Drug manegement of ECD

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Erdheim-Chester Disease

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- A rare form of non-Langerhans' cell histiocytosis of unknown origin, characterized by xanthogranulomatous infiltration of bones and soft tissues with foamy, "lipid-laden", histiocytes, mononuclear cells and fibrosis
- ECD histiocytes express CD68 but lack typical markers of LCH (S-100, CD1a)
- Clinical findings and symptoms depend on the affected organs and by the extension and severity of infiltration
- Prognosis is variable and depends on extra-skeletal involvement

Campochiaro C et al, Eur J Int Med 2015
Warner ME, Mayo Clin Proc. 2001;76:529-532

Erdheim-Chester Disease

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- ECD clinical spectrum extends from indolent forms with sole bone localization to life-threatening variants with multi-organ involvement

- Treatment must be patient - tailored, according to the specific clinical and radiological features characterizing the individual

Diamond EL et al. Blood. 2014 Jul 24;124(4):483-92
Campochiaro C et al, Eur J Int Med 2015

Erdheim-Chester Disease

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Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease

Eli L. Diamond,[1] Lorenzo Dagna,[2] David M. Hyman,[3] Giulio Cavalli,[2] Filip Janku,[4] Juvianee Estrada-Veras,[5] Marina Ferrarini,[6] Omar Abdel-Wahab,[7] Mark L. Heaney,[8] Paul J. Scheel,[9] Nancy K. Feeley,[9] Elisabetta Ferrero,[6] Kenneth L. McClain,[10] Augusto Vaglio,[11] Thomas Colby,[12] Laurent Arnaud,[13] and Julien Haroche[13]

Diamond EL et al. Blood. 2014 Jul 24;124(4):483-92

Erdheim-Chester Disease treatment

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- No clinical randomized trial available to date

- Many different pharmacological approaches have been developed in time

Diamond EL et al. Blood. 2014 Jul 24;124(4):483-92
Campochiaro C et al, Eur J Int Med 2015

ECD: treatment

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3 main drug categories are used in ECD treatment:

- Anti metabolites
- Interferon (IFN)-α
- Anti-cytokine directed therapies
- Targeted therapy: BRAF and MEK inhibitors

Diamond EL et al. Blood. 2014 Jul 24;124(4):483-92
Campochiaro C et al, Eur J Int Med 2015

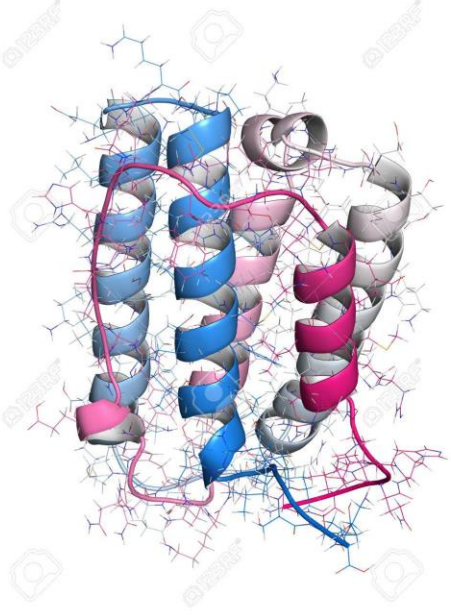
ECD treatment

anti-metabolites

- Cladribine
- Methotrexate

Interferon-α

IFN-α has the largest amount of supporting evidence of efficacy in ECD treatment



Diamond EL et al. Blood. 2014 Jul 24;124(4):483-92
Campochiaro C et al, Eur J Int Med 2015

Interferon-α

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IFN-α efficacy was first pointed out in 2005

Successful treatment of Erdheim-Chester disease, a non–Langerhans-cell histiocytosis, with interferon-α

Fadi Braiteh, Cynthia Boxrud, Bita Esmaeli, and Razelle Kurzrock

Erdheim-Chester disease is a rare non-Langerhans histiocytosis with multisystem involvement. To date, there is no standard treatment for this disorder, and more than half of the patients succumb within 3 years. Because interferon-α promotes the terminal differentiation of histiocytes and dendritic cells, we hypothesized that this molecule would be a useful therapy for Erdheim-Chester disease. We therefore treated 3 patients with advanced disease with interferon-α at a starting dose of 3 to 6 × 10^6 units, which was later reduced, during maintenance, to 1 × 10^6 units subcutaneous 3 times per week. Marked improvement was noted in all patients, with substantial retro-orbital disease regression within 1 month. Improvement in bone lesions, pain, diabetes insipidus, and other manifestations was gradual over many months. Responses were durable (3+ to 4.5+ years). Our observations suggest that this well-tolerated therapy has a significant effect on the course and outcome of Erdheim-Chester disease. (Blood. 2005;106:2992-2994)

Interferon-α

- IFN-α represents I line therapy in uncomplicated forms of ECD

- Limited efficacy in life-threatening forms

Interferon-α

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- Standard dose
  - IFNα 9 mIU/wk (3 injections weekly)
  - PEG-IFNα 135 µg/wk
- High dose
  - IFNα ≥ 18 mIU/wk (3 injections weekly)
  - PEF-IFNα ≥ 180 µg/wk
- Tolerance with high-dose
  - 54% no adverse events
  - Severe asthenia 41%
  - Myalgia 15%
  - Pruritus 4%
  - Thrombocytopenia 4%
  - Depression 8%
  - Discontinuation 13%

- No significant difference in side effects between standard and high dose

Interferon-α

- "Flu"-like symptoms
  - Napping and resting when required
  - Maintaining daily schedule and keeping active
  - Acetominophen
    - 1 g 1 hour before injection and 3-4 hours after
  - Judicious timing
    - Predictable time after injection
- Injection site irritation
  - Inject with sufficient force
  - Beyond the superficial skin layer into sc tissue
  - Rotate injection site
- Interferon-induced autoimmunity
  - Thyroid / SLE / Thrombocytopenia

Interferon-α

- Neuropsychiatric manifestations
  - Depression
    - Up to 16% of pts
    - Major manifestations→ discontinution and psychiatrist
    - Mild depression
      - Citalopram 20 mg → titrated upwards
      - Psychological and psychiatric support
  - Fatigue
    - Adequate fluid balance
    - Behavioral strategies
    - Social support network
    - Paroxetine
  - Insomnia
    - Behavioral strategies → sleep hygiene
    - Zolpidem 10 mg
    - Trazodone 25 to 150 mg
  - Hair loss
    - Transient

Anti-cytokine therapies

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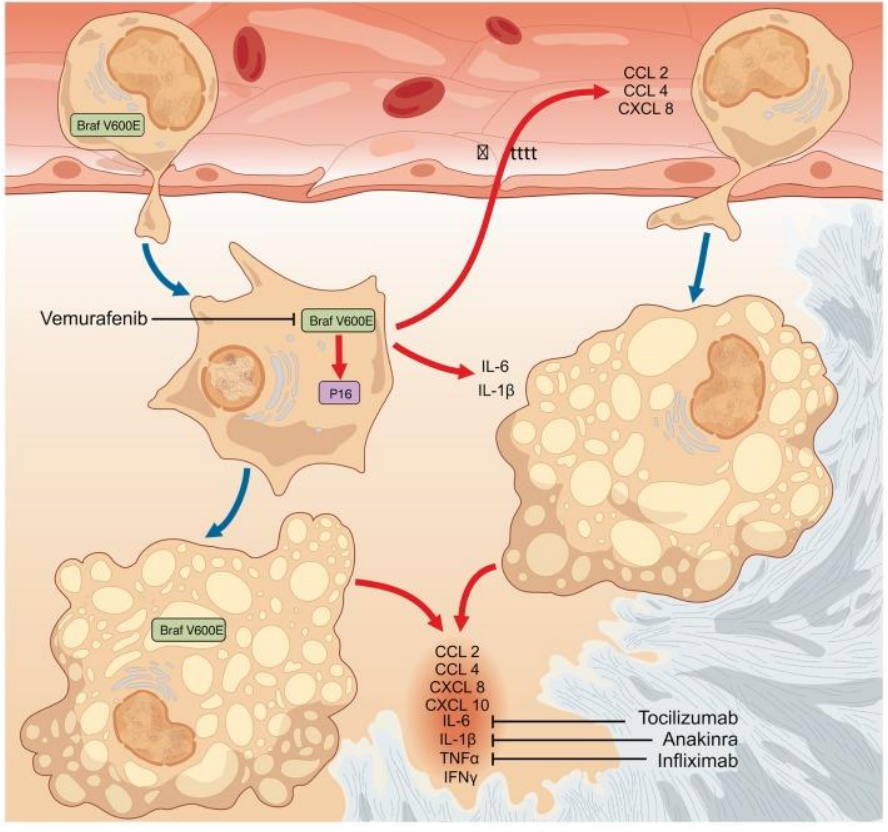
- ECD is charcterized by a typical pro-inflammatory cytokine pattern: increased IFN-α, IL-12, MCP-1; reduced IL-4 and IL-7
- Often elevated CRP and ESR

Diamond EL et al. Blood. 2014 Jul 24;124(4):483-92
Campochiaro C et al, Eur J Int Med 2015

Anti-cytokine therapies



Cavalli et al, Frontiers in Immunology, 2014

Anti-cytokine therapies

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- Conflicting data, anecdoctal reports of efficacy
- Good tolerability profile
- II/III line treatment

IL-1R antagonist: anakinra

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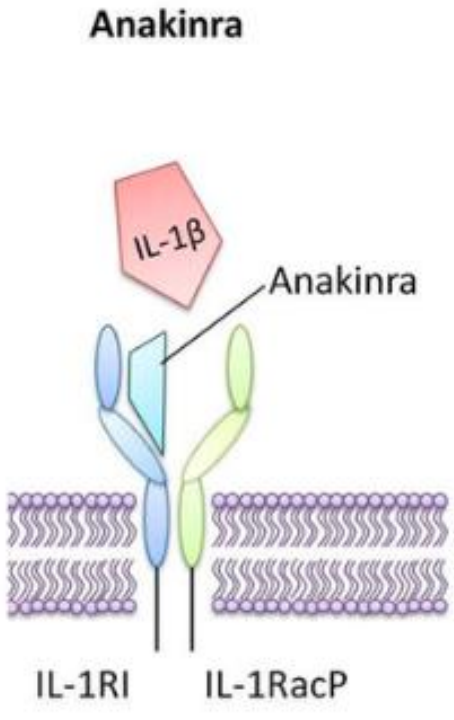

IL-1R antagonist: anakinra

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- About 50% clinical-response rate; variable effect on lesions progression

Goyal et al, British Journal of Hematology, 2017
Aubart et al, Blood, 2016
Diamond et al, Blood, 2016

- Possible role in combined treatment with BRAF and MEK inhibitors to lower targeted therapy toxicity

Franconieri, Acta Oncologica, 2016

IL-1R antagonist: anakinra

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Treating Heart Inflammation With Interleukin-1 Blockade in a Case of Erdheim–Chester Disease

Alessandro Tomelleri[1], Giulio Cavalli[1], Giacomo De Luca[1], Corrado Campochiaro[1], Teresa D'Aliberti[2], Moreno Tresoldi[2] and Lorenzo Dagna[1]*

IL-1R antagonist: anakinra

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- Remarkable record of safety
  - Short half-life of 6 h → prompt discontinuation
- Risk for virus-type, non-life-threatening upper airway infections
- Rare opportunist infections
- Daily s.c. administrations
  - Often cause injection site reactions
  - Usually resolve within 14 days
  - Topical steroid
  - Anti-H1 drugs

TNF-α inhibitors

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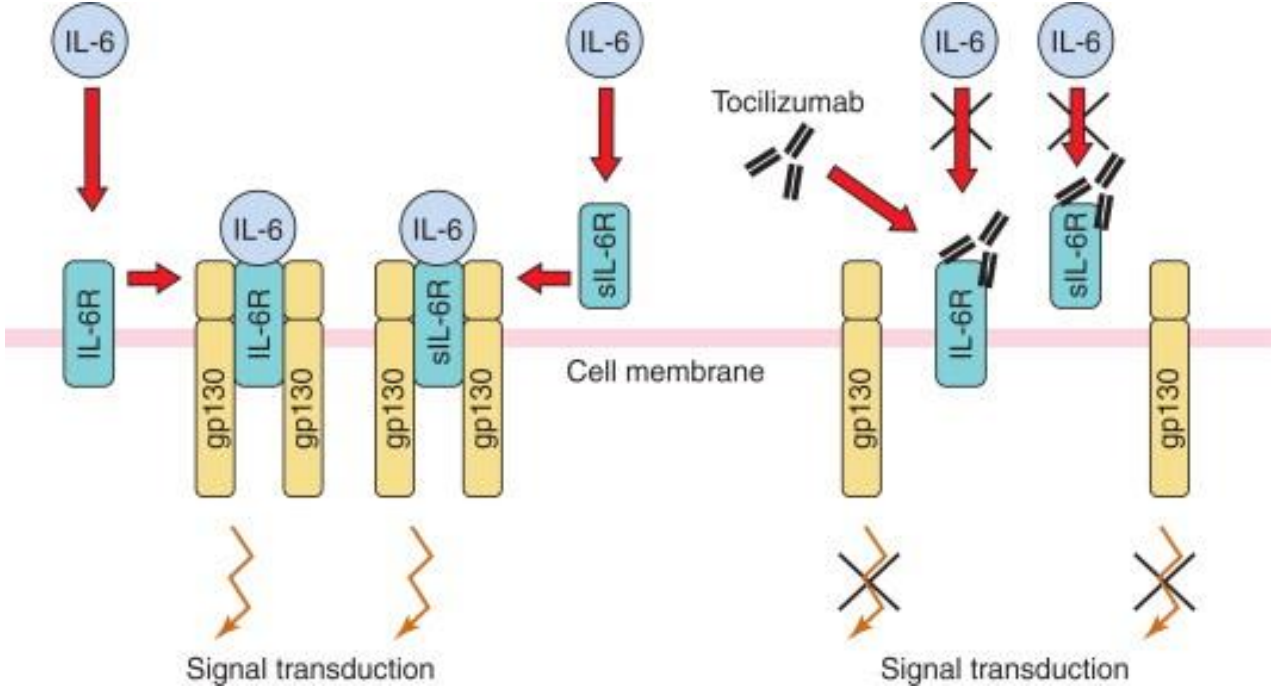
- Infliximab: most studied TNF-α inhibitor in ECD
- Variable efficacy and favorable tolerability profile

Aubart, Annals of Rheumatic Diseases, 2018
Goyal et al, British Journal of Hematology, 2017

- Considerable efficacy in case of ECD with cardiovascular involvement

Dagna et al, Journal of Clinical Oncology, 2012

IL6-R inhibitor: tocilizumab



IL6-R inhibitor: tocilizumab

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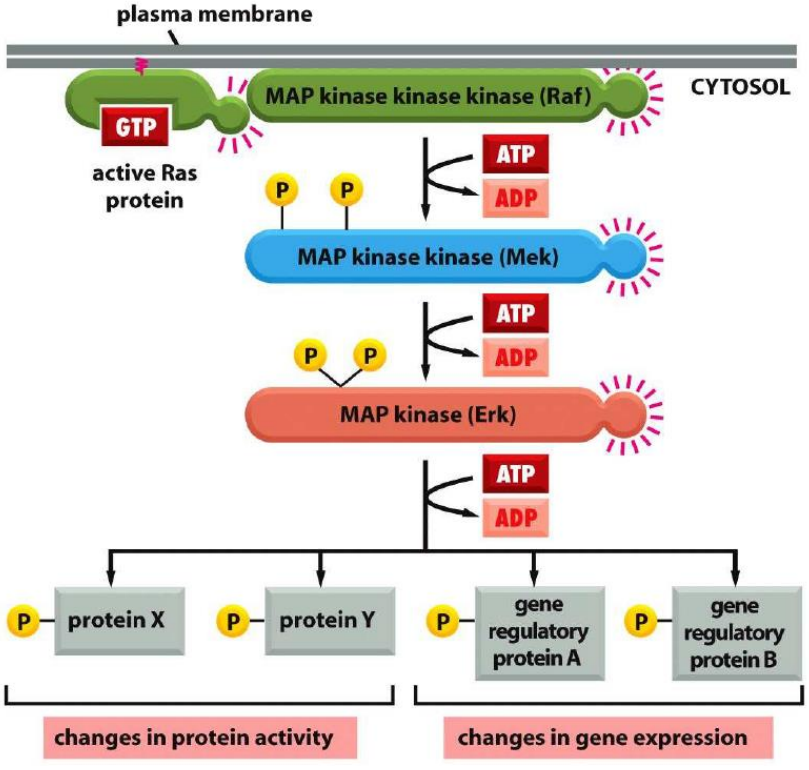
- Only a single study to date analyzed the use of tocilizumab in ECD

- Good efficacy for bone, retroperitoneal and heart lesions. No efficacy in case of central nervous system involvement.

Berti et al, Oncoimmunology, 2017

ECD: targeted therapy



Diamond EL et al. Blood. 2014 Jul 24;124(4):483-92
Campochiaro C et al, Eur J Int Med 2015

ECD: targeted therapy

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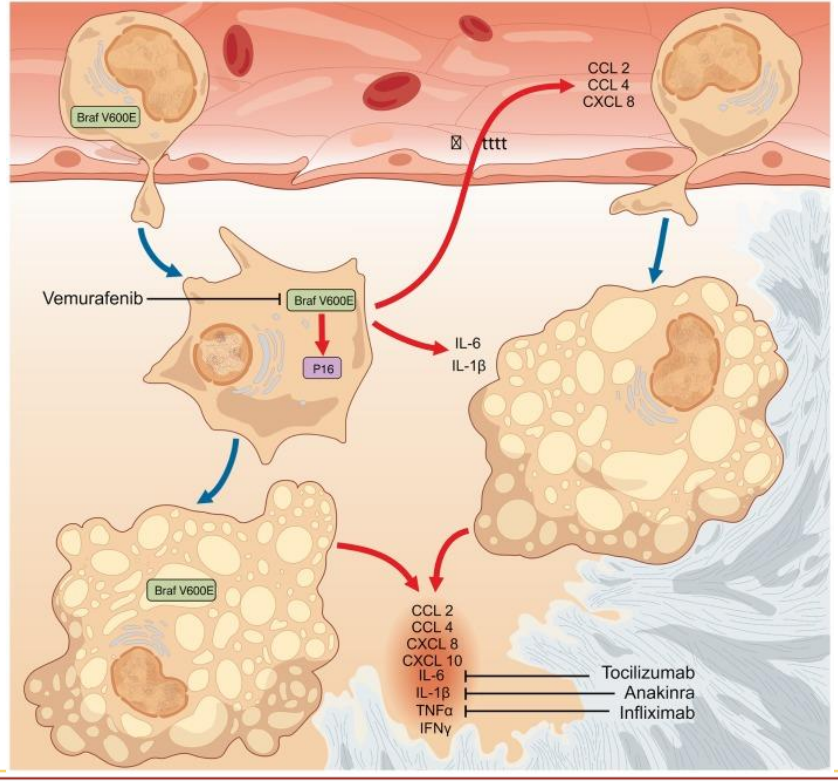
- A significant proportion of patient with ECD has a mutation in the BRAF gene

- In patients with the mutation, a variable fraction of cells in the ECD lesions are mutated the others are not

Cangi G et al ARD 2015
Diamond EL et al. Nature 2019

ECD: targeted treatment



Cavalli et al, Frontiers in Immunology, 2014

ECD: targeted therapy

In patients without BRAF mutation, other alterations have been identified in genes codifying for key-elements of the same pathway:

- ARAF
- KRAS, NRAS
- MEK1

Diamond EL et al. Nature 2019

ECD: targeted therapy

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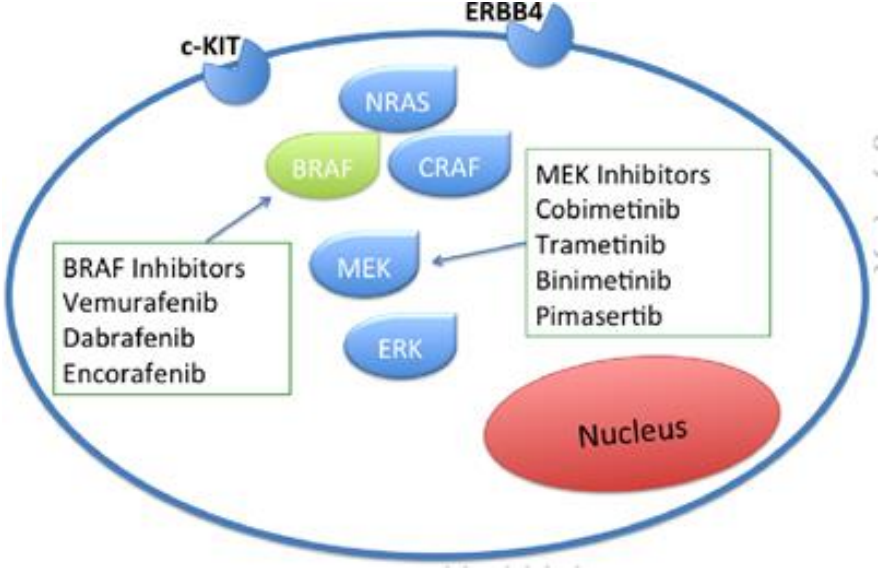
2 classes of targeted drugs



ECD: targeted therapy

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- Both BRAF and MEK inhibitors have been developed for the treatment of metastatic melanoma

- High efficacy and significant toxicity, justifiable by the poor prognosis of this malignant condition

ECD: targeted therapy

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- In the last years these drugs have been exploited for ECD treatment

- The BRAF inhibitor vemurafenib and the MEK blocker cobimetinib are the most used ones

ECD: targeted therapy

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- Vemurafenib is prescribed in patients with life-threatening (CNS or heart involvement) forms of ECD in whose bioptic hystiocites V600E mutation BRAF is identified

- Cobimetinib is prescribed in patients with life-threatening forms BRAF wild-type or who have controindications or developed intolerance to vemurafenib

ECD: targeted therapy

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- Both vemurafenib and cobimetinib are administered at a lower dosage in ECD than in melanoma to reduce toxicity

- Vemurafenib is given at the dosage of 960 mg/day (instead of 1920 mg) and cobimetinib at 40 mg/day (instead of 60 mg) for 21 days/month

ECD: targeted therapy

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- Vemurafenib most common adverse reactions: prolonged QT interval, acneiform rash and photosensitivity, gastrointestinal symptoms, renal insufficiency

- Cobimetinib most common adverse reactions: acneiform rash and photosensitivity, diarrhea, cardiomyopathy

ECD: targeted therapy

- Data available to date confirm the dramatic clinical and radiogical efficacy of cobimetinib and vemurafenib in ECD

- However, these therapies can be associated with high toxicity and must therefore should be considered in more severe forms

Aubart et al, Blood, 2019
Diamond et al, Nature, 2019

Management of Skin Toxicities

Erythema nodosum-type rash	• Emolients, topical steroids, analgesia • Consider oral steroids: prednisolone 0.5 mg/kg/day (up to 60 mg/kg/day) for 5–7 days [Sinha *et al.* 2012] • Consider interrupting KI • Seek dermatology advice
Photosensitivity	• Prophylactic sunscreen SPF >30 (UVB) plus 5* (UVA) rating; cover up • Treat burns as appropriate
Squamous papillomas/warts	• If problematic, refer to dermatologist for cryotherapy or curettage
Keratoacanthoma, SCC	• Refer urgently to dermatologist for intervention, particularly if rapidly enlarging or symptomatic
Dry skin	• Soap substitutes, emolients
Folliculitis or cysts	• Soap substitutes • Antibiotics – topical or systemic • Consider excision for symptomatic, uninfected cysts

Management of GI effects (diarrhea)

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- Common side effect: 25% incidence
- Mild to moderate
- Mainly outpatient
- Dietary modifications
  - Bananas
  - Rice
  - Apples
  - Toast
- Stop lactose-containing products

Management of ostheoarticular complaints

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- Arthralgia usually in the first months
- Incidence 56%
- Any joint can be affected
- Pain may be intermittent or constant
- Overt polyarthritis may develop after 1 week
- May be self-limiting

Management of cardiac complications

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- **<u>QTc prolongation</u>** (vemurafenib)
  - Observed in 2% of pts in registration studies
    - 2 pts developed cardiac arrhythmia
      - Both had hypertension and iscaemic heart disease
    - Median time to development 1.9 months
    - Always check magnesium levels
      - Treatment not recommended in pts with known low Mg
    - Check QTc before starting vemurafenib
      - < 500 ms

Renal complications

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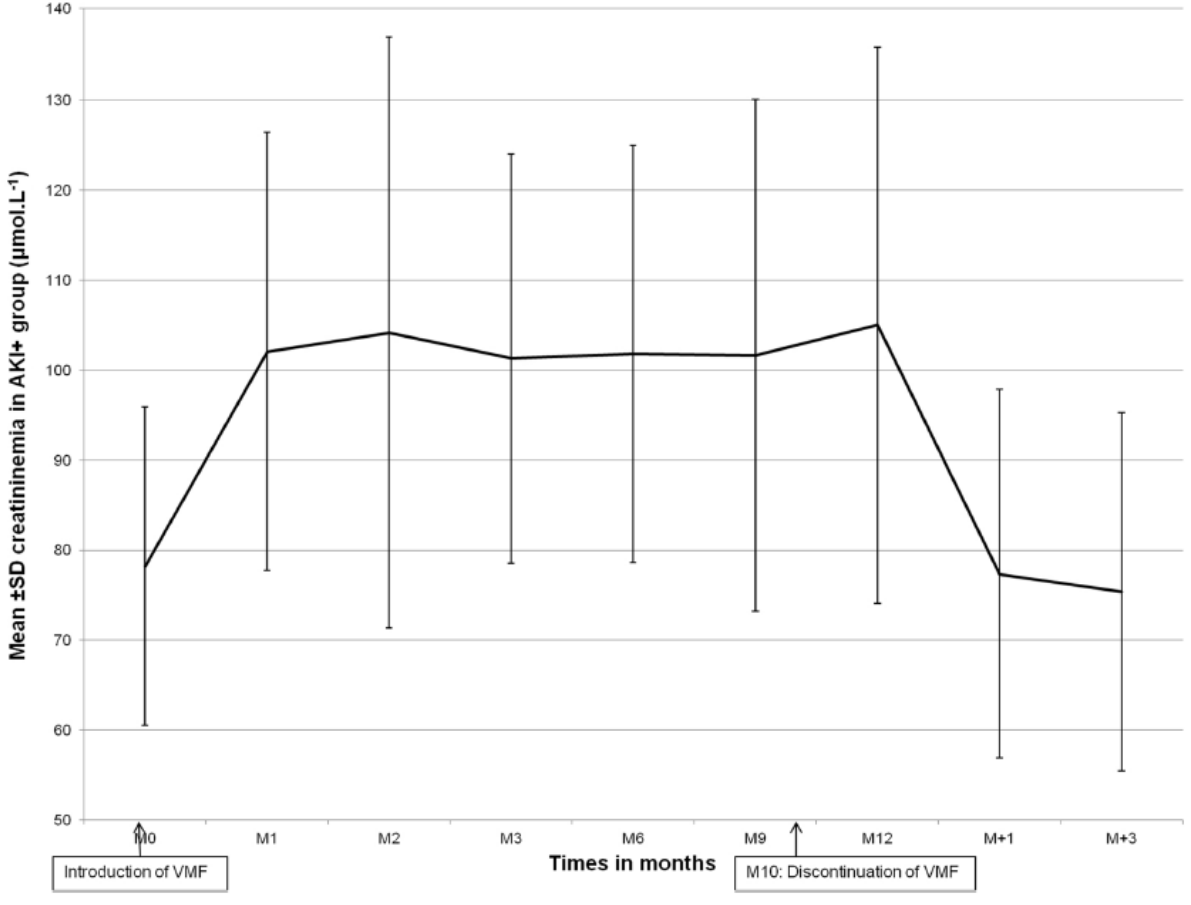
- Retrospective data on 74 pts
  - Common 60%
  - Stage I AKI
  - During the first 3 months of treatment
  - Serum creatinine initially rose to reach a stable concentration
  - Acceptable?
  - More frequent in male patients
  - Acute tubular damage → tubular interstitial nephritis
  - When stopped → complete renal recovery after 3 months

Renal complications



Other complications

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- Hypertension
  - Check regularly blood pressure
- Hyperglycemia
  - 2 – 6%
  - Usually in pts already diabetic
- Liver abnormalities
  - 13%
  - Elevation ALP, bilirubin and transaminases
- Hemorrhagic complications (cobimetinib)

Combined treatment

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Combined treatment with anticytokine drug(s) could reduce vemurafenib and cobimetinib toxicity, making targeted therapy more tolerable

Superior efficacy and tolerance of reduced doses of vemurafenib plus anakinra in Erdheim-Chester disease: Towards the paradigm of combined targeting and immune therapies

Fréderic Franconieri, Nicolas Martin-Silva, Hubert de Boysson, Françoise Galateau-Salle, Jean-François Emile, Boris Bienvenu & Achille Aouba

Diabetes Insipidus

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- Desmopression (dDAVP)
  - Intranasal (pref), oral, sublingual or parenteral
  - Decreased absorption with meals (40 – 50%)
  - 5% absorbed from the gut
  - 0.1 mg intranasal ≅ 2.5 – 5 mg oral
- Long-term data
  - No attenuation of antidiuretic effect
  - No side effect
  - No antibody formation

Pain Management

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- **Acetomoniphen (paracetamol)**
  - First-line up to 4 g/day
  - Combined with opiod medications to reduce the amount of opioid needed
- **NSAIDs**
  - Avoid if CKD
  - Interference with platelet aggregation
  - Evaluate cardiovascular risk factors
- **Opiods**
  - Start with low dose of immediate-release/short-acting agents
  - Titrate the dose by slowing increasing it
    - No > than 25 – 50 % of the total daily dose
    - Linear dose response curve
  - Tramadol and tapentadol
    - μ and monoamine receptors
    - Neuropathic and chronic musculoskeletal pain

Opioid Side Effects

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- Monitor patients for
  - Constipation
    - Laxative prescription
    - Combination with naloxone
  - Nausea and vomiting
    - Titrate the dose slowly
  - Sedation
    - Reduce dosage
    - Avoid combination with sedative drugs
  - Impaired psychomotor function
    - Reduce dosage
    - Avoid drugs with monoamine antagonist action
  - Urinary retention
    - Prefer short half-life agents (fentanyl)
    - Combination with naloxone

Conclusions

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- There is no absolute and un universal consensus about the correct pharmacological approach for ECD treatment

- A patient-tailored therapy is necessary: clinical, radiological and pathological features must be taken in consideration on a case by case basis

Conclusions (II)

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- IFN-α represents the I line treatment in indolent forms with isolated bone localization

- Life-threatening forms require targeted therapies such as those with vemurafenib and cobimetinib, both associated with high efficacy and toxicity

Conclusions (III)

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- In recent years many progresses have been made, leading to the development of new therapeutic approaches which have dramatically increased ECD life-span

- A better knowledge of ECD pathogenesis is necessary in order to develop new drugs to further improve quality of life and prognosis in ECD patients

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