



2013
ERDHEIM-CHESTER
DISEASE



INTERNATIONAL
MEDICAL SYMPOSIUM
HOSTED BY THE ECD GLOBAL ALLIANCE



ECD Global Alliance

Supporting Those Affected by Erdheim-Chester Disease

www.erdheim-chester.org P.O. Box 775, DeRidder, LA 70634 337-515-6987

October 31, 2013

Welcome to San Diego and the first ever International ECD Medical Symposium!

Thank you for your involvement and attendance. It is our hope that this meeting will mark the beginning of an annual event for presentation of new scientific findings and research related to Erdheim-Chester Disease. Through sharing of information and working together, the ECD Global Alliance believes common treatment protocols can emerge and cross-institutional scientific studies might be established. We believe this will bring about better treatment options and someday a cure for this devastating and puzzling disease.

We hope you will find this event helpful to your work, and that you might meet colleagues who share similar interests and find collaboration opportunities.

The ECD Community is extremely grateful for all you do to help bring hope into the lives of patients and their families. If we can help you in any way, please let us know.

Enjoy your visit to sunny San Diego!

*The ECD Global Alliance
Board of Directors
- Kathy*

Erdheim-Chester Disease
International Medical Symposium
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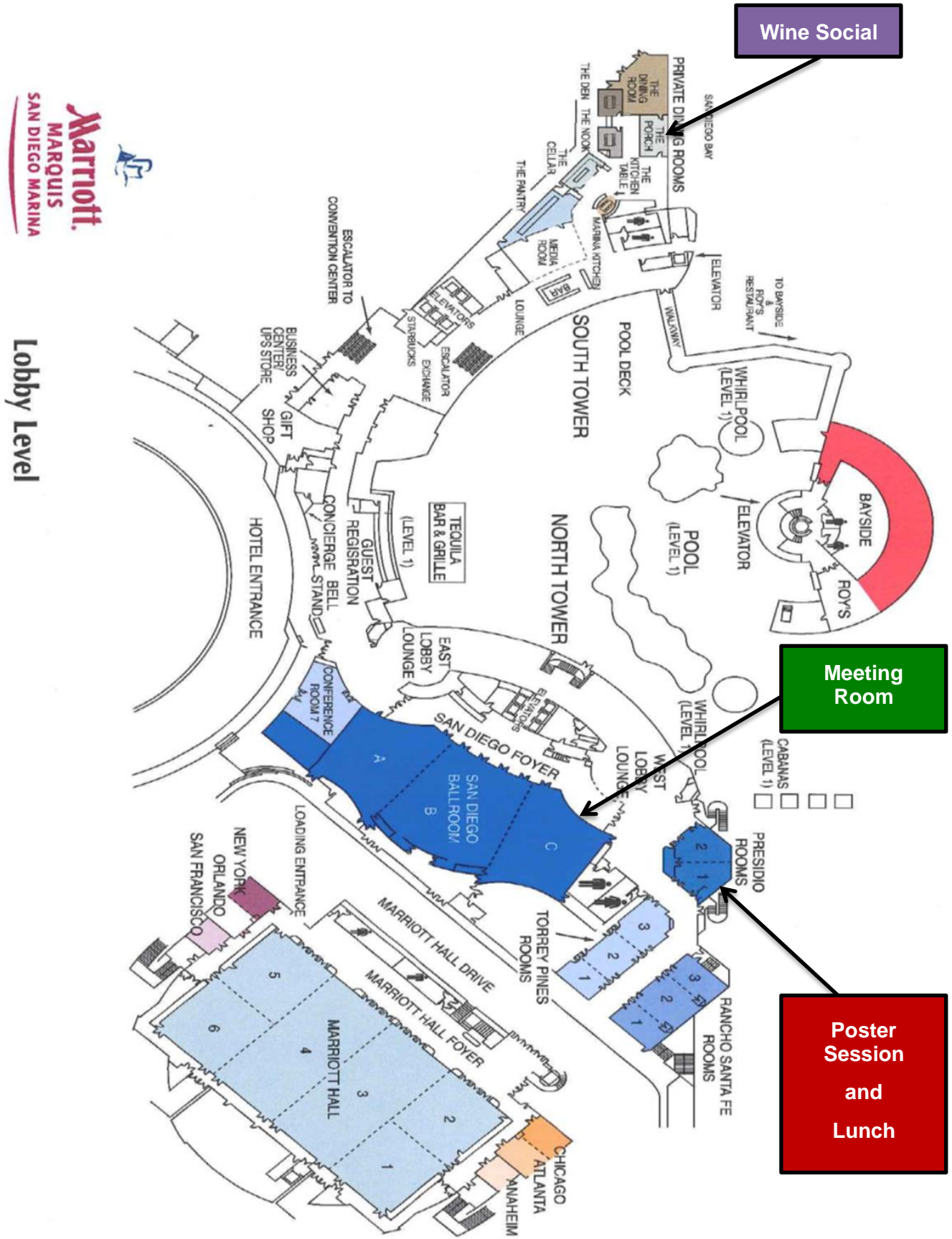
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A. Marriott Marquis and Marina Conference Location Map



B. Symposium Agenda

| October 30, 2013 | | |
|--|---------------------------------------|----------------|
| ECD Global Alliance Wine Social & Pre-registration | | |
| 1 st Floor - North Tower | | |
| Time | Activity | Location |
| 4:00 – 6:00 pm | Poster Set up | Presidio Rooms |
| 5:00 – 8:00 pm | Medical Symposium Pre-Registration | The Porch |
| 6:00 – 8:00 pm | Wine Social | The Porch |

| October 31, 2013 | | | |
|-------------------------------------|---|---|----------------------|
| ECD International Medical Symposium | | | |
| 1 st Floor - North Tower | | | |
| Time | Activity | Presenter | Location |
| 7:00 – 8:00 am | Registration and Breakfast | | San Diego Ballroom C |
| 8:00 - 8:15 am | Opening/Welcome/ 2 min Film | <u>Juvianee Estrada-Veras, MD</u> , Genetics, NIH, Bethesda, MD, USA | San Diego Ballroom C |
| 8:15 – 8:30 am | History / State of ECD Knowledge | <u>Julien Haroche, MD, PhD</u> , Internal Medicine, Hôpital Pitié-Salpêtrière, Paris, FRANCE | San Diego Ballroom C |
| 8:30 – 9:30 am | Pathology/Immunology (Oral Presentations) Moderator: <u>Tom Colby, MD</u> , Pathology, Mayo Clinic, Scottsdale, AZ, USA | <ol style="list-style-type: none"> 1. “Analysis of BRAF-V600E in Lesions and Circulating Cells in Langerhans Cell Histiocytosis and Erdheim-Chester Disease”, <u>Ken McClain, MD, PhD</u>, Pediatric - Hematology and Oncology, Baylor College of Medicine, Texas Children's Cancer Center, Houston, TX, USA 2. “Inflammation in Erdheim-Chester disease: toward the identification of therapeutic targets”, <u>Marina Ferrarini, MD</u>, Internal Medicine, San Raffaele Scientific Institute, Milan, ITALY 3. “Expression of the Receptor CD163 on Histiocytes in Patients with Erdheim Chester Disease Allows for Targeting of Therapeutics to These Cells”, <u>Kate Matthews, David Bell, PhD</u>, Therapure Biopharma, Mississauga, Ontario, CANADA | San Diego Ballroom C |

| Time | Activity | Presenter | Location |
|---------------------|---|--|-------------------------|
| 9:30 - 10:30 am | Patient Series Studies / Retrospective View (Oral Presentations) Moderator: <u>Timothy Vollmer</u> , MD, Neurology, University of Colorado Denver, Aurora, CO, USA | <ol style="list-style-type: none"> 1. “The heterogeneous clinical presentations and manifestations of Erdheim-Chester disease: review of the literature and of 10 new cases”, <u>Giulio Cavalli, MD</u>, Internal Medicine and Clinical Immunology, Vita-Salute San Raffaele University and School of Medicine, San Raffaele Scientific Institute, Milan, ITALY 2. “Cardiovascular involvement in Erdheim-Chester Disease: a Magnetic Resonance Imaging study on seven patients”, <u>Davide Gianfreda, MD</u>, Nephrology, University Hospital of Parma, Parma, ITALY 3. “Outcomes of Patients with Erdheim-Chester Disease Treated at MD Anderson Cancer Center”, <u>Filip Janku, MD, PhD</u>, Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA | San Diego Ballroom C |
| 10:30 - 10:45 am | Break | | San Diego Ballroom C |
| 10:45 – 11:45 am | Patient Series Studies / Retrospective Views (Oral Presentations) Moderator: <u>Timothy Vollmer</u> , MD, Neurology, University of Colorado Denver, Aurora, CO, USA | <ol style="list-style-type: none"> 4. “Erdheim-Chester disease: a monocentric series of 96 patients”, <u>Julien Haroche, MD, PhD</u>, Internal Medicine, Hôpital Pitié-Salpêtrière, Paris, FRANCE 5. “Whole transcriptome analysis in Erdheim-Chester disease: a multicenter collaborative analysis of 58 patients unveils new pathogenic pathways”, <u>Laurent Arnaud, MD, PhD</u>, Internal Medicine, Hôpital Pitié-Salpêtrière, Paris, FRANCE 6. “Erdheim Chester Disease: The NIH Experience Thus Far”, <u>Juvianee Estrada-Veras, MD</u>, Genetics, NIH, Bethesda, MD, USA | San Diego Ballroom C |

| Time | Activity | Presenter | Location |
|------------------|--|--|----------------------|
| 11:45 – 12:30 pm | Poster Presentations | <ol style="list-style-type: none"> 1. “Erdheim Chester Disease: Case study of 27 year old female with lung and rib involvement”, <u>Thomas Colby, MD</u>, Pathology, Mayo Clinic, Scottsdale, AZ, USA 2. “Three cases of newly diagnosed ECD with rapidly progressive involvement of the CNS treated with high-dose intravenous methotrexate”, <u>Eli Diamond, MD</u>, Neurology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA 3. “Pathogenetic role of cyto-chemokine molecules in pericardial fluid of ECD patients with cardiac involvement and their capability to induce chemotaxis and endothelial activation in vitro”, <u>Elisabetta Ferrero, PhD</u>, Oncology, San Raffaele Scientific Institute, Milan, ITALY 4. “Outcomes Measures of pain, mobility, balance, and grip strength in patients with Erdheim- Chester Disease”, <u>Ana Acevedo, MD</u>, Physiatrist , NIH, Bethesda, MD, USA | Presidio Rooms |
| 12:30 – 1:30 pm | Lunch | | Presidio Rooms |
| 1:30 – 2:50 pm | <p>Treatment Studies (Oral Presentations)</p> <p>Moderator: <u>Achille Aouba, MD</u>, Hematology, Hôpital Necker-Enfants Malades, Paris FRANCE</p> | <ol style="list-style-type: none"> 1. “ECD pathogenesis, diagnosis and treatment, including the preliminary results of the on-going clinical trial with the IL-6-inhibitor tocilizumab”, <u>Lorenzo Dagna, MD</u>, Internal Medicine, San Raffaele Scientific Institute, Milan, ITALY 2. “The Role of Rehabilitation Medicine in Erdheim-Chester Disease”, <u>Ana Acevedo, MD</u>, Physiatrist, NIH, Bethesda, MD, USA 3. “Sirolimus plus prednisone for Erdheim-Chester disease: a pilot trial”, <u>Davide Gianfreda, MD</u>, Nephrology, University Hospital of Parma, Parma, ITALY 4. “Medium and long-term efficacy of vemurafenib in Erdheim-Chester disease”, <u>Julien Haroche, MD, PhD</u>, Internal Medicine, Hôpital Pitié-Salpêtrière, Paris, FRANCE | San Diego Ballroom C |
| 2:50 – 3:10 pm | Break | | San Diego Ballroom C |

| Time | Activity | Presenter | Location |
|-------------------|---|--|----------------------|
| 3:10 – 4:00 pm | Centers of Excellence Panel Panel Chair: <u>Omar Abdel-Wahab, MD</u> , Hematology/Oncology, Sloan-Kettering, New York, NY USA | Panelists: 1. <u>Lorenzo Dagna, MD</u> – Internal Medicine, San Raffaele Scientific Institute, Milan, ITALY 2. <u>Eli Diamond, MD</u> – Neurology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA 3. <u>Juvianee Estrada-Veras, MD</u> – Genetics, National Institutes of Health, Bethesda, MD USA 4. <u>Marina Ferrarini, MD</u> – Internal Medicine, San Raffaele Scientific Institute, Milan, ITALY 5. <u>Julien Haroche, MD, PhD</u> – Internal Medicine, Publique-Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Paris FRANCE | San Diego Ballroom C |
| 4:00 – 4:45 pm | Treatment Protocols Panel Panel Chairs: <u>Lorenzo Dagna, MD</u> , Internal Medicine, San Raffaele Scientific Institute, Milan, ITALY <u>Filip Janku, MD, PhD</u> , Oncology, MD Anderson, Houston, TX USA | Panelists: 1. <u>Robert Arceci, MD, PhD</u> – Pediatric Oncology, Phoenix Childrens Hospital, Phoenix, AZ USA 2. <u>Mark Heaney, MD, PhD</u> – Oncology, Columbia University Medical Center, New York, New York, USA 3. <u>David Hyman, MD</u> – Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA 4. <u>Filip Janku, MD, PhD</u> – Oncology, MD Anderson, Houston, TX USA 5. <u>Paul Scheel, MD</u> – Nephrology, Johns Hopkins, Baltimore, MD USA 6. <u>Augusto Vaglio, MD, PhD</u> – Nephrology, University of Parma, Parma ITALY | San Diego Ballroom C |
| 4:45 – 5:00 pm | Symposium Conclusion | <u>Omar Abdel-Wahab, MD</u> -- Hematology/Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA | San Diego Ballroom C |
| 5:00 pm | Thank You & Photo Opportunity | ECD Global Alliance, Kathy Brewer | San Diego Ballroom C |

C. Pathology/Immunology Oral Presentation Abstracts

1. Title: Analysis of BRAF-V600E in Lesions and Circulating Cells in Langerhans Cell Histiocytosis and Erdheim-Chester Disease.

Authors: M Berres, P Lim, T Peters, J Price, A Shih, P Lupo, K Heym, J Hicks, K McClain, M Merad and C Allen

Institution: Pediatric - Hematology and Oncology, Baylor College of Medicine, Texas Children's Cancer Center, Houston, TX, USA

Presenter: Ken McClain, MD, PhD

Langerhans Cell Histiocytosis (LCH) is a clonal lymphoproliferative disorder characterized by inflammatory lesions with characteristic CD207+ dendritic cells (DCs). LCH has variable clinical presentations ranging from single lesions to potentially fatal multi-system “High Risk” disease. The etiology of LCH remains elusive, with debate of LCH as an inflammatory versus malignant disorder unresolved. The first recurrent somatic genetic mutation in LCH, BRAF-V600E, was recently reported in over half of all LCH and Erdheim-Chester Disease (ECD) lesions (Badalian-Very et al., 2010; Haroche et al., 2012). In this study, we investigate the clinical significance of BRAF-V600E and identify cells carrying the mutation to determine the pathogenesis of LCH. Two patients with ECD were also included in this study.

Lesions from 100 patients with LCH and 2 with ECD were genotyped, and 61% percent of the LCH patients carried the V600E mutation, which localized to the infiltrating CD207+ DCs; one of the two ECD patients carried the V600E mutation. In 16 LCH patients with more than one lesion, BRAF status remained fixed, suggesting somatic mutation is an early event. BRAF-V600E did not define specific clinical risk groups or impact overall survival, but it was associated with approximately two-fold higher risk of relapse ($p=0.04$). Furthermore, the cellular compartment carrying the mutation correlated with disease severity: The ability to detect BRAF-V600E in circulating mononuclear cells defined High-Risk LCH with 100% sensitivity/87% specificity. The ability to detect BRAF-V600E in circulating blood cells in patients with High-Risk LCH defined clinically detectable disease with 97% sensitivity/100% specificity. Analysis of sorted populations localized the BRAF-V600E to CD11c+ and CD14+ fractions in peripheral blood, and to rare CD34+ cells in bone marrow. CD34+ cells from bone marrow aspirate patients with High-Risk LCH were purified and grown in CFU assays. BRAF-V600E colonies were identified, proving LCH can arise from hematopoietic stem cells. Circulating cells with BRAF were not detected in the patient with ECD, who had multifocal bone disease.

We therefore hypothesize that High-Risk LCH arises from somatic mutation of hematopoietic stem cells or immature myelomonocytic precursor cell, where Low-Risk disease arises from somatic mutation of tissue-restricted DC precursors. Based on these results, we propose classifying LCH as an “inflammatory myeloid neoplasia”. We speculate ECD may follow similar model of pathogenesis. Furthermore, BRAF-V600E “barcode” may be clinically useful as a diagnostic tool, a factor in clinical risk-stratification, and as a marker of residual disease for patients with LCH and ECD with hematopoietic organ disease.

2. Title: Inflammation in Erdheim-Chester disease: toward the identification of therapeutic targets.

Author: Dr. Marina Ferrarini, MD

Institution: Vita-Salute San Raffaele University, Dept. of Oncology, San Raffaele Scientific Institute, Via Olgettina 60, Milan, Italy 20132

Presenter: Dr. Marina Ferrarini, MD

Chronic inflammation and a BRAFV600E mutation in histiocytes are recognized as major pathogenetic events in ECD. Notably, both may be targeted by specific inhibitors already available in the clinical practice. We will discuss data on cyto-chemokine production by ECD histiocytes and monocytes, their pathogenetic role, as well as on the development of a novel 3-D culture model to assess the impact of cytokine- vs BRAF-inhibition on ECD lesions.

3. Title: The Expression of the Receptor CD163 on Histiocytes in Patients with Erdheim Chester Disease Allows for Targeting of Therapeutics to These Cells.

Authors: Kate Matthews; David Bell, PhD

Institution: Therapure Biopharma Inc, Mississauga, ON, Canada

Presenters: Kate Matthews; David Bell, PhD

Recently, numerous reports have demonstrated that the histiocytes from ECD patients express CD163 (the hemoglobin-haptoglobin receptor). This allows for the possibility of targeting CD163⁺ cells in order to treat ECD. Therapure is uniquely positioned to assist in the development of treatments for ECD as it has several drugs that have been chemically conjugated to hemoglobin as a means of specifically targeting the drug payload to CD163⁺ cells while reducing systemic toxicity. Therapure's TBI 301 has been shown *in vitro* and in animal models to reduce the production of pro-inflammatory cytokines while TBI 302 is cytotoxic to receptor bearing cells. Therapure intends to first demonstrate targeting of CD163+ histiocytes with both TBI 301 and TBI 302 as a means of demonstrating the potential efficacy of these compounds.

D. Patient Series Studies / Retrospective View Oral Presentation Abstracts

1. Title: The Heterogeneous Clinical Presentations and Manifestations of Erdheim-Chester Disease: Review of the Literature and of 10 New Cases.

Authors: G. Cavalli, B. Guglielmi, A. Berti, C. Campochiaro, M.G. Sabbadini, L. Dagna

Institution: Department of Internal Medicine and Clinical Immunology, Vita-Salute San Raffaele University, San Raffaele Scientific Institute, Milan, Italy

Presenter: Giulio Cavalli, MD

Background: Erdheim-Chester disease (ECD) is an inflammatory disease of unknown etiology, characterized by the infiltration of tissues by non-Langerhans histiocytes. Although rare, ECD is a largely overlooked disease, mostly affecting middle-aged men. Its clinical spectrum at presentation is broad, since the infiltration of different organs leads to the development of protean manifestations. Current literature identified bone, central nervous system and retroperitoneal as the most common localizations of ECD. Still, the clinical picture at the time of onset is often substantially different, and seldom specific for ECD. Thus, the diagnosis is particularly challenging at onset. Furthermore, as successive manifestation can occur over years, the clinical picture may be a slowly forming mosaic, and a long-lasting dilemma.

Objectives: To characterize the clinical presentation of ECD at the time of onset and the evolution of the clinical picture over time, with particular regards to those symptoms that first induced patients to seek medical attention.

Methods: We analyzed the presentation at the time of onset, at diagnosis, and the subsequent clinical manifestations in a cohort of 16 ECD patients followed up at our institution. We performed the same analysis on the cases reported in the English-language medical literature. Moreover, we divided the cumulative cohort of patients in three age groups (<40, 40-69, >70 years), and performed the same analyses on the different subgroups.

Results and discussion: ECD typically manifests with bone pain, diabetes insipidus, neurological and/or constitutional symptoms, regardless of the age of presentation. Interestingly, diabetes insipidus and constitutional symptoms due to ECD, if not present early in the course, only rarely develop. However, there are seeming variations in ECD presentation and course in different age groups, with more severe manifestations becoming progressively more prevalent over time. In particular, patients aged less than 40 years only rarely endured pulmonary, cardiac or retroperitoneal involvement. In middle-aged patients, pulmonary and cardiac manifestations become more frequent. In the elderly, the incidence of cardiac manifestations reached its peak. Physicians should be aware of the extraordinarily heterogeneous clinical presentations and manifestations of this rare but overlooked disease, in order to include ECD in the differential diagnosis of several conditions, in particular when multi-organ involvement is present.

References: Veyssier-Belot C et al. Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases. *Medicine* 1996. Haroche J et al. Erdheim-Chester disease. *Curr Opin Rheumatol* 2012. Cavalli G et al. The multifaceted clinical presentations and manifestations of Erdheim-Chester disease. *Ann Rheum Dis* 2013

2. Title: Cardiovascular Involvement In Erdheim-Chester Disease: A Magnetic Resonance Imaging Study on Seven Patients.

Authors: Davide Gianfreda, MD¹, Enrica Rossi, MD², Lorenzo Buttarelli, MD², Chiara Martini², Augusto Vaglio, MD³, Massimo De Filippo, MD².

Institutions: ¹Department of Clinical and Experimental Medicine, University of Parma; ²Department of Radiology, University Hospital of Parma; ³Department of Clinical and Experimental Medicine, University Hospital of Parma

Presenter: Augusto Vaglio, MD, PhD

Purpose. Erdheim-Chester Disease (ECD) is a rare non-Langherans form of histiocytosis, characterized by xanthomatous or xanthogranulomatous infiltration of tissues by foamy histiocytes, surrounded by fibrosis. ECD is a multisystemic disease and its clinical course depends mostly on cardiovascular manifestations, that are responsible for poor prognosis and death. In order to assess the cardiovascular extent of the disease, we studied 7 consecutive cases with biopsy-proven ECD by magnetic resonance imaging (MRI).

Materials and Methods. The patients underwent cardiac and thoracic aorta MRI. Images were acquired with a 1,5T RM, using T2W with and without fat suppression, long and short axis cine B-TFE and late gadolinium enhancement sequences evaluated by dedicated software.

Results. Four patients (57%) showed abnormal heart imaging. Four patients had myocardium involvement with typical pseudo-mass aspects in the anterior and lateral walls of right atrium. In three cases it extended to the right atrioventricular sulcus, sheathing the right coronary artery; only in one case both coronary arteries were surrounded by periarterial infiltration. None of the cases showed signs of coronary stenosis. One case also presented atrial septal thickening. In three cases imaging studies recognized pericardial effusion; just in one case it was massive (50mm), even if without signs of cardiac tamponade. The pericardium facing the right ventriculum was thickened in two cases.

Imaging showed a mild cardiomegaly in one patient, but no atrial enlargement was detected. In no case we recognized cardiac insufficiency or cardiac signs of systemic hypertension. No patients had valvular defects.

The angiography assessment suggested the presence of periaortic fibrosis with “coated aspect” in two cases. In these, epiaortic vessels were surrounded by irregular, non stenosing fibrosis.

Conclusions: Our study confirms the frequent cardiovascular involvement in ECD. A systematic cardiac and aortic evaluation by MRI would be indicated in patients with ECD.

3. Title: Outcomes of Patients with Erdheim-Chester Disease Treated at MD Anderson Cancer Center.

Authors: ¹Filip Janku, ¹Javier Munoz, ²Luis E. Fayad, ³Patrick P. Lin, ⁶Philip R. Cohen, ⁴Bitu Esmali, ⁵Sharon R. Hymes, ¹Tiffany L. Jackson, ¹Tamara G. Barnes, ⁷Razelle Kurzrock

Institutions: ¹Departments of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), ²Lymphoma/Myeloma Oncology, ³Orthopedic Oncology, ⁴Ophthalmology, ⁵Dermatology, MD Anderson Cancer Center, Houston, TX

⁶Division of Dermatology, University of California San Diego, San Diego, CA

⁷Moore's Cancer Center, University of California San Diego, La Jolla, CA

Presenter: Filip Janku, MD, PhD

Background: Erdheim-Chester disease (ECD) is a rare form of non-Langerhans histiocytosis characterized by xanthogranulomatous infiltration of foamy macrophages. There is no standard treatment for this disorder and previous literature reports suggest that more than half the patients die in less than three years from presentation.

Methods: We reviewed the records of consecutive patients with ECD who were referred to the MD Anderson Cancer Center starting in August 1999.

Results: We identified a total of 16 patients (9 men, median age at diagnosis 50 years [range, 26-76 years]). Common findings included involvement of the following: bone (13/16, 81%), pulmonary (11/16, 69%), cardiac (11/16, 69%), central nervous system (9/16, 56%), renal/adrenal involvement (9/16, 56%), and skin (2/16, 13%). Diabetes insipidus was diagnosed in 9/16 (56%) of patients. Targeted next-generation sequencing of 182 cancer-related genes performed in 3 patients with adequate archival tissue demonstrated a *BRAF* V600E mutation in 2 patients and *NTRK1* rearrangement in 1 patient. Patients received a median of 2 (range, 0-4) therapies. Interferon- α (IFN) or pegylated IFN was given to 9 patients (median time to treatment failure [TTF] 44.9 months; 95% CI 0-100.7), imatinib to 8 patients (median TTF 1.8 months; 95% CI 0-11.2), and anakinra to 4 patients (median TTF not reached after a median follow-up of 14.2 months). The *BRAF* kinase inhibitor vemurafenib was given to one patient with a *BRAF* V600E mutation; however, treatment was discontinued after 1.3 months due to intolerance (despite a decrease in FDG uptake on the PET/CT). At a median follow-up of 49.5 months from diagnosis, median overall survival was not reached (only 3 patients died).

Conclusion: Patients with ECD present most frequently with bone involvement and can be treated with several lines of therapy. Our data indicate that expected survival is longer than previously reported.

4. Title: Erdheim-Chester Disease: A Monocentric Series Of 96 Patients.

Authors: Julien Haroche, Laurent Arnaud, Fleur Cohen-Aubart, Baptiste Hervier, David Saadoun, Nathalie Costedoat-Chalumeau, Sophie Besnard, Kim Ly, Michel Pavic, Jean-Gabriel Fuzibet, Loïc Raffray, Zahir Amoura

Institution: Internal Medicine Department. Hospital Pitié-Salpêtrière, University Paris 6, AP-HP, 47-83 bd de l'Hôpital, 75013, Paris, France.

Presenter: Julien Haroche, MD, PhD

Background/Purpose: Erdheim-Chester disease (ECD) is a rare non-Langerhans form of histiocytosis characterized by an infiltration of foamy CD68+ CD1a- histiocytes. More than 500 cases of this disease have been reported since its first description in 1930.

Methods: The aim of this study was to describe a single-centre series of 96 consecutive ECD patients hospitalized at least once between 1992 and 2013 in the department of internal medicine of Pitié-Salpêtrière hospital, Paris, France.

The geographic origin of patients referred to our tertiary care centre is international: 75 are french residents, while 21 patients come from Germany, UK, Eire, Belgium, Spain, Portugal, Israel, Norway and South Africa.

Results: Patients were 75 men and 21 women. Median age at diagnosis was 54.6 years (5-81 yr). In the present series the mean diagnostic delay is 2 yr (0-35yr). Mean follow-up between diagnostic and last news is 37.3 months (1.63-376 months). Fifty-five patients (56%) had peri-renal. Forty patients (42%) had a peri-aortic sheathing of the whole aorta ("coated aorta"), 33 (34%) a pericardial involvement, 29 (30%) a coronary involvement, 20 (21%) a reno-vascular hypertension, 34 (35%) a pseudotumoral infiltration of the right atrium. Twenty-two patients (23%) had an exophthalmos, 24 (25%) a xanthelasma often in peri-orbital spaces, 29 (30%) a diabetes insipidus, and 38 (40%) an involvement of the central nervous system (CNS), among which 17 (18%) with a cerebellar involvement. Twenty-one patients (22%) had hydronephrosis, 35 (36%) a pulmonary involvement, often asymptomatic. Seventy-four patients (80%) had high C-reactive protein values.

Eighty-seven patients (91%) have been treated with interferon alpha (IFN α) or Pegylated IFN α , with high doses when facing CNS and/or cardiac involvements. Twenty-two patients died (23%). We were able to identify a BRAFV600E mutation among 27 of the 53 patients (51%) among which tissue samples were exploitable. Seven of these patients with multisystemic ECD, refractory and/or intolerant to IFN α , have been treated with BRAF inhibitors (vemurefenib) with spectacular and sustained responses.

Conclusion: We report the world largest's monocentric series of ECD patients. The prognosis, which largely depends on the presence of CNS involvement, is variable. First line of treatment remains IFN α , which use is associated with improved survival in ECD is an independent prognostic factor of survival of ECD. Nevertheless, long-term therapy with IFN α may be poorly tolerated, and the place of BRAF inhibition, particularly for BRAFV600E mutated patients with life-threatening forms of the disease, should be studied in larger scale.

5. Title: Whole Transcriptome Analysis In Erdheim-Chester Disease: A Multicenter Collaborative Analysis Of 58 Patients Unveils New Pathogenic Pathways.

Authors: Laurent Arnaud¹, Julien Haroche¹, Lorenzo Dagna², Augusto Vaglio³, Bruno Faivre⁴, Karim Dorgham⁴, Baptiste Hervier¹, Fleur Cohen-Aubart¹, Guy Gorochov⁴ and Zahir Amoura¹

Institutions: ¹Department of internal medicine, Hopital Pitié-Salpêtrière, AP-HP & UPMC Univ Paris 06, Paris, France & Institut National de la Santé et de la Recherche Médicale, INSERM UMR-S 945, Paris, France.

²Vita-Salute San Raffaele University School of Medicine and San Raffaele Scientific Institute, Milano, Italy.

³University of Parma, Parma, Italy.

Presenter: Laurent Arnaud, MD, PhD

Background/Purpose: To date, gene expression profiling has not been performed in Erdheim-Chester disease (ECD), a rare, non-Langerhans form of histiocytosis. The aim of this study was to analyze the transcriptome of ECD compared to healthy individuals, as a manner to identify new pathways involved in the pathogenesis of the disease as well as new therapeutic targets.

Methods: Total RNA was extracted from peripheral blood mononuclear cell (PBMC) obtained in 58 patients with biopsy-proven ECD and 36 healthy individuals. Complementary DNA (cDNA) was hybridized in Illumina Human HT-12[®] v4 Expression Bead Chips. Statistical analysis of Microarray (SAM) algorithm with Benjamini and Hochberg multiple testing correction was used to determine the statistical significance of the differences in gene expression while controlling the false-discovery rate. Cluster analysis was also performed with JMP8 software. Differentially expressed genes were analyzed to identify potential functional pathways using Ingenuity[®] Pathway Analysis (IPA).

Results: Gene expression analysis using SAM showed 265 significantly down- or up-regulated transcripts between ECD patients and controls. Cluster analysis of these transcripts by similarity on gene expression patterns identified several clusters containing only ECD patients, healthy individuals, or both, underlining the strong heterogeneity of the disease. The set of genes statistically different between ECD and healthy individuals was further analyzed with IPA Analysis, which revealed a role for genes related to growth factor and cytokine activities, cyclin-dependant cell-cycle genes, regulation of phosphate homeostasis, DNA packaging, transcription regulation, and mRNA stability.

Conclusion: This large multicenter collaborative transcriptome analysis of 58 patients with Erdheim-Chester disease reveals that complex gene expression patterns are involved in the pathogenesis of the disease. This may be seen as a significant advance in this rare disease with poor prognosis and non-formally codified therapeutic management.

6. Title: Erdheim Chester Disease: The NIH Experience Thus Far.

Authors: Estrada-Veras, Juvianee; Gahl, William

Institution: Medical Genetics Branch, Section Human Biochemical Genetics, Office of the Clinical Director, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA.

Presenter: Juvianee Estrada-Veras, MD

Background. Erdheim-Chester Diseases (ECD) is a rare non-Langerhans cell histiocytosis which etiology and pathogenesis are still poorly understood. It has been reported mainly in adult males over the age of 40 years, although females are affected as well. Childhood cases are rare. The clinical characteristics of ECD range from asymptomatic to multisystemic involvement affecting the bones, retroperitoneal space, pituitary stalk, cerebellum, brainstem, retro-orbital space, heart, lungs and other systems. After diagnosis, the disease progresses rapidly without treatment, causing fatal outcomes due to severe lung disease, chronic renal failure, cardiomyopathy and other complications. The diagnosis relies upon imaging studies and specific pathologic findings in biopsies of affected organs, i.e., fibrosis and infiltration of the affected tissues with foamy histiocytes, lymphocytes, and plasma cells. Immunohistochemistry reveals cells positive for CD68 and negative for CD1a and S-100. There is no standard treatment for ECD, although chemotherapy, radiation, stem cell transplantation, alpha-interferon, steroids, monoclonal antibodies and sirolimus have been proposed. Therapy with BRAF inhibitors is promising in a subset of patients with ECD that harbor the BRAF V600E. Symptomatic improvement has been reported with these therapies, but in a number of cases, response is disappointing.

Methods. The longitudinal progression and natural history of ECD have been reported, but this is an area that merits more observation. Its etiology and pathogenesis are poorly understood. We are clinically evaluating patients with ECD at the National Institutes of Health Clinical Center under NHGRI study 11-HG-0207 "Clinical and Basic Investigations into Erdheim-Chester disease" (clinicaltrials.gov identifier: NCT01417520). Patients with ECD are admitted to the NIH Clinical Center for one week. During this period we obtain cells, plasma, urine, DNA and perform other basic studies in order to better understand the pathogenesis. Clinical manifestations will also be studied in order to define the clinical spectrum. Patients are seen and evaluated by our clinical services such as neurology, cardiology, rehabilitation medicine, ophthalmology and nutrition. Imaging studies are performed as well.

Conclusions. Up to date, 34 patients from the USA and other countries have been enrolled and 32 have been seen and evaluated. Data is currently being gathered and analyzed.

E. Poster Presentations

1. Title: Erdheim Chester Disease: Case Study Of 27 Year Old Female with Lung and Rib Involvement.

Authors: Thomas V. Colby MD, John Muhm MD

Institution: Pathology, Mayo Clinic, Scottsdale, AZ, USA

Presenter: Thomas V. Colby, MD

A case of Erdheim-Chester disease encountered in a 25-year-old woman is presented. The patient had carried a diagnosis of diabetes insipidus since age five and had been treated with desmopressin since her teenage years.

She presented three months prior to surgical lung biopsy with dyspnea on exertion which progressively worsened. She was noted to have bilateral pulmonary infiltrates and CT scan was showed diffuse pleural thickening, upper lobe bullous/emphysematous changes, marked lower lobe diffuse septal thickening, and coalescent linear parenchymal consolidation. Surgical lung biopsy showed a fibrosing process exquisitely limited to lymphatic routes in the pleura, septa and along bronchovascular bundles. The appearance was strongly suggestive of Erdheim-Chester disease.

The CT scan was re-reviewed and in retrospect a region of bony sclerosis was noted in one of the ribs and this finding was considered consistent with Erdheim-Chester disease.

The case is presented as an unusual example of ECD presenting with pulmonary complaints and occurring in a young woman with a history of diabetes insipidus. In retrospect the symptoms of ECD in this patient may have been present since age five.

2. Title: Three Cases of Newly Diagnosed ECD with Rapidly Progressive Involvement of the CNS Treated with High-Dose Intravenous Methotrexate.

Author: Eli Diamond, MD

Institution: Memorial Sloan-Kettering Cancer Center, Neurology Department, 1275 York Ave, New York, New York 10065

Presenter: Eli Diamond, MD

Involvement of the central nervous system (CNS) is a cause of morbidity and is a poor prognostic factor for ECD. We present three cases of newly diagnosed ECD with rapidly progressive involvement of the CNS treated with high-dose intravenous methotrexate. Clinical stabilization was achieved. Outcomes and toxicities will be discussed. This regimen may have a role in initial treatment of CNS disease in some cases of ECD.

3. Title: Pathogenetic Role of Cyto-Chemokine Molecules in Pericardial Fluid of ECD Patients with Cardiac Involvement and Their Capability to Induce Chemotaxis and Endothelial Activation In Vitro.

Author: Elisabetta Ferrero, PhD

Institution: Vita-Salute San Raffaele University, Dept. of Oncology, San Raffaele Scientific Institute, Via Olgettina 60, Milan, Italy 20132

Presenter: Elisabetta Ferrero, PhD

ECD is characterized by tissue infiltration with foamy histiocytes, paralleled by cyto-chemokine release. To investigate the pathogenetic role of these molecules, we determined their expression in pericardial fluid of ECD patients with cardiac involvement and their capability to induce chemotaxis and endothelial activation in vitro. Inhibition of this latter phenomenon with Infliximab discloses a key role of TNFalpha; as well as the possibility to target this molecule to treat cardiac ECD.

4. Title: Outcomes Measures of Pain, Mobility, Balance, and Grip Strength in Patients with Erdheim-Chester Disease.

Author: Ana T. Acevedo, MD¹; Juvanee Estrada-Veras, MD²; John Collins, PhD³; William Gahl, MD, PhD²

Institution: 1- Rehabilitation Medicine Department, NIH-CC, Bethesda, MD.; 2- National Human Genome Research Institute-NIH, Section Human Biochemical Genetics-Office of the Clinical Director, Bethesda, MD.; 3- Rehabilitation Medicine Department, Biostatistics section, NIH-CC, Bethesda, MD.

Presenter: Juvanee Estrada-Veras, MD

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis. It is a systemic disease with a wide range of clinical manifestations such as skeletal involvement with bone pain, retroperitoneal fibrosis, interstitial lung disease, central nervous system and/or cardiopulmonary involvements. Sometimes this disease may present with no symptoms. Patients may experience fatigue, weakness, balance and coordination problems which may impact their day-to-day function and quality of life. To assess pain, mobility, balance and grip strength in patients with ECD, outcomes measures were obtained in these categories in 20 patients evaluated at the NIH Clinical Center under NHGRI protocol 11-HG-0207. The outcome measures included the fatigue severity scale, the comparative pain scale, Time up and go test, single leg stance, functional reach and bilateral grip strength measures. The results of findings are analyzed and presented with recommendations for future research opportunities. It is our understanding that this may be one of the first reports evaluating functional outcomes measures in patients with ECD.

F. Treatment Studies Oral Presentation Abstracts

1. Title: ECD Pathogenesis, Diagnosis and Treatment, Including the Preliminary Results of the on-Going Clinical Trial with the IL-6-Inhibitor Tocilizumab.

Author: Lorenzo Dagna, MD

Institution: Vita-Salute San Raffaele University, Dept. of Internal Medicine and Clinical Immunology, San Raffaele Scientific Institute, Via Olgettina 60, Milan, Italy 20090

Presenter: Lorenzo Dagna, MD

Recent advances in understanding ECD suggest that at least two distinct but possibly interconnected events (i.e., a full-blown chronic inflammation and the occurrence of the BRAFV600E mutation in histiocytes) are implicated. The presentation will cover the most recent data generated by our group on ECD pathogenesis, diagnosis and treatment, including the preliminary results of the on-going clinical trial with the IL-6-inhibitor tocilizumab.

2. Title: The Role of Rehabilitation Medicine in Erdheim-Chester Disease.

Author: Ana T. Acevedo, MD¹

Institution: Department of Rehabilitation and Physical Medicine, National Institutes of Health Clinical Center, Bethesda, MD.

Presenter: Juvianee Estrada- Veras, MD

Erdheim Chester disease (ECD) is a rare form of non- Langerhans histiocytosis which etiology and pathophysiology are still poorly understood and are current areas of active research. ECD is a systemic disease with a wide range of clinical manifestations including skeletal abnormalities with bone pain, central nervous system and/or cardiovascular involvements, interstitial lung disease, retroperitoneal fibrosis with perirenal and/or ureteral obstruction/dysfunction, exophthalmoses, diabetes insipidus and other manifestations which individually and/or collectively may impact the patient's day to day function and quality of life.

Rehabilitation medicine's approach in patients with ECD is to thoroughly evaluate how the clinical manifestations of the disease as well as pre-existing and co-existing conditions are affecting the patient's day to day function. Assessing functional mobility, self care skills, safety risks, physical conditioning and general well-being are of outmost importance to optimize patients' quality of life.

Patients often complain of incapacitating fatigue, chronic pains, balance and coordination problems and need for physical help from their caregivers. The disease may affect the patients physically, emotionally and behaviorally and psychosocial status and alter their role within their family, work structures and communities.

Here we will provide an overview of the rehabilitation team and rehabilitative tactics and strategies that may be of benefit to patients with ECD. We will also discuss preliminary findings of outcomes measures of fatigue, pain, grip strength and mobility obtained in a small sample of patients with ECD evaluated at the National Institutes of Health Clinical Center under the NHGRI protocol 11-HG-0207 which studies Clinical and Basic Investigations into Erdheim Chester Disease.

3. Title: Sirolimus Plus Prednisone for Erdheim-Chester Disease: A Pilot Trial.

Author: Davide Gianfreda, MD¹, Federico Alberici, MD², Maricla Galetti, PHD², Maria Nicastro, PHD², Carlo Buzio, MD², Augusto Vaglio, MD²

Institution: ¹Department of Clinical Medicine, Nephrology and Health Sciences, University of Parma; ²Department of Clinical Medicine, Nephrology and Health Sciences, University Hospital of Parma

Presenter: Augusto Vaglio, MD

Introduction and aims. Erdheim-Chester disease (ECD) is an extremely rare form of non-Langerhans cell histiocytosis, characterised by tissue infiltration of CD68+ CD1a- “foamy” histiocytes. The etiopathogenesis of ECD is unclear: while most authors suggest the hypothesis of an inflammatory disease, others claim it is a neoplastic disorder. ECD often has a progressive and fatal course (3-year mortality 25-60%). There is no established treatment for ECD. Interferon- α is often used but it has severe side effects and poor efficacy on CNS and cardiovascular lesions.

The mTOR inhibitor sirolimus (SRL) is an immunosuppressive drug with known anti-neoplastic properties. We tested the efficacy and safety of a combination of prednisone (PDN) and SRL in a series of patients with multisystemic, active ECD. We also assessed mTOR activity in patients’ biopsies and PBMCs, in order to get predictors of treatment efficacy.

Patients and methods. We enrolled all patients with active, multisystemic ECD (either at first diagnosis or with progressive disease refractory to other treatments) referred to our Department between 2003 and 2011.

PDN was given at the initial dose of 0.75 mg/kg/day for 1 month, tapered to 2.5-5 mg/day over 6 months; SRL was given at a daily dose of 2-3 mg, with a target trough level of 8-10 ng/mL. If disease stabilization or remission was achieved, the treatment was continued chronically. The response to treatment was assessed by means of clinical examination and appropriate laboratory and imaging studies (CT, MRI, PET/CT, bone scintigraphy).

Where available, frozen tissue biopsies (two from retroperitoneal tissue and one from skin) were used to assess mTOR activity: for this purpose, the levels of phospho-p70S6K (Thr389) and phospho-mTOR (ser 2448) in total proteins extracted from the biopsies were determined by Western blotting.

Results. Nine consecutive ECD patients were enrolled. Of them, six were newly diagnosed and untreated, whereas the remaining three were refractory to previous treatments (interferon- α , PDN and colchicine, PDN and cyclophosphamide). The median follow-up from diagnosis was 41 months (range 12-164). At the end of the follow-up, seven patients were alive and experienced quiescent disease; of the remaining two, one died 12 months after diagnosis because of progressive CNS involvement, and one 25 months after diagnosis because of small cell lung cancer (treatment with PDN and SRL for ECD was conducted for 15 months and stopped when cancer was diagnosed).

One of two patients had a complete cardiac response (complete remission of pericarditis), 1/2 a complete response in the lungs and 2/5 a complete remission in cutaneous lesions. Partial

responses were observed at the following sites: long bones in 2/8 cases, CNS in 1/2 cases, retroperitoneum-perirenal space in 5/7 cases, hypothalamic-pituitary axis in 1/4 cases, skin in 1/5 cases. One patient had a progression in retroperitoneal involvement.

Treatment-related toxicity was generally mild, with Cushingoid changes, other common steroid-related side-effects and hypercholesterolemia/hypertriglyceridemia being the most frequent adverse events. One patient had to stop treatment because of pneumonia caused by sirolimus.

The three available biopsies analyzed exhibited high levels of expression of phospho-p70S6K and phospho-mTOR, confirming that the mTOR pathway is activated in ECD. Moreover, PBMCs isolated from one of these patients reflected the expression pattern of retroperitoneal tissue, suggesting that an important source of mTOR-activated signalling is mononuclear cells. Because of the paucity of available tissue and PBMC samples, we could not evaluate whether mTOR activity assessment was a predictor of response to SRL.

Conclusion. The combination of PDN and SRL is a potential treatment approach for patients with multisystemic ECD; it usually induces disease stabilization and in some cases objective responses, and has a good tolerability. The mTOR pathway seems to be activated in ECD lesions; further studies are needed to explore whether phospho-p70S6K and phospho-mTOR tissue expression predict response to SRL therapy.

4. Title: Medium and Long-Term Efficacy of Vemurafenib in Erdheim-Chester Disease.

Authors: F Cohen Aubart; L Arnaud; F Charlotte, B Hervier; S Besnard; S Barete; B Graffin; F Lifermann; JP Ory; K Hoang Xuan; N Benameur; JF Emile, Z Amoura; J Haroche

Institution: Internal Medicine Department. Hospital Pitié-Salpêtrière, University Paris 6, AP-HP, 47-83 bd de l'Hôpital, 75013, Paris, France

Presenter: Julien Haroche, MD, PhD

Introduction: Erdheim-Chester disease (ECD) is a rare, non-Langerhans form of histiocytosis of unknown origin. Between then and January 2013, more than 500 cases were reported.

First-line of treatment is interferon-alpha (IFN α) which is effective in more than half of cases, but may be poorly tolerated. Moreover, some patients are refractory and progression of disease can be associated with impairment of functional and vital prognosis. Half of ECD patients have the *BRAF*^{V600E} mutation. Vemurafenib, an inhibitor of mutant BRAF, has shown some efficacy against 2 diseases (metastatic melanoma and hairy-cell leukemia) associated with the *BRAF*^{V600E} mutation. Here, we report the middle and long term efficacy of vemurafenib in the treatment of ECD, with a particular focus on the CNS involvement, in an open-label prospective use.

Patients and methods: We conducted a prospective open-label phase 2 study from April 2012 to June 2013. All ECD patients harboring the *BRAF*^{V600E} mutation and refractory to at least one first-line treatment were eligible for receiving vemurafenib. The assessment of patients was as follows: initial evaluation, month (M) 1, M3, M6, M9 and M12 including complete physical examination, routine biological markers (such as C-reactive protein (CRP)), para-aortic CT-scan, cardiac MRI, cerebral MRI, 18^{FDG} PET-CT scan. The principal criterion of judgement was the normalisation of 18^{FDG} PET-CT scan at M6. Secondary criteria were: normalisation of 18^{FDG} PET-CT scan at M12; CRP values; quantification of the heart infiltration, of the peri-aortic sheathing and of cerebral infiltration at M3, M6 and M12. The side effects were also listed. Patients also had a monthly dermatological examination and electrocardiogram.

Results: Nine patients (4 women, 5 men) were included. One man was lost to follow-up. The mean age at beginning of treatment was 58.3 years (extremes: 33-78). The mean duration of evolution of the disease was 8.1 years. The mean duration of follow-up under vemurafenib was 13 months (extremes: 3-13). Prior treatments were corticosteroids (n=6), IFN α or peg IFN α (n=7), anakinra (n=2), rituximab (n=1), infliximab (n=1), cladribine (n=1).

The main characteristics of patients were: retro-peritoneal fibrosis (n=5), heart involvement (n=4), CNS involvement (n=5), hypothalamo-hypophyseal involvement (n=5), xanthelasmas (n=2), other cutaneous manifestations (n=2). Four patients also had langerhans cell histiocytosis histology (overlap forms of histiocytosis).

For the first 3 patients the initial regimen was 4 tablets b.i.d (=1920 mg/d) which is the dose recommended for melanoma. Due to the cutaneous side-effects, we had to taper doses to 2 tablets b.i.d (=960 mg/d) at M1, and we chose for the 5 next patients to initiate treatment at this posology. For the 3 patients who reached one year of treatment we tapered the dose to 1 tablet b.i.d (=480 mg/d) due to arthralgias for 2 of them and lack of progression of disease in all.

All patients had elevated CRP values at the initiation of treatment. All but one patient normalized their 18^{FDG} PET-CT scan at M3, and CRP values returned within normal values. MRI of the heart showed disappearance of the "pseudo-tumoral" infiltration of right atrium in 2 patients. We also

found in 4 patients a substantial regression of the infra-tentorial or retro-orbital infiltrations and the disappearance of the gadolinium uptake in all patients.

For each patient, the most important Standardized Uptake Value (SUV) values on serial 18FDG PET-CT scan constantly diminished over time and sometimes went back to normal values.

Side effects were mainly dermatological: keratosis pilaris (n=4), keratoacanthoma (n=2), simple naevi (n=2), photosensitivity (n=3), alopecia and depilation (n=8), cutaneous squamous cell carcinoma (n=1), arthralgias (n=4).

Conclusions: Vemurafenib seems effective to treat ECD patients refractory to first-line treatment, particularly in case of severe cardiac and CNS involvements. Despite cutaneous side effects, we believe BRAF inhibition should be considered in a larger cohort of BRAFV600E-associated histiocytosis patients, particularly those with life-threatening disease. The therapeutic response seems to maintain at 13 months for the first three patients, and should be confirmed among the other ones.



“Supporting those affected by Erdheim-Chester Disease”