Case Series

Efficacy and tolerability of osimertinib with dabrafenib and trametinib in *BRAF* V600E acquired *EGFR*-mutant non-small cell lung cancer: a case series

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Background: Acquired mutations within bypass pathways including *BRAF* V600E have been observed in post-osimertinib progression in *EGFR*-mutant non-small cell lung cancer (NSCLC). The combination of dabrafenib and trametinib is currently Food and Drug Administration-approved in *BRAF* V600E-mutant NSCLC. However, the application of osimertinib and dabrafenib and trametinib in the setting of acquired *BRAF* V600E mutation resistance from osimertinib therapy has not been clearly defined. In this case series, we evaluate the efficacy and tolerability of continued osimertinib in combination with dabrafenib and trametinib in *BRAF* V600E acquired *EGFR*-mutant NSCLC.

Case Description: We retrospectively reviewed our clinical patient cohort at the University of California San Diego and patients from published case studies. Individuals who had metastatic *EGFR*-mutant lung adenocarcinoma treated with osimertinib at any line whom subsequently developed an acquired *BRAF* V600E mutation confirmed by next-generation sequencing were included for analysis. All patients had subsequent dabrafenib and trametinib in combination with osimertinib after detection of the novel *BRAF* V600E mutation post-osimertinib therapy. We identified three cases from our practice and nine cases from literature review. In our study cohort (n=12), we observed a median progression-free survival of 7 months on triplet therapy (osimertinib, dabrafenib, and trametinib) post progression on osimertinib, median overall survival of 46.2 months, and 60% partial response on first scan after treatment initiation. Dose reductions were required in 5/12 patients due to adverse events and treatment discontinuation in 2/12 patients. The most common adverse events were pyrexia and rash, and two cases of pneumonitis were observed (grade 1 & unreported grade).

Conclusions: We concluded that the addition of combination dabrafenib and trametinib can be tolerable and effective in patients with acquired *BRAF* V600E mutation post progression on osimertinib. This study supports molecular profiling at osimertinib progression and provides additional information on the appropriate sequencing of targeted therapies in the EGFR tyrosine kinase inhibitor resistance setting.

Keywords: Non-small cell lung cancer (NSCLC); dabrafenib; trametinib; *BRAF* V600E; EGFR; case series

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Introduction

Osimertinib, a third-generation tyrosine kinase inhibitor (TKI), is the current standard of care for metastatic EGFR-positive non-small cell lung cancer (NSCLC). The medicine has been positioned to the front-line setting based on the FLAURA trial which demonstrated a superior overall survival, central nervous system (CNS) response, and improved drug tolerability compared to first- and second-generation EGFR-TKIs (1,2). Characterizing acquired resistance for this drug class can be a challenge, and therapy selection post-progression remains an unmet need. A subgroup analysis of the AURA3 trial reported acquired alterations in the post-osimertinib progression setting. The most common acquired genetic aberrations include *MET* amplification (19%), *EGFR* C797S (14%), *HER2* amplification (5%), *PIK3CA* amplification (4%), and *BRAF* V600E (4%) (3).

Acquired osimertinib resistance can occur due to genetic alterations in bypass signaling pathways and drug binding sites (4). *MET* amplification and *PIK3CA* mutations allow for aberrant alternative bypass signaling via the MAPK and PI3K signaling pathways respectively. *ALK* fusions, *RET* fusions, and *BRAF* mutations have been observed in post-treatment samples and demonstrate acquired genomic heterogeneity through the selective pressure of EGFR-TKI therapy (5).

Highlight box

Key findings

- The combination therapy of osimertinib with dabrafenib and trametinib has demonstrated responses in some patients being treated for *EGFR*-mutant non-small cell lung cancer (NSCLC) with acquired *BRAF* V600E resistance.

What is known and what is new?

- The presence of the *BRAF* V600E mutation in *EGFR*-mutant NSCLC can be associated with acquired resistance on therapy.
- The manuscript adds additional data is provided here about the durability of response, tolerability, and potential resistance mechanisms as associated with the combination.
- The manuscript adds additional information is provided about the safety of combining osimertinib with dabrafenib and trametinib.

What is the implication, and what should change now?

- Prospective, controlled clinical trials are necessary to evaluate the efficacy and safety of the combinational therapy. Preclinical work characterizing pathway synergy, redundancy, and other mechanisms of resistance are needed.

BRAF V600E mutations are detected in 2.8% of lung adenocarcinoma (6). In 2017, the combination of dabrafenib and trametinib therapy was Food and Drug Administration-approved for metastatic *BRAF* V600E-mutant NSCLC (7). The approval was based on the phase II multicenter clinical trial assessing dabrafenib and trametinib in pretreated and treatment-naïve *BRAF* V600E-mutant metastatic NSCLC excluding for pretreated *EGFR* or *ALK*-mutant patients and active brain metastasis (8). Grade 3 and 4 adverse events occurred in 69% of subjects including pyrexia, transaminase elevation, hypertension and vomiting. In addition, serious adverse events which occurred in more than 2 patients included hepatitis, pyrexia, and reduced ejection fraction. From an updated report, the pretreated cohort of *BRAF* V600E mutant patients had an overall response rate (ORR) of 68.4%, median progression-free survival (mPFS) of 10.2 months, and median overall survival (mOS) of 18.2 months (9).

The application of dabrafenib and trametinib in the setting of acquired *BRAF* V600E mutation resistance from EGFR-TKI therapy has not been clearly defined. In this case series, we evaluated cases in the literature and our own patient cohort to assess the efficacy and tolerability of osimertinib in combination with dabrafenib and trametinib in acquired *BRAF* V600E mutation *EGFR*-mutant NSCLC. We present this article in accordance with the AME Case Series reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-629/rc).

Case presentation

Patient data was reviewed at our institution (University of California San Diego) and through published case reports at global sites which included Asia and Europe (10-17). Patients at the University of California San Diego provided consent for data review and the project was approved by our Institutional Review Board standards. We included individuals who had metastatic *EGFR*-mutant lung adenocarcinoma treated with osimertinib at any line whom subsequently developed a *BRAF* V600E mutation confirmed by next-generation sequencing (NGS). All subjects had combination therapy of osimertinib with dabrafenib and trametinib (triplet therapy) after post-osimertinib progression. For patients treated at the University of California San Diego, we determined response based on RECIST v1.1 criteria. We reviewed the literature by using PubMed and Google Scholar database (*Table 1*). Keywords for our review included: *EGFR*-mutant NSCLC, lung adenocarcinoma, *BRAF* V600E, post-osimertinib, EGFR TKI, resistance

Table 1 The search strategy summary

Items	Specification
Date of search	December 31, 2023
Databases and other sources searched	PubMed, Google Scholar
Search terms used	*EGFR*-mutant NSCLC, lung adenocarcinoma, *BRAF* V600E, post-osimertinib, EGFR TKI, resistance mechanism, acquired resistance, dabrafenib, trametinib
Timeframe	January 1, 2018–December 31, 2023
Inclusion and exclusion criteria	Inclusion: primary *EGFR*-mutant NSCLC with new *BRAF* V600E mutation detected on NGS biopsy after osimertinib; treated with dabrafenib/trametinib after progression; case published in peer-reviewed journal
	Exclusion: cases that lacked PFS, OS, ORR data
Selection process	Authors conducted the selection independently

NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; NGS, next-generation sequencing; PFS, progression-free survival; OS, overall survival; ORR, overall response rate.

Table 2 Baseline characteristics of cohort

Characteristics	Value
Patients, n	12
Age at diagnosis (years)	
Median	65
Range	50–71
Gender, n (%)	
Male	8 (67)
Female	4 (33)
Smoking history, n (%)	
Former smoker	1 (8)
Never smoker	11 (92)
Stage of cancer at diagnosis, n (%)	
Stage III	1 (8)
Stage IV	11 (92)
Lines of therapy prior to osimertinib/dabrafenib/trametinib, n (%)	
1	2 (17)
2	5 (42)
3+	5 (42)

mechanism, acquired resistance, dabrafenib, and trametinib.

Twelve patients were included in our analysis (*Table 2*). In particular, we identified three patients who fit the criteria mentioned above within our clinical practice at the University of California San Diego. Furthermore, we reviewed eight case studies which described nine subjects who fit the criteria for study entry. All patients were diagnosed with stage IV lung adenocarcinoma with the exception of one diagnosed at stage III with progression to stage IV. The median age of diagnosis was 65 years with a range from 50 to 71 years. We observed that ten patients had an *EGFR* exon 19 deletion and two had an *EGFR* L858R mutation. The majority of the cohort were never smoking patients and 7 had two or fewer lines of therapy before dabrafenib and trametinib initiation. Eight of 12 patients received combination osimertinib with dabrafenib and trametinib immediately after osimertinib progression. The remaining four patients received platinum doublet (n=2) or taxane (n=2) prior to initiating dabrafenib and trametinib. Six patients received a first-generation TKI and subsequent osimertinib, while two patients received osimertinib as first-line EGFR directed therapy. Ten of 12 patients had biopsy performed directly after progression on osimertinib, while two had biopsy post-osimertinib and chemotherapy.

In ten patients with reported response outcomes, six had a partial radiographic response on combination osimertinib with dabrafenib and trametinib while four had stable disease. No complete responses were reported. The mPFS was determined to be 7 months with a range of 1 to 14 months (*Figure 1*). Of those patients, three did not reach disease progression at study cut-off. The mOS was observed to be 46.2 months (22 to 103 months). The median time to onset of response was 1.75 months (0.5 to 3 months). Of the two cases with CNS metastasis, one patient had shrinkage of brain tumor after starting triplet therapy while the other had further CNS progression on therapy.

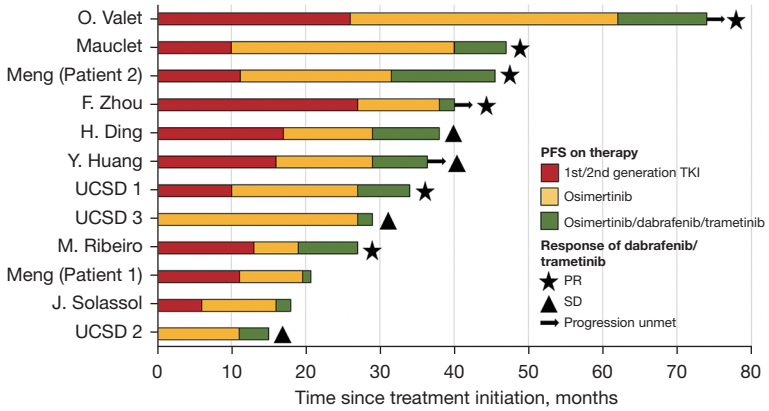

Figure 1 Swimmer plot representing the PFS at each line of therapy including first- or second-generation TKI, monotherapy osimertinib, and dabrafenib with trametinib treatment. PFS is defined as radiographic progression or death. PR is defined as at least a 30% decrease in the sum of the diameters of target lesions and SD is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease. First authors of patient case reports labeled. Arrow indicates patients that continued osimertinib and dabrafenib and trametinib at the time of last follow-up. UCSD, University of California San Diego; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; PR, partial response; SD, stable disease.

We describe two patients from our clinical practice that were treated with dabrafenib and trametinib post-osimertinib (*Figure 2*). Our first patient had a partial response of the right hilar and subcarinal lymph nodes. Serial plasma circulating tumor DNA analyses showed clearance of *BRAF* V600E by plasma NGS analyses after starting triplet therapy. After radiographic disease progression, the known resistance mutation *EGFR* C797S was detected signifying resistance through *EGFR*. Our second patient had a stable radiographic response with initial decline of *BRAF* V600E cfDNA from 1.8% to 0.5% on dabrafenib and trametinib. After radiographic disease progression on triplet therapy, *BRAF* V600E cfDNA increased from 0.5% to 0.7%.

The most common dosage regimen in our series was osimertinib 80 mg once daily (QDay), dabrafenib 150 mg twice a day (BID) and trametinib 2 mg qday (*Figure 3*). One patient discontinued osimertinib while on *BRAF/MEK* inhibition therapy until after progression. Dose reductions were required in five patients due to adverse events. Of the 12 cases, triplet therapy had to be discontinued in two patients due to toxicity. The most common reported side-effect after starting *BRAF/MEK* inhibition was pyrexia in six patients (50%) (*Table 3*). Pneumonitis was observed in two patients (grade 1 & unknown grade) while a single event of grade 2 thrombocytopenia and hepatitis was also reported. One patient from the University of California San Diego cohort was transitioned from dabrafenib, trametinib, and osimertinib to encorafenib, binimetinib, and osimertinib with improved tolerability.

A description of three cases from University of California San Diego are provided below.

Subject 1

A 70-year-old female, non-smoking patient presented with a worsening cough. She was found to have a poorly differentiated lung adenocarcinoma with *EGFR* exon 19 deletion identified by tissue polymerase chain reaction. Positron emission tomography-computed tomography (PET-CT) showed left upper lobe mass, axillary, supraclavicular, hilar, subcarinal lymph node involvement, and malignant pleural effusion. Brain magnetic resonance imaging (MRI) was negative. She was stage IV at diagnosis and initiated anti-cancer treatment with erlotinib. A repeat plasma NGS 2 months after the initiation of erlotinib showed clearance of the *EGFR* variant allele frequency. Approximately 2 years later, she had a progression of the disease in the chest and a new plasma sequencing analysis showed the re-identification of *EGFR* ex19del and a new *EGFR* T790M. She initiated therapy with osimertinib and had stable disease with no further side effects for approximately 1 year, when she progressed again in the chest. At this time, a third liquid biopsy was ordered and the result showed *BRAF* V600E in addition to *EGFR* exon 19 deletion but suppression of the *EGFR* T790M. Based on this genomic profile, dabrafenib 75 mg and trametinib 2 mg were added

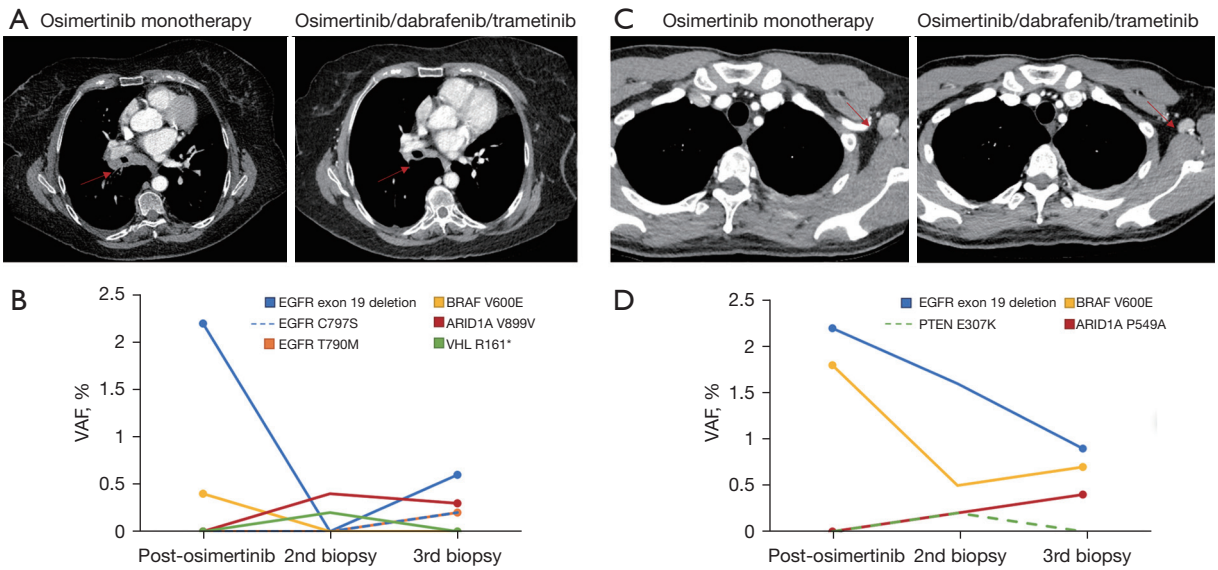

Figure 2 Circulating tumor DNA dynamics on combination therapy. (A) Patient #1: CT imaging comparison of post-osimertinib treatment and concurrent dabrafenib/trametinib after 1 month. Red arrow depicts right hilar lymph node that decreased from 1.7 cm × 1.9 cm to 1.1 cm × 0.9 cm in size. (B) Patient #1: liquid biopsy with VAF change post-osimertinib. Subsequent liquid biopsies taken 21 and 24 months after post-osimertinib biopsy. (C) Patient #2: CT imaging comparison of post-osimertinib treatment and concurrent dabrafenib/trametinib after 1 month. Red arrow depicts left axillary lymph node that decreased from 1.7 to 1.1 cm in size. (D) Patient #2 liquid biopsy with VAF change post-osimertinib. Subsequent liquid biopsies taken 1 and 5 months after post-osimertinib biopsy. VAF, variant allele frequency; CT, computed tomography.

Patient	Osimertinib	Dabrafeni	Trametinib	Pyrexia	Rash	Diarrhea	Fatigue	Nausea	Paronychia	Pneumonitis	Appetite loss	CPK elevation	Dysgeusia	Hepatitis	Pleural effusion	Pleuritic pain	Thrombocytopenia	Vomiting
UCSD 1	80 mg QDay	75 mq BID	2 mg QDay															
UCSD 2	80 mg QDay	75 mg BID	0.5 mg BID															
UCSD 3	80 mg QDay	75 mg BID	2 mg QDay															
Y. Huang	80 mg Qday	150 mg BID	1 mg QDay															
Meng (Patient 1)																		
Meng (Patient 2)	80 mg QDay	50 mg BID	0.5 mg BID															
F. Zho	80 mg QDay	150 mg BID	2 mg QDay															
H. Ding	80 mg QDay	150 mg BID	2 mg QDay															
M. Ribeiro	80 mg QDay	75 mg BID	1 mg QDay															
J. Solassol		150 mg BID	2 mg QDay															
O. Valet	80 mg QDay	150 mg BID	2 mg QDay															
Mauclet	80 mg QDay	150 mg BID	2 mg QDay															

Dose reduction or discontinuation | Grade not reported | Grade 1 | Grade n2 | Grade 3

Figure 3 Adverse events noted on therapy. Dosage of osimertinib, dabrafenib, and trametinib for each subject. Reported new side-effects after addition of anti-*BRAF* and anti-*MEK* therapy represented by shaded boxes. UCSD, University of California San Diego; QDay, once daily; BID, twice a day; CPK, creatine phosphokinase.

to osimertinib 80 mg. She tolerated the three-medicine combination well for approximately 6 months, however subsequently had a progression in axillary lymph nodes and underwent radiation for oligometastatic disease. She was found to have new brain metastases approximately 1 year after the initiation of osimertinib. Osimertinib was increased to 160 mg, and she underwent stereotactic radiosurgery for those lesions. She subsequently had progression in the chest again and repeat plasma NGS showed rising allele frequencies for the mutations *EGFR* ex19del, T790M, and a new *EGFR* C797S but continued suppression of *BRAF* V600E. She passed away approximately

Table 3 Adverse events

Treatment-related adverse event	Any grade	Grade 1	Grade 2	Grade 3
Total	12 [100]	4 [33]	5 [42]	1 [8]
Pyrexia	6 [50]	–	3 [25]	–
Rash	3 [25]	1 [8]	1 [8]	–
Diarrhea	2 [17]	2 [17]	–	–
Fatigue	2 [17]	2 [17]	–	–
Nausea	2 [17]	–	1 [8]	–
Paronychia	2 [17]	–	–	–
Pneumonitis	2 [17]	1 [8]	–	–
Appetite loss	1 [8]	–	–	–
CPK elevation	1 [8]	–	–	1 [8]
Dysgeusia	1 [8]	–	–	–
Hepatitis	1 [8]	–	–	–
Pleural effusion	1 [8]	–	–	–
Pleuritic pain	1 [8]	–	–	–
Thrombocytopenia	1 [8]	–	1 [8]	–
Vomiting	1 [8]	–	1 [8]	–

Data are expressed as n [%]. CPK, creatine phosphokinase.

5.5 years after diagnosis due to the progression of the metastatic brain lesions without significant change in Eastern Cooperative Oncology Group (ECOG) status.

Subject 2

A 55-year-old male, former smoking patient was diagnosed with stage IV *EGFR* exon 19 deletion lung adenocarcinoma with pleural effusion. He was admitted with worsening shortness of breath from the pulmonary nodules and pleural effusion. The patient then started on osimertinib, which was well tolerated but subsequently had progression on scans about 1 year into therapy. Plasma NGS revealed an *EGFR* exon 19 deletion with a *BRAF* V600E resistance mutation. Based on the genomic findings, the patient started dabrafenib and trametinib. He stopped after a few months due to fever, fatigue, and body aches. Subsequently, the patient started encorafenib and binimetinib and then escalated to 450 and 45 mg, respectively, due to slight progression on the scan. The patient had been on encorafenib 450 mg daily and binimetinib 45 mg BID for 7 months, and he tolerated the medicines well but then transitioned to osimertinib and capmatinib based on *MET* amplification identified (CN8). He did not have a change in ECOG status. He developed new brain metastasis and passed away 2 years after diagnosis due to cancer progression in the chest and the resulting respiratory failure.

Subject 3

A 71-year-old male, never smoking patient presented with back pain. On his initial X-ray imaging, a compression fracture was identified on the L2 vertebra. A follow-up MRI of the L-spine showed multiple lesions within the lumbar spine and sacrum signifying stage IV disease, and a CT scan also showed bilateral sub centimeter lung nodules. A biopsy of the left pelvis metastasis confirmed the diagnosis of *EGFR* L858R lung adenocarcinoma. He started on osimertinib and completed palliative radiotherapy to T12–L4. He tolerated osimertinib without issues and had no active disease for 2 years until he had new lower back pain and spine MRI, which showed progressing disease in the bone. Plasma NGS at the same time identified *BRAF* V600E along with several new *EGFR* mutations (*EGFR* L718Q, *EGFR* L792V & *EGFR* L718V). The patient was then changed to dabrafenib and trametinib in combination

with osimertinib. The patient had constipation and headache during therapy without change in ECOG status. He continued to have back pain with cancer progression and passed away 3 years after diagnosis due to brain metastasis and associated leptomeningeal disease.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for the publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

From our study, we conclude that osimertinib in combination with dabrafenib and trametinib can have a significant ORR, mPFS and mOS. Specifically, the cohort had a clinically meaningful 60% ORR and mPFS of 7 months in the treatment refractory setting. A recent publication included three cases with time on the combination of osimertinib, dabrafenib, and trametinib to be 1, 9, and 23 months (5).

Multiple clinical trials are currently investigating the use of osimertinib concurrent with other targeted therapies in the resistance setting. The INSIGHT 2 study is assessing the addition of tepotinib after *MET* amplification (copy number ≥5) resistance to first-line osimertinib (18). The confirmed ORR was 54.5% in the tepotinib with osimertinib group and 8.3% in the tepotinib only group. These findings suggest that subclonal cellular populations remain dependent on *EGFR* and can be sensitive to osimertinib even in the setting of acquired resistance oncogenes. In addition, the acquired *EGFR* C797S mutation in our patient after combination therapy suggest continued *EGFR* dependence in subclonal mutant populations supporting the continued use of EGFR-TKI in the resistance setting. Since our cohort included published case reports, there may be a publication bias selecting for patients with response on triplet therapy. Further prospective evaluation is required to best understand efficacy and dosing strategies for dabrafenib and trametinib concurrent with osimertinib. Currently, the ORCHARD clinical trial is evaluating a cohort of osimertinib and selumetinib for *BRAF* V600E or *BRAF* fusion acquired resistance to osimertinib.

It is important to highlight the adverse events that were seen on triplet therapy. Two cases of pneumonitis were reported, and this required corticosteroids in one case and discontinuation of the triplet therapy in the other. Major toxicities were uncommon as only 1 grade 3 (creatine phosphokinase elevation) and no grade 4 toxicities were reported. The high number of dose reductions suggest that a dose escalation strategy may be preferential to avoid treatment limiting toxicities. Additional studies are needed to evaluate the combination of encorafenib and binimetinib with osimertinib as there may be different adverse events across the various *BRAF*/*MEK* combinations.

Toxicity of combination osimertinib with non-*EGFR* targeted therapy has been evaluated in prospective studies. The TATTON trial evaluated combinatory osimertinib with savolitinib in patients with *MET* amplification after EGFR-TKI progression (19). The savolitinib arm at 300 mg qday versus 600 mg qday dosing had an incidence of grade 3 or worse adverse events of 38% and 57% respectively. Combinatory strategies can be tolerable, but special consideration for additional toxicity is required for triple targeting agents.

We demonstrate the importance of genomic sequencing in the setting of osimertinib resistance to identify acquired actionable mutations. Two patients at University of California San Diego received a serial plasma biopsy strategy to understand subclonal evolution on triplet therapy. In both cases, there was initial *BRAF* V600E circulating tumor DNA (ctDNA) clearance after triplet therapy initiation coinciding with radiographic tumor shrinkage. For patient 1, we observed the ctDNA rise of a novel *EGFR* C797S mutation which is a known acquired resistance mutation from osimertinib selective pressure (4,20). The detection of a novel *EGFR* C797S mutation while on triplet therapy suggests that osimertinib may continue to drive resistance with on-target effects. In summary, serial biopsies can show the clearance of *BRAF* V600E cfDNA on *BRAF*/*MEK* inhibition and can be utilized to observe the rise of potential resistance mutations in this setting.

Conclusions

In this case series, we conclude that combination osimertinib, dabrafenib, and trametinib therapy can be efficacious and tolerable in *BRAF* V600E acquired *EGFR*-mutant NSCLC; however, attention to the adverse event profile of the triplet regimen is an important consideration. Molecular testing post-osimertinib progression to identify possible actionable mutations is a standard of care post-progression on EGFR-TKIs. At the time of publication, there is no prospective clinical trial assessing the combination of *BRAF*/*MEK* inhibition in patients with acquired *BRAF* V600E

mutation post-osimertinib. Currently the ORCHARD clinical trial is evaluating osimertinib and selumetinib post-progression on osimertinib with *BRAF* V600E or *BRAF* fusion mediated resistance. We propose that additional clinical trials investigating triplet combination therapy after osimertinib progression may be considered with *BRAF/MEK* inhibitors (21). Further work is needed to understand the significance of targeted therapy sequencing in the treatment of both primary and acquired oncogene driven cancers.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-629/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-629/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-629/coif). H.H. has received consulting fees from Janssen and Astrazeneca and honoraria from Janssen, Astrazeneca, Neogenomics, and Foundation Medicine. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for the publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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