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Prophylaxis and Management of Skin Toxicities with Amivantamab (Rybrevant) and Lazertinib (Lazcluze) Treatment: The COCOON Protocol

Description: This document outlines an evidence-based approach to the prevention of dermatologic toxicities, informed by the Phase 2 COCOON trial[1], along with management strategies for patients receiving amivantamab and lazertinib for EGFR-mutant advanced non–small cell lung cancer (NSCLC).

Background: Amivantamab is an intravenously administered bispecific antibody that targets the extracellular domains of EGFR and MET, while lazertinib is an oral, third-generation EGFR tyrosine kinase inhibitor.[2,3] In August 2024, the combination received FDA approval for the first-line treatment of adult patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 L858R substitutions.[4] This approval was supported by the Phase 3 MARIPOSA trial,[5] which demonstrated that amivantamab plus lazertinib significantly improved median progression-free survival compared with osimertinib (23.7 vs. 16.6 months; hazard ratio [HR], 0.70; $P < 0.001$). With longer follow-up, the combination was also associated with a statistically significant improvement in overall survival (OS), with median OS not yet reached in the combination arm versus 36.7 months with osimertinib (HR, 0.75; 95% CI, 0.61–0.92; $P < .005$).[6]

Safety and adverse events (AEs) vs. osimertinib[5,7]

- *Dermatologic AEs:*
  - Rash: 86% vs. 48%
  - Nail toxicity: 71% vs. 34%
  - Dry skin: 25% vs. 18%
  - Pruritus: 24% vs. 17%
- Other AEs
  - Infusion-related reactions: 63% vs. 0%
  - Edema: 43% vs. 8%
  - Hypoalbuminemia: 89% vs. 22%
  - Venous thromboembolism: 36%[5], with few patients on anticoagulation[6]
    - However, COCOON[1] prospectively required 4 months of prophylactic anticoagulation in all patients at treatment initiation (6.5% average rate of VTE)
      - ➢ Refer to prescribing information for anticoagulation guidance[2,3]

COCOON Trial: Evaluation of Proactive Dermatologic Toxicity Management[1]

- Phase 2 trial evaluated proactive skin toxicity management with amivantamab plus lazertinib in EGFR-mutant advanced NSCLC.
- A regimen of oral antibiotics, topical agents, moisturizers, and antiseptic washes significantly reduced grade ≥2 skin and nail toxicities within the first 12 weeks.
  - *See regimen details on page 2.*
- The trial also showed a reduction in the impact of dermatologic symptoms on quality of life.[8]

PQI Process:

- Confirm treatment indication and initial amivantamab and lazertinib dosing: [2,3]
  - Upon receiving the treatment order, verify the presence of an EGFR exon 19 deletion or exon 21 L858R substitution via FDA-approved test.
  - Amivantamab: weight-based intravenous dosing
    - Patient weight <80 kg: 1050 mg; ≥80 kg: 1400 mg
      - Administer weekly for weeks 1–5 (first dose split over two days), then every two weeks starting week 7
  - Lazertinib: 240 mg orally once daily, with or without food
    - Available in 80 mg and 240 mg tablets
- Recommended prophylactic dermatologic supportive care – COCOON protocol[1,7]:
  - Ensure the following prescribed and over-the-counter supportive care agents are obtained prior to treatment initiation.

Intervention	Timing/Duration	Purpose	Instructions
Doxycycline or minocycline 100 mg	Weeks 1 – 12 (first 3 months), BID	Prevent/mitigate rash and paronychia	Take twice daily for 12 weeks starting week 1
Topical clindamycin lotion 1%	Nightly, starting on Week 13	Prevent/mitigate scalp rash	Apply to scalp nightly at bedtime starting week 13
Chlorhexidine 4% wash	Once daily	Prevent/mitigate paronychia and nail infections	Apply to fingernails and toenails daily
Ceramide-based, non-comedogenic moisturizer	At least once daily	Maintain skin barrier, prevent dryness, fissures	Apply to face and body at least once daily

- Management of dermatologic AEs
  - Refer to the most recent version of Common Terminology Criteria for Adverse Events (CTCAE) to assess AE grading and severity[9]
  - Consult the prescribing information and Proactive Therapy Management Guide for comprehensive guidance on dose modifications and AE management.[2,3,7]

	Severity-Based Dermatology Management: Amivantamab and Lazertinib[2,3,7]	
Severity	Amivantamab	Lazertinib
Grade 1	• Supportive care • Reassess after 2 weeks; consider dose reduction if no improvement in rash	• Supportive care
Grade 2	• Supportive care • Reassess after 2 weeks; consider dose reduction if no improvement in rash	• Supportive care • If no improvement after 2 weeks: reduce amivantamab dose and continue lazertinib at same dose • Reassess every 2 weeks; if still no improvement, reduce lazertinib dose until ≤ Grade 1, then may resume previous dose
Grade 3	• Hold amivantamab • Supportive care • Resume amivantamab at reduced dose once rash improves to ≤ Grade 2 • Permanently discontinue if no improvement within 2 weeks	• Hold lazertinib • Supportive care • Resume lazertinib at same or reduced dose and amivantamab at reduced dose once ≤ Grade 2 • Discontinue both agents if no improvement within 2 weeks

Grade 4	• Permanently discontinue amivantamab	• Supportive care • Permanently discontinue amivantamab • Hold lazertinib until ≤ Grade 2 or baseline, then resume lazertinib at reduced dose

    - If skin reactions develop:[1,2]
        - Start topical corticosteroids and topical and/or oral antibiotics (if not already on).
        - Grade 3 reactions: add oral corticosteroids and consider Dermatology consult.
        - See also: NCODA PQI: Managing EGFR Inhibitor Rash
- Order Set Optimization:
    - To streamline implementation, consider integrating dermatologic supportive care items into the initial treatment order set to ensure timely initiation.

Patient-Centered Activities:

- Dermatologic side effect anticipation
    - Prepare patients for common, early-onset skin and nail side effects that are typically manageable with supportive care.
- Supportive medications
    - Provide a personalized medication calendar and emphasize adherence to the full prophylactic regimen.
- Skin care and sun protection
    - Recommend daily use of non-comedogenic moisturizers and SPF ≥ 30, sun avoidance during and up to 2 months post-treatment, and protective clothing.[2,3,7]
- Monitoring and adjustments
    - Encourage early reporting of symptoms and reassure patients that dose modifications can support tolerability.
- Emotional well-being
    - Recognize and address the emotional impact of visible side effects.

References:

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3. Lazcluze™ (lazertinib) [package insert]
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6. Girard N. *Amivantamab plus lazertinib (MARIPOSA): updated overall survival results*. Presented at: European Lung Cancer Congress (ELCC) 2025; March 26–29, 2025; Paris, France.
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8. Feldman J, Cho BC, Li W, et al. Dermatologic prophylaxis and impact on patient-reported outcomes in first-line EGFR-mutant advanced NSCLC treated with amivantamab plus lazertinib: results from the Phase 2 COCOON trial. Poster presented at: American Society of Clinical Oncology Annual Meeting; May 30–June 3, 2025; Chicago, IL, and Virtual.
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