

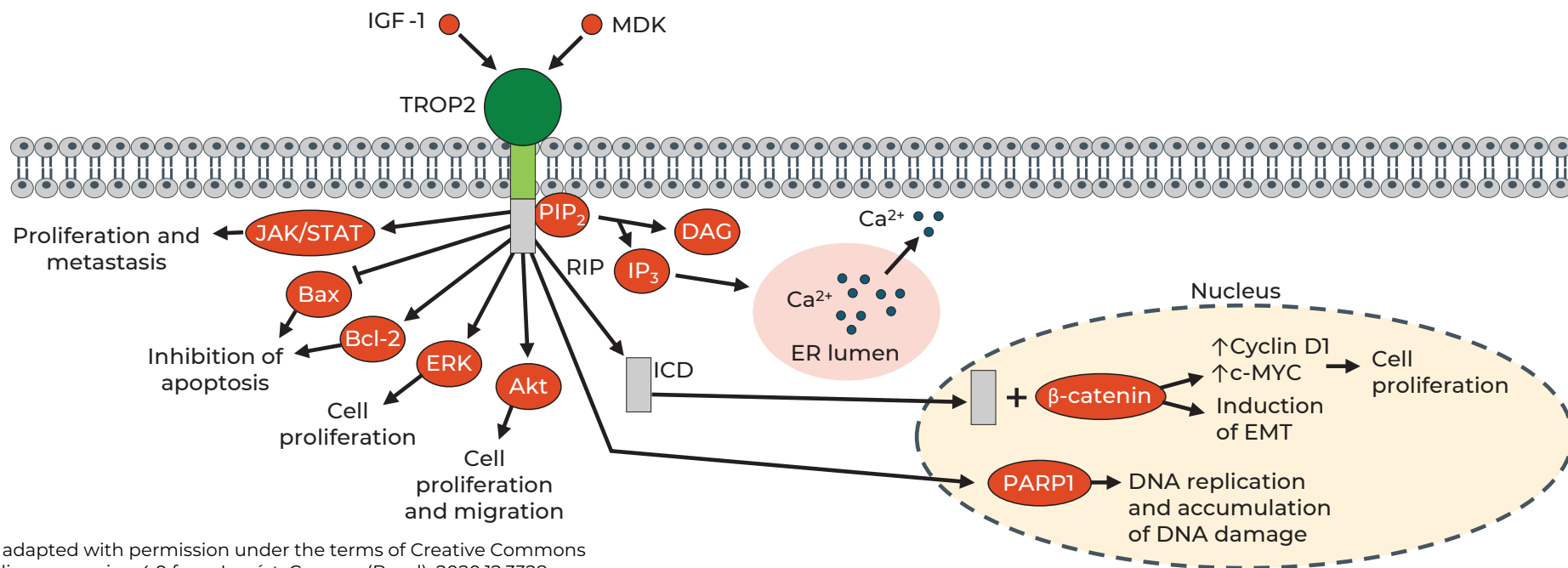
Managing the Toxicities of TROP2 Antibody–Drug Conjugates in Lung Cancer

Components of TROP2 ADCs

TROP2

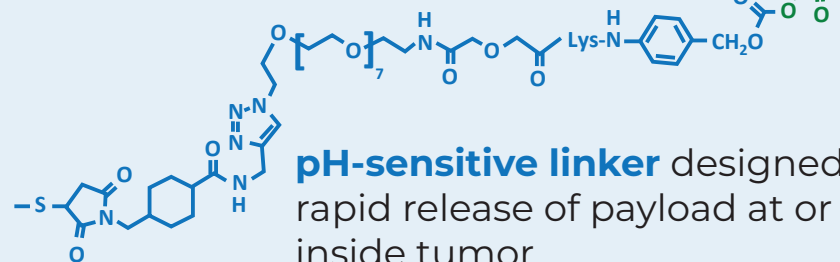
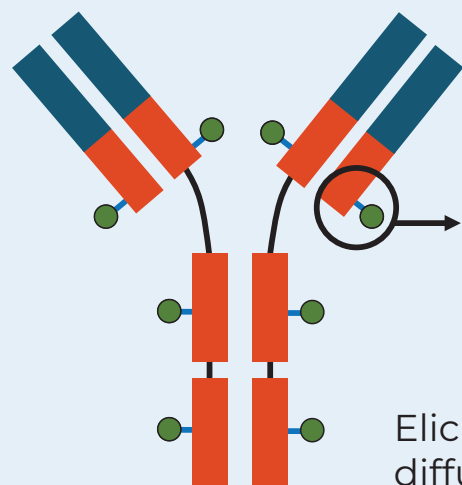
- TROP2 is a transmembrane protein highly expressed on the surface of epithelial cells
- TROP2 is expressed across lung cancer subtypes, including both nonsquamous and squamous NSCLC
- TROP2-targeted ADCs deliver highly cytotoxic payloads to cells expressing TROP2
- 2 TROP2 ADCs, sacituzumab govitecan and datopotamab deruxtecan, demonstrate efficacy in advanced NSCLC
- Toxicity can be a concern when using TROP2 ADCs because of (1) TROP2 expression in normal tissues and (2) potential off-target effects of the high-potency payloads

TROP2 Signaling Pathway¹

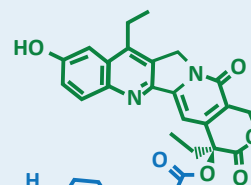


Sacituzumab Govitecan

RS7 (anti-TROP2 IgG1k antibody)



pH-sensitive linker designed for rapid release of payload at or inside tumor



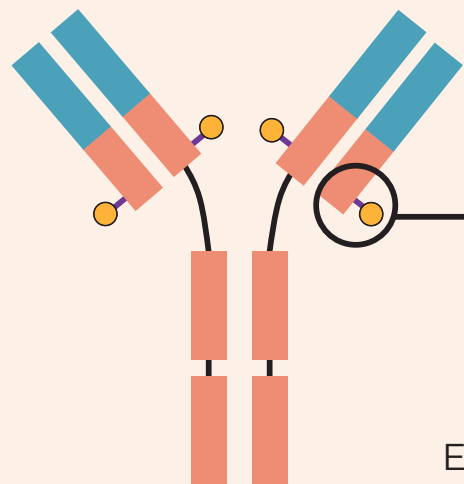
Topoisomerase I inhibitor payload (SN-38)

Metabolite of irinotecan with 100- to 1000-fold greater potency

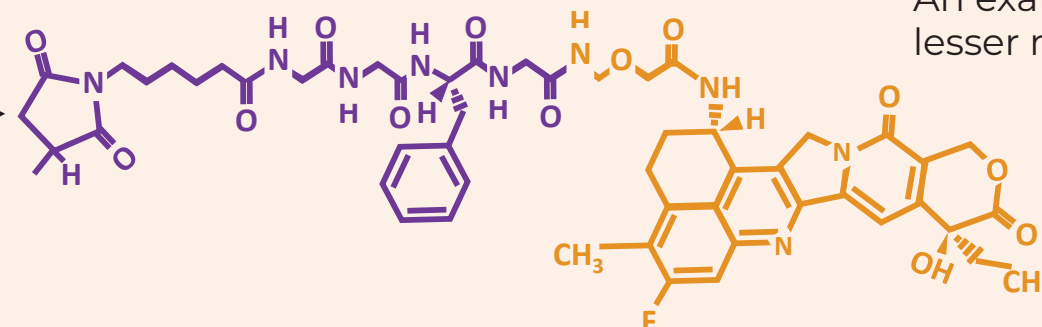
Elicits a bystander effect whereby SN-38, once released, diffuses into neighboring TROP2-negative cells

Datopotamab Deruxtecan

Datopotamab (anti-TROP2 IgG1 antibody)



Tetrapeptide-based linker
cleaved by lysosomal proteases in tumor cells



Topoisomerase I inhibitor payload (DXd)

An exatecan derivative with lesser myelotoxicity

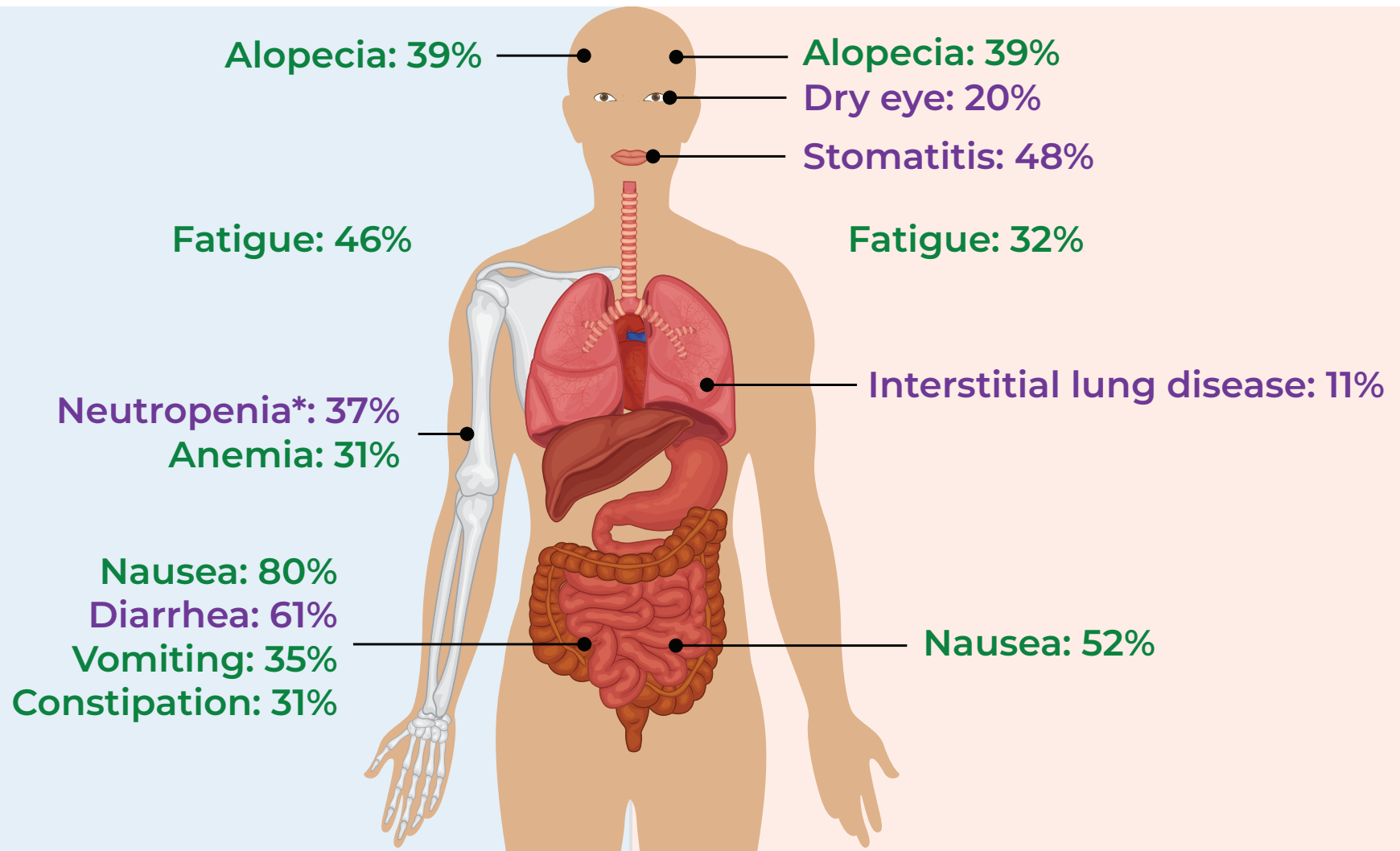
Elicits a bystander effect whereby DXd, once released, diffuses into neighboring TROP2-negative cells

Common and Notable Toxicities Associated With TROP2 ADCs^{2,3}

- The **common** AEs tend to occur at an incidence of >30% (all grades)
- The **notable** AEs are unique to either of the ADCs and require concerted management

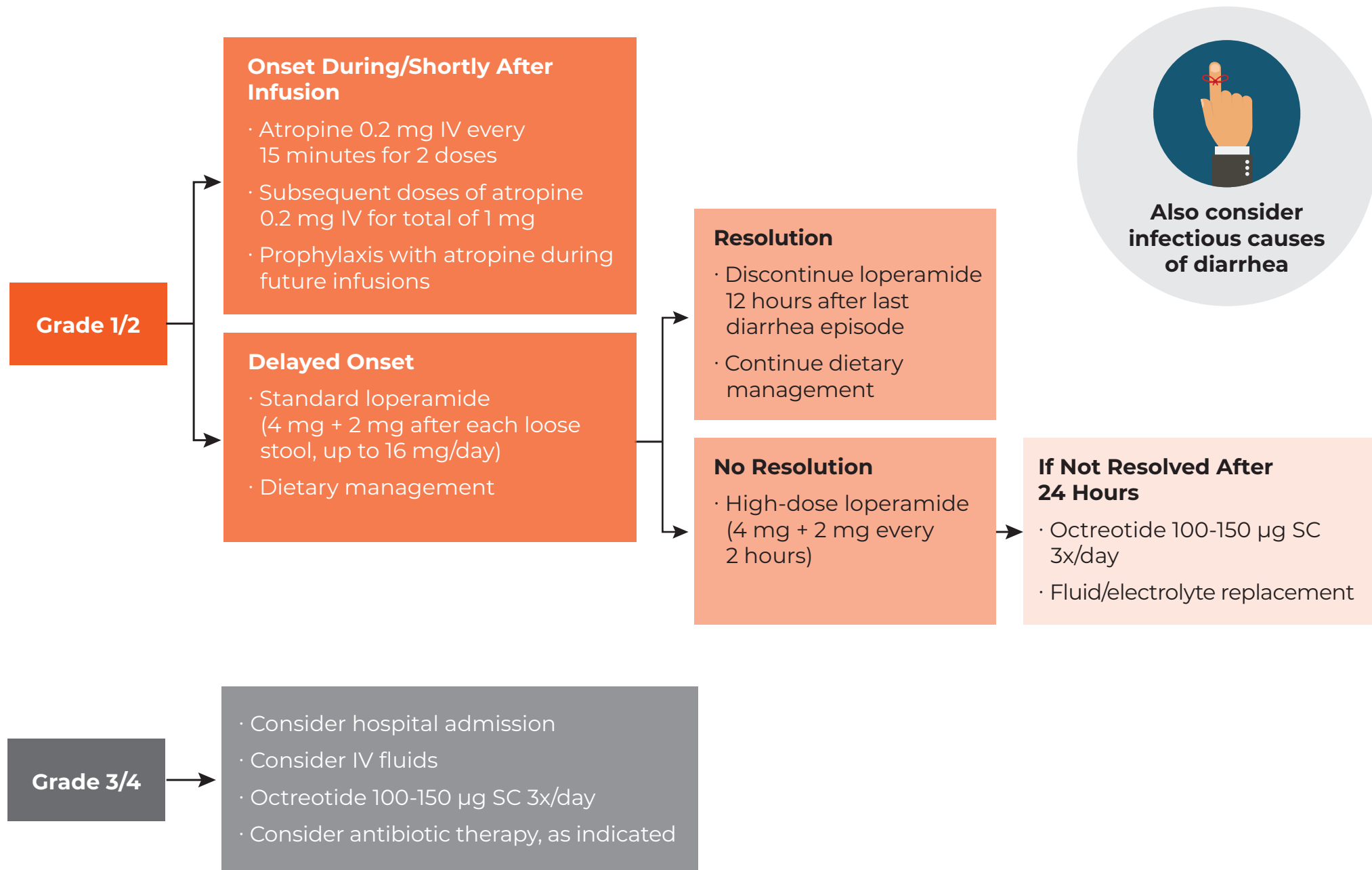
Sacituzumab Govitecan

Datopotamab Deruxtecan



*Most common severe AE.

Management of Diarrhea⁴



Management of Neutropenia⁴

ANC <1500/mm³ on Day 1 of any cycle, ANC <1000/mm³ on Day 8 of any cycle, or neutropenic fever

Hold treatment until improved

Severe Neutropenia

- Grade 4 neutropenia (ANC <500/mm³) lasting ≥7 days
- Grade 3 febrile neutropenia (ANC <1000/mm³ and fever ≥38.5°C)
- Grade 3/4 neutropenia that delays dosing by 2-3 weeks for recovery to grade ≤1

First Occurrence

- Hold treatment until grade ≤1
- Assess ANC weekly for grade 3 and biweekly for grade 4
- Consider supportive care
 - For onset on Day 1, administer G-CSF on Days 4-5 or 4-6, but avoid use 24 hours before and after sacituzumab govitecan infusion
 - For onset on Day 8, pegylated G-CSF 24-48 hours post infusion
- When grade ≤1, reduce dose by 25% (to 7.5 mg/m²)
- If delay lasts >3 weeks, discontinue treatment

Second Occurrence

- Same process as before
- However, when grade ≤1, reduce dose by 50% (to 5 mg/m²)

Third Occurrence

- Discontinue treatment

At time of scheduled treatment, grade ≥3 neutropenia (ANC <1000/mm³) that delays dosing beyond 3 weeks for recovery to grade ≤1

Discontinue treatment

Management of Stomatitis



What to Look for

- Lips and mucosa appear redder than usual
- Visible sores on the oral mucosa
- Mouth pain, which may affect chewing and swallowing
- Changes in ability to taste

Grade 1



Grade 2



Grade 3



Grade 4



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Management

Grade	Management Recommendation
1: asymptomatic or mild symptoms	• Maintain dose • Optimize supportive medications*
2: moderate pain/ulceration that does not interfere with oral intake	• Consider dose delay or reduction • Optimize supportive medications*
3: severe pain/ulceration interfering with oral intake	• Delay dose until resolved to grade ≤ 1 or baseline • Optimize supportive medications* • Consider dose reduction by 1 level if supportive medications already were optimized
4: oral intake not possible; life-threatening consequences	• Discontinue drug

*Supportive medications should provide adequate pain relief (eg, viscous lidocaine rinses).

Preventive Measures



- Bland mouth rinses
- Steroid-containing mouth rinses (eg, dexamethasone 0.1 mg/mL, swish 10 mL for 1-2 minutes 4x/day, then spit out)
- Ice chips



powered by cea

Management of Ocular Toxicities



What to Look for

Dry eye

- Eye redness
- Stinging
- Burning or scratchy sensation
- Sensation of having something in eye
- Sensitivity to light
- Blurred vision

Keratitis

- Eye pain
- Excess tears or discharge from eye
- Difficulty opening eyelid due to pain or irritation
- Decreased vision

Management

Grade	Management Recommendation
1: asymptomatic; clinical or diagnostic observations only	• Maintain dose • Ensure use of artificial tears and no contact lenses • Consider ophthalmology assessment
2: symptomatic with moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or ≤ 3 lines of decreased vision from known baseline)	• Obtain ophthalmology assessment • Delay dose until resolved to grade ≤ 1
3: symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or > 3 lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting self-care ADL	• Obtain ophthalmology assessment • Delay dose until resolved to grade ≤ 1, then reduce by 1 dose level
4: perforation; best corrected visual acuity of 20/200 or worse in the affected eye	• Obtain ophthalmology assessment • Discontinue drug

Preventive Measures



- Daily use of artificial tears
- Avoid contact lenses
- Instruct patients to report any eye issues

Management of ILD



What to Look for

- Shortness of breath, particularly on exertion
- Dry cough
- Chest discomfort
- Fatigue

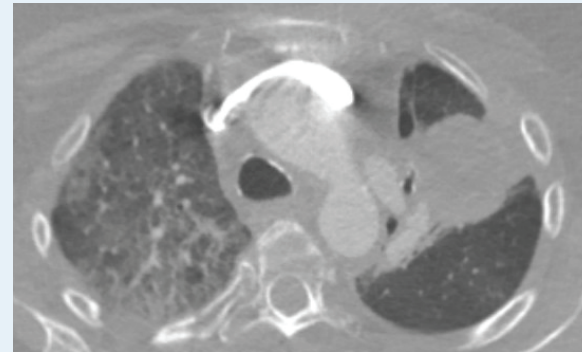


Image courtesy of Rebecca Heist, MD, MPH.

Management

Grade	Management Recommendation
1: asymptomatic; clinical or diagnostic observations only	• Consider observation • Consider oral prednisone 0.5 mg/kg/day
2: symptomatic; limiting instrumental ADL	• Oral prednisone 1 mg/kg/day • Increase to 2 mg/kg/day or switch to IV if no improvement after 5 days
3: severe symptoms; limiting self-care ADL or life-threatening respiratory compromise	• Hospitalization • IV methylprednisolone 1-2 mg/kg, or consider high dose at 1-g pulse x 3 days followed by taper, if needed
For all grades	• Oxygen supplementation for hypoxia • Supportive treatment for prolonged corticosteroid use • Consider infliximab, mycophenolate mofetil, IVIG, or other immunosuppressant if corticosteroid refractory

Management of ILD (Continued)

Workup for Suspected ADC-Related ILD⁵



- Discontinue the ADC and start corticosteroids according to grade
- History and physical exam
- Laboratory tests
 - CBC, liver and kidney function tests, electrolytes, CRP, ESR, procalcitonin, LDH, other
 - Analysis for infection based on suspected pathogen (blood culture, expectorated sputum, urinary antigens, β -D-glucan, other)
 - Tumor markers and autoimmune antibodies, if indicated
- High-resolution CT scan of chest
- Pulmonology consult with pulmonary function testing
- Bronchoscopy and BAL $\pm$ transbronchial lung biopsy

Differential Diagnosis



- Infectious pathogen
- Cancer progression
- ILD related to other drugs
- RT-induced pneumonitis (for patients receiving concomitant RT)

ADC, antibody–drug conjugate; ADL, activities of daily living; AE, adverse event; ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; CBC, complete blood count; CRP, C-reactive protein; DXd, deruxtecan; EMT, epithelial-to-mesenchymal transition; ER, endoplasmic reticulum; ESR, erythrocyte sedimentation rate; G-CSF, granulocyte colony-stimulating factor; IgG1, immunoglobulin G1; ICD, intracellular domain; ILD, interstitial lung disease; IVIG, IV immunoglobulin; LDH, lactate dehydrogenase; NSCLC, non-small-cell lung cancer; RT, radiation therapy.

References

1. Lenárt. Cancers (Basel). 2020;12:3328.
2. Heist. J Clin Oncol. 2017;35:2790.
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