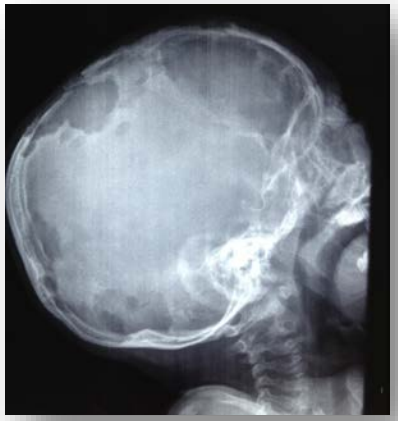
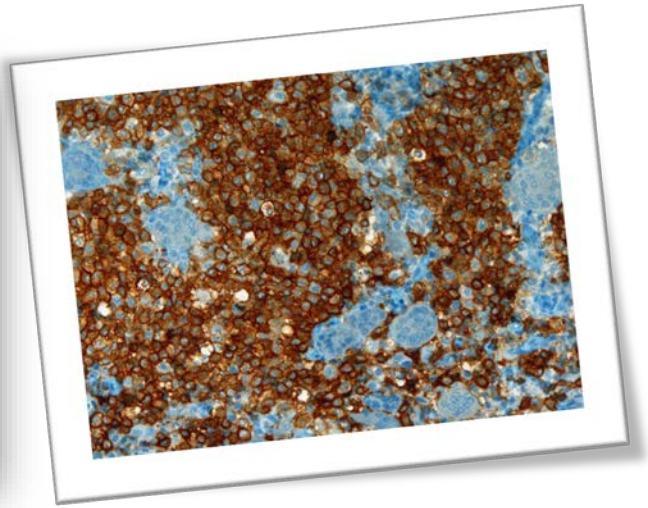
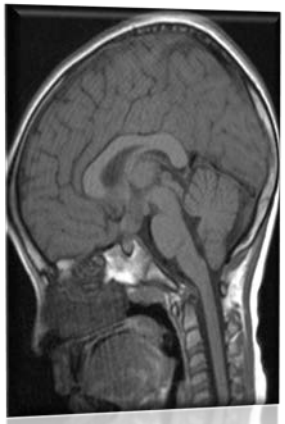
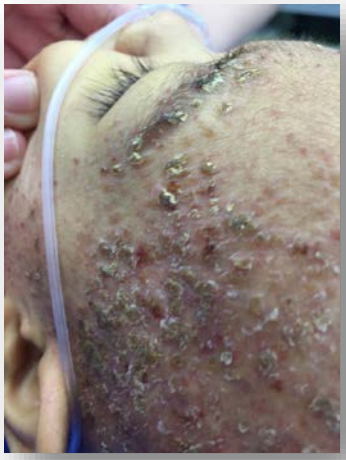





Langerhans Cell Histiocytosis

Past, Present and Future

The 54th TSH Annual Meeting: "Hematology: Basics and Beyond"
1-2 May, 2019

Chalinee Monsereenusorn, MD

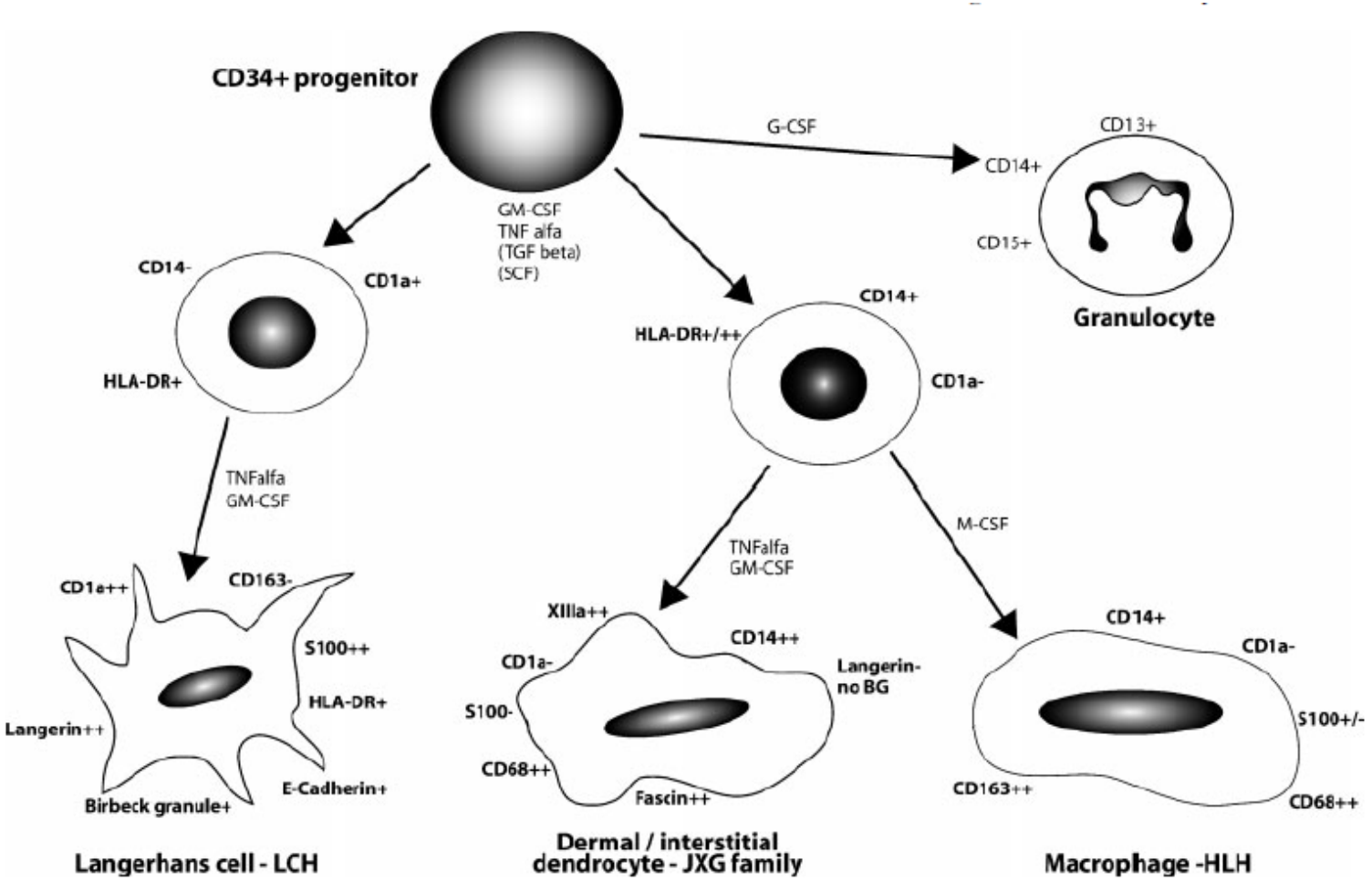
Assistant Professor
Division of Hematology-Oncology, Department of Pediatrics,
Phramongkutklao Hospital and College of Medicine

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Outlines

- Introduction
- Biology
- Epidemiology
- Clinical presentations
- Investigations
- Diagnostic histopathology
- Clinical classification
- Prognosis
- Treatment

Histiocyte developmental pathway



Pediatric Cancer & Hematologic Disorder
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Weitzman et al., Pediatr Blood Cancer 2005; 45: 256-64

Classification of histiocytosis syndrome in children

Class	Syndrome
I Dendritic/histiocytic disorder	• Langerhans cell histiocytosis (LCH) • Non-LCH o Erdheim-Chester Disease – primary in adult o Juvenile xanthogranuloma (JXG) – occur in children and adult
II Macrophage/monocytoid disorder	• Rosai-Dorfman Disease • Hemophagocytic lymphohistiocytosis (HLH) o Primary HLH – genetic disorder o Secondary HLH- infectious associated hemophagocytic syndrome (IAHS)
III Malignant disorder	• Malignant histiocytosis (histiocytic sarcoma) • Monocytic/myelomonocytic leukemias

Adapted from http://www.cancer.gov/cancertopics/pdq/treatment/lchistio/HealthProfessional

Langerhans Cell Histiocytosis

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

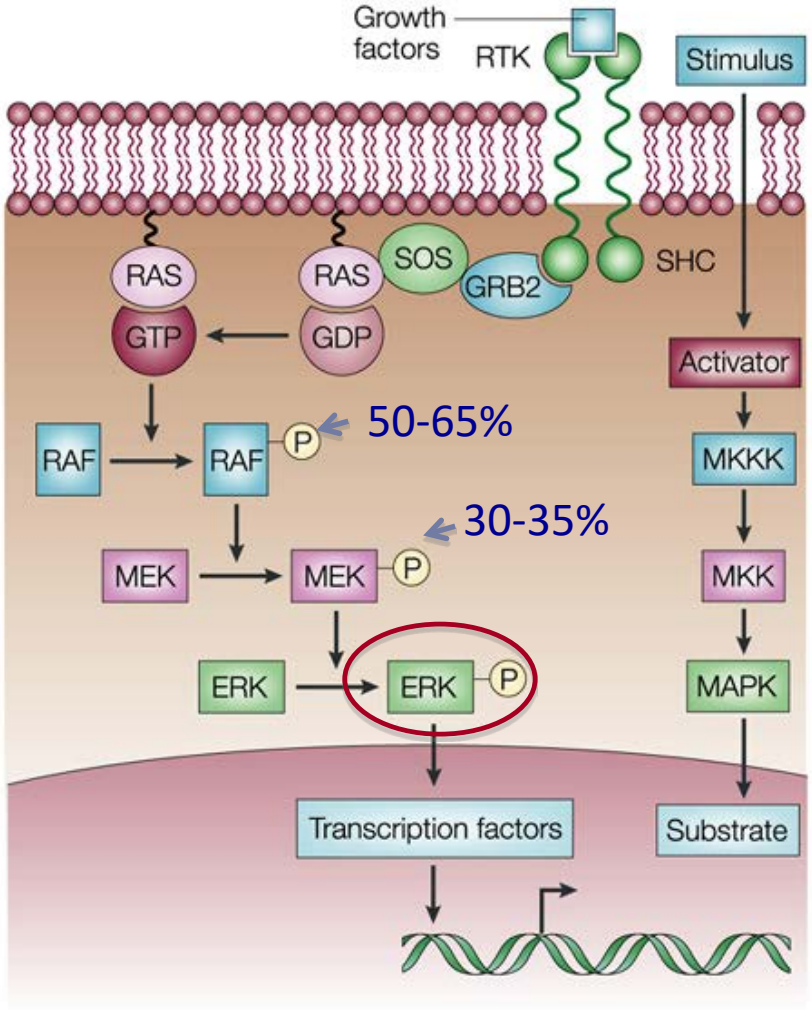
Eosinophilic Granuloma
Skin Disease
Poliostotic Bone Disease
Hand-Schuler-Christian
Multi-systemic Disease
Letterer-Siwe

Biology

- Inflammatory response *vs.* Oncogenic event ???
- Originate from a myeloid-derived precursor
- Uncontrolled clonal periforation of CD1a+/CD207+ cells
- Activation of the MAPK/ERK signaling pathway
  - 60-70% somatic mutation in BRAF (BRAFV600E)
  - 10-25% Others
    - Mutation in MAP2K1
    - Mutation in ARAF
  - ¼ Unknown

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

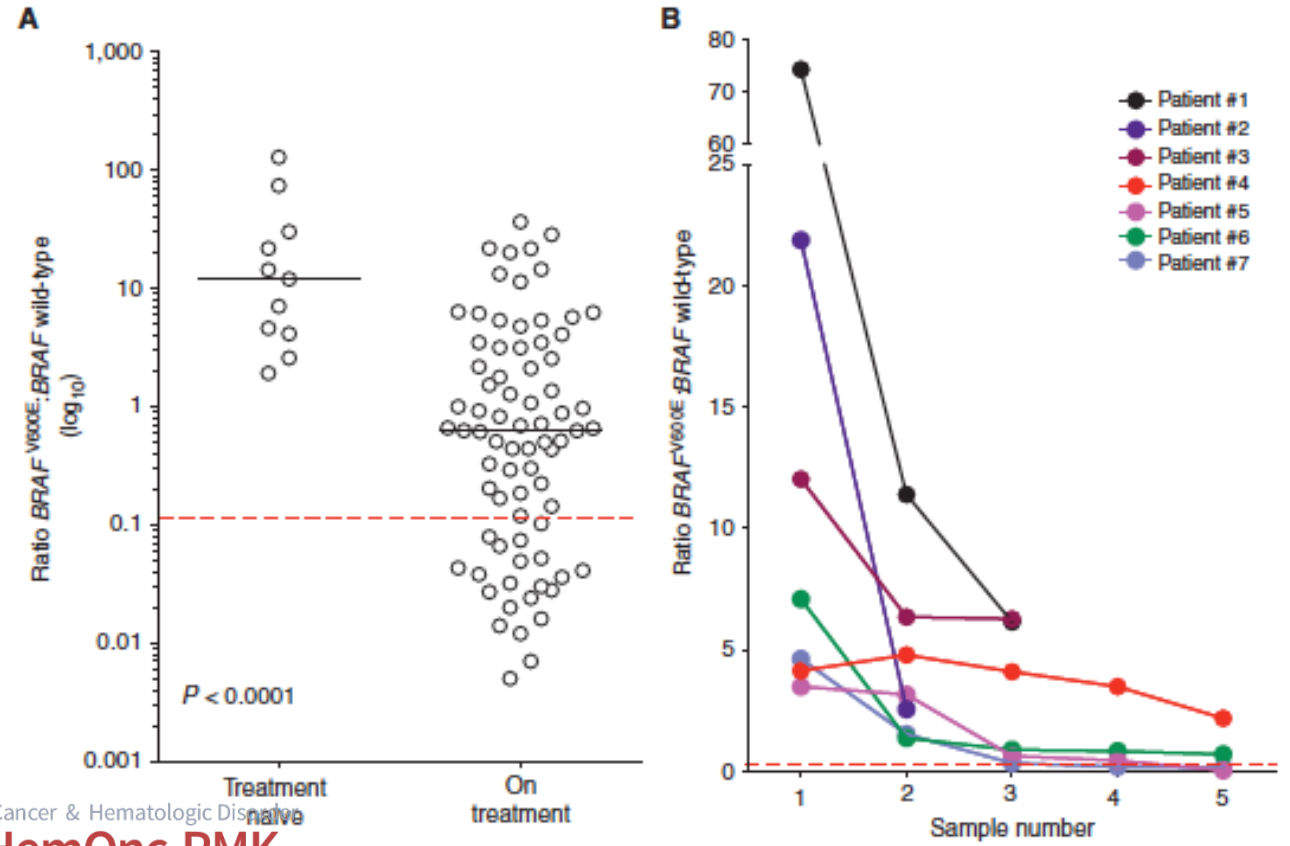
RAS-RAF-MEK-ERK Signaling



Chin et al, Nat Rev Cancer 2003; 559

Prospective Blinded Study of *BRAF*^{V600E} Mutation Detection in Cell-Free DNA of Patients with Systemic Histiocytic Disorders

David M. Hyman[1], Eli L. Diamond[2], Cecile Rose T. Vibat[3], Latifa Hassaine[3], Jason C. Poole[3], Minal Patel[4], Veronica R. Holley[5], Goran Cabrilo[5], Timothy T. Lu[3], Maria E. Arcila[6], Young Rock Chung[7], Raajit Rampal[4], Mario E. Lacouture[8], Neal Rosen[9], Funda Meric-Bernstam[5], José Baselga[1,7], Razelle Kurzrock[10], Mark G. Erlander[3], Filip Janku[5], and Omar Abdel-Wahab[4,7]

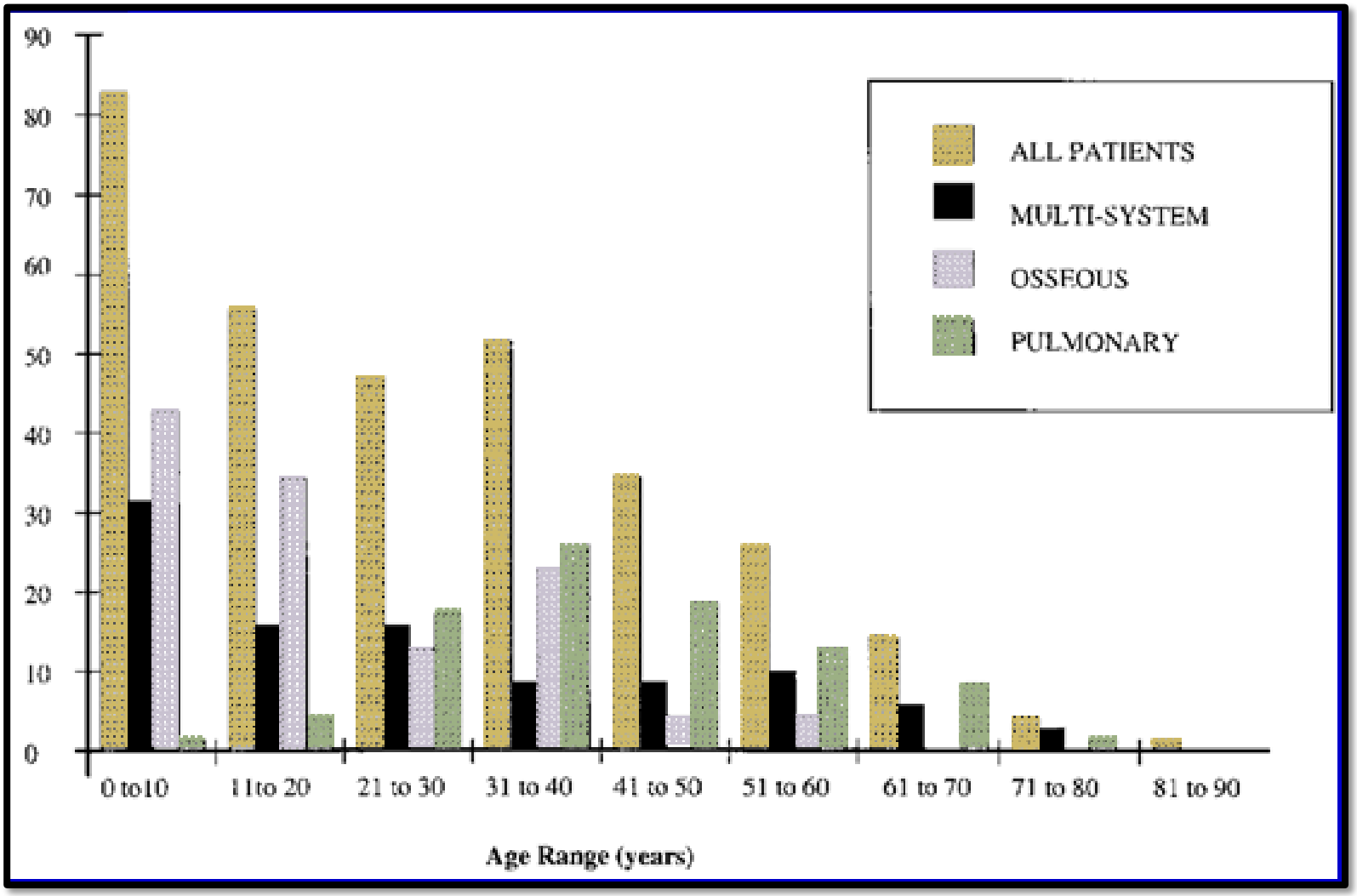


Hyman et al., Cancer Discov 2015; 5: 64-71

Epidemiology of LCH

- Rare
- 8-9 cases per million/year in children
  - Same in adults
- 1/10th the incidence of childhood leukemia
- Male:Female ratio is 1:1
- Median age presentation is 30 months
- Patients may present from birth to the 9th decade

Age distribution of LCH patients



Pediatric Cancer & Hematologic Disorder
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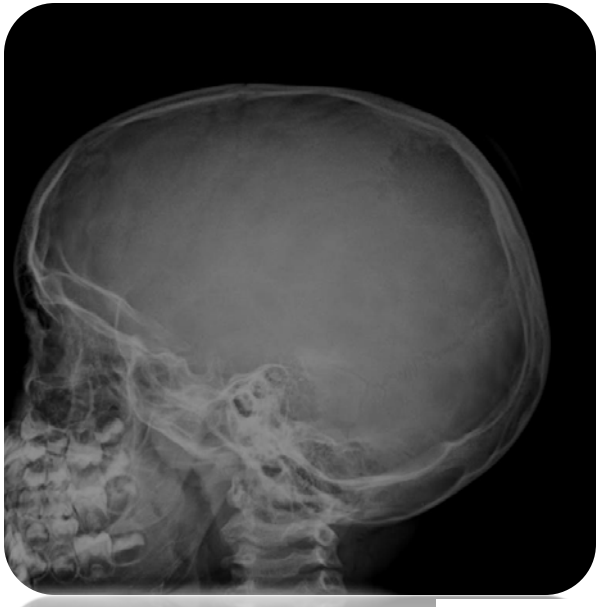
Howarth et al., Cancer 1999; 85: 2278-90

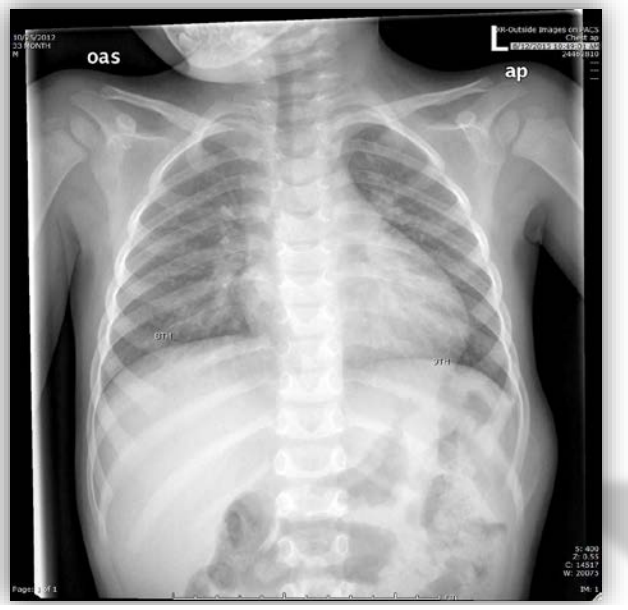
Epidemiology of LCH

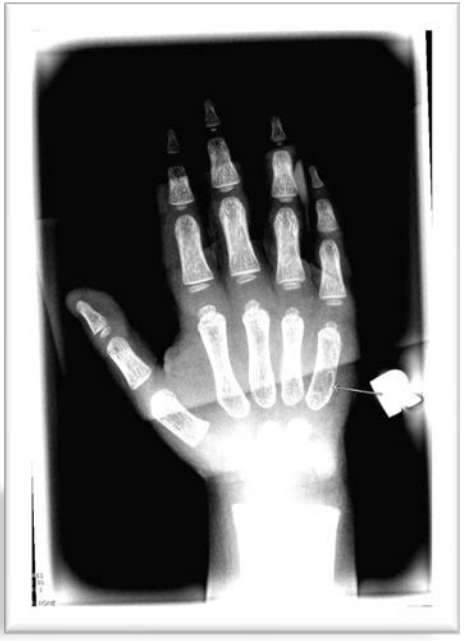
Points for Consideration

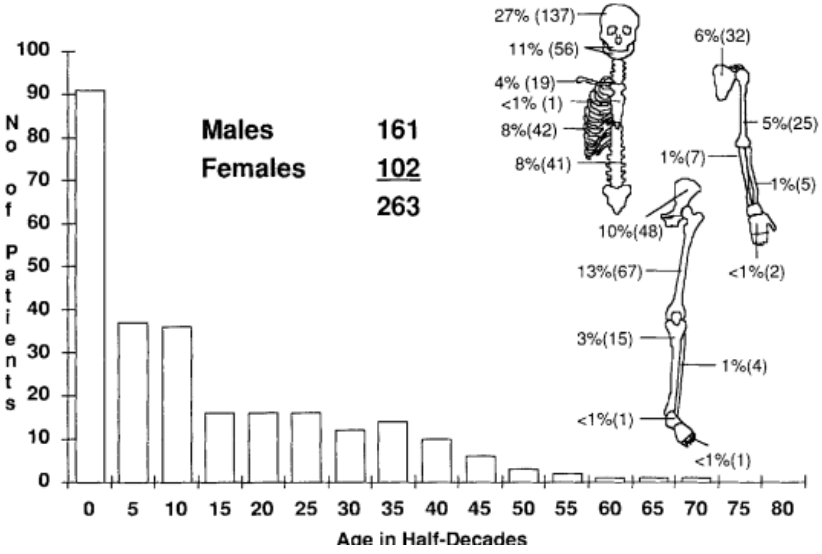
- Population-based studies may be used to describe patterns of incidence
  - Higher incidence in first year, with rapid decline and plateau
  - Significantly higher incidence in Hispanics and lower in Blacks (infants)
  - Higher incidence associated with socioeconomic exclusion (education and crowding)
- Some of these findings may provide clues to causation and deserve further evaluation (epidemiology + genomics)
- <u>Given age distribution, perinatal and early life exposures should be explored</u>

Organ system involvement in LCH



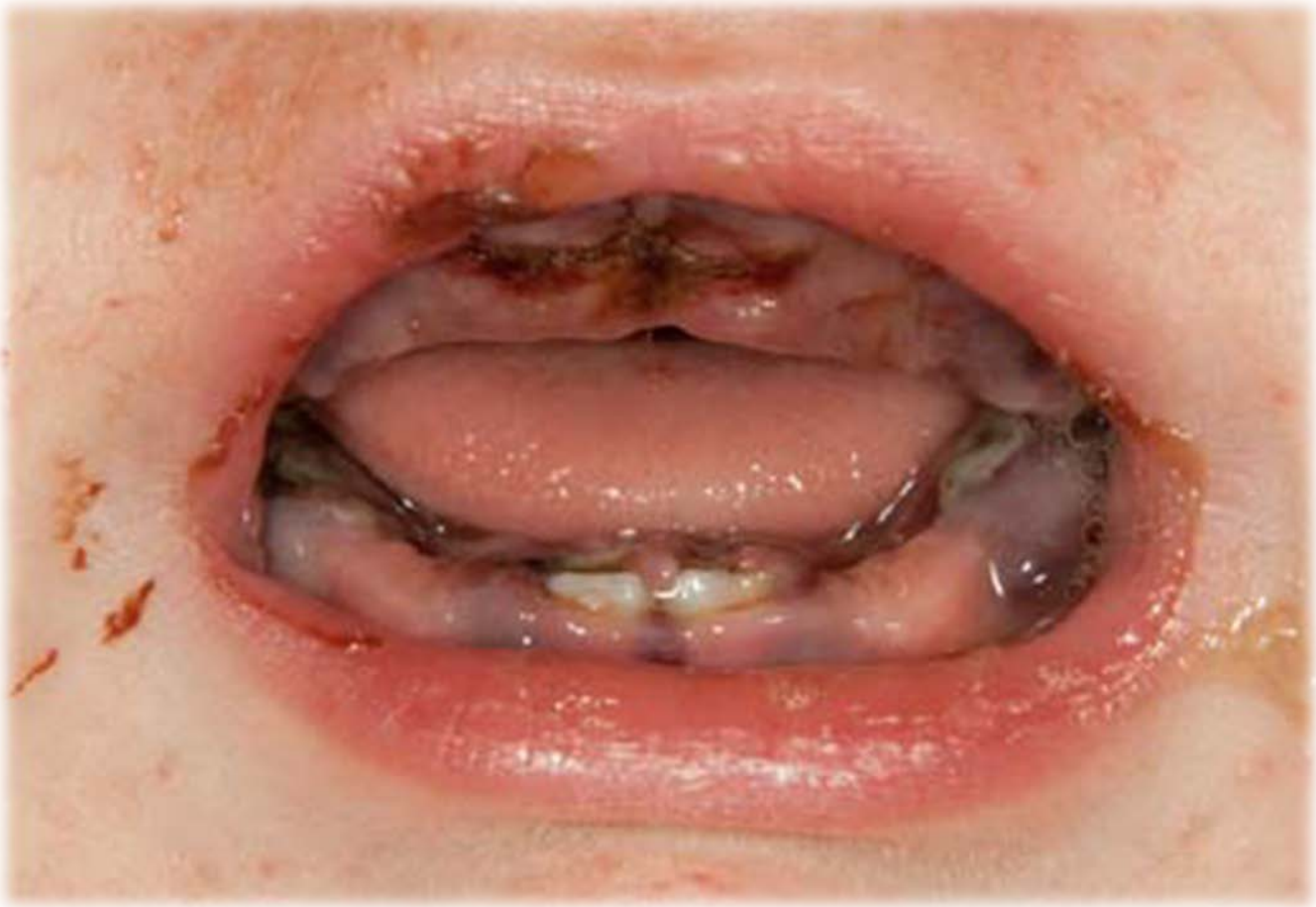






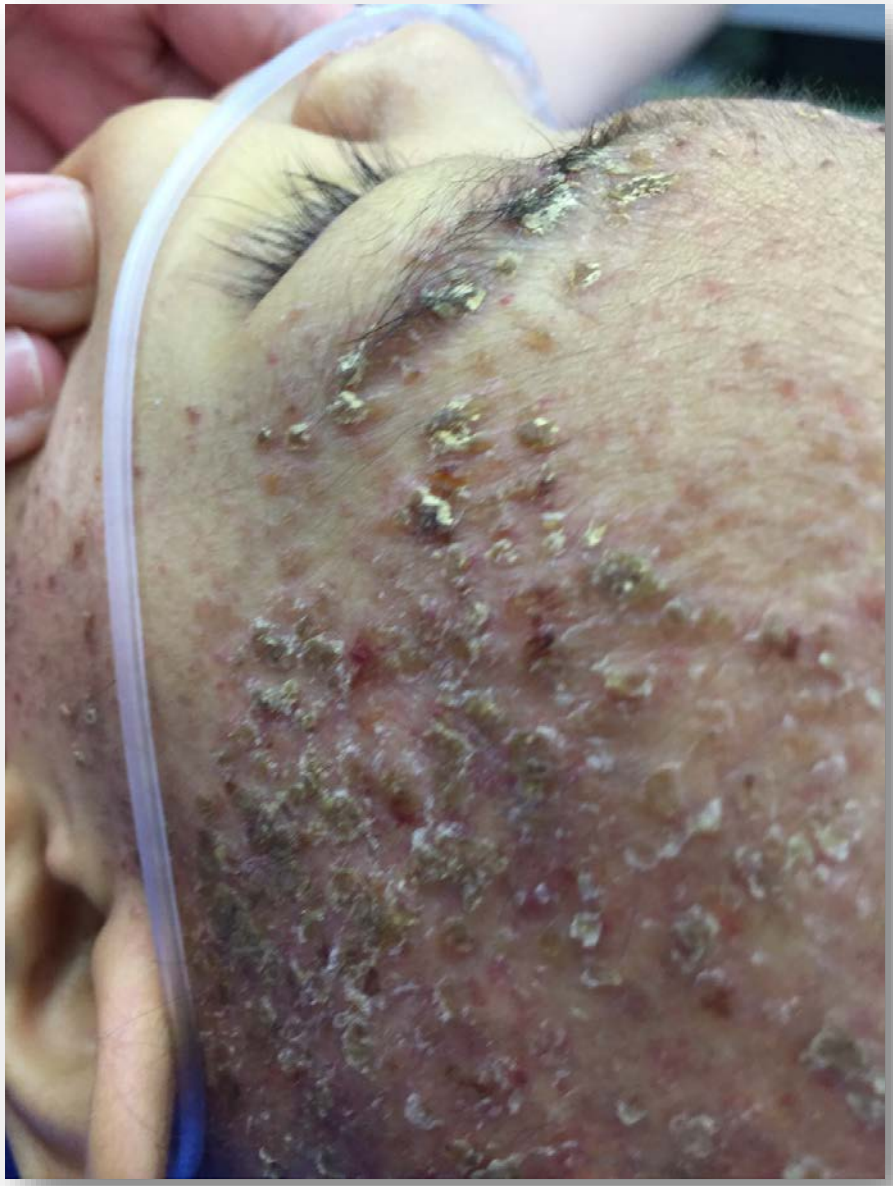
Kilpatrick et al., Cancer 2006

Organ system involvement in LCH



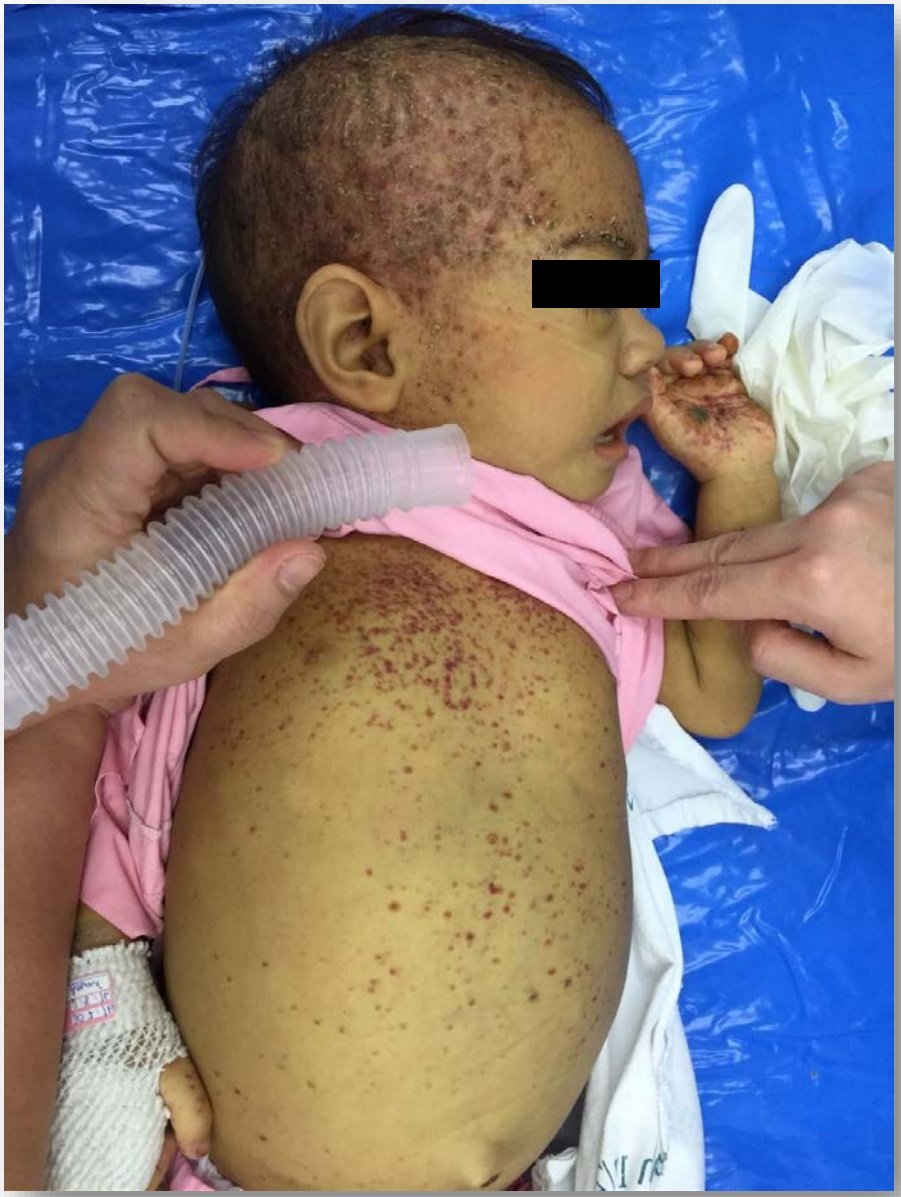
Floating teeth

Organ system involvement in LCH



Parental permission for educational propose only

Organ system involvement in LCH



Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

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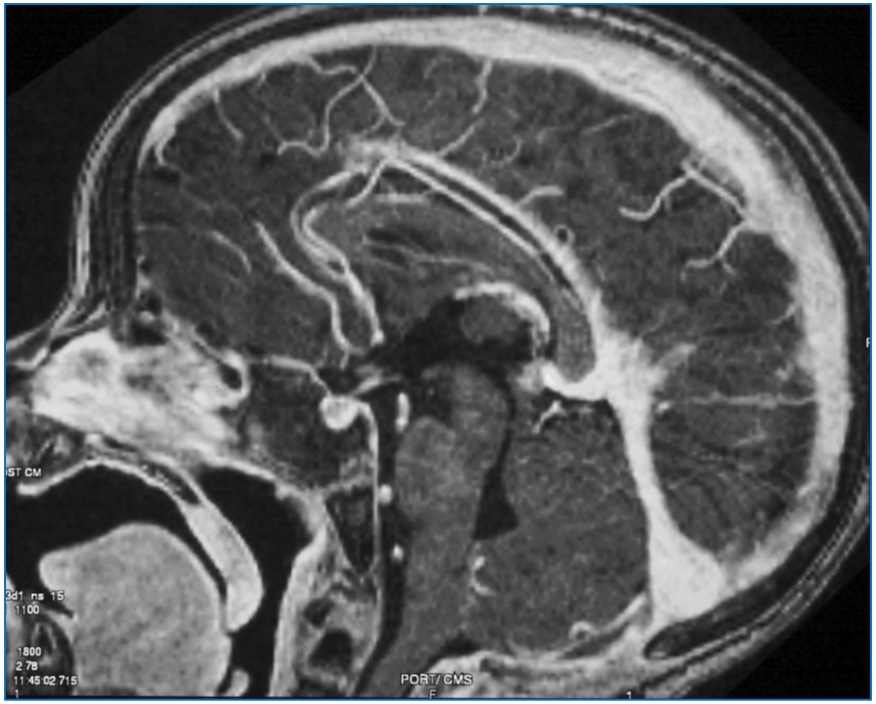
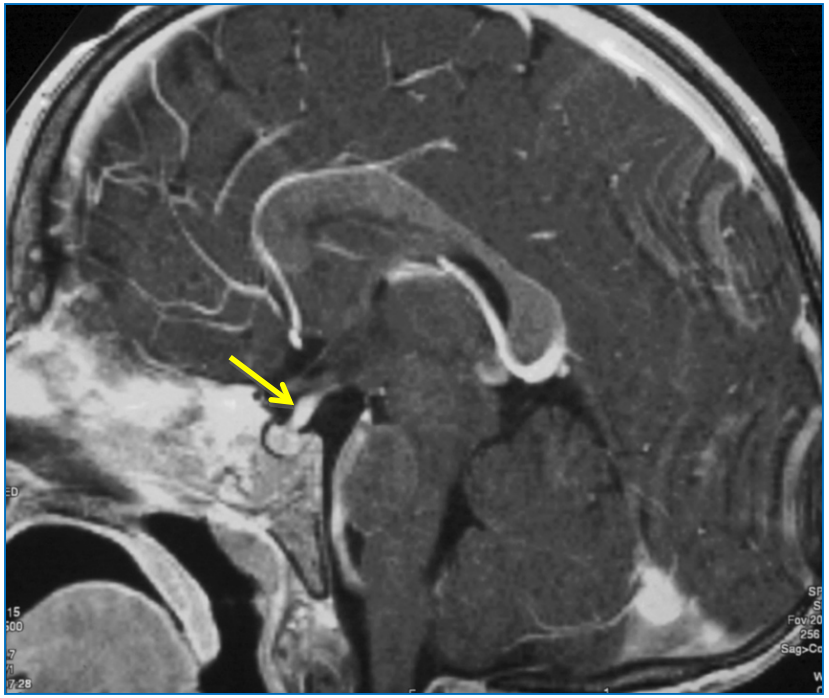
Organ system involvement in LCH

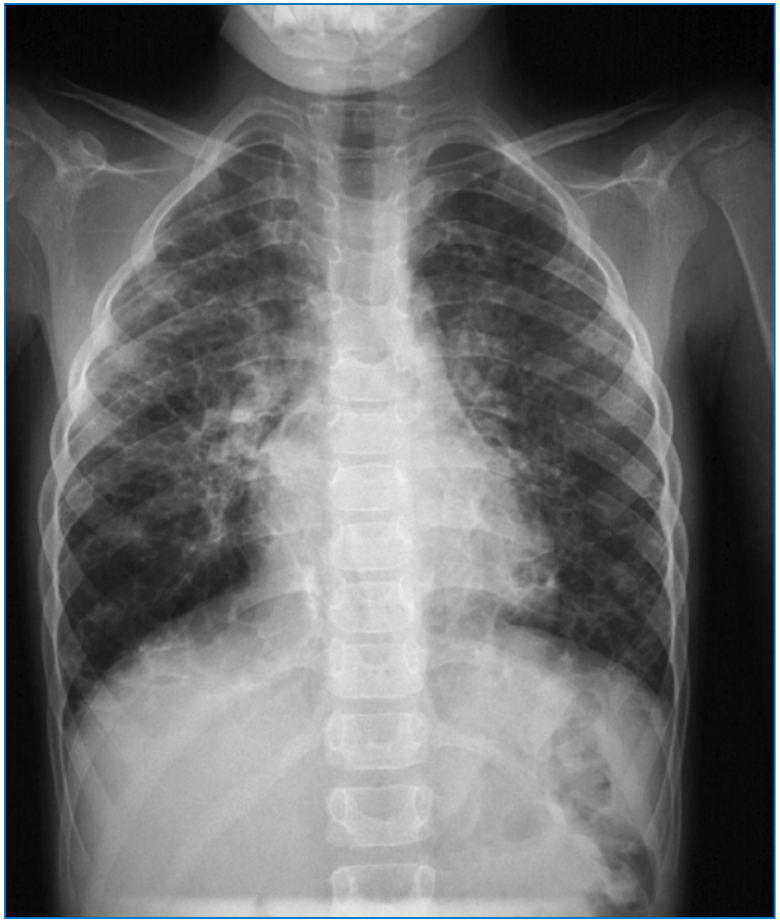


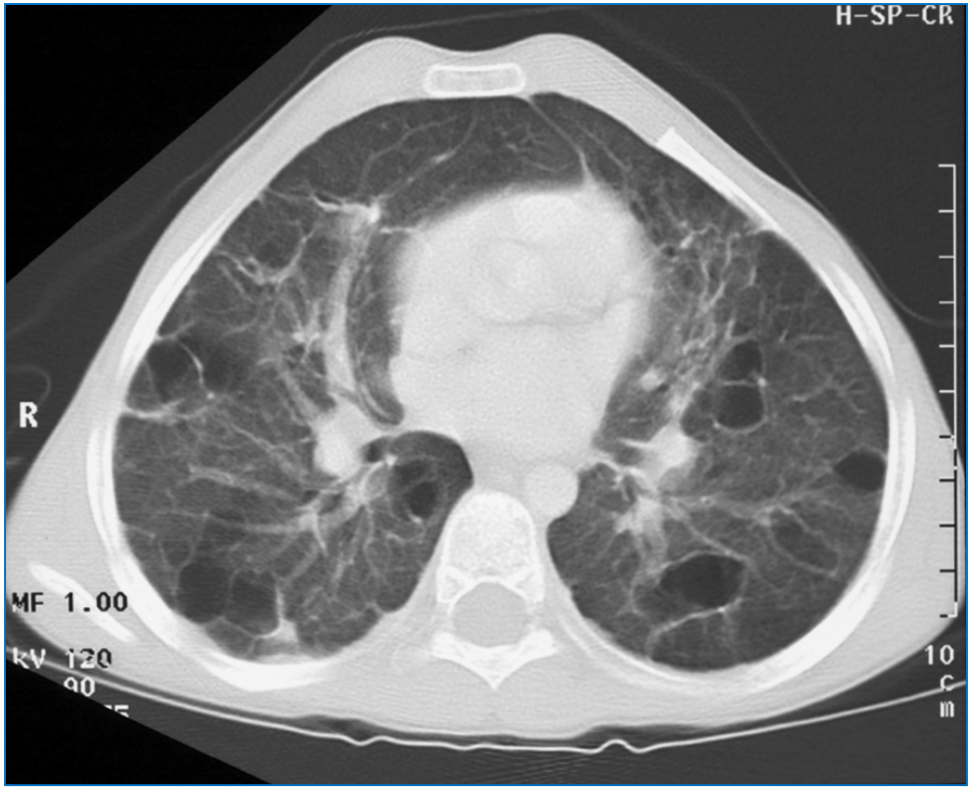


Neuro-Endocrine Involvement

- DI:
  - MCM symptom of CNS involvement
  - Before, during, after (median 10-12 months)
  - Skull lesions and extraosseous disease
  - MRI: absent post pituitary bright signal, thickened infundibulum
  - Unreversible
- Other deficits:
  - GH deficiency > ACTH def > alt puberty
  - Precoccious/delayed puberty
- Neurologic Sequelae:
  - Neuro-degenerative disease
  - Intelectual deficits

Organ system involvement in LCH



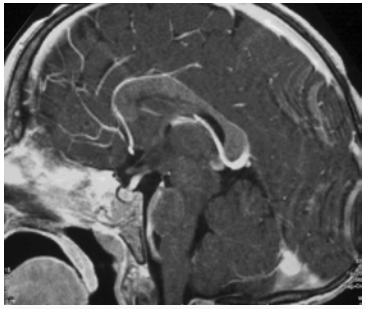


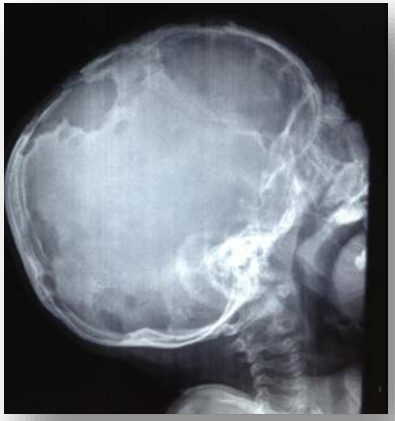
Pulmonary LCH

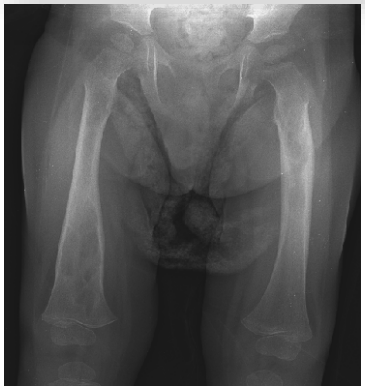
- Incidence and prevalence unknown
  - “15 LCH vs 274 Sarcoidosis”
- Mainly among whites
- 90-95% adults
- 90-95% smokers
- Reticulonodular pattern

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

Organ system involvement in LCH







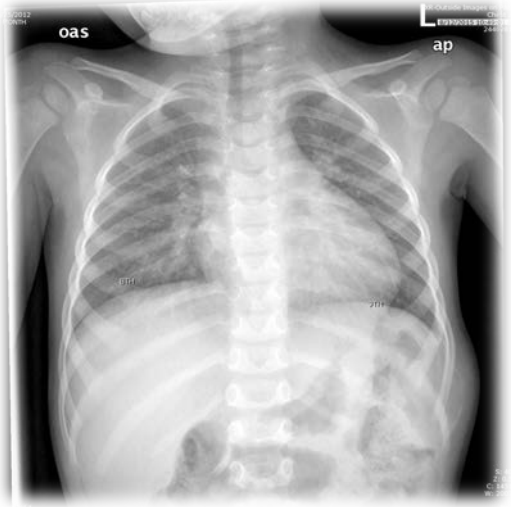
Brain	Neuroendocrine deficits Neurodegeneration
Skull and craniofacial bones	
Chest	Lung disease (infants, smokers) Thymus
Abdomen	Liver Spleen GI tract
Skeleton	Bones
Skin	Cradle cap, seborrhea
Hematopoietic system	pancytopenia, hypersplenism
Lymph nodes	

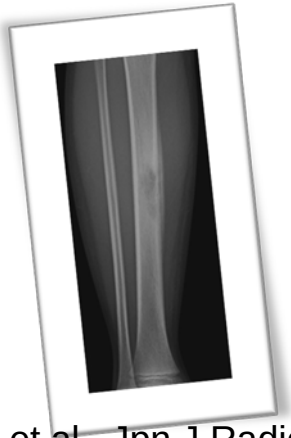
Organ system involvement in LCH

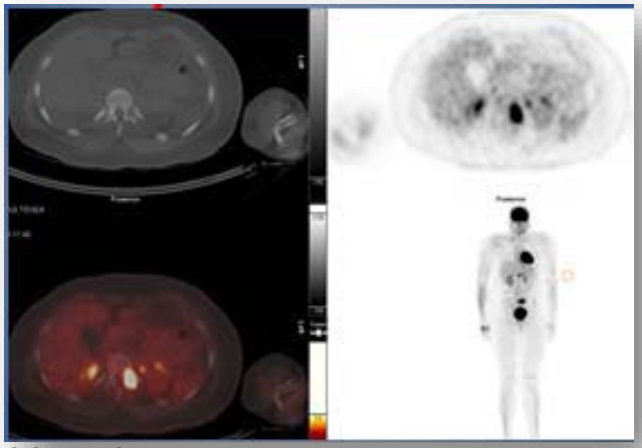
Site	% of cases involved
Bone	80
Skin	60
Liver, spleen, LN	33
Bone marrow	30
Lungs	25
Orbit	25
Orodental	20
Otological	20
DI	15
GI tract	<5

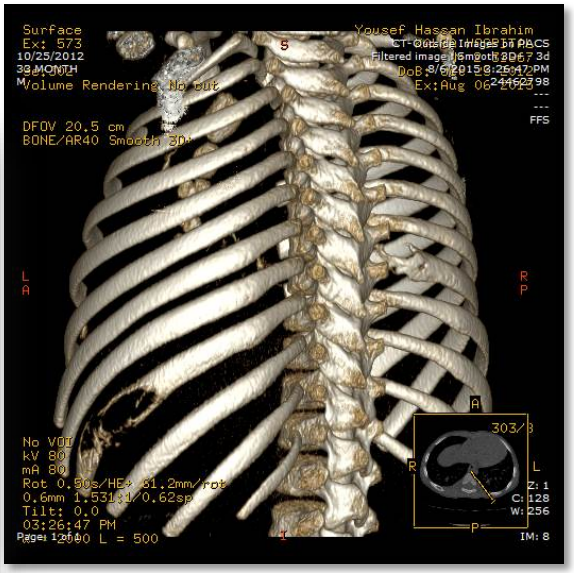
Investigations

- 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





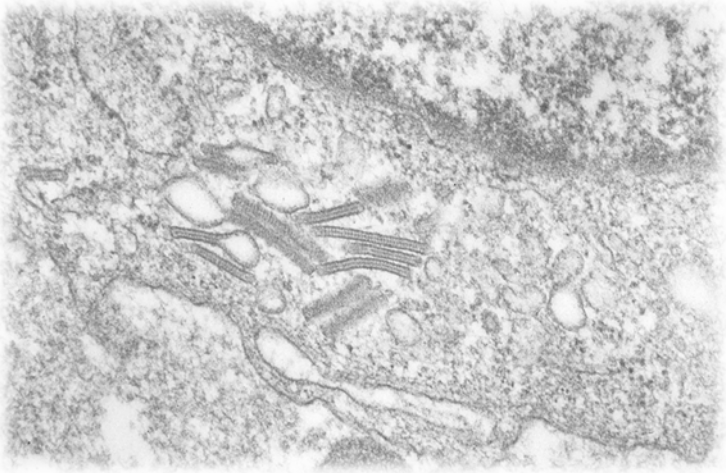


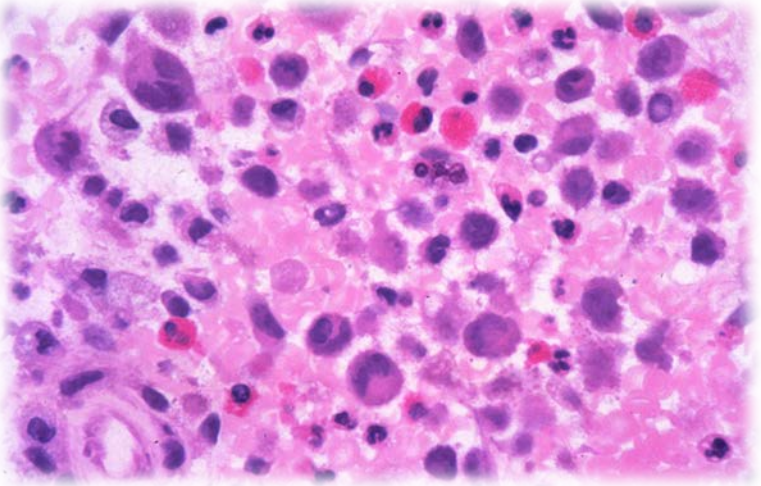


*Agarwal et al., Jpn J Radiol; 2016, 34:267–76

Diagnostic Histopathology

- Uniform regardless of clinical severity:
  - Diagnosis:
    - CD1a, Langerin (CD 207), S-100
    - EM: Birbeck granules





Criteria diagnosis

- Presumptive diagnosis: LM characteristics compatible
- Designated diagnosis
  - LM plus
  - ≥2 supplemental positive stains for
    - Adenosine triphosphatase
    - S-100 protein
    - α-D-Mannosidase
    - Peanut lectin

- Definitive diagnosis
  - LM plus
  - Birbeck granules in the lesional cell by EM

    and/or
  - Positive staining of CD1a antigen and/or CD207 (Langerin) staining on the lesional cell

Clinical Classification of LCH patients

- LCH-III (2001-2008)

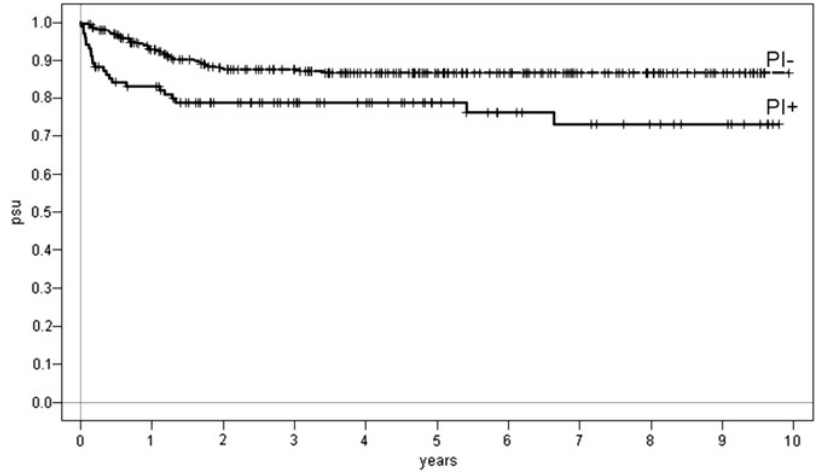
Clinical Group	Involved system	Involved organs
1	Multisystem "*Risk*" patients	Any "Risk*" organ involvement
2	Multisystem "*Low risk*" patients	≥ 2 organ without "Risk*" organ involvement
3	Single system • Multifocal or • Special site#	≥ 2 lesions in one organ or In special site#
-	Single system Unifocal or localized	1 lesion in one organ

*Risk organs consist of *Lung, liver, spleen, bone marrow or haematological* dysfunction

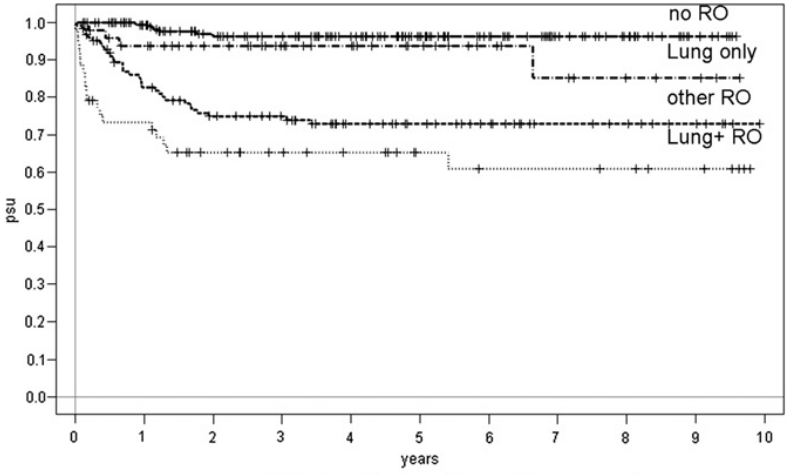
Special site are *intracranial soft tissue extension* or *vertebral lesions with intraspinal soft tissue extension*

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

Clinical Classification of LCH patients

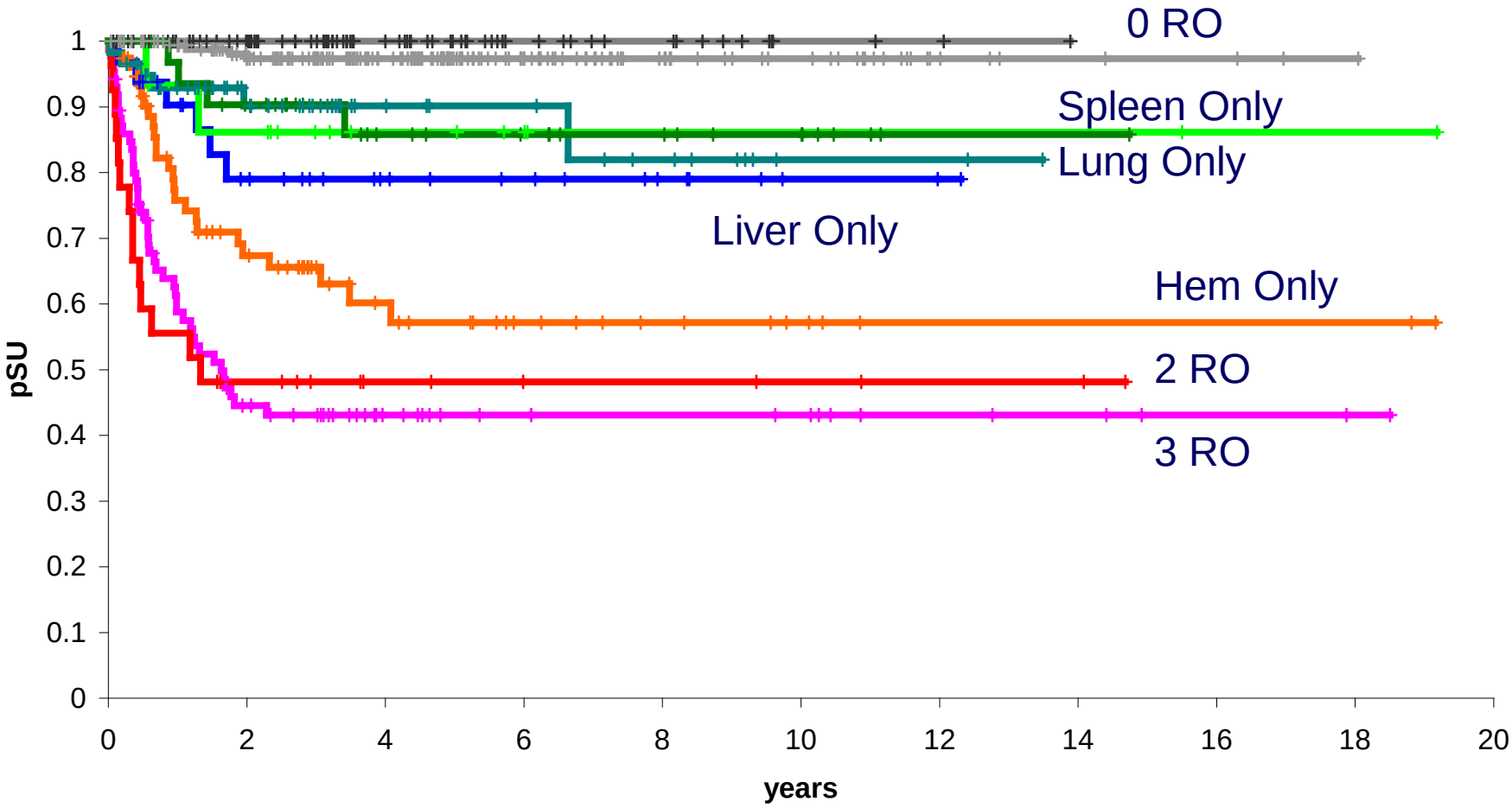
- LCH-IV (2011)

Clinical Classification	Involved System	Involved Organs
Multisystem LCH (MS-LCH) (Group 1)	≥ 2	RO+/- (e.g. hemato, liver, and/or spleen)
Single System LCH (SS-LCH) (Group 2)	1 (UF/MF)	• Bone UF (single bone) or MF (>1 bone) • Skin • LN (excluding draining LN of another LCH lesion) • Lungs • Special site (eg. Vertebrae, spine) • "CNS-risk" • Central nervous system (CNS) • Other (e.g. thyroid, thymus)

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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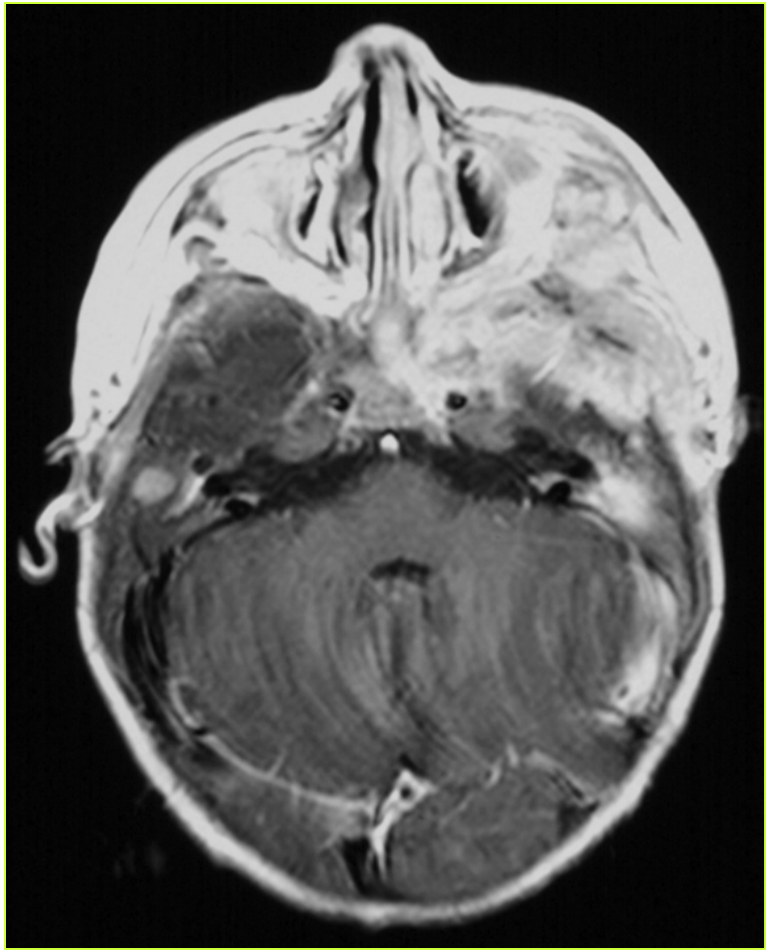
Data from LCH Studies
Provided by Vienna Data Center

CNS-Risk Lesions

Facial bones or Anterior or Medial Cranial Fossa:

- Skull base
- Mastoid
- Temporal
- Maxilla
- Sphenoidal
- Ethmoidal
- Cygomatic bone
- Orbits

With intracranial extension or could not be excised



3 x risk of CNS disease

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

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

HISTIOCYTE SOCIETY

Treatment

Single system (SS)

Bone
or
Skin
or
LN
or
Lung

Unifocal (UF)

Multifocal (MF)
Or
UF-CNS risk/special site

Multisystem (MS)

RO-

RO+

Liver
Spleen
Heme

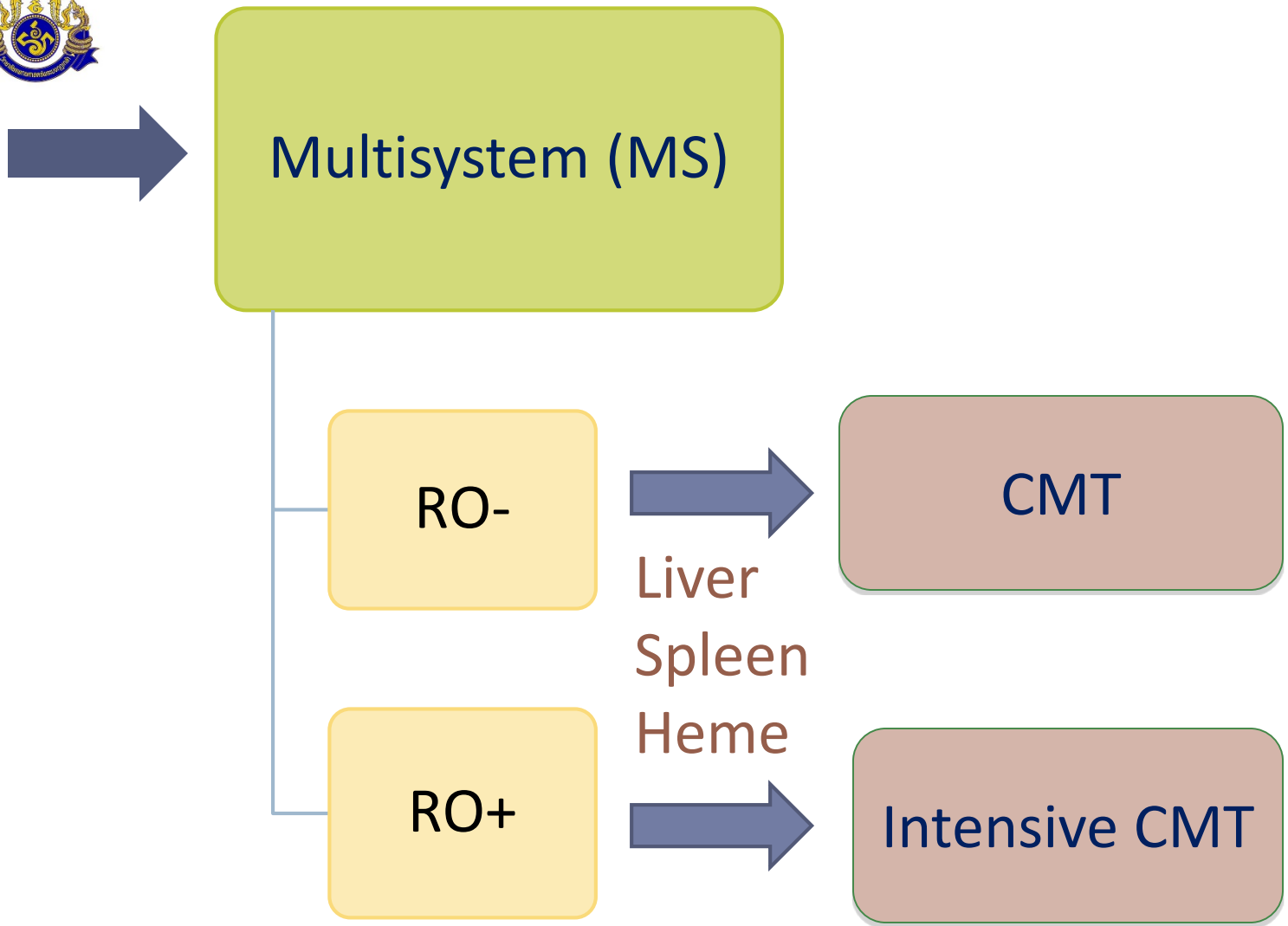
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Single system (SS)

Bone
or
Skin
or
LN
or
Lung

Unifocal (UF) → Observation
Local Therapy

Multifocal (MF)
Or
UF-CNS risk/special site → CMT


Multisystem (MS)
RO-
RO+
Liver
Spleen
Heme
CMT
Intensive CMT

Indications for Systemic Therapy

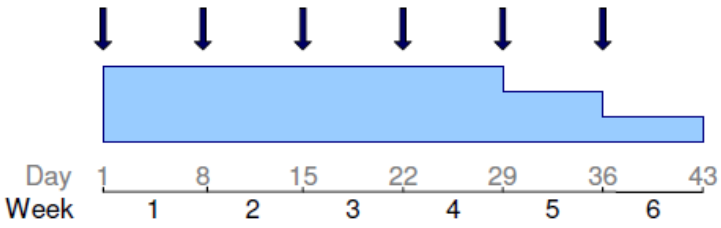
- SS-LCH with
  - CSN-risk lesions
  - Multifocal bone lesions
  - “Special Site” lesions
- MS-LCH with/without involvement of risk organs

Unifocal lesion

- Observe
- ~30% of UF bone lesion develop MFB within 2 years
- If remission → relapse UF bone→ local control or systemic CMT
- Eosinophilic granuloma had PGE overexpression → role for indomethacin
- Local control
  - Biopsy
  - Curettage
  - Excision
  - Intralesional or topical steroid
  - Radiotherapy
  - Options: bisphosphanate, indomethacin, NSAIDS

MF Or UF-CNS risk/special site

Initial Treatment: Course 1

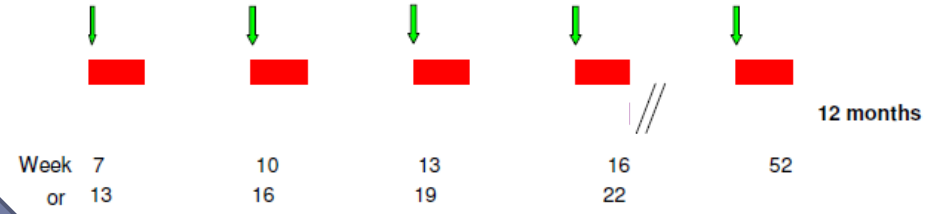


LEGEND:

PRED 40 mg/m²/day orally, weekly reduction after week 4

VBL 6 mg/m² i.v. bolus

Continuation Treatment



LEGEND:

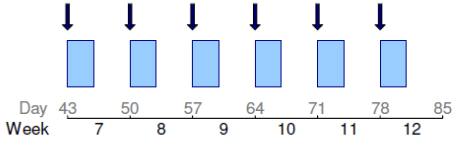
PRED 40 mg/m2/d orally day 1-5 of week (7, 10), 13, 16, 19, ...52

VBL 6 mg/m2/d i.v. bolus q3 weeks

Immediate response or worse

Once systemic CMT applied → no need for surgery

Initial Treatment: Course 2



LEGEND:

PRED 40 mg/m²/day orally, weekly for 3 days i.v. bolus

VBL 6 mg/m² i.v. bolus

Aim: ↓ disease reactivation

No 6-MP

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Histiocyte Society Evaluation and Treatment Guidelines, April 2009 from www.histiocytesociety.org

MS-LCH

History of LCH treatment

LCH-I (1991-1995)

VBL/VP-16 + HD-MP x 6 mo

- Same clinical effectiveness
- High incidence of 2nd malignancy and toxicity in VP-16 group
- "Risk" = Heme, lung, liver spleen and age at Dx <2 y
- Survival related to response to treatment at week 6
- Treatment response at 6th weeks was low compared to historical → need treatment intensification
- Disease reactivation was higher compared to historical → need prolongation of treatment

Gadner et al., J Pediatr 2001; 138: 728-34
Minkov et al., Klin Padiatr 2000; 212: 139-144
Minkov et al., Med Pediatr Oncol 2002; 39: 581-5

MS-LCH
History of LCH treatment

LCH-II (1996-2001)

Induction: VBL+PRED+VP-16 x 6 wk

Continuation: PRED+VBL+6-MP±VP-16 x 6 mo

- Intensive Rx upfront (3 drugs) esp. VP-16 improve outcome???
- No significant improvement of overall response, survival and disease reactivation
- RO+ had significant improvement
- Age at Dx < 2y was not independent RF

Gadner et al., Blood 2008; 111: 2556-62

MS-LCH

History of LCH treatment

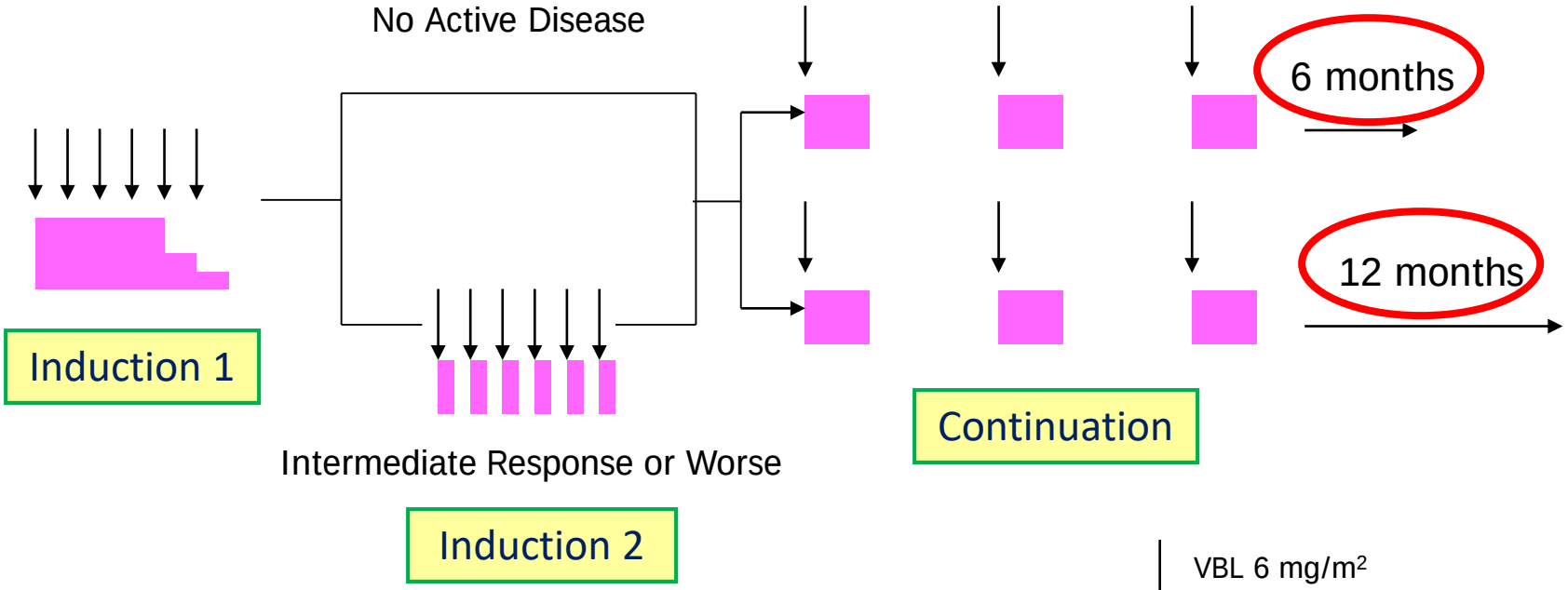
LCH-III (2001-2008)

- Upfront 2 drugs – no VP-16
- Age of Dx < 2y was removed from RF
- Treatment intensity tailored by RO+/-

LCH III for MS LCH

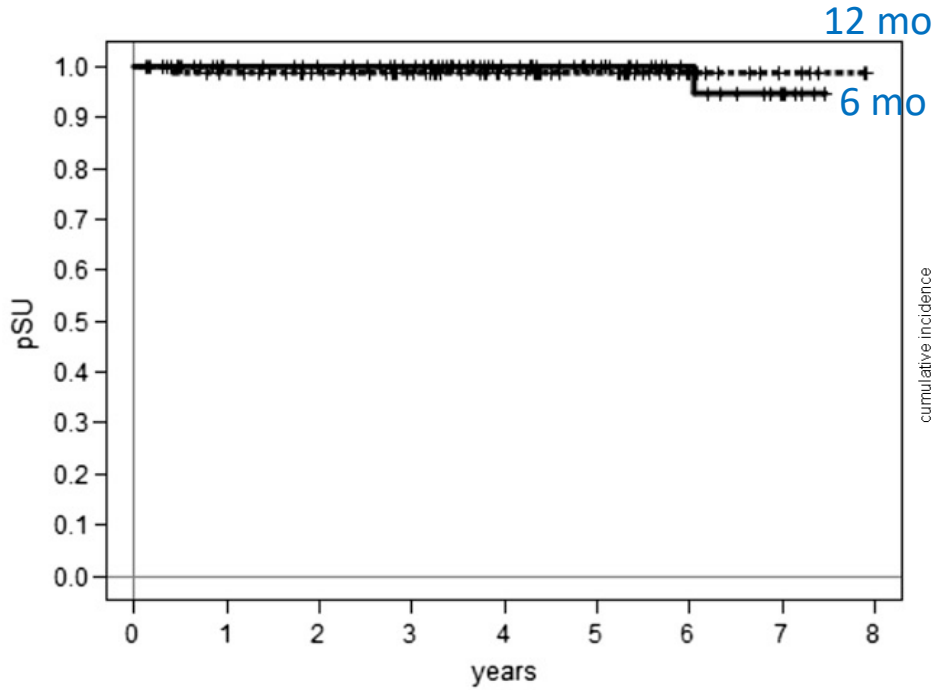
- Group 2: Low-risk patients
  - Survival ~100%
  - *The Problem:* Reactivations
  - The Question: Does prolongation of therapy decrease reactivation rates?
  - Treatment:
    - PRD+VBL
    - Randomization: continuation 6 vs 12 months

LCH-III Protocol for Group 2: MS-Low Risk Patients

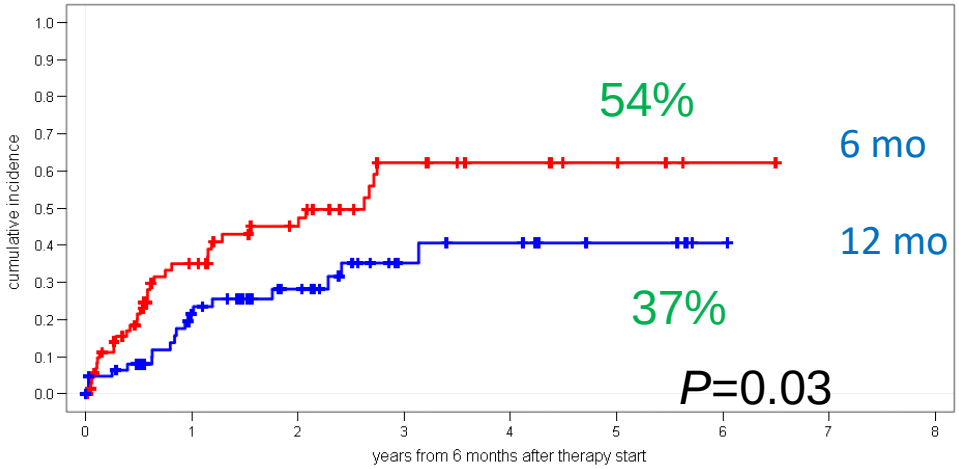


Therapy prolongation improves outcome in RO- MS LCH

- Survival



- Reactivations



Benefit in decreased disease reactivation in prolongation of therapy

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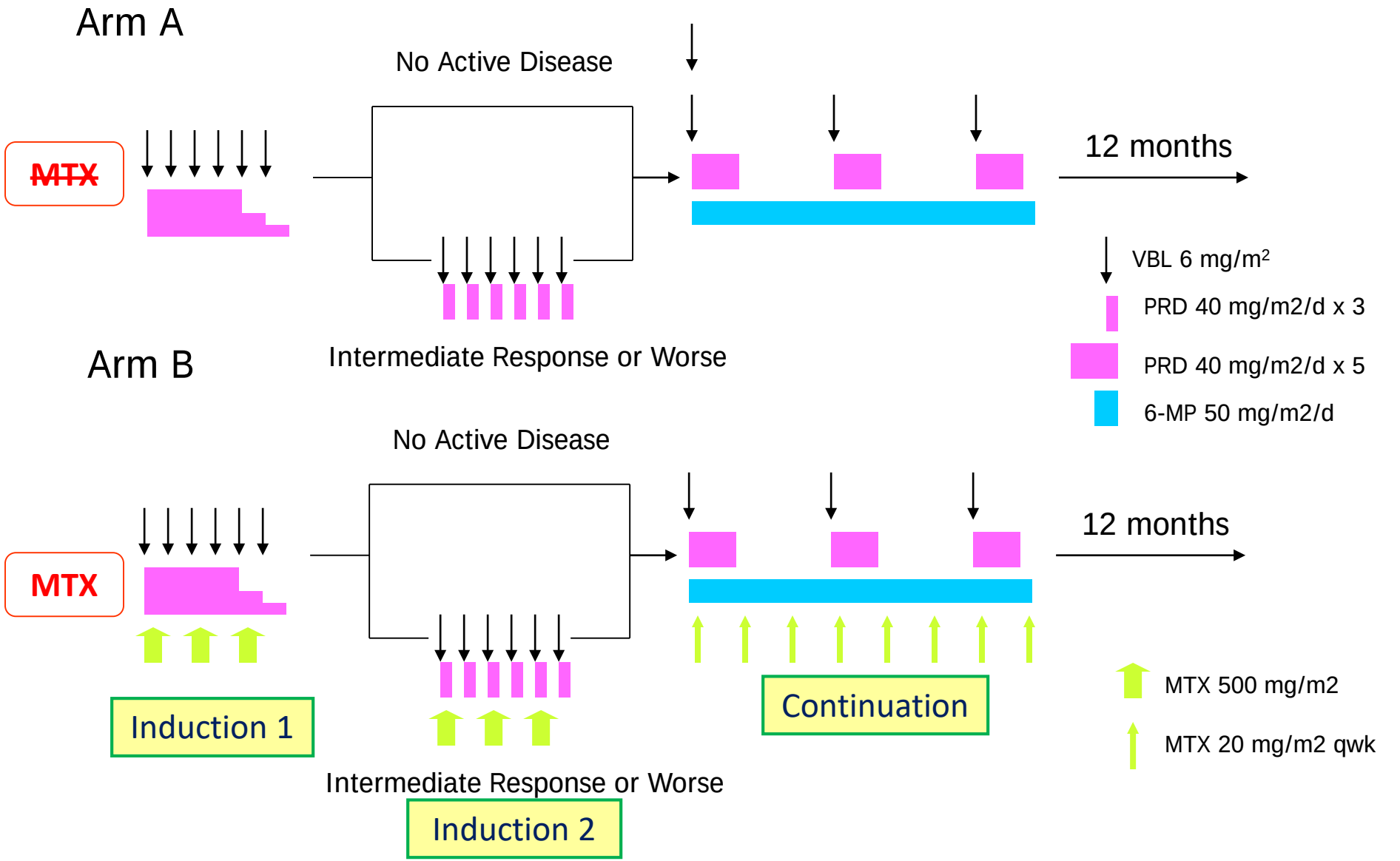
Gadner et al., Blood 2013; 121: 5006-14

LCH III for MS LCH

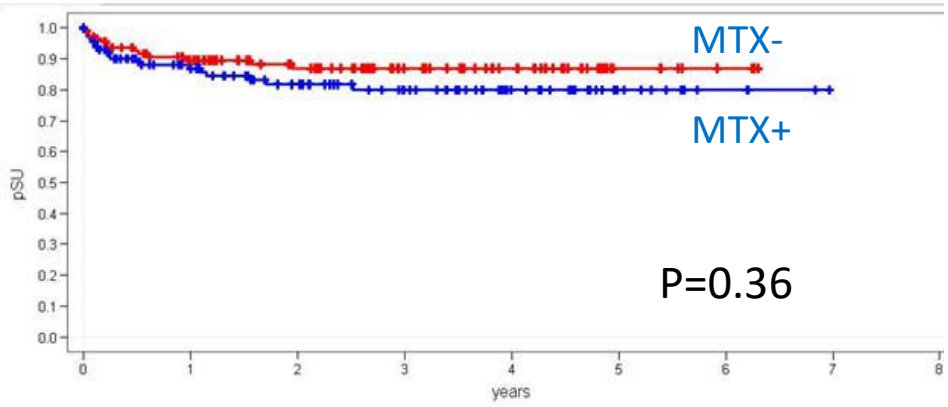
- Group 1: “Risk” patients
  - *The Problem:* Survival
  - The Question: Does the addition of MTX improve survival?
  - Treatment:
    - Randomization PRD+VBL+6-MP +/- MTX
    - Duration: 12 months

LCH-III Protocol for Group 2: MS-"Risk" Patients



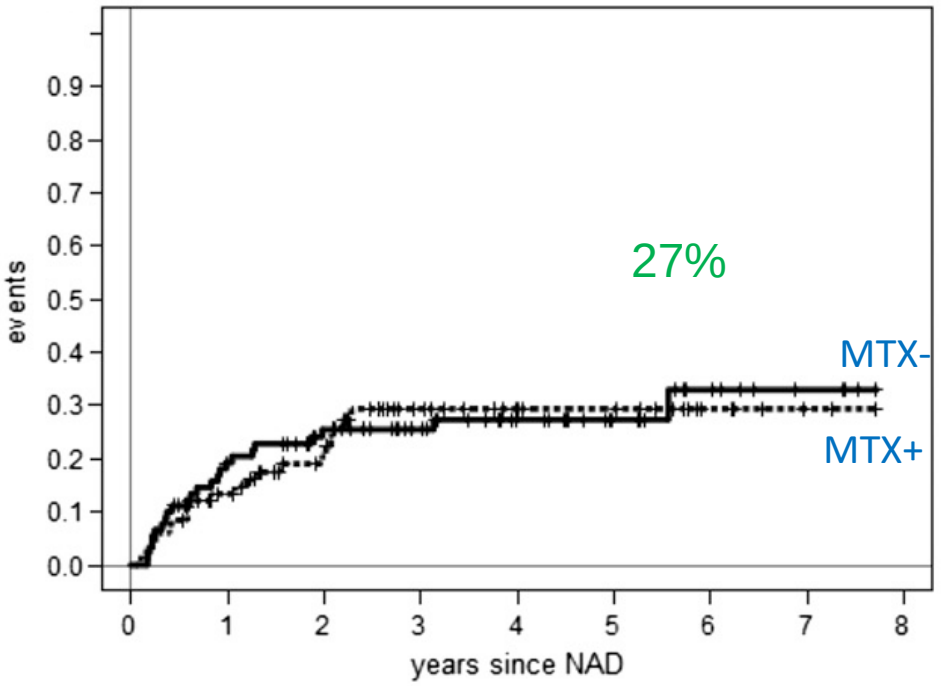
Addition MTX in RO+MS LCH

- 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

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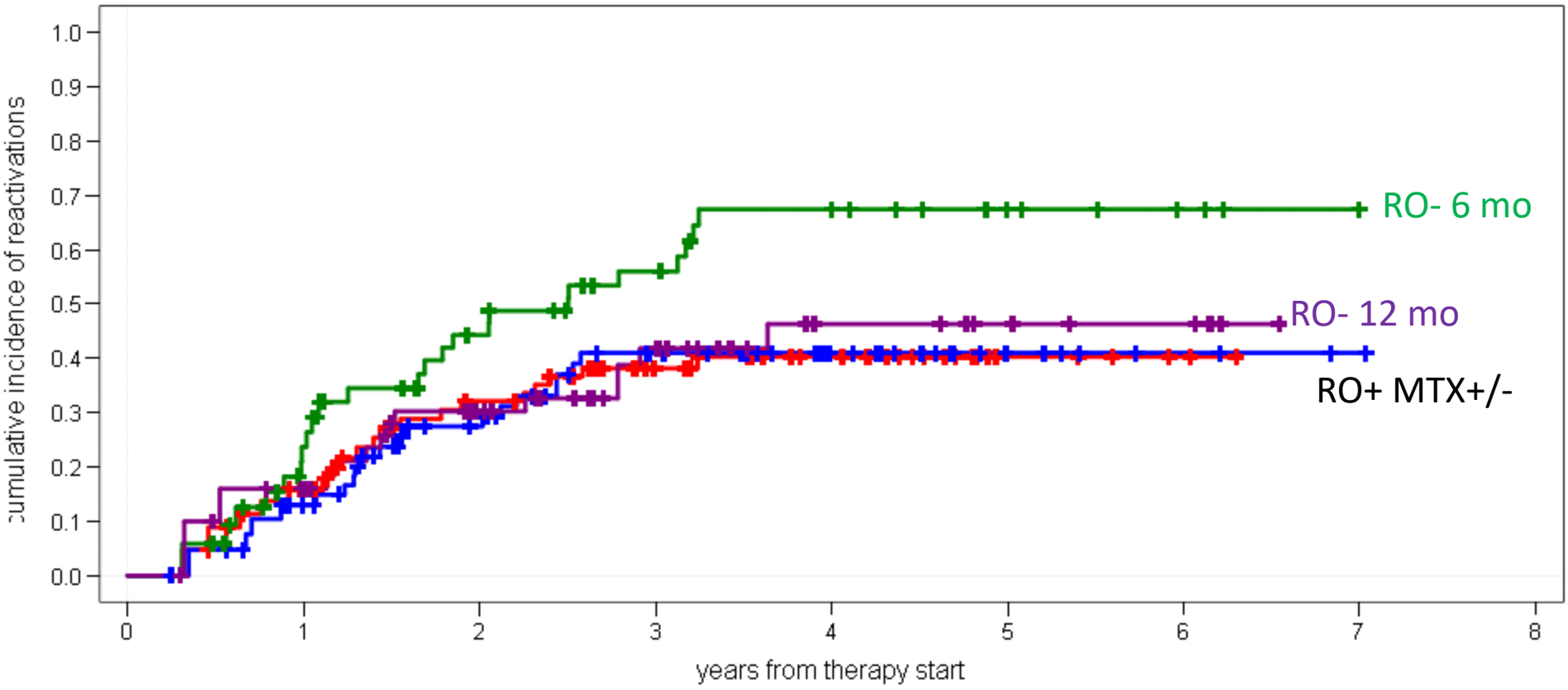
Gadner et al., Blood 2013; 121: 5006-14

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

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

Current study: LCH IV for SS-, MS-LCH

- Opened: 2011

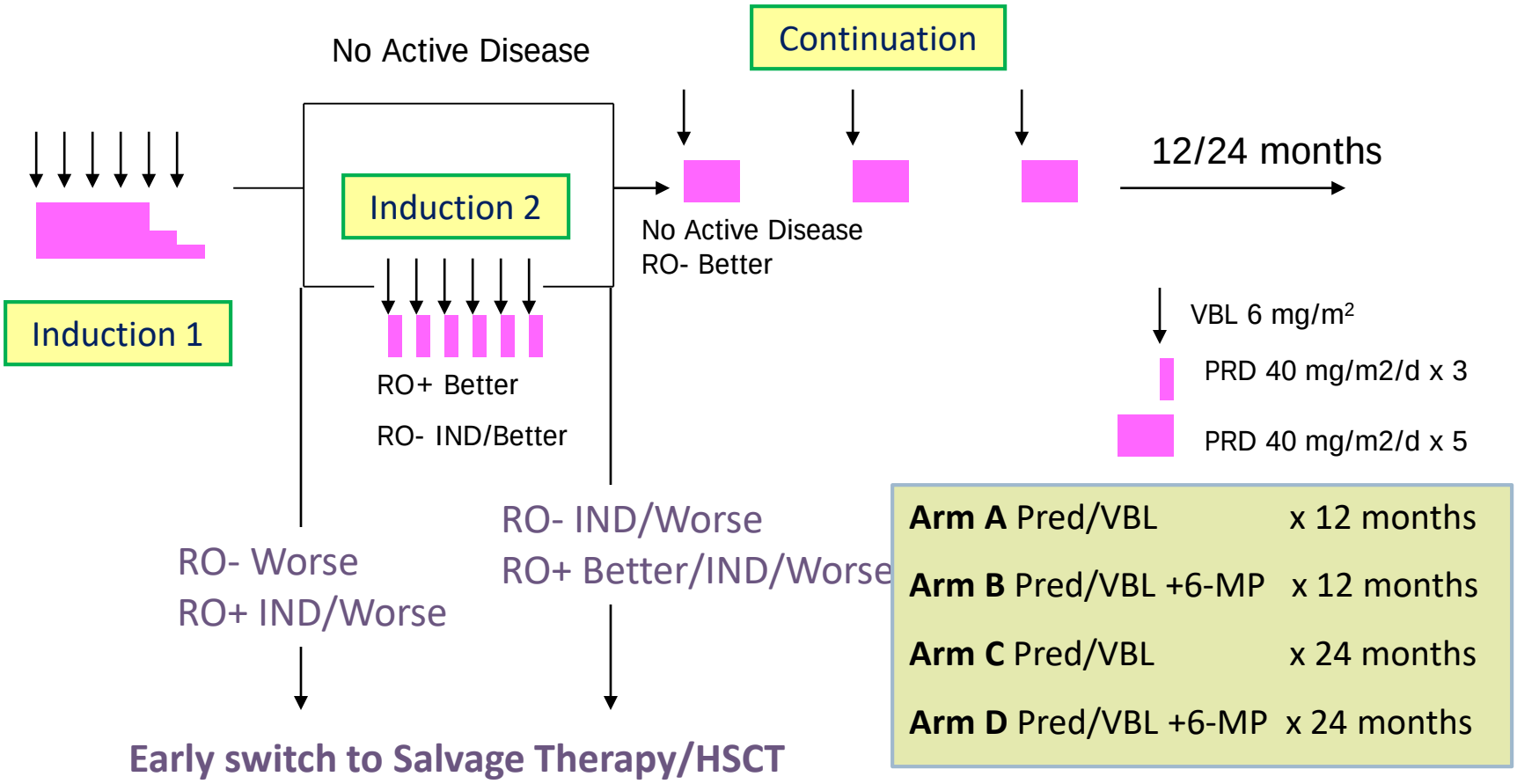
Clinical Classification	Involved System	Involved Organs
Multisystem LCH (MS-LCH) (Group 1)	≥ 2	RO+/- (e.g. hemato, liver, and/or spleen)
Single System LCH (SS-LCH) (Group 2)	1 (UF/MF)	• Bone UF (single bone) or MF (>1 bone) • Skin • LN (excluding draining LN of another LCH lesion) • Lungs • Special site (eg. Vertebrae, spine) • "CNS-risk" • Central nervous system (CNS) • Other (e.g. thyroid, thymus)

Current study: LCH IV for MS 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

LCH-IV – Stratum I front line therapy

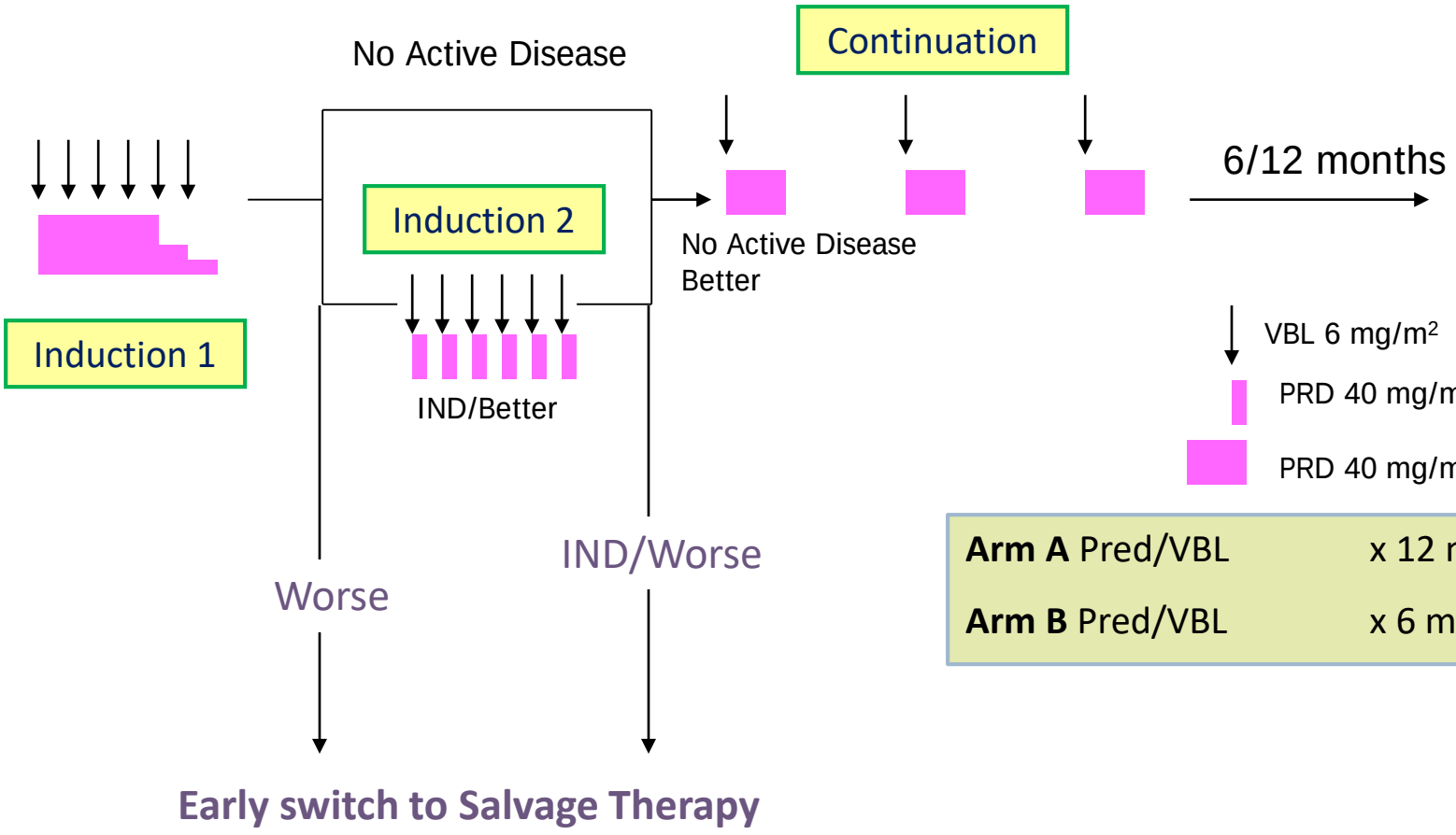
Group 1-Multi-System LCH



Arm A Pred/VBL	x 12 months
Arm B Pred/VBL +6-MP	x 12 months
Arm C Pred/VBL	x 24 months
Arm D Pred/VBL +6-MP	x 24 months

LCH-IV – Stratum I front line therapy

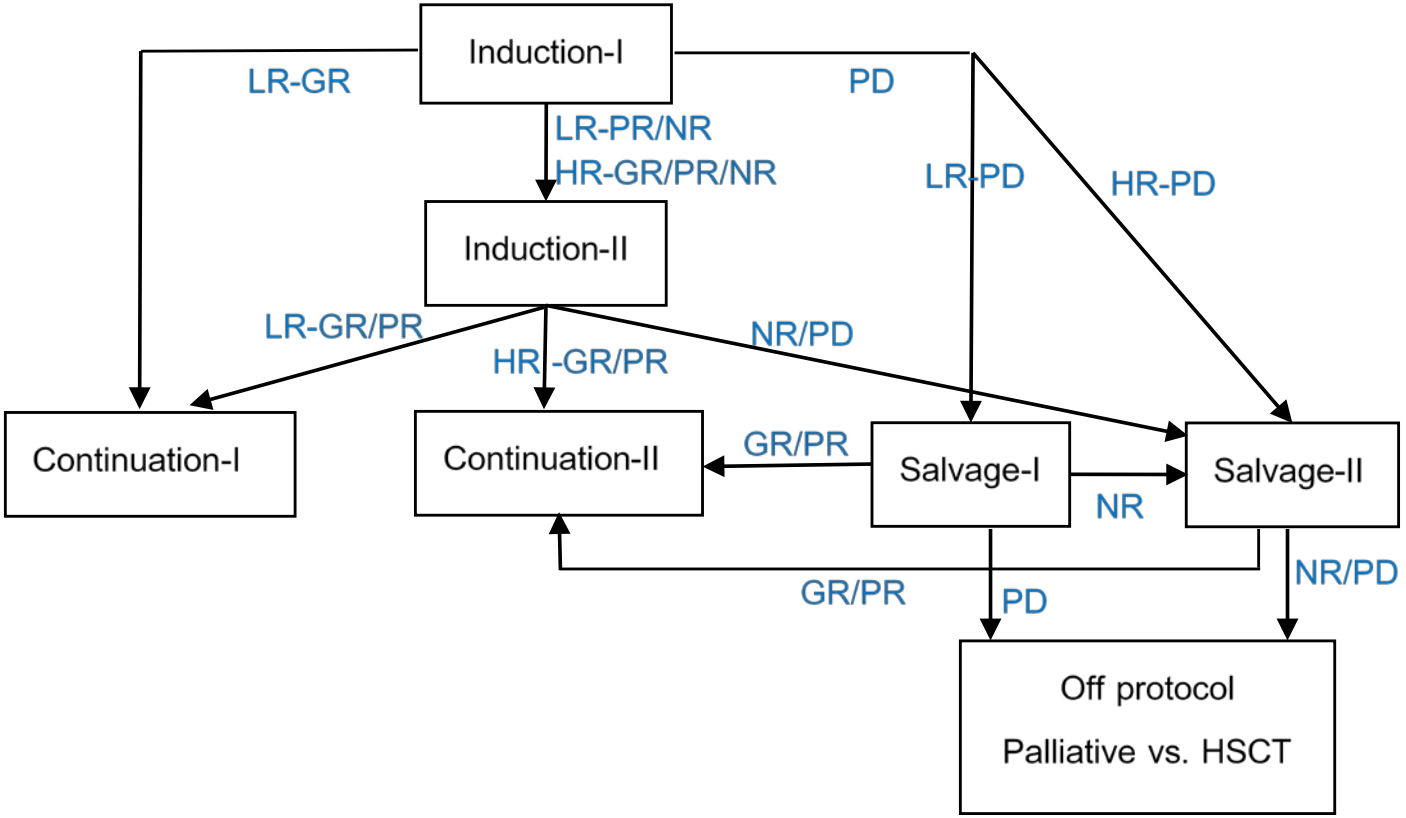
Group II-Single-System LCH



Arm A Pred/VBL	x 12 months
Arm B Pred/VBL	x 6 months

THAI POG
Thai Pediatric Oncology Group

LCH treatment Guideline



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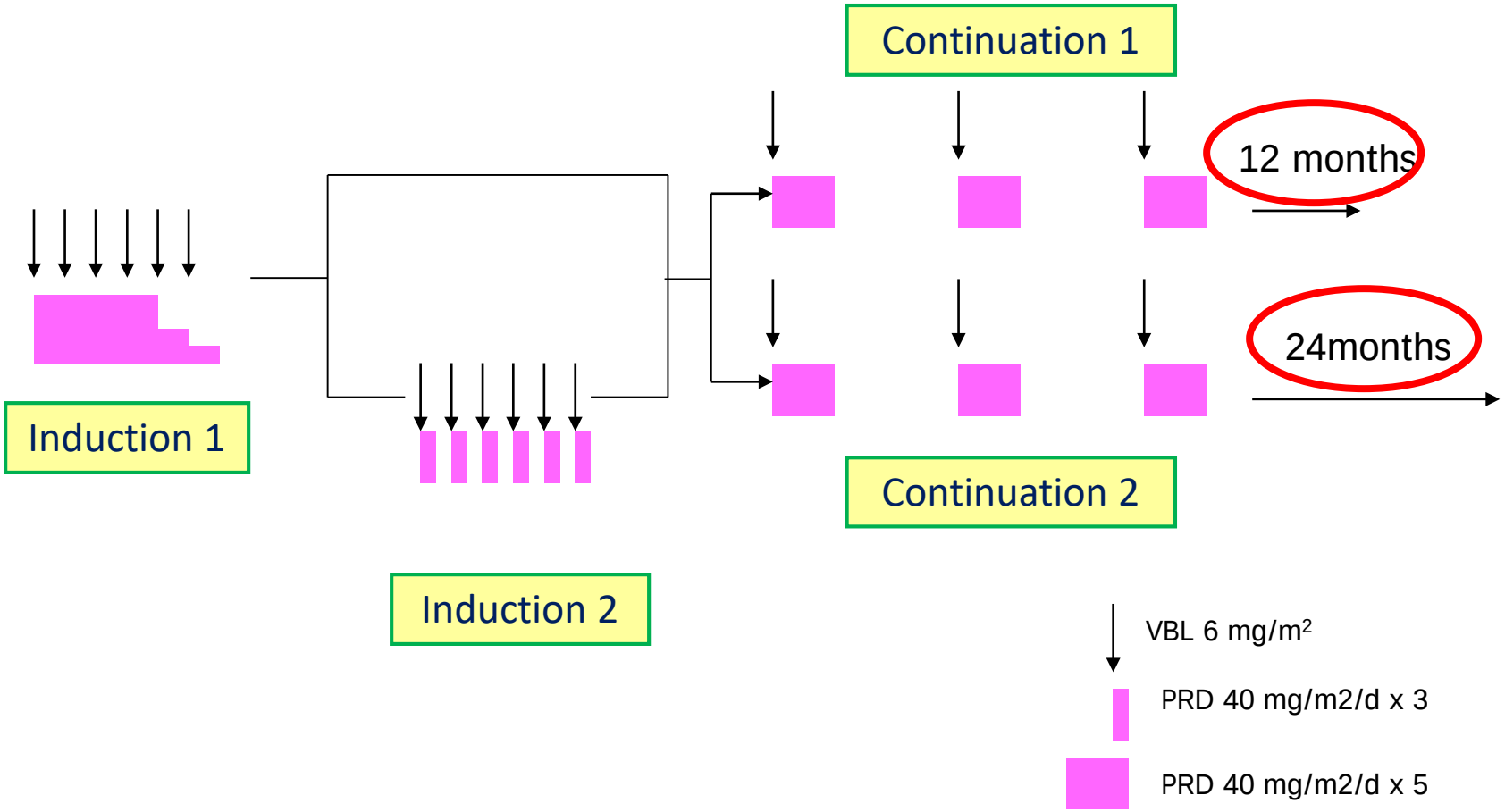
GR; good response, PR; partial response, NR; not response, PD; progressive disease

Indication for Treatment

- Low risk LCH (LR)
  - SS-LCH with
    - CSN-risk lesions
    - Multifocal bone lesions
    - “Special Site” lesions
  - MS-LCH without “risk organs”
- High risk LCH (HR)
  - MS-LCH with “risk organs”

LCH treatment Guideline



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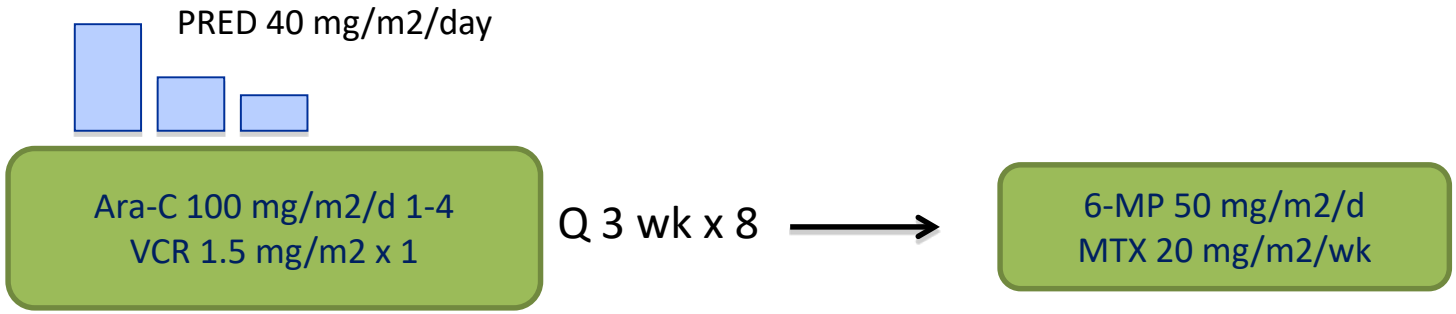
Gadner et al., Blood 2013; 121: 5006-14
LCH-IV Study Protocol

LCH treatment Guideline

Salvage I regimen

For LR with progressive disease



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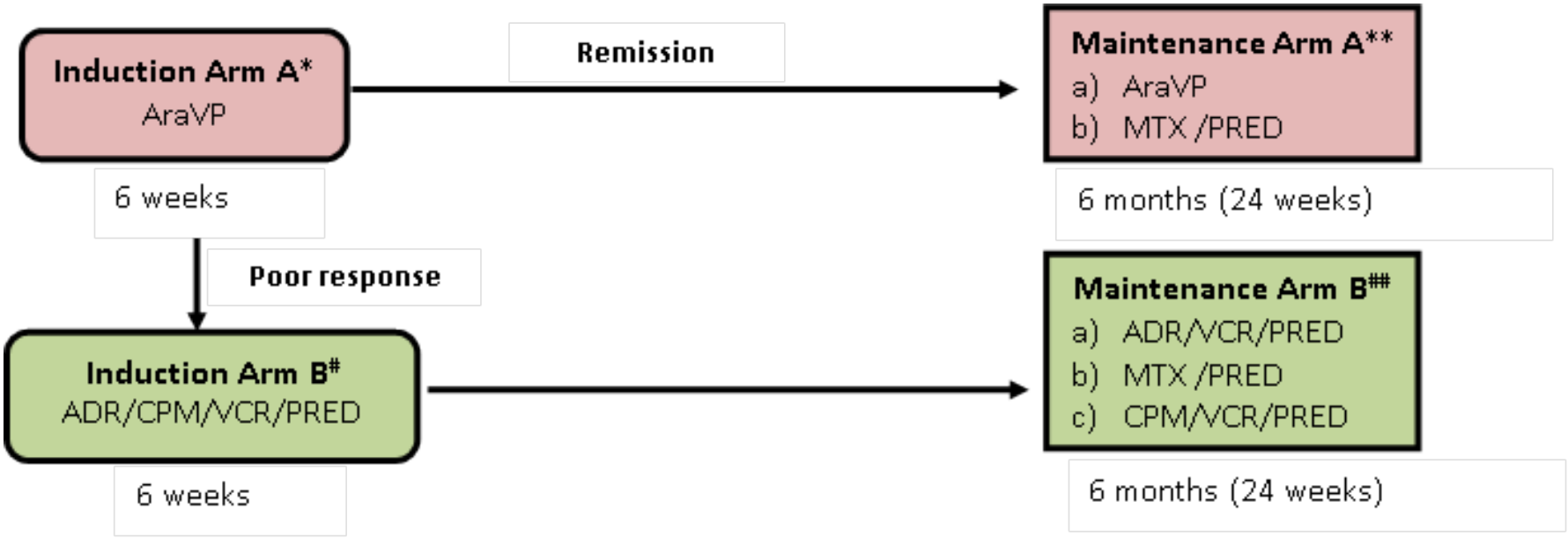
LCH-IV – Stratum II Second line therapy
RO- LCH Reactivation

LCH 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

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

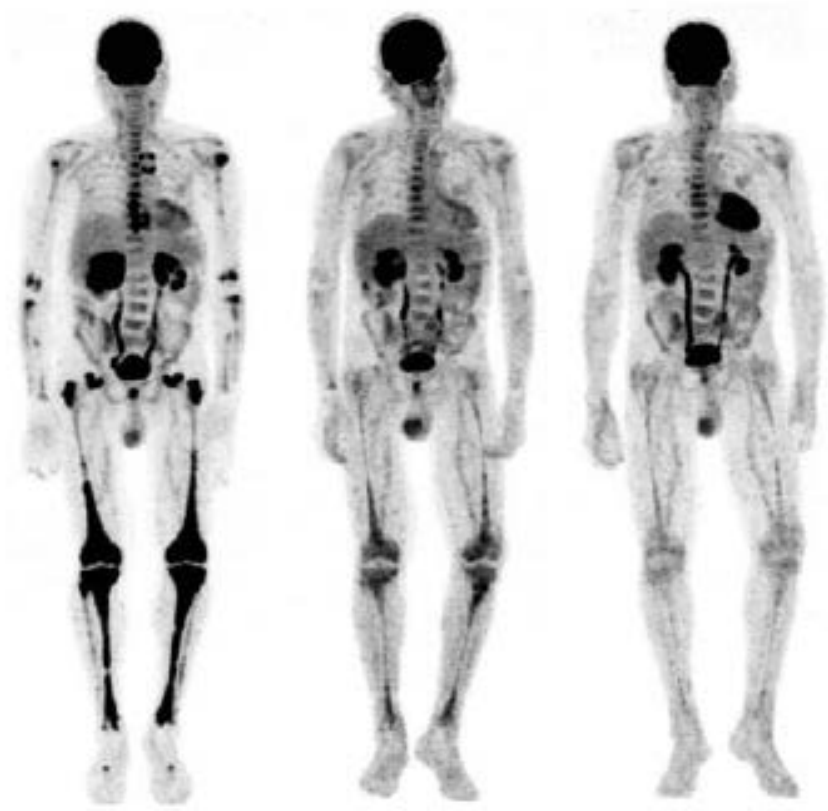
MS-LCH <u>without</u> risk organ involvement	MS-LCH <u>with</u> risk organ involvement
1. Cladribine 2. 6-MP with methotrexate 3. Bisphosphonate (local skin and bone) 4. Clofarabine 5. Imatinib mesylate	1. Cytarabine with cladribine 2. Clofarabine 3. BRAF inhibitor 4. Hematopoietic stem cell transplantation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

Targeted therapy for LCH with BRAF mutation

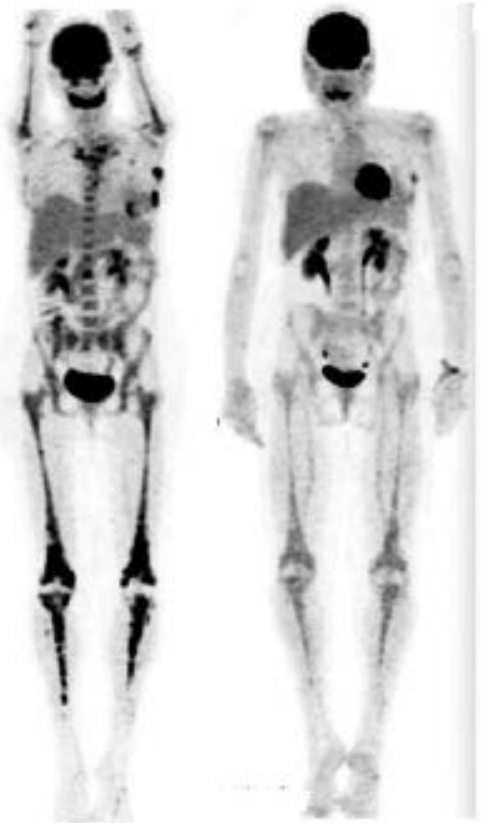
HAROCHE et al

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

The Prevalence, Clinical Characteristics, Management and Outcomes of Children with Langerhans Cell Histiocytosis in Thailand

chalinee_monsereenusorn@pedpmk.org

Conclusions

- LCH is a neoplastic proliferation of Langerin + myeloid dendritic cells → recruitment of activated lymphocytes
- Wide spectrum of clinical presentations that combine features of neoplastic proliferation with inflammation
- Challenges:
  - Patients with MFB have excellent prognosis but high tendency for disease reactivation (30-50%)
  - Treatment of patients with RO+ disease → Intensive upfront therapy
  - Reactivations → prolongation of therapy
  - Relapse in RO+

for

children with cancer

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