Targeting Resistance in EGFRm NSCLC with HER3-Directed ADCs in the Community Setting

A PATIENT/CLINICIAN DECISION SUPPORT AID

What is Shared Decision-Making?

Shared decision-making (SDM) occurs when a healthcare provider and a patient work together to make a healthcare decision that is best for the patient. Optimal decision making takes into account evidence-based information about available options; the provider's knowledge and experience; and the patient's values, goals, and preferences. Patients and their families/caregivers who are engaged in an SDM process are more likely to arrive at a treatment decision that works best for all those involved.

What Are the Best Practices for Discussing the Risk/Benefits of Therapy?

For patients and clinicians alike, it is essential to weigh the risks and benefits of different treatment options and to be aware of the potential for both acute and long-term side effects of different treatment options. Individual patient goals and preferences should be considered, including desire for curative treatment. The effects of treatment options on patient quality of life and independence are crucial. The American Society of Clinical Oncology recommends several strategies that may help to appropriately weigh the balance of risks and benefits of different treatment options, including:

- Getting a second opinion
- Understanding the latest guideline recommendations
- Incorporating other decision-making tools
- Encouraging patient discussions with people they trust (family, social workers, clergy, etc.)
- Understanding statistical data for key outcomes and what these may mean (or not mean) for each individual patient

Additional considerations can be found at the American Cancer Society website:
https://www.cancer.org/cancer/managing-cancer/making-treatment-decisions/making-decisions.html

The AXIS 6 Ease ("Es") to SDM

ENSURE

Ensure you see and treat the patient as an individual not a disease.

ELEVATE

Elevate the patient-centric experience and improve satisfaction with care.

ENABLE

Enable a long-term personal connection with your patients.

ESTABLISH

Establish co-created treatment plans that align medical evidence with patient preferences to foster adherence and optimize outcomes

ELICIT

Elicit patient/caregiver preferences, values, and goals for therapy.

EVALUATE

Evaluate the risk/benefits and costs of treatment so that they are aligned with patient expectations.

What Is the Role of HER3 in NSCLC?

- HER3 is a member of the ERRB/HER protein kinase family
- HER family members heterodimerize with HER3
- Downstream signaling leads to cell proliferation, cancer cell survival
- HER3 expression can mediate resistance to targeted therapy
- HER3 mutations and genomic alterations are not commonly seen
- HER3 expression is typically determined by IHC and quantified using H-score
- HER3 expression by IHC is seen in 83% of NSCLCs
- High levels of expression are associated with progression and metastases
- HER3 testing is currently not recommended

Efficacy of Patritumab Deruxtecan

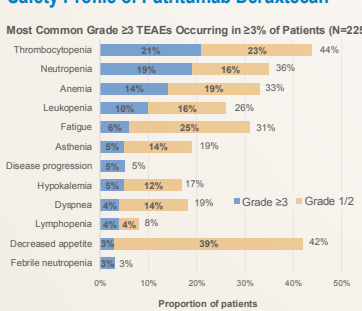
HERTHENA-Lung02

Confirmed Responses and Survival		Prior EGFR TKI (any) and PBC (N = 225)	Subset With Prior 3rd-Gen EGFR and PBC (n = 209)
cORR (95% CI), %		28.4 (22.6-24.8)	28.2 (22.2-24.9)
Best overall response (BICR), n (%)	**CR**	1 (0.4)	1 (0.5)
	PR	63 (28.0)	58 (27.8)
	SD	102 (45.3)	93 (44.5)
	PD	43 (19.1)	41 (19.6)
	NE	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), %		6.0 (4.4-7.2)	6.4 (4.4-7.2)
PFS, median (95% CI), %		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.8 (11.2-12.6)	11.8 (10.9-12.6)

Median study follow-up, 13.1 (range, 9.0-21.6) months

BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; NE, not established; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Safety Profile of Patritumab Deruxtecan



- Hematologic toxicities were transient, typically occurred during early treatment, and were not associated with clinical sequalae
- Adjudicated cases of interstitial lung disease (ILD) occurred in 5.3% of patients and were mainly grades 1 or 2 in severity

Management of TEAEs Associated With HER3-Directed ADCs

ILD/Pneumonitis

What to look for:

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

Promptly investigate any evidence of suspected ILD/ pneumonitis with high-resolution CT, pulmonologist consult, and blood cultures/CBC

Grade and Description	Protocol Management Recommendations
1. Asymptomatic; clinical or diagnostic observations only	• Hold patritumab deruxtecan until resolution to grade 0 – If AE resolved in ≤28 days, resume with same dose of patritumab deruxtecan – If AE resolves in >28 days, resume with reduced dose of patritumab deruxtecan • Consider corticosteroid treatment (eg, prednisone ≥0.5 mg/kg/day)
2. Symptomatic; limiting instrumental ADL	• Permanently discontinue patritumab deruxtecan • Promptly initiate corticosteroid treatment (eg, ≥1 mg/kg/day prednisone or equivalent) and continue for ≥14 days followed by gradual taper for ≥4 weeks
3. Severe symptoms; limiting self-care ADL or **4. Life-threatening respiratory compromise**	• Permanently discontinue patritumab deruxtecan • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by ≥1 mg/kg/day of prednisone (or equivalent) and continue for ≥14 days followed by gradual taper for ≥4 weeks
For all grades	• Oxygen supplementation for hypoxia • Monitor closely for worsening symptoms, re-image as clinically indicated • Supportive treatment for prolonged corticosteroid use • Consider infliximab, mycophenolate mofetil, IVIG, etc if corticosteroid refractory

ADL, activity of daily living; AE, adverse event.

Dose reductions: Starting Dose 5.6 mg/kg Q3W → Reduction 1: 4.8 mg/kg → Reduction 2: 3.2 mg/kg → Discontinue

Clinically Significant Nausea and Vomiting

- Premedicate with 3-drug regimen for CINV (eg, dexamethasone + 5-HT_3 receptor antagonist + NK1 receptor antagonist)
- Onset may be delayed: Provide patient with take-home antiemetics (eg, dexamethasone, ondansetron)
- Manage with antiemetics, dose reductions; withhold if high grade until resolved to grade ≤1

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