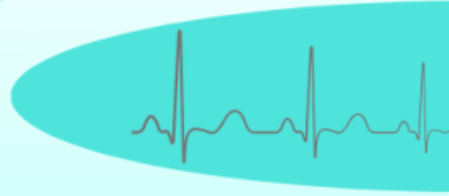


# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas

25 de noviembre 2025 | Nh Collection Sevilla



## Síndrome Hemofagocítico *Linfohistoicitosis Hemofagocítica*

**Jesús Corral, MD**

**Director de la UGC Oncología Médica  
Director del Programa Oncohematología  
Hospital Universitario de Jerez-INIBICA**



Unidad Oncología Médica  
Hospital Universitario de Jerez



INSTITUTO DE INVESTIGACIÓN E  
INNOVACIÓN BIOMÉDICA DE CÁDIZ

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Disclosure

- I have received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations:

AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, F. Hoffmann-Roche, Eli Lilly, MSD, Takeda, Janssen, GSK, Novartis, Merck, Amgen, BeOne, Sanofi, Regeneron, Biocartis, Daiichi Sankyo, Pierre Fabre & Pfizer.

- I declare no conflict of interest.

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Outlook

- Introduction
- HLH & Cancer
- Treatment algorithm proposal
- Conclusions

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas

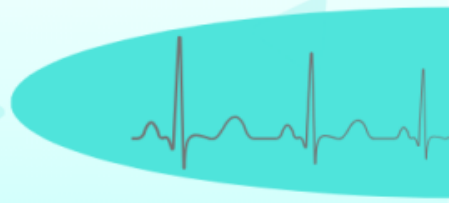


## Outlook

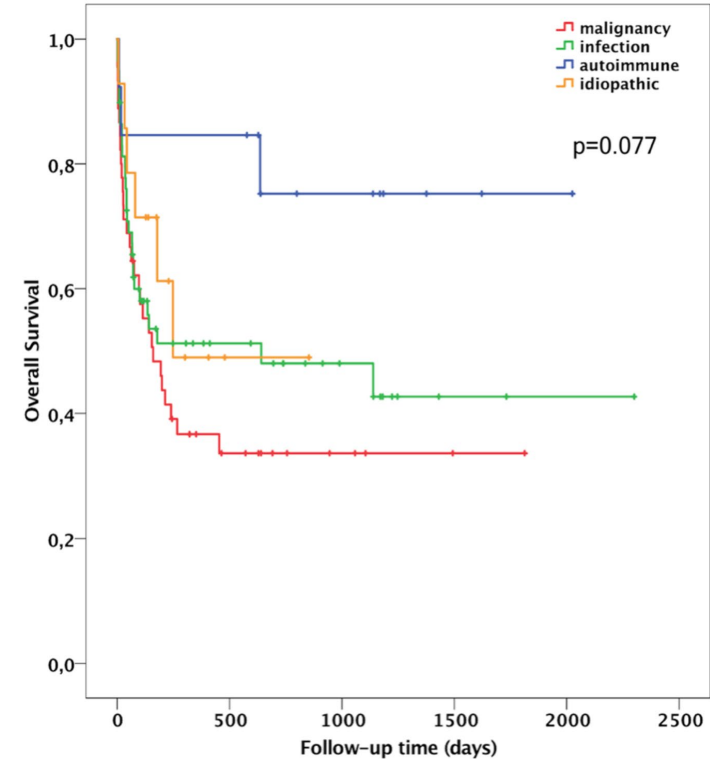
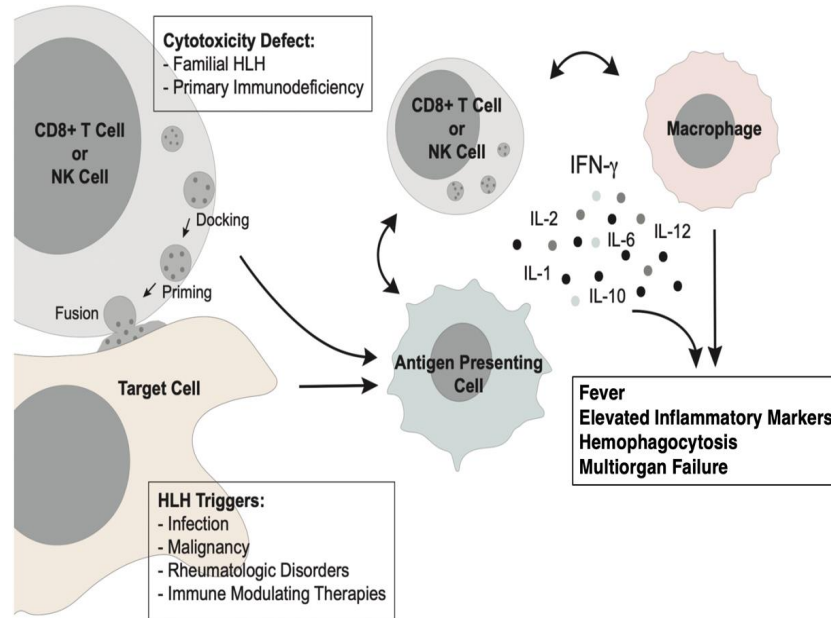
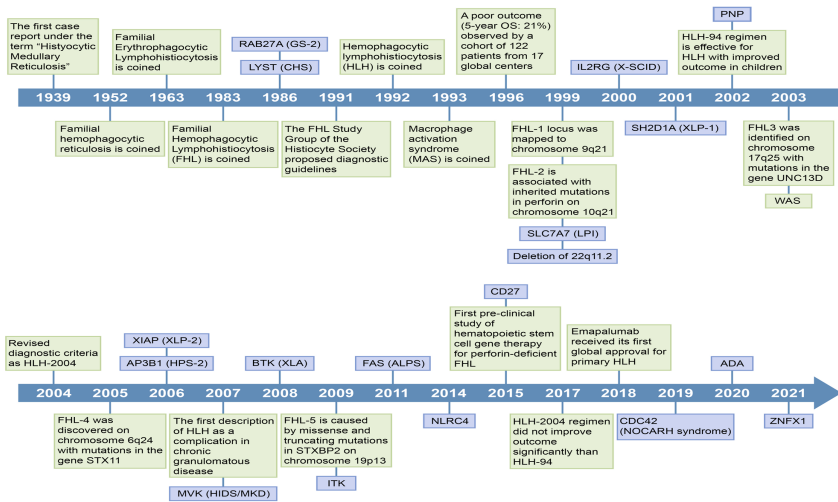
- Introduction**
- HLH & Cancer
- Treatment algorithm proposal
- Conclusions

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Introduction: HLH overview

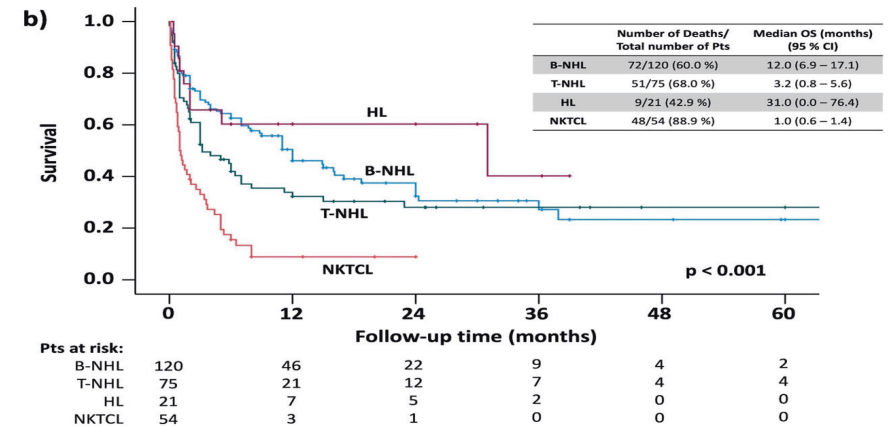
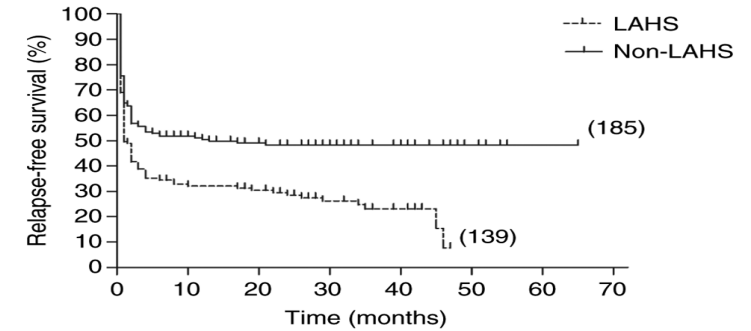
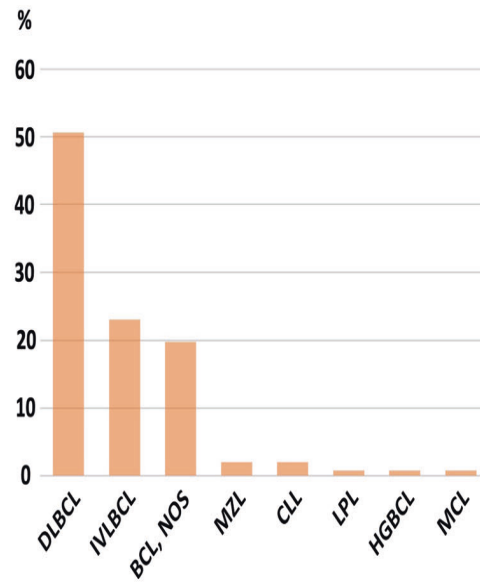
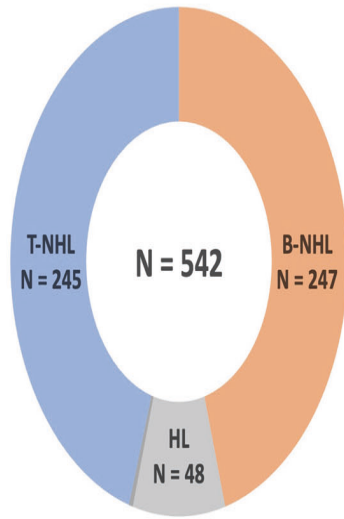
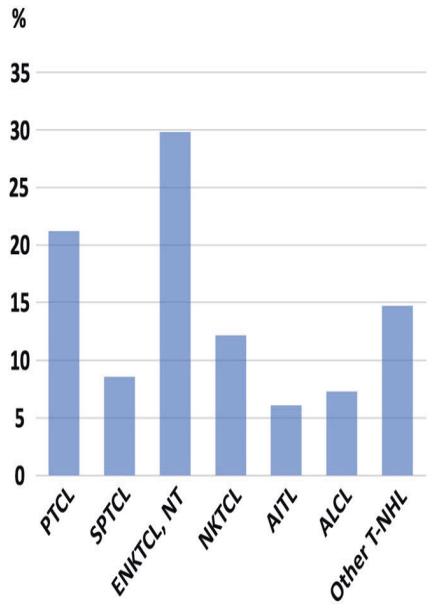


# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Introduction: HLH & Haematological tumors

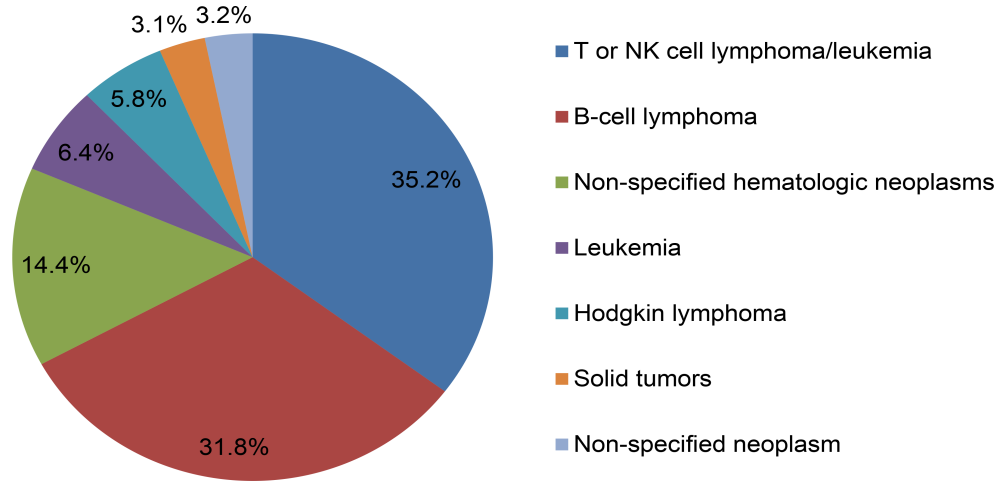


# II Jornada del paciente con cáncer en situación crítica

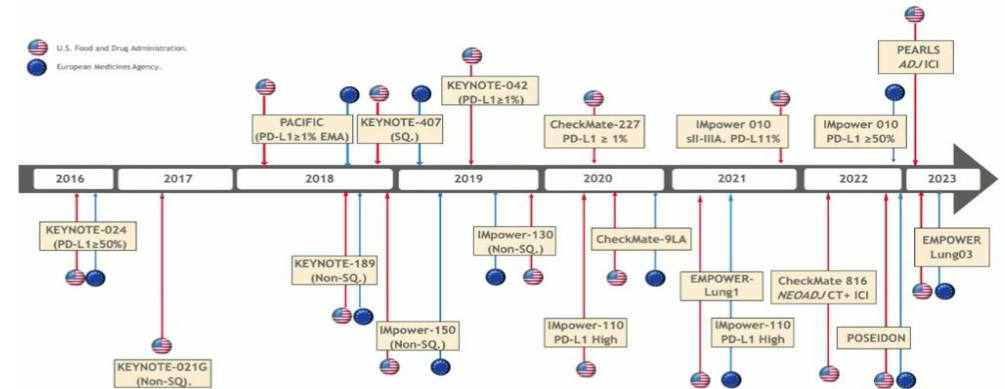
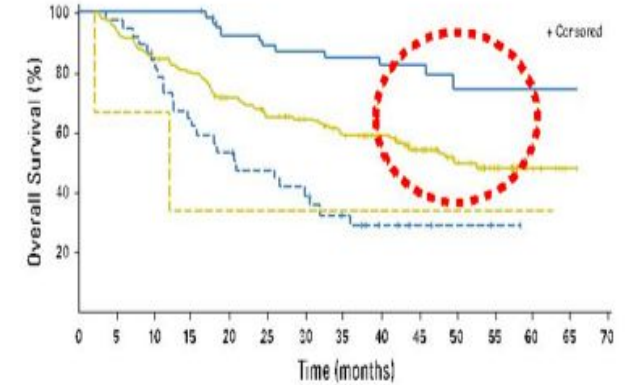
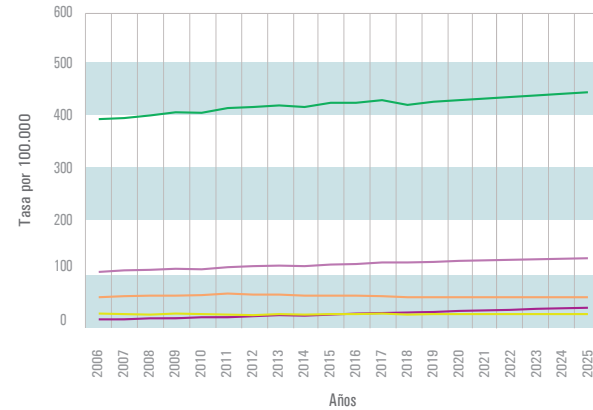
Coordinación en la instauración de medidas de soporte agresivas



## Introduction: *HLH & Solid tumors*



Wilms tumor, germ cell tumor, lung cancer, colon cancer, prostate cancer, hepatocellular carcinoma, squamous cell carcinoma

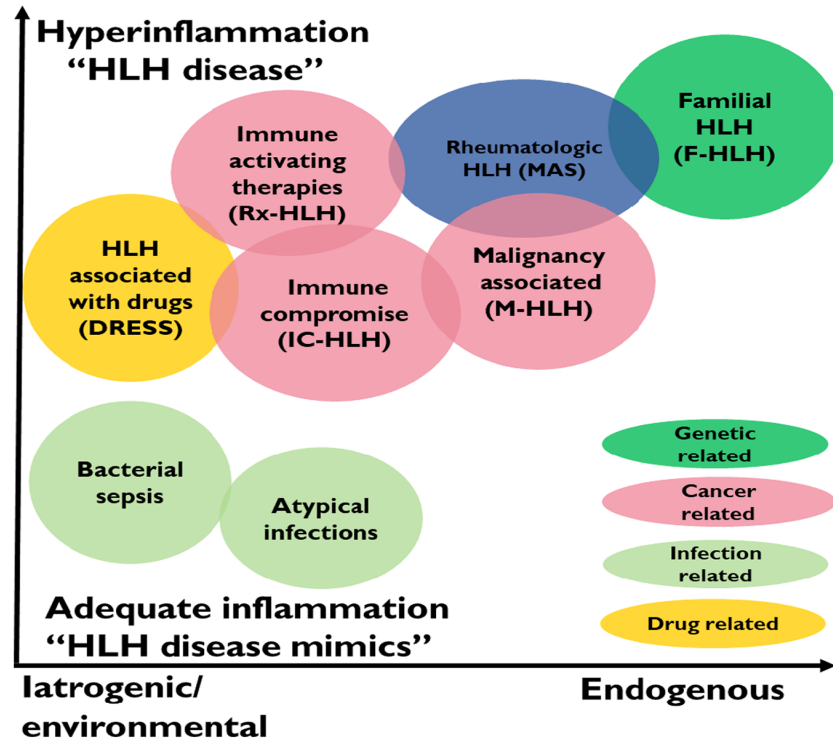


# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Introduction: *HLH* Diagnosis challenge



### HLH-2004 diagnostic criteria

| Feature                                       | Cut off                      |
|---|------------------------------|
| 1. Fever                                      |                              |
| 2. Splenomegaly                               |                              |
| 3. Cytopenia                                  | ≥2 cell lines                |
| Hemoglobin                                    | < 90 g/L (neonates <100 g/L) |
| Platelets                                     | <100x10 <sup>9</sup> /L      |
| Neutrophils                                   | <1x10 <sup>9</sup> /L        |
| 4. Hyperferritinemia                          | >500 μg/L                    |
| 5. Hypofibrinogenemia or hypertriglyceridemia | < 1.5 g/L<br>> 3 mmol/L      |
| 6. Elevated soluble CD25                      | > 2400 U/mL                  |
| 7. Hemophagocytosis                           | Bone marrow, other tissues   |
| 8. Reduced or absent NK cytotoxicity          |                              |

### Other features

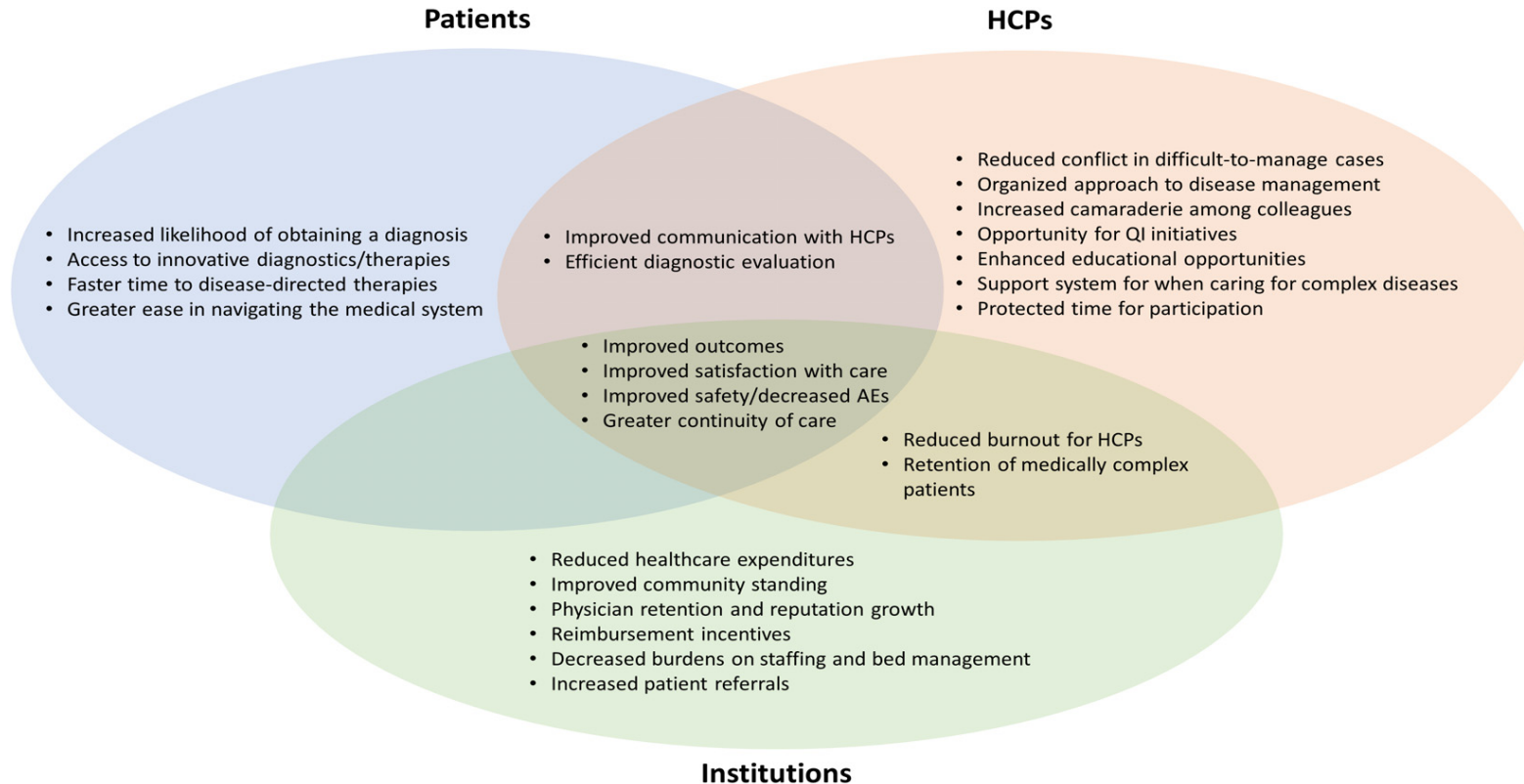
- Elevated transaminases and bilirubin
- Elevated lactate dehydrogenase
- Elevated d-dimers
- Elevated cerebrospinal fluid cells and/or protein

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas

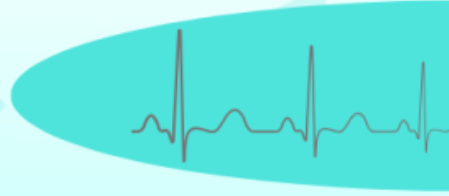


## Introduction: *Multidisciplinary approach*



# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Introduction: Collaborative consortium



# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Outlook

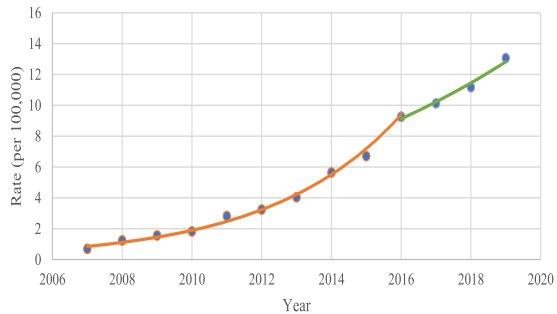
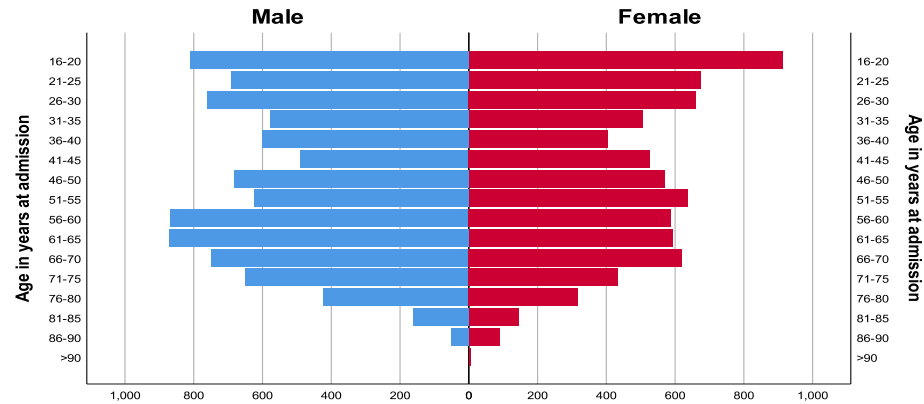
- Introduction
- HLH & Cancer**
- Treatment algorithm proposal
- Conclusions

# II Jornada del paciente con cáncer en situación crítica

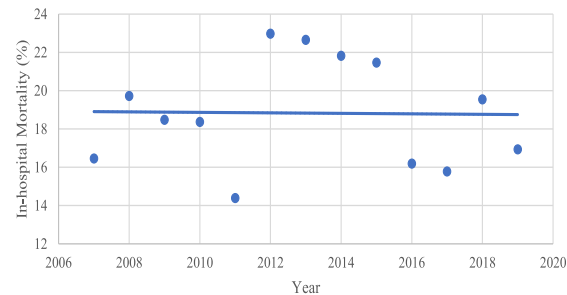
Coordinación en la instauración de medidas de soporte agresivas



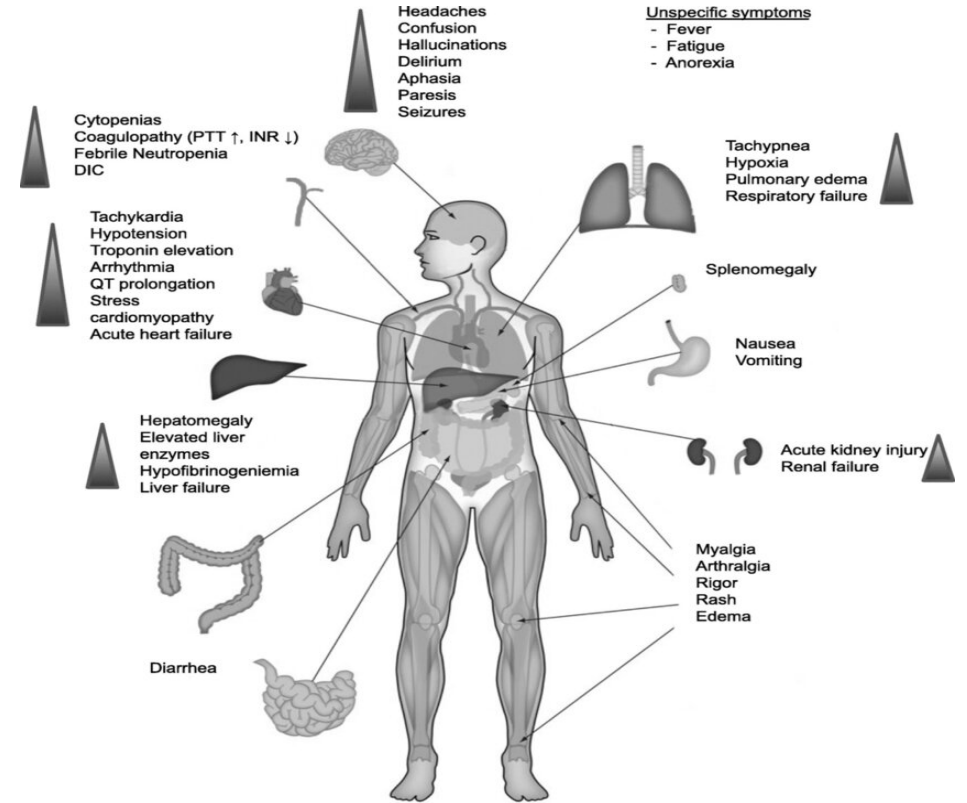
## HLH & Cancer: *Underdiagnosed disease*



● 2007-2016 APC = 30.47;  $p < 0.0001$  ● 2016-2019 APC = 11.03;  $p = 0.20$

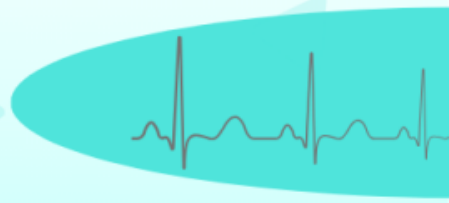


● 2007-2019 slope = -0.01;  $p = 0.95$

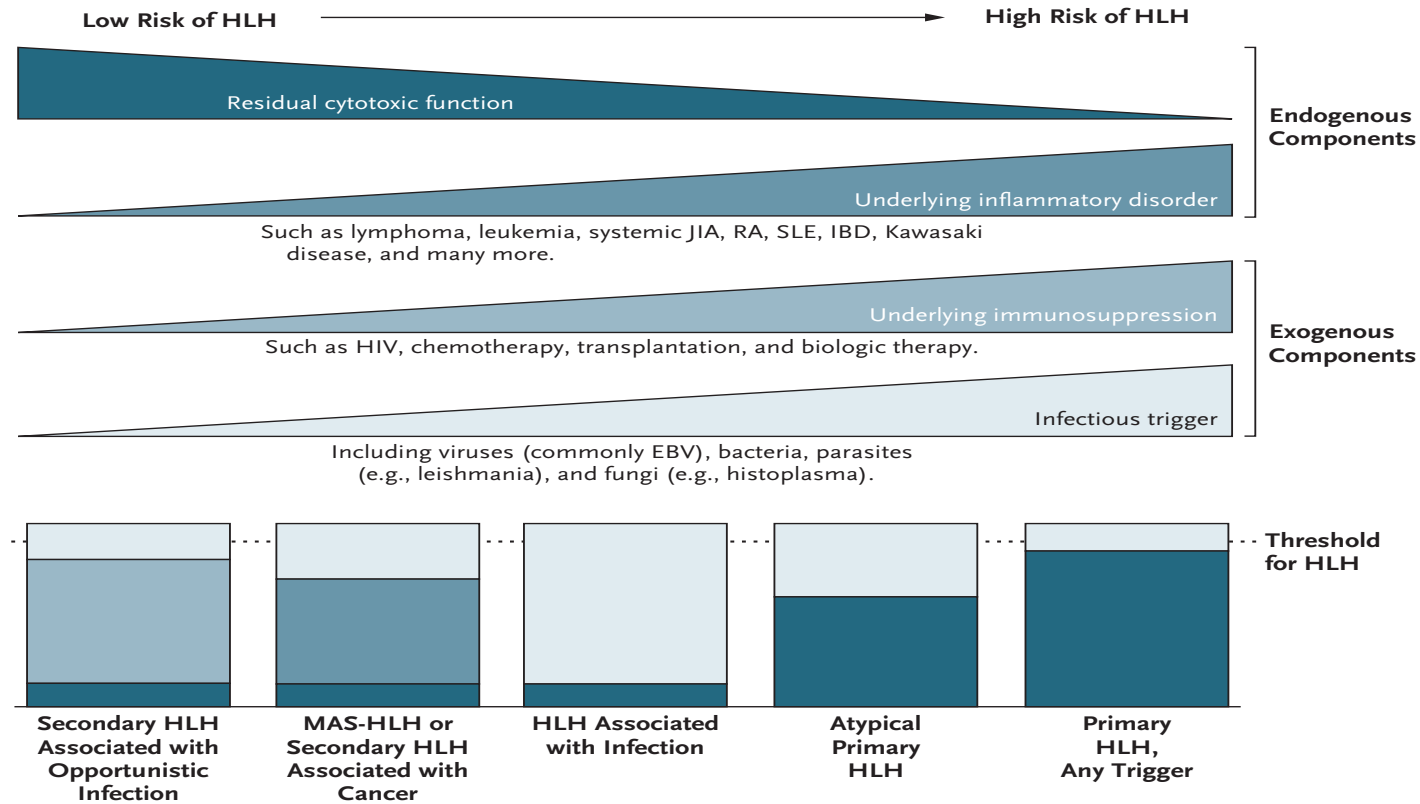


# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas

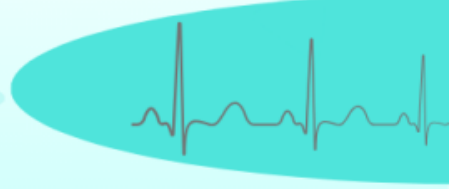


## HLH & Cancer: *Brisse model*

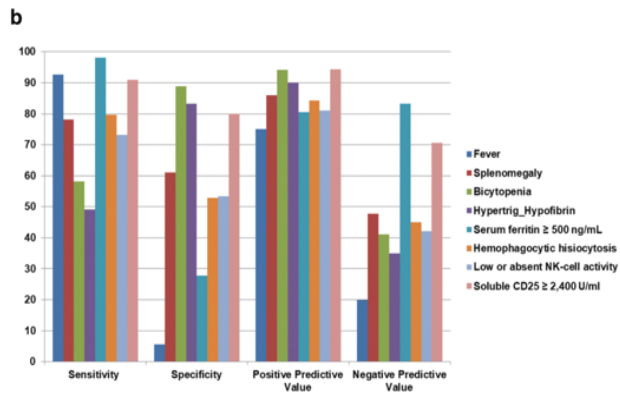
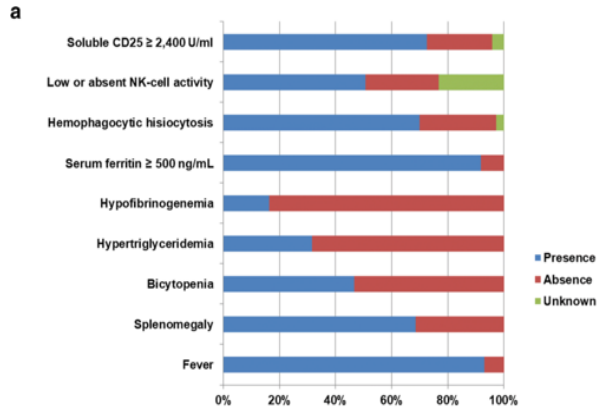


# II Jornada del paciente con cáncer en situación crítica

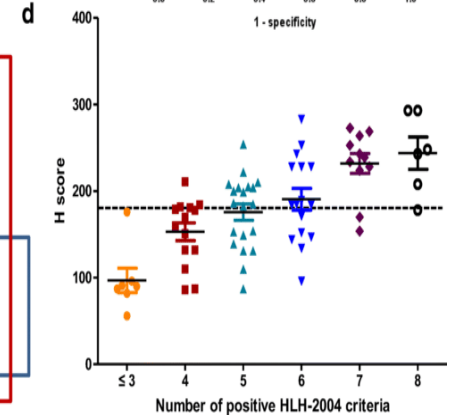
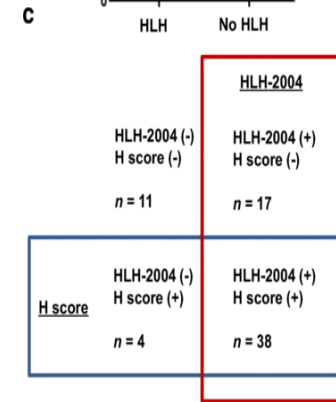
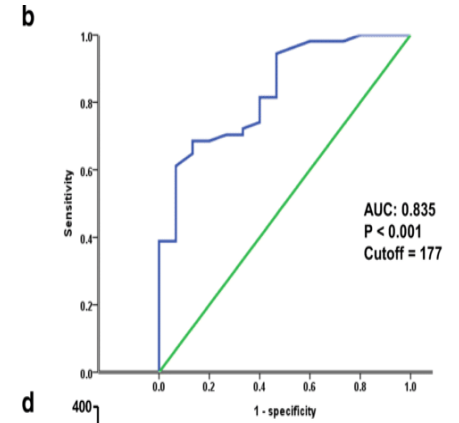
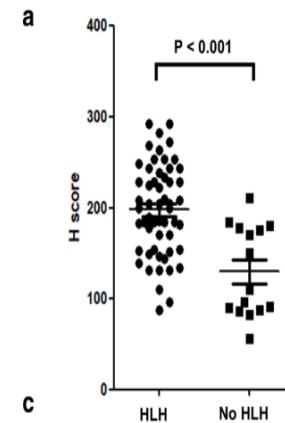
Coordinación en la instauración de medidas de soporte agresivas



## HLH & Cancer: Updated diagnosis criteria



| Parameter   | No. of points (criteria for scoring)   | Patient's score at admission |
|---|--|------------------------------|
| Known underlying immunosuppression                | 0 (no) or 18 (yes)   | 0                            |
| Temperature ( $^{\circ}$ C)                       | 0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)   | 33                           |
| Organomegaly                                      | 0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly) | 23                           |
| No. of cytopenias                                 | 0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)                               | 24                           |
| Ferritin (ng/ml)                                  | 0 (<2000), 35 (2000–6000), or 50 (>6000)   | 35                           |
| Triglyceride (mmol/l)                             | 0 (<1.5), 44 (1.5–4), or 64 (>4)   | 44                           |
| Fibrinogen (g/l)                                  | 0 (>2.5) or 30 ( $\leq$ 2.5)   | 30                           |
| Serum glutamic oxaloacetic transaminase (IU/l)    | 0 (<30) or 19 ( $\geq$ 30)   | 19                           |
| Hemophagocytosis features on bone marrow aspirate | 0 (no) or 35 (yes)   | 0                            |
| <b>TOTAL</b>                                      | <b>-</b>   | <b>208</b>                   |

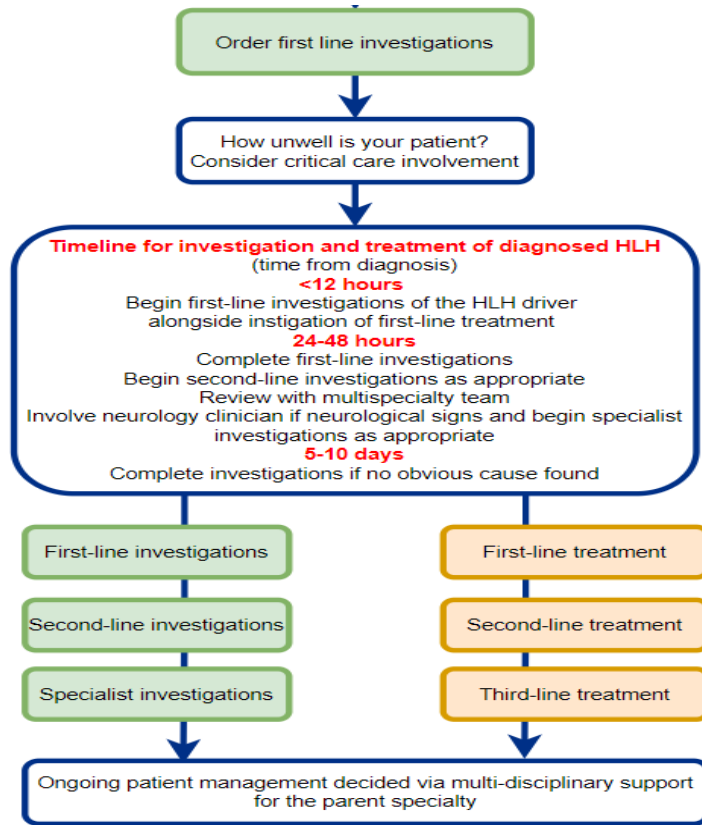


# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## HLH & Cancer: Quick surveillance flowchart



### High Index of Suspicion for HLH:

ill-appearing adult with fever/sepsis, hyperferritinemia, and bi/pancytopenia, especially with an unknown cause and if clinically deteriorating

#### Recommended Screening Evaluation, Expected Results within 24h:

Physical Exam: vital signs, abdominal exam for hepatosplenomegaly, neurological exam<sup>1</sup>, history-directed exam for infection, malignancy, and/or autoimmunity

#### Labs:

- complete blood count with differential, peripheral blood smear
- metabolic panel (liver/renal panel, albumin), lactate dehydrogenase, fasting triglycerides
- coagulopathy panel (activated partial thromboplastin time, prothrombin time, fibrinogen)
- inflammatory markers (e.g., ferritin, C-reactive protein)
- pregnancy test if applicable
- blood cultures, lactate, respiratory viral panel, COVID
- other history/physical exam-directed infectious, malignancy, or rheumatologic workup

If concerning for HLH (e.g., recurrent fever, high ferritin/LDH, cytopenias, abnormal liver function, hypoalbuminemia):

If not concerning for HLH, repeat as clinically indicated, especially if the patient continues to deteriorate, since HLH labs may not be initially positive

Refer to a tertiary care center, and/or

Perform First Pass Evaluation: complete HLH-2004 diagnostic workup and evaluate for malignancy<sup>2</sup>

#### Labs:

- soluble IL2R (sCD25), NK-cell cytotoxicity activity assay, antinuclear antibody (ANA) test
  - nucleic acid tests for EBV, CMV, VZV, HSV, and HIV; viral hepatitis serologies; rule out tuberculosis
- Imaging: computed tomography (CT) +/- positron emission tomography (PET) of at least the chest, abdomen, and pelvis
- Pathology: biopsy of suspicious masses; peripheral blood flow cytometry and/or bone marrow biopsy as clinically appropriate
- Consultation: hematology/oncology, rheumatology, and/or infectious disease to assist in diagnosis

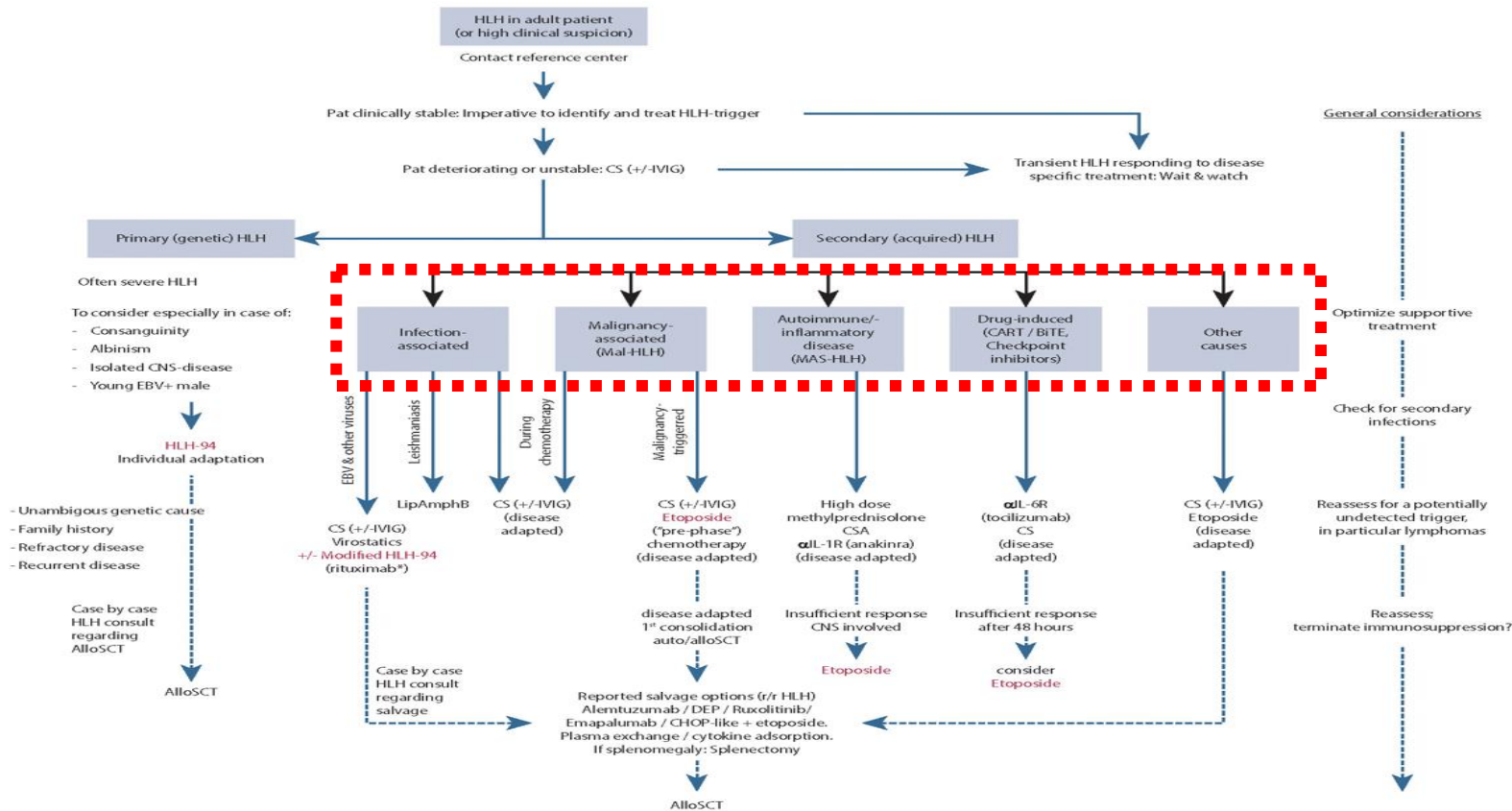
Extended Diagnostic Evaluation<sup>3</sup>: if HLH is confirmed, but the underlying etiology is not yet uncovered  
Consider: sCD163, serum CXCL9, T-lymphocyte subsets, quantitative immunoglobulins, tumor markers  
Other infections: fungal/parasite serologies, HHV-6, HHV-8, non-tuberculous mycobacteria  
Biopsy and/or culture any tissue with clinical changes suggestive of occult malignancy/infection  
Consider genetic testing<sup>4</sup>

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## HLH & Cancer: *PNTs* value

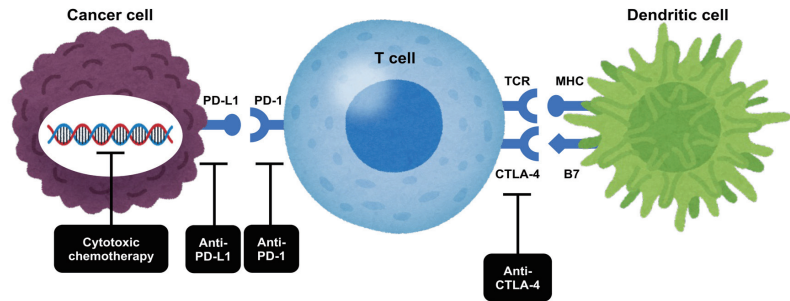


# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## HLH & Cancer: ICI AEs



Hematologic complications of immune checkpoint inhibitors (%)

| Anemia  | Neutropenia   | Thrombocytopenia  |
|---|---|---|
| Grade I-V: 36.49% (30.23-42.75)<br>Grade III-V: 4.14% (3.85-4.42) | Grade I-V: 29.73% (24.82-34.64)<br>Grade III-V: 5.29% (3.86-6.73) | Grade I-V: 17.95% (15.04-20.87)<br>Grade III-V: 1.58% (1.06-2.11) |

| Country of primary source | Total number of ICI-related safety reports | Number of ICI-related HLH safety reports | ICI-related HLH reporting rate (%) |
|---------------------------|--|--|------------------------------------|
| France                    | 3526                                       | 14                                       | 0.4                                |
| Japan                     | 6421                                       | 11                                       | 0.2                                |
| Germany                   | 1901                                       | 3  | 0.2                                |
| Switzerland               | 830  | 1  | 0.1                                |
| Canada                    | 1279                                       | 1  | 0.08                               |
| US of America             | 24'998                                     | 8  | 0.03                               |

### Cancer type

|                                     |         |
|-------------------------------------|---------|
| Melanoma                            | 21 (55) |
| Lung cancer                         | 5 (13)  |
| Bladder cancer                      | 3 (8)   |
| Renal cell carcinoma                | 2 (5)   |
| Hodgkin disease                     | 1 (3)   |
| Transitional cell carcinoma         | 1 (3)   |
| Adenocarcinoma gastric              | 1 (3)   |
| Thymoma                             | 1 (3)   |
| T cell lymphoblastic leukemia acute | 1 (3)   |
| Not reported                        | 2 (5)   |

### Drugs

|   |         |
|---|---------|
| Anti-CTLA-4 (ipilimumab) monotherapy            | 7 (18)  |
| Anti-PD-1 monotherapy                           |         |
| nivolumab                                       | 14 (37) |
| pembrolizumab                                   | 7 (18)  |
| Anti-PD-L1 monotherapy                          |         |
| Atezolizumab                                    | 1 (3)   |
| ipilimumab and nivolumab combination therapy    | 5 (13)  |
| nivolumab and ipilimumab sequential therapy     | 3 (8)   |
| pembrolizumab and ipilimumab sequential therapy | 1 (3)   |

In clinical practice, ICI-related HLH arises with a delayed timing with respect to initiation of ICI treatment, presents clinical, haematological and coagulation features similar to those of HLH with different etiology, rarely is associated with other irAEs and concomitant viral infections, and resolved in the majority of cases.

Keeping in mind these findings, clinicians should consider ICIs' involvement in the onset of HLH whenever they diagnose a disease of this group of syndromes in cancer patients treated with ICIs.

**Same treatment approach?  
HLH-2004 protocol sense?**

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Outlook

- Introduction
- HLH & Cancer
- Treatment algorithm proposal**
- Conclusions

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Treatment algorithm proposal: *Guidelines*

### Consensus-Based Guidelines for the Recognition, Diagnosis, and Management of Hemophagocytic Lymphohistiocytosis in Critically Ill Children and Adults

Early aggressive critical care interventions are often required to manage the multisystem organ failure associated with hemophagocytic lymphohistiocytosis.

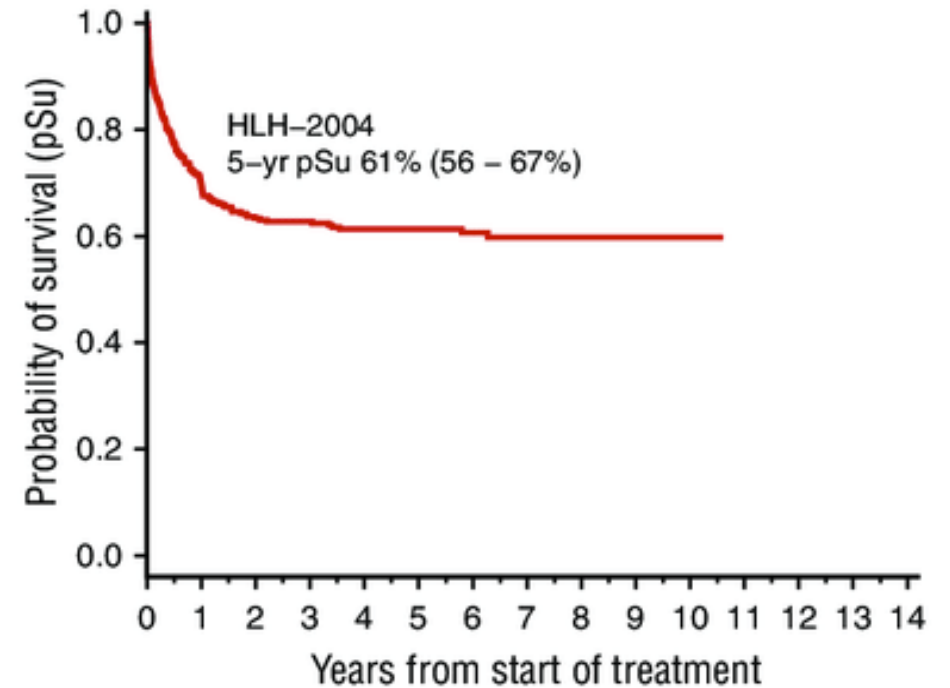
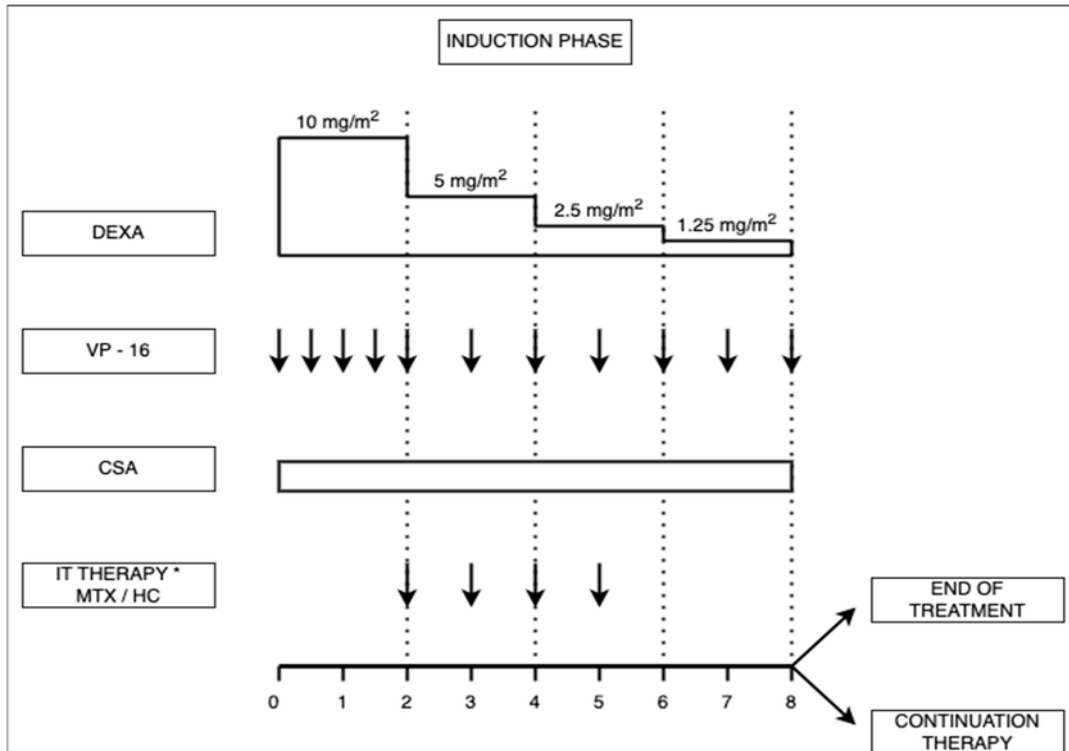
| Proposed Severity of Secondary HLH in ICU-Admitted Patients |  | Therapy  |
|---|--|--|
| Mild  | No evidence of organ dysfunction except coagulation/hematologic system   | <b>See Statement 9 Text and Supplementary Material (<a href="http://links.lww.com/CCM/G882">http://links.lww.com/CCM/G882</a>) for Recommendations</b><br><br>Consider addition of corticosteroid therapy (58)<br>Dexamethasone 10mg/m <sup>2</sup> daily divided every 12hr (17, 58, 68) or equivalent methylprednisolone dosing (2mg/kg/d) (58); consider addition of anakinra 2–10mg/kg/d, divided in two to four daily doses (subcutaneous or IV) (22, 56, 62, 64, 65)<br>Addition of etoposide with dose reduction as follows (35, 66, 67)<br>100 mg/m <sup>2</sup> once weekly in older teens<br>75 mg/m <sup>2</sup> once weekly in adults<br>50 mg/m <sup>2</sup> once weekly in the elderly |
| Moderate  | Evidence of moderate organ dysfunction (SOFA or pSOFA score 2 or less per organ system excluding coagulation/hematologic system)<br><br>Possible need for supplemental oxygen  |  |
| Severe  | Evidence of severe organ dysfunction (SOFA or pSOFA Score 3 or more of at least one organ system excluding coagulation/hematologic system) and/or any need for organ replacement therapy due to organ failure, including positive-pressure ventilation, renal replacement therapy, vasopressors, and extracorporeal life support |  |

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas

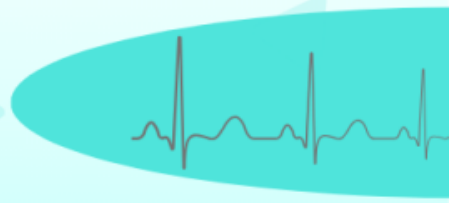


## Treatment algorithm proposal: *1st Step therapy*



# II Jornada del paciente con cáncer en situación crítica

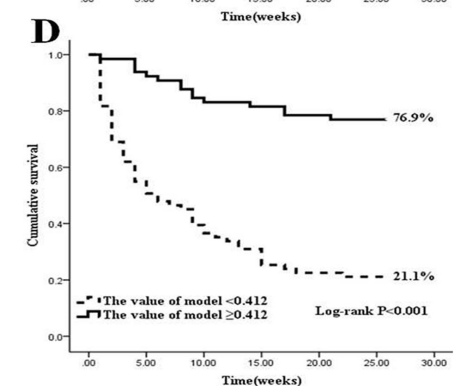
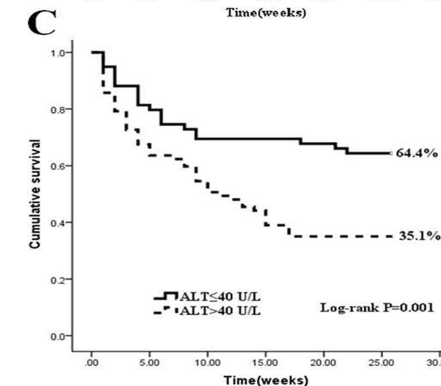
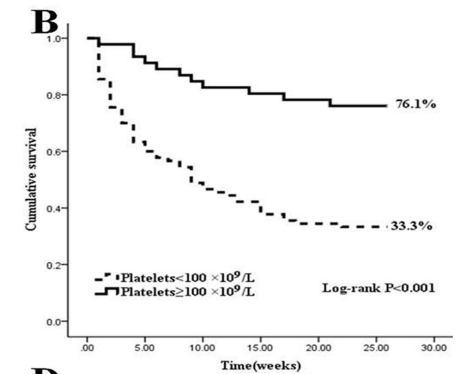
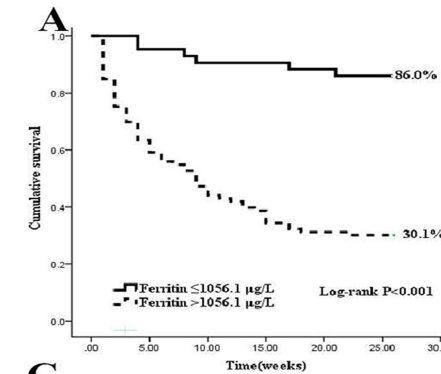
Coordinación en la instauración de medidas de soporte agresivas



## Treatment algorithm proposal: *Underlying malignancy?*

| HLH Type                  | Severity  | Therapy  |
|---------------------------|---|--|
| Malignancy-associated HLH | HLH-triggered organ damage (e.g., cytopenias, cholestatic icterus, pulmonary infiltrates, encephalopathy, or renal failure) | Two-step approach (11, 67)<br>Etoposide (75–100mg/m <sup>2</sup> ), corticosteroids, and IVIG<br><b>Once stabilized, start cancer-directed therapy</b> |
| Adjunctive therapies      | IVIG (18, 35, 56)   | General anti-inflammatory and antiviral effects  |
|                           | Plasmapheresis (71)   | Anti-inflammatory effects; use with caution if giving a monoclonal antibody  |
|                           | Cytokine adsorption columns (72)  | Anti-inflammatory effects  |

decisions are made on a case-by-case basis, weighing whether the patient requires immediate inflammation-directed therapy or is sufficiently stable to receive chemotherapy directly.



# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Treatment algorithm proposal: *Monitoring request*

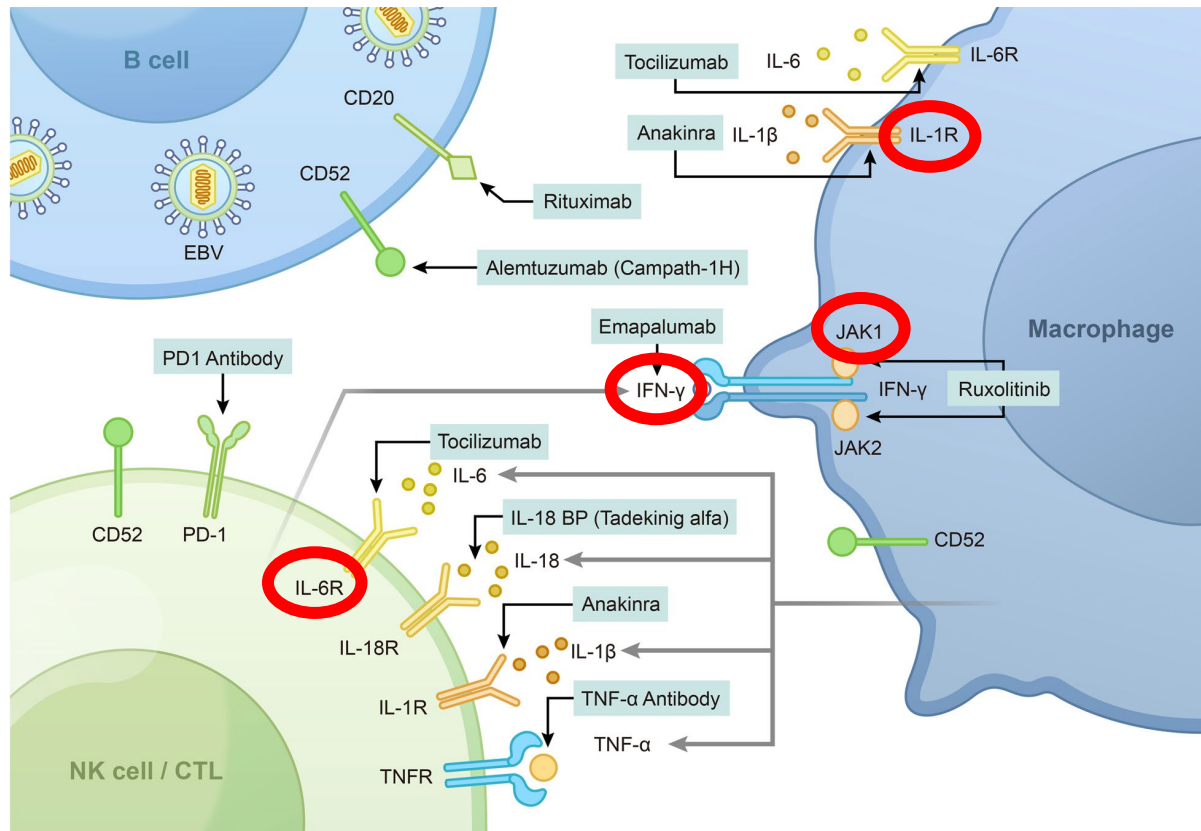
|                                     |   | Therapy  |
|-------------------------------------|---|--|
| <b>Proposed Response to Therapy</b> |   | <b>See Statement 9 Text and Supplementary Material (<a href="http://links.lww.com/CCM/G882">http://links.lww.com/CCM/G882</a>) for Recommendations</b> |
| Response                            | Improvement in ferritin, normalization of temperature, and clinical stabilization (i.e., no worsening organ dysfunction) within 48–72 hr after start of therapy   | Continue full treatment of trigger; reassess disease daily, and wean therapy as tolerated  |
| Nonresponse                         | Lack of improvement in ferritin, persistent fever, and/or lack of clinical improvement > 48–72 hr after start of therapy  | Reevaluate triggers to ensure they are treated; consider adding additional HLH-directed therapy  |
| Progression                         | Increasing ferritin and/or persistent fever > 48–72 hr after start of therapy. Increasing need for support of organ dysfunction (i.e., positive-pressure ventilation, renal replacement therapy, increasing blood product replacement, and/or need for vasopressors and extracorporeal life support) at any point | Aggressively reevaluate triggers to ensure they are treated; highly consider the addition of other or additional HLH-directed therapies                |

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Treatment algorithm proposal: 2nd Step therapy



| Target   | Drug               | Type of Drug                | Preclinical | Phase I            | Phase II | Phase III | Identifier  | Ref. |
|----------|--------------------|-----------------------------|-------------|--------------------|----------|-----------|-------------|------|
| JAK 1/2  | Ruxolitinib        | JAK 1/2 inhibitors          |             | Not yet recruiting |          |           | NCT05137496 | NA   |
|          | Methylprednisolone |                             |             | Not yet recruiting |          |           |             |      |
| IL-1     | Anakinra           | IL-1R antagonists           |             | Not yet recruiting |          |           | NCT02780583 | 116  |
|          | Methylprednisolone |                             |             | Not yet recruiting |          |           |             |      |
| IL-2     | rhIL-2             | Recombinant hIL-2 protein   |             | Recruiting         |          |           | NCT02569463 | NA   |
| IFN-γ    | Emapalumab         | Anti-IFNγ mAb               |             | Completed          |          |           | NCT03311854 | NA   |
| IL-1     | Anakinra           | IL-1R antagonist            |             | Completed          |          |           | NCT04339712 | NA   |
| IL-6     | Tocilizumab        | Anti-IL-6 mAb               |             | Completed          |          |           |             |      |
| IL-18    | Tadekinig alfa     | IL-18BP                     |             | Recruiting         |          |           | NCT03512314 | NA   |
| IL-2R    | Rituximab          | Anti-CD20 mAb               |             | Recruiting         |          |           | NCT05384743 | NA   |
| IL-1     | Anakinra           | IL-1R antagonist            |             | Completed          |          |           | NCT03322225 | 117  |
| IFN-γ-1β | Imukin             | Recombinant hIFN-1b protein |             | Completed          |          |           |             |      |

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas

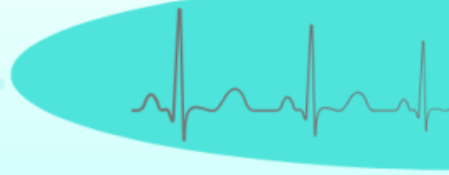


## Treatment algorithm proposal: *Exciting results*

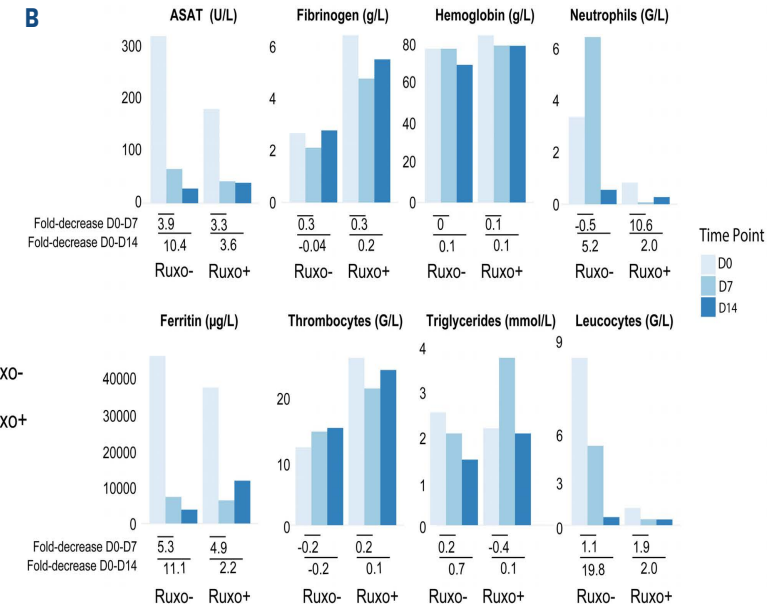
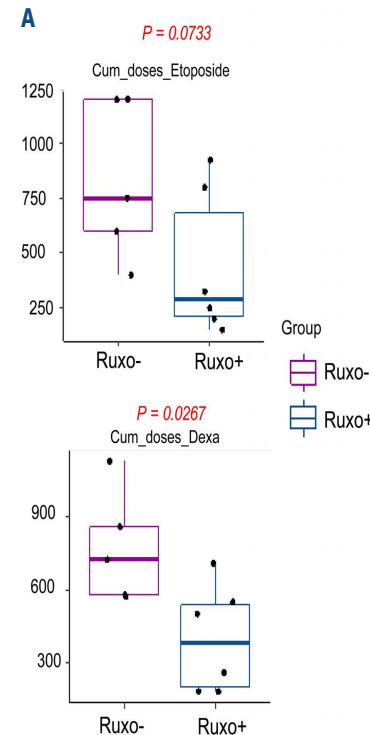
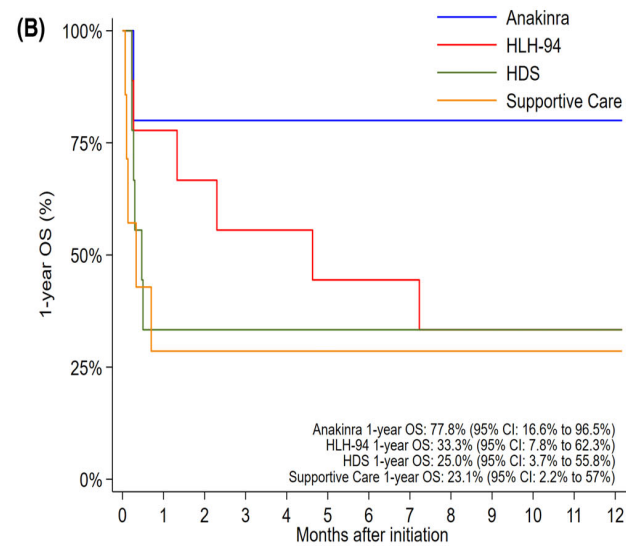
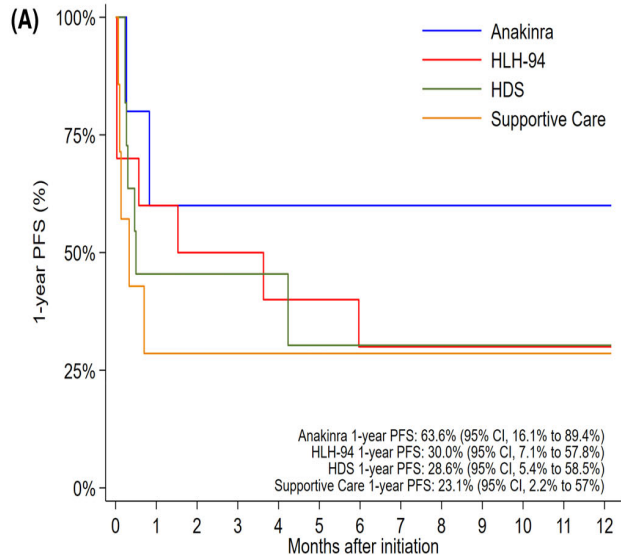
| Treatment  | Number of Patients | Type of HLH  | Complete Response/<br>Partial Response | Overall Response | Number of Patients Who Achieved HSCT or Subsequent Chemotherapy | Rate of Survival         |
|--|--------------------|--|--|------------------|---|--------------------------|
| Alemtuzumab (Marsh, et al) <sup>45</sup>                                 | 22                 | 8 F-HLH<br>5 EBV-HLH<br>2 CMV-HLH<br>7 I-HLH   | 0%/64%                                 | 64%              | 77%   | 64%                      |
| DEP (Wang, et al) <sup>44</sup>  | 63                 | 29 Mal-HLH<br>22 EBV-HLH<br>4 F-HLH<br>8 I-HLH   | 27%/49.2%                              | 76.2%            | 13 (44.8%)  | 60.4%                    |
| L-DEP (Wang, et al) <sup>53</sup>  | 28                 | EBV-HLH  | 32%/53.5%                              | 85.7%            | 13 (54.1%)  | 76.9%<br>(post HSCT)     |
| Ruxolitinib (Ahmed, et al) <sup>60</sup>                                 | 5                  | Secondary HLH  | 100%                                   | 100%             | NA  | 100%                     |
| Ruxolitinib (Boonstra, et al) <sup>61*</sup>                             | 13                 | 5 Infectious-HLH<br>4 MAS-HLH<br>5 I-HLH   | 38.4%/38.4%                            | 77%              | NA  | 76.9%                    |
| Ruxolitinib with and without glucocorticoids (Wang, et al) <sup>59</sup> | 34                 | 1 F-HLH<br>25 EBV-HLH<br>2 MAS<br>6 I-HLH  | 14.7%/58.8%                            | 73.5             | NA  | 55.9%                    |
| DEP-Ru (Wang, et al) <sup>62</sup>                                       | 54                 | 28 EBV-HLH<br>5 MAS<br>3 Mal-HLH<br>6 F-HLH<br>1 Pregnancy-HLH<br>1 Drug-HLH<br>2 Infect-HLH | 15.1%/58.5%                            | 73.6%            | 32 (59.2%)  | NA                       |
| Emapalumab (Locatelli, et al) <sup>55</sup>                              | 34                 | 27 F-HLH<br>7 I-HLH  | 21%/32%                                | 65%              | 22 (64.7%)  | 69% (90.9%<br>post HSCT) |
| Nivolumab (Liu, et al) <sup>64</sup>                                     | 7                  | EBV-HLH  | 71.4%/14.2%                            | 85.6%            | NA  | 71.4%                    |

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas

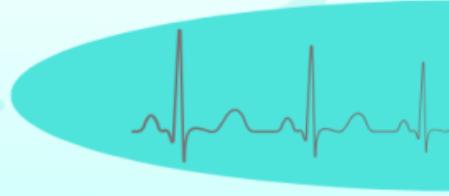


## Treatment algorithm proposal: *Next Future*

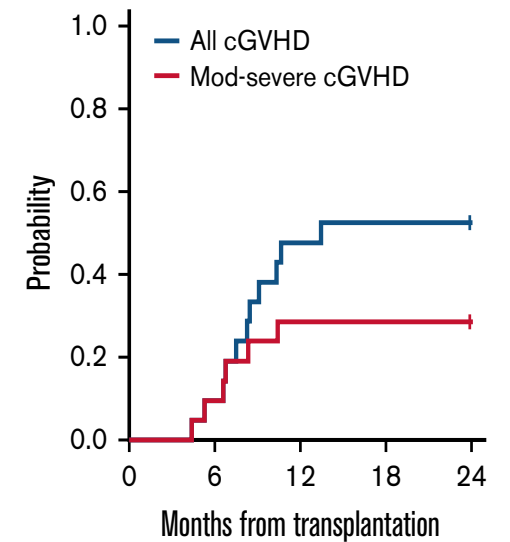
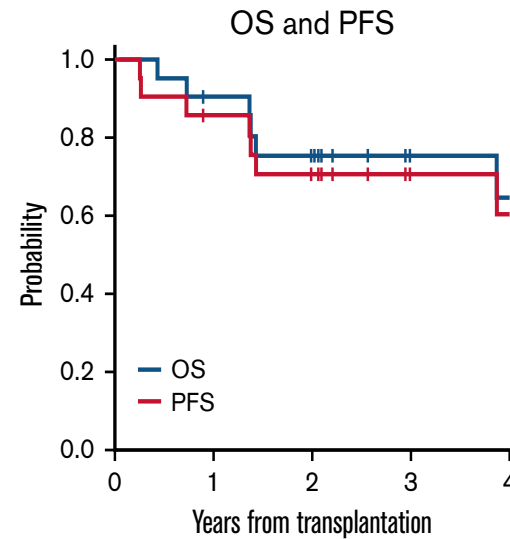
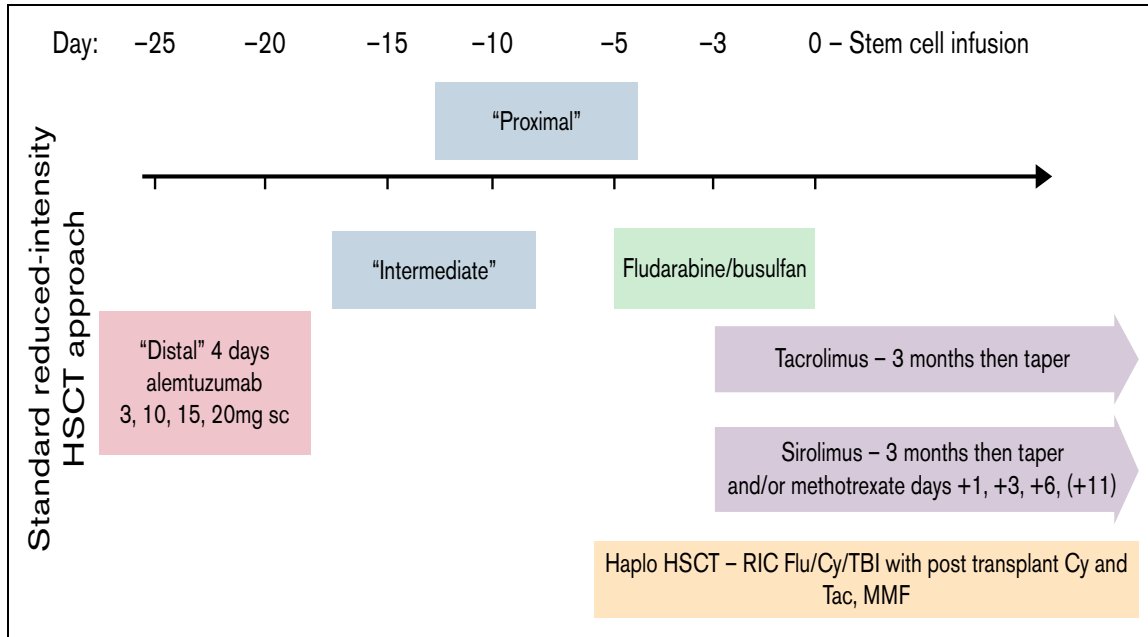


# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Treatment algorithm proposal: *The last bullet=HSCT*

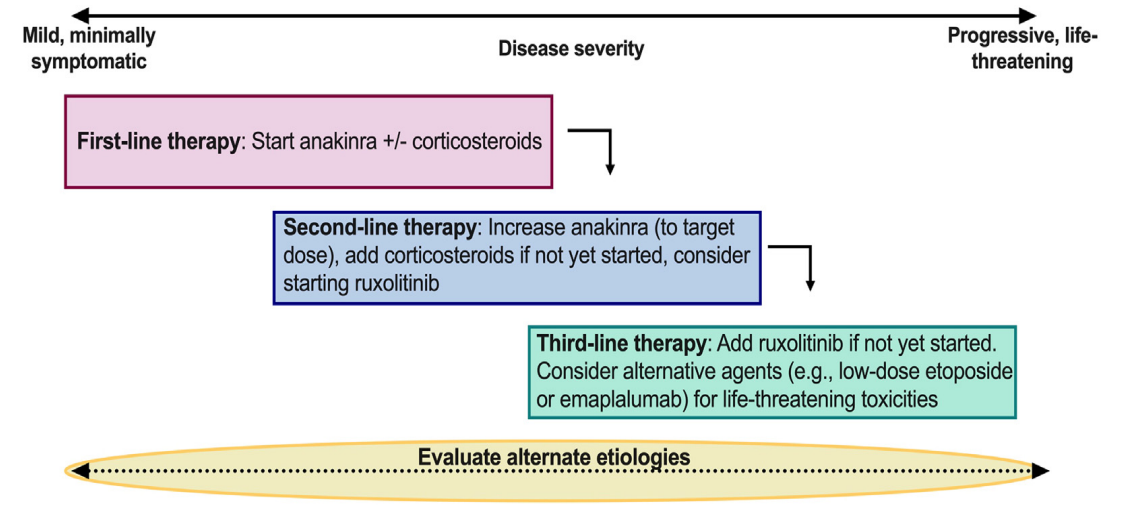
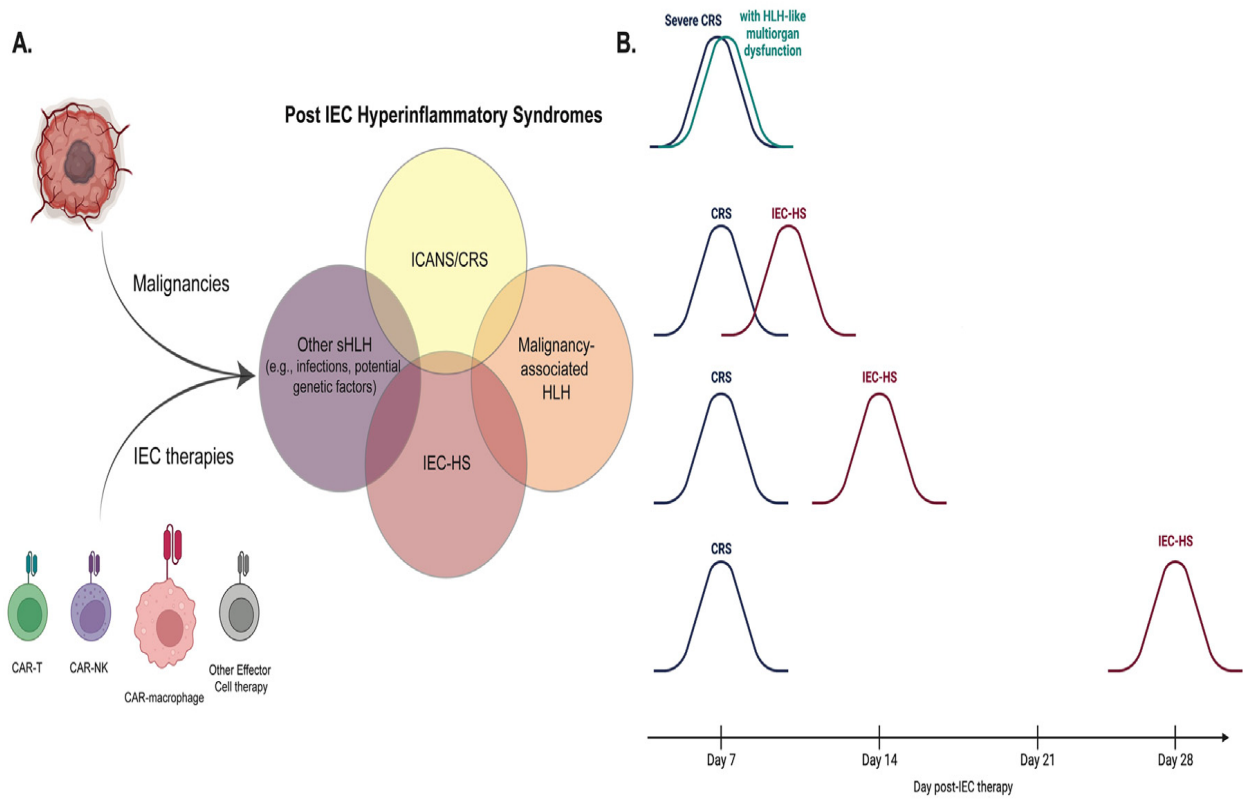


# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Treatment algorithm proposal: *IEC-HS*



# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Outlook

- Introduction
- HLH & Immunotherapy
- Treatment algorithm proposal
- Conclusions**

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



## Conclusions: *Take-home messages*

- ✓ **Adult malignancy-associated HLH remains a severe underdiagnosed disease**
- ✓ **Early multidisciplinary & collaborative work-up is crucial with prognosis outcome**
- ✓ **Investigational effort should be focused on mHLH (including treatment-related) vs other etiology HLH distinction**
- ✓ **Despite recent advantages, improvements are strongly needed concerning diagnosis & registry (IA tools), together with new treatment approaches (clinical trials)**

# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas



**Conclusions: *It could happen to you***



# II Jornada del paciente con cáncer en situación crítica

Coordinación en la instauración de medidas de soporte agresivas

25 de noviembre 2025 | Nh Collection Sevilla



# GRACIAS

*[jesuscorraljaime@hotmail.com](mailto:jesuscorraljaime@hotmail.com)*

*[jesus.corral.jaime.sspa@juntadeandalucia.es](mailto:jesus.corral.jaime.sspa@juntadeandalucia.es)*



Unidad Oncología Médica  
Hospital Universitario de Jerez



INSTITUTO DE INVESTIGACIÓN E  
INNOVACIÓN BIOMÉDICA DE CÁDIZ