

ORIGINAL ARTICLE

Osimertinib–Savolitinib in Advanced NSCLC after Progression during EGFR-TKI Therapy

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ABSTRACT

BACKGROUND

Savolitinib is an oral, potent, highly selective MET–tyrosine kinase inhibitor (TKI). Combination therapy with savolitinib and osimertinib, an epidermal growth factor receptor (EGFR)–TKI, has shown activity in patients with *EGFR*-mutated, advanced non–small-cell lung cancer (NSCLC) with *MET* overexpression, *MET* amplification, or both, after progression during EGFR-TKI therapy.

METHODS

In this international, phase 3, open-label trial, we randomly assigned, in a 1:1 ratio, patients with *EGFR*-mutated, locally advanced or metastatic NSCLC with *MET* overexpression (staining intensity of 3+ for MET in ≥90% of tumor cells on immuno-histochemical analysis), *MET* amplification (≥10 gene copies on fluorescence in situ hybridization), or both whose disease had progressed during osimertinib therapy to receive osimertinib (at a dose of 80 mg once daily) plus savolitinib (300 mg twice daily) or intravenous platinum–pemetrexed. The primary end point was progression-free survival, as assessed by blinded independent central review. Secondary end points included overall survival and safety.

RESULTS

Of the 1746 patients screened, 338 were randomly assigned to receive osimertinib–savolitinib (171 patients) or platinum–pemetrexed (167 patients). Osimertinib–savolitinib led to significantly longer progression-free survival than platinum–pemetrexed (hazard ratio for disease progression or death, 0.55; 95% confidence interval [CI], 0.42 to 0.72; $P < 0.001$), as well as significantly longer overall survival (hazard ratio for death, 0.68; 95% CI, 0.50 to 0.91; $P = 0.01$; final analysis). The Kaplan–Meier estimate of 12-month progression-free survival was 36% in the osimertinib–savolitinib group and 10% in the platinum–pemetrexed group, and the estimate of 12-month overall survival was 70% and 53%, respectively. The most frequently reported adverse events that occurred during treatment in the osimertinib–savolitinib group were peripheral edema (in 49% of the patients), anemia (in 26%), and diarrhea (in 26%). Grade 3 or higher adverse events during treatment were reported in 64% of the patients in the osimertinib–savolitinib group and in 63% of those in the platinum–pemetrexed group.

CONCLUSIONS

Osimertinib–savolitinib led to significantly longer progression-free and overall survival than platinum–pemetrexed among patients with *EGFR*-mutated, locally advanced or metastatic NSCLC with *MET* overexpression, *MET* amplification, or both that had progressed during osimertinib therapy (Funded by AstraZeneca; SAFFRON ClinicalTrials.gov number, NCT05261399.)

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OSIMERTINIB IS A THIRD-GENERATION, irreversible, oral epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitor (TKI), with demonstrated efficacy in patients with *EGFR*-mutated non–small-cell lung cancer (NSCLC), including in those with central nervous system (CNS) metastases.^{1,2} Osimertinib, with or without pemetrexed and a platinum-based agent (platinum–pemetrexed), is recommended as a first-line treatment for *EGFR*-mutated advanced NSCLC^{3–6}; however, most patients will eventually have disease progression.^{7,8} *MET* amplification and *MET* protein (also known as hepatocyte growth factor receptor or c-MET) overexpression are together the most commonly reported alterations after disease progression during treatment with osimertinib among patients with *EGFR*-mutated advanced NSCLC.^{8–13} The reported prevalence of *MET* amplification after disease progression among patients receiving osimertinib therapy ranges from approximately 7 to 18%.^{8–11} In the SAVANNAH trial, the estimated prevalence of *MET* overexpression, *MET* amplification, or both was 34%, on the basis of a high *MET* cutoff (*MET* staining intensity of 3+ in ≥90% of tumor cells on immunohistochemical [IHC] analysis, ≥10 *MET* gene copies on fluorescence in situ hybridization [FISH], or both),¹² whereas in the CHRYSALIS-2 trial, *MET* overexpression was reported in approximately 31 to 40% of the patients on the basis of a lower *MET* cutoff (IHC 3+ staining intensity in ≥25% of tumor cells).¹⁴ Estimates vary across populations, testing methods, sample types, and *MET* cutoffs.¹⁵ Current evidence suggests that the development of *MET*-mediated resistance is associated with poor outcomes,^{16,17} and targeted treatment options for patients who have disease progression during osimertinib therapy remain limited.⁵ Thus, an unmet clinical need for improved outcomes remains for patients with *MET* overexpression, *MET* amplification, or both after disease progression during *EGFR*-TKI treatment.¹⁸

Savolitinib is an oral, potent, highly selective, CNS-penetrant *MET*-TKI^{19–21} with demonstrated activity in patients with advanced or metastatic NSCLC with *MET* exon 14 skipping alterations.²² In the SAVANNAH trial, osimertinib plus savolitinib (osimertinib–savolitinib) showed clinically meaningful and durable responses in patients with *EGFR*-mutated advanced NSCLC with *MET* overexpression, *MET* amplification, or both, who had

disease progression during first-line therapy with osimertinib. The percentage of patients in this trial with an investigator-assessed confirmed objective response was 56% (95% confidence interval [CI], 45 to 67), and the median duration of response was 7.1 months (95% CI, 5.6 to 9.6).¹⁸ In the SACHI trial, treatment with osimertinib–savolitinib improved progression-free survival as compared with platinum–pemetrexed among patients in China with *EGFR*-mutated, *MET*-amplified locally advanced or metastatic NSCLC that had progressed during *EGFR*-TKI treatment (hazard ratio for progression or death, 0.34; 95% CI, 0.23 to 0.49; $P < 0.001$).²³ These data support further investigation of osimertinib–savolitinib for the treatment of patients with advanced NSCLC with *MET* overexpression, *MET* amplification, or both after disease progression during osimertinib therapy.

Here, we report the results of the SAFFRON trial, an international, open-label, phase 3 trial designed to evaluate the efficacy and safety of osimertinib–savolitinib as compared with platinum–pemetrexed in patients with *EGFR*-mutated locally advanced or metastatic NSCLC with *MET* overexpression, *MET* amplification, or both after disease progression during osimertinib therapy.

METHODS

PATIENTS

Eligible patients were 18 years of age or older (or ≥19 years of age in South Korea) and had histologically or cytologically confirmed locally advanced or metastatic NSCLC that was not amenable to curative treatment, with tumors harboring an *EGFR*-TKI–sensitizing mutation (*EGFR* exon 19 deletion or exon 21 codon p.Leu858Arg point mutation), an *EGFR* p.Thr790Met resistance mutation, or both. Patients were also required to have *MET* overexpression (*MET* IHC 3+ staining intensity in ≥90% of tumor cells; scores range from 0 to 3+, with higher scores indicating higher staining intensity), *MET* amplification (≥10 *MET* gene copies on FISH), or both. *MET* status was determined by central laboratory testing of tumor tissue obtained at screening in patients with disease progression that occurred during first-line or second-line use of osimertinib as the most recent treatment. The cutoffs for *MET* IHC and FISH were identified in preliminary analyses of the

phase 2 SAVANNAH trial.¹² Additional details regarding MET testing are provided in the Supplementary Appendix (available with the full text of this article at NEJM.org). Asymptomatic and stable brain metastases were allowed.

TRIAL OVERSIGHT

The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol, available at NEJM.org. Details regarding trial oversight are provided in the Supplementary Appendix.

TRIAL DESIGN AND TREATMENT

The trial design is shown in Figure S1 in the Supplementary Appendix. Patients were randomly assigned in a 1:1 ratio to receive oral osimertinib (at a dose of 80 mg once daily) plus oral savolitinib (300 mg twice daily) or intravenous platinum–pemetrexed. Platinum–pemetrexed consisted of pemetrexed (500 mg per square meter of body-surface area) plus either cisplatin (75 mg per square meter) or carboplatin (a pharmacologically guided dose defined as an area under the concentration–time curve of 5 mg per milliliter per minute) administered on day 1 of each 21-day cycle for four cycles, followed by maintenance treatment with pemetrexed (500 mg per square meter once every 3 weeks). Treatment continued until the occurrence of disease progression, which was assessed by investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; until the occurrence of unacceptable toxic effects; or until another discontinuation criterion was met. Crossover between treatment groups was not allowed. Further details of the trial design are provided in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, defined as the time from randomization until disease progression or death from any cause in the absence of progression, as assessed by blinded independent central review according to RECIST, version 1.1. Secondary end points included overall survival, which was defined as the time from randomization until death from any cause; progression-free survival in patients with MET overexpression; and safety. Additional details regarding the trial end points (Table S1) and end-

point assessments are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The efficacy analysis was performed in the full analysis population, which included all the patients who had undergone randomization, and in the MET-overexpressed analysis population (with overexpression defined by MET IHC 3+ staining intensity in $\geq 90\%$ of tumor cells). An exploratory analysis was conducted in the MET-amplified analysis population (with amplification defined by ≥ 10 MET gene copies on FISH). The safety analysis population included all the patients who had undergone randomization and received at least one dose of a trial treatment.

The assumption of proportionality was assessed by examining plots of complementary log–log (event times) versus log (time). Progression-free survival was analyzed by means of a log-rank test stratified according to line of therapy (second-line vs. third-line), baseline brain metastases (yes vs. no), and race (Asian vs. non-Asian). Progression-free survival in prespecified subgroups was analyzed with the use of an unstratified Cox proportional-hazards model.

For the primary analysis of progression-free survival, we calculated that 227 events of disease progression or death would provide the trial with 90% power to detect a significant difference between the two groups, assuming a treatment effect hazard ratio of 0.65 and a two-sided significance level of 5%. To control the type I error rate at 5% (two-sided), a sequential multiple-testing procedure was used (Fig. S2). The primary end point — progression-free survival, as assessed by blinded independent central review in the full analysis population — was tested first; if significance was shown, then progression-free survival in the MET-overexpressed analysis population and overall survival in the full analysis population would be tested, followed by overall survival in the MET-overexpressed analysis population. No multiplicity adjustment was planned for additional secondary or subgroup analyses; therefore, the widths of the confidence intervals were unadjusted and should not be used to infer definitive treatment effects. The data-cutoff date was July 6, 2026. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENT

Between August 3, 2022, and September 25, 2025, a total of 1746 patients were screened for eligibility. Of the 1373 patients who underwent screening and were evaluable for *MET* aberrations (by IHC or FISH), 480 (35%) had *MET* overexpression, *MET* amplification, or both. Overall, 338 eligible patients were randomly assigned to the osimertinib–savolitinib group (171 patients) or to the platinum–pemetrexed group (167 patients). A total of 170 patients in the osimertinib–savolitinib group and 145 in the platinum–pemetrexed group received at least one dose of the trial treatment; 23 patients did not receive any trial treatment (Fig. S3).

The demographic and clinical characteristics of the patients at baseline were generally balanced between the two groups (Table 1). The percentage of patients with brain metastases at baseline was 31% in both groups (53 patients in the osimertinib–savolitinib group and 51 in the platinum–pemetrexed group), and 84% of the patients in both groups (143 and 141 patients, respectively) had received one previous line of therapy. Previous anticancer treatments are listed in Table S2. Among the patients who underwent randomization, a total of 242 patients (72%) had *MET* overexpression, and a total of 245 patients (72%) had *MET* amplification (Table 1); 151 patients (45%) had both overexpression and amplification, 91 (27%) had overexpression only (positive for *MET* overexpression and negative or unknown status for *MET* amplification), and 94 (28%) had amplification only (positive for *MET* amplification and negative or unknown status for *MET* overexpression). On the basis of available data, the demographic and clinical characteristics of the patients in this trial were generally representative of patients with *EGFR*-mutated NSCLC (Table S3); however, the majority of the trial patients were enrolled from Asian countries. Consequently, some racial and ethnic subgroups were underrepresented, with only 1 Black patient enrolled.

At data cutoff, among patients who received at least one dose of a trial treatment, 45 (26%) in the osimertinib–savolitinib group and 3 (2%) in the platinum–pemetrexed group continued to receive any trial treatment; 43 patients (25%) in the osimertinib–savolitinib group continued to receive

both osimertinib and savolitinib. The median duration of total treatment exposure was 8.3 months (range, 0.5 to 37.3) for osimertinib, 8.3 months (range, 0.7 to 37.3) for savolitinib, and 4.1 months (range, 0.7 to 21.0) for pemetrexed; additional details are provided in the Supplementary Appendix. The most common reason for treatment discontinuation was disease progression, which occurred in 52% of the patients in the osimertinib–savolitinib group and 76% of those in the platinum–pemetrexed group.

EFFICACY

In the full analysis population, median progression-free survival, as assessed by blinded independent central review, was significantly longer with osimertinib–savolitinib (7.6 months; 95% CI, 5.6 to 9.7) than with platinum–pemetrexed (5.4 months; 95% CI, 4.2 to 5.8); the hazard ratio for disease progression or death was 0.55 (95% CI, 0.42 to 0.72; $P < 0.001$; overall data maturity for progression-free survival, 68%) (Fig. 1A). The Kaplan–Meier estimate of the percentage of patients who were alive and free from disease progression at 12 months was 36% (95% CI, 28 to 44) in the osimertinib–savolitinib group and 10% (95% CI, 6 to 17) in the platinum–pemetrexed group. The results for investigator-assessed progression-free survival are shown in Figure S4, and the hazard ratios for disease progression or death across prespecified subgroups are shown in Figure S5.

In the *MET*-overexpressed analysis population, which included 124 patients in the osimertinib–savolitinib group and 118 patients in the platinum–pemetrexed group, median progression-free survival, as assessed by blinded independent central review, was significantly longer with osimertinib–savolitinib (8.5 months; 95% CI, 5.7 to 11.1) than with platinum–pemetrexed (5.6 months; 95% CI, 4.4 to 6.7); the hazard ratio for disease progression or death was 0.51 (95% CI, 0.37 to 0.71; $P < 0.001$) (Fig. 1B). Although this end point was not formally tested for statistical significance in accordance with the multiple-testing procedure, progression-free survival, as assessed by blinded independent central review in the *MET*-amplified analysis population (129 patients in the osimertinib–savolitinib group and 116 in the platinum–pemetrexed group) was consistent with that observed in the *MET*-overexpressed analysis population. Median progression-free survival was

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Full Analysis Population).*

Characteristic	Osimertinib–Savolitinib (N = 171)	Platinum–Pemetrexed (N = 167)
Sex — no. (%)		
Female	110 (64)	109 (65)
Male	61 (36)	58 (35)
Median age (range) — yr	64 (34–86)	64 (37–86)
Race — no. (%)†		
Asian	107 (63)	110 (66)
Non-Asian	61 (36)	46 (28)
Smoking status — no. (%)		
Current	3 (2)	6 (4)
Former	51 (30)	47 (28)
Never	117 (68)	114 (68)
ECOG performance-status score — no. (%)‡		
0	60 (35)	49 (29)
1	111 (65)	118 (71)
Histologic type — no. (%)		
Adenocarcinoma	170 (99)	165 (99)
Small-cell carcinoma§	0	1 (1)
Undetermined	1 (1)	1 (1)
EGFR mutation type at randomization — no. (%)¶		
Exon 19 deletion	111 (65)	116 (69)
L858R	59 (35)	50 (30)
Other	1 (1)	1 (1)
Extent of disease at baseline — no. (%)		
Locally advanced	9 (5)	8 (5)
Metastatic	162 (95)	159 (95)
Brain metastases at baseline — no. (%)	53 (31)	51 (31)
Previous lines of therapy — no. (%)		
1	143 (84)	141 (84)
≥2**	28 (16)	26 (16)
MET overexpression or MET amplification (or both)††		
MET IHC 3+ staining intensity in ≥90% of tumor cells	124 (73)	118 (71)
≥10 MET gene copies on FISH	129 (75)	116 (69)
MET IHC 3+ staining intensity in ≥90% of tumor cells and ≥10 MET gene copies on FISH	83 (49)	68 (41)

* Percentages may not total 100 due to rounding. EGFR denotes epidermal growth factor receptor, FISH fluorescence in situ hybridization, IHC immunohistochemical, and L858R exon 21 codon p.Leu858Arg.

† Race was reported by the patients. Data were missing or not reported for 3 patients in the osimertinib–savolitinib group and 11 patients in the platinum–pemetrexed group.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

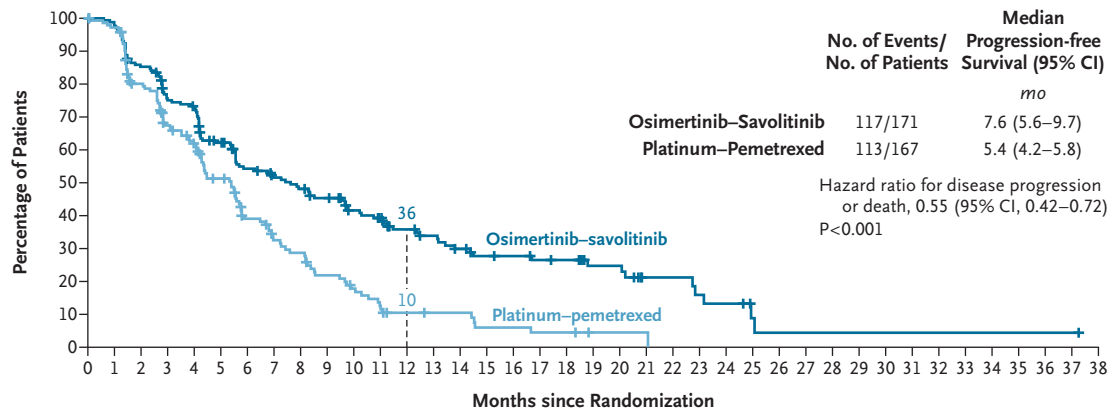
§ One patient had the histologic type reported as small-cell carcinoma owing to a data-entry issue; the correct histologic type was squamous-cell carcinoma (protocol deviation). The patient underwent randomization but did not receive a dose of osimertinib–savolitinib or platinum–pemetrexed.

¶ Patients with both exon 19 deletion and L858R were included in the exon 19 deletion group. Patients who had a positive test for L858R but a negative test for exon 19 deletion were included in the L858R group. Patients who had neither a positive test for exon 19 deletion nor L858R were included in the “Other” category. Other EGFR mutations included p.Thr790Met (in the absence of exon 19 deletion and L858R), which was detected in one patient in the osimertinib–savolitinib group and in one patient in the platinum–pemetrexed group.

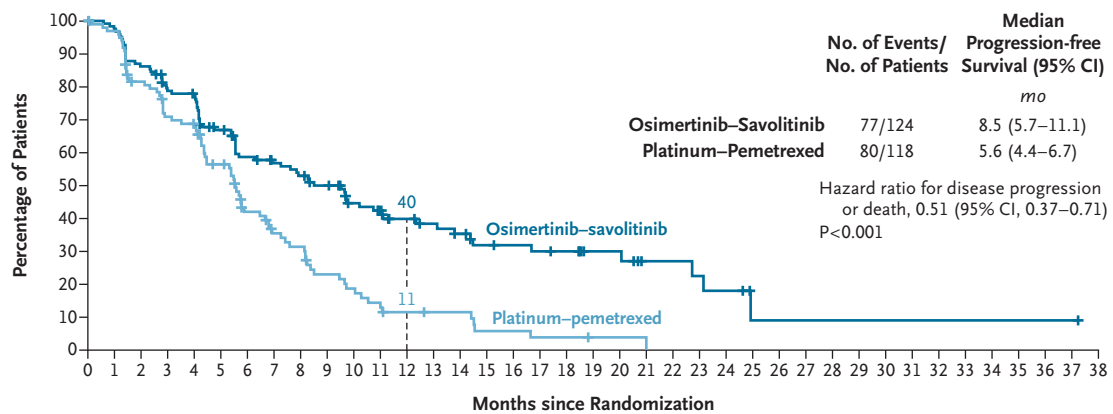
|| The presence of brain metastases was assessed by the investigator.

** One patient in the platinum–pemetrexed group had received three previous lines of therapies, as recorded in the electronic case report form.

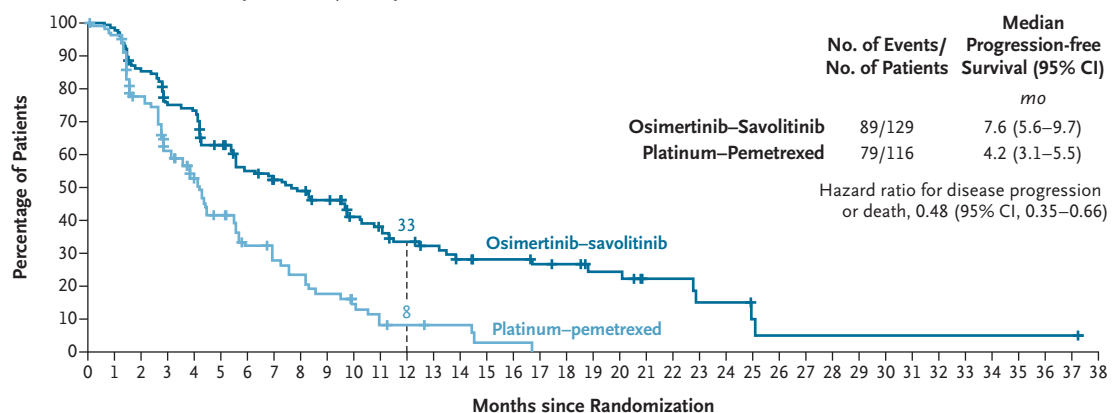
†† In two patients (one in each group), neither MET overexpression nor MET amplification was reported on the basis of the protocol-defined cutoffs (MET IHC 3+ staining intensity in ≥90% of tumor cells and ≥10 MET gene copies on FISH); this was reported as a protocol deviation in each case. The number of patients with MET IHC 3+ staining intensity in at least 90% of tumor cells and at least 10 MET gene copies on FISH are not mutually exclusive and patients may be included in both categories, as appropriate.

A Progression-free Survival in the Full Analysis Population**No. at Risk**

Osimertinib-savolitinib	171	144	120	82	70	54	39	29	24	21	14	8	5	1	1	1	1	1	0
Platinum-pemetrexed	167	109	77	43	30	17	8	7	4	3	1	0	0	0	0	0	0	0	0

B Progression-free Survival in the MET-Overexpressed Analysis Population**No. at Risk**

Osimertinib-savolitinib	124	106	92	64	55	40	29	22	17	15	10	6	4	1	1	1	1	1	0
Platinum-pemetrexed	118	77	63	33	23	13	7	6	3	2	1	0	0	0	0	0	0	0	0

C Progression-free Survival in the MET-Amplified Analysis Population**No. at Risk**

Osimertinib-savolitinib	129	108	91	63	54	39	28	20	19	16	11	6	4	1	1	1	1	1	0
Platinum-pemetrexed	116	72	42	23	16	9	4	3	1	0	0	0	0	0	0	0	0	0	0

Figure 1 (facing page). Kaplan–Meier Estimates of Progression-free Survival.

Shown are Kaplan–Meier estimates of progression-free survival in the full analysis population (Panel A), in the MET-overexpressed analysis population (Panel B), and in the MET-amplified analysis population (Panel C), as assessed by blinded independent central review according to RECIST, version 1.1. MET overexpression was defined by a MET staining intensity of 3+ in at least 90% of tumor cells on immunohistochemical analysis, and MET amplification was defined by the presence of at least 10 MET gene copies on fluorescence in situ hybridization. Tick marks indicate censored data, and vertical dashed lines indicate the times of landmark analyses of progression-free survival. Progression-free survival rates and associated 95% confidence intervals were based on Kaplan–Meier estimates. Progression-free survival in the full analysis population and in the MET-overexpressed analysis population were formally tested for significance in accordance with a multiple-testing procedure (Panels A and B). No formal statistical testing was performed in the MET-amplified analysis population in accordance with a prespecified multiple-testing procedure; the widths of the confidence intervals have not been adjusted and should not be used to infer definitive treatment effects (Panel C). The median duration of follow-up for progression-free survival for all the patients in the full analysis population, the MET-overexpressed analysis population, and the MET-amplified analysis population was 5.6 months (range, 0 to 37.3), 6.6 months (range, 0 to 37.3), and 5.6 months (range, 0 to 37.3), respectively, in the osimertinib–savolitinib group and 3.5 months (range, 0 to 21.1), 4.2 months (range, 0 to 21.1), and 2.8 months (range, 0 to 16.7) in the platinum–pemetrexed group.

7.6 months (95% CI, 5.6 to 9.7) in the osimertinib–savolitinib group and 4.2 months (95% CI, 3.1 to 5.5) in the platinum–pemetrexed group (hazard ratio for disease progression or death, 0.48; 95% CI, 0.35 to 0.66) (Fig. 1C).

At the data cutoff, 180 patients in the full analysis population had died (data maturity for overall survival, 53%); median overall survival was significantly longer with osimertinib–savolitinib (17.8 months; 95% CI, 15.6 to 23.7) than with platinum–pemetrexed (12.9 months; 95% CI, 10.6 to 16.8), and the hazard ratio for death was 0.68 (95% CI, 0.50 to 0.91; $P=0.01$; final analysis) (Fig. 2). The Kaplan–Meier estimate of 12-month overall survival was 70% (95% CI, 62 to 76) in the osimertinib–savolitinib group and 53% (95% CI, 44 to 61) in the platinum–pemetrexed group. In the MET-overexpressed analysis population, the hazard ratio for death was 0.74

(95% CI, 0.51 to 1.08; $P=0.12$), and in the MET-amplified analysis population, the hazard ratio for death was 0.55 (95% CI, 0.38 to 0.77; not formally tested for statistical significance in accordance with the multiple-testing procedure; see the Results section and Fig. S6 in the Supplementary Appendix). Data for patients in the full analysis population who received subsequent anticancer treatments are reported in Table S4.

In the full analysis population, 88 of 171 patients (51%) in the osimertinib–savolitinib group and 45 of 167 (27%) in the platinum–pemetrexed group had a confirmed objective response, as assessed by blinded independent central review. Additional results for tumor response end points are provided in the Results section of the Supplementary Appendix and in Table S5, Fig. S7, and Fig. S8.

SAFETY

A summary of adverse events is provided in Table 2. Adverse events of any cause that occurred during treatment were reported in 169 of 170 patients (99%) in the osimertinib–savolitinib group and in 140 of 145 (97%) in the platinum–pemetrexed group. The most frequently reported adverse events of any grade that occurred during treatment were peripheral edema (in 49% of the patients), anemia (in 26%), and diarrhea (in 26%) in the osimertinib–savolitinib group, and anemia (in 54%), nausea (in 37%), and decreased platelet count (in 31%) in the platinum–pemetrexed group (Table 3). Among the adverse events of any cause that occurred during treatment, adverse events of grade 3 or higher and serious adverse events were reported in 64% and 41% of the patients, respectively, in the osimertinib–savolitinib group and in 63% and 28% of those in the platinum–pemetrexed group (Tables S6 and S7). Adverse events that led to treatment discontinuation were reported in 14% of the patients in the osimertinib–savolitinib group and in 8% of those in the platinum–pemetrexed group (Table S8).

Adverse events that occurred during treatment and led to death were reported in 12 patients (7%) in the osimertinib–savolitinib group and in no patients in the platinum–pemetrexed group (Table S9). Overall, 9 of 12 patients with fatal events had documented disease progression before death or had disease progression or NSCLC cited as a primary or secondary cause of death. The results for commonly reported, grade 3 or

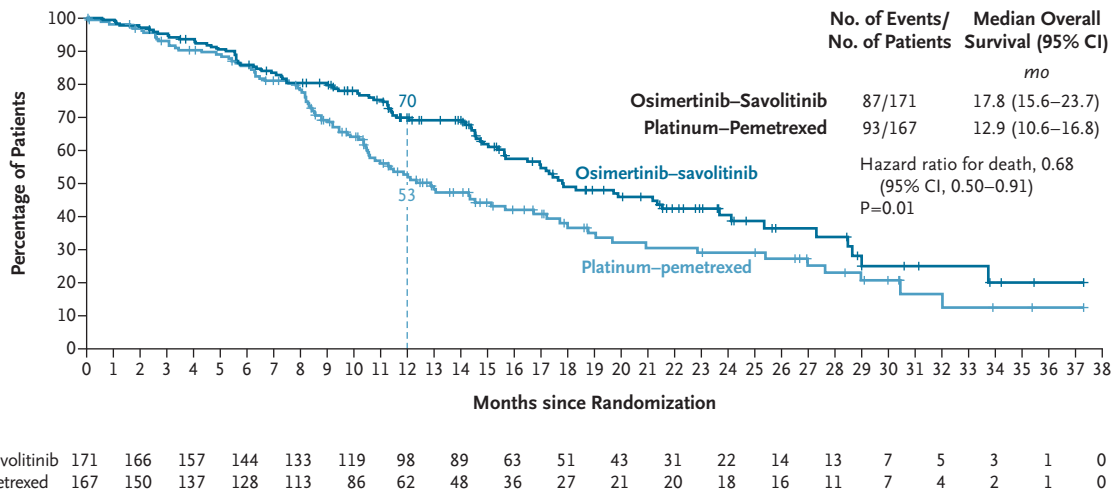


Figure 2. Overall Survival (Full Analysis Population).

Shown are the Kaplan–Meier estimates of overall survival (defined as the time from randomization until death from any cause) in the full analysis population (formally tested for significance in accordance with a multiple-testing procedure). The boundary to declare statistical significance was $P < 0.03047$. Although the Kaplan–Meier plot indicates nonproportionality, the hazard ratio can still be meaningfully interpreted as an average hazard ratio over time. The median duration of follow-up for overall survival for all the patients in the full analysis population was 14.2 months (range, 0.6 to 37.3) in the osimertinib–savolitinib group and 10.2 months (range, 0 to 37.3) in the platinum–pemetrexed group. Tick marks indicate censored data. Landmark overall survival rates and associated 95% confidence intervals were based on Kaplan–Meier estimates. Data for patients not known to have died at the time of the analysis were censored at the last recorded date on which the patient was known to be alive.

higher, and serious treatment-related adverse events are reported in Tables S10, S11, and S12, respectively.

DISCUSSION

In the SAFFRON trial, osimertinib–savolitinib showed a statistically significant and clinically meaningful progression-free survival benefit over platinum–pemetrexed among patients with *EGFR*-mutated, locally advanced or metastatic NSCLC with *MET* overexpression (*MET* IHC 3+ staining intensity in $\geq 90\%$ of tumor cells), *MET* amplification (≥ 10 *MET* gene copies on FISH), or both. The hazard ratio for disease progression or death was 0.55 (95% CI, 0.42 to 0.72; $P < 0.001$), which corresponds to a 45% reduction in the risk of disease progression or death with osimertinib–savolitinib as compared with platinum–pemetrexed. Furthermore, overall survival was significantly longer with osimertinib–savolitinib than with platinum–pemetrexed in this *MET*-selected patient population; the hazard ratio for death was 0.68 (95% CI, 0.50 to 0.91; $P = 0.01$), which corresponds to a 32% reduction in the risk of

death with osimertinib–savolitinib as compared with platinum–pemetrexed.

The efficacy results from this trial are consistent with those from previous trials of osimertinib–savolitinib involving patients who had disease progression during *EGFR*-TKI therapy. In the SAVANNAH trial, osimertinib–savolitinib (savolitinib dose, 300 mg twice daily) was associated with a median investigator-assessed progression-free survival of 7.4 months (7.5 months, as assessed by blinded independent central review) in patients with *EGFR*-mutated advanced NSCLC with *MET* overexpression, *MET* amplification, or both.¹⁸ In the SACHI trial, among patients with *EGFR*-mutated advanced NSCLC with *MET* amplification, the median progression-free survival was 8.2 months in the osimertinib–savolitinib group (savolitinib dose, 600 mg for patients weighing ≥ 50 kg or 400 mg for patients weighing < 50 kg) and 4.5 months in the platinum–pemetrexed group; the hazard ratio for death was 0.84 (95% CI, 0.55 to 1.29; data maturity for overall survival, 40%).²³

The treatment landscape for patients with NSCLC who have received previous treatment

Table 2. Summary of Adverse Events (Safety Analysis Population).*

Event	Osimertinib–Savolitinib (N=170)	Platinum–Pemetrexed (N=145)
	<i>number of patients (percent)</i>	
Any adverse event that occurred during treatment	169 (99)	140 (97)
Grade ≥ 3 adverse event	108 (64)	91 (63)
Serious adverse event	69 (41)	40 (28)
Adverse event leading to death	12 (7)	0
Adverse event of special interest	119 (70)	76 (52)
Grade ≥ 3 adverse event of special interest	38 (22)	18 (12)
Serious adverse event of special interest	24 (14)	7 (5)
Adverse event of special interest leading to death	3 (2)	0
Adverse event leading to treatment discontinuation	23 (14)	12 (8)
Adverse event leading to treatment interruption	99 (58)	50 (34)
Adverse event leading to dose reduction	45 (26)	31 (21)
Adverse event leading to dose modification	104 (61)	64 (44)
Any adverse event possibly related to trial treatment†	158 (93)	134 (92)
Grade ≥ 3 adverse event	68 (40)	75 (52)
Serious adverse event	24 (14)	23 (16)
Adverse event leading to death	1 (1)	0
Adverse event of special interest	94 (55)	61 (42)
Grade ≥ 3 adverse event of special interest	22 (13)	9 (6)
Serious adverse event of special interest	11 (6)	1 (1)
Adverse event of special interest leading to death	0	0
Adverse event leading to treatment discontinuation	21 (12)	9 (6)
Adverse event leading to dose modification	82 (48)	55 (38)

* The safety analysis population included all the patients who had undergone randomization and received at least one dose of a trial treatment. Adverse events are reported for those with an onset, or those that had worsened, on or after the date of the first trial dose, up to and including 35 days after the date of the administration of the last trial dose or up to the day before the start of a subsequent anticancer treatment, whichever was first. Patients with multiple events in the same category were counted once per category regardless of the number of occurrences.

† An adverse event was considered by the trial investigator to be related to the trial treatment if there was a reasonable possibility that the event was caused by the treatment.

with osimertinib has evolved since the initiation of the SAFFRON trial, when platinum-based chemotherapy alone was the standard of care. Evidence supporting the use of other treatment combinations after disease progression during EGFR-TKI therapy includes data from the COMPEL trial,²⁴ which showed improved progression-free and overall survival among patients who continued treatment with osimertinib while adding chemotherapy than among those who received placebo plus chemotherapy (median progression-free survival, 8.4 months in the osimertinib plus chemotherapy group vs. 4.4 months in the placebo plus chemotherapy group; median overall survival,

15.9 vs. 9.8 months, respectively). The OptiTROP-Lung04 trial showed longer progression-free and overall survival among patients receiving sacituzumab tirumotecan than among those receiving platinum-based chemotherapy (median progression-free survival, 8.3 months in the sacituzumab tirumotecan group vs. 4.3 months in the platinum-based chemotherapy group; 18-month overall survival, 66% vs. 48%, respectively).²⁵ The pooled data for the TROPION-Lung05 and TROPION-Lung01 trials showed clinically meaningful activity with datopotamab deruxtecan after EGFR-TKI and platinum-based chemotherapy (median progression-free survival, 5.8 months; me-

dian overall survival, 15.6 months).²⁶ However, these studies did not select patients for MET alterations after disease progression during EGFR-TKI therapy; therefore, conclusions in patients with NSCLC who have MET overexpression, MET amplification, or both are limited.

In the MARIPOSA-2 trial, median progression-free survival, as assessed by blinded independent central review was 6.3 months with amivantamab–chemotherapy and 4.2 months with chemotherapy alone among patients with EGFR-mutated advanced NSCLC after disease progression during osimertinib therapy (irrespective of resistance mechanism).²⁷ At the second interim analysis, no significant difference in overall survival was observed between the two groups.²⁸ Median progression-free survival in a subgroup of 12 patients with MET amplification (identified by genomic sequencing of baseline circulating tumor DNA [ctDNA]) who received amivantamab–chemotherapy in the MARIPOSA-2 trial was only 4.4 months, a finding consistent with previous reports of poor outcomes in patients with MET-driven resistance.^{16,17} These data highlight the evolving range of treatment options for patients after disease progression during osimertinib therapy and the continued need for biomarker testing, with the results of the SAFFRON trial supporting osimertinib–savolitinib as a biomarker-directed combination treatment for MET-mediated resistance.

The efficacy outcomes in the MET-overexpressed analysis population (all 242 patients with MET IHC 3+ staining intensity in ≥90% of tumor cells) and MET-amplified analysis population (all 245 patients with ≥10 MET gene copies on FISH) were consistent with those in the full analysis population. The hazard ratio for disease progression or death among the 84 patients who were positive for MET overexpression and negative for MET amplification (excluding those with unknown status for MET amplification) was 0.69; the hazard ratio among the 77 patients who were positive for MET amplification and negative for MET overexpression (excluding those with unknown status for MET overexpression) was 0.67. These results were consistent with the result reported in the overall population. These findings suggest that all MET-selected subgroups may derive benefit from osimertinib–savolitinib. Although the populations of patients with MET

overexpression and MET amplification overlap, a substantial distinction exists between them, with more than half the randomly assigned patients in this trial found to be positive by means of IHC or FISH alone; 45% of the patients had MET overexpression and MET amplification, 27% had MET overexpression only, and 28% had MET amplification only. Therefore, both IHC and FISH testing have utility in this clinical setting.

Plasma-based approaches may not have adequate sensitivity to detect MET-mediated resistance to EGFR-TKIs,²⁹ and previous evidence suggests that tissue-based testing after disease progression is more sensitive than liquid biopsy for accurate detection of MET amplification³⁰; these considerations support the use of the tissue biopsy-based approach in the SAFFRON trial. The frequency of MET-mediated resistance detected by liquid biopsy may also vary according to first-line treatment. In the FLAURA2 trial, the percentage of patients with MET amplification detected by plasma ctDNA testing after first-line treatment with osimertinib plus platinum–pemetrexed or with osimertinib alone was similar (12% vs. 11%),³¹ whereas in the MARIPOSA trial, MET amplification was reported in a lower percentage of patients receiving first-line amivantamab–lazertinib than those receiving osimertinib (3% vs. 13%).³² Further data, particularly from tissue-based testing, are needed to characterize resistance mechanisms following these regimens. The American Society of Clinical Oncology and European Society for Medical Oncology guidelines recommend tissue rebiopsy in the event of disease progression, when possible, in order to identify histologic transformation and targetable resistance mechanisms.^{3–6} Although in some instances biopsy may be precluded by procedural risks or yield insufficient tissue for testing,³³ repeat biopsy of tissue remains important for identifying actionable resistance mechanisms, including MET overexpression, MET amplification, or both, to inform biomarker-directed treatments such as osimertinib–savolitinib.

The most frequently reported adverse events that occurred during treatment in the osimertinib–savolitinib group were peripheral edema, anemia, and diarrhea; these events were mostly of low grade. The incidence of peripheral edema, a common MET-TKI class effect,³⁴ was generally consistent with that observed with other MET

Table 3. Adverse Events That Occurred during Treatment and Were Reported in at Least 10% of Patients in Either Group (Safety Analysis Population).*

Event	Osimertinib–Savolitinib (N=170)		Platinum–Pemetrexed (N = 145)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	<i>number of patients (percent)</i>			
Peripheral edema	83 (49)	13 (8)	12 (8)	0
Anemia	45 (26)	9 (5)	78 (54)	26 (18)
Diarrhea	44 (26)	2 (1)	11 (8)	0
Nausea	43 (25)	6 (4)	53 (37)	2 (1)
Increased creatine kinase	40 (24)	14 (8)	0	0
Hypoalbuminemia	39 (23)	1 (1)	12 (8)	0
Paronychia	36 (21)	2 (1)	2 (1)	0
Increased aspartate aminotransferase	33 (19)	3 (2)	34 (23)	3 (2)
Decreased platelet count	31 (18)	0	45 (31)	13 (9)
Increased alanine aminotransferase	31 (18)	4 (2)	42 (29)	7 (5)
Increased blood creatinine	29 (17)	0	7 (5)	0
Vomiting	27 (16)	4 (2)	23 (16)	4 (3)
Decreased white-cell count	26 (15)	5 (3)	39 (27)	19 (13)
Pyrexia	24 (14)	0	10 (7)	1 (1)
Constipation	22 (13)	1 (1)	30 (21)	0
Increased amylase	22 (13)	1 (1)	10 (7)	0
Decreased appetite	21 (12)	1 (1)	37 (26)	2 (1)
Fatigue	21 (12)	1 (1)	24 (17)	3 (2)
Hypocalcemia	20 (12)	1 (1)	4 (3)	0
Decreased neutrophil count	19 (11)	4 (2)	42 (29)	26 (18)
Dyspnea	19 (11)	1 (1)	11 (8)	1 (1)
Pneumonia	19 (11)	11 (6)	7 (5)	4 (3)
Hyponatremia	18 (11)	4 (2)	10 (7)	3 (2)
Rash	18 (11)	1 (1)	9 (6)	0
Muscle spasms	17 (10)	0	0	0
Stomatitis	17 (10)	0	10 (7)	0
Urinary tract infection	17 (10)	2 (1)	7 (5)	0
Neutropenia	14 (8)	3 (2)	25 (17)	15 (10)
Thrombocytopenia	14 (8)	0	16 (11)	2 (1)
Headache	11 (6)	1 (1)	17 (12)	2 (1)
Asthenia	7 (4)	0	25 (17)	3 (2)
Leukopenia	7 (4)	1 (1)	15 (10)	5 (3)

* Adverse events are reported for those with an onset, or those that had worsened, on or after the date of the first trial dose, up to and including 35 days after the date of the administration of the last trial dose or up to the day before the start of a subsequent anticancer treatment, whichever was first. Patients with multiple events in the same category were counted once per category regardless of the number of occurrences. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 29.0. Adverse events occurring in at least 10% of the patients in any group are listed in descending order of frequency in the osimertinib–savolitinib group.

inhibitors,^{35,36} and anemia and diarrhea are commonly associated with EGFR-TKIs.⁵⁻⁷ Treatment discontinuation rates were low and in line with previous trials of combination therapies with EGFR-TKIs and MET-TKIs.^{18,23,37,38}

Fatal adverse events were more common in the osimertinib–savolitinib group than in the platinum–pemetrexed group. Treatment exposure was approximately twice as long in the osimertinib–savolitinib group as in the platinum–pemetrexed group, which reflects, in part, the possibility for patients in the osimertinib–savolitinib group to continue treatment beyond disease progression. Indeed, of the 12 patients in the osimertinib–savolitinib group who had fatal adverse events, 9 had documented disease progression before death or had disease progression or NSCLC cited as a primary or secondary cause of death. Osimertinib–savolitinib appears to have a favorable safety profile as compared with available and investigational therapies, including amivantamab–chemotherapy, sacituzumab tirumotecan, and datopotamab deruxtecan.²⁵⁻²⁷ In the MARIPOSA-2 trial, amivantamab–chemotherapy was associated with hematologic, EGFR- and MET-related, dermatologic, and infusion-related adverse events.²⁷ In the OptiTROP-Lung04 trial, sacituzumab tirumotecan was predominantly associated with hematologic events, alopecia, and stomatitis.²⁵ In the pooled analysis of the TROPION-Lung05 and TROPION-Lung01 trials, the most common adverse events with datopotamab deruxtecan were stomatitis, alopecia, and nausea.²⁶

Results from this trial support osimertinib–savolitinib as an effective biomarker-directed treatment regimen that can extend the duration of oral therapy while preserving intravenous or subcutaneous options for subsequent lines of therapy. The prevalence of acquired *MET* amplification after therapy with osimertinib alone or after osimertinib with chemotherapy was similar,³¹ which suggests a possible benefit of osimertinib–savolitinib in both treatment settings. The SAFFRON trial also builds on evidence for continuing osimertinib therapy beyond disease progression; in the COMPEL trial, continuation of osimertinib with the addition of chemotherapy was associated with longer progression-free survival than chemotherapy alone in *EGFR*-mutated advanced NSCLC after progression during first-line osimertinib.²⁴ These data reinforce osimertinib as backbone treatment

and a biomarker-directed, oral combination treatment option through lines of therapy for *EGFR*-mutated advanced NSCLC.

SAFFRON is an open-label trial; therefore, the results should be interpreted in the context of possible systematic bias related to knowledge of treatment assignment.³⁹ More patients assigned to receive platinum–pemetrexed than those assigned to receive osimertinib–savolitinib did not begin treatment, which may reflect a preference for a chemotherapy-free regimen. However, the risk of bias was limited by keeping the sponsor unaware of the treatment assignments and through the use of blinded independent central review and a central randomization system.

In this trial, osimertinib–savolitinib led to significantly longer progression-free and overall survival than platinum–pemetrexed among patients with *EGFR*-mutated locally advanced or metastatic NSCLC with *MET* overexpression, *MET* amplification, or both after disease progression during osimertinib therapy. Together, *MET* overexpression and *MET* amplification are among the most common alterations after disease progression on osimertinib,⁸⁻¹³ which highlights the need for routine tissue rebiopsy and *MET* testing in the event of progression to identify patients who may benefit from biomarker-directed treatment.

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