Preventing Moderate to Severe Dermatologic Adverse Events in First-Line *EGFR*-Mutant Advanced NSCLC Treated With Amivantamab Plus Lazertinib: Early Success of the COCOON Trial

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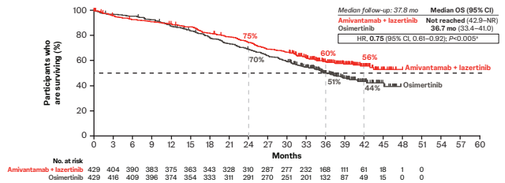
Background

- Epidermal growth factor receptor (EGFR)-targeted therapies have been associated with dermatologic adverse events (AEs), which are often treated reactively in clinical practice[1-3]
- First-line amivantamab + lazertinib is U.S. Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved for *EGFR*-mutant advanced non-small cell lung cancer (NSCLC) based on the results of the phase 3 MARIPOSA study (NCT04487080; **Figure 1**)[4,5]
  - The first onset of dermatologic AEs often occurs in the first 4 months of treatment (**Figure 2**)[6]
  - Early management of dermatologic AEs is expected to allow patients to remain on treatment longer with amivantamab + lazertinib
- COCOON (NCT06120140) prospectively evaluated a simple prophylactic regimen to prevent moderate to severe *EGFR*-related dermatologic AE

FIGURE 1: MARIPOSA final OS[6]



[a]In total, 390 deaths had occurred in the amivantamab + lazertinib (173 deaths) and osimertinib (217 deaths) arms. P-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified Cox regression model.
CI, confidence interval; Ex19del, exon 19 deletion; HR, hazard ratio; NR, not reached; OS, overall survival.

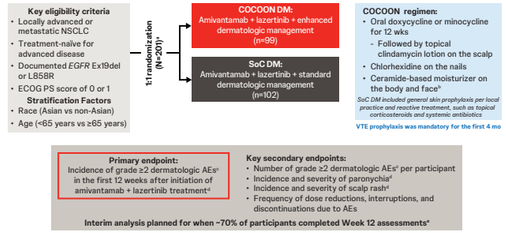
FIGURE 2: First onset of key AEs[6]

AE, adverse event.

Methods

- The COCOON study design is presented in **Figure 3**

FIGURE 3: Phase 2 COCOON study design



COCOON (ClinicalTrials.gov Identifier: NCT06120140).
[a]Planned enrollment of 200 participants was estimated to provide a power of 82% to detect a 35% difference in DAEIs.
[b]La Roche Posay Lipikar AP+M moisturizer was used in COCOON.
[c]Preferred terms included rash, dermatitis acneiform, pruritus, skin fissures, acne, folliculitis, erythema, eczema, maculopapular rash, skin exfoliation, skin lesion, skin irritation, dermatitis, rash erythematous, rash macular, rash papular, rash pruritic, rash pustular, dermatitis contact, dermatitis exfoliative generalized, drug eruption, dyshidrotic eczema, eczema asteatotic, and paronychia.
[d]Severity per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.
[e]All analyses were performed using the safety analysis set.
AE, adverse event; DAEI, dermatologic adverse events of interest; DM, dermatologic management; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; SoC, standard of care; VTE, venous thromboembolism.

Results

Study participants

- Baseline characteristics were well balanced across arms (**Table 1**)
- At a median follow-up of 4.2 months, 138 participants received ≥1 dose of amivantamab + lazertinib (safety analysis set) and had ≥12 weeks of follow-up
  - Due to limited follow-up at the interim analysis, efficacy results will be reported at a future congress. All analyses were performed using the safety analysis set. 138 participants had the opportunity to receive treatment for 12 weeks; however, some discontinued prior to Week 12
- The median duration of amivantamab + lazertinib treatment was **4.2 months** with **COCOON dermatologic management (DM)** vs **4.1 months** with **standard-of-care (SoC) DM**
  - In the COCOON DM arm, 48 participants received doxycycline for a median duration of 2.7 months, and 24 participants received minocycline for a median duration of 2.8 months

TABLE 1: Baseline demographics and clinical characteristics

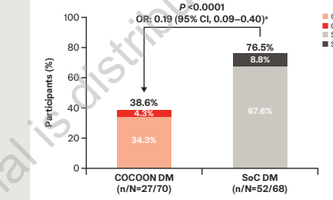
Characteristic, n (%)	COCOON DM (n=70)	SoC DM (n=68)[a]
Median age, years (range)	62.5 (36–78)	62.5 (37–83)
Female	42 (60)	37 (54)
Race[b]		
Asian	52 (74)	49 (72)
White	17 (24)	19 (28)
ECOG PS 1	44 (63)	36 (53)
History of smoking	24 (34)	21 (31)
History of brain metastases	23 (33)	27 (40)
EGFR mutation type		
Ex19del	35 (50)	37 (54)
L858R	35 (50)	31 (46)

Note: percentages may not sum to 100 due to rounding.
[a]2 participants randomized to SoC DM did not meet inclusion criteria at C1D1 and discontinued the study prior to receiving amivantamab + lazertinib.
[b]1 participant in the COCOON DM arm was American Indian or Alaska Native.
ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; SoC, standard of care.

Efficacy

- COCOON DM reduced grade ≥2 dermatologic AEs by 50% vs SoC DM (**Figure 4**)
- In the first 12 weeks:
  - 2-fold reduction in grade ≥2 dermatologic AEs with **COCOON DM** vs **SoC DM (38.6%** vs **76.5%)**
  - 2-fold reduction in grade 3 dermatologic AEs with **COCOON DM** vs **SoC DM (4.3%** vs **8.8%)**
  - 3-fold reduction in the number of participants who reported 2 or more different grade ≥2 dermatologic AEs with **COCOON DM** vs **SoC DM (6%** vs **18%)**

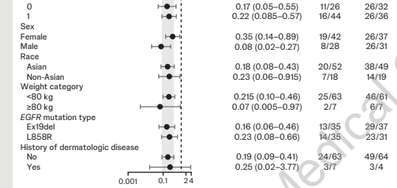
FIGURE 4: COCOON: Primary endpoint reached at first analysis



[a]OR was generated by a logistic model, adjusted by race and age (continuous).
CI, confidence interval; DM, dermatologic management; OR, odds ratio; SoC, standard of care.

- Consistent reductions in grade ≥2 dermatologic AEs were observed across all subgroups (**Figure 5**)

FIGURE 5: Benefit of COCOON DM by predefined subgroups

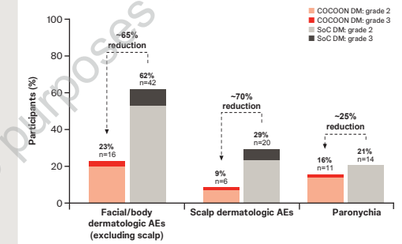


Subgroup	OR (95% CI)[a]	Events/N COCOON DM	Events/N SoC DM
All participants[a]	0.19 (0.09–0.40)	27/70	52/68
Age category			
<65 years	0.28 (0.11–0.71)	17/41	28/39
≥65 years	0.11 (0.03–0.375)	10/29	24/29
ECOG PS score			
0	0.17 (0.05–0.55)	11/26	26/32
1	0.22 (0.085–0.57)	16/44	26/36
Sex			
Female	0.35 (0.14–0.89)	19/42	26/37
Male	0.08 (0.02–0.27)	8/28	26/31
Race			
Asian	0.18 (0.08–0.43)	20/52	38/49
Non-Asian	0.23 (0.06–0.915)	7/18	14/19
Weight category			
<80 kg	0.215 (0.10–0.46)	25/63	46/61
≥80 kg	0.07 (0.005–0.97)	2/7	6/7
EGFR mutation type			
Ex19del	0.16 (0.06–0.46)	13/35	29/37
L858R	0.23 (0.08–0.66)	14/35	23/31
History of dermatologic disease			
No	0.19 (0.09–0.41)	24/63	49/64
Yes	0.25 (0.02–3.77)	3/7	3/4

Note: Gray box indicates 95% CI of OR for all participants.
[a]Safety analysis set.
[b]Unadjusted OR.
CI, confidence interval; DM, dermatologic management; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; OR, odds ratio; SoC, standard of care.

- In the first 12 weeks, substantial reductions in grade ≥2 dermatologic AEs were observed on different body locations with COCOON DM compared to SoC DM, including a 70% reduction in scalp dermatologic AEs (**Figure 6**)

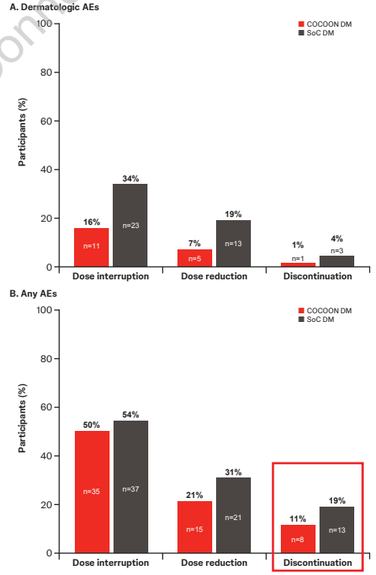
FIGURE 6: Grade ≥2 dermatologic AEs by body location



AE, adverse event; DM, dermatologic management; SoC, standard of care.

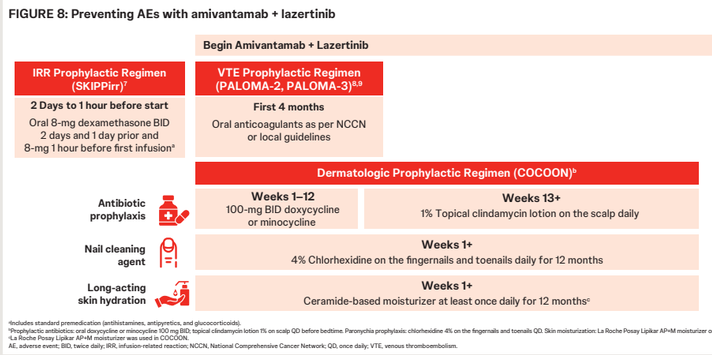
- Participants using the COCOON DM regimen had lower rates of amivantamab or lazertinib discontinuations due to AEs (11% vs 19% for SoC; **Figure 7**)
- Venous thromboembolism was observed in **6%** of participants with **COCOON DM** vs **7%** with **SoC DM**

FIGURE 7: Dose modifications of amivantamab/lazertinib due to AEs



AE, adverse event; DM, dermatologic management; SoC, standard of care.

FIGURE 8: Preventing AEs with amivantamab + lazertinib



[a]Includes standard premedication (antihistamines, antipyretics, and glucocorticoids).
[b]Prophylactic antibiotics and doxycycline or minocycline 100 mg BID; topical clindamycin lotion 1% on scalp QD before bedtime. Paronychia prophylaxis: chlorhexidine 4% on the fingernails and toenails QD. Skin moisturization: La Roche Posay Lipikar AP+M moisturizer on the body and face at least QD.
[c]La Roche Posay Lipikar AP+M moisturizer was used in COCOON.
AE, adverse event; BID, twice daily; IRR, infusion-related reaction; NCCN, National Comprehensive Cancer Network; QD, once daily; VTE, venous thromboembolism.

Key takeaway

The prophylactic COCOON DM regimen, with widely available and easy-to-use agents, significantly reduced the incidence and severity of dermatologic AEs with amivantamab + lazertinib

Conclusions

At the first pre-planned interim analysis, **the primary endpoint was met: The prophylactic COCOON DM regimen significantly reduced the incidence of grade ≥2 dermatologic AEs** vs SoC DM in the first 12 weeks

- Preferred terms included rash, dermatitis acneiform, pruritus, skin fissures, acne, folliculitis, erythema, eczema, maculopapular rash, skin exfoliation, skin lesion, skin irritation, dermatitis, rash erythematous, rash macular, rash papular, rash pruritic, rash pustular, dermatitis contact, dermatitis exfoliative generalized, drug eruption, dyshidrotic eczema, eczema asteatotic, and paronychia
- Incidence of **grade ≥2 dermatologic AEs was reduced by 50%** with COCOON DM vs SoC DM (*P*<0.0001)
- **Grade 3 dermatologic AEs were reduced by >50%** with COCOON DM vs SoC DM
- **>3-fold reduction in moderate to severe scalp dermatologic AEs** with COCOON DM compared with SoC DM

~50% reduction in discontinuations due to AEs with COCOON DM vs SoC DM allows participants to remain on treatments

The COCOON DM and SoC DM arms are fully enrolled (N=201) with additional results planned at upcoming congresses

- A subcutaneous arm and further prophylactic and reactive regimens are being evaluated (**Figure 8**)

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