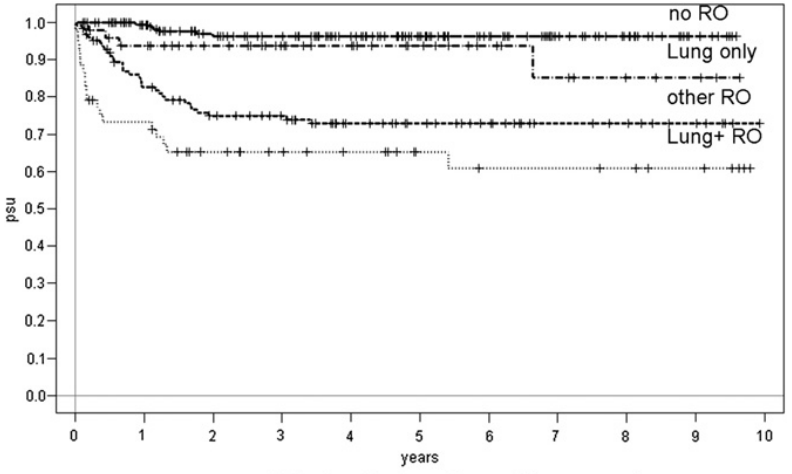
JLSG-96 protocol for LCH patients
Morimoto et al., Cancer 2006; 107: 613-9

Pulmonary involvement in MS LCH

- In multivariate analysis, pulmonary involvement was not an independent prognostic factor
- Therefore, it was excluded from the definition of risk organ involvement in MS-LCH.



	Patients	Events	5-yrs. pSU	*P*-value
PI-	318	38	0.87±0.02	.004
PI+	102	23	0.79±0.04	



	Patients	Events	5-yrs. pSU	*P*-value
no RO	192	6	0.96±0.01	
Lung only	49	4	0.94±0.03	.096
RO only	126	32	0.73±0.04	
Lung+RO	53	19	0.65±0.07	.070

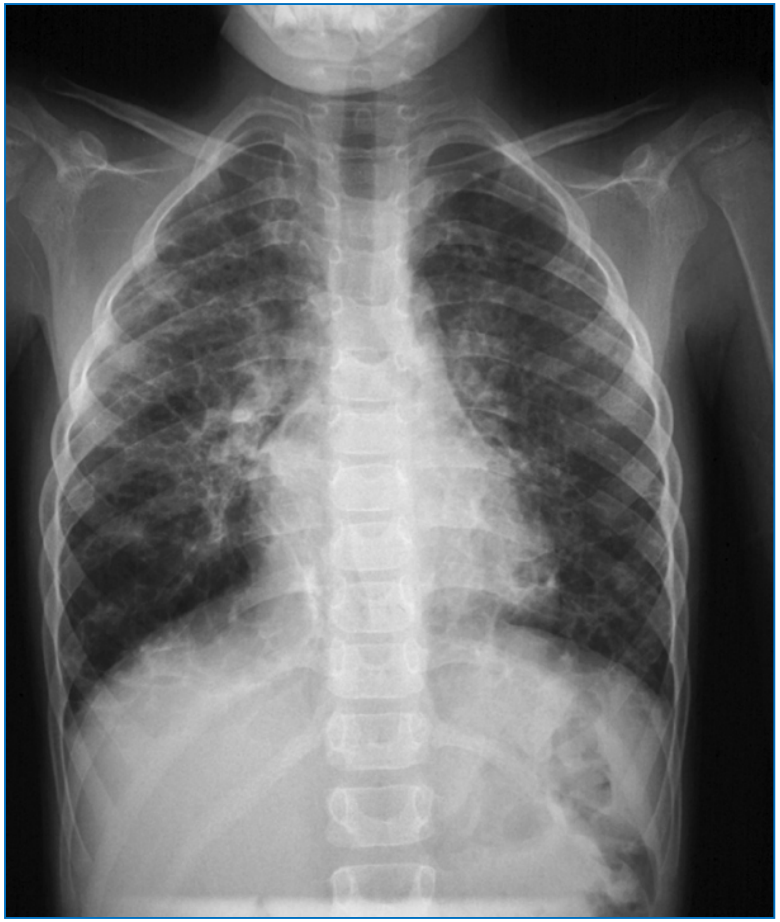
Ronceray et al., J Pediatr 2012; 161: 129-33 e1-3

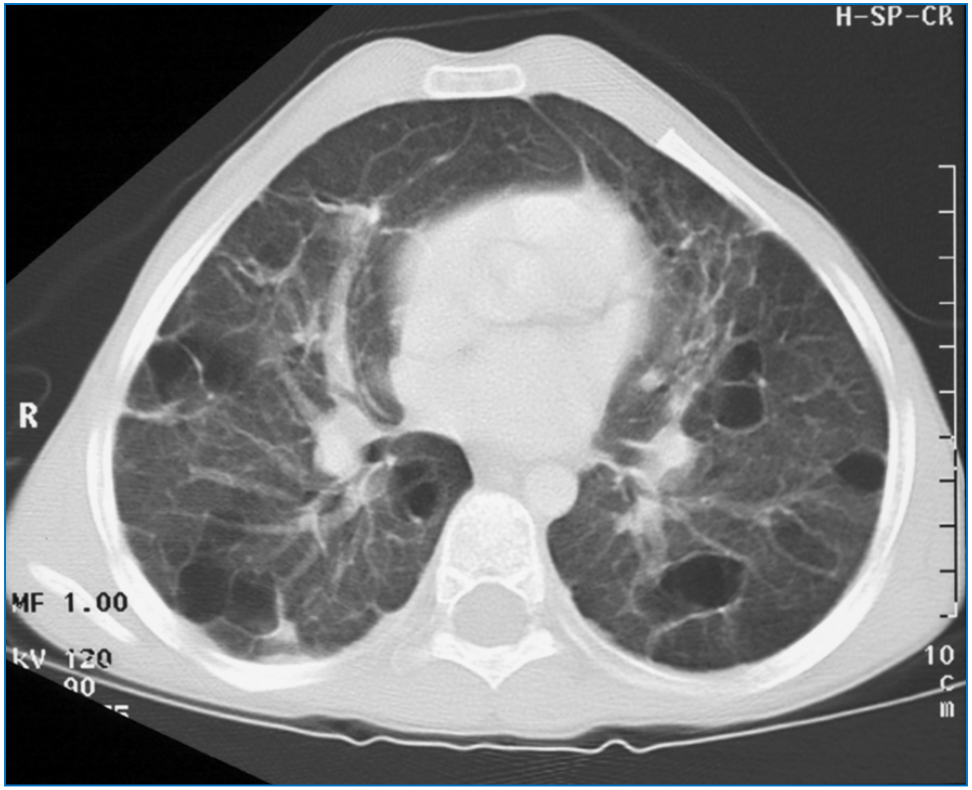
Pulmonary LCH
Pediatric vs. adult

	Pediatric	Adult
Sites	Mostly as part of MS-LCH	Mostly isolated lung
Smoking	No association	90-95% association
Pneumothorax at 1st presentation	Not common	Common (32%)
Radiological findings	Cystic lesion Reticulonodular pattern	
	CPA and lower lungs	Spare CPA and lower lungs

Barclay M, Devaney R, Bhatt JM. Breathe. 2020 Jun 1;16(2).

Lung involvement in LCH





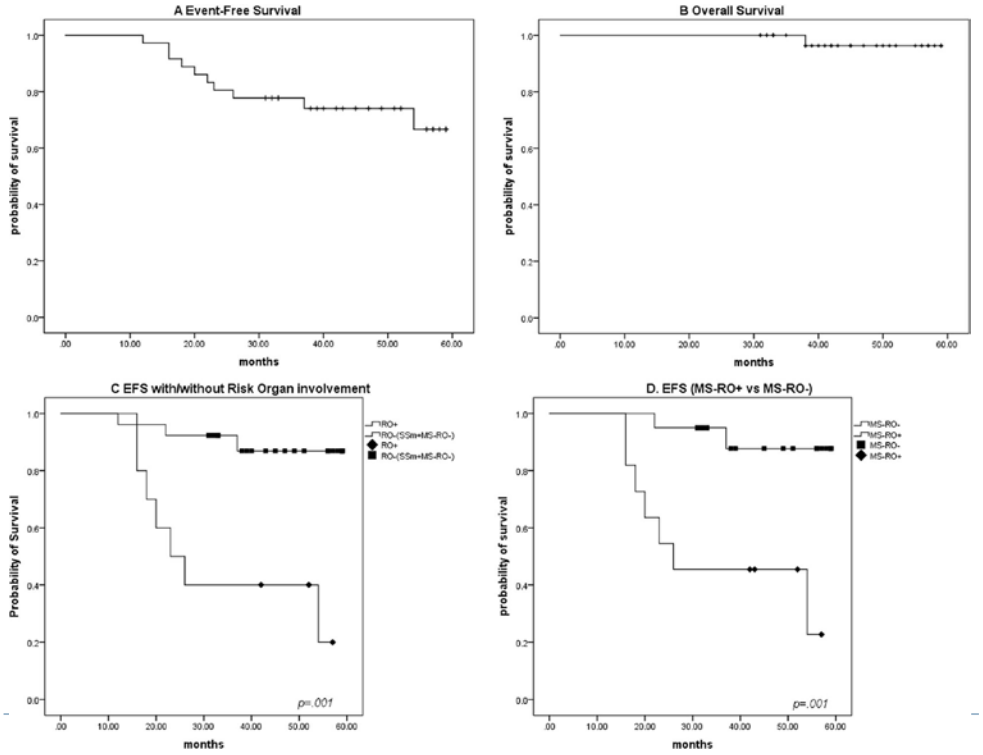
Han et al. BMC Cancer (2020) 20:433
https://doi.org/10.1186/s12885-020-06872-8

BMC Cancer

RESEARCH ARTICLE Open Access

The combination of methotrexate and cytosine arabinoside in newly diagnosed adult Langerhans cell histiocytosis: a prospective phase II interventional clinical trial

Xiao Han†, Mingqi Ouyang†, Minghui Duan*, Wei Zhang, Tienan Zhu, Jian Li, Shujie Wang and Daobin Zhou



Conclusions

- LCH is a neoplastic proliferation of Langerin + myeloid dendritic cells → recruitment of activated lymphocytes
- FDG PET-CT scan had greater accuracy to detect LCH disease
- Liver and hematopoietic involvement are worse prognosis factors in MS-LCH
- Patients with MFB have excellent prognosis but high tendency for disease reactivation (30-50%)
- Reactivations → prolongation of therapy
- BRAF inhibitor and HSCT are the future direction to improve outcome in refractory LCH

for

children with cancer

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