ASP PALERMO
AZIENDA SANITARIA PROVINCIALE

Concorso pubblico, per titoli ed esami, per la copertura di n. 4 posti a tempo pieno ed indeterminato di Dirigente Medico di Oncologia

Prova ORALE

VERBALE N. 5 DEL 27 LUGLIO 2023

L'anno duemilaventitre, il giorno 27 del mese di luglio alle ore 9,00 presso i locali della Direzione Generale Aziendale dell'ASP di Palermo, via G. Cusmano, 24 Palermo 2 piano, si è riunita la Commissione esaminatrice del concorso pubblico, per titoli ed esami, per la copertura di n. 1 posto a tempo pieno e indeterminato di Dirigente Medico di Oncologia, nominata con Deliberazione n. 188 del 16/02/2023, per procedere all'espletamento della prova orale.

La Commissione presente risulta così composta:
- Presidente: Dott.ssa Termini Rosanna Direttore Medico presso U.O.C. Geriatria P.O. G.F. Ingrassia presso ASP di Palermo;
- Componente: Dott. Paolo Tralongo Direttore U.O.C. Oncologia presso Ospedale Umberto I Siracusa presso ASP Siracusa;
- Componente: Dott. Stefano Vitello Direttore U.O.C. Oncologia Medica presso P.O. S. Elia (CL) presso ASP di Caltanissetta;
- Segretario: Dr.ssa Giglio Fabiola, Collaboratore Amministrativo Professionale in servizio presso il Dipartimento Risorse Umane c/o ASP Palermo.

Il Presidente, constatata la regolare costituzione della Commissione, essendo presenti tutti i componenti e il segretario, dichiara aperti i lavori.

Il Segretario dichiara di aver provveduto a convocare a mezzo pec tutti i 7 (sette) candidati che sono stati ammessi alla prova orale, dopo avere fatto visionare le note di trasmissione al Presidente e ai Componenti, indica nel presente verbale le note di seguito descritte:

	Cognome	Nome	Nota protocollo
1.	CARUSO	PAOLO	ASP 246169/2023 del 26 luglio 2023
2.	CATARELLA	MARIA TERESA	ASP 246170/2023 del 26 luglio 2023
3.	CURABA	ANNABELLA	ASP 246171/2023 del 26 luglio 2023
4.	MARCHESE	ANTONELLA	ASP 246172/2023 del 26 luglio 2023
5.	SANTANELLI	GIULIA	ASP 246173/2023 del 26 luglio 2023
6.	SCIUME'	CALOGERO	ASP 246174/2023 del 26 luglio 2023
7.	VACCARO	GIOVANNI IGNAZIO	ASP 246175/2023 del 26 luglio 2023

Il Segretario procede all'appello dei candidati e li fa firmare nel foglio presenza (Allegato A).
Sono le ore 9,10 la Commissione procede all'individuazione delle domande per la prova orale cui sottoporre i candidati che hanno superato la prova pratica.
La Commissione decide di far effettuare la prova orale predisponendo n. 8 quesiti numerati di pari difficoltà, come da "Allegato B", parte integrante del presente verbale.
Vengono quindi predisposti n. 8 quesiti che vengono ripiegati ed inseriti in un'unica busta.
I candidati sceglieranno all'interno della busta 1 quesito.
I quesiti estratti non saranno riproposti.
All'unanimità la Commissione decide che per candidato sarà formulata n. 1 domanda.
Alle ore 9,30 i candidati vengono ammessi nei locali degli esami.
I colloqui avvengono in aula aperta al pubblico.
Il presidente precisa ai candidati le modalità di estrazione delle domande e specifica che saranno chiamati a partire dalla Lettera estratta che è la S.
La Commissione procede a comunicare ai candidati i criteri di valutazione della prova orale ribadendo che la stessa verterà su materie inerenti alla disciplina a concorso.
Quanto ai criteri di valutazione saranno articolati sempre nel rispetto del punteggio previsto dall'avviso e dalla normativa che va da 14 a 20 punti ed in particolare, viene specificato che la valutazione, verterà secondo i criteri definiti e trascritti nel verbale n. 1 di giorno 29 GIUGNO 2023 cui si rimanda e che terranno conto:

a) della pertinenza cui sarà attribuito un punteggio da 0 a 7;
b) della completezza cui sarà attribuito un punteggio da 0 a 7;
c) della correttezza del linguaggio cui sarà assegnato un punteggio da 0 - 6.

Per ciò che riguarda l'inglese e l'informatica, le stesse saranno valutate sotto forma di idoneità senza attribuzione di relativo punteggio.
Per ciò che riguarda l'informatica, sono stati individuati 8 quesiti indicati al presente verbale (Allegato C). Il candidato dovrà rispondere alla domanda estratta.
E' stato individuato 1 brano in inglese indicato al presente verbale, si tratta di una rivista scientifica "The New England Journal of Medicine"(Allegato D).
Ai candidati sarà chiesto di leggere e tradurre una frase in inglese dell'articolo.
I quesiti estratti non saranno riproposti.
Vengono predisposte n.2 buste, ognuno con l'indicazione dell'Area (Oncologia e Informatica) e vengono inseriti rispettivamente nelle suddette buste i quesiti.
Alle ore 9,32 i candidati che hanno superato la prova pratica sono invitati ad iniziare la prova orale.
Il presidente precisa ai candidati che saranno chiamati in base alla Lettera estratta che è la S.
La prova orale si apre alle ore 9,35 con il primo candidato.

Alle ore 9,35 la **Dr.ssa Santanelli Giulia:**
estrae la domanda n. 5 dal titolo "L'aumento della sopravvivenza dei tumori ha portato all'evidenza di nuovi bisogni: quali e come intervenire".
Con riferimento alla materia di informatica, sorteggia la domanda n.2 "AL FINE DI CREARE UNA PASSWORD IL PIÙ POSSIBILE SICURA QUALE CRITERIO È CONSIGLIABILE USARE ?"
Il Presidente chiede al candidato di leggere e tradurre la frase in inglese della rivista scientifica The New England Journal of Medicine.

Alle ore 9,50 il **Dr. Sciumè Calogero:**
estrae la domanda n. 2 dal titolo "Come può la collaborazione funzionale tra ospedale e territorio migliorare la performance in campo oncologico".
Con riferimento alla materia di informatica, sorteggia la domanda n.4 "AVENDO APERTO UN DOCUMENTO COL PROGRAMMA DI VIDEOSCRITTURA MICROSOFT WORD, È POSSIBILE SUDDIVIDERE LO SCHERMO AL FINE DI VISUALIZZARNE DUE PARTI?"
Il Presidente chiede al candidato di leggere e tradurre la frase in inglese della rivista.

Alle ore 10,05 il **Dr. Vaccaro Giovanni Ignazio:**
estrae la domanda n. 6 dal titolo "La terapia antalgica nei pazienti oncologici"
Con riferimento alla materia di informatica, sorteggia la domanda n. 5 "CHE COSA OCCORRE FARE SE SI SOSPETTA CHE LA PROPRIA PASSWORD SIA DI PUBBLICA CONOSCENZA?"
Il Presidente chiede al candidato di leggere e tradurre la frase in inglese della rivista.

Alle ore 10,20 il **Dr. Caruso Paolo:**
estrae la domanda n. 4 dal titolo "L'immunoterapia: meccanismo d'azione, impiego e tossicità"
Con riferimento alla materia di informatica, sorteggia la domanda n. 7 "WRITER, CALC E BASE FANNO PARTE DEI PROGRAMMI?"
Il Presidente chiede al candidato di leggere e tradurre la frase in inglese della rivista.

Alle ore 10,35 la **Dr.ssa Catarella Maria Teresa:**
estrae la domanda n. 8 dal titolo "La *fatigue* nel paziente oncologico"
Con riferimento alla materia di informatica, sorteggia la domanda n.6 "WORD PER WINDOWS PERMETTE DI MODIFICARE LE "IMPOSTAZIONI DI PAGINA". IN CHE COSA CONSISTE TALE OPERAZIONE?"
Il Presidente chiede al candidato di leggere e tradurre la frase in inglese della rivista.

Alle ore 10,50 la **Dr.ssa Curaba Annabella:**
estrae la domanda n.1 dal titolo "Approccio al paziente geriatrico oncologico"
Con riferimento alla materia di informatica, sorteggia la domanda n.3: "ATTRAVERSO LA POSTA ELETTRONICA, È POSSIBILE INVIARE UN DOCUMENTO WORD?"
Il Presidente chiede al candidato di leggere e tradurre la frase in inglese della rivista .

Alle ore 11,05 la **Dr.ssa Marchese Antonella:**
estrae la domanda n.7 dal titolo "Ruolo del PDTA nella gestione della malattia oncologica"
Con riferimento alla materia di informatica, sorteggia la domanda n.8 " IN WORD, SE SI VUOLE INSERIRE UN'INTERRUZIONE DI PAGINA ALL'INTERNO DI UN DOCUMENTO, DOPO AVER POSIZIONATO IL CURSORE NEL PUNTO IN CUI SI VUOLE INSERIRE L'INTERRUZIONE DI PAGINA BISOGNA".
Il Presidente chiede al candidato di leggere e tradurre la frase in inglese della rivista.

Alle ore 11,10 la Commissione congeda i candidati.
Alle ore 11,15 la Commissione si riunisce per stabilire i punteggi attribuibili ai candidati della prova orale e attribuisce:

Alla Dr.ssa Santanelli Giulia il punteggio pari a 16/20;
Al Dr. Sciumè Calogero il punteggio pari a 16/20;
Al Dr. Vaccaro Giovanni Ignazio il punteggio pari a 15/20;
Al Dr. Caruso Paolo il punteggio pari a 17/20;
Alla Dr.ssa Catarella Maria Teresa il punteggio pari a 16/20.
Alla Dr.ssa Curaba Annabella il punteggio pari a 17/20;
Alla Dr.ssa Marchese Antonella il punteggio pari a 16/20.

La Commissione accede alla piattaforma informatica ove vengono caricati i punteggi della prova pratica ed orale.
Viene stilata la graduatoria composta dai candidati che hanno superato la prova parte integrante del presente verbale con il relativo punteggio (Allegato "E") e tale elenco viene affisso.
La Commissione dichiara conclusi i lavori, delegando il Segretario alla trasmissione degli atti relativi al concorso in argomento al Dipartimento Risorse Umane per i successivi adempimenti di competenza.
Alle ore 12,30 si concludono i lavori della Commissione.
Del che si redige il presente verbale composto da numero 4 (QUATTRO) pagine che, letto e confermato, viene sottoscritto come segue:

Dr.ssa Rosanna Termini	Presidente	
Dott. Paolo Tralongo	Componente	
Dott. Stefano Vitello	Componente	
Dott.ssa Fabiola Giglio	Segretario	

Allegato _____A_____

ASP PALERMO

REPORT PARTECIPANTI AVVISO DI CONCORSO PUBBLICO, PER TITOLI ED ESAMI, PER LA COPERTURA A TEMPO PIENO E INDETERMINATO DI N. 1 POSTI DI DIRIGENTE MEDICO DI ONCOLOGIA

Allegato

FOGLIO PRESENZA DEI CANDIDATI ALLA PROVA ORALE DI GIORNO 27 Luglio 2023

	Cognome	Nome	Codice Fiscale	Data Nascita	Documento di Identità	Firma del candidato
1	CARUSO	PAOLO				
2	CATARELLA	MARIA TERESA				
3	CURABA	ANNABELLA				
4	MARCHESE	ANTONELLA				
5	SANTANELLI	GIULIA				
6	SCIUME	CALOGERO				
7	VACCARO	GIOVANNI IGNAZIO				

Allegato B

Azienda Sanitaria Provinciale di Palermo

Commissione esaminatrice concorso pubblico, per titoli ed esami, per la copertura di n. 1 posto a tempo pieno ed indeterminato di Dirigente Medico di Oncologia

DOMANDE PER PROVA ORALE
27 Luglio 2023

1. Approccio al paziente geriatrico oncologico
2. Come può la collaborazione funzionale tra ospedale e territorio migliorare la performance in campo oncologico
3. Preservazione della fertilità nel paziente oncologico
4. L'immunoterapia: meccanismo d'azione, impiego e tossicità
5. L'aumento della sopravvivenza dei tumori ha portato all'evidenza di nuovi bisogni: quali e come intervenire
6. La terapia antalgica nei pazienti oncologici
7. Ruolo del PDTA nella gestione della malattia oncologica
8. La *fatigue* nel paziente oncologico

Regione Siciliana

Azienda Sanitaria Provinciale di Palermo

Commissione esaminatrice concorso pubblico, per titoli ed esami, per la copertura di n. 1 posto a tempo pieno e indeterminato di Dirigente Medico di Oncologia

QUESITI PROVA D'INFORMATICA – GIORNO 27 Luglio 2023

Allegato ___C___

1) COME DEVE ESSERE COMPOSTA UNA PASSWORD PERCHÉ GARANTISCA LA MASSIMA SICUREZZA?

2) AL FINE DI CREARE UNA PASSWORD IL PIÙ POSSIBILE SICURA QUALE CRITERIO È CONSIGLIABILE USARE ?

3) ATTRAVERSO LA POSTA ELETTRONICA, È POSSIBILE INVIARE UN DOCUMENTO WORD?

4) AVENDO APERTO UN DOCUMENTO COL PROGRAMMA DI VIDEOSCRITTURA MICROSOFT WORD, È POSSIBILE SUDDIVIDERE LO SCHERMO AL FINE DI
VISUALIZZARNE DUE PARTI:?

5) CHE COSA OCCORRE FARE SE SI SOSPETTA CHE LA PROPRIA PASSWORD SIA DI PUBBLICA CONOSCENZA?

6) Word per Windows permette di modificare le "impostazioni di pagina".In che cosa consiste tale operazione?

7) Writer, Calc e Base fanno parte dei programmi:?

8) In Word, se si vuole inserire un'interruzione di pagina all'interno di un documento, dopo aver posizionato il cursore nel
punto in cui si vuole inserire l'interruzione di pagina bisogna:

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Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K.H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, and J.-C. Soria, for the FLAURA Investigators*

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ORIGINAL ARTICLE

Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K.H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, and J.-C. Soria, for the FLAURA Investigators*

ABSTRACT

BACKGROUND

Osimertinib is a third-generation, irreversible tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR-TKI) that selectively inhibits both EGFR-TKI–sensitizing and *EGFR* T790M resistance mutations. A phase 3 trial compared first-line osimertinib with other EGFR-TKIs in patients with *EGFR* mutation–positive advanced non–small-cell lung cancer (NSCLC). The trial showed longer progression-free survival with osimertinib than with the comparator EGFR-TKIs (hazard ratio for disease progression or death, 0.46). Data from the final analysis of overall survival have not been reported.

METHODS

In this trial, we randomly assigned 556 patients with previously untreated advanced NSCLC with an *EGFR* mutation (exon 19 deletion or L858R allele) in a 1:1 ratio to receive either osimertinib (80 mg once daily) or one of two other EGFR-TKIs (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily, with patients receiving these drugs combined in a single comparator group). Overall survival was a secondary end point.

RESULTS

The median overall survival was 38.6 months (95% confidence interval [CI], 34.5 to 41.8) in the osimertinib group and 31.8 months (95% CI, 26.6 to 36.0) in the comparator group (hazard ratio for death, 0.80; 95.05% CI, 0.64 to 1.00; P=0.046). At 3 years, 79 of 279 patients (28%) in the osimertinib group and 26 of 277 (9%) in the comparator group were continuing to receive a trial regimen; the median exposure was 20.7 months and 11.5 months, respectively. Adverse events of grade 3 or higher were reported in 42% of the patients in the osimertinib group and in 47% of those in the comparator group.

CONCLUSIONS

Among patients with previously untreated advanced NSCLC with an *EGFR* mutation, those who received osimertinib had longer overall survival than those who received a comparator EGFR-TKI. The safety profile for osimertinib was similar to that of the comparator EGFR-TKIs, despite a longer duration of exposure in the osimertinib group. (Funded by AstraZeneca; FLAURA ClinicalTrials.gov number, NCT02296125.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Ramalingam at the Winship Cancer Institute of Emory University, 1365 Clifton Rd., Atlanta, GA 30322, or at ssramal@emory.edu.

*A complete list of the investigators in the FLAURA trial is provided in the Supplementary Appendix, available at NEJM.org.

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RAMA_1

In patients with advanced or metastatic non–small-cell lung cancer (NSCLC) with mutations in the gene encoding epidermal growth factor receptor (*EGFR*) that are sensitive to tyrosine kinase inhibitors (TKIs) (exon 19 deletions or L858R point mutations), guidelines recommend treatment with an EGFR-TKI.[1-4] The clinical practice guidelines of the National Comprehensive Cancer Network recommend osimertinib as the preferred EGFR-TKI option for first-line treatment in such patients.[4]

Osimertinib is a third-generation, irreversible, oral EGFR-TKI that selectively inhibits both EGFR-TKI–sensitizing and *EGFR* p.Thr790Met (T790M) resistance mutations and has shown efficacy in patients with NSCLC who have central nervous system (CNS) metastases.[5-9] The FLAURA trial was a double-blind, phase 3 trial involving patients with previously untreated advanced NSCLC with *EGFR* mutations that compared the efficacy and safety of osimertinib with that of two other EGFR-TKIs, gefitinib or erlotinib (with both drugs included in the comparator group).[9]

The primary analysis (data cutoff on June 12, 2017) showed significantly longer progression-free survival with the osimertinib regimen than with the comparator regimen (median duration, 18.9 months vs. 10.2 months; hazard ratio for disease progression or death, 0.46; P<0.001). At the time of the primary analysis, overall survival data were immature (data maturity, 25%) but showed a trend toward longer overall survival with osimertinib (hazard ratio for death, 0.63; P=0.007).[9] The safety profile of osimertinib was similar to that of the comparator EGFR-TKIs, and the rates of serious adverse events were lower with osimertinib.[9] On the basis of these efficacy and safety data, the indication for osimertinib was extended to include first-line treatment in patients with advanced NSCLC whose tumors have sensitizing *EGFR* mutations.[10,11] Here, we report the results of the planned final analysis of overall survival.

METHODS

PATIENTS

Full details regarding the FLAURA trial have been published previously[9] and are provided in the trial protocol, available with the full text of this article at NEJM.org. In brief, eligible patients were 18 years of age or older (20 years or older in Japan), had locally advanced or metastatic NSCLC with an *EGFR* mutation (exon 19 deletion or L858R), had not previously received treatment for advanced disease, and were eligible to receive first-line treatment with gefitinib or erlotinib. Patients with known or suspected CNS metastases were eligible to participate if their condition was neurologically stable.

TRIAL OVERSIGHT

The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference on Harmonisation), applicable regulatory requirements, and the policy on bioethics and human biologic samples of the trial sponsor, AstraZeneca. All the patients provided written informed consent.

The trial was funded by the sponsor and was designed by the principal investigators (first and last authors) and the sponsor. The sponsor was responsible for the collection and analysis of the data and had a role in data interpretation. All the authors had full access to all the data. The first draft of the manuscript was written by the first and last authors, with medical-writing support funded by the sponsor; all the authors reviewed the manuscript before it was submitted for publication. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol.

TRIAL DESIGN AND TREATMENT

In this double-blind, phase 3 trial, patients were stratified according to *EGFR* mutational status (exon 19 deletion or L858R) and race (Asian or non-Asian) and were randomly assigned in a 1:1 ratio to receive either oral osimertinib (at a dose of 80 mg once daily) or a comparator oral EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily) until disease progression, unacceptable toxicity, or withdrawal of consent. Patients in the comparator group (a combination of those who received either gefitinib or erlotinib) were eligible for crossover to open-label osimertinib after disease progression had been objectively confirmed on blinded independent central review (or by investigator assessment if disease progression occurred after the primary data cutoff) and after post-progression documentation of the presence of a T790M resistance mutation on local or central testing.

END POINT

Overall survival was a key secondary end point in the trial. According to the protocol, after the analysis of the primary end point of progression-free survival had been performed (data cutoff, June 12, 2017), central collection of progression events, defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, was stopped.

TRIAL ASSESSMENTS

After the primary data cutoff, tumor assessments were performed in accordance with clinical practice, and scans were no longer centrally collected. Assessments for survival were made every 6 weeks after objective disease progression up to the time of the final analysis of overall survival. Overall survival was defined as time from randomization until death from any cause. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

STATISTICAL ANALYSIS

The final analysis of overall survival was planned after approximately 318 deaths had occurred in the full analysis set. We used the Kaplan–Meier method with a log-rank test, stratified according to race (Asian vs. non-Asian) and mutational status (exon 19 deletion vs. L858R), to compare overall survival in the two groups; the Breslow approach was used to handle tied events. The hazard ratio and confidence interval were obtained directly from a stratified log-rank test.[12] Data from patients who had not died at the time of the analysis were censored on the basis of the last recorded date that the patient was known to be alive.

We calculated that the trial would have a power of 72% to determine a hazard ratio of less than 0.75 (indicating a longer duration of median overall survival, from 25.0 to 33.3 months) with a two-sided significance level of 0.05. The Lan–DeMets approach that approximates the O'Brien–Fleming spending function was used to maintain an overall two-sided 5% type I error rate across the interim and final analyses of overall survival. The P value that was observed at the interim analysis of overall survival was not significant. This finding did not preclude further planned testing of overall survival, and according to the Lan–DeMets approach, a two-sided P value of 0.0495 was considered to indicate statistical significance for the final analysis of overall survival. A 95.05% confidence interval for the final analysis of the hazard ratio for overall survival was calculated because of the remaining alpha of 0.0495 after the interim analysis. All other confidence intervals are reported as 95%, since all P values reported for overall survival are nominal and not part of the multiple-testing strategy. The data cutoff for the final analysis was June 25, 2019.

We used a Cox proportional-hazards model to analyze overall survival in predefined subgroups. There had to be at least 20 deaths in a subgroup for it to be included in the analysis. In the subgroup analysis, all hazard ratios and 95% confidence intervals were adjusted for trial group, subgroup, and a treatment-by-subgroup interaction term for each subgroup. Additional details regarding the statistical analysis are provided in the Supplementary Appendix, available at NEJM.org.

RESULTS

PATIENTS AND TREATMENT

From December 2014 through March 2016, a total of 556 patients underwent randomization (279 to receive osimertinib and 277 to receive a comparator EGFR-TKI) and received at least one dose of a trial drug. In the comparator group, 183 patients (66%) received gefitinib and 94 patients (34%) received erlotinib as their assigned treatment. The demographic characteristics of the patients at baseline have been reported previously.[9] The enrollment and outcomes in the two groups are presented in Figure S1 in the Supplementary Appendix.

At the time of the data cutoff, the median duration of treatment exposure was 20.7 months (range, 0.1 to 49.8) in the osimertinib group and 11.5 months (range, 0.0 to 50.6) in the comparator group. The number of patients who were continuing to receive the assigned trial drug at the time of the data cutoff was 61 (22%) in the osimertinib group and 13 (5%) in the comparator group.

EFFICACY

At the time of data cutoff, 321 deaths had occurred (58% maturity), representing the planned number of events and maturity. All the patients had the opportunity to have a follow-up of 39 months; the median duration of follow-up for overall survival was 35.8 months in the osimertinib group

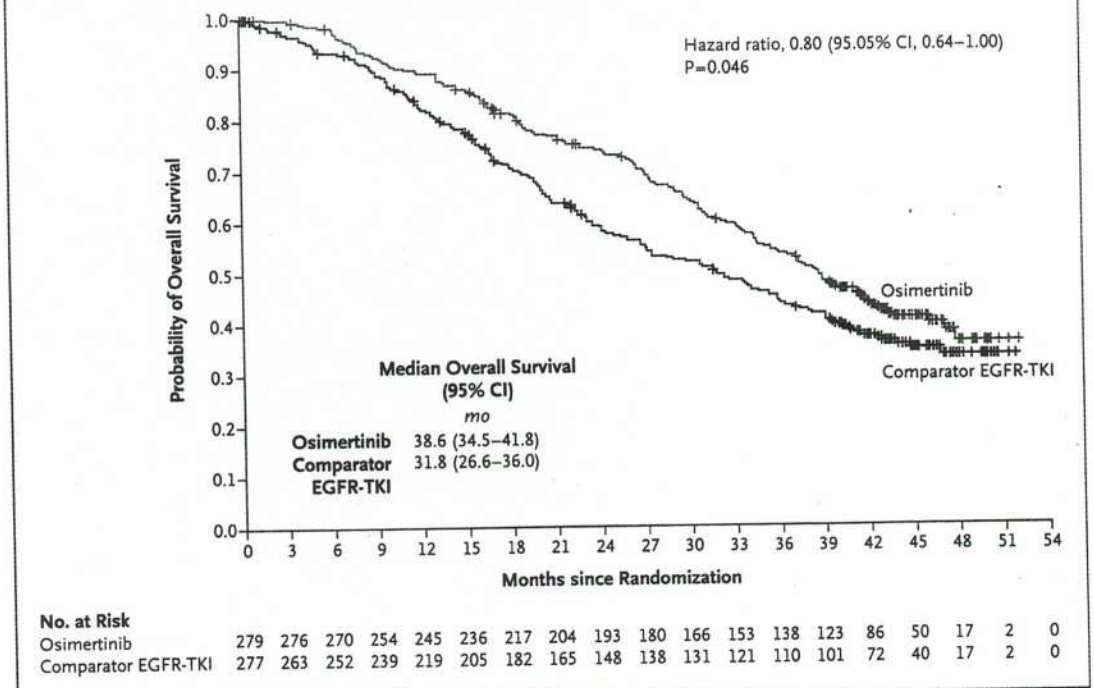

Figure 1. Overall Survival.

Shown is the Kaplan–Meier estimate of overall survival in the full analysis set. Censored data are indicated by tick marks. Data from patients who had not died at the time of the analysis were censored on the basis of the last recorded date on which the patient was known to be alive. CI denotes confidence interval, and EGFR-TKI tyrosine kinase inhibitor of epidermal growth factor receptor.

and 27.0 months in the comparator group. The median overall survival was 38.6 months (95% confidence interval [CI], 34.5 to 41.8) in the osimertinib group and 31.8 months (95% CI, 26.6 to 36.0) in the comparator group (hazard ratio for death, 0.80; 95.05% CI, 0.64 to 1.00; P=0.046) (Fig. 1). Survival rates and the number of patients continuing to receive the first-line trial drug were consistently higher in the osimertinib group than in the comparator group at months 12, 24, and 36 (Table 1).

Table 1. Overall Survival and Continuation of First-Line Trial Drug.*

Variable	Osimertinib (N=279)	Comparator EGFR-TKI (N=277)
Overall survival — % (95% CI)		
At 12 mo	89 (85–92)	83 (77–87)
At 24 mo	74 (69–79)	59 (53–65)
At 36 mo	54 (48–60)	44 (38–50)
Patients continuing to receive first-line trial drug — no. (%)		
At 12 mo	194 (70)	131 (47)
At 24 mo	118 (42)	45 (16)
At 36 mo	78 (28)	26 (9)

* In the comparator group, patients received one of two tyrosine kinase inhibitors of epidermal growth factor receptor (EGFR-TKI): gefitinib or erlotinib.

The overall survival benefit with osimertinib as compared with the comparator EGFR-TKIs was consistent across most predefined subgroups, with varying magnitude of benefit (Fig. 2). The confidence intervals were overlapping within and across all subgroups. The largest numerical between-group differences in the hazard ratios for overall survival were observed between Asian and non-Asian patients. The Kaplan–Meier estimates for the subgroup comparison between Asian and non-Asian patients and between mutational status (exon 19 deletion vs. L858R) are provided in Figure S2.

SUBSEQUENT THERAPIES

In total, 133 patients (48%) in the osimertinib group and 180 (65%) in the comparator group started a first subsequent anticancer therapy after

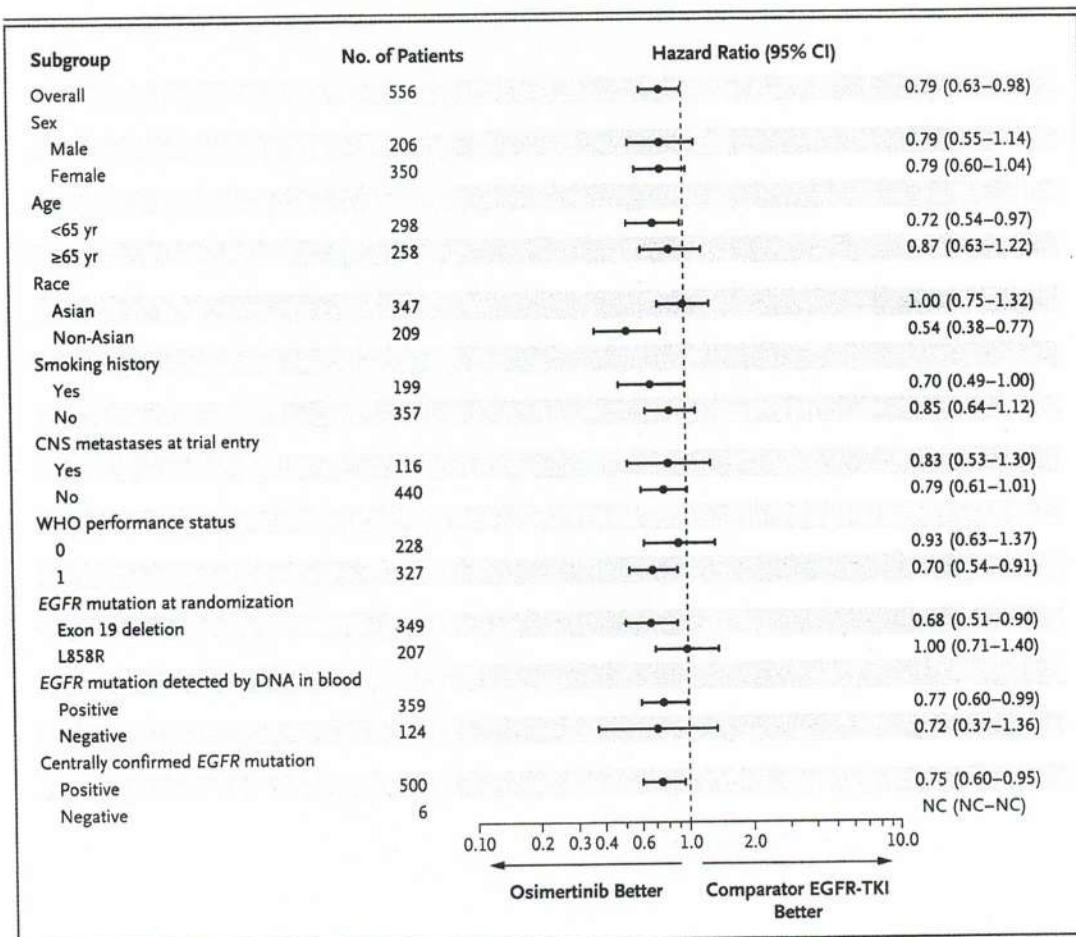

Figure 2. Subgroup Analyses of Overall Survival.

Shown is a forest plot of the subgroup analyses, which were performed with the use of a Cox proportional-hazards model that included the trial group, the subgroup covariate of interest, and the treatment-by-subgroup interaction. A hazard ratio of less than 1.00 indicates a lower risk of death with osimertinib than with the comparator EGFR-TKI. The overall population analyses were performed with the use of both a log-rank test stratified according to the *EGFR* mutational status and race and an unstratified Cox proportional-hazards model. The unstratified model was used to analyze the subgroups. If there were fewer than 20 events in a subgroup, the subgroup analysis was not performed. The *EGFR* mutational status at randomization was determined on local or central testing. Data were missing for 1 patient regarding World Health Organization (WHO) performance status and for 73 patients regarding the detection of the *EGFR* mutation in circulating tumor DNA. CNS denotes central nervous system, and NC could not be calculated.

the discontinuation of the assigned treatment. Of these patients, 85 of 180 (47%) in the comparator group received osimertinib as the first subsequent therapy (Fig. 3A); these patients made up 31% of the 277 who had been assigned to the comparator group. Among all the patients who underwent randomization, the number of those who received a second subsequent therapy was 72 of 279 (26%) in the osimertinib group and 92 of 277 (33%) in the comparator group. Among the patients who received a first subsequent therapy, the number of those who received a second subsequent therapy was 72 of 133 (54%) in the osimertinib group and 92 of 180 (51%) in the comparator group (Fig. 3B). (Additional data regarding the time until the first and second subsequent therapies or death and the subsequent therapies received are provided in the Results section in the Supplementary Appendix and in Fig. S3 and Tables S3 and S4.)

SAFETY

In the analysis of overall survival, the safety profile of osimertinib was consistent with the safety

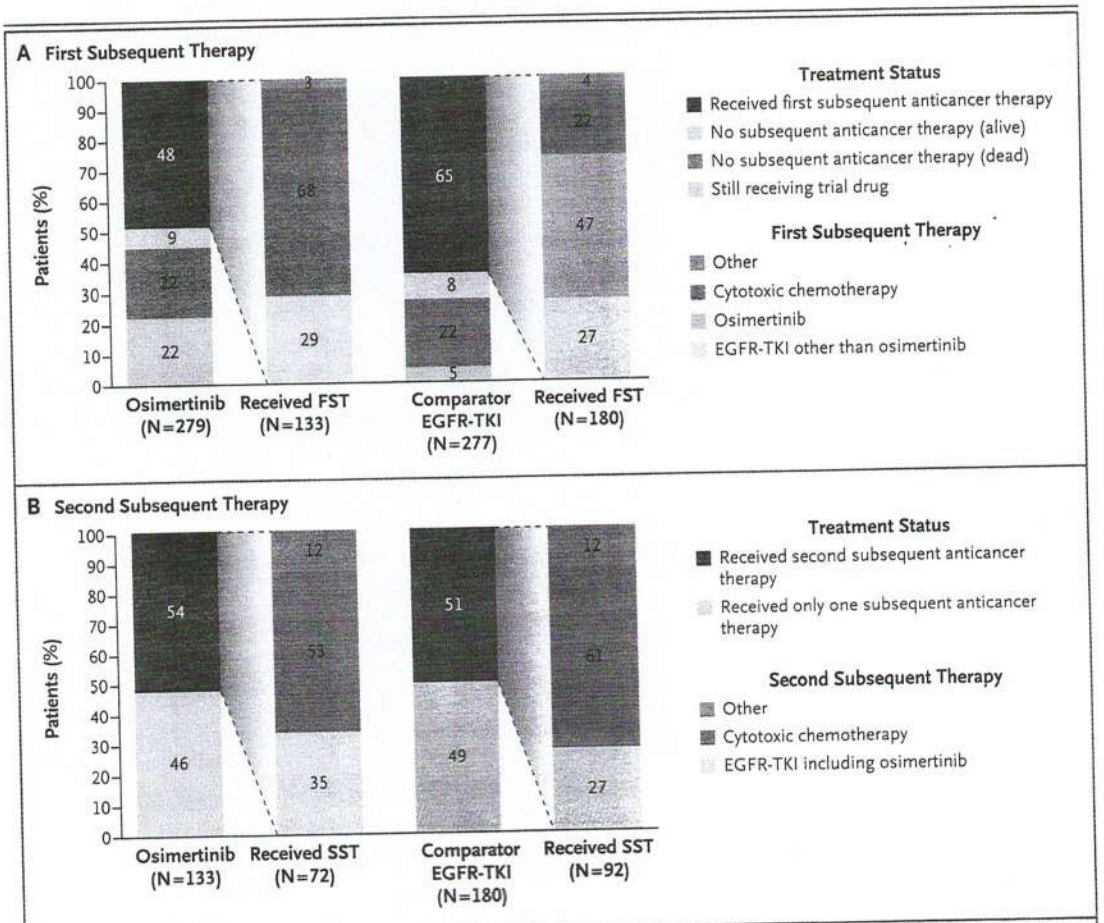

Figure 3. Summary of First and Second Subsequent Therapies Received.

Shown are bar plots illustrating the percentage of patients who received a first subsequent therapy (FST) (Panel A) and a second subsequent therapy (SST) (Panel B) after the discontinuation of their assigned treatment. The linked bar plot shows the type of therapy that the patients subsequently received. "Other" therapy refers to a treatment that did not include either chemotherapy or an EGFR-TKI. The majority of patients who underwent cytotoxic chemotherapy received a platinum-based chemotherapy regimen. Percentages may not total 100 because of rounding.

profile in the primary analysis. Overall, 98% of the patients in the two trial groups had at least one adverse event (Table 2). Adverse events that were deemed to be possibly related to the trial drug are listed in Table S5. Adverse events of grade 3 or higher were reported in 42% of the patients in the osimertinib group and in 47% of those in the comparator group (Table S6). Serious adverse events were reported in 27% of the patients in each trial group (Table S7). A decrease in the ejection fraction was reported in 13 patients (5%) in the osimertinib group and in 5 (2%) in the comparator group, with no associated symptoms reported. QT prolongation on electrocardiography was reported in 28 patients (10%) in the osimertinib group and in 12 patients (4%) in the comparator group. There were no new reports of interstitial lung disease, which was reported in 6 patients (2%) in the osimertinib group and in 4 (1%) in the comparator group, or of pneumonitis, which was reported in 5 (2%) and 2 (1%), respectively.[9]

Fatal adverse events were reported in 9 patients (3%) in the osimertinib group and in 10 (4%) in the comparator group. None of the deaths in the osimertinib group and 2 in the comparator group were deemed by investigators to be treatment-related.

In the osimertinib group, dose interruptions occurred in 120 patients (43%), dose reductions in 14 (5%), and permanent discontinuation of treatment because of adverse events in 41 (15%); in the comparator group, the corresponding num-

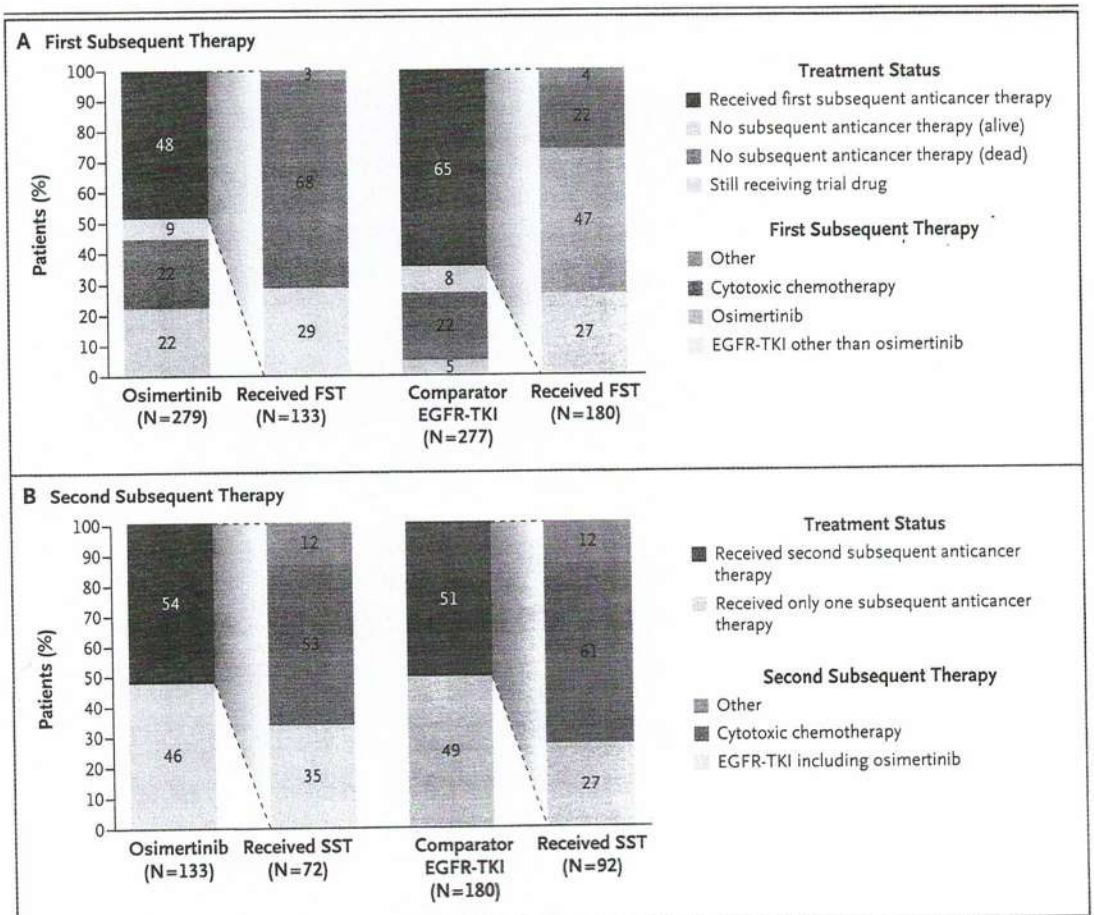

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Table 2. Adverse Events.*

Adverse Event	Osimertinib (N=279)				Comparator EGFR-TKI (N=277)			
	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
	number of patients (percent)							
Diarrhea	167 (60)	119 (43)	41 (15)	7 (3)	162 (58)	118 (43)	35 (13)	7 (3)
Rash or acne†	164 (59)	132 (47)	29 (10)	3 (1)	219 (79)	111 (40)	88 (32)	20 (7)
Nail effects†	108 (39)	61 (22)	45 (16)	2 (1)	95 (34)	58 (21)	35 (13)	2 (1)
Dry skin†	106 (38)	89 (32)	16 (6)	1 (<1)	102 (37)	78 (28)	21 (8)	3 (1)
Stomatitis	82 (29)	66 (24)	14 (5)	1 (<1)	60 (22)	51 (18)	8 (3)	1 (<1)
Decreased appetite	66 (24)	32 (11)	27 (10)	7 (3)	58 (21)	29 (10)	24 (9)	5 (2)
Cough	60 (22)	42 (15)	18 (6)	0	50 (18)	33 (12)	17 (6)	0
Nausea	55 (20)	37 (13)	18 (6)	0	55 (20)	31 (11)	23 (8)	0
Constipation	51 (18)	42 (15)	9 (3)	0	39 (14)	29 (10)	10 (4)	0
Pruritus	50 (18)	41 (15)	8 (3)	1 (<1)	44 (16)	30 (11)	14 (5)	0
Renal symptoms‡	50 (18)	32 (11)	13 (5)	3 (1)	32 (12)	24 (9)	7 (3)	1 (<1)
Fatigue	45 (16)	25 (9)	17 (6)	3 (1)	35 (13)	23 (8)	10 (4)	2 (1)
Anemia	44 (16)	22 (8)	15 (5)	7 (3)	27 (10)	19 (7)	5 (2)	3 (1)
Dyspnea	42 (15)	28 (10)	12 (4)	2 (1)	22 (8)	10 (4)	9 (3)	3 (1)
Vomiting	41 (15)	32 (11)	9 (3)	0	32 (12)	24 (9)	4 (1)	4 (1)
Headache	39 (14)	29 (10)	8 (3)	2 (1)	25 (9)	17 (6)	8 (3)	0
Back pain	36 (13)	22 (8)	14 (5)	0	29 (10)	15 (5)	14 (5)	0
Upper respiratory tract infection	36 (13)	20 (7)	16 (6)	0	23 (8)	12 (4)	11 (4)	0
Pyrexia	32 (11)	28 (10)	4 (1)	0	12 (4)	9 (3)	2 (1)	1 (<1)
Insomnia	31 (11)	23 (8)	8 (3)	0	21 (8)	12 (4)	9 (3)	0
Nasopharyngitis	31 (11)	17 (6)	14 (5)	0	16 (6)	11 (4)	5 (2)	0
Prolonged QT interval	28 (10)	12 (4)	12 (4)	4 (1)	12 (4)	7 (3)	3 (1)	2 (1)
Increase in aspartate aminotransferase	28 (10)	19 (7)	7 (3)	2 (1)	69 (25)	39 (14)	18 (6)	12 (4)
Musculoskeletal pain	28 (10)	19 (7)	9 (3)	0	14 (5)	8 (3)	6 (2)	0
Alopecia	22 (8)	18 (6)	4 (1)	0	35 (13)	31 (11)	4 (1)	0
Increase in alanine aminotransferase	19 (7)	11 (4)	6 (2)	2 (1)	74 (27)	30 (11)	19 (7)	21 (8)

* Listed are adverse events that were reported in at least 10% of the patients in either trial group. The safety analyses included all the patients who had received at least one dose of a trial drug (safety analysis set). Some patients had more than one adverse event. In the osimertinib group, the only grade 4 adverse events were stomatitis and renal symptoms (1 patient each); the only grade 5 adverse event was renal symptoms (1 patient). In the comparator group, the only grade 4 adverse event was an increase in the alanine aminotransferase level (4 patients); the only grade 5 adverse event was diarrhea (1 patient). In the comparator group, 1 patient had an adverse event of diarrhea of unknown grade, and 1 patient had an adverse event of nausea of unknown grade.

† This category is a grouped term.

‡ The most common renal adverse events in the two trial groups were an increase in the blood creatinine level, acute kidney injury, proteinuria, dysuria, and hematuria.

bers were 113 (41%), 10 (4%), and 50 (18%). (Additional details regarding adverse events are provided in the Results section in the Supplementary Appendix.)

DISCUSSION

In the FLAURA trial, a double-blind, randomized phase 3 trial involving untreated patients with

Table 2. Adverse Events.*

Adverse Event	Osimertinib (N=279)				Comparator EGFR-TKI (N=277)			
	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
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Nail effects†	108 (39)	61 (22)	45 (16)	2 (1)	95 (34)	58 (21)	35 (13)	2 (1)
Dry skin†	106 (38)	89 (32)	16 (6)	1 (<1)	102 (37)	78 (28)	21 (8)	3 (1)
Stomatitis	82 (29)	66 (24)	14 (5)	1 (<1)	60 (22)	51 (18)	8 (3)	1 (<1)
Decreased appetite	66 (24)	32 (11)	27 (10)	7 (3)	58 (21)	29 (10)	24 (9)	5 (2)
Cough	60 (22)	42 (15)	18 (6)	0	50 (18)	33 (12)	17 (6)	0
Nausea	55 (20)	37 (13)	18 (6)	0	55 (20)	31 (11)	23 (8)	0
Constipation	51 (18)	42 (15)	9 (3)	0	39 (14)	29 (10)	10 (4)	0
Pruritus	50 (18)	41 (15)	8 (3)	1 (<1)	44 (16)	30 (11)	14 (5)	0
Renal symptoms‡	50 (18)	32 (11)	13 (5)	3 (1)	32 (12)	24 (9)	7 (3)	1 (<1)
Fatigue	45 (16)	25 (9)	17 (6)	3 (1)	35 (13)	23 (8)	10 (4)	2 (1)
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