

The Real-Life Efficacy And Safety of Osimertinib In Pretreated Advanced Non-Small Cell Lung Cancer Patients With T790M Mutation: A Turkish Oncology Group Study

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Research Article

Keywords: Osimertinib, disease, discontinuation, TTD, ORR

Posted Date: May 7th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-486874/v1>

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Version of Record: A version of this preprint was published at Journal of Cancer Research and Clinical Oncology on July 31st, 2021. See the published version at <https://doi.org/10.1007/s00432-021-03748-7>.

Abstract

Introduction: Osimertinib, an irreversible third-generation EGFR-TKI, is the standard of care for second-line treatment of T790M-mutant advanced NSCLC patients whose progressed after first-line EGFR-TKI therapy. In this multicenter study, we aimed to determine the real-life efficacy and safety of Osimertinib in pretreated advanced NSCLC patients with T790M mutation.

Materials and Methods: This retrospective trial included advanced T790M-mutant pretreated NSCLC patients who received Osimertinib from 24 different centers in Turkey. Primary endpoint was time-to-treatment discontinuation (TTD). Secondary endpoints were objective response rate (ORR), overall survival (OS), and safety.

Results: Of 163 patients 68.7% had EGFR exon 19 deletion and 22.7% had exon 21 L858R mutation. Osimertinib was given as second-line treatment in 96 patients (58.9%) and third-line in 48 patients (29.4%). After median of 13 months disease follow-up, median TTD was 21.6 months with an 82.2% ORR. Estimated median OS was 32.1 months. Grade 3-4 adverse events were seen in 11.7% of the patients.

Conclusion: Osimertinib is a highly effective option in second or third-line treatment of NSCLC patients with T790M mutation, with a favorable safety profile.

Introduction

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related morbidity and mortality (1). In the last decade, survival expectancy has dramatically changed for some patient subgroups with the identification of druggable driver mutations which suitable for targeted therapies (2). Activating mutation in the gene which encodes the proteins of the Epidermal growth factor receptor (EGFR) constitutes one of the most important treatment targets, and pooled prevalence of exon 19 and exon 21 mutations in NSCLC patients is reported approximately 32% by previous studies (3).

Until recently, first-generation EGFR tyrosine kinase inhibitors (TKIs) (Erlotinib, Gefitinib), and second-generation TKI, Afatinib were the standard of care options for first-line treatment of advanced NSCLC with EGFR exon 19 deletion and 21 mutations. However, resistance seen in 10–14 months to these TKIs was the most important determinant to limited efficacy in terms of duration of response (DoR) and progression-free survival (PFS) for most of the patients (2). T790M mutation occurs in exon 20 of the EGFR gene, converts ATP-binding pocket of the receptor to a nonpolar, hydrophobic state which interferes with drug-binding and causes a lack of efficacy (4). This point mutation was demonstrated in 60% of the patients at the time of progression (5).

Osimertinib is an irreversible, third-generation EGFR-TKI which is also effective in patients with T790M mutation (4). AURA3 was a phase 3 trial that randomized 419 patients with T790M-positive advanced NSCLC, who had disease progression after first-line EGFR-TKI therapy (6). This study demonstrated a

significant PFS advantage (median 10.1 vs. 4.4 months) with Osimertinib treatment compared to platinum-pemetrexed combination chemotherapy. Objective response rate (ORR) was achieved in 71% of the patients who received Osimertinib. Median overall survival (OS) was 26.8 months with Osimertinib, however, the updated analysis did not show a significant OS benefit, mainly secondary to a remarkable cross-over rate (67% of the patients in the chemotherapy group) to Osimertinib arm (7). Osimertinib became the standard of care for second-line treatment of T790M-mutant advanced NSCLC patients whose disease progressed after first-line EGFR-TKI therapy, based on the results of the AURA3 trial(2).

Recently, Osimertinib achieved a longer OS compared to first-generation EGFR-TKIs (median 38.6 vs. 31.8 months) in the treatment-naive advanced NSCLC population with exon 19 deletions and L858R mutations (8). However, there are many patients who have not progressed under first-line treatment with first or second-generation TKIs. Furthermore, Osimertinib may not be accessible because of many reasons related to approval policy, reimbursement issues, insurance coverage, etc., in the first-line treatment for many patients worldwide, as well as in our country. This status emphasizes the importance of sequential strategy and second-line efficacy.

Randomized phase 3 trials are the most important tools to assess the efficacy and safety of a new treatment agent or strategy. These studies may have strict inclusion and exclusion criteria which usually under represents patients with poor performance and elderly. They also have close follow-up and monitorization rules, and a tendency to over or underestimate some factors regarding efficacy and safety profile, some of which may not be clinically so meaningful. Studies which evaluated the outcomes of real-life patients who received the treatment agent may help to close this gap.

In this multicenter study, we aimed to determine the real-life efficacy and safety of Osimertinib in pretreated advanced NSCLC patients with T790M mutation, in Turkey.

Materials And Methods

This multicenter, retrospective trial included pathologically and radiologically confirmed T790M-mutant, pretreated, advanced NSCLC patients who received Osimertinib between January 2016 and January 2021. There were only six patients who received Osimertinib in first-line treatment regardless of the T790M mutation.

The study was performed in 24 different centers in Turkey with collaboration of the Turkish Oncology Group. Data were obtained from patients' files and electronic databases of the hospitals. The EGFR and/or T790M mutation was analyzed either in the tumor tissue sample or in plasma circulating tumor DNA (ctDNA) by local laboratories of each center.

Primary endpoint was time-to-treatment discontinuation (TTD) and calculated from the date of the initiation of Osimertinib treatment to discontinuation of the drug or death. Secondary endpoints were OS, response rate according to the criteria of RECIST version 1.1 by the investigator, and safety. OS was defined as the time from initiation of Osimertinib to death from any cause. Adverse events were assessed

by using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

All statistical procedures were performed with SPSS 22.0 (SPSS Inc, Chicago, Illinois). The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Categorical variables were compared using the Chi-square or Fisher's exact test, where appropriate. Differences in continuous values between the two groups were assessed with Student's *t*-test for normally distributed variables and non-parametric Mann-Whitney *U* tests for non-normally distributed variables as appropriate. In normally distributed parameters, the correlation coefficients and their significance were calculated using the Pearson test and in non-normally or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. Survival curves were obtained by the Kaplan-Meier method, and the log-rank test was used to compare survival differences. A *P* value < 0.05 was considered to statistically significant. A 5% type-1 error level was used to infer statistical significance.

Local Clinical Research Ethics Committee's approval was obtained.

Results

Patient Characteristics

Median age of 163 patients at the time of diagnosis was 57 (min-max: 26–79), and it did not significantly differ between male and female. The 59.5% of the patients were female. Approximately all of the patients had adenocarcinoma (98.1%) histology. EGFR exon 19 del mutation were seen in 68.7% of the patients. Of 163 patients with advanced disease, 153 (93.9%) had metastatic disease. There were 49 patients (30.1%) who had brain metastasis. Demographic and clinical features of the patients are summarized in Table 1.

Table 1
Demographic and Clinical Characteristics of the Patients

Feature	%, n	Feature	%, n
Sex	59.5%, n = 97	ECOG Performance	23.3%, n = 38
Female	(58, 29–79)	0	52.8%, n = 86
(median age, min-max)	40.5%, n = 66	1	11.7%, n = 19
Male	(56, 26–79)	≥ 2	12.3%, n = 20
(median age, min-max)		NA	
Tumor Histology	98.1%, n = 160	Smoking Status	69.3%, n = 113
Adenocarcinoma	< 1%, n = 1	Non-Smoker	24.5%, n = 41
Squamous cell	1.2%, n = 2	Previous exposure	5.5%, n = 9
NOS		Active smoker	
Metastatic Site	75.5%, n = 123	No. of Previous Regimens	3.7%, n = 6
Lung	59.5%, n = 97	0	58.9%, n = 96
Bone	41.7%, n = 68	1	29.4%, n = 48
Pleura	30.1%, n = 49	2	5.5%, n = 9
Brain	19.6%, n = 32	3	2.4%, n = 4
Liver		≥ 4	
Type of EGFR Mutation	96.3%, n = 157	Previous TKI	79.8%, n = 130
T790M	68.7%, n = 112	Erlotinib	6.1%, n = 10
Exon 19 deletion	22.7%, n = 37	Gefitinib	6.7%, n = 11
Exon 21 L858R	3.7%, n = 6	Afatinib	3.7%, n = 6
Other		NA	

There was no significant difference in terms of EGFR mutation subtype between female and male patients. Non-smokers were significantly more frequent ($p < 0.05$) in female patient group (85.6%, n = 83) compared to males (45.5%, n = 30).

Previous Anticancer Treatments

There were only 6 patients who received Osimertinib as first-line treatment regardless of T790M mutation. All other patients (n = 157) had T790M mutation. There were 96 patients (58.9%) who received Osimertinib as second-line and 48 patients (29.4%) as \geq third-line treatment. Among 151 patients who received first- or second-generation EGFR-TKI before Osimertinib, Erlotinib was given to 86% (n=130), while 6.6% (n = 10) got Gefitinib and 7.2% (n = 11) got Afatinib. Median duration of exposure to previous

TKI treatment was calculated as 16 months (min-max: 1–85 months), irrespective of the agent that used or disease status (Table 1).

Efficacy and Safety Outcomes of Osimertinib

After median follow-up of 13 months (min-max:1.1–52.2 months), response assessment obtained from 161 patients. Complete response (CR) was achieved in 11 patients (6.7%) and ORR was 82.2% with Osimertinib treatment. There were only 6 patients (3.7%) whose best response to treatment was progressive disease (PD) (Table 2).

Table 2
Response Assessment to Osimertinib Treatment

Treatment Response	%, n
Complete Response (CR)	6.7%, n = 11
Partial Response (PR)	75.5%, n = 123
Objective Response Rate (ORR)	82.2%, n = 134
Stable Disease (SD)	12.9%, n = 21
Disease Control Rate (DCR)	95%, n = 155
Progressive Disease (PD)	3.7%, n = 6

Seventy-five events occurred in terms of TTD and median TTD with Osimertinib treatment was 21.6 months (95% CI, 17.4 to 25.7 months) (Fig. 1). In the pretreated population (n = 157), median TTD was also 21.6 months (95% CI, 17.4 to 25.8 months).

In patient subgroup (n = 96) that received Osimertinib as second-line treatment, median TTD was 22.7 months (95% CI, 14.7 to 30.7 months). Similarly, patients (n = 61) who received Osimertinib as third-line or later achieved a median TTD of 21.6 months (95% CI, 17.1 to 26 months).

There was a significant TTD difference between patient groups with exon 19 del (n = 112) and with exon 21, L858R mutation (n = 37). Median TTD was 25.3 months (95% CI, 21.1 to 29.5 months) vs. 15.1 months (95% CI, 5.4 to 24.9 months) in patients with 19 del and L858R mutation, respectively (p = 0.045). Also, a significant TTD difference was demonstrated between gender, in favor of female patients with a median of 24 vs. 15.1 months (p = 0.021). TTD was significantly shorter in patients with brain metastasis compared to without brain metastasis (median of 11.4 vs 24 months, respectively, p = 0.045) (Table 3). There were no significant TTD differences in terms of smoking status, ECOG performance status, presence, or grade of any side effects.

Table 3
Time to Treatment Discontinuation and Overall Survival in Patient Subgroups

Patient Subgroups (n of Events / n)	TTD months (median, 95% CI range)	p
Age < 65 (57/124)	21.6 (17.5–25.6)	0.63
Age ≥ 65 (18/39)	19.2 (8.3–30.1)	
Female (39/97)	24 (19.6–28.4)	0.021
Male (36/66)	15.1 (7.6–22.6)	
Nonsmoker (49/113)	21.6 (17.3–25.9)	0.13
Smoking History (26/50)	16 (3–28.9)	
2nd Line Osimertinib (40/96)	22.7 (14.7–30.7)	0.81
≥ 3rd Line Osimertinib (33/61)	21.6 (17.1–26)	
Exon 19 deletion (50/112)	25.3 (21.1–29.5)	0.045
Exon 21 L858R (20/37)	15.1 (5.4–24.9)	
Brain Metastasis (-) (49/114)	24 (19.4–28.6)	0.045
Brain Metastasis (+) (26/49)	11.4 (6.2–16.7)	
Patient Subgroups (n of Events / n)	OS months (median, 95% CI range)	p
Age < 65 (37/124)	35.5 (23.8–47.1)	0.18
Age ≥ 65 (14/39)	32.1 (22.1–42.2)	
Female (26/97)	35.5 (22.1–48.8)	0.063
Male (25/66)	24.2 (14.5–34)	
Nonsmoker (31/113)	35.5 (21.4–49.5)	0.038
Smoking History (20/50)	27.7 (15.9–39.4)	
2nd Line Osimertinib (29/96)	27.7 (22.7–32.7)	0.35
≥ 3rd Line Osimertinib (20/61)	32.1 (19–45.3)	
Exon 19 deletion (32/112)	32.1 (26.5–37.8)	0.075
Exon 21 L858R (15/37)	20.1 (18.1–22.2)	
Brain Metastasis (-) (31/114)	32.1 (26.5–37.8)	0.021
Brain Metastasis (+) (20/49)	17.3 (13.9–20.7)	

A total of 51 patients (31.2%) died. Estimated median OS was calculated as 32.1 months (95% CI, 22.1 to 42.2 months) (Fig. 2). As expected, patients with brain metastasis had significantly shorter OS compared with patients who had no brain metastasis (median OS of 17.3 vs. 32.1 months, respectively, p = 0.021).

There was a trend in OS in favor of female gender, and exon 19 del mutation compared with L858R, but these differences have failed to reach statistical significance (Table 3).

The tolerability and safety of Osimertinib were assessed. At least one side effect reported in 51.5% (n = 84) of the patients. Rate of grade 3 or 4 side effects was 11.7% (n = 19). Most common side effects were fatigue (33.1%), decreased appetite (32.5%), skin toxicity (28.8%), diarrhea (17.2%), and paronychia (12.9%). Grade 3 pneumonitis was seen only in one patient. None of the patients experienced an adverse event leading to death or permanent discontinuation of the drug. Drug dose was reduced in 9 patients (5.5%), and treatment was interrupted temporarily in 9 patients.

Discussion

In this real-life study, as a primary endpoint; Osimertinib demonstrated a quite impressive TTD with a median of 21.6 months, in pretreated advanced EGFR-mutant NSCLC patients. Secondary endpoints were also consistent with 82.2% of ORR, and estimated-median OS of 32.1 months, with a favorable safety profile.

AURA3 was an international, phase 3 study that randomized 419 patients with T790M-mutant advanced NSCLC to second-line Osimertinib or chemotherapy arms (6). The study reported a median of 10.1 months PFS with Osimertinib treatment. Demographic and clinical features of the patient population were similar in terms of age (62 and 57), sex (female, 62% and 59%), rate of CNS involvement (33% and 30%), and EGFR mutation subtypes (exon 19 del, 68% and 68%) in AURA3 and our study, respectively (6). However, in the Osimertinib arm of the AURA3 study, 65% of the patients were Asian, 83% of the patients had adenocarcinoma histology (in our study it was 98%), 96% had only one-line of previous treatment (in our study it was 59%) (6). Moreover, our study group had received more previous treatment lines before Osimertinib.

In this context, the survival outcomes of other real-life studies varied between median 9.4 and 14.5 months of PFS, in the second-line treatment of advanced NSCLC with T790M mutation (9–14). The Spanish Lung Cancer Group reported a median of 9.4 months PFS in 155 patients, and this was a very close to the PFS reported in the pivotal phase 3 trial (6, 10). Other studies from different regions and ethnicities like China, Japan, France, and Poland demonstrated slightly better real-life outcomes than the AURA3 trial with approximately median 11–14 months of PFS (9, 11–14). In general, outcomes of real-life experiences with the different classes of drugs just like cytotoxic chemotherapy, barely exceed the success of pivotal studies. Because patients often have more comorbidities and worse performance status than patient population strictly selected in phase 3 studies. However, targeted agents typically could demonstrate similar or better results in several studies. Clinicians' increasing experience in the management of treatment side effects and sustainable clinical benefit observed in some patient groups might contribute to these results.

Median 21.6 months of TTD in our study was a quite different outcome than the PFS results of phase 3 AURA3 or other real-life studies. Of course, these two different end-points did not refer to the same

situation, and they could not be compared directly in any clinical scenario. Indeed, our aim mostly emphasizes the distinct features of the TTD and PFS as study end-points. Unlike other studies, TTD did not identify the disease progression as “an event” according to RECIST criteria, and includes patient subgroups in which clinicians decided to continue the treatment post-progression.

Importance of TTD was demonstrated in a recent study that analyzed 18 different randomized studies with 8947 NSCLC patients (15). Five of these 18 studies included 1151 patients who received targeted TKI therapy for EGFR-mutant NSCLC. Median TTD exceeded median PFS by 2 months (13.4 versus 11.4 months) in this subgroup. Also, the rate of “late TTD” (identified as TTD – PFS \geq 3 months) was 12.4% in EGFR-mutant patients and this rate was higher than chemotherapy and immunotherapy studies (15). Another study from Spain which included 91 patients who received post-progression treatment after second or third-line Osimertinib therapy for T790M mutation-positive disease, reported a median of 6.4 months post-progression PFS with Osimertinib treatment in 50 (54%) patients (16). Both post-progression PFS and OS were significantly longer in the post-progression Osimertinib arm compared with other treatments in this study (16).

The other determinant that might improve the TTD could be inclusion of local ablative therapies (LAT) to patient care. As one of the weaknesses of our study, our database did not include the percentages of patients who received LAT. However, it is a routine part of daily clinical practice especially for patients whose disease showed oligoprogression and/or isolated CNS progression (17). A recent study by Zeng et al., included 108 patients (n = 83 for the second-line Osimertinib) who had oligo-residual disease (\leq 5 metastatic lesions) and treated with Osimertinib, demonstrated a PFS advantage in patients (n = 14) who had received LAT compared with others (NR vs 12.8 months, p = 0.01) (18). In this small patient subgroup (n = 8 for first-line Osimertinib, and n = 6 second-line Osimertinib) in which administered LAT to their Osimertinib treatment, 3-year PFS rate was reported as 54.5% (18).

Main reasons of choosing TTD as our primary end-point were also the weaknesses of our study. TTD was more suitable for a retrospective study that did not perform a central assessment of treatment response and included many centers around the country which may have different clinical approaches and LAT practices. But at the same time, it might reflect directly the sustainable and real-life beneficial effects of treatment to allow the post-progression continuation and other interventions to the treatment process. Clinicians’ choice to hold on to the drug throughout median 21.6 months was quite understandable in this very special patient subgroup who did not have too many treatment options after Osimertinib treatment, rather than chemotherapy which has highly suspicious efficacy in third or later-lines.

TTD was significantly longer in favor of women, patients with Exon 19 deletion, and patients without brain metastasis compared to men, Exon 21 L858R mutation, and patients with brain metastasis, respectively. There was greater risk reduction observed in female gender and patients with Exon 19 del mutation, with both first-line and second-line Osimertinib treatment, in pivotal phase 3 studies (6, 19). Also, our results were compatible with a recent meta-analysis by Lee et al. that demonstrated 50% greater benefit in Exon 19 del mutation than Exon 21 L858R mutation (p < 0.01), and 27% greater benefit in

women than men ($p = 0.02$) with first or second-generation EGFR-TKIs compared with chemotherapy (20). Real-life studies from Poland and France also reported significant PFS advantage in patients with Exon 19 del mutation (11, 12).

Brain metastasis is a worse prognostic factor for NSCLC and drug penetrance to CNS remains a problem even for highly effective therapies like Osimertinib (21). TTD in patients with brain metastasis is significantly shorter than patients without brain metastasis, however, median 11.4 months of TTD was similar to the AURA3 trial's 8.5 months of PFS (6). In our study, patients with asymptomatic brain metastasis might be under-represent in our brain metastatic subgroup because of the lack of periodic brain MRI screening in daily clinical practice.

In the pivotal phase 3 trial, 71% of the patients achieved ORR and 93% DCR with Osimertinib (6). In our study, ORR was higher (82%) and DCR was similar with 95%. Studies from Europe already reported lower rates with approximately 40–50% of ORR (10, 12). No data was indicating that the Turkish population might be more “sensitive” to this treatment than Western population. Our study did not perform a central assessment for radiological review, and patient-selection bias always has to be taken into consideration as a possible determinant of a retrospective study.

After median 13 months follow-up, estimated median OS was 32.1 months (median 27.7 months for second-line and 32.1 months for ≥ 3 -lines of treatment). Median OS of the Osimertinib arm in AURA3 trial was 26.8 months (7). Real-life results showed a median OS of 20 months in the western population and 24 months in the Asian population (11, 14). In a phase 2 study, 3-year OS rate was 54% in Japanese patients (22). In another study, median OS from the failure of first-line EGFR-TKI was reported as 42.6 months in patients who had T790M mutation with a history of Osimertinib use (23). Relatively short follow-up period, risk of patient-selection bias, and also possible differences in the sequential therapies might have affected our OS results.

Safety profile was favorable with only 5.5% of temporary drug interruption. Most common side effects were similar with recent data. Rates of any adverse events and grade 3–4 adverse events were lower than the AURA3 study (6). Clinicians' tendency to underestimate the side effects –especially grade 1 and 2– which will not influence treatment strategy, might be a possible reason in daily clinical practice. For example, grade 1–2 pneumonitis was seen in 9 of 279 patients in AURA3 however it was none in our study. Probably, asymptomatic grade 1 events might be underestimated and the symptoms of grade 2 events might be explained with other clinical entities. But grade ≥ 3 pneumonitis was seen in one patient in both studies (6).

In conclusion, Osimertinib is a highly effective therapy in second-line treatment of NSCLC patients with T790M mutation, with a favorable safety profile.

Declarations

Funding: No role for any funding source.

Conflicts of Interest: The authors declare no conflicts of interest

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Figures

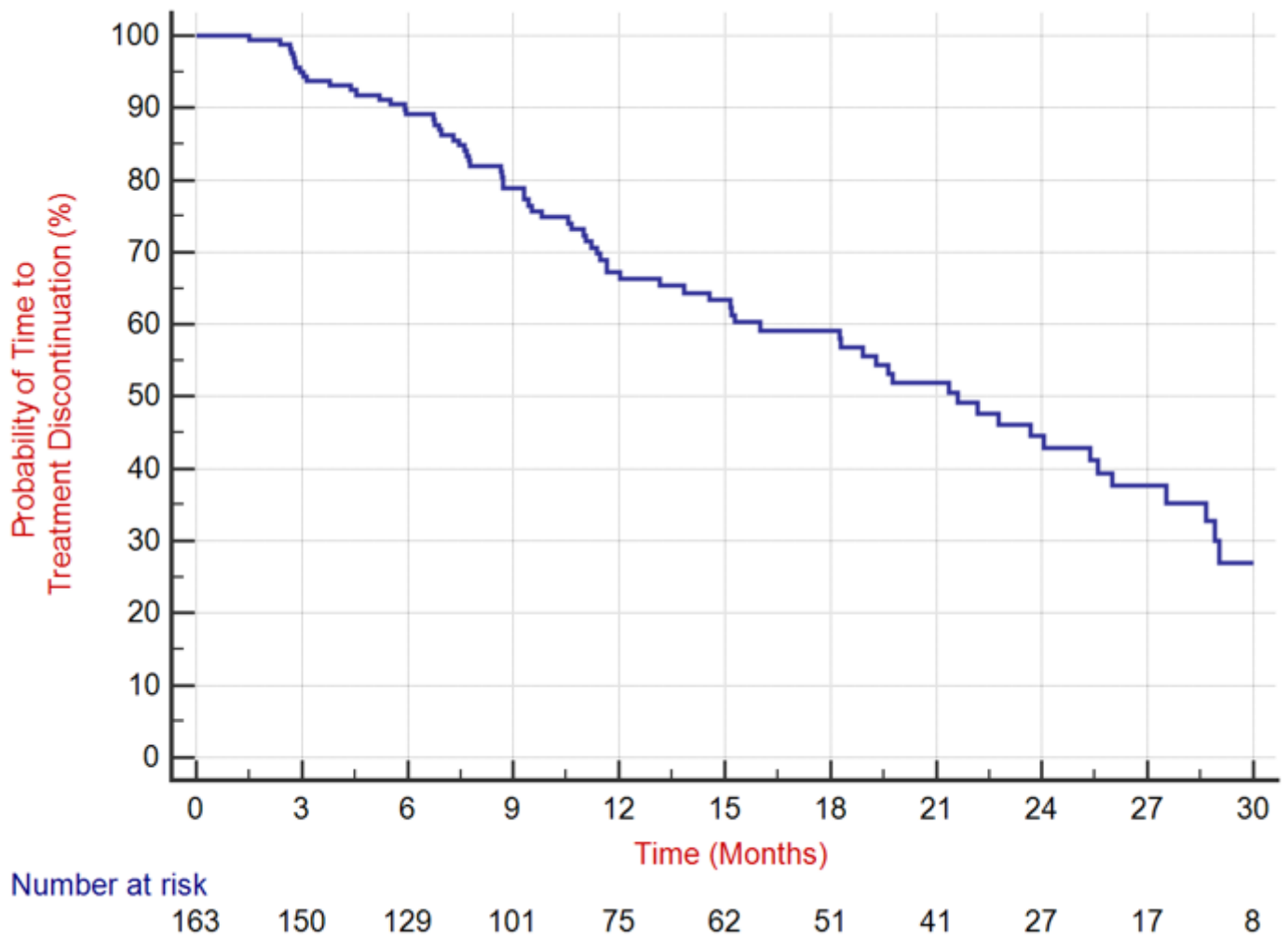


Figure 1

Time to Treatment Discontinuation with Osimertinib Treatment

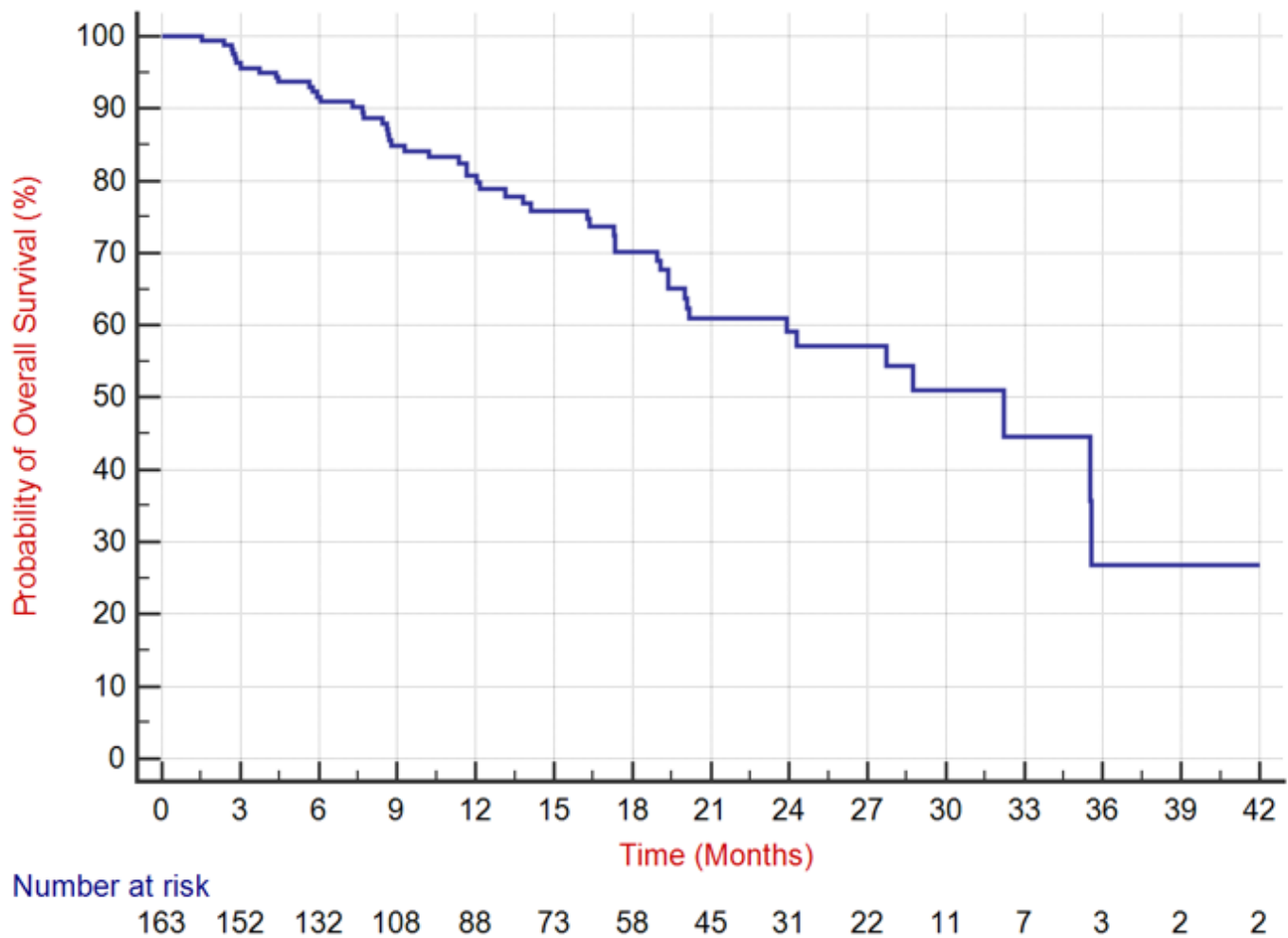


Figure 2

Overall Survival with Osimertinib Treatment