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Datopotamab deruxtecan (DATROWAY): Prophylaxis and Management of Adverse Events

Description:
The purpose of this PQI is to provide clinical guidance on the safe use, recommended monitoring, and adverse-event management of datopotamab deruxtecan (DATROWAY).

Background[1]:
Datopotamab deruxtecan is a Trop2-directed antibody-drug conjugate linked to a topoisomerase-I inhibitor payload (DXd). After binding to Trop2-expressing tumor cells and internalization, the cytotoxic payload is released leading to DNA damage and apoptosis.

- FDA-approved indications (adult patients):
  - Locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) after an EGFR-directed therapy and platinum chemotherapy.
  - Unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior endocrine-based therapy and chemotherapy.
- Frequent adverse events (AEs) (≥ 20% across pooled safety): stomatitis, nausea, fatigue, alopecia, constipation, decreased appetite, dry eye, keratitis, rash, vomiting, musculoskeletal pain; common lab changes include decreased hemoglobin, lymphocytes, leukocytes, calcium, and lactate dehydrogenase; increased ALT/AST, lactate dehydrogenase, and alkaline phosphatase
- AE patterns to note:
  - Interstitial lung disease (ILD)/pneumonitis risk is higher in the NSCLC population (~7%; 0.6% Grade 3, 0.4% Grade 4, 1.7% fatal events; median onset ~1.4 months) vs the breast-cancer population (~3.6%; 0.7% Grade 3, 0.2% fatal – 1 patient; median onset ~2.8 months). Emphasize early recognition and prompt steroids.
  - Ocular AEs (e.g., dry eye, keratitis) occur in ~36% overall (2.2% Grade 3, 1 patient Grade 4); median onset ~2.3 months.
  - Stomatitis occurs in about 63% of patients (Grade 3, 8%, Grade 4, 1 patient); median onset ~0.5 months. Advise patients to use a steroid-containing mouthwash for prophylaxis and treatment of stomatitis.

PQI Process:

- Patient Identification[1]
  - EGFR-mutated NSCLC: Confirm presence of an EGFR mutation using tumor or plasma testing; once confirmed, repeat testing is generally unnecessary. Verify prior exposure to an EGFR-directed therapy and a platinum-based regimen.
  - HR+/HER2- breast cancer: Confirm HR+/HER2- status and prior endocrine-based therapy and chemotherapy in the advanced setting.
- Dosing & Schedule[1]
  - Datopotamab deruxtecan 6 mg/kg IV once every 3 weeks (21-day cycle)
    - Max dose: 540 mg for ≥90 kg
    - Administer until progression or unacceptable toxicity

        - If a dose is missed/delayed, give as soon as possible and maintain the 3-week interval.
- Premedication & Concomitant Support[1,2]
    - Antihistamine (e.g., diphenhydramine 25-50 mg; oral or IV) and antipyretic (e.g., acetaminophen 650-1000 mg) 30-60 minutes prior to each infusion
    - Antiemetic per institutional practice (e.g., 5-HT3 antagonist) prior to each infusion and thereafter as needed
        - Datopotamab deruxtecan is considered highly emetogenic per NCCN guidelines
    - Lubricant eye drops (preservative-free), multiple times daily throughout treatment (ideally at least 4 times daily and as needed)
    - Encourage holding ice chips or ice water in the mouth during infusion to reduce stomatitis risk
    - Steroid-containing mouthwash (e.g., dexamethasone solution) 4 times daily and as needed
        - In the absence of a prophylactic steroid-containing mouthwash, daily use of inert, bland mouth rinses (e.g., with a non-alcoholic and/or bicarbonate-containing mouthwash, 4-6 times a day) is recommended

Table 1. Infusion & Observation Guidance:

First infusion	▪ Administer infusion over 90 minutes ▪ Observe patients during the infusion and for at least 1 hour following the initial dose for signs or symptoms of infusion-related reactions
Second infusion	▪ If first infusion was tolerated, administer over 30 minutes ▪ Observe patients during the infusion and for at least 1 hour after infusion
Subsequent infusion	▪ Administer over 30 minutes if prior infusions were tolerated ▪ Observe patients during the infusion and for at least 30 min after infusion

- Required Baseline/On-Treatment Eye Care (performed by an ophthalmologist or optometrist) [1]
    - Comprehensive ophthalmic exam (visual acuity, slit-lamp with fluorescein, intraocular pressure, and fundoscopy) at treatment initiation, annually during therapy, at end of treatment, and as needed for symptoms
- Administration Pearls[1]
    - Administer in a setting prepared to manage infusion reactions. Use an in-line 0.2-micron filter, protect from light during infusion, and avoid mixing with other drugs/lines. No IV push/bolus
    - Reconstitute with sterile water, dilute with 5% Dextrose injection, do not us sodium chloride
- Dose Modifications (general framework)[1,2]
    - Dose-reduction steps: first reduction to 4 mg/kg (max 360 mg for patients ≥90 kg); second dose reduction to 3 mg/kg (max 270 mg for patients ≥90 kg); if not tolerated at 3 mg/kg, discontinue. Do not re-escalate after a reduction.

Table 2. Adverse Event Management[1]

Adverse Event	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Stomatitis/Oral Mucositis	Continue therapy, supportive care, steroid mouthwash, ice chips.	Hold until ≤G1; restart at same dose if first occurrence; reduce dose if recurrent.	Hold until ≤G1; resume at reduced dose with enhanced supportive care.	Discontinue permanently.
ILD/Pneumonitis	Asymptomatic radiographic findings: hold*; consider steroids; resume once resolved.	Symptomatic: discontinue permanently; start systemic corticosteroids.	Same as Grade 2.	Same as Grade 2.
Keratitis	Supportive care with lubricant eye drops; continue therapy.	Hold until resolved; resume at same or reduced dose.	Hold until improved; resume at reduced dose.	Discontinue permanently (e.g., corneal perforation).
Infusion-Related Reactions	Reduce infusion rate by 50% if IRR suspected and monitor patient closely	Interrupt infusion, give supportive care meds; restart infusion at 50% rate if resolved.	Discontinue permanently.	Discontinue permanently (e.g., anaphylaxis).
Nausea/Vomiting	Premedicate with antiemetics; continue therapy.	Escalate supportive meds, maintain hydration.	Hold if uncontrolled, resume once stabilized with antiemetics.	Consider discontinuation if unmanageable.
Hematologic Toxicities	Monitor CBCs; continue therapy.	Monitor CBCs; continue therapy.	Hold until recovery; resume at reduced dose, consider growth factors.	Discontinue if recurrent or unable to recover.

*If ILD/pneumonitis resolved in ≤28 days, maintain current dose; if resolved in > 28 days, reduce one dose level (see Table 2 in PI)[1]

Patient-Centered Activities:

- NSCLC emphasis: ILD risk is higher—report cough, shortness of breath, or fever immediately; don't self-treat with OTC cough meds[2]
- Eye care: Use preservative-free lubricant drops several times daily; avoid contact lenses unless cleared; keep scheduled eye exams; call with pain, photophobia, blurred vision, or gritty sensation[1]
- Mouth care: Begin steroid mouthwash on day 1 and continue throughout treatment; ice chips during infusion; avoid irritating foods; call if develop painful sores that interfere with eating; suggest patients to swish for 1-2 minutes with oral solution and then spit out; encourage patients to brush with a soft toothbrush and continue flossing, if already part of their routine.[2]
- Review common side effects: nausea, fatigue, alopecia, constipation, stomatitis, eye changes
    - Reproductive health: Discuss contraception during and after therapy per label guidance; avoid breastfeeding during treatment and for 1 month after last dose[1]

- When to call urgently: New/worsening breathing symptoms; fever; vision changes or eye pain; inability to maintain hydration due to mouth pain
- Patient Support Materials
    - DATROWAY4U website - https://www.datroway4u.com/
    - Patient support materials https://datrowayhcp.com/support-resources/care-team-corner.

References:

1. Datroway (datopotamab deruxtecan-dlnk) Prescribing Information. Daiichi Sankyo/AstraZeneca; Revised June 2025.
2. Datroway HCP. Managing Adverse Reactions. Daiichi Sankyo/AstraZeneca; 2025. Available at: https://datrowayhcp.com/managing-adverse-reactions

Supplemental Information:

Table 3. Comparison of Indications[1]

Feature	Breast Cancer (HR+/HER2-)	NSCLC (EGFR-mutated)
Population	Unresectable/metastatic HR+/HER2- after endocrine therapy + chemo	Locally advanced/metastatic EGFR-mutated after EGFR TKI + platinum chemo
ILD Incidence	~3.6% (0.7% Grade 3, 0.2% fatal – 1 patient)	~7% (0.6% Grade 3, 0.4% Grade 4, 1.7% fatal)
Median ILD Onset	~2.8 months	~1.4 months
Ocular AEs	36% incidence (keratitis, dry eye)	36% incidence (keratitis, dry eye)
Unique Concern	Mucositis and eye care	Heightened ILD vigilance, mucositis and eye care