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MANEJO DE LA TOXICIDAD DE LOS NUEVOS TRATAMIENTOS EN

TUMORES UROLÓGICOS

Valencia, 23 de abril de 2024

Organizado por: GUARD CONSORTIUM

Manejo práctico de la toxicidad pulmonar

Belén Safont Muñoz

Neumóloga. Hº General Valencia

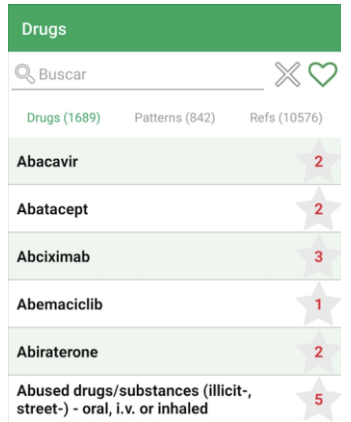
Organizado por: GUARD CONSORTIUM

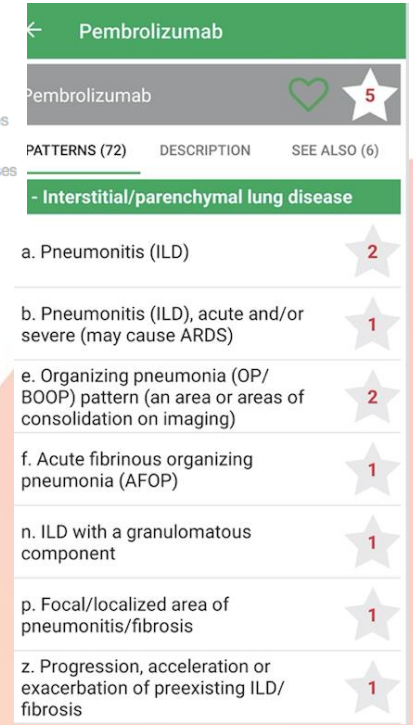
INCIDENCIA: 1º causa de DIILD (23% al 51%)

Type of anticancer drug	Incidence of DILD reported in the literature (%)
Chemotherapeutic agents[6]	1.0–40.0
TKIs[7–10]	0.4–5.3
mTOR inhibitors[11, 12]	3.0–54.0
ICIs[13–17]	0.9–3.6
ADCs[18, 19]	1.9–15.8

Class	Estimated DIILD incidence (range)[a]
Bleomycin[1]	7%-21%
EGFR inhibitors[1,2]	0.3%-6%
HER2 inhibitors (including ADCs)[3-5]	2.4% (up to 15.8% with T-DXd)
BRC/ABL tyrosine kinase inhibitors[6-8]	Unknown (imatinib and dasatinib); ≥1/1,000 to <1/100 (nilotinib)
ALK inhibitors[9]	2.5% (95% CI: 1.7%-3.6%)
BRAF inhibitors[10]	2.4% (trametinib); data not shown
PI3K inhibitors[11]	3%-25%
FLT3 inhibitors[12]	7%-8.5%
TRK/ROS1 inhibitors[13]	Data not shown
VEGFR inhibitors[14]	0.37% (bevacizumab in combination with FOLFOX and FOLFIRI)
Immune checkpoint inhibitors[1]	1.1%-3.6%
CDK4/6 inhibitors[15]	0.3%-2.1%
mTOR inhibitors[16]	11%
PARP inhibitors[17,18]	0.79%-2.0%

PNEUMOTOX ON LINE





CITOTÓXICOS

Drug name	Frequency (%)
Paclitaxel (Taxol®)	0.54
Docetaxel hydrate (Taxotere®)	0.1
Amrubicin hydrochloride (Calsed®)	2.2
Gemcitabine hydrochloride (Gemzar®)	1.50
Pemetrexed (Alimta®)	3.6
Vinorelbine (Navelbine®)	2.45
Irinotecan (Campto®, Topotecin®)	1.30
Peplomycin sulfate (Pepleo®)	6.90
Bleomycin (Bleo)	10.20
Cisplatin (Briplatin®, Randa®)	0.38
Carboplatin (Paraplatin®)	0.1
S-1 (TS-1)	0.3

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P Conte. ESMO Open 2022;7:100404

Kubo K.Respir Investig 2013;51:260

MANEJO DE LA TOXICIDAD PULMONAR

Patient screening	Close monitoring	Suspected anticancer drug-induced ILD	Treatment and management
Identify high-risk population	**Early detection**	**Early diagnosis**	**Early treatment**
Risk factors Underlying disease Age Lung lesions Low body surface area Renal dysfunction Combination therapy Investigations Chest imaging and other laboratory tests	Signs and symptoms Cough (especially dry cough), dyspnea/shortness of breath/rales Investigations Chest imaging and other laboratory tests	Signs and symptoms Cough (especially dry cough), dyspnea/shortness of breath/rales Investigations Chest imaging, other laboratory tests, bronchoscopy if necessary Differential diagnosis Infections, tumor progression, radiation pneumonitis, and abnormal function of other organs	Grading of DILD ASCO guidelines of immune-related adverse events/CTCAE v5.0 Management Treat based on DILD grading. Commonly used drugs are glucocorticoids.

Comité EPI

DD:infección
*FBC
*ATB empírico

Patient-related risk factors

Major risk factors:

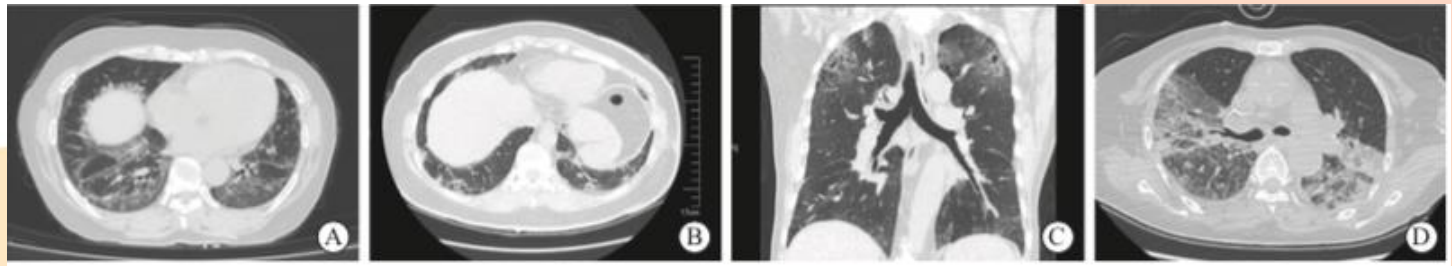
- History of cigarette smoking (≥50 packs/year)
- Pre-existing lung disease (such as IPF, COPD and bronchiectasis)
- Previous DIILD
- ECOG PS ≥2 at cancer diagnosis
- Advanced stage of the underlying cancer

Other risk factors:

- Increased age
- Male gender
- Asian ethnicity
- Prior thoracic radiotherapy
- Prior chemotherapy
- Underlying pulmonary neoplasm
- Comorbidities (e.g. kidney failure, diabetes)
- Genetic predisposition/Family history (e.g. cytochrome P450 enzyme polymorphisms and HLA allelic variants)
- Alcohol consumption

Cancer treatment-related risk factors

- Cumulative dose (bleomycin) and treatment duration[a]
- Combinations of anticancer drugs
- Interaction with concomitant non-anticancer drugs



NINE NO HP DAD

Dai HP. Curr Med Sci 2023;43:1

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CLASIFICACIÓN DE LA GRAVEDAD

CTCAE v5.0

Grado	Severidad clínica
Grado 1 (leve)	Asintomático, sólo Δ RX
Grado 2 (moderada)	Síntomas leves que no afectan la calidad de vida
Grado 3 (severa)	Síntomas con afectación calidad de vida y limitación ABVD (independiente del grado de Δ RX) Posibilidad de O2
Grado 4 (muy severa)	Síntomas severos que condicionan hospitalización Posibilidad de soporte ventilatorio
Grado 5 (fatal)	Muerte

Table 4 Grading of pulmonary toxicity in ASCO guideline on the management of immune-related adverse events[52]

Grade	Description
G1	Asymptomatic; confined to one lobe of the lung or 25% of the lung parenchyma; clinical or diagnostic observations only
G2	Symptomatic; involving more than one lobe of the lung or 25%–50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL
G3	Severe symptoms; hospitalization required; involving all lung lobes or >50% of lung parenchyma; limiting self-care ADL; oxygen indicated
G4	Life-threatening respiratory compromise; urgent intervention indicated (tracheotomy or intubation)

ASCO: American Society of Clinical Oncology; ADL: activity of daily living

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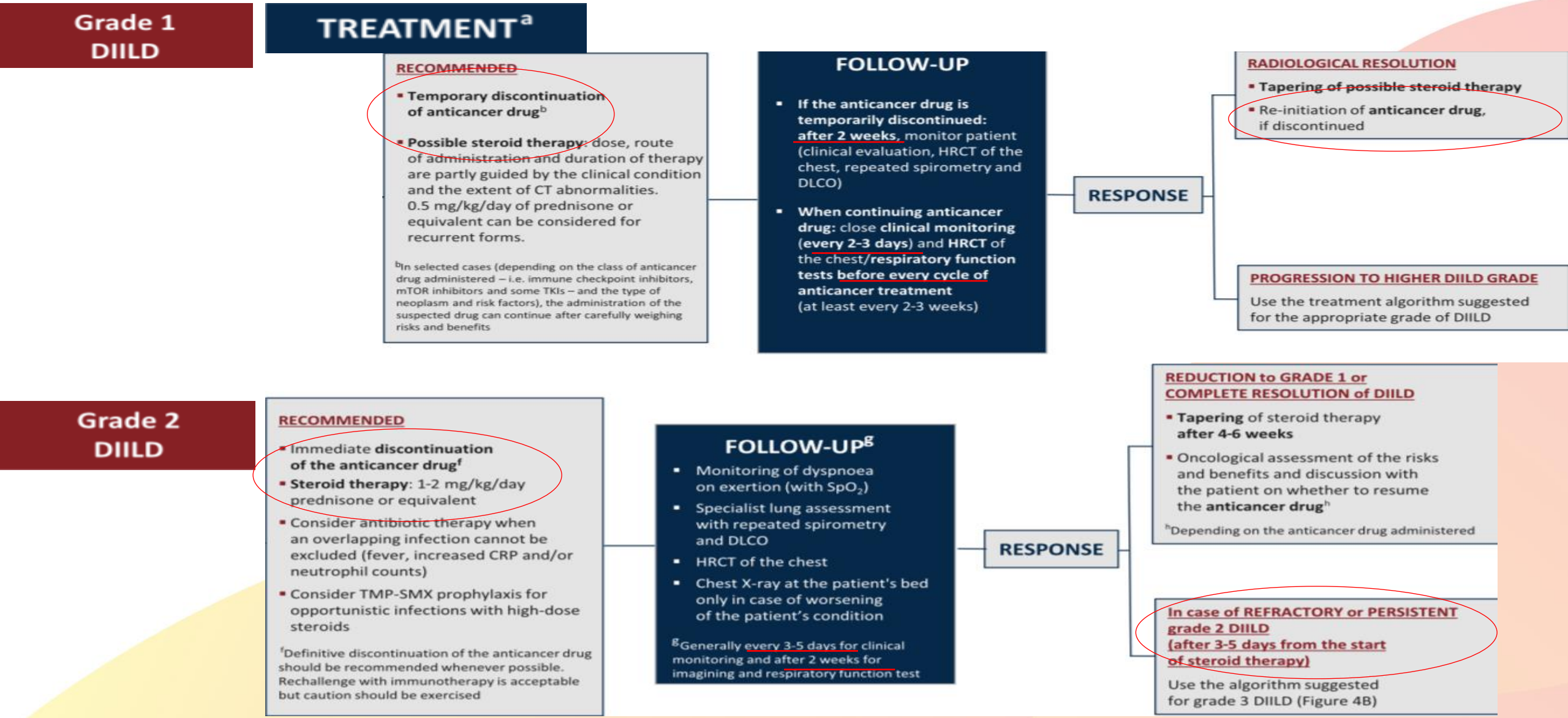
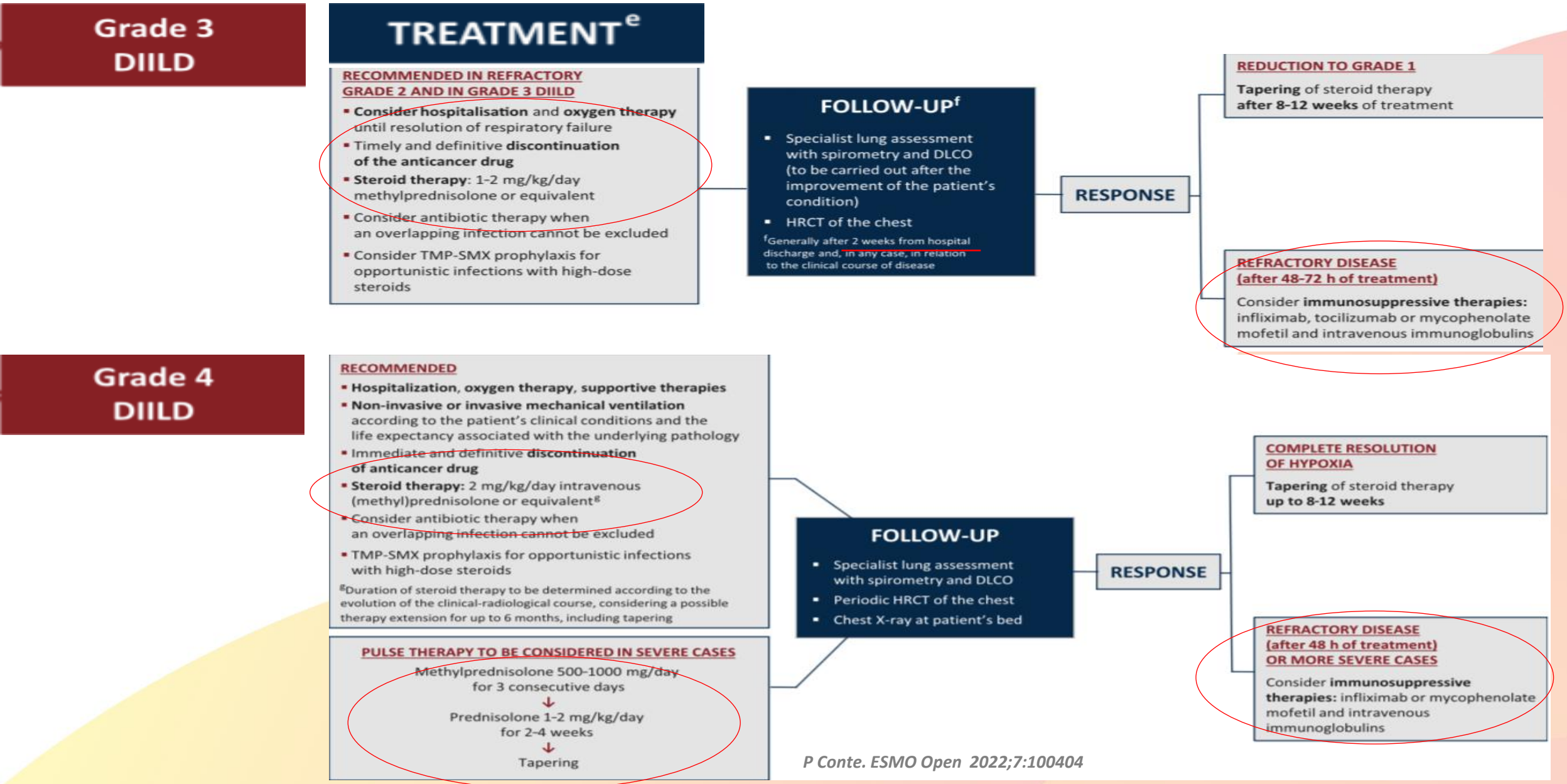
TRATAMIENTO Y SEGUIMIENTO



P Conte. ESMO Open 2022;7:100404

TRATAMIENTO Y SEGUIMIENTO



P Conte. ESMO Open 2022;7:100404

ANTICUERPOS INMUNOCONJUGADOS (ADC)

- Enfortumab vedotin: vida real 15%
- F.RIESGO:
  - EPI previa
  - Deterioro renal moderado/grave

Severidad	Modificación del tratamiento
GRADO 1	Interrumpir hasta resolución - Si ≤28d, reintroducir dosis - Si >28d, reducir la dosis un nivel Considerar GC (0.5mg/kg)
GRADO ≥2	Retirada permanente Iniciar GC (1mg/kg) ≥14d resolución completa y ↓dosis

https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf
Yoon S. Eur J Cancer 2022:174:81-89
Tarantino P. JAMA Oncol 2021;7:1873-1881
Endo Y. Curr Oncol 2024;31:759-768

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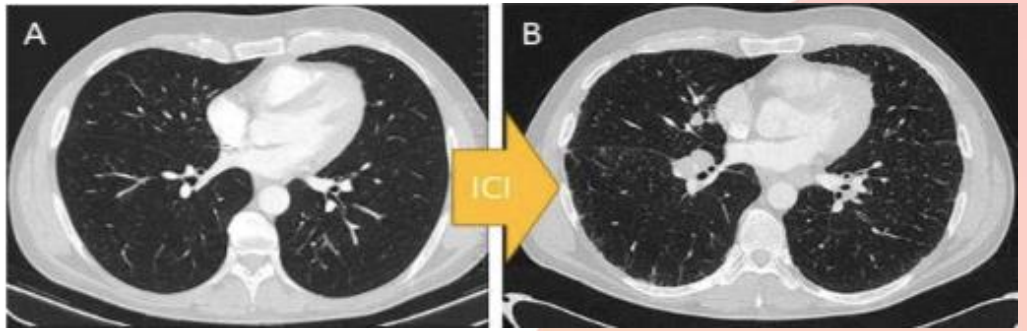
INHIBIDORES DE PUNTO DE CONTROL INMUNITARIO

- F.RIESGO:
  - EPI previa
  - Neoplasia pulmonar y células renales

- Otra presentación: sarcoidosis-like



Chanson M. Eur J Cancer 2021;158:208-216

G1	**-Eliminar temporalmente o mantener con monitorización** -Control semanal clínico, SpO2, RX/TC +/- PFR/DLCO c/3- 4s → **Reanudar**, si resolución o mejoría RX → Si no mejora → G2
G2	-**Eliminar hasta ≤G1** y PDN 1-2mg/día -Revalorar ≤ 1v/sem, TC c/ 3-4s → Si no mejoría a las 48-72h→ G3 → Si mejoría, disminuir 5-10mg cada 4-6s
G3	-**Suspender permanentemente** -Metilprednisolona ev 1 - 2 mg/Kg/d → Si no mejora 48h valorar +IS (MMF, infliximab, Igs, ciclofosfamida) → Si mejoría, continuar tratamiento hasta ≤G1 y reducir cada 4-6s
G4	

Shannon VR. Support Care Cancer 2020;28:6145
Chneider BJ. J Clin Oncol 2021; 39:4073
Dai HP. Curr Med Sci 2023;43:1-12

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INHIBIDORES mTOR

- Metanálisis everolimus y temsirolimus (n=2233)
- Toxicidad pulmonar 12%
- Grado 3-4: 3%

Iacovelli R. Acta Oncol. 2012;51:873

G1	-Vigilar (RX/TCAR) cada 2 ciclos
G2	-Reducir everolimus 5mg/d 3sem y TC y PFR en cada ciclo * si ≤G1 en <3s: AUMENTAR * Si persiste: SUSPENDER
G3	SUSPENDER + GC y TC y PFR en cada ciclo *Si G1 o resolución, valorar reintroducir a las 2s a 5mg/d
G4	SUSPENDER PERMANENTEMENTE + GC

Porta C. Eur J Cancer 2011;47:1287. Experiencia FIII RECORD-1
Alvarez RH. Oncologist. 2018;23:660

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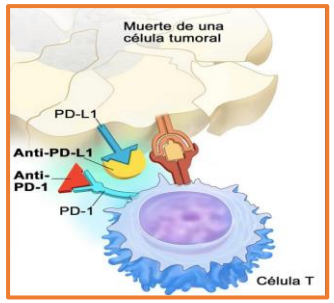
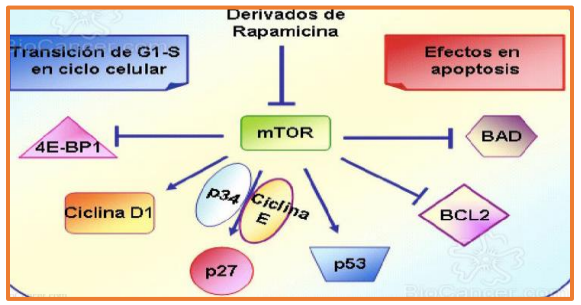
MANTENIMIENTO, REDUCCIÓN O REINTRODUCCIÓN DE DOSIS

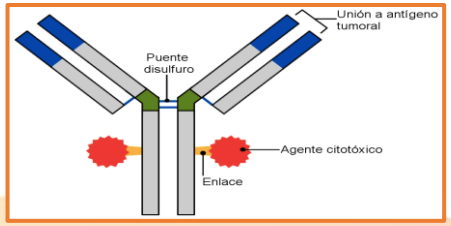
- Inhibidores de puntos de control inmunitario (ICI)
- Mantener y reintroducir



- Inhibidores mTOR
- Mantener, reintroducir o reducir dosis



- Ac. inmunoconjugados (ADC)
- Reintroducir o reducir dosis



- Inh TK (Dasatinib)
- Reintroducir

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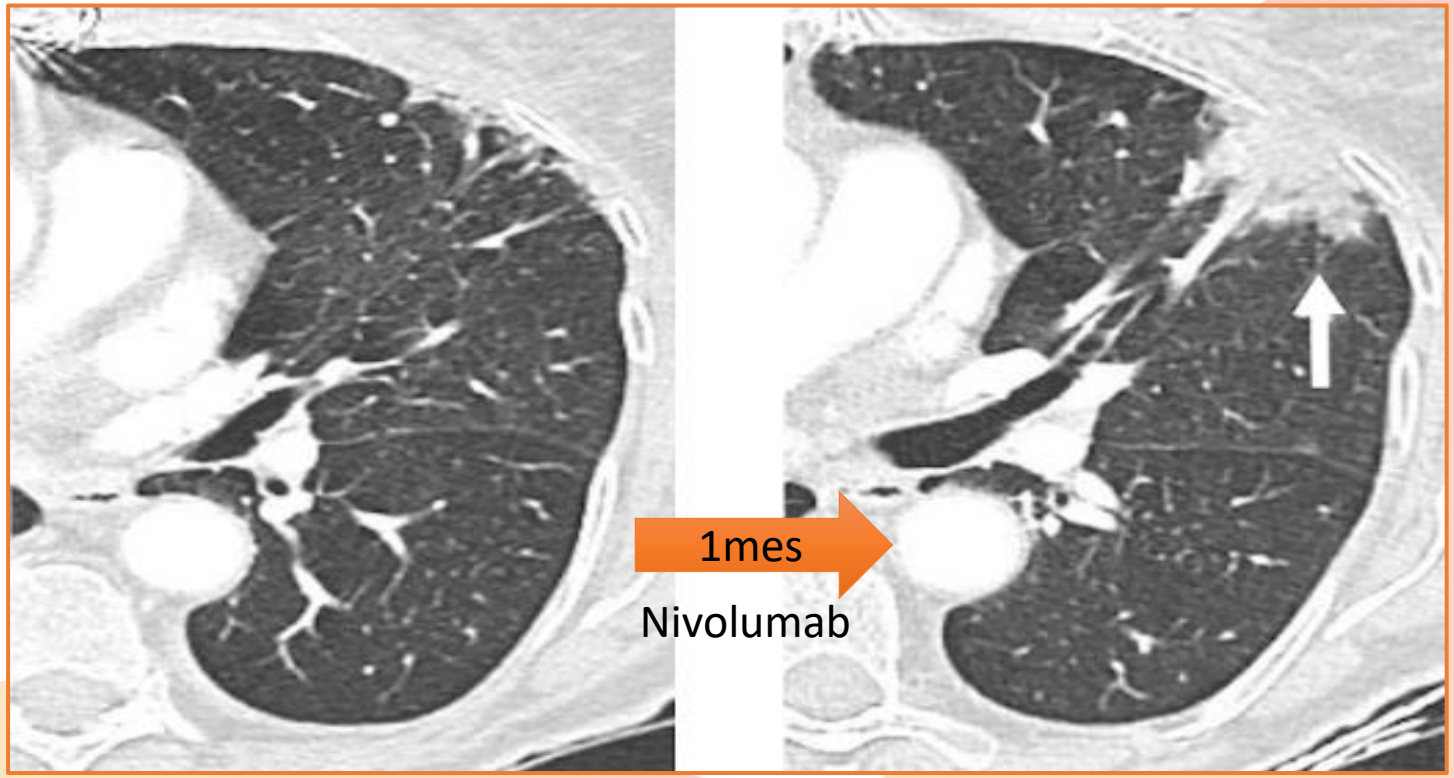
NEUMONITIS POR RECUERDO DE RT

- Carmustina
- Doxorrubicina
- Etopósido
- Gefitinib
- Gemcitabina
- Paclitaxel
- Trastuzumab
- Adriamicina
- ICIs (19%)



Vahid B. Chest 2008;133:528-38
Cousin F. Radiother Oncol 2021;157:47

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MORTALIDAD: 14-51%

- Citotóxicos: 21%
- ICI 17%
- Agentes dirigidos molecularmente: 9.5%

FR MORTALIDAD:

- Presentación aguda
- PAFI
- Necesidad de VMI → mortalidad 69%
- Sexo masculino
- Edad >65 años
- EPI preexistente
- Mayor extensión radiológica
- Patrones radiológicos: DAD (HSP 47, KL-6), NIU (KL-6)

Schwaiblmair M. Open Respir Med J. 2012; 6: 63
Skeoch S. J Clin Med. 2018; 7: 356
Spagnolo P. European Respiratory Journal 2022
Kaku S. J Cancer Res Clin Oncol 2022;148:1737

Skeoch S. J Clin Med. 2018; 7: 356
Kakugawa T. Respir Res 2013;14:133
Ohnishi H. Thorax 2003;58:872
JR Cleverley. Clin Radiol 2002;57:292

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FACTORES PREDICTORES DE MORTALIDAD (GRADO 3-4)

- n=19132 → n=126: Incidencia : 0.62% (c. pulmón 2,5%)
- Mortalidad 18%

F.PRONÓSTICOS	HR	IC 95%
TC DAD	3.59	1.17-11.03
EPI previa	3.20	1.27-8.1
ECOG >2	3.81	1.10-13.17

- Tasa de mortalidad DAD vs no DAD: 53,3% vs 13,3%
- Md supervivencia DAD: 10 días (rango: 2-65 días)

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Kaku S. J Cancer Res Clin Oncol 2022;148:1737

CONCLUSIONES → DIAGNÓSTICO PRECOZ

- Importancia de valorar factores individuales de riesgo
- Concienciación del paciente acerca de los síntomas
- Exploraciones complementarias: PFR iniciales y imagen tórax
- Seguir los algoritmos diagnósticos y terapéuticos
- Revisión de casos en Comité multidisciplinar de enf. pulmonar intersticial

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¡Gracias!

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