Sociedad Andaluza de Oncología Medica

I Reunión de manejo de los efectos secundarios inmunomediados

Córdoba, 13 de noviembre de 2019

Salón de usos múltiples del Edificio IMIBIC, Hospital Universitario Reina Sofía.
- Avda. Menéndez Pidal s/n. 14004 Córdoba -

CASO CLÍNICO:
Una Tóxica Respuesta

Dr. Pedro Sánchez Mauriño

Unidad de Oncología Médica

Hospital Universitario Reina Sofía

ANAMNESIS

- Varón 63 años
- No HTA, no DM ni DLP. No AMC
- Sin cardiopatías ni broncopatías.
- **ICTUS/AVC recientes**
- Antecedentes Quirúrgicos: No
- Hábitos tóxicos: Exfumador (desde septiembre 2018; 40 paq/año).

- Tratamiento habitual: bemiparina 10.000 sc día, AAS 150 mg día, losartan 25 mg día, atorvastatina 80mg día.

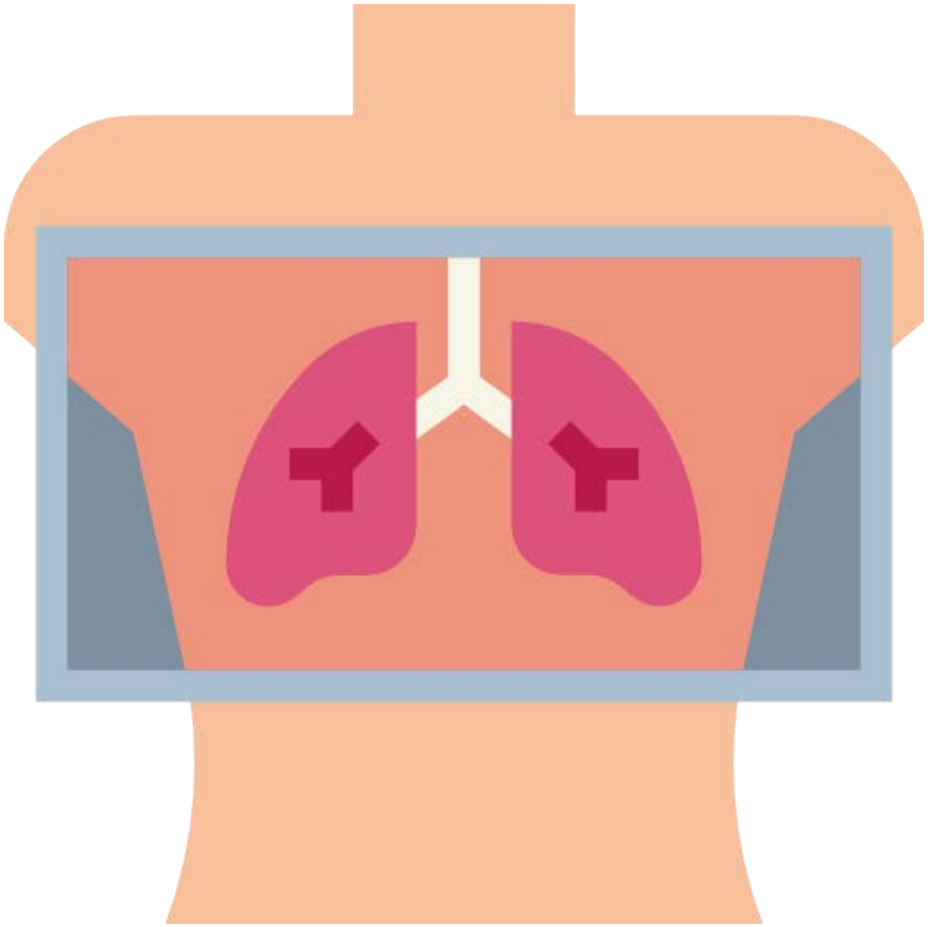
- 1º Síntoma (Diciembre 2018)

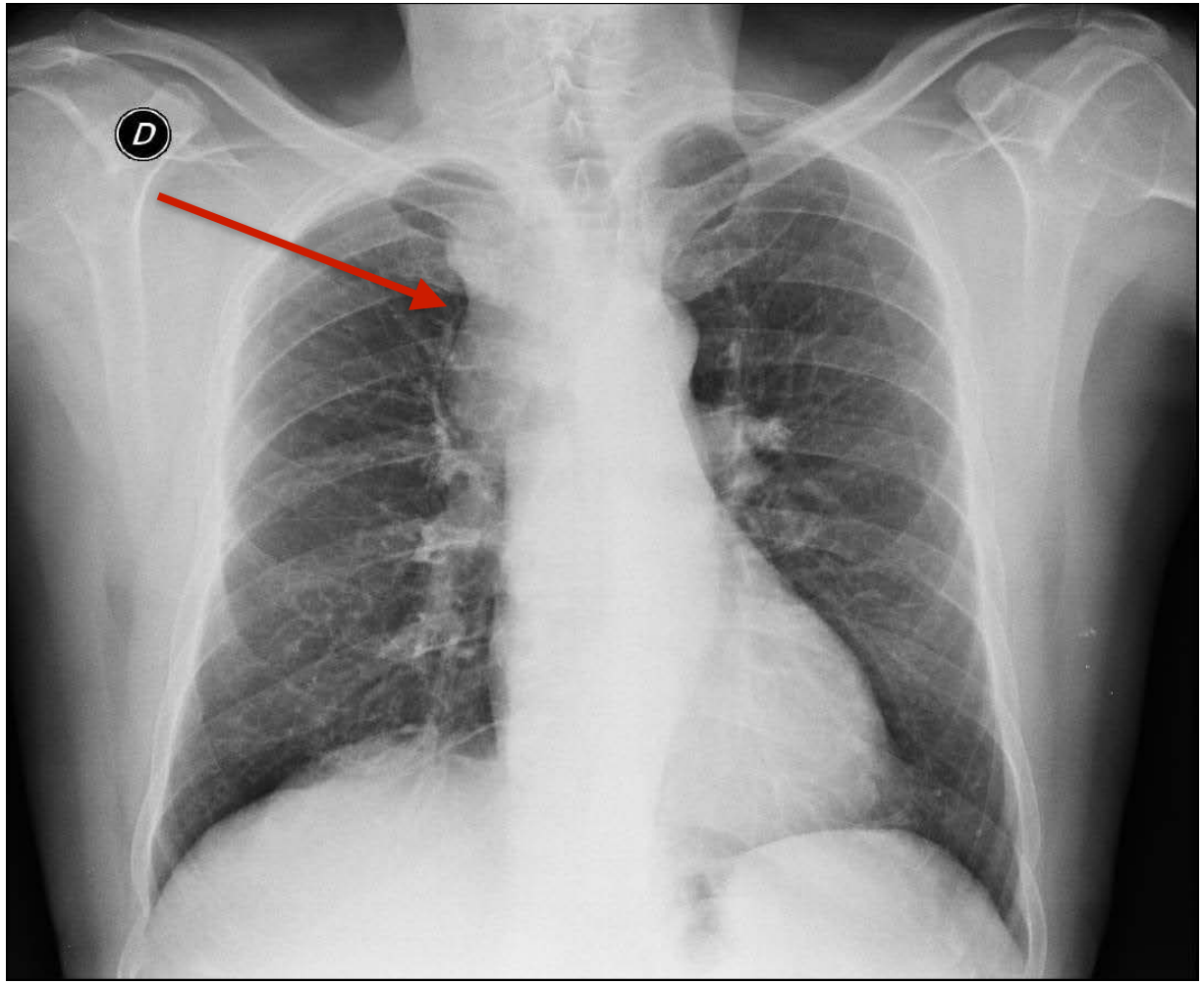
Sensación vertiginosa, alteración en la marcha y disartria.

* RM de craneo: Lesiones con restricción de la difusión asociada, compatibles con infartos isquémicos agudos.

Diagnostico: ICTUS isquémico

DIAGNOSTICO





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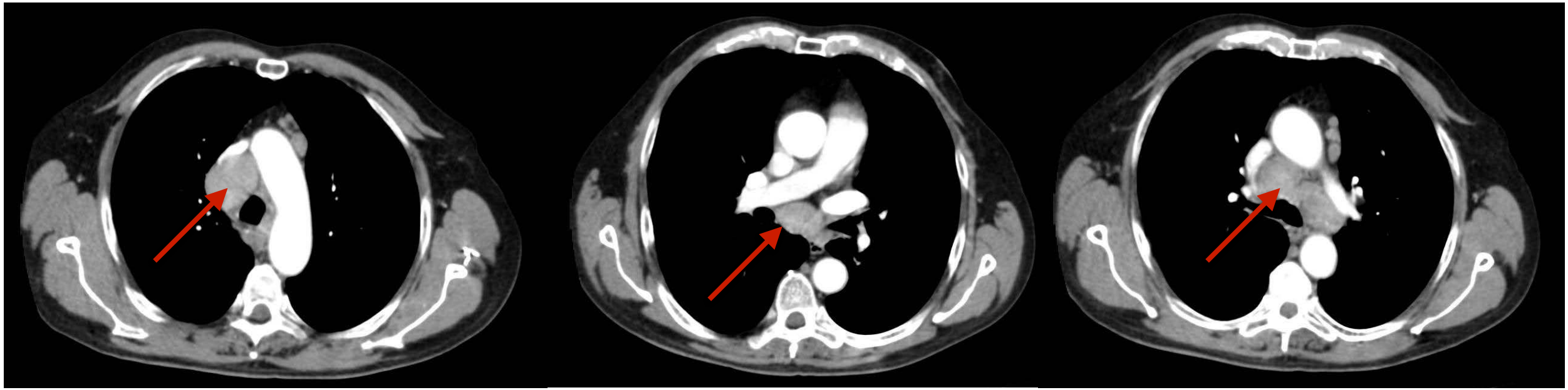
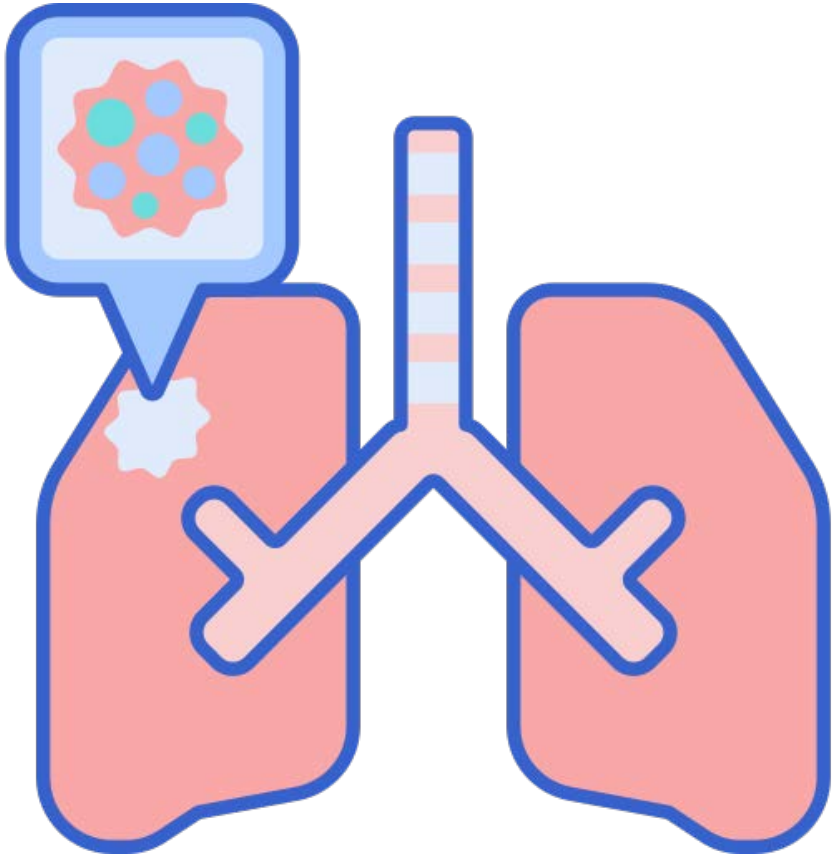


Adenopatías paratraqueales y subcarinales de hasta 4 centímetros, sospechosas de malignidad.

Sin alteraciones en el parénquima pulmonar ni otros hallazgos significativos

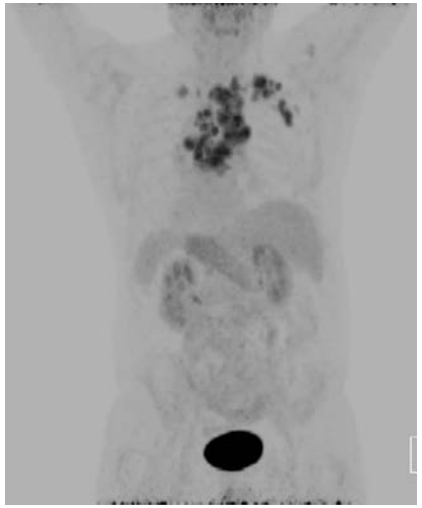
DIAGNÓSTICO HISTOLÓGICO

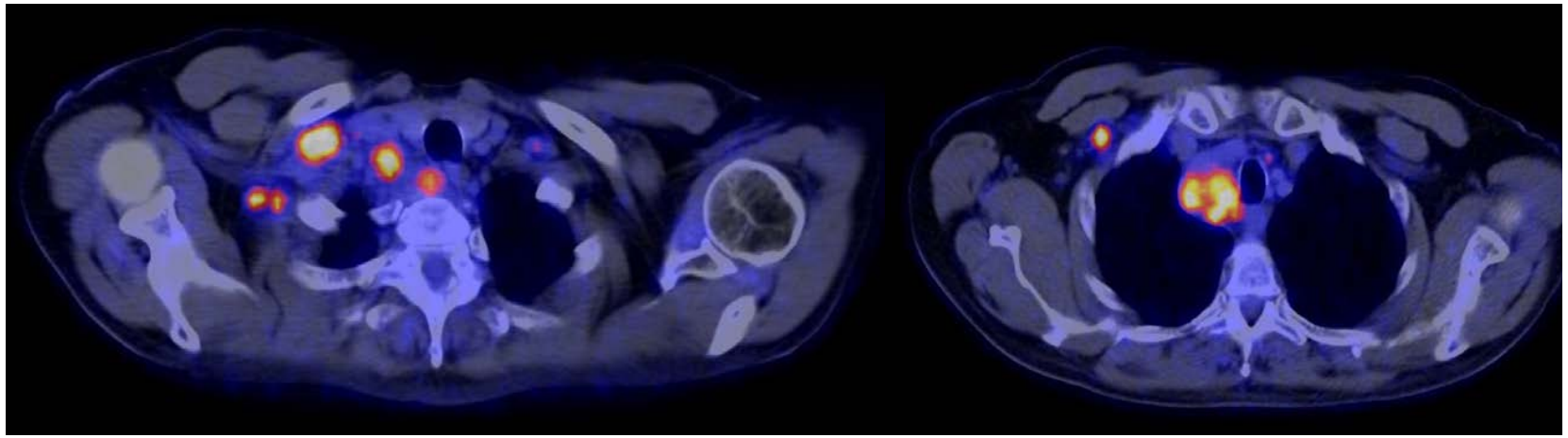


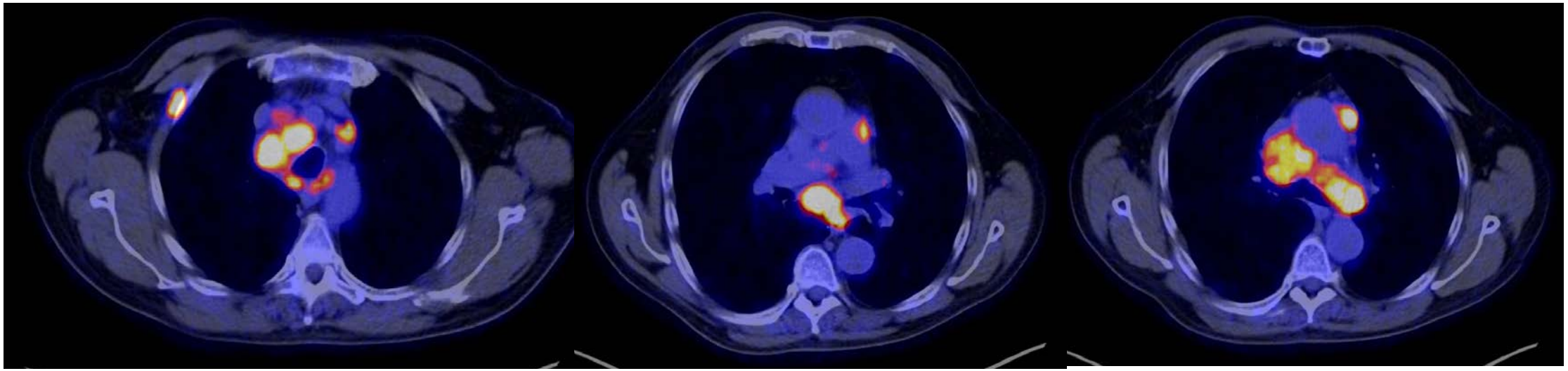
Carcinoma de células no pequeñas de pulmón, subtipo adenocarcinoma

P40-, TTF1+, EGFR -, ALK-, ROS1-, PDL1+ 90%

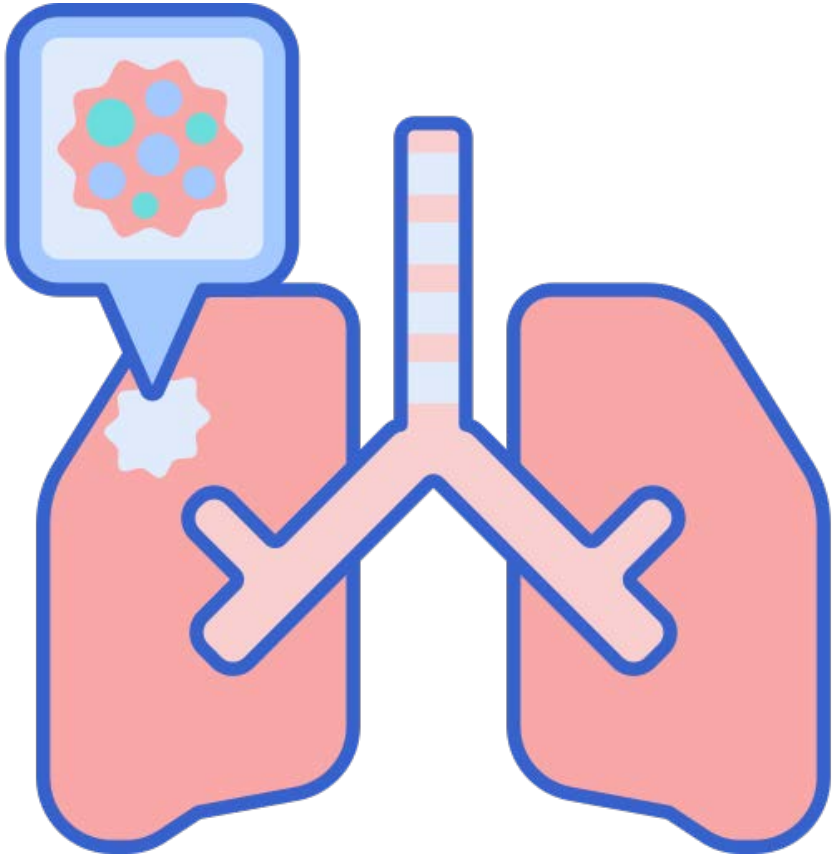
DIAGNÓSTICO







DIAGNÓSTICO HISTOLÓGICO



Carcinoma de células no pequeñas de pulmón, subtipo adenocarcinoma

P40-, TTF1+, ALK-, ROS1-, PDL1+ 90%

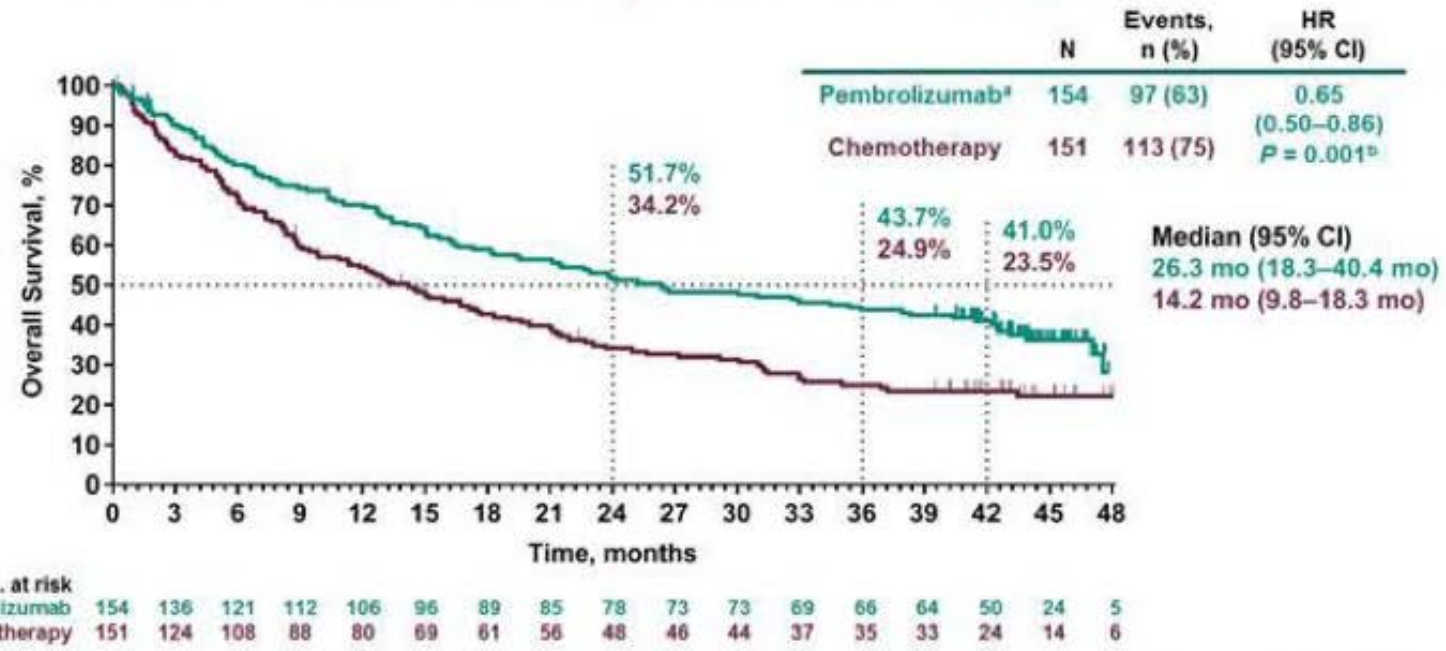
Estadio IV (TxN3M1)

TRATAMIENTO

KeyNote-024: Pembrolizumab 1ºL

Reck KN024 WCLC 201

Overall Survival: Updated Analysis

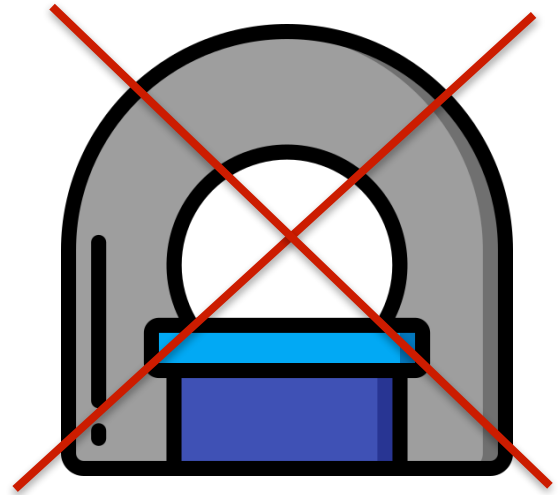


	N	Events, n (%)	HR (95% CI)
Pembrolizumab[a]	154	97 (63)	0.65 (0.50–0.86) P = 0.001[b]
Chemotherapy	151	113 (75)	

Median (95% CI)
26.3 mo (18.3–40.4 mo)
14.2 mo (9.8–18.3 mo)

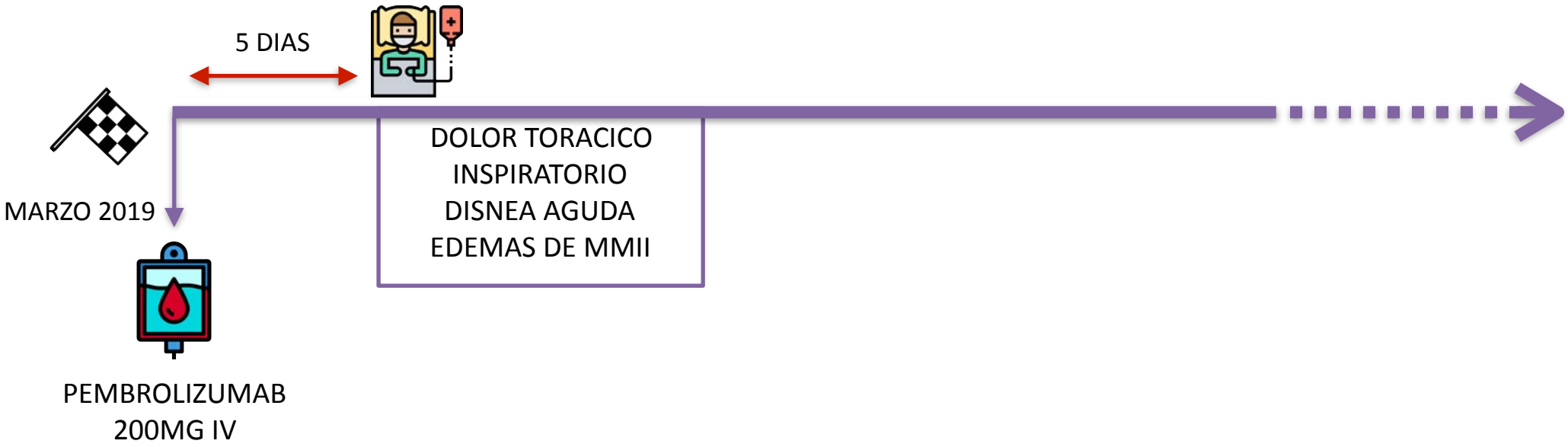
No. at risk																	
Pembrolizumab	154	136	121	112	106	96	89	85	78	73	73	69	66	64	50	24	5
Chemotherapy	151	124	108	88	80	69	61	56	48	46	44	37	35	33	24	14	6

[a]Effective crossover rate from chemotherapy to anti–PD-L1 therapy, 64.9% (98 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 21 patients received subsequent anti–PD-L1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-L1 therapy). [b]Nominal P value.
Data cutoff: February 15, 2019

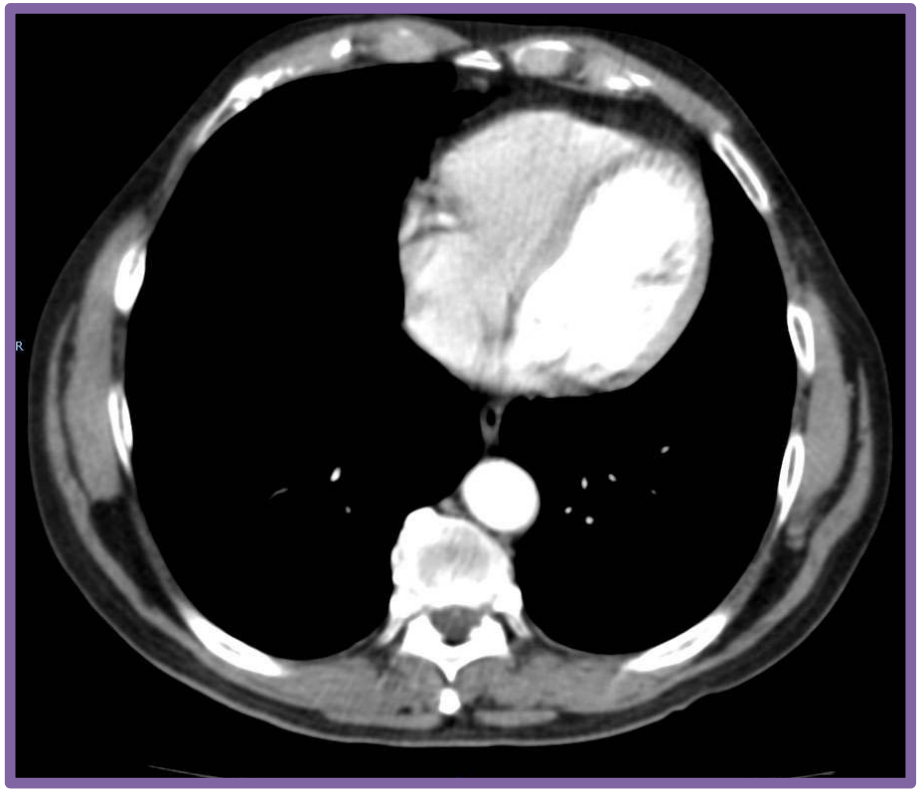


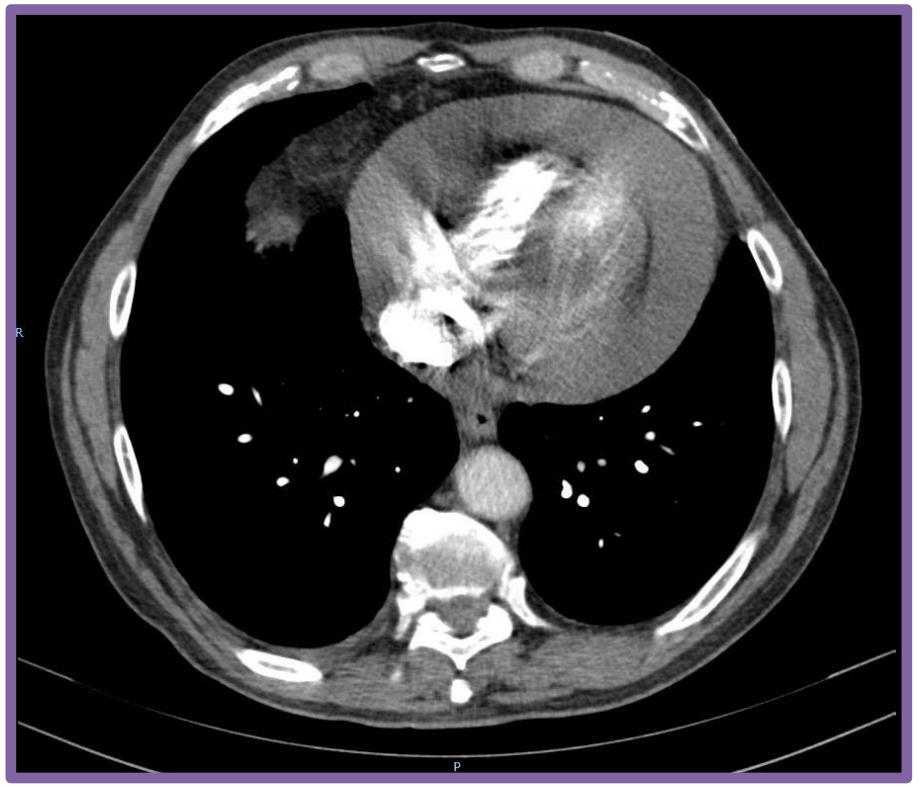
TRATAMIENTO

TRATAMIENTO



DERRAME PERICARDICO





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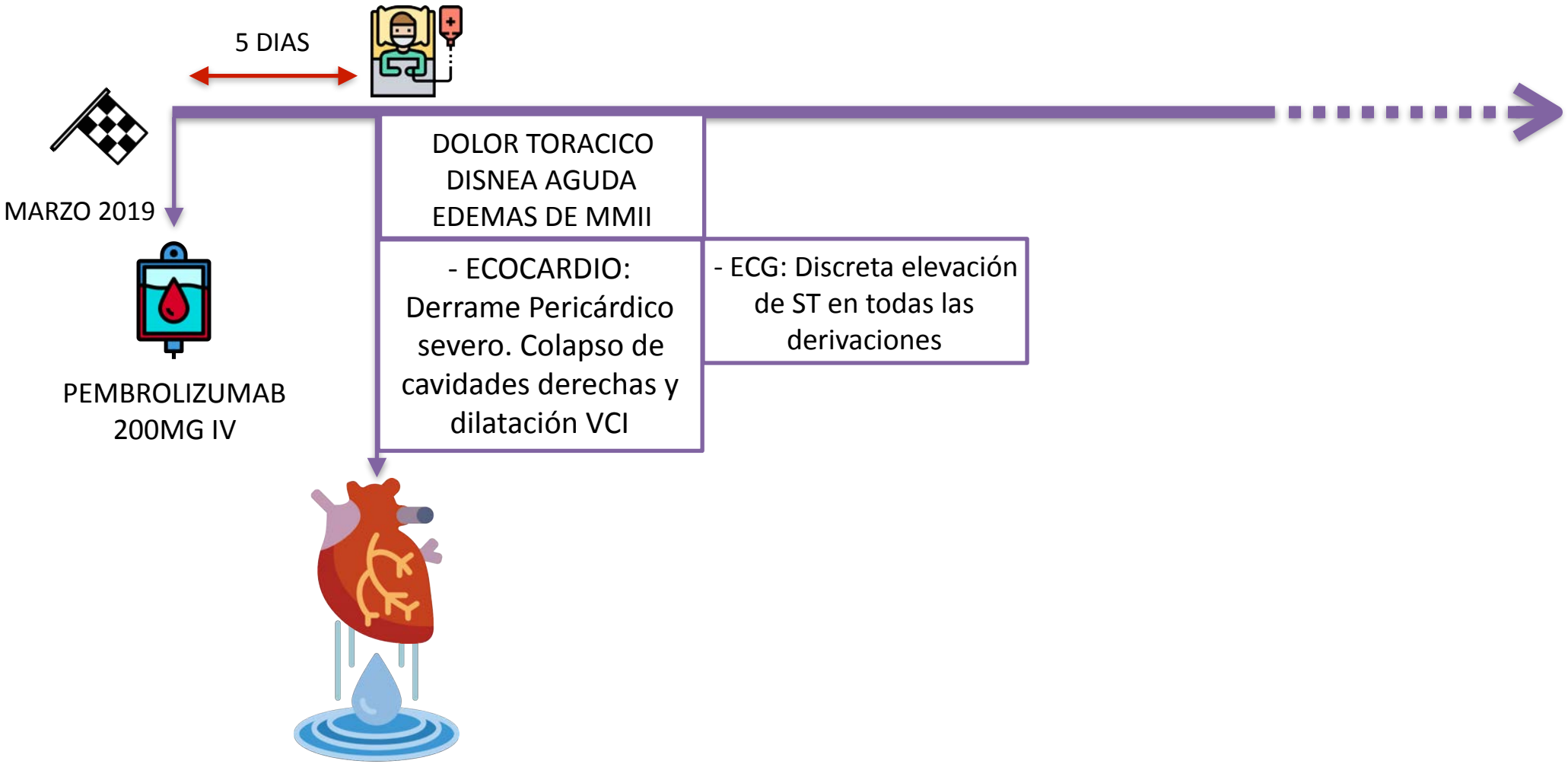

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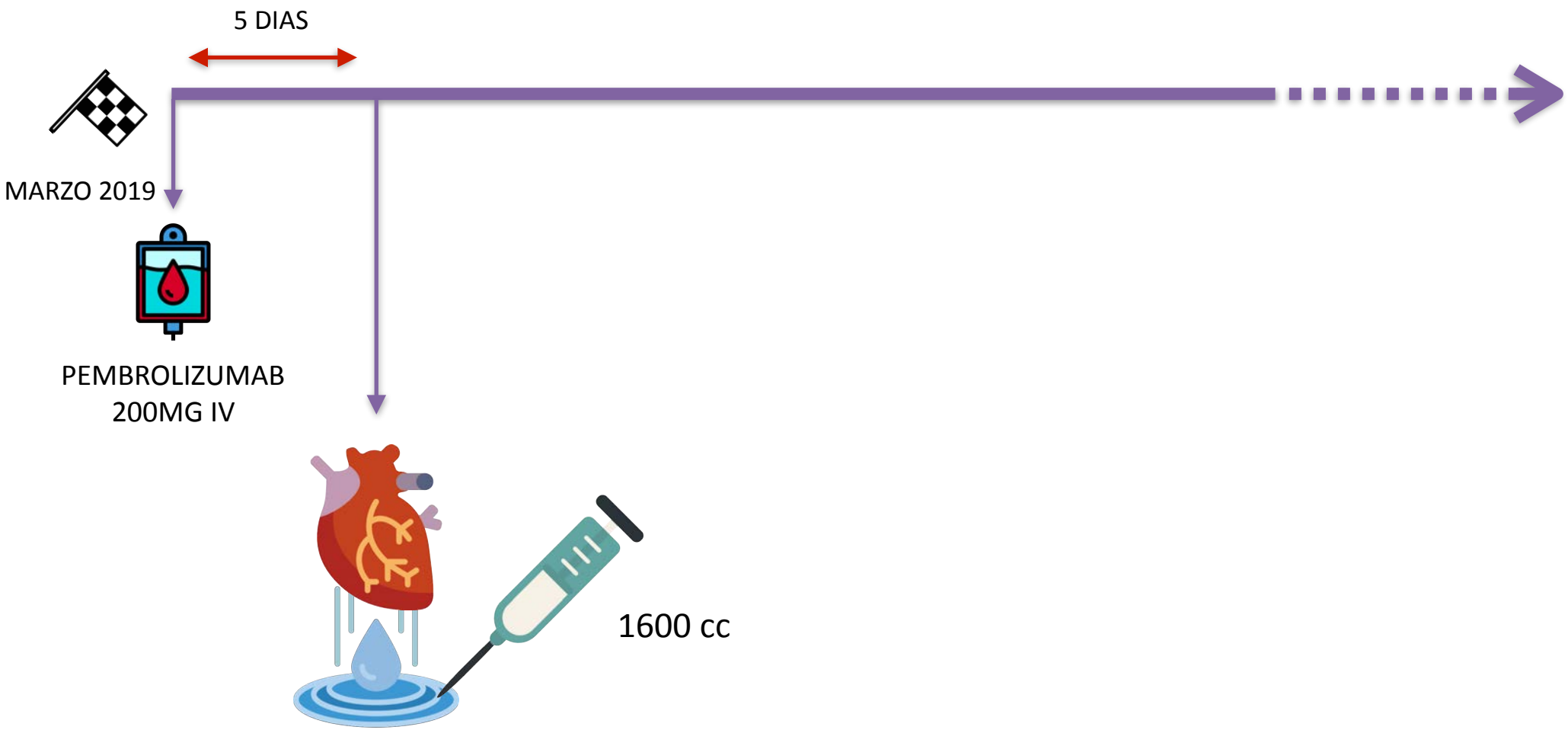

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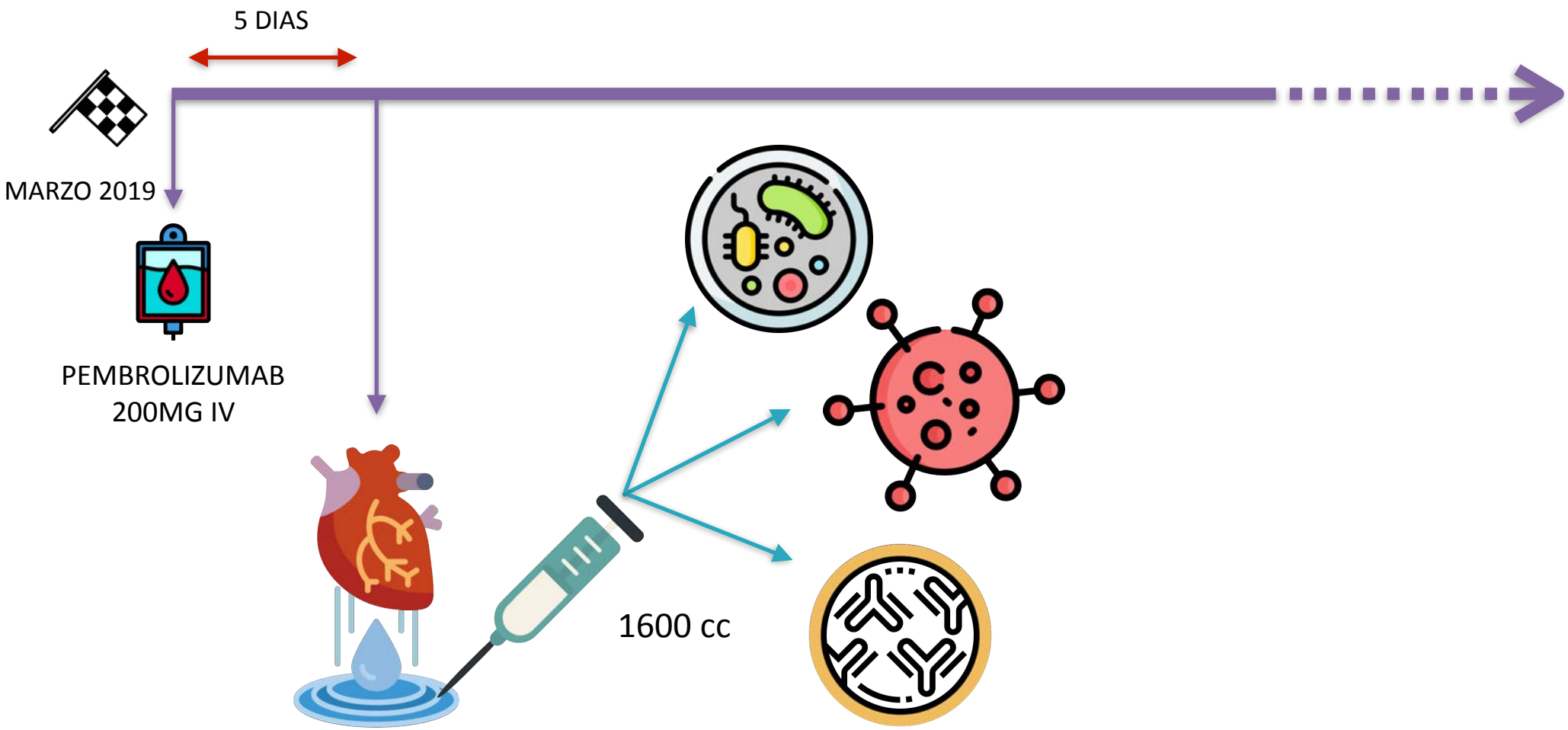

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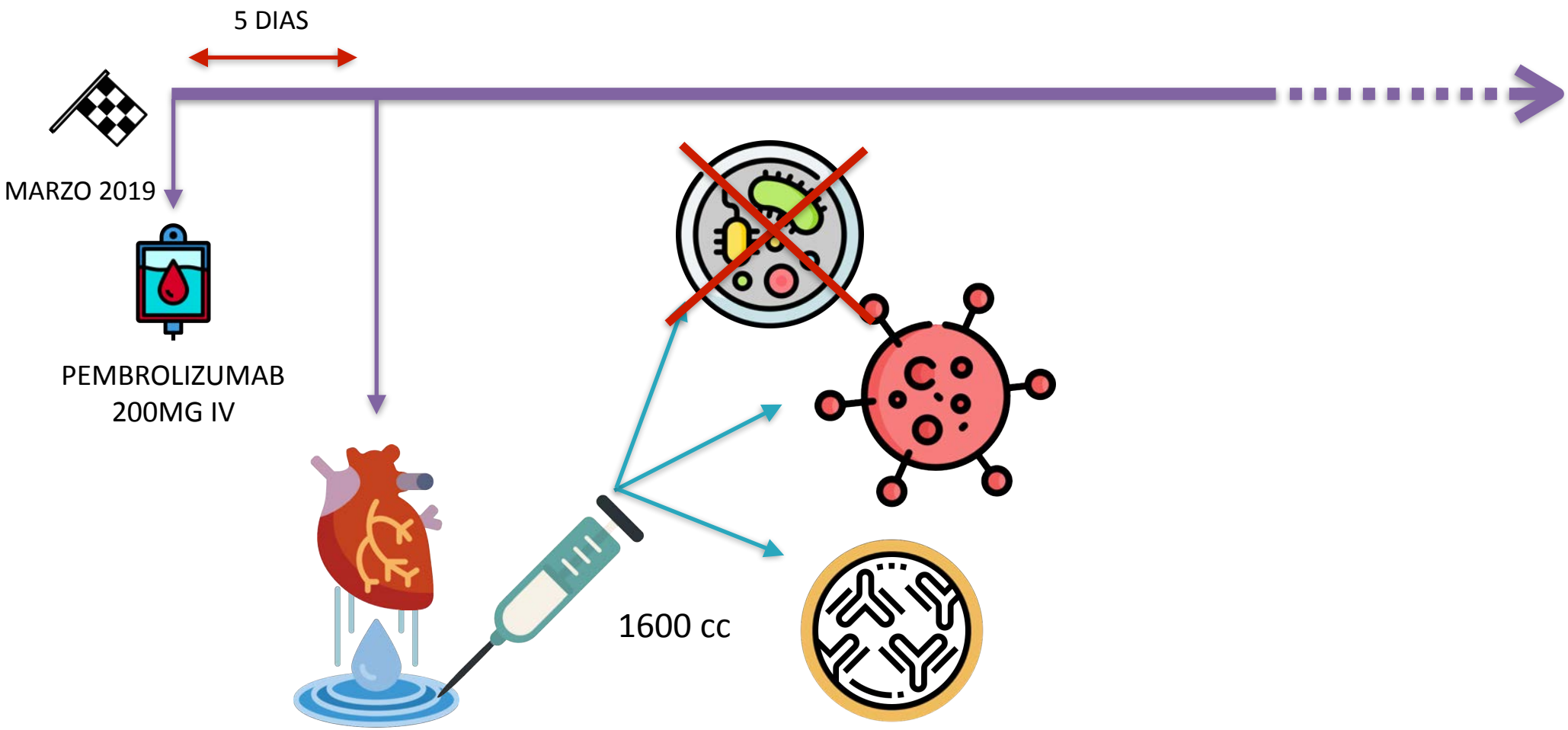

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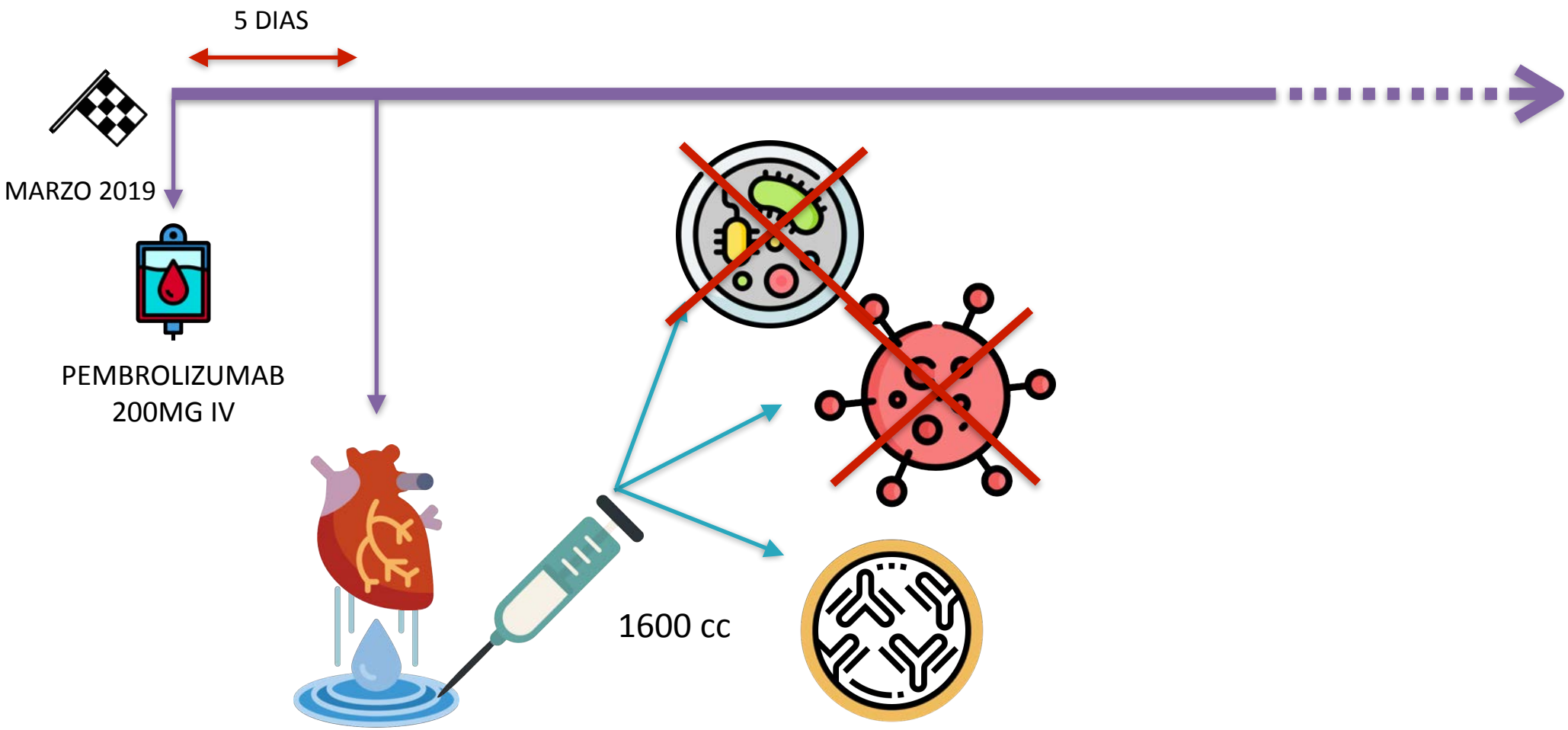
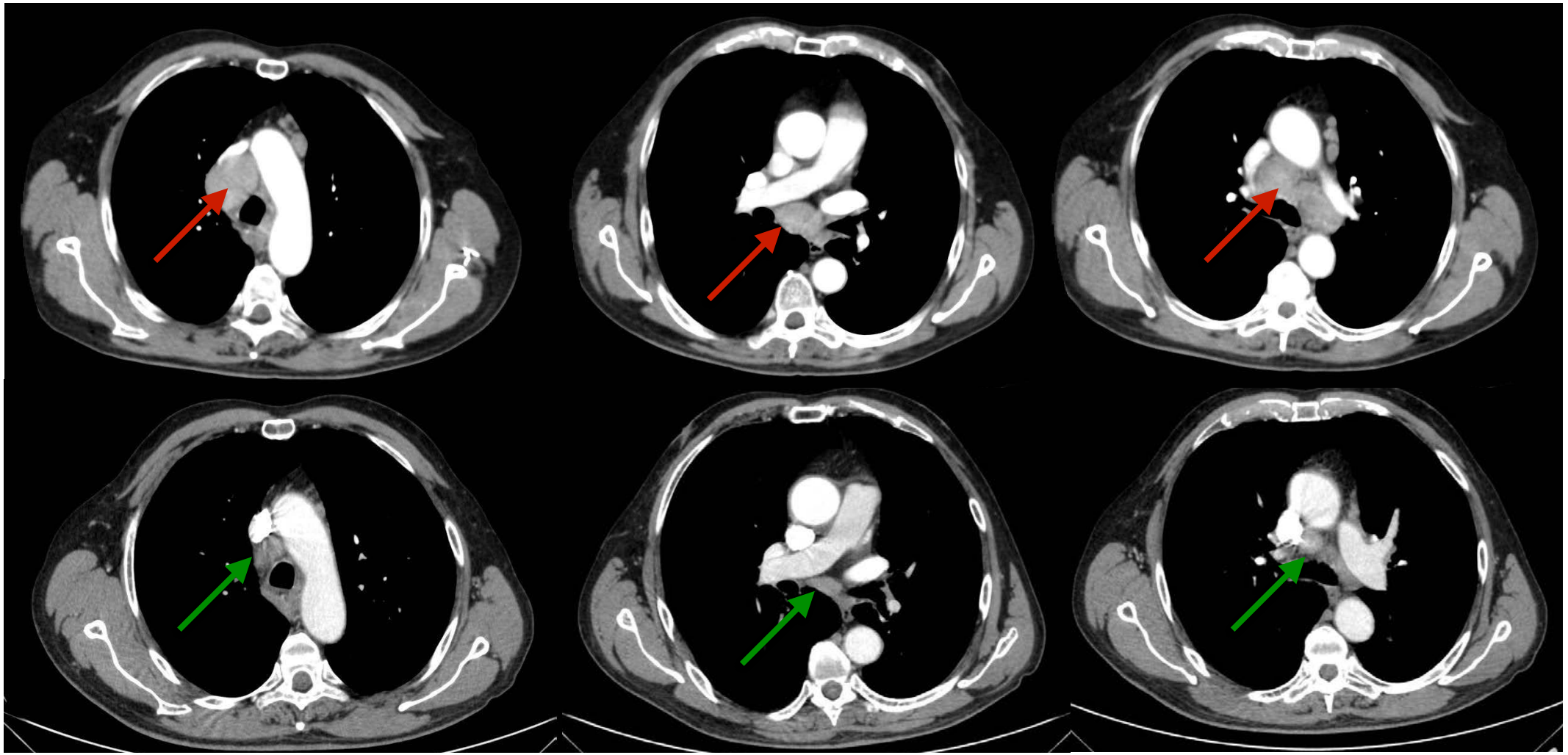


TAC RE-ESTADIFICACIÓN



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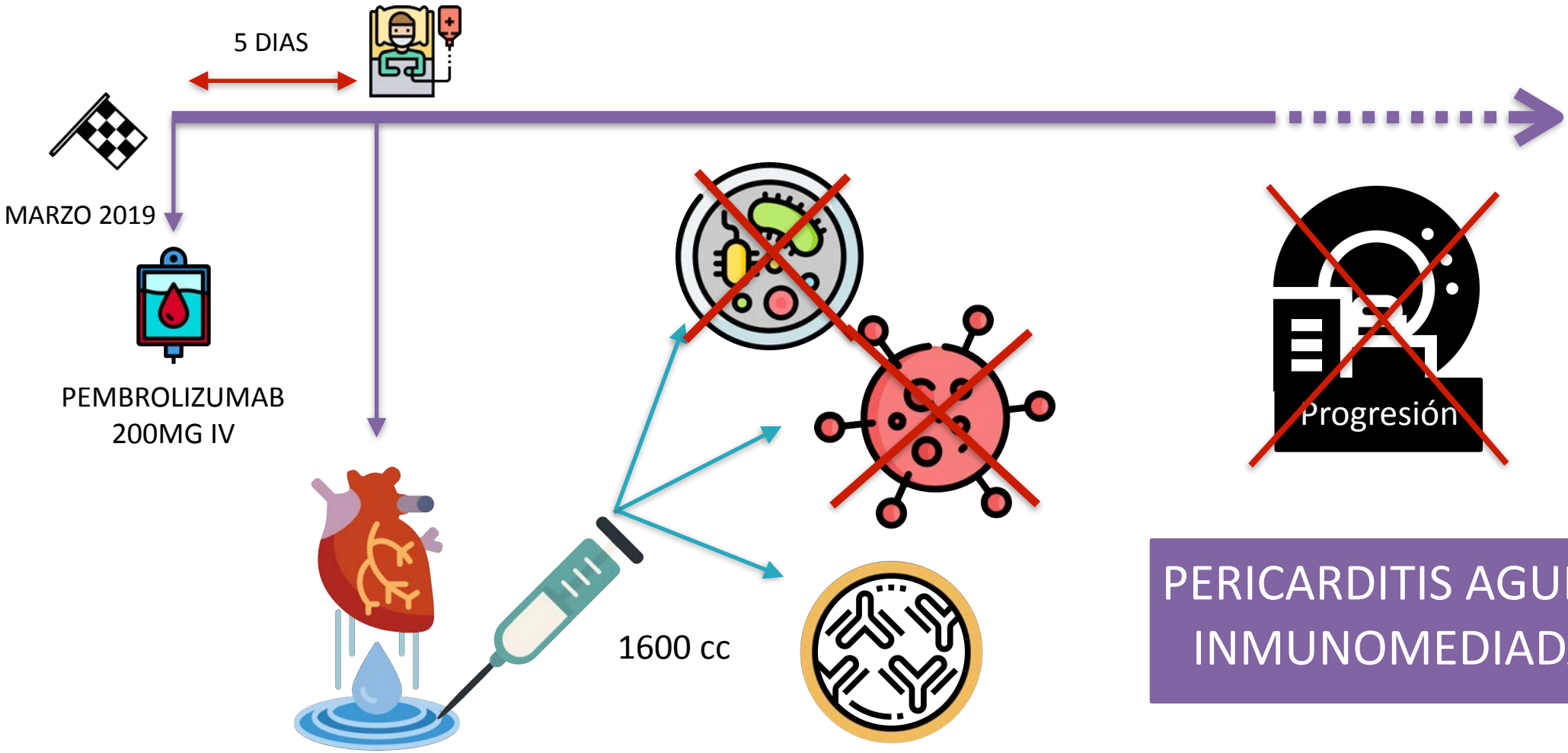

PERICARDITIS AGUDA INMUNOMEDIADA

CLINICAL PRACTICE GUIDELINES

Rare immune-related toxicities

Cardiac toxicity

Summary of recommendations	
Circumstances	Cardiac side effects have been reported to occur after treatment with ipilimumab, pembrolizumab and nivolumab and the incidence is higher with the combination of ipilimumab and nivolumab compared with nivolumab alone
Management	• Early consultation with a cardiologist is recommended • High-dose corticosteroids should be instituted rapidly if ICPi-induced cardiac side effects are suspected • Escalation to other immunosuppressive drugs, such as infliximab, MMF and ATG, is recommended if symptoms do not respond promptly to steroids

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9.1 Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis

Definition: Signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue

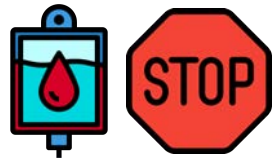
Grading	Management
G1: Abnormal cardiac biomarker testing, including abnormal ECG	All grades warrant work-up and intervention given potential for cardiac compromise
G2: Abnormal screening tests with mild symptoms	Consider the following:
G3: Moderately abnormal testing or symptoms with mild activity	Hold ICPi and permanently discontinue after G1
G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms) Admit patient, cardiology consultation Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin

Brahmer. J Clin Oncol. 2018 Jun 10;36(17):1714-1768

EVOLUCIÓN CLÍNICA

5 DIAS

MARZO 2019

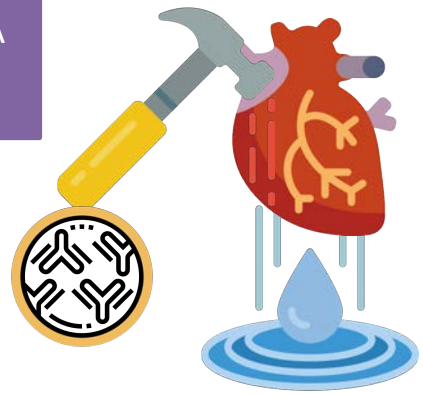


Colchicina 0,5mg cada 12h

Suspende IT

Dexametasona ciclo corto/pauta descendente

PERICARDITIS AGUDA INMUNOMEDIADA Grado III/IV



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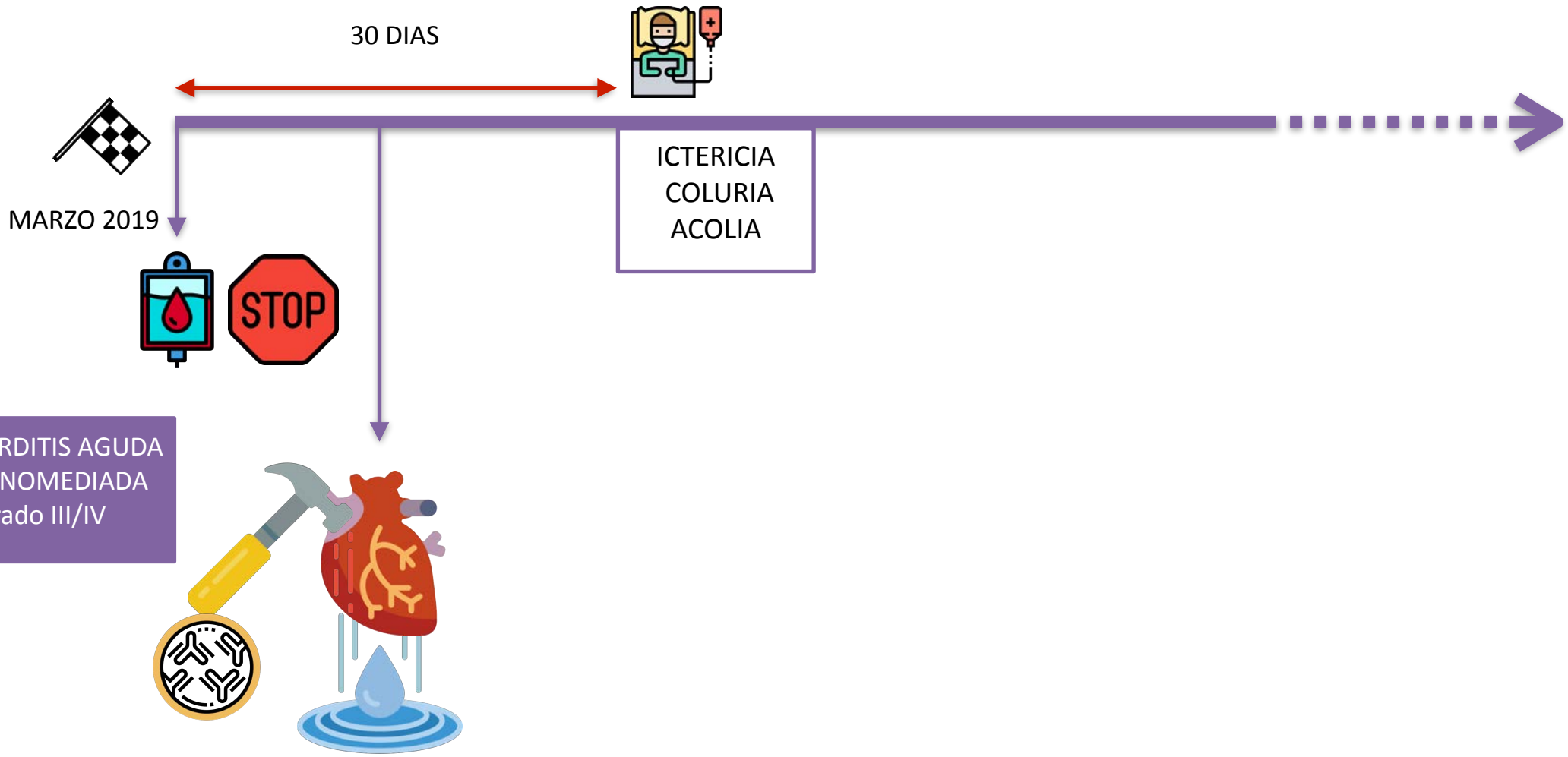
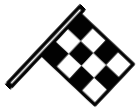


EVOLUCIÓN CLÍNICA

30 DIAS



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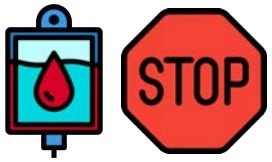
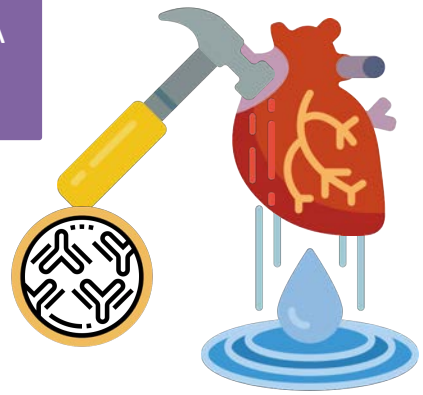


ICTERICIA
COLURIA
ACOLIA

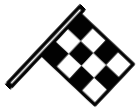
Analítica		
Bilirrubina Total	7,3	mg/100ml
Bilirrubina Directa	5,1	mg/100ml
AST	683	mU/ml
ALT	761	mU/ml
GGT	1100	mU/ml
F. Alcalina	894	mU/ml
Serología Hepat	Negativa	

PERICARDITIS AGUDA
INMUNOMEDIADA
Grado III/IV



EVOLUCIÓN CLÍNICA

30 DIAS



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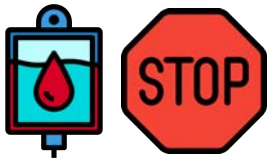

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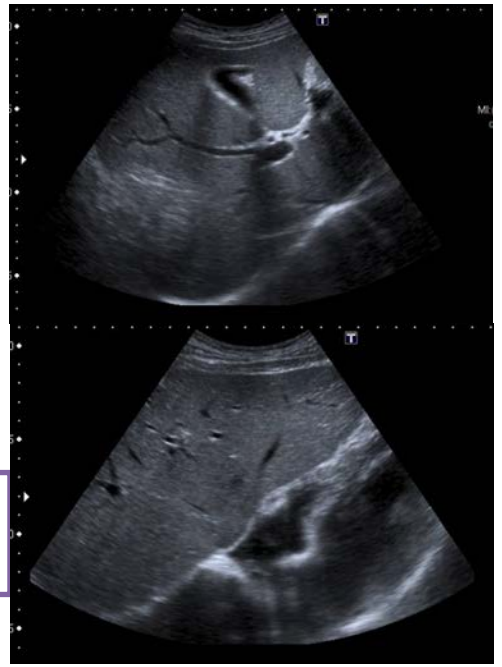
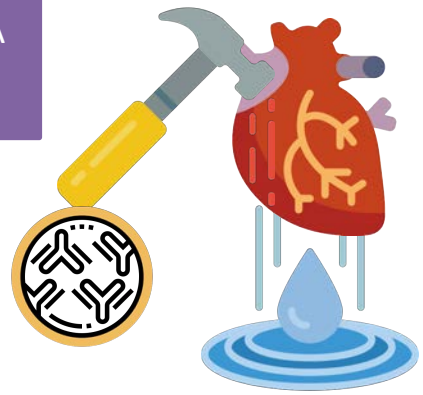


PERICARDITIS AGUDA
INMUNOMEDIADA
Grado III/IV



NO CONSUMOS FÁRMACOS

ECOGRAFÍA: SIN LESIONES
NI DILATACION VIA BILIAR

EVOLUCIÓN CLINICA

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ICTERICIA
COLURIA
ACOLIA

Dexametasona
(equival metilpred 2mg/Kg)

PERICARDITIS AGUDA
INMUNOMEDIADA
Grado III/IV

HEPATITIS
INMUNOMEDIADA
Grado III

EVOLUCIÓN CLINICA

30 DIAS

MARZO 2019

ICTERICIA
COLURIA
ACOLIA

Dexametasona
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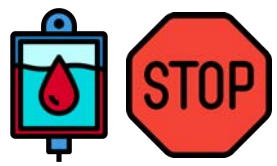
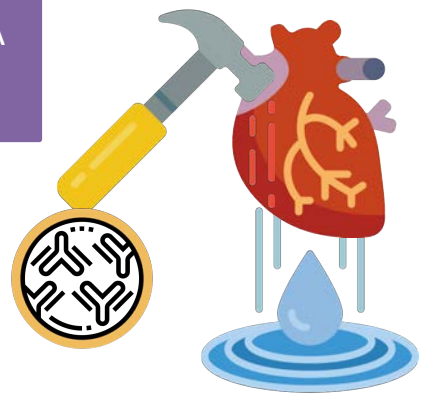
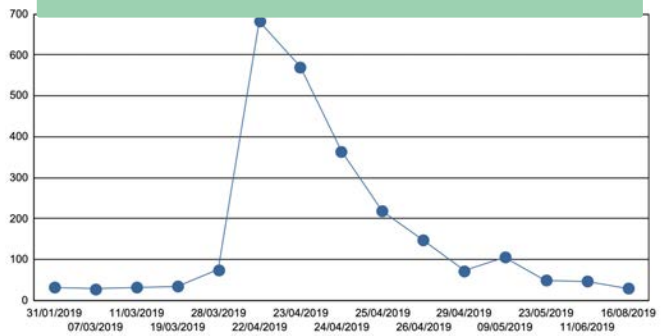


PERICARDITIS AGUDA
INMUNOMEDIADA
Grado III/IV

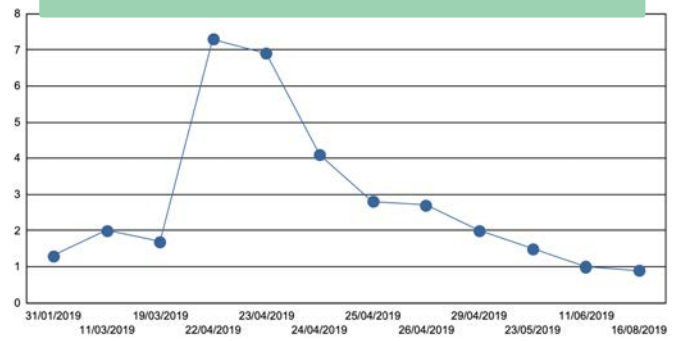


HEPATITIS
INMUNOMEDIADA
Grado III

Histórico valores AST



Histórico valores Bilirrubina



CLINICAL PRACTICE GUIDELINES

Immune related hepatotoxicity

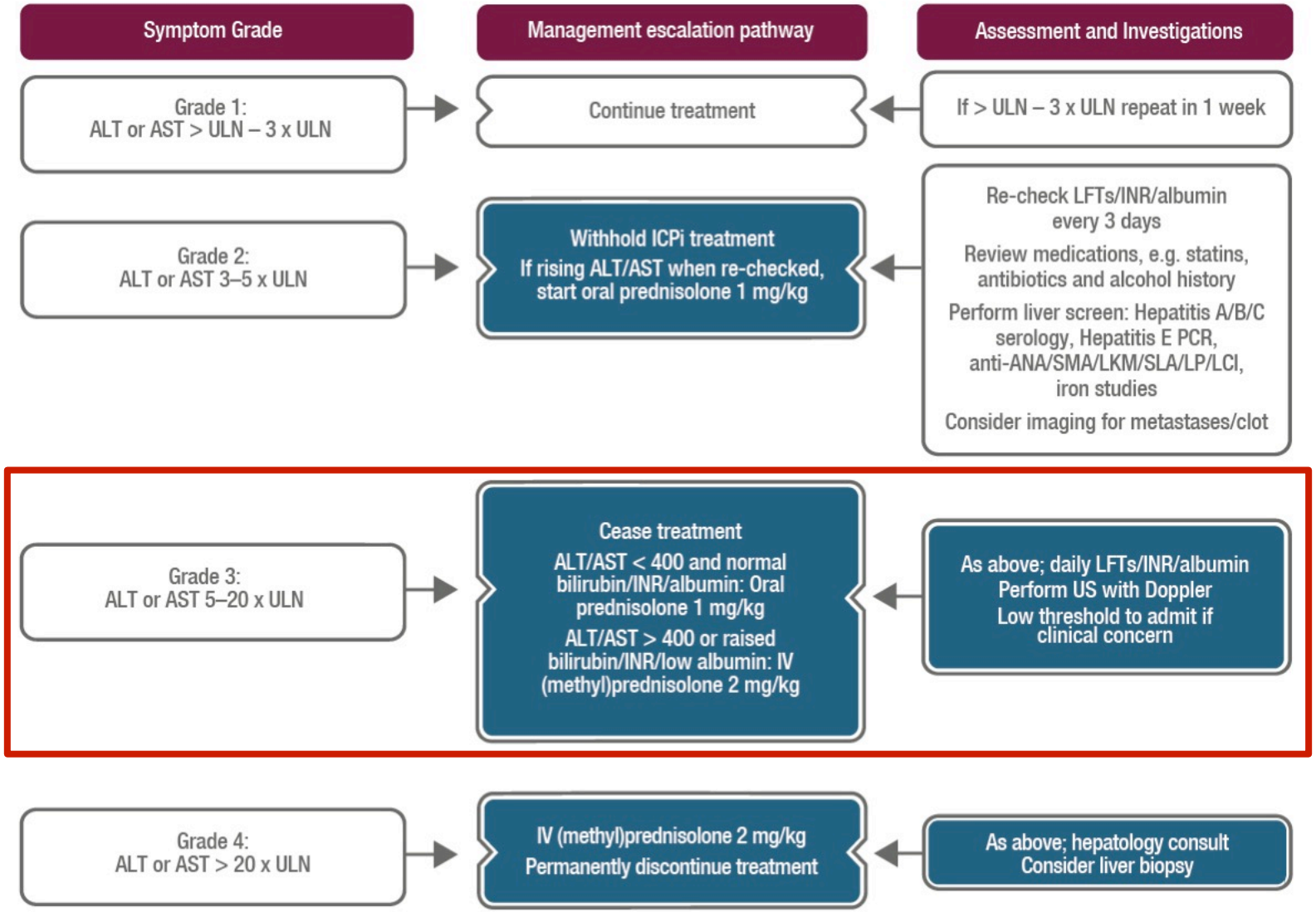
ICPi-related toxicity: Management of hepatitis

Steroid wean:

- Grade 2: Once grade 1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone ≤ 10 mg
- Grade 3/4: Once improved to grade 2, can change to oral prednisolone and wean over 4 weeks; for grade 3, re-challenge only at consultant discretion

Worsening despite steroids:

- If on oral change to IV (methyl)prednisolone
- If on IV add MMF 500–1000 mg bid
- If worse on MMF, consider addition of tacrolimus
- A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis



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2.2 Hepatitis	
G1: Asymptomatic (AST or ALT > ULN to 3.0 × ULN and/or total bilirubin > ULN to 1.5 × ULN)	Continue ICPi with close monitoring; consider alternate etiologies Monitor laboratories one to two times weekly Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT > 3.0 to ≤ 5 × ULN and/or total bilirubin > 1.5 to ≤ 3 × ULN)	Hold ICPi temporarily and resume if recover to G1 or less on prednisone ≤ 10 mg/d For grade 2 hepatic toxicity with symptoms, may administer corticosteroid 0.5-1 mg/kg/d prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days Increase frequency of monitoring to every 3 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab from other studies) In follow-up, may resume ICPi treatment followed by taper only when symptoms improve to G1 or less and corticosteroid ≤ 10 mg/d; taper over at least 1 month Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs
G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 × ULN and/or total bilirubin 3-10 × ULN)	Permanently discontinue ICPi Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency) Laboratories at daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 × ULN and/or elevated TB 3 × ULN Increase frequency of monitoring to every 1-2 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-α agents as systemic immunosuppressants If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 × ULN and/or total bilirubin > 10 × ULN)	Permanently discontinue ICPi Administer 2 mg/kg/d methylprednisolone equivalents If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil Monitor laboratories daily; consider inpatient monitoring Avoid the use of infliximab in the situation of immune-mediated hepatitis Hepatology consult if no improvement was achieved with corticosteroid Corticosteroid taper can be attempted around 4-6 weeks when symptoms improve to G1 or less; re-escalate if needed; optimal duration unclear Consider transfer to tertiary care facility if necessary
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations is moderate.	

Brahmer. J Clin Oncol. 2018 Jun 10;36(17):1714-1768

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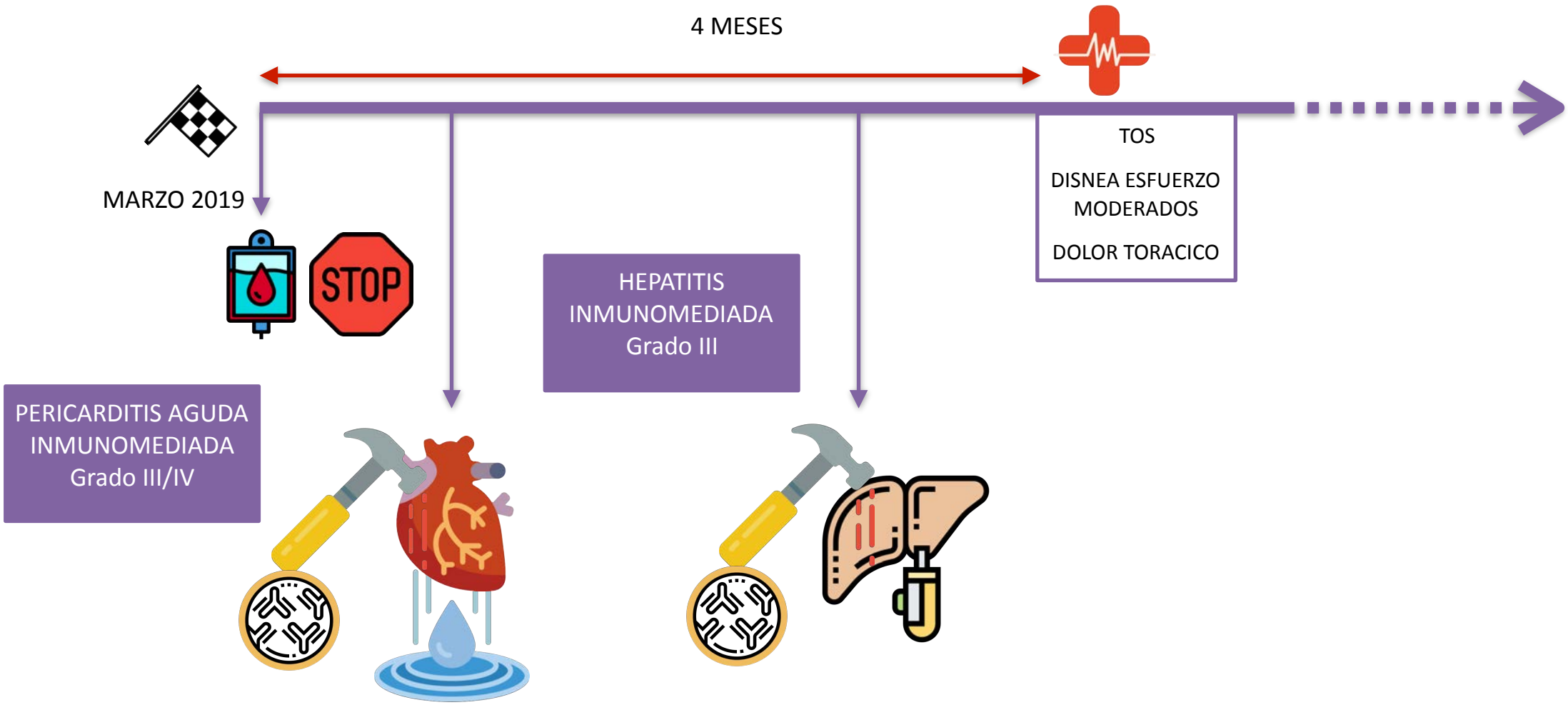


EVOLUCIÓN CLÍNICA

4 MESES

MARZO 2019

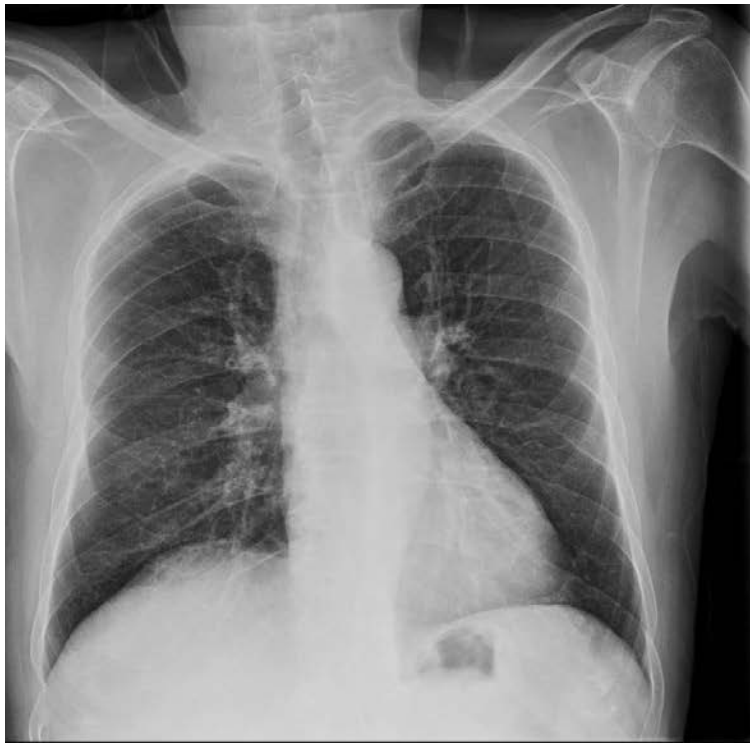
TOS

DISNEA ESFUERZO MODERADOS

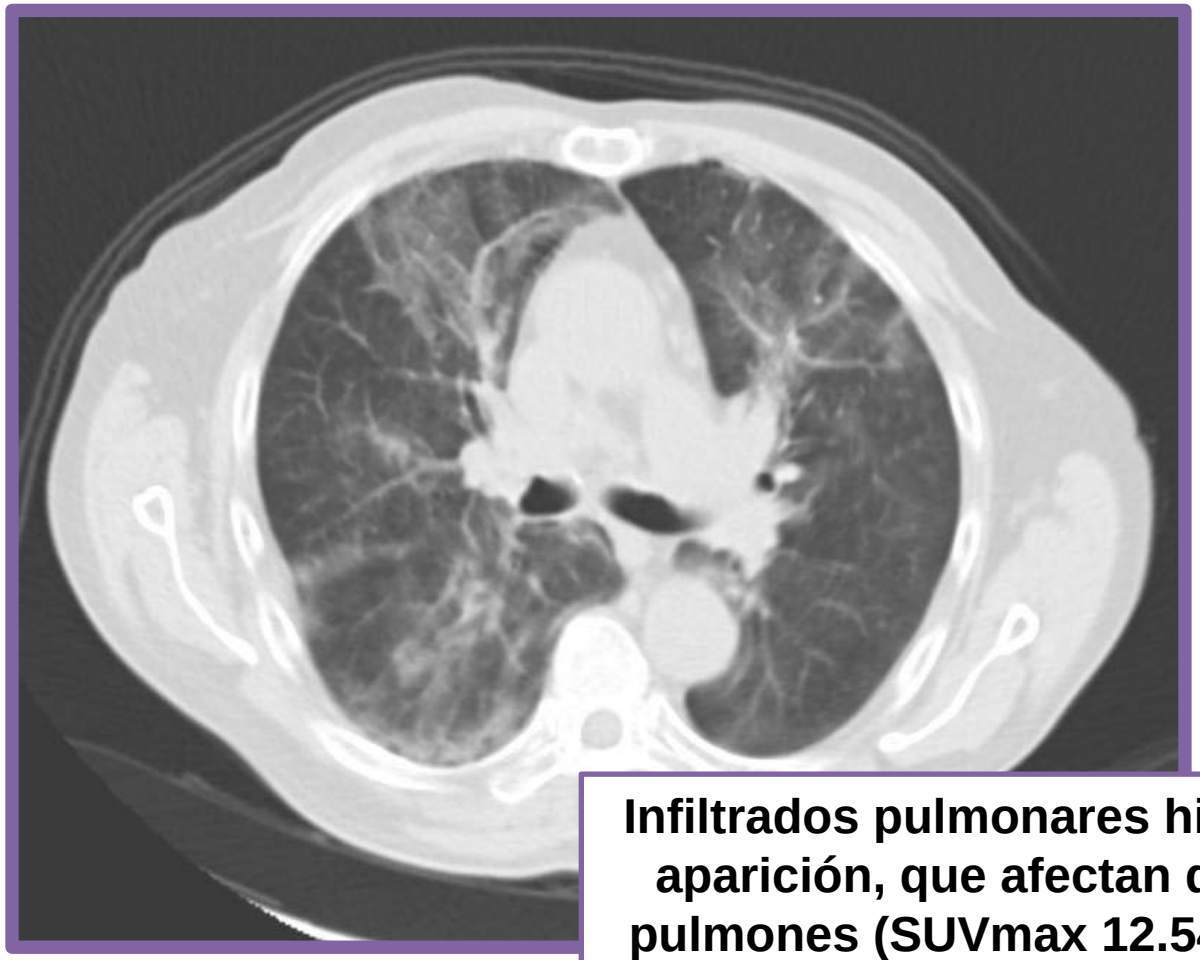
DOLOR TORACICO

HEPATITIS INMUNOMEDIADA Grado III

PERICARDITIS AGUDA INMUNOMEDIADA Grado III/IV

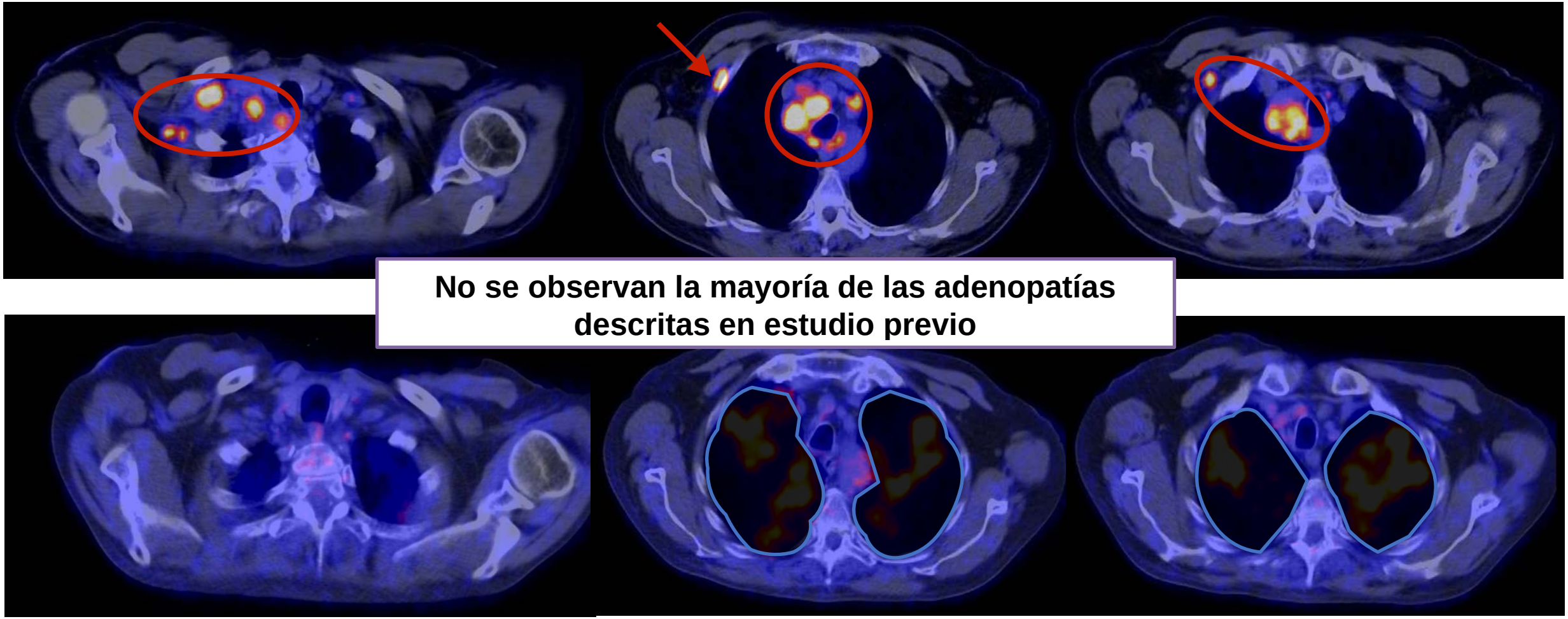


PET/CT Seguimiento



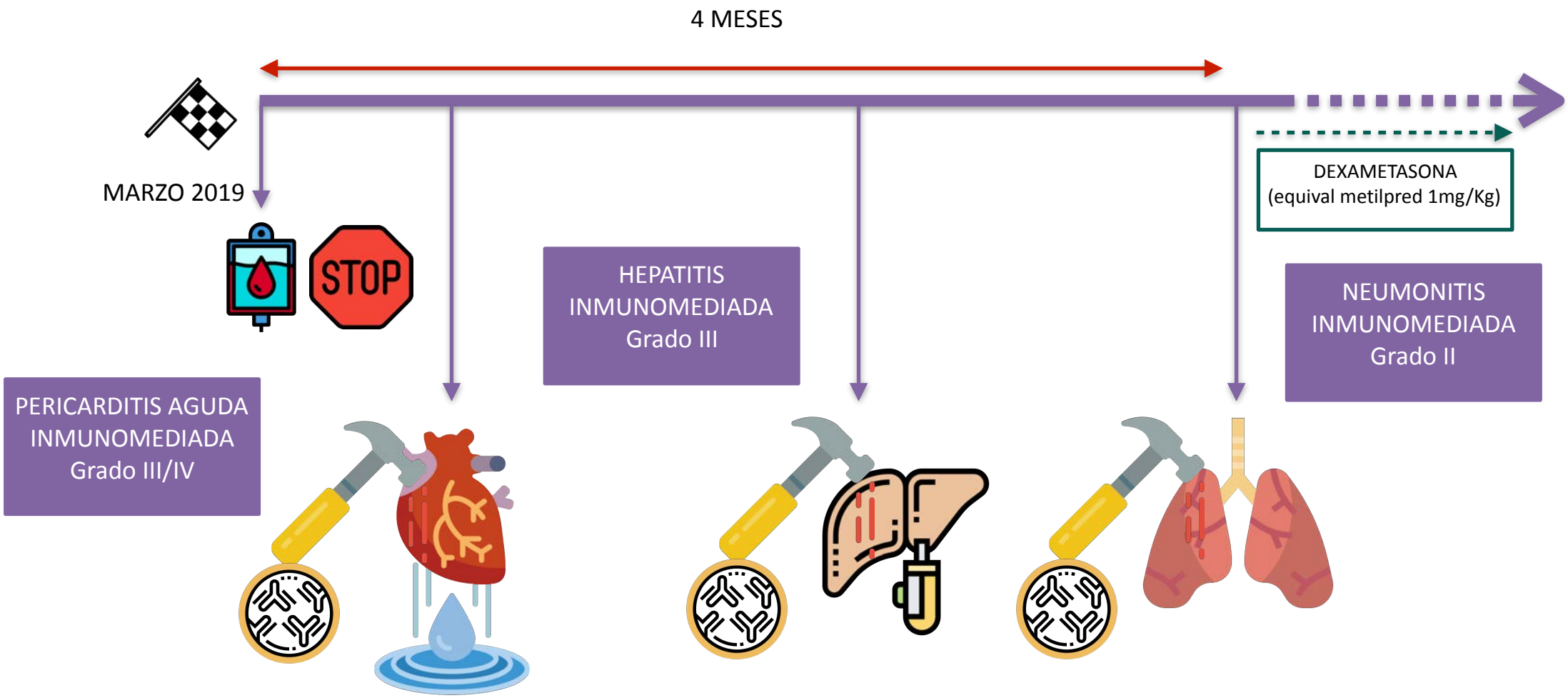
Infiltrados pulmonares hipermetabólicos de nueva aparición, que afectan de forma extensa ambos pulmones (SUVmax 12.54) de probable naturaleza inflamatoria vs infecciosa

PET/CT Seguimiento

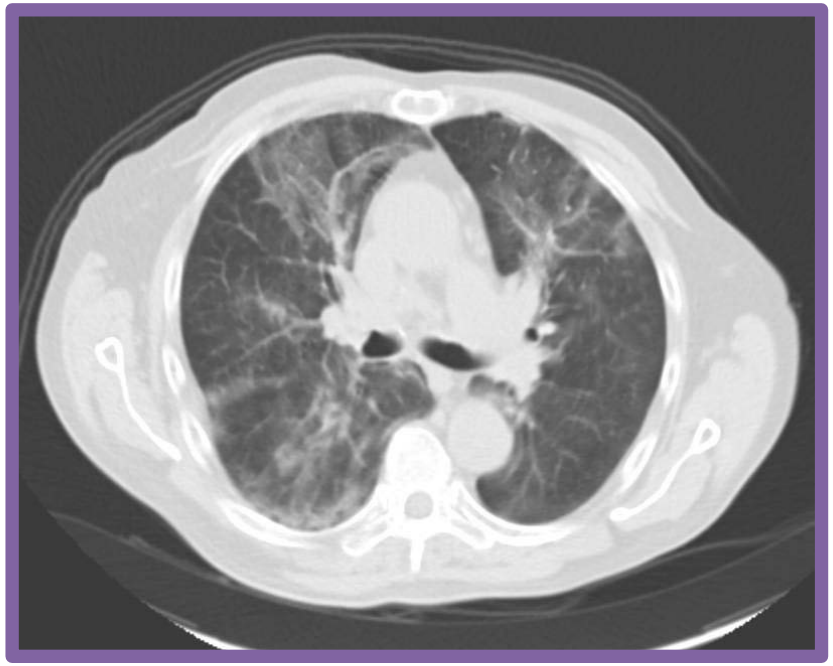


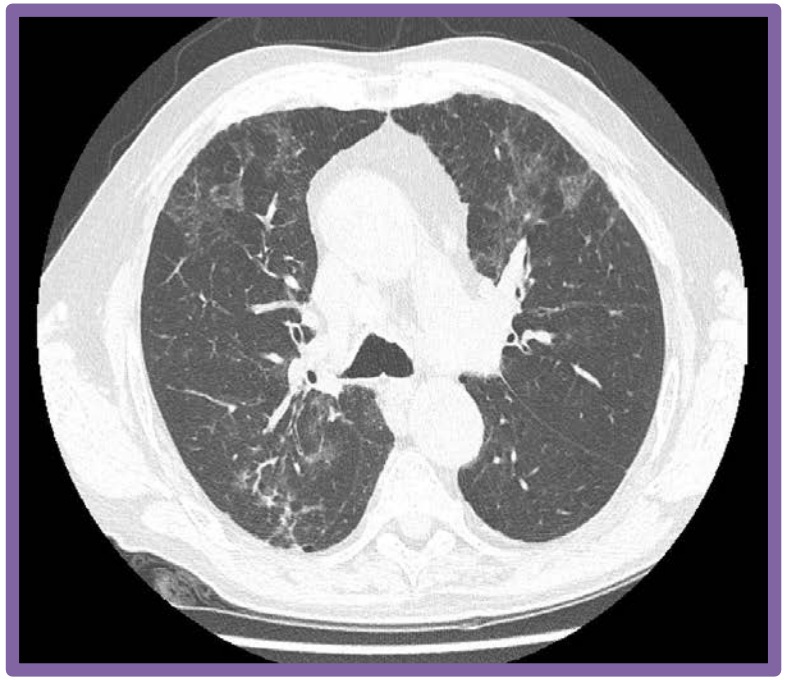
No se observan la mayoría de las adenopatías descritas en estudio previo

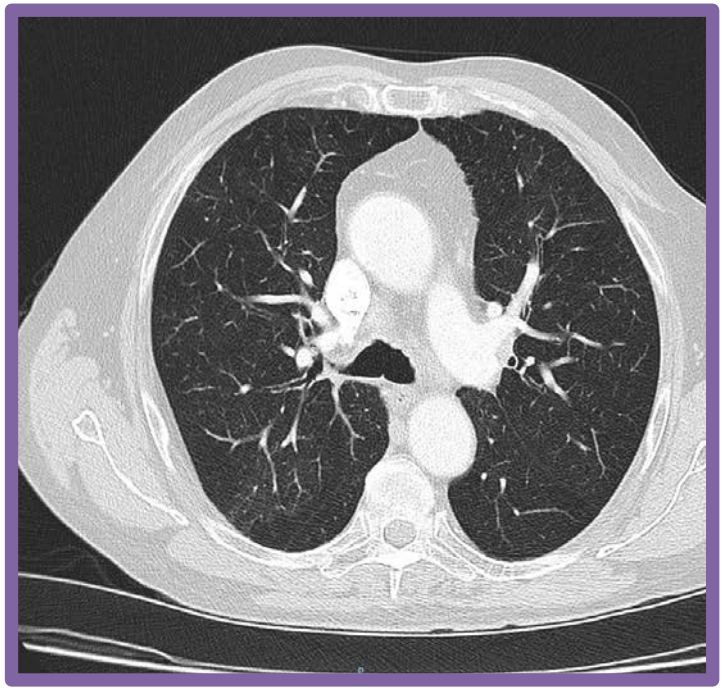
EVOLUCIÓN CLÍNICA



Seguimiento Neumonitis







CLINICAL PRACTICE GUIDELINES

Immune related pneumonitis toxicities

Any new respiratory symptom require prompt investigation to formally exclude lung toxicity and all patients presenting with pulmonary symptoms should be assessed by CT

Summary of recommendations	
Radiological features	• Ground glass opacities • A cryptogenic organising pneumonia-like appearance • Interstitial pneumonia pattern • Characteristics of hypersensitivity pneumonitis
Lung biopsy	Generally not required for patient management, unless there is doubt as to the aetiology of pulmonary infiltrates, when a VATS biopsy is the method of choice
Bronchoscopy with BAL	Supports the identification of infections and is recommended in any symptomatic pneumonia

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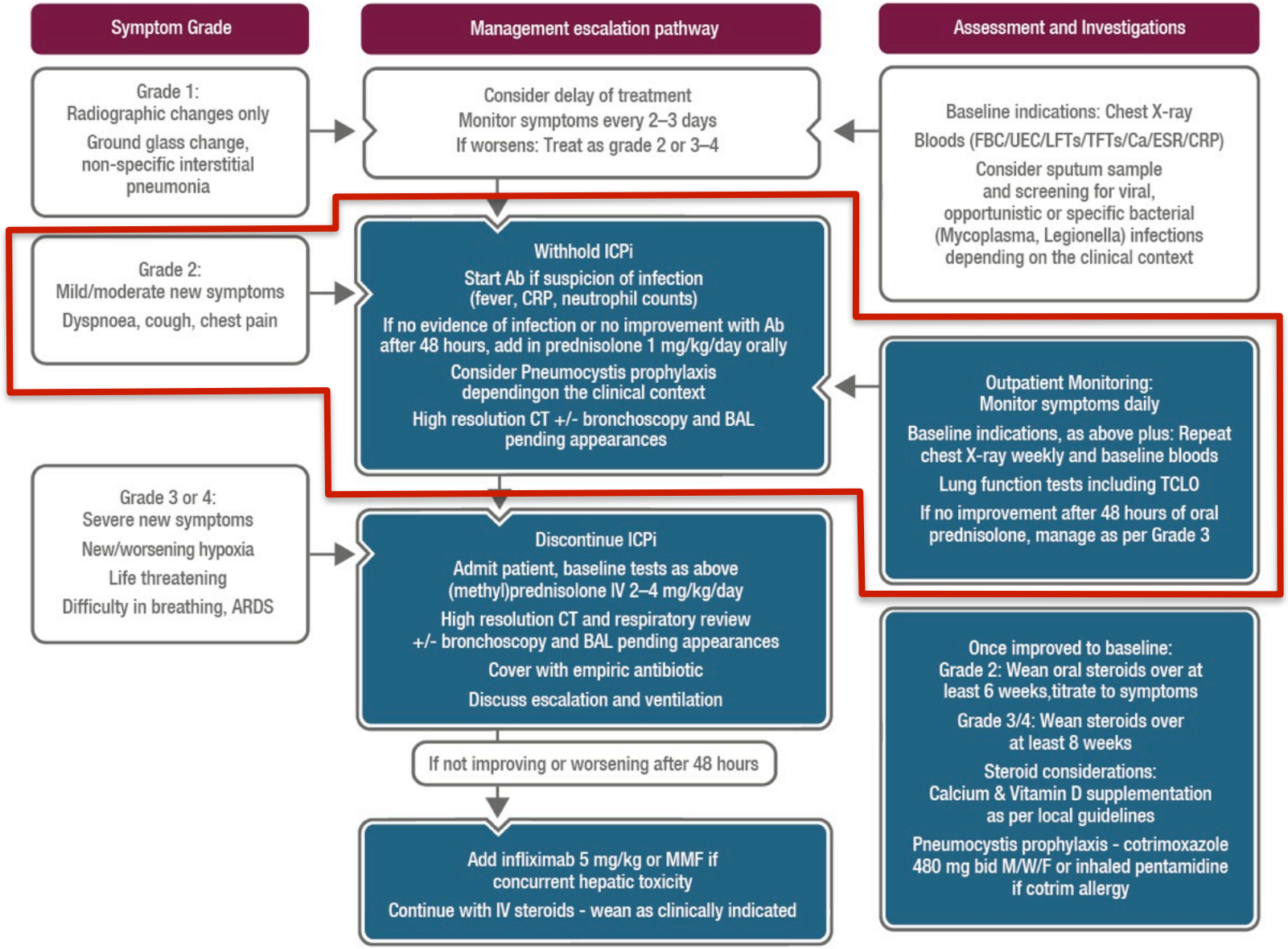
CLINICAL PRACTICE GUIDELINES

Immune related pneumonitis toxicities

ICPi-related toxicity: Management of pneumonitis

History:
Pulmonary hypertension/respiratory; disease/connective tissue disease; Influenza/Mycobacterium; tuberculosis exposure; Smoking history; Travel history; Allergy history including exposure to home/occupational aeroallergens

Differential Diagnosis:
Pneumonia (including atypical, pneumocystis, tuberculosis); Lymphangitis; Usual interstitial pneumonias; Pulmonary oedema; Pulmonary emboli; Sarcoidosis



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3.1 Pneumonitis

Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging)
No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis

Diagnostic work-up
Should include the following: CXR, CT, pulse oximetry
For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity

Grading	Management
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management

Brahmer. J Clin Oncol. 2018 Jun 10;36(17):1714-1768

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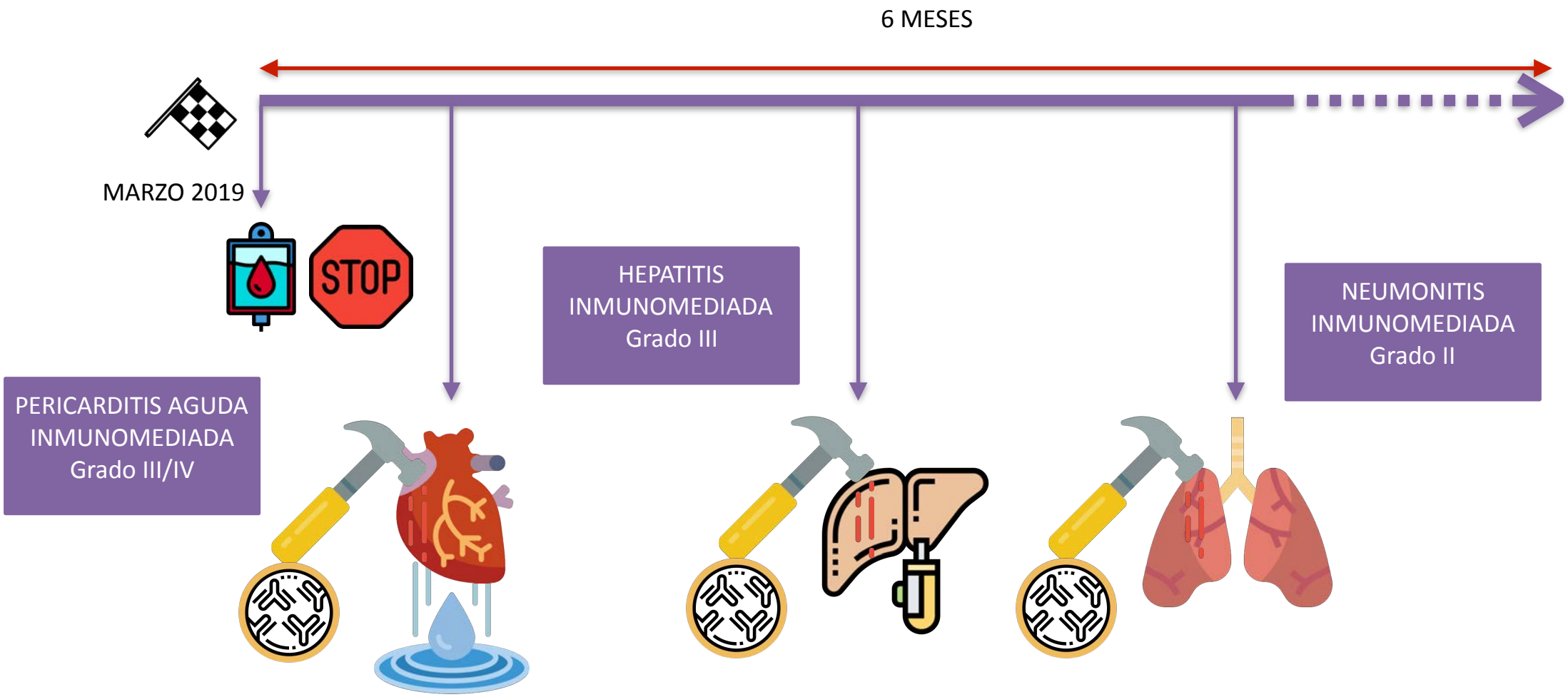
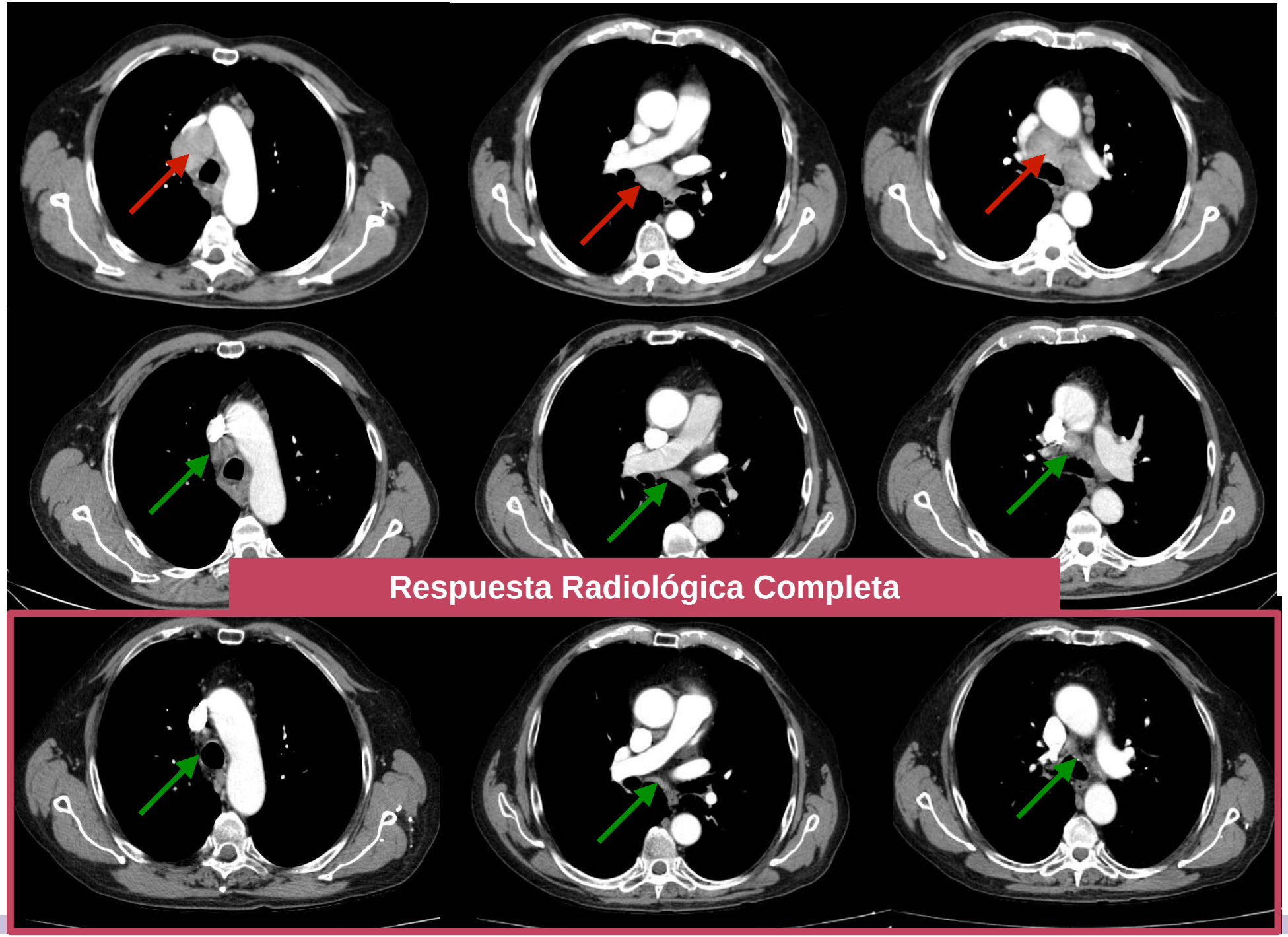
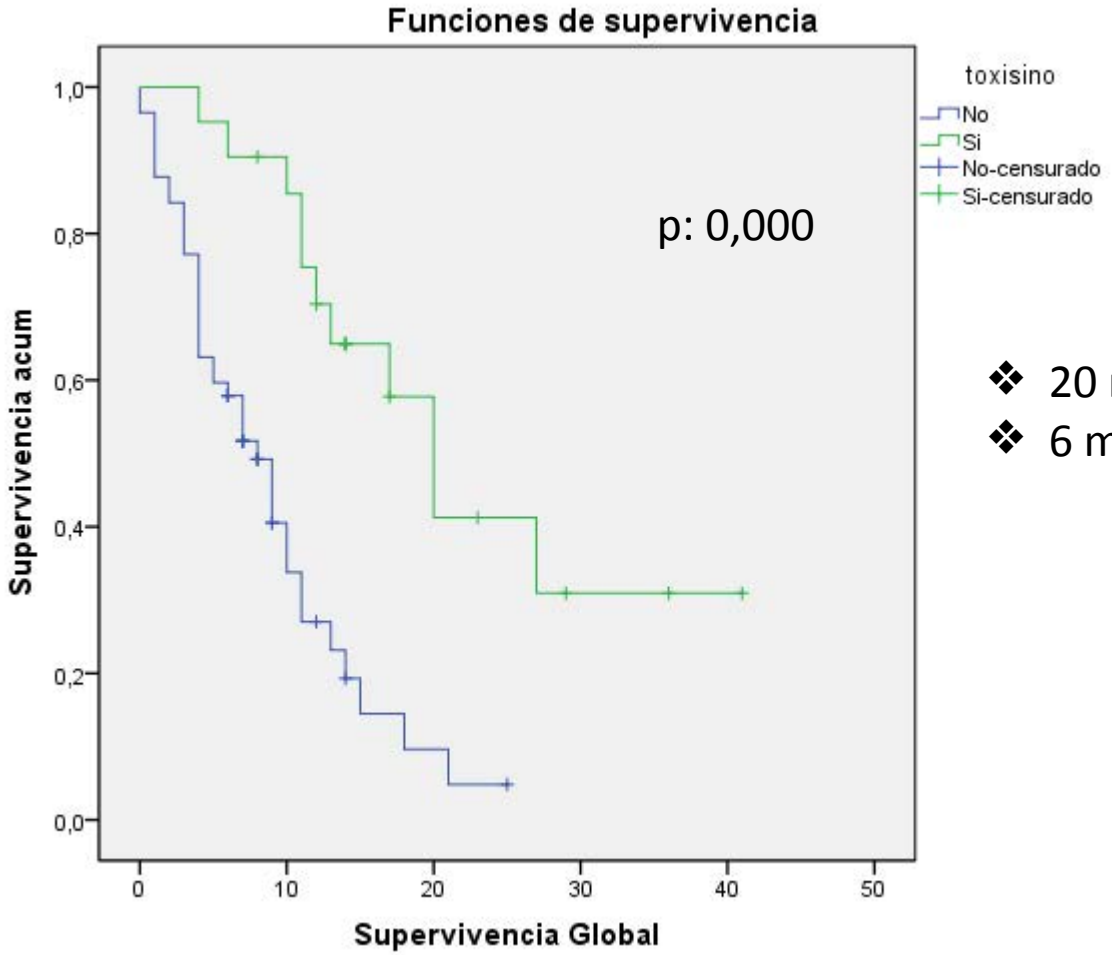



Respuesta Radiológica Completa

EN NUESTRO HOSPITAL



- 20 meses para los pacientes que desarrollaron toxicidad.
- 6 meses para los pacientes que no desarrollaron toxicidad.

Tabla de contingencia Presencia de toxicidad * Respuesta a la inmuno

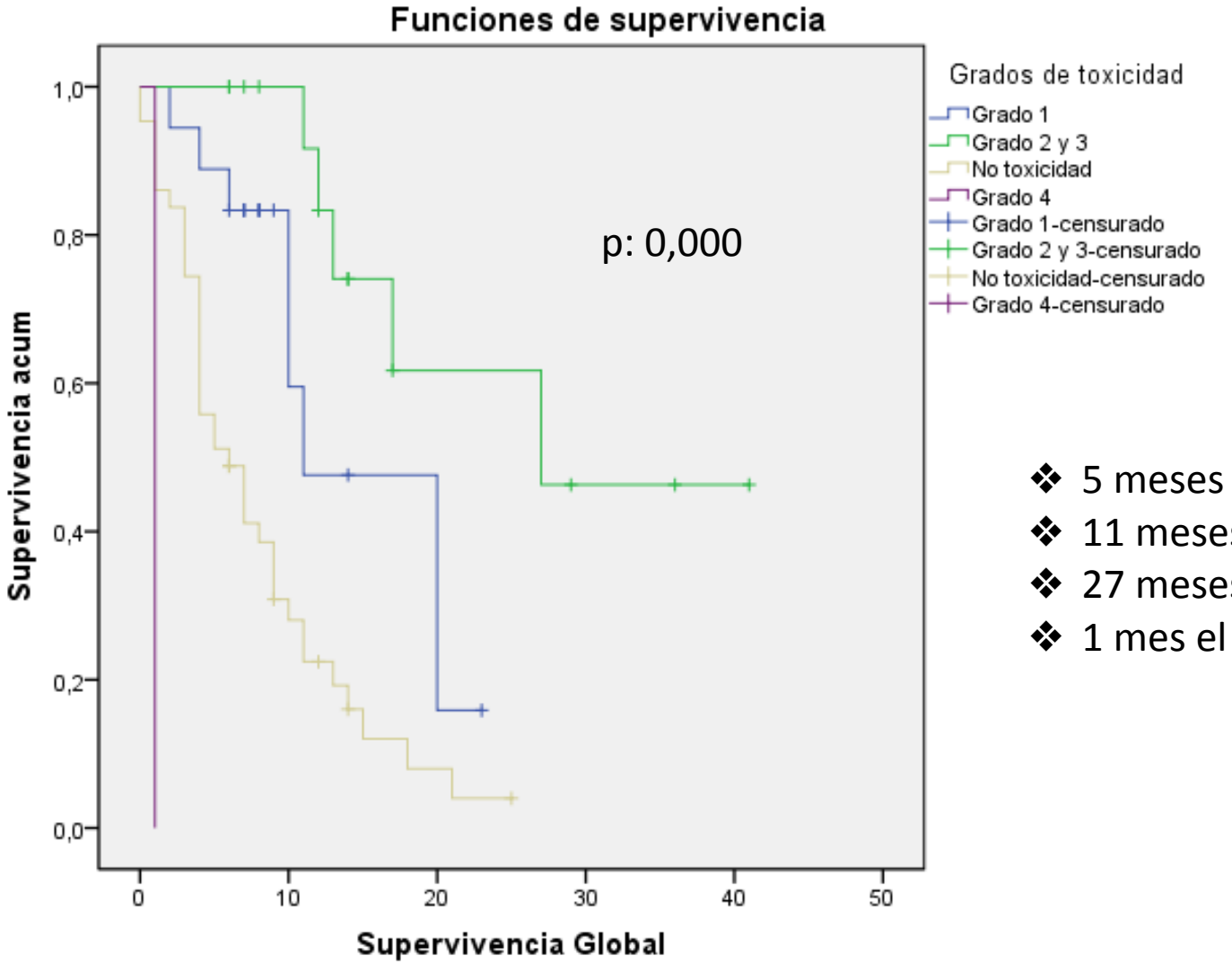
Recuento

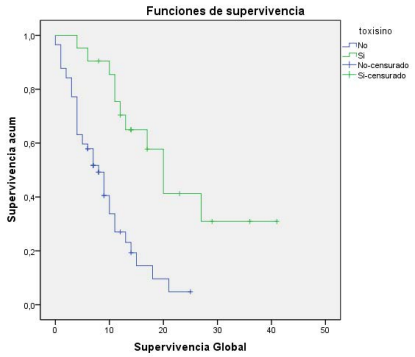
		Respuesta a la inmuno		Total
		No	Sí	
Presencia de toxicidad	No	18	16	34
	Si	7	26	33
Total		25	42	67

p: 0,007

DIAPOSITIVA CEDIDA DR. GARCÍA DURÁN

EN NUESTRO HOSPITAL





- 5 meses para los pacientes que no desarrollaron toxicidad.
- 11 meses para los pacientes con toxicidad G1
- 27 meses para los pacientes con toxicidad G2/3
- 1 mes el paciente con toxicidad G4

DIAPOSITIVA CEDIDA DR. GARCÍA DURÁN

I Reunión de manejo de los efectos secundarios inmunomediados

Córdoba, 13 de noviembre de 2019

Sociedad Andaluza de Oncología Medica