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- To report a novel post-hoc analysis evaluating the long-term safety of the FLAURA2 combination arm across mutually exclusive treatment periods defined by patient-level exposure to study medications (induction [plat, pem and osi]; pem maintenance [pem and osi] and osi-only)

- By characterizing safety according to individual treatment exposure, this novel analysis provides clinically meaningful insight into the longitudinal safety of the FLAURA2 regimen, supporting informed treatment decisions throughout a patient's treatment journey
- With prolonged treatment, the frequency of grade ≥ 3 AE onset progressively declined over successive treatment periods; AE profiles remained consistent with the known safety profiles of the individual agents administered during each period
- Median durations of the pem-maintenance and osi-only periods exceeded 12 and 17 months, respectively
- Renal AEs mostly occurred during pem maintenance; events were of mild-to-moderate severity and manageable with standard medical practice
- Overall, these findings reinforce the favorable long-term benefit-risk profile of the FLAURA2 regimen

Why did we perform this research?

- The FLAURA2 study compared the addition of chemotherapy (platinum–pemetrexed) to osimertinib versus osimertinib alone as a first treatment for patients with epidermal growth factor receptor (EGFR)-mutated advanced non-small cell lung cancer (NSCLC).^{1,2}
- Previous results showed that the osimertinib + platinum–pemetrexed helped patients live longer without their cancer worsening and helped them live longer overall compared with using osimertinib alone.^{1,2} Based on these results, osimertinib + platinum–pemetrexed is a preferred first treatment option for patients with EGFR-mutated advanced NSCLC.^{3,4}
- Here, we report detailed safety outcomes with osimertinib + platinum–pemetrexed from the FLAURA2 study

How did we perform this research?

- Patients with previously untreated EGFR-mutated advanced NSCLC were randomly assigned to receive either osimertinib + platinum–pemetrexed or osimertinib alone
- In the group that received combination treatment, osimertinib was given once daily and platinum–pemetrexed every 3 weeks for 4 cycles. Following this, patients continued osimertinib and pemetrexed until the cancer grew or spread, until death, or until treatment had to be stopped for another reason, such as unacceptable side effects
- Because the number and type of treatments changed over time, we analyzed the occurrence of side effects in the combination group during different treatment periods: the induction period, when patients received platinum, pemetrexed, and osimertinib; the pemetrexed-maintenance period, when patients received pemetrexed and osimertinib; and the osimertinib-only period, when patients received osimertinib alone

- Overall, 276 patients received treatment in the combination group. Following the limited (~3-month) induction period, patients were able to continue pemetrexed and osimertinib treatment for a long time. The median (middle value of an ordered list sorted from smallest to largest) durations of the pemetrexed-maintenance and osimertinib-only periods exceeded 12 and 17 months, respectively
- The side effects that we analyzed started most frequently during the induction period, where patients were receiving three medications. In general, the side effects decreased in onset frequency and severity in the pemetrexed-maintenance (two-medication) and osimertinib-only (single-medication) periods
- Onset of side effects that resulted in patients stopping osimertinib was low throughout all treatment periods, suggesting the addition of platinum–pemetrexed did not prevent patients from remaining on osimertinib treatment
- Reported side effects were as expected based on the known side-effect profiles of the individual medications.⁵⁻⁸ For example:

- The side effects of osimertinib + platinum–pemetrexed were consistent with what is already known about the individual medications, and could be managed with dose changes and / or with additional medical support
- Together with previously reported survival outcomes,^{1,2} these results support osimertinib + platinum–pemetrexed as a preferred first treatment option for patients with EGFR-mutated advanced NSCLC

- More information on the FLAURA2 study can be found at ClinicalTrials.gov: <https://clinicaltrials.gov/study/NCT04035486>

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Osi + plat–pem is a preferred 1L treatment option for patients with EGFR-mutated advanced NSCLC based on the findings from FLAURA2.¹⁻⁴ The addition of plat–pem significantly improved PFS and OS versus osi mono:

- **PFS HR:** 0.62 (95% CI 0.49, 0.79); $p < 0.001$
- **OS HR:** 0.77 (95% CI 0.61, 0.96); $p = 0.02^2$

Median osi exposure was longer with osi + plat–pem versus osi mono (30.5 vs 21.2 months).² The combination arm also exhibited a long osi-only treatment period (median pem exposure, 8.3 months)²

Combination therapies are inherently associated with a greater AE burden than osi mono.^{1,2,9,10} As the treatment paradigm shifts toward 1L intensification,^{3,4} a detailed understanding of longitudinal safety is important for evaluating the benefit–risk profile of combination strategies and informing treatment selection, patient counselling, and shared decision-making

Results and interpretation

- As reported previously, 279 patients were randomized to receive osi + plat+pem and 278 to receive osi mono.¹ The safety analysis set for the combination arm comprised 276 patients who received ≥ 1 dose of osi and ≥ 1 dose of plat / pem¹
- Overall, 276, 201, and 206 patients from the combination arm were evaluated in the induction, pem-maintenance, and osi-only periods, respectively. The median (range) duration of each period was 2.8 (0.1–4.1), 12.4 (0.7–56.1), and 17.8 (0.4–56.8) months, respectively (**Figure 2**)

The area of the spheres is proportional to the median duration of each period

Median (range) duration:
2.8 (0.1–4.1) months

Plat + pem + osi

Median (range) duration:
12.4 (0.7–56.1) months

Pem + osi

Median (range) duration:
17.8 (0.4–56.8) months

Osi

- Onset frequency of AEs considered causally related to treatment by the investigator (any grade / grade ≥ 3) was highest during the induction period (93% / 43%) (**Figure 3**)
- Onset frequency of AEs considered causally related to treatment decreased progressively across the pem-maintenance (90% / 25%) and osi-only (58% / 14%) periods

- Onset frequencies of AEs leading to osi discontinuation were consistently low throughout the study (4%, 3%, and 8% during the induction, pem-maintenance, and osi-only periods, respectively; **Figure 4A**)
- Onset frequency of AEs leading to oxi dose reduction were also consistently low throughout the study (5%, 3%, and 4% during the induction, pem-maintenance, and osi-only periods, respectively; **Figure 4B**)
- Onset frequency of AEs leading to plat dose reduction was 18% during the induction period, and onset frequencies of AEs leading to pem dose reduction were 17% and 14% during the induction and pem-maintenance periods, respectively (**Figure 4B**)

A

Patients with AE onset leading to oA discontinuation (%)

Treatment	Percentage (%)
Osi	4%
Osi + Pem	3%
Osi + Pem + Plat	8%

B

Patients with AE onset leading to dose reduction (%)

Treatment Period	Treatment	Percentage (%)
Induction period* (n=276)	Plat	18%
	Pem	17%
	Osi	5%
Pem-maintenance period* (n=201)	Pem	14%
	Osi	3%
Osi-only period* (n=206)	Osi	4%

The flowchart illustrates the patient selection process and the treatment arms for the Osi 80 mg (QD)* study. It begins with a box labeled 'Patients with EGFR-mutated advanced NSCLC N=557'. An arrow leads from this box to a blue circle containing 'R 1:1', indicating a randomization process. From the 'R 1:1' circle, two arrows branch out: one points to a green box labeled 'Osi 80 mg (QD)*' and the other points to an orange box labeled 'Osi 80 mg (QD) + pem 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles of plat-based treatment)'. The orange box is connected by an arrow to a larger orange box labeled 'Maintenance osi 80 mg (QD) + pem 500 mg/m² (Q3W)*'. Below the flowchart, a section titled 'The novel post-hoc analysis is based on the combination arm' contains a table with two rows: 'Treatments administered' and 'Definition of period'. The table has four columns: 'Induction period', 'Pem-maintenance period', and 'Osi-only period'. The 'Induction period' column is further divided into 'Plat + pem + osi' and 'First dose of plat to last dose of plat + a 21-day plat washout period'. The 'Pem-maintenance period' column is divided into 'Pem + osi' and 'Last dose of plat + 22 days to the last dose of pem + a 21-day pem washout period'. The 'Osi-only period' column is divided into 'Osi' and 'Latest of the last dose of pem (or plat) + 22 days to the last dose of osi + a 28-day osi washout period'.

Patients with EGFR-mutated advanced NSCLC N=557

R 1:1

Osi 80 mg (QD)*

Osi 80 mg (QD) + pem 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles of plat-based treatment)

Maintenance osi 80 mg (QD) + pem 500 mg/m² (Q3W)*

The novel post-hoc analysis is based on the combination arm

	Treatment period ¹		
	Induction period	Pem-maintenance period	Osi-only period
Treatments administered	Plat + pem + osi	Pem + osi	Osi
Definition of period	First dose of plat to last dose of plat + a 21-day plat washout period	Last dose of plat + 22 days to the last dose of pem + a 21-day pem washout period	Latest of the last dose of pem (or plat) + 22 days to the last dose of osi + a 28-day osi washout period

*Treatment continued until disease progression or another discontinuation criterion was met; treatment beyond progression was permitted if the investigator judged the patient had continued clinical benefit. †A treatment wash-out period was included after each treatment end date to ensure that relevant AEs attributable to a given treatment period were included in the safety assessment for that period. The washout period was 21 days for plat and pem, and 28 days for osi.

Onset frequency of AEs indicative of renal toxicity was higher during the perm-maintenance period than during the induction and osi-only periods (**Figure 5**)

- AEs indicative of renal toxicity were predominantly grade 1 or 2, with only one grade 3 event (reported during induction) and no grade 4 or 5 events
- Onset frequencies of AEs indicative of anemia, neutropenia, and thrombocytopenia were highest during the induction period (**Figure 6**)
- While grade 3 AEs indicative of anemia, neutropenia, and thrombocytopenia were common during the induction period, grade 4 events were infrequent and no grade 5 events were reported
- Onset frequencies of AEs indicative of GI and skin / nail toxicity were also generally highest during induction (**Figure 6**)
 - AEs indicative of GI and skin / nail toxicity were predominantly grade 1 or 2, with few grade 3 and no grade 4 or 5 events
- Less frequently reported AEs, including the predefined AESIs of cardiac effects and LDL / pneumonitis, and summaries for additional AEs indicative of fatigue, VTEs, and febrile neutropenia, are provided in **Supplementary Table 1 (scan QR code)**

Grade	Induction (n=276)	Perm-maintenance (n=201)	Osi-only (n=206)
Grade 3	1	0	0
Grade 1 / 2	6	19	10

*Includes AEs with an onset date within the treatment period noted. Patients with multiple events in the same category during a given treatment period were counted only once for that category and period. Patients who experienced events in different categories or treatment periods were counted once in each relevant category and period. AEs indicative of renal toxicity included preferred terms for blood creatinine increased, creatinine renal clearance decreased, and glomerular filtration rate decreased.

AEs indicative of hematological toxicity

Proportion with AE onset (%)

Grade 3
Grade 1/2

Induction (n=276)*

Pem-maintenance (n=201)*

Osi-only (n=206)*

AEs indicative of anemia

Grade	Induction (n=276)*	Pem-maintenance (n=201)*	Osi-only (n=206)*
Grade 3	16%	6%	3%
Grade 1/2	22%	19%	8%
Total	38%	25%	11%

AEs indicative of neutropenia

Grade	Induction (n=276)*	Pem-maintenance (n=201)*	Osi-only (n=206)*
Grade 3	3%	3%	4%
Grade 1/2	13%	11%	9%
Grade 1/2	19%	14%	8%
Total	35%	28%	13%

AEs indicative of thrombocytopenia

Grade	Induction (n=276)*	Pem-maintenance (n=201)*	Osi-only (n=206)*
Grade 3	2%	<1%	<1%
Grade 1/2	11%	12%	8%
Grade 1/2	16%	2%	8%
Total	29%	15%	9%

AEs indicative of GI toxicity

Proportion with AE onset (%)

Grade 3

Grade 1/2

Osi-only

Diarrhea

Grade	Induction (n=276)*	Pem-maintenance (n=201)*	Osi-only (n=206)*
Grade 3	2%	1%	1%
Grade 1/2	30%	24%	12%
Total	32%	25%	13%

Stomatitis

Grade	Induction (n=276)*	Pem-maintenance (n=201)*	Osi-only (n=206)*
Grade 3	<1%	6%	5%
Grade 1/2	20%	6%	5%
Total	21%	6%	5%

Decreased appetite

Grade	Induction (n=276)*	Pem-maintenance (n=201)*	Osi-only (n=206)*
Grade 3	3%	1%	6%
Grade 1/2	21%	9%	6%
Total	24%	10%	6%

Nausea

Grade	Induction (n=276)*	Pem-maintenance (n=201)*	Osi-only (n=206)*
Grade 3	1%	15%	6%
Grade 1/2	36%	15%	6%
Total	37%	15%	6%

Vomiting

Grade	Induction (n=276)*	Pem-maintenance (n=201)*	Osi-only (n=206)*
Grade 3	1%	14%	4%
Grade 1/2	19%	14%	4%
Total	20%	14%	5%

Category	Period 1	Period 2	Period 3	Period 4
AEs indicative of rash	39%	2%	21%	9%
AEs indicative of dry skin	15%	9%	8%	<1%
AEs indicative of pruritus	10%	17%	12%	1%
AEs indicative of pruritus	4%	5%	3%	3%

*Indicates AEs with an onset date within the treatment period noted. Patients with multiple events in the same category during a given treatment period were counted only once for that category and period. Patients who experienced events in different categories or treatment periods were counted once in each relevant category and period. AEs indicative of hematological toxicity included AEs indicative of anemia (comprising anemia and hemoglobin decreased preferred terms), neutropenia (neutropenia and neutrophil count decreased), and thrombocytopenia (thrombocytopenia and platelet count decreased). AEs indicative of GI toxicity included diarrhea, stomatitis, decreased appetite, nausea and vomiting (reported as preferred terms). AEs indicative of skin / nail toxicity included AEs indicative of rash (rash, acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash erythematous, rash follicular, rash maculopapular, rash papular, rash pruritic, rash pruritic, rash pustular, rash vesicular, and skin erosion preferred terms), dry skin (dry skin, eczema, skin fissures, xerosis, and xerosis), paronychia (paronychia, nail-bed disorder, nail-bed infection, nail-bed inflammation, nail discoloration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychia, onychoclasia, onycholysis, onychomadness, and onychomatous), and pruritus (pruritus and erythema pruritic).

- To provide context for the findings in the combination arm, an additional post-hoc analysis was conducted to compare temporal patterns of AEs indicative of hematological and renal toxicity between the combination and osi mono arms using cumulative incidence and occurrence-over-time analyses (**Supplementary Figures 1 to 4; scan QR code**)

This study (NCT04035486) was funded by AstraZeneca. Medical writing support, under the direction of the authors, was provided by Gayle Wall, PhD, of Ashfield MedComms, an Inizio company, and Caroline Allinson, BSc, as contracted by Ashfield MedComms, an Inizio company, in accordance with Good Publications Practice (GPP) guidelines (<http://www.ismpp.org/gpp-2022>), and funded by AstraZeneca.

1L, first-line; AE, adverse event; ASES, AE of special interest; AUC, area under the curve; CI, confidence interval; CNS, central nervous system; CT, computed tomography; CTAEC, Common Terminology Criteria for Adverse Events; EGFR, epidermal growth factor receptor; Ex1del9, exon 19 deletion; GI, gastrointestinal; HR, hazard ratio; LD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; mono, monotherapy; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; osi, osimertinib; pem, pemetrexed; PFS, progression-free survival; platinum; Q3W, every 3 weeks; QD, once daily; R, randomized; VTE, venous thromboembolism; WHO, World Health Organization performance status.

Prof Lee reports grants or contracts from Amgen, AstraZeneca, F. Hoffmann-La Roche, Merck KGaA, and Novartis; travel expenses from AstraZeneca.

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Poster presented at the World Conference on Lung Cancer (WCLC); Seoul, Republic of Korea; September 12–15, 2026