*The Oncologist*, 2022, **27**, 903–e834
https://doi.org/10.1093/oncolo/oyac193
Advance access publication 1 October 2022
**Clinical Trial Results**

# A Phase II Trial on Osimertinib as a First-Line Treatment for *EGFR* Mutation-Positive Advanced NSCLC in Elderly Patients: The SPIRAL-0 Study

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## Abstract

**Background:** Osimertinib is one of the standard first-line treatments for advanced non-small cell lung cancer in patients with epidermal growth factor receptor (*EGFR*) mutations, because it achieves significantly longer progression-free survival (PFS) than conventional first-line treatments (hazard ratio: 0.46). However, the efficacy and safety of osimertinib as a first-line treatment for patients aged ≥75 years remain unclear.

**Methods:** This phase II study was performed to prospectively investigate the efficacy and safety of osimertinib for elderly patients with *EGFR* mutation-positive advanced non-small cell lung cancer. The primary endpoint was 1-year PFS rate; secondary endpoints were overall response rate (ORR), PFS, overall survival (OS), and safety.

**Results:** Thirty-eight patients were included in the analysis. The 1-year PFS rate was 59.4% (95% confidence interval [CI], 46.1%-72.7%), which did not meet the primary endpoint (the threshold 1-year PFS rate of 50% predicted using data from the NEJ003 study). The most common grade 3/4 adverse events were rash/dermatitis acneiform/ALT increased/hypokalemia (2 patients, 5%). Seven patients developed pneumonitis (17.5%). There were no other cases of treatment discontinuation due to adverse events other than pneumonitis.

**Conclusion:** Although this study did not meet the primary endpoint, osimertinib was tolerable for elderly patients with EGFR mutation-positive advanced non-small cell lung cancer. (Japan Registry of Clinical Trials [JRCT] ID number: jRCTs071180007).

**Key words:** non-small cell lung cancer; EGFR-TKI; osimertinib; elderly patients.

Received: 8 April 2022; Accepted: 23 August 2022.

### Lessons Learned

- This phase II study was performed to prospectively investigate the efficacy and safety of osimertinib for elderly patients with *EGFR* mutation-positive advanced non-small cell lung cancer (NSCLC).
- The 1-year progression-free survival (PFS) rate was 59.4% (95%CI 46.1-72.7), which did not meet the primary endpoint (the lower CI meeting a threshold 1-year PFS rate of 50%).
- Osimertinib is expected to be tolerable for elderly patients with *EGFR* mutation-positive advanced NSCLC.

## Discussion

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have become the first-line treatment for *EGFR* mutation-positive non-small cell lung cancer (NSCLC). Several EGFR-TKIs have been approved for the treatment of inoperable or postoperative recurrent *EGFR* mutation-positive NSCLC. In a meta-analysis of 6 eligible trials (gefitinib = 3, erlotinib = 3) including 1231 patients, 632 received EGFR-TKI and 599 received chemotherapy, median progression-free survival (PFS) was 11 months in treatment-naïve patients versus 5.6 months in the chemotherapy group (Fig. 1).[1]

Osimertinib is a third-generation EGFR-TKI with potent inhibitory effects not only for EGFR-TKI sensitizing mutations, but also for the T790M resistance *EGFR* mutation. It achieved significantly longer PFS (18.9 months) than EGFR-TKIs (10.2 months) in the FLAURA study (hazard ratio [HR]: 0.46).[2] Based on these findings, osimertinib has been approved as one of the standard first-line treatments for *EGFR* mutation-positive NSCLC.

The number of elderly patients with lung cancer is increasing.[3] In Japan, 45,000 patients aged ≥75 years were estimated to have died of lung cancer in 2016.[4] Osimertinib exhibits strong tyrosine kinase inhibitory activity by targeting the EGFR-TKI sensitizing mutations and the EGFR T790M, EGFR-TKI resistance mutation, but rarely suppresses the tyrosine kinase activity of wild-type EGFR.[5] As a consequence, osimertinib may be superior in activity and in terms of toxicity compared with conventional EGFR-TKIs with lower selectivity. In the FLAURA study, adverse events (AEs) of grade 3 or higher were less frequent with osimertinib than with standard EGFR-TKIs (34% vs. 45%). We hypothesized that osimertinib may be safer for elderly patients with *EGFR* mutation-positive lung cancer than conventional EGFR-TKIs. A subset analysis of patients aged ≥65 years was performed in the FLAURA study; however, the efficacy and safety of osimertinib for patients aged ≥75 years with *EGFR* mutation-positive NSCLC currently remains unclear. We herein performed a phase II study to investigate the efficacy and safety of osimertinib as a first-line treatment for elderly Japanese patients (≥75 years) with *EGFR* mutation-positive advanced NSCLC.

In the present study, the 1-year PFS rate was 59.4%, which did not meet the primary endpoint based on the lower bound of the CI. However, the incidence of the most common AEs of grade 3 or higher was 5%. Other than pneumonitis, there were no cases of treatment discontinuation due to AEs. Although pneumonitis occurred more frequently than other AEs, all patients recovered after appropriate therapy. The present study suggests that osimertinib is tolerable and has potential as a first-line treatment for elderly patients with *EGFR* mutation-positive advanced NSCLC.

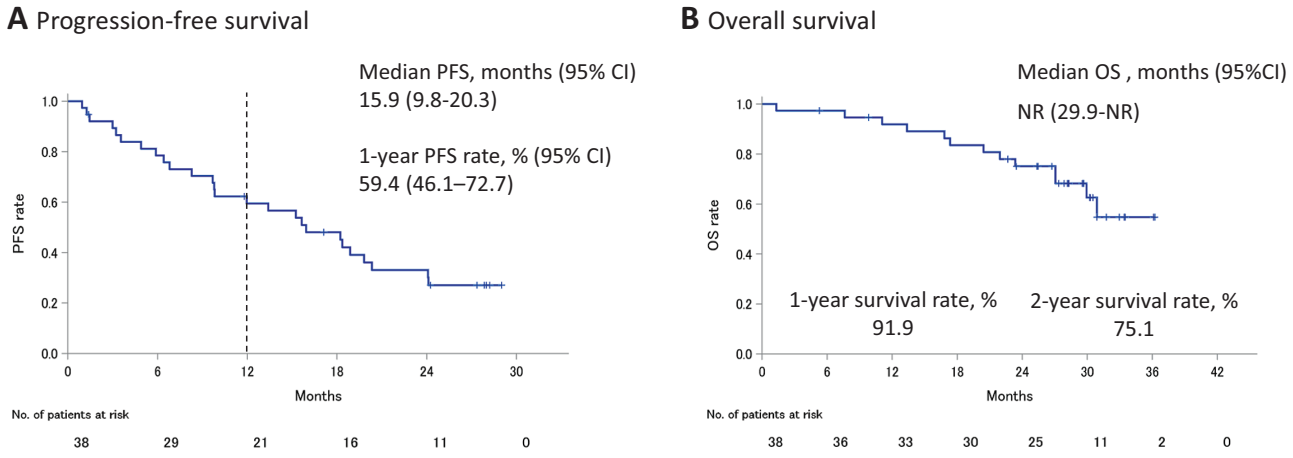


**Figure 1.** Kaplan-Meier plot. (**A**) Kaplan-Meier survival curves for PFS. (**B**) Kaplan-Meier survival curves for OS. Abbreviations: PFS, progression-free survival; CI, confidence interval; OS, overall survival; NR, not reached.

| Trial Information | |
|---|---|
| Disease | Lung cancer—NSCLC |
| Stage of disease/treatment | Metastatic/advanced |
| Prior therapy | None |
| Type of study | Phase II, single arm |
| Primary endpoint | 1-year PFS rate |
| Secondary endpoints | Overall response rate, PFS, overall survival, safety |
| Investigator's analysis | Correlative endpoints not met but clinical activity observed |

## Additional Details of Endpoints or Study Design

### Inclusion Criteria

Inclusion criteria were as follows: (a) age ≥75 years at the time of providing informed consent; (b) histologically or cytologically confirmed NSCLC; (c) patients with inoperable or postoperative recurrent stage IIIB/IIIC or IV NSCLC; (d) an EGFR mutation (the exon 19 deletion, L858R point mutation) associated with EGFR-TKI sensitivity; (e) treatment-naïve patients (preoperative and/or postoperative treatment is permitted); (f) patients capable of receiving oral drugs; (g) patients with at least one measurable lesion according to the RECIST v1.1 criteria; (h) an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; (i) patients with normal major organ functions (including bone marrow, hepatic, and renal functions) and who satisfy the following criteria in a test conducted within 2 weeks prior to registration (white blood cell count ≥3000 to ≤12 000/$mm^3$, neutrophil count ≥1500/$mm^3$, platelet count ≥100 000/$mm^3$, hemoglobin ≥9.0 g/dL, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤100 IU/L, total bilirubin ≤1.5 mg/dL, creatinine ≤2.0 mg/dL, or $SpO_2$ [room air] ≥90%); (j) patients expected to survive for at least 3 months; (k) patients who completed wash-out periods for previous treatments of at least the following duration as of the treatment initiation date (registration was allowed on and after the same day of the week as the day after the following periods): chemotherapy (preoperative/postoperative adjuvant chemotherapy), longer than 4 weeks after the last administration date; definitive thoracic radiotherapy, longer than 12 weeks after the last radiation date; surgery/intervention (inclusive of thoracic drainage), longer than 4 weeks after the last surgery/intervention date; (l) patients who provided written informed consent by their own free will.

### Exclusion Criteria

Exclusion criteria were as follows: (a) complications of pulmonary disorders, such as idiopathic pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, active radiation pneumonitis, and drug-induced pneumonia; (b) patients receiving (or unable to discontinue by the time the protocol treatment was scheduled to start) a CYP3A4 inhibitor treatment (for not less than 1 week) and/or any drugs/herbal supplements that function as an inducer of CYP3A4 (for not less than 3 weeks); (c) complications of infectious diseases requiring the intravenous administration of antibacterial or antifungal agents; (d) patients with any of the following QTc-prolongation risks: a mean corrected QT interval at rest of >470 ms (Fridericia's correction: QTc); clinically important abnormalities (such as a complete left bundle branch block, third-degree heart block, and second-degree heart block) in the rhythm, conduction, or waveform of electrocardiograms at rest; any factors that increase the risk of QTc prolongation or arrhythmia (including cardiac failure, hypokalemia, long QT syndrome congenital, a family history of long QT syndrome or unexplained sudden death in first-degree relatives ≤40 years, or any concomitant drug that is known to prolong the QT interval); (e) pregnant, lactating, or possibly pregnant women; (f) active multiple primary cancers (synchronous multiple cancers or asynchronous multiple cancers with a cancer-free period of not more than 5 years; however, lesions such as carcinoma *in situ* and intramucosal carcinoma deemed to be cured by local treatment were not included as active multiple cancers); (g) symptomatic brain metastasis; (h) uncontrolled diabetes mellitus; (i) clinically important complications (such as uncontrolled heart disease, severe arrhythmia in need of medication, and persistent watery diarrhea); (j) judged as ineligible to participate in this study by the investigator.

### Endpoint

The primary endpoint was the 1-year PFS rate. Secondary endpoints were the overall response rate (ORR), PFS, overall survival (OS), and safety.

### Statistical Analysis

The 1-year PFS rate and its 2-sided 95% CI were calculated using Wilson's method. Effectiveness was regarded as the lower limit of the estimated CI exceeding the threshold 50% PFS at 1 year. ORR and its 2-sided 95% CI were calculated (Wilson's method). The Kaplan-Meier method was used to evaluate survival curves for PFS and OS as well as medians and annual values. The Brookmeyer and Crowley method was used to estimate CI for median values, and Greenwood's formula to estimate the standard error for annual values.

### Ethics

The present study was conducted in accordance with ethical principles originating in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the Ethical Guidelines for Medical and Health Research Involving Human Subjects (December 22, 2014), and the Ethical Guidelines for Human Genome/Gene Analysis Research (March 29, 2001). This study received ethical approval from the Certified Review Board of the Clinical Research Network Fukuoka Certified Review Board, Fukuoka, Japan (The last edition version 4.1, December 13, 2021). The trial was subject to supervision and management by the Ethics Committee. All patients provided written informed consent.

| Drug Information | |
|---|---|
| Generic/working name | Osimertinib |
| Company name | AstraZeneca |
| Drug type | Small molecule |
| Drug class | EGFR |
| Dose | 80 mg daily |
| Unit | Milligrams (mg) |
| Route | Oral (p.o.) |
| Schedule of administration | Osimertinib was administered at a dose of 80 mg orally once daily until disease progression or a discontinuation criterion was met |

| Patient Characteristics | |
|---|---|
| Number of patients, male | 15 |
| Number of patients, female | 23 |
| Stage | IIIC: 1, IV: 26, recurrence after surgery: 11 |
| Age, median(range) | 80 (75-87) years |
| Performance status: ECOG | 0: 16<br>1: 21<br>2: 1<br>3: 0<br>4: 0 |
| Cancer types or histologic subtypes | Adenocarcinoma, 37; squamous cell carcinoma, 1. |

| Primary Assessment Method | |
|---|---|
| Title | 1-year PFS rate |
| Number of patients screened | 41 |
| Number of patients enrolled | 41 |
| Number of patients evaluable for toxicity | 40 |
| Number of patients evaluated for efficacy | 38 |
| Evaluation nethod | RECIST 1.1 |
| Median duration assessments, PFS | 15.9 months (9.8-20.3 CI) |
| Median duration assessments, OS | Not reached (29.9-not reached) |
| Outcome notes | The median follow-up period was 27.6 months. The 1-year PFS rate was 59.4% (95% CI, 46.1-72.7%). Median PFS was 15.9 months (95% CI: 9.8-20.3 months) (Fig. 1). Median OS was not reached (Fig. 1). One- and 2-year survival rates were 91.9% and 75.1%, respectively. |

| Secondary Assessment Method | |
|---|---|
| Title | **ORR** |
| Number of patients screened | 41 |
| Number of patients enrolled | 41 |
| Number of patients evaluable for toxicity | 40 |
| Number of patients evaluated for efficacy | 38 |
| Evaluation method | RECIST 1.1 |
| Response assessment, CR | 4 (10.5%) |
| Response assessment, PR | 26 (68.4%) |
| Response assessment, SD | 5 (13.2%) |
| Response assessment, PD | 3 (7.9%) |
| Outcome notes | The responses of 38 patients were evaluated.ORR was 78.9% (95% CI, 63.7-88.9%). Four, 26, 5, and 3 patients showed a complete response, partial response, stable disease, and progressive disease, respectively. |

| Assessment, Analysis, and Discussion | |
|---|---|
| Completion | Study completed |
| Investigator's assessment | Correlative endpoints not met but clinical activity observed |

To the best of our knowledge, this is the first prospective clinical trial to investigate the efficacy and safety of osimertinib as a first-line treatment for elderly Japanese patients (≥75 years) with EGFR mutation-positive advanced NSCLC. Patients characteristics are summarized in Table 1.

The 1-year PFS rate, the primary endpoint of the present study, was estimated to be 70% using data from the FLAURA study,[2] while the threshold 1-year PFS rate was set at 50% using data from the NEJ003 study on gefitinib in elderly patients with EGFR mutation-positive lung cancer in Japan.[6] In the present study, the 1-year PFS rate was 59.4%, which did not meet the primary endpoint because the one-sided 90% lower CI corresponding to a significance level of 5% was <50% (the 1-year PFS rate was 59.4% with 95% CI, 46.1%–72.7%).

Clinical studies examined the effects of EGFR-TKIs in elderly patients with EGFR mutation-positive advanced NSCLC. The NEJ003 study on gefitinib in elderly patients reported median PFS of 12.3 months.[6] Prolonged PFS (14.2 months) was achieved in a phase II study (NEJ027) on afatinib; however, dose adjustments were required in most cases.[7] Moreover, a phase II study on erlotinib revealed Prolonged PFS (15.5 months) in elderly patients ≥75 years with EGFR mutation-positive advanced NSCLC in Japan.[8] PFS in the present study was 15.9 months, which was equivalent to or longer than that in previous clinical studies on first- and second-generation EGFR-TKIs in elderly patients. Although the median OS was not reached, the 2-year OS rate (75.1%) in the present study was also equivalent to or longer than those in previous clinical studies on erlotinib and afatinib in elderly patients (60.6% and 78.3%, respectively).[7,9]

One possible reason why the present study was unable to meet the primary endpoint was the high percentage of smokers. A preclinical study on nicotine indicated the development of resistance to EGFR-TKIs.[10,11] A meta-analysis of real-world data revealed longer PFS in non-smokers than in smokers.[12] The percentage of smokers in the present study was high at 47.4%, in contrast to 35% in the FLAURA study, 26% in the NEJ003 study, 28% in the phase II study on erlotinib, and 32% in the phase II study on afatinib.

The overall incidence of AEs in the present study (95%) was similar to that in the FLAURA study and the Japanese subset of the FLAURA study (98% vs. 100%, respectively),[13] while that of AEs of grade 3 or higher in the present study (35%) was similar to that in the FLAURA study (34%) and lower than that in the FLAURA Japanese subset (47.7%), with the incidence of the most common AEs of grade 3 or higher being 5%. All toxicities are listed in Table 2. Common AEs in the FLAURA study were diarrhea (58% at all grades, 2% at grade 3 or higher) and rash acneiform (58% at all grades, 1% at grade 3 or higher) in the osimertinib group. In the present study, these AEs were less frequent than in the FLAURA Japanese subset (diarrhea, 32.5% vs. 56.9% and rash acneiform, 42.5% vs. 46.2%). With other EGFR-TKIs, the incidence of diarrhea and rash did not significantly differ between elderly and young patients.[8,10] Cytopenic conditions, such as anemia (87.5% in the present study vs. 18.5% in the FLAURA Japanese subset), leukopenia (30% in the present study vs. 21.5% in the FLAURA Japanese subset), and platelet count decreased (77.5% in the present study vs. N/A in the FLAURA Japanese subset), were more common in the present study than in the FLAURA Japanese subset.[13] The incidence of cytopenia was higher for osimertinib than for first-generation TKIs in the FLAURA study, suggesting that it is a characteristic AE of osimertinib. A high rate of cytopenia was also observed in the SPIRAL study, a phase II study previously conducted by our study group on elderly patients with T790M-positive NSCLC.[14] In the elderly, organ function declines and the incidence of hematological toxicities increases.[15] Although a grade 3 AE was observed in only one patient (platelet count decreased) and complications due to cytopenia, such as infection and hemorrhage, were not observed, cytopenia is an AE for which caution is required during the administration of osimertinib to elderly patients. Other common AEs included electrolyte abnormalities, hypoalbuminemia, hepatic disorders, and creatinine increased; however, these AEs of grade 3 were observed in less than 5% of patients. Furthermore, the rate of treatment discontinuation due to AEs was lower than that reported in the FLAURA Japanese subset (17.5% vs 26.2%)[13] and there were no cases of treatment discontinuation due to AEs other than pneumonitis.

Pneumonitis is an important AE of EGFR-TKIs. In the FLAURA study, pneumonitis developed in 4% of all patients and 12.3% of the Japanese subset of patients.[13] In the present study, pneumonitis occurred more frequently than in the Japanese subset of patients in the FLAURA study. Previous studies identified an older age as a risk factor for the development of pneumonitis[16,17] In the SPIRAL study,[14] pneumonitis developed in 11.1% of patients, which was a higher incidence than that in the AURA3 study in patients of all ages with T790M mutation-positive lung cancer.[18] Similarly, phase II studies on first- and second-generation EGFR-TKIs demonstrated that the incidence of pneumonitis was higher in elderly patients than in young patients.[7,8,19] Moreover, prospective and retrospective observational studies on osimertinib reported a similar incidence of pneumonitis to that in the present study (18% and 17.4%, respectively).[20,21] Therefore, pneumonitis needs to be considered when administering osimertinib to elderly patients. However, only one case was grade 3 or higher in the present study, and all patients recovered after the discontinuation of osimertinib or administration of corticosteroid therapy.

The present study did not meet the primary endpoint; however, osimertinib is expected to exert the same effects as first- and second-generation EGFR-TKIs in elderly patients. Although caution is required for the development of pneumonitis, osimertinib is tolerable and has potential as a first-line treatment option for elderly patients with EGFR mutation-positive advanced NSCLC.

## Funding

This study was sponsored by AstraZeneca.

## Conflict of Interest

**Yuko Tsuchiya-Kawano:** Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, Kyowa Kirin, Boehringer-Ingelheim (H); **Minoru Fukuda:** AstraZeneca, Eli Lilly Japan (RF), AstraZeneca, Bristol Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Kyowa Kirin, MSD, Nippon Kayaku, Novartis, Pfizer, Taiho, Takeda (H); **Shigeru Tanzawa:** AstraZeneca (RF), AstraZeneca, Eli Lilly Japan, Chugai Pharmaceutical, Taiho Pharmaceutical (H); **Koichi Takayama:** AstraZeneca (C/A, H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

## Data Availability

The data underlying this article are available in the article and in its online supplementary material.

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## Tables

**Table 1.** Patient characteristics ($n$ = 38).

| Characteristic | *n* (%) |
|---|---|
| Age, years | |
| Median (range) | 80 (75-87) |
| ≥80 years | 19 (50%) |
| <80 years | 19 (50%) |
| Sex | |
| Male | 15 (39.5%) |
| Female | 23 (60.5%) |
| ECOG performance status | |
| 0 | 16 (42.1%) |
| 1 | 21 (55.3%) |
| 2 | 1 (2.5%) |
| Histology | |
| Adenocarcinoma | 37 (97.3%) |
| Squamous cell carcinoma | 1 (0.27%) |
| Stage | |
| IIIC | 1 (2.6%) |
| IV | 26 (68.4%) |
| Recurrence after surgery | 11 (28.9%) |
| *EGFR* mutation status | |
| Exon 19 deletion | 16 (42.1%) |
| L858R | 22 (57.9%) |
| Smoking history (ex-smoker) | 18 (47.4%) |
| Site of metastasis | |
| Lung | 14 (36.8%) |
| Pleural dissemination | 13 (34.2%) |
| Brain | 10 (26.3%) |
| Bone | 14 (36.8%) |
| Liver | 2 (5.3%) |
| Adrenal grand | 2 (5.3%) |
| Comorbidity | |
| Yes | 22 (57.9%) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

**Table 2.** Adverse events.

| AEs | NC/NA, % | Grade 1, % | Grade 2, % | Grade 3, % | Grade 4, % | Grade 5, % | All grades, % |
|---|---|---|---|---|---|---|---|
| Fatigue | 62.5 | 27.5 | 12.5 | 0 | 0 | 0 | 40 |
| Rash acneiform | 57.5 | 27.5 | 10 | 5 | 0 | 0 | 42.5 |
| Dry skin | 50 | 40 | 10 | 0 | 0 | 0 | 50 |
| Paronychia | 67.5 | 22.5 | 7.5 | 2.5 | 0 | 0 | 32.5 |
| Pruritus | 65 | 32.5 | 0 | 2.5 | 0 | 0 | 35 |
| Anorexia | 50 | 30 | 17.5 | 2.5 | 0 | 0 | 50 |
| Diarrhea | 67.5 | 30 | 2.5 | 0 | 0 | 0 | 32.5 |
| Mucositis oral | 65 | 30 | 5 | 0 | 0 | 0 | 35 |
| Pneumonitis | 82.5 | 2.5 | 12.5 | 2.5 | 0 | 0 | 17.5 |
| White blood cell decreased | 70 | 15 | 15 | 0 | 0 | 0 | 30 |
| Neutrophil count decreased | 72.5 | 22.5 | 5 | 0 | 0 | 0 | 27.5 |
| Platelet count decreased | 22.5 | 72.5 | 2.5 | 2.5 | 0 | 0 | 77.5 |
| Anemia | 12.5 | 60 | 27.5 | 2.5 | 0 | 0 | 87.5 |
| Hypoalbuminemia | 0 | 77.5 | 22.5 | 0 | 0 | 0 | 100 |
| Aspartate aminotransferase increased | 40 | 52.5 | 5 | 2.5 | 0 | 0 | 60 |
| Alkaline aminotransferase increased | 47.5 | 42.5 | 5 | 5 | 0 | 0 | 52.5 |
| Creatinine increased | 32.5 | 57.5 | 10 | 0 | 0 | 0 | 67.5 |
| Hyponatremia | 35 | 60 | 5 | 0 | 0 | 0 | 65 |
| Hypocalcemia | 50 | 45 | 5 | 0 | 0 | 0 | 50 |
| Hypokalemia | 72.5 | 22.5 | 0 | 5 | 0 | 0 | 27.5 |
| Hypermagnesemia | 88.2 | 11.2 | 0 | 0 | 0 | 0 | 11.2 |
| Electrocardiogram QT corrected interval prolonged | 90 | 5 | 2.5 | 2.5 | 0 | 0 | 10 |

Abbreviation: NC/NA, no change from baseline/no adverse event.