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Concurrent use of aspirin with osimertinib is associated with improved survival in advanced *EGFR*-mutant non-small cell lung cancer

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Abstract

Background: Osimertinib is the treatment of choice for advanced *EGFR*-mutant non-small cell lung cancer (NSCLC). However, novel strategies to improve the duration of disease control are still urgently needed. Aspirin has been shown to decrease cancer incidence and improve outcomes in various malignancies. Therefore, we evaluated a cohort of patients who received osimertinib with or without concurrent use of aspirin to assess whether the addition of aspirin may lead to improved clinical outcomes.

Methods: MD Anderson Cancer Center GEMINI database was retrospectively queried for *EGFR*-mutant NSCLC patients who received osimertinib with or without concurrent use of aspirin for progression-free survival (PFS) and overall survival (OS).

Results: A total of 365 patients were identified including 77 which had concurrent use of aspirin. Patients in the aspirin-osimertinib group had significantly improved PFS (21.3 vs 11.6 months; HR, 0.52; 95% CI, 0.38 - 0.70) and OS (Not reached vs 32.3 months; HR, 0.56; 95% CI, 0.35 - 0.91) compared to osimertinib group. In subgroup analyses, the aspirin-associated PFS benefit was observed in patients with and without central nervous system (CNS) metastases, as well as in osimertinib first-line setting and in subsequent line setting. The median PFS in *EGFR* 19Del patients was longer than *EGFR* L858R patients with osimertinib, and when aspirin was added, the median PFS significantly improved in both groups regardless of lines of therapy. The benefit from aspirin was independent of age, gender, *TP53* mutational status, or PD-L1 positivity.

Conclusion: Concurrent aspirin use with osimertinib in *EGFR*-mutant NSCLC patients was associated with improved survival, regardless of lines of therapy, CNS metastatic status, *EGFR* mutation type, age, gender, *TP53*, and PD-L1 status.

Keywords

Non-small cell lung cancer; aspirin; osimertinib; *EGFR*; *TP53*; PD-L1

1. Introduction:

The treatment for advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) mutations has evolved since the initial discovery of this oncogene-driver. [1-3] With the development of newer generations of tyrosine kinase inhibitors (TKIs), patients' clinical benefit, measured by progression-free survival (PFS) and overall survival (OS), continues to improve. [4-6] Recently, osimertinib, a third-generation irreversible *EGFR* TKI, has demonstrated significant efficacy in metastatic *EGFR*-mutant NSCLC. In the AURA3 (NCT02151981) trial, osimertinib showed improved progression-free survival (PFS 10.1 vs 4.4 months) and objective response rate (ORR 71% vs 31%) when compared with platinum-pemetrexed in T790M-positive advanced NSCLC after first-line *EGFR* TKI.

[7] Subsequently, the phase III FLAURA trial (NCT02296125) demonstrated a significant PFS (18.9 vs 10.2 months) and OS (38.6 vs 31.8 months) benefit when compared with erlotinib or gefitinib in the treatment-naïve patients.[8, 9] Currently in the United States, osimertinib is indicated both as the first-line treatment for metastatic *EGFR*-mutant NSCLC and as the subsequent treatment for patients with metastatic *EGFR* T790M-positive NSCLC after progression on other *EGFR* TKI therapy.

Despite the high rate of initial response, resistance to osimertinib inevitably emerges and patients ultimately succumb to the disease. [10-12] Therefore, therapeutic strategies that can further improve upon osimertinib in *EGFR*-mutant NSCLC patients are still urgently needed. Extensive efforts are being made on therapeutic combinations that might increase the long-term efficacy of osimertinib. For example, since the addition of anti-angiogenics have shown PFS benefit,[13, 14] ongoing trials are evaluating osimertinib with ramucirumab[15] or bevacizumab[16]. Also, the addition of chemotherapy with gefitinib demonstrated OS benefit compared to gefitinib alone,[17] so a large randomized phase 3 trial of osimertinib with chemotherapy to compare to osimertinib alone is now enrolling. [18] Although promising, these combinations come with a high risk of toxic effects and increased financial burden for patients. Identification of therapeutic strategies which are low-cost, have low toxicity, and improve osimertinib efficacy are beneficial to the patients and field.

There is evidence from observational studies that aspirin, a nonselective cyclooxygenase (COX) inhibitor, commonly used in patients with cardiovascular disease, is beneficial in reducing the incidence, metastasis, or the risk of death in various cancers.[19-22] In a recent study in patients with chronic hepatitis, the use of aspirin was associated with decreased incidence of liver cancer (4% vs 8.3%; HR 0.69; 95% CI, 0.62 - 0.76) in over 55, 000 patients.[23] In an analysis of over 10 million patients, aspirin use was associated with significantly reduced lung cancer risk (HR, 0.89; 95% CI, 0.84 - 0.94).[24] Furthermore, in a lung cancer preclinical study, Ogawa et al showed that cyclooxygenase (COX)-derived prostaglandin E2 (PGE2) is associated with poor prognosis by inducing tumor growth and metastasis, and aspirin use reduced the rate of metastasis to regional lymph nodes[25].

In *EGFR*-mutant NSCLC, a few lines of evidence indicate a potential benefit from aspirin usage to delay or overcome resistance from EGFR TKIs. Li et al. showed that aspirin use overcame acquired resistance to *EGFR*-TKI through inhibiting proliferation and promoting apoptosis of cancer cells using *in vitro* and *in vivo* models.[26] Han et al. reported that the combination of aspirin and osimertinib could induce strong antiproliferative and pro-apoptotic effects through inhibition of Akt/FoxO3a signaling component phosphorylation and increased Bim expression to promote apoptosis used in osimertinib-resistant NSCLC cell lines. Furthermore, they demonstrated that the use of aspirin was associated with improved median PFS (15.3 vs 9.3 months; $p = 0.023$) in a retrospective analysis of 45 patients with *EGFR* T790M mutant NSCLC.[27, 28] With aspirin being an inexpensive and relatively safe medication, it is of great interest to understand whether the concurrent use of aspirin enhances osimertinib's benefit for *EGFR*-mutant NSCLC in a larger patient population. Here, we identified a cohort of 365 patients with advanced *EGFR*-mutant NSCLC treated with osimertinib and compared the clinical outcome of patients who had

concurrent use of aspirin to the ones without. We further analyzed the impact of concurrent aspirin use in different clinical subgroups as well as different molecular subgroups.

2. Materials and Methods

2.1 Study population

We queried the GEMINI database, a University of Texas MDACC Lung Cancer Moon Shot funded internal database, and identified patients with advanced *EGFR*-mutant lung cancers treated with osimertinib from March 2014 to July 2019. We collected patient demographics, clinical characteristics, reasons for aspirin use, survival data, and tumor molecular profiles (data cut-off was in October 2019, when the dataset was locked for the outcome analysis, Figure. 1). The reasons for aspirin use were divided into 4 categories which were defined as below: 1. Primary prevention: for the individuals with 10-year risk of cardiovascular disease ≥ 30%; 2. Secondary prevention: for the individuals with established cardiovascular disease (as well as those who had deep venous thrombosis or atrial fibrillation); 3. Mild pain; 4. Unclear reason. The written informed consent was collected from all of the patients and the studies were conducted following ethical guidelines including the Declaration of Helsinki and U.S. Common Rule. Eligibility criteria included histologic or cytologic confirmation of NSCLC, recurrent or metastatic disease, *EGFR*-mutant, and receipt of osimertinib. Patients with osimertinib as adjuvant therapy or induction therapy, lost to follow-up after osimertinib commenced, withdrawn from treatment because of toxicity, receipt of osimertinib < 1 cycle were excluded from the analysis. The study was approved by the Institutional Review Boards at MDACC.

2.2 Genomic profiling

The genomic profiling data were collected through molecular pathology reports. The cancer gene mutations including *EGFR, TP53* were determined by next-generation sequencing panels of tumor tissue DNA (at MDACC Molecular Diagnostics Laboratory or FoundationOne - Foundation Medicine Inc.) or circulating tumor DNA (Guardant360 panel - Guardant Health). PD-L1 expression was assessed by immunohistochemistry using 22C3 pharmDx and quantified as a percentage of tumor cells expressing PD-L1 (TPS) at MDACC Molecular Diagnostics Laboratory.

2.2 Statistical analysis

Progression-free survival (PFS) was calculated from the date osimertinib treatment began to disease progression by the physician’s judgment, or death, whichever occurred first. Overall survival (OS) was defined as the time from the beginning of osimertinib treatment to death from any cause. The response was extracted from clinical notes, based on physician’s evaluation. Patients alive or the absence of disease progression at last follow-up were censored for analyses. The Kaplan–Meier method was used to estimate PFS and OS. The log-rank test was used to compare between-group differences. Fisher’s exact test was used to evaluate the impact of gender, smoking status, performance status, central nervous system (CNS) status, disease stage and previous lines of TKI therapy. The median age was determined by the Mann-Whitney test. All statistical analyses were performed on SPSS 24.0 statistical software package and $p < 0.05$ was considered statistically significant.

3. Results:

3.1 Patient characteristics

We identified a total of 395 patients with advanced *EGFR*-mutant NSCLC, whose tumor was not amenable to local treatment and had received osimertinib as systemic therapy (Figure. 1). Among them, 30 patients were excluded due to the following reasons: osimertinib used as adjuvant therapy or induction therapy (n = 7), lost to follow-up (n = 15), receipt of osimertinib < 1 cycle (28 days) (n = 8). In the total evaluable cohort of 365 patients, 77 patients received concurrent aspirin with osimertinib for at a minimum of one month (referred to as aspirin-osimertinib group hereafter). Among the 77 patients with aspirin use, 22 (29%) were treated for primary prevention, 38 (49%) for secondary prevention, 10 (13%) for treatment of mild pain, and remaining 7 (9%) for unclear reasons (Supplemental Table 1). There were no significant bleeding events in the aspirin-osimertinib group. Other common aspirin side effects (such as thrombocytopenia and gastrointestinal symptoms) are overlapping with osimertinib side effects, and therefore, they cannot be appropriately attributed. The remaining 288 patients received osimertinib without aspirin use (referred to as osimertinib alone group). The two groups were well-balanced in gender, histology, smoking status, disease stage, performance status and lines of TKI therapy (Table. 1). There were two differences between the two groups: (1) the incidence of CNS metastases prior to osimertinib treatment was lower in the aspirin-osimertinib group (27% vs 43%, $p = 0.013$), and (2) patients were older in the aspirin-osimertinib group (median age 69 vs 62 years; $p < 0.001$; Table 1). These differences are in line with clinical expectations as patients with brain metastases are less likely to use aspirin due to the concern of intracranial hemorrhage and older patients are more likely to use aspirin for treatment or prevention of cardiovascular diseases.

3.2 Concurrent use of aspirin with osimertinib was associated with improved survival

At the data cut-off on October 30, 2019, 64 (83% of 77) patients in the aspirin-osimertinib group and 207 (72% of 288) in the osimertinib alone group were still alive. The median follow-up was 14.3 months. The median PFS in the aspirin-osimertinib group (n = 77) was significantly longer than that in the osimertinib alone group (n = 288) (21.3 vs 11.6 months; HR, 0.52; 95% CI, 0.38 - 0.70; $p < 0.001$; Fig. 2A). Multivariable analysis showed that treatment with aspirin was independently associated with longer PFS (Table 2). The median OS in the aspirin-osimertinib group has not been reached after a follow up of 46.9 months, while the osimertinib alone group was 32.3 months, which also represents a significant difference (HR, 0.56; 95% CI, 0.35 - 0.91; $p = 0.049$; Fig. 2B).

As osimertinib was approved for both first- and subsequent-line treatment in *EGFR*-mutant NSCLC, we next performed subgroup analyses to evaluate aspirin's benefit in different lines of osimertinib treatment. The median PFS of first-line osimertinib treatment in aspirin-osimertinib group (n = 38) has not been reached, while osimertinib alone group (n = 117) was 14.0 months (HR, 0.35; 95% CI, 0.20 - 0.62; $p = 0.007$; Fig. 3A). The median PFS of subsequent-line osimertinib treatment in aspirin-osimertinib group and osimertinib alone group was 19.6 months versus 10.9 months (HR, 0.50; 95% CI, 0.35 - 0.72; $p = 0.002$, Fig. 3B).

Next, we assessed whether the patients with CNS metastases also benefit from aspirin use. In our cohort of 365 patients, 145 (40%) had CNS metastasis at the time of osimertinib initiation. The PFS for patients who had baseline CNS metastasis was 21.3 months in the aspirin-osimertinib group (n = 21) compared to 9.1 months in the osimertinib alone group (n = 124) (HR, 0.43; 95% CI, 0.27 - 0.69; p = 0.006, Fig. 3C). For patients with no brain metastasis, the PFS was 20.7 versus 14.9 months in the aspirin-osimertinib (n = 56) and the osimertinib alone (n = 164) group respectively (HR, 0.50; 95% CI, 0.33 - 0.76; p = 0.005; Fig. 3D). For the 21 patients with CNS metastasis who had concurrent aspirin use with osimertinib, none of the patients had intracranial bleeding.

We also analyzed whether key clinical characteristics may impact the additional benefit from aspirin. The median PFS in females were 32.9 months versus 12.5 months (HR, 0.33; 95% CI, 0.22 - 0.50; p < 0.001; Supplemental Fig. 1A) in the aspirin-osimertinib (n = 44) and the osimertinib alone (n = 190) groups, respectively. In males (n = 33 vs 98), median PFS was 16.9 months versus 10.5 months (HR, 0.59; 95% CI, 0.37 - 0.95; p = 0.052; Supplemental Fig. 1B. In addition, we found that the PFS in the elderly group (age ≥ 60 years, n = 65 vs 175) were 21.3 versus 12.5 months (HR, 0.47; 95% CI, 0.33 - 0.68; p < 0.001; Supplemental Fig. 1C), while in the younger group (age < 60 years, n = 12 vs 113) were 20.7 versus 11.1 months (HR, 0.50; 95% CI, 0.25 - 0.98, p = 0.123; Supplemental Fig. 1D), respectively. No statistical significance in the younger group may be due to the limited sample size.

3.3 *EGFR* mutation type, *TP53* and PDL1 status were not associated with the differential benefit of aspirin

It is known that lung cancers with *EGFR* exon 19 deletions (19Del) have a better prognosis than L858R mutations on exon 21.[29, 30] In our cohort, the 19Del patients (n = 212) had a better median PFS of 16.9 months compared to 13.0 months in L858R patients (n = 125, HR, 0.67; 95% CI, 0.50 - 0.91; p = 0.005; Fig. 4A), consistent with prior reports. When stratified by *EGFR* mutation type, we found that the median PFS of 19Del patients in the aspirin-osimertinib group (n = 50) was 20.7 compared to 14.2 months (HR, 0.49; 95% CI, 0.33 - 0.75; p = 0.006; Fig. 4B) in the osimertinib alone group (n = 162); whereas in L858R patients (n = 22 vs 103) the median PFS were 21.3 versus 11.5 months (HR, 0.44; 95% CI, 0.27 - 0.70; p = 0.009; Fig. 4B). We further analyzed the PFS for patients treated with osimertinib with or without aspirin in the first-line setting with regards to either 19Del or L858R. As shown in Supplemental Fig. 2, the median PFS was significantly longer in patients with 19Del in aspirin-osimertinib group (n = 22) compared to osimertinib alone group (n = 60) (Not reached vs 21.4 months; HR, 0.24; 95% CI, 0.10 - 0.60; p = 0.036). The same trend was observed in the L858R group (n = 13 vs 46), although the difference did not reach significance (16.3 vs 12.5 months; HR, 0.52; 95% CI, 0.22 - 1.77; p = 0.216). In patients with *EGFR* T790M mutation (n = 31 vs 114), the median PFS were 20.7 versus 13.5 months (HR, 0.44; 95% CI, 0.29 - 0.66; p = 0.001; Supplemental Fig. 3). These data suggest that the additional benefit from aspirin was not dependent on *EGFR* mutation type.

Other than the *EGFR* mutation type, in some reports, co-occurring mutation of *TP53* also impacts prognosis in EGFR-mutant NSCLC.[31, 32] In our cohort, we found no significant difference in median PFS between *TP53* mutant patients (n = 185) *and TP53* wild type (n =

92) with 13.1 versus 12.2 months (HR, 1.28; 95% CI, 0.94 - 1.73; p = 0.125; Fig. 4C). When analyzed by *TP53* mutation status, the median PFS in *TP53* wild type patients (n = 21 vs 71) were 21.7 versus 11.1 months (HR, 0.54; 95% CI, 0.29 - 0.99; p = 0.045, Fig. 4D), and the median PFS in *TP53* mutant patients (n = 37 vs 148) were 17.6 versus 10.5 months (HR, 0.50; 95% CI, 0.33 - 0.76; p = 0.001; Fig. 4D) in aspirin-osimertinib versus osimertinib alone treated patients, respectively. These data suggest that the concurrent aspirin use confers benefit regardless of the *TP53* mutational status.

Studies have shown that the clinical benefit with osimertinib was unaffected by PD-L1 expression status, [33] which was consistent with the results of our study (p = 0.293; Supplemental Fig. 4A), but aspirin might suppress cancer cell growth through PD-L1 related pathways.[34] We therefore evaluated whether PD-L1 status impacted the additional benefit of aspirin treatment in patients treated with osimertinib. Using equal or greater than 1% as the cut-off for being positive, the median PFS in PD-L1 positive patients (n = 27 vs 115) were 16.9 versus 10.2 months (HR, 0.61; 95% CI, 0.37 - 0.98; p = 0.071; Supplemental Fig. 4B). Similarly, the median PFS of PD-L1 negative patients in the aspirin-osimertinib group (n = 20) had not been reached yet, while the PFS in the osimertinib alone group (n = 73) was 11.1 months (HR, 0.42; 95% CI, 0.22 - 0.79; p = 0.036; Supplemental Fig. 4C), suggesting that the aspirin-osimertinib group had better median PFS regardless of PD-L1 status.

4. Discussion

In this study, we reviewed a cohort of patients with metastatic *EGFR*-mutated NSCLC treated with osimertinib with or without concurrent use of aspirin at MDACC. Our results demonstrated that the addition of aspirin to standard osimertinib therapy prolonged PFS and OS in *EGFR*-mutant NSCLC patients. Aspirin therapy with first-line osimertinib treatment (median PFS not yet reached) conferred the longest PFS in all subgroups analyzed. Furthermore, patients from different age groups, gender, *EGFR* mutation type, *TP53* and PD-L1 status all benefited from the concurrent use of aspirin.

In this real-world dataset, it is worth noting that the PFS of first-line osimertinib alone group (14.0 months) was inferior to that from FLAURA trial [9] (18.9 months). This difference is likely due to different patient populations. Our real-world first-line osimertinib cohort (n = 117) included 17 patients (14.5%) with prior systemic chemotherapy or immunotherapy (anti-PD-1), 44 patients (37.6%) with CNS metastasis and 32 (30%) patients with performance status greater or equal to 2, all of which might be contributing factors to an inferior clinical outcome.

Due to the nature of the real-world retrospective study, this cohort of 365 patients had nearly 40% of patients having CNS metastasis at the time of osimertinib initiation. It could be related to physician’s choice due to the established efficacy of osimertinib in EGFR-mutant NSCLC patients with CNS metastases.[35-38] Our cohort demonstrated that the PFS in the osimertinib alone group was consistent with AURA3 in patients with measurable CNS metastasis (8.9 months).[39, 40] Interestingly, in the FLAURA study when osimertinib was used as first-line therapy, the median CNS PFS in patients with measurable and/or non-measurable CNS lesions treated with osimertinib was significantly better than that of the

AURA3 trial, with CNS PFS not-reached (95% CI, 16.5 months to not reached). [41] We found when aspirin was added to the osimertinib treatment of CNS metastasis patients, the PFS emerged a substantial improvement to months from 9.1 months (p = 0.006). This significant improvement of PFS could be due to multiple factors. Our aspirin-osimertinib CNS group was small with only 21 patients. Furthermore, among them, 7 were treated as first line. 18 of the 21 patients received Gamma Knife or whole brain radiation therapy; 2 of the remaining 3 patients who did not have radiation achieved CR to osimertinib and 1 was asymptomatic with SD to osimertinib (Supplemental Table 2). Therefore, small sample size, first-line setting benefit and radiation therapy may all have contributed to the good outcome in this group of patients. Although our cohort was small at 21 patients with CNS metastasis and concurrent aspirin use, there was no intracranial bleeding, suggesting it is safe to use aspirin for *EGFR*-mutant NSCLC with controlled CNS metastasis to gain the potential PFS benefit.

It is known that patients with *EGFR* 19Del had better survival than *EGFR* L858R mutation, when treated with first-generation[42] and second-generation[43] *EGFR* TKI. One study showed that the significant OS benefit in *EGFR* 19Del group compared to *EGFR* L858R group (33.3 vs 26.4 months, p = 0.028) may be contributed by higher proportion of the *EGFR* T790M in the 19Del group compared to the L858R group (50.4% vs 36.5%, p = 0.043).[30] In this study, we also found that with the use of third-generation TKI (osimertinib), the median PFS in *EGFR* 19Del patients was significantly longer than *EGFR* L858R patients. Interestingly, when aspirin was added, the median PFS significantly improved in both groups to a similar duration (20.7 vs 21.3 months). When only first-line use of osimertinib was evaluated, removing the T790M rate as a confounding factor, the aspirin use continued to confer PFS benefit for both 19Del and L858R groups.

It is known that female patients often demonstrate better outcomes than males from *EGFR* TKI therapy.[44] Our data was generally in line with the prior report showing that the median PFS for females was significantly longer than that for males (32.9 vs 16.9 months, p = 0.036) when aspirin was added. To identify other potential confounding factors contributing to the long PFS in the female group, such as age, lines of therapy or mutation subtype, we further compared the female and male groups of patients. We found that 19Del was more common in females compared to males (75% vs 51%) within our cohort (Supplemental Table 3). What remains unclear is the magnitude of benefit that female patients derive from aspirin compared to the males. Although there was evidence that aspirin interacts with estrogen-related biological process [45-47] to reduce breast cancer risks for females, how the aspirin produces additional benefit in female patients receiving *EGFR* TKI still requires additional preclinical and clinical investigation.

The biological mechanisms underlying our observation that aspirin prolongs PFS for osimertinib are unclear, but could be from more than one process. Aspirin is a nonselective and irreversible inhibitor of COX-1 and COX-2 enzymes, and hence has many effects on human body. COX-2 enzymes are highly expressed in lung neoplasia[48] and shown as a potential contributor to *EGFR* TKI resistance,[49] possibly through epithelial-to-mesenchymal transition (EMT) that is related to prostaglandin E2 (PGE2) production downstream of COX-2.[50, 51] Previous studies have shown that aspirin inhibits the

cyclooxygenase activity of the COX enzymes which leads to the decrease of PGE2 to suppress EMT. Decreased EMT potential has preventive or therapeutic effects in lung carcinogenesis[52] and overcomes TKI resistance in human *EGFR*-mutant NSCLC cell lines.[53] Other than suppressing PGE2 and MET, aspirin's impact on apoptosis pathways could also be contributing to the additional cancer cell growth control. He et al. reported that the combination of aspirin and osimertinib significantly inhibited *EGFR*-mutant tumor cell growth through inhibition of Akt/FoxO3a signaling component phosphorylation and increased Bim expression to promote apoptosis.[27] Din et al. revealed that aspirin induced apoptosis through NFkB nuclear translocation, independent of p53 status. [54] In our study, we also found that aspirin's benefit was independent of *TP53* status.

Our study is the first to explore the clinical benefit of concurrent use of aspirin with osimertinib for patients with advanced NSCLC harboring *EGFR* mutations. In this real-world cohort of 365 patients, we found that *EGFR*-mutant NSCLC patients had prolonged PFS and OS from concurrent use of aspirin with osimertinib. Aspirin at low dose is relatively safe and inexpensive. An ongoing prospective randomized clinical trial (NCT04184921) will provide more direct evidence to advocate the use of aspirin with osimertinib in advanced *EGFR*-mutant lung cancer patients.

5. Conclusion

In summary, our study demonstrates that the addition of aspirin to osimertinib treatment in *EGFR*-mutated NSCLC patients significantly prolongs PFS and OS. The benefit remains regardless of lines of therapy, the presence of CNS metastasis, gender, age, *EGFR* mutation type, *TP53* status or PD-L1 status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations:

NSCLC	non-small cell lung cancer
PFS	progression-free survival
OS	overall survival

NR	Not reached
CNS	central nervous system
TKIs	tyrosine kinase inhibitors
COX	nonselective cyclooxygenase
ORR	objective response rate
EMT	epithelial-to-mesenchymal transition
PGE2	prostaglandin E2.

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Highlights

- Concurrent aspirin use with osimertinib in *EGFR*-mutant NSCLC patients was associated with improved progression-free survival.
- The benefit is independent of lines of therapy, CNS metastasis, *EGFR* mutation type, *TP53* status, PD-L1 status, age or gender.
- With aspirin use, the progression-free survival in L858R patients are similar to the *EGFR* 19Del patients.

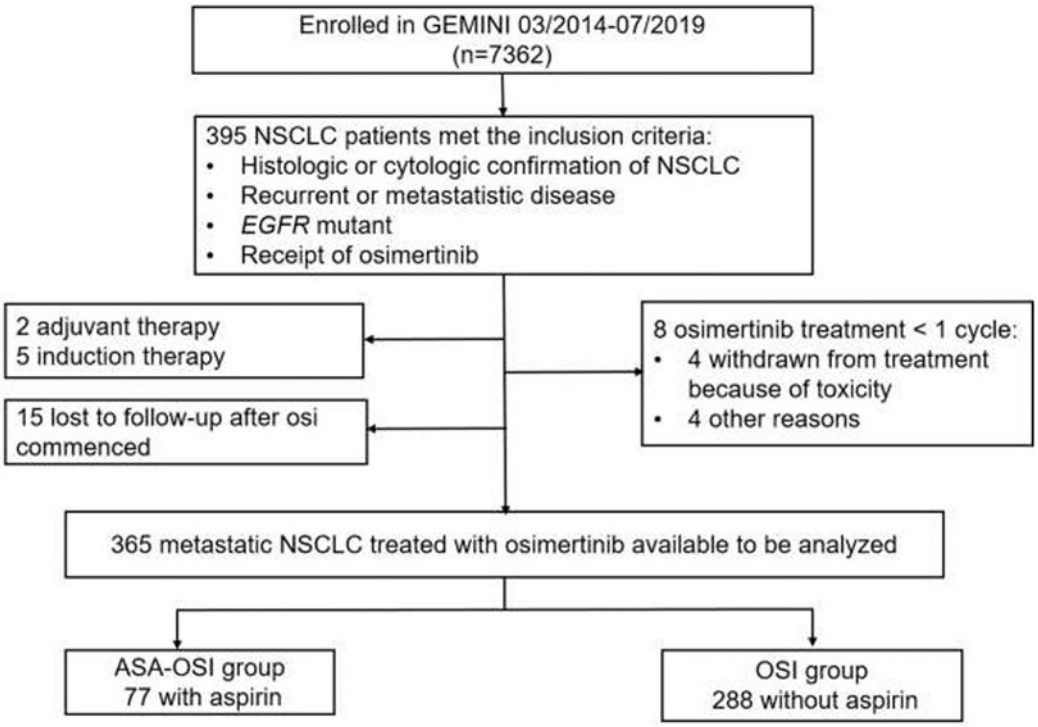

Figure 1. Consort diagram for the retrospective cohort.
ASA-OSI: aspirin-osimertinib. OSI: osimertinib.

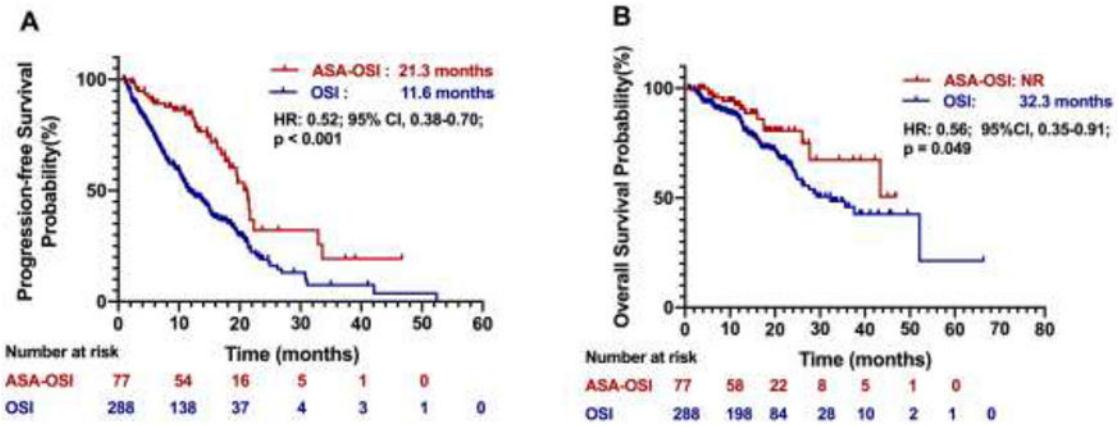

Figure 2. Kaplan-Meier analyses of progression-free survival and overall survival.

(A) Progression-free survival of patients in the ASA-OSI versus the OSI alone group, (B) Overall survival of patients in the ASA-OSI versus the OSI alone group. ASA-OSI: aspirin-osimertinib. OSI: osimertinib.

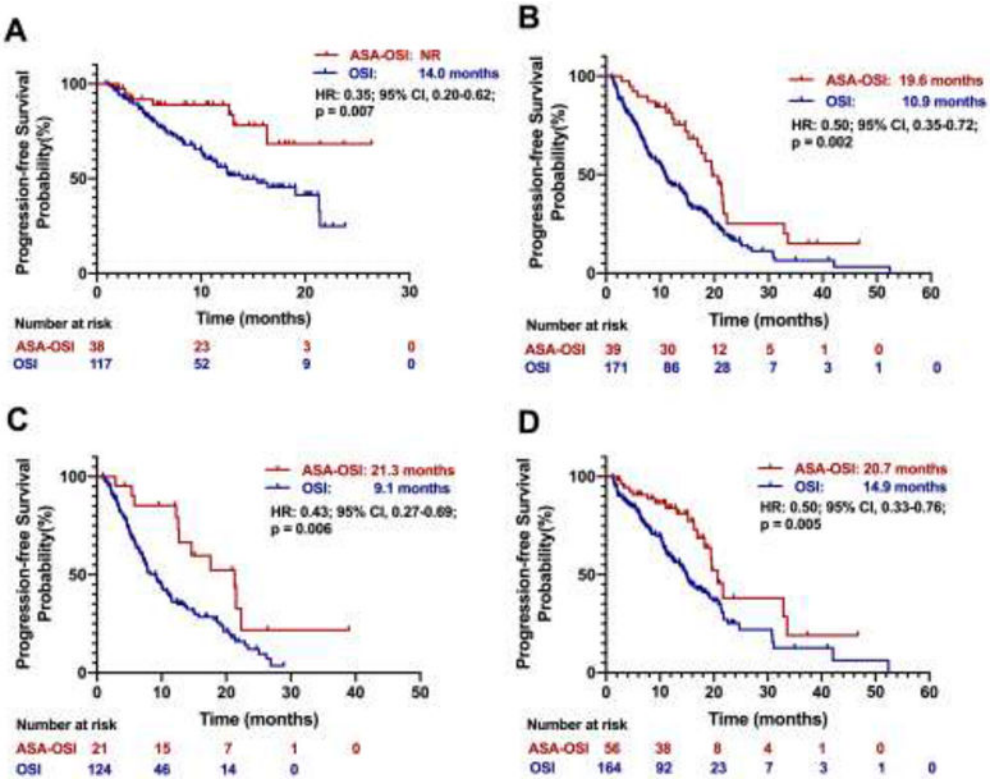

Figure 3. Kaplan–Meier estimates of progression-free survival for subgroups.

(A) Progression-free survival in osimertinib as the first-line treatment patients; (B) Progression-free survival in osimertinib as the subsequent-line treatment patients; (C) Progression-free survival in patients with baseline CNS metastases; (D) Progression-free survival in patients without baseline CNS metastases. CNS: central nervous system. ASA-OSI: aspirin-osimertinib. OSI: osimertinib.

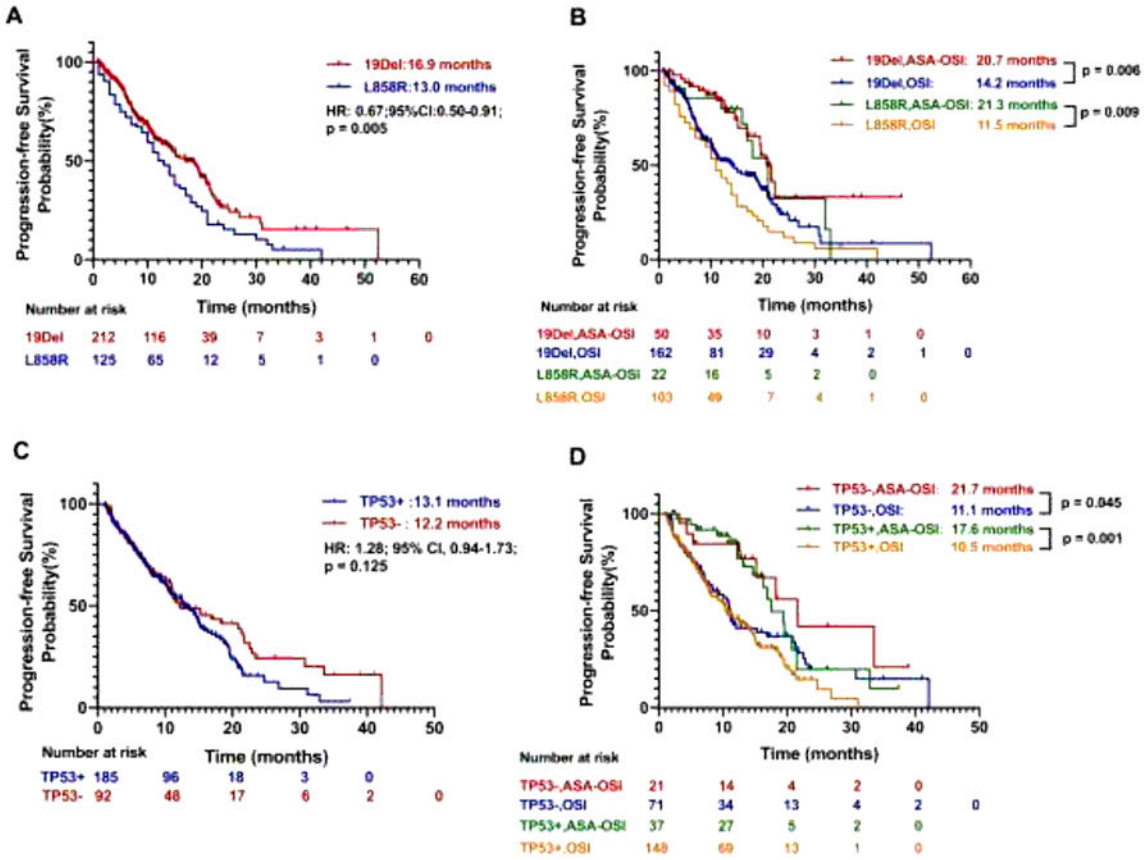

Figure 4. Kaplan–Meier estimates of progression-free survival based on gene status.

(A) Progression-free survival by *EGFR* 19Del versus L858R mutation; (B) Progression-free survival by *EGFR* 19Del versus L858R mutation and aspirin usage; (C) Progression-free survival by TP53 mutation status; (D) Progression-free survival by *TP53* mutation status and aspirin usage. ASA-OSI: aspirin-osimertinib. OSI: osimertinib.

Table 1.

Patient demographics

	Overall	ASA-OSI group	OSI group	p Value
No. of patient	365	77	288	NA
Median age, year (range)	63 (27 - 87)	69 (41 - 87)	62 (27 - 82)	< 0.001
Gender n (%)				
Male	131 (35.9)	33 (43.0)	98 (35.0)	0.181
Female	234 (64.1)	44 (57.0)	190 (65.0)	
Histology n (%)				
Adenocarcinoma	352 (96.4)	74 (96.1)	278 (96.5)	0.858
Squamous cell carcinoma	6 (1.6)	1 (1.3)	5 (1.7)	
Other	7 (1.9)	2 (2.6)	5 (1.7)	
Smoking status n (%)				
Never	259 (71.0)	50 (65.0)	209 (73.0)	0.205
Former/current	106 (29.0)	27 (35.0)	79 (27.0)	
Performance status n (%)				
0 - 1	236 (64.7)	50 (64.9)	186 (64.6)	0.883
2	32 (8.8)	6 (7.8)	26 (9.0)	
3 - 4	14 (3.8)	2 (2.6)	12 (4.2)	
Not known	83 (22.7)	19 (24.7)	64 (22.2)	
CNS disease n (%)				
Yes	145 (39.7)	21 (27.0)	124 (43.0)	0.013
No	220 (60.3)	56 (73.0)	164 (57.0)	
Disease stage n (%)				
Recurrence	78 (21.4)	20 (26.0)	58 (20.0)	0.276
Metastasis	287 (78.6)	57 (74.0)	230 (80.0)	
Lines of TKI therapy n (%)				
1	155 (42.5)	38 (49.0)	117 (41.0)	0.195
≥ 2	210 (57.5)	39 (51.0)	171 (59.0)	
Previous lines of therapy n (%)				
0	132 (36.2)	32 (41.6)	100 (34.7)	0.272
1	139 (38.1)	30 (39.0)	109 (37.8)	
2	53 (14.5)	11 (14.3)	42 (14.6)	
≥ 3	41 (11.2)	4 (5.1)	37 (12.8)	

Abbreviations: ASA-OSI - aspirin-osimertinib, OSI – osimertinib, CNS – central nervous system, TKI – tyrosine kinase inhibitor.

Table 2.

Univariate and multivariate analyses for progression-free survival cohort

	Univariate analysis		Multivariate analysis	
Parameter	**HR (95% CI)**	**p value**	**HR (95%CI)**	**p value**
Aspirin use				
Yes vs. No	0.48 (0.32 - 0.71)	< 0.001	0.45 (0.30 - 0.66)	< 0.001
CNS				
No vs. Yes	0.60 (0.45 - 0.81)	0.001	0.58 (0.44 - 0.76)	< 0.001
Age				
< 60 vs. ≥ 60	1.18 (0.88 - 1.56)	0.260	0.73 (0.55 - 0.96)	0.027
Performance status				
0 - 1 vs. ≥ 2	0.25 (0.16 - 0.38)	< 0.001	0.25 (0.17 - 0.28)	< 0.001
Smoke status				
Never vs. Former/current	0.98 (0.71 - 1.35)	0.90	1.09 (0.8 - 1.47)	0.570
Gender				
Male vs. Female	1.33 (0.99 - 1.78)	0.062	1.22 (0.92 - 1.61)	0.170
Lines of TKI therapy				
Line 1 vs. Line ≥ 2	0.81 (0.59 - 1.11)	0.190	0.68 (0.50 - 0.93)	0.015

Abbreviations: CNS – central nervous system, TKI – tyrosine kinase inhibitor