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SHORT COMMUNICATION

Afatinib in patients with solid tumors with neuregulin 1 (*NRG1*) fusions: a case series from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

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Background: TAPUR is a phase II basket trial evaluating the antitumor activity of commercially available targeted agents in patients with advanced cancer and targetable genomic alterations. Results of four patients with various tumors with *NRG1* fusions treated with afatinib are reported.

Patients and methods: Eligible patients had advanced cancer, measurable disease (RECIST), Eastern Cooperative Oncology Group performance status 0-2, adequate organ function, tumors with *NRG1* fusions, and no standard treatment options. The primary endpoint was disease control (DC), defined as objective response (OR) or stable disease (SD) of at least 16 weeks' duration (SD16+). Secondary endpoints included OR, duration of response, duration of SD, and safety.

Results: Four patients were enrolled from February 2020 to July 2021; all had solid tumors [colorectal cancer ($n = 2$), non-small-cell lung cancer ($n = 1$), and pancreatic adenocarcinoma ($n = 1$)] with an *NRG1* fusion. All patients were evaluable for efficacy. One partial response and two SD16+ were observed. One patient was still alive as of October 2024 with SD of 134 weeks' duration. No patients had a drug-related grade 3-5 adverse event (AE) or serious AE.

Conclusion: Though the sample size was small, afatinib demonstrated promising activity in patients with advanced solid tumors with *NRG1* fusions, including durable DC warranting additional study.

Key words: case series, afatinib, *NRG1* fusion

INTRODUCTION

Gene fusions involving *ERG*, *ALK*, *RET*, *FGFR*, and others have been shown to drive tumorigenesis in various cancers.[1] *NRG1* fusions are rare but actionable genomic alterations reported in <1% of cancers.[2] *NRG1* fusions activate the erythroblastic leukemia viral oncogene (ERBB) signaling pathway and promote tumor growth.[2] The highest incidence of *NRG1* fusions has been reported in breast cancer (0.301%), cholangiocarcinoma (0.263%), and non-small-cell lung cancer (NSCLC; 0.232%).[3] NRG1 binds to ERBB3/4 to activate the ERBB signaling pathway and promote cell survival, proliferation, migration, and differentiation.[4]

ERBB-targeting agents demonstrated clinical activity in patients with tumors harboring *NRG1* fusions. The ERBB2/3 bispecific antibody zenocutuzumab was recently approved by the Food and Drug Administration (FDA) for patients with advanced NSCLC or pancreatic adenocarcinoma (PDAC) harboring *NRG1* fusions.[5] Afatinib is a tyrosine kinase inhibitor that binds to and inhibits the activity of epidermal growth factor receptor (EGFR), ERBB2, and ERBB4.[6]

Case studies reported clinical responses to afatinib in patients with tumors harboring *NRG1* fusions including lung cancer, colorectal cancer (CRC), PDAC, and hepatocellular carcinoma.[7-13] A retrospective analysis of patients with solid tumors harboring *NRG1* fusions reported a 37.5% overall response rate to afatinib.[14] Most patients receiving afatinib had NSCLC (40.3%) or PDAC (15.3%), and the objective response (OR) rates (ORRs) were 48.3% and 9.1%, respectively. Two of three patients with CRC had complete responses (CRs) to afatinib and four of eight patients with cholangiocarcinoma had partial responses (PRs) to afatinib.[14]

The TAPUR Study is a prospective, phase II, pragmatic, basket clinical trial designed to identify signals of antitumor activity of commercially available targeted agents in patients with advanced cancers that harbor targetable

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genomic alterations. This single-arm, open-label trial describes the efficacy and toxicity of targeted therapies outside of their approved indications. In this analysis, the results of four patients with solid tumors harboring *NRG1* fusions treated with afatinib are reported.

PATIENTS AND METHODS

The rationale, general design, and eligibility criteria of the TAPUR Study (ClinicalTrials.gov: NCT02693535) have been previously reported.[15] The methods specific to the data collection and analysis of a cohort, defined in TAPUR as a group of patients with the same tumor genomic target, tumor type, and study treatment received, have been previously reported for other cohorts.[16]

Patients

Eligible patients were required to meet both general and drug-specific eligibility criteria. General eligibility criteria include advanced or metastatic solid tumors, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2, and a protocol-specified genomic target identified by a Clinical Laboratory Improvement Amendments-certified and College of American Pathologists or NY State-accredited laboratory. Solid tumors were required to be measurable as per RECIST version 1.1.[17] To match to afatinib, patients with solid tumors must have had a tumor harboring an *NRG1* fusion and must not have had NSCLC with pathogenic mutations in *ALK*, *BRAF*, *EGFR*, or *ROS1*.

Genomic tests used to identify patients for this study are listed in Table 1. Patients self-administered a 40-mg tablet of afatinib daily until clinical and/or radiographic evidence of progressive disease (PD), withdrawal due to unacceptable toxicity, patient preference, or physician recommendation to discontinue.

Study endpoints

The primary endpoint was disease control (DC), based on investigator assessment, and defined as OR or stable disease (SD) of at least 16 weeks' duration (SD16+) from the initiation of study treatment as determined by RECIST version 1.1.[17] Secondary endpoints were OR, progression-free survival, overall survival, duration of response (DOR), duration of SD, and safety. DOR was defined as the time from the participant's first documented response until disease progression. Duration of SD was defined as time from the initiation of study treatment until disease progression. Radiographic assessment and clinical evaluation for response were carried out at 8 and 16 weeks after treatment initiation, and every 12 weeks thereafter while the patient was on treatment. A central independent review of imaging was not carried out. All serious adverse events (SAEs) and grade 3-5 treatment-related adverse events (AEs) were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical considerations

Patients in the TAPUR Study were placed in multiple parallel cohorts defined by study drug, tumor type, and genomic target. Each cohort used the same optimal Simon's two-stage design,[18] with a null hypothesized DC rate of 15% versus the alternative of 35%. Power and α levels were set at 85% and 10%, respectively. The study design required 10 patients to be enrolled in a cohort for stage I, and if fewer than 2 patients had DC, the cohort was permanently closed for futility. Otherwise, the cohort expanded to stage II and enrolled 18 additional patients. This cohort was closed due to slow enrollment after 2 years before completing stage I enrollment according to a prespecified cohort closure rule. Since the cohort closed before the completion of stage I, the primary endpoint of DC is presented individually for each patient and is not summarized.

Due to the small sample size, times to progression and times to death (TTD) are reported for each patient individually. All patients receiving at least one dose of treatment were included in the safety analysis. Analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC) and R 4.2.2 (R Core Team; R Foundation for Statistical Computing, Vienna, Austria).

Trial oversight

The study protocol was approved by a central institutional review board (IRB) and, in some cases, by a local IRB at

Table 1. Baseline demographic and clinical characteristics of patients with solid tumors with *NRG1* fusion ($N = 4$)

Characteristic	Case			
	No. 1	No. 2	No. 3	No. 4
Age (years)	58	47	49	70
Sex	Female	Female	Male	Female
Race	White	White	Black	White
Ethnicity	Non-Hispanic	Hispanic	Non-Hispanic	Non-Hispanic
Smoking status	Nonsmoker	Nonsmoker	Nonsmoker	Nonsmoker
Primary origin of tumor	Lung	Colon	Pancreas	Colon
ECOG PS	0	1	1	0
Prior lines of therapy (*n*)	3	3	5	1
Prior lines of radiation (*n*)	1	0	0	0
Genomic test	FoundationOne CDx	Genetrails Solid Tumor Fusion Gene Panel	Caris MI Profile X	FoundationOne CDx

ECOG PS, Eastern Cooperative Oncology Group performance status.

participating sites. Patients provided written consent before any screening activities or data collection began. The study was designed by American Society of Clinical Oncology (ASCO) staff with input from ASCO volunteer members, patient advocates, and participating pharmaceutical companies. The TAPUR Data and Safety Monitoring Board (DSMB) is an ASCO-appointed board that reviews all cohorts for futility after stage I enrollment is completed and recommends closure or expansion to stage II and release of data when the primary endpoint is met in all patients in each cohort. After this cohort was closed, the DSMB reviewed and released the findings.

CASE PRESENTATIONS

Case No. 1

A 58-year-old white, non-Hispanic, non-smoking female presented with NSCLC (adenocarcinoma) and started treatment on TAPUR in December 2020 (Table 1). This patient had an ECOG PS of 0 and had received three prior systemic therapies, including carboplatin and pemetrexed from February 2019 to April 2019, durvalumab from June 2019 to April 2020, and nivolumab (dates unknown) with a best response of PD to nivolumab. Genomic testing was carried out 11 months before enrolling in the TAPUR Study using a FoundationOne CDx (Foundation Medicine, Cambridge, MA) assay and revealed a *CD74—NRG1* fusion. Best percent change in target lesion size from baseline was 31% (Figure 1). The patient had PR that lasted 24 weeks and progressed after 32 weeks on treatment (Figure 2). Percent change in tumor burden over time is shown in Figure 3. TTD was 67 weeks (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.104545). No AEs or SAEs were reported. This patient died in April 2022.

Case No. 2

A 47-year-old white, Hispanic female presented with metastatic colorectal adenocarcinoma (left sided) and started treatment on TAPUR in February 2020 (Table 1). This patient had an ECOG PS of 1 and had received three prior therapies including FOLFOX from September 2017 to March 2018, surgical resection of their omentum, umbilicus, bladder, and left ovary in May 2018, and FOLFOX plus bevacizumab from August 2019 to December 2019, experiencing SD of 14 weeks as their best response to FOLFOX plus bevacizumab. Genomic testing was carried out using the Genetrails Solid Tumor Fusion Gene Panel (Knight Diagnostic Laboratories, Portland, OR) 7 months before enrolling in the TAPUR Study and revealed a *MATN—NRG1* fusion. This patient was tested for *KRAS* alterations, and none were found. Best percent change in target lesion size from baseline was 17% (Figure 1). This patient had SD that lasted 136 weeks and she then underwent resection of a remaining target lesion in September 2022 and ended treatment. This patient is still alive and has not progressed as of October 2024 (Figure 2). Percent change in tumor burden over time is shown in Figure 3. No AEs or SAEs were reported.

Case No. 3

A 49-year-old black, non-Hispanic male presented with PDAC and started treatment on TAPUR in July 2021 (Table 1). This patient had an ECOG PS of 1 and five prior therapies including FOLFOXIRI from April 2019 to November 2019, gemcitabine and nab-paclitaxel from December 2019 to February 2020, SGN-CD228A (a CD228-directed antibody—drug conjugate) from March 2020 to July 2020, surgery on their liver in March 2021, and MCLA-128 [a bispecific antibody that targets human epidermal growth factor receptor 2 (HER2) and HER3] from September 2020 to June 2021, experiencing SD of 20 weeks as best response to MCLA-128. Genomic testing was carried out using a Caris Molecular Intelligence Profile X (Caris Life Sciences, Irving, TX) panel 10 months before enrolling in the TAPUR Study and revealed an *ATP1B1—NRG1* fusion. This patient's tumor was tested for *KRAS* alterations, and none were found. Best percent change in target lesion size from baseline was 9% (Figure 1). This patient had SD that lasted 64 weeks

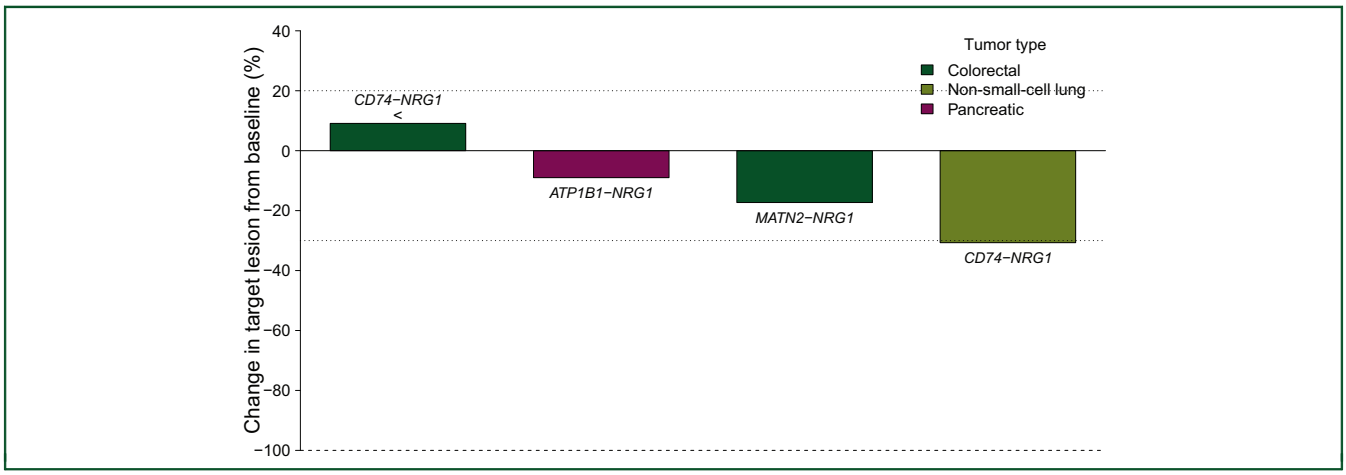

Figure 1. Best percent change from baseline in target lesions ($n = 4$). Color coding in the plot indicates tumor origin. *NRG1* fusion is reported above/below bars. <, stable target lesions, but clinical progression assessed by treating physician at the same evaluation.

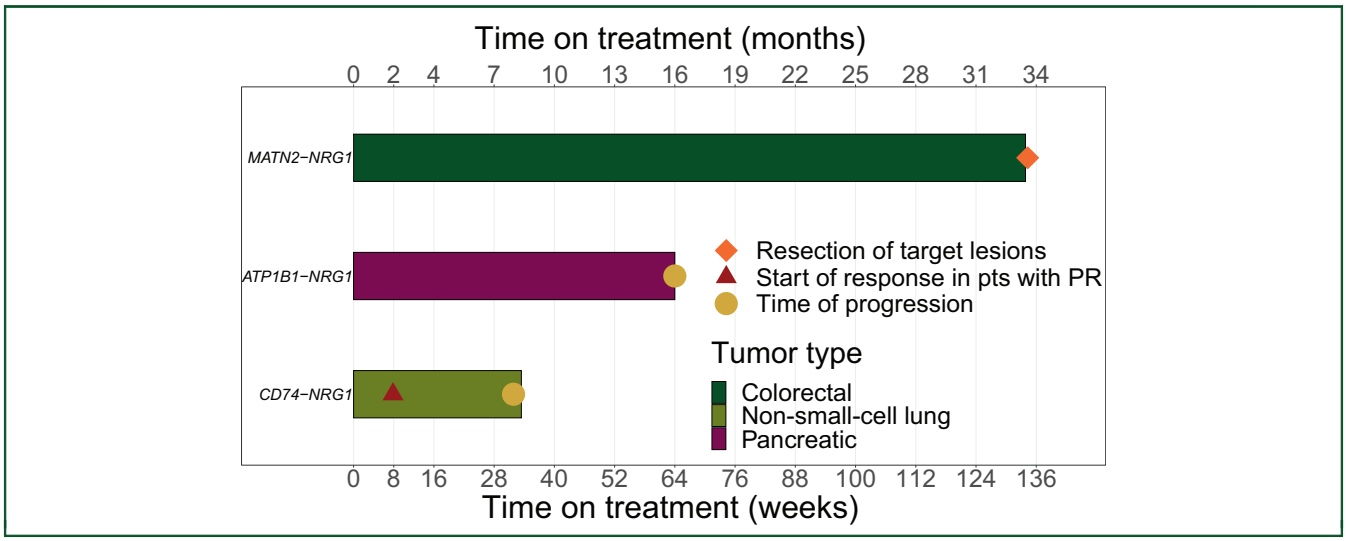

Figure 2. Time on treatment of three patients with SD16+ or OR. Color coding in the plot indicates tumor origin.
OR, objective response; PR, partial response; pts, patients; SD16+, stable disease of at least 16 weeks' duration.

(Figure 2). Percent change in tumor burden over time is shown in Figure 3. TTD was 94 weeks (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.104545). No AEs or SAEs were reported.

Case No. 4

A 70-year-old white, non-Hispanic female presented with CRC (sidedness unknown) and started treatment on TAPUR in March 2021 (Table 1). This patient had an ECOG PS of 0 and one prior systemic therapy regimen of oxaliplatin (November 2020 to January 2021) plus capecitabine (November 2020 to February 2021) with a best response of PD. Genomic testing was carried out on the patient's tumor tissue using the FoundationOne CDx (Foundation Medicine) assay 4 months before enrolling in the TAPUR Study and revealed a *CD74—NRG1* fusion. This patient's tumor was tested for *KRAS* alterations, and none were found. Best percent change in target lesion size from baseline was 9%, and progression was based on clinical assessment and not radiographic evidence (Figure 1). Percent change in tumor burden over time is shown in Figure 3. This patient had a best response of PD and progressed at 8 weeks. TTD was 35 weeks (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.104545). No AEs or SAEs were reported. This patient died in November 2021.

For each patient, genomic co-alterations in their tumor tissue are reported in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.104545.

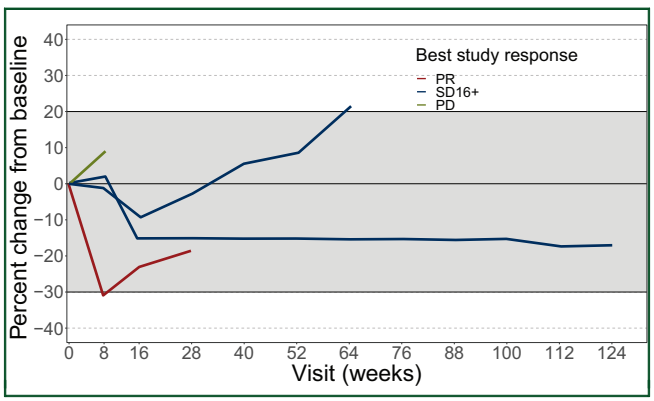

Figure 3. Percent change from baseline of tumor burden during afatinib treatment in four patients with solid tumors with *NRG1* fusions. Color coding in the plot indicates best response observed during the period of observation.
PD, progressive disease; PR, partial response; SD16+, stable disease of at least 16 weeks' duration.

DISCUSSION

This study demonstrated durable responses to afatinib in three patients with tumors harboring *NRG1* fusions (NSCLC, CRC, and PDAC).

One patient with NSCLC with a *CD74—NRG1* fusion had a PR that lasted 24 weeks. This aligns with a retrospective analysis by Liu et al. that reported a 48.3% ORR to afatinib in patients with NSCLC with *NRG1* fusions.[14] Also, a case series demonstrated PR in four patients with lung cancer with *NRG1* fusions.[8] Several case reports have also demonstrated durable responses to afatinib in patients with lung cancer harboring *NRG1* fusions.[7,10-13] Our data also align with the recent FDA approval of zenocutuzumab for patients with advanced NSCLC with *NRG1* fusions.

NRG1 fusions have a prevalence of 0.1%-0.5% in gastrointestinal tumors.[2] We observed SD of 64 weeks' duration in a patient with PDAC with an *NRG1* fusion aligning with case reports.[9,12] Liu et al. reported a 9.1% ORR in patients with PDAC with *NRG1* fusions treated with afatinib.[14] Notably, zenocutuzumab was recently approved by the FDA for patients with advanced PDAC with *NRG1* fusions based on a study by Schram et al. that demonstrated a 44% ORR in this patient population.[5]

Liu et al. also demonstrated CRs to afatinib in two of three patients with CRC harboring *NRG1* fusions.[14] Other studies reported significant responses to afatinib across five patients with CRC (three had *KRAS* co-mutations, two had

KRAS wild type) harboring an *NRG1* fusion.[8,12,19] Our study included two patients with CRC harboring *NRG1* fusions: one patient demonstrated prolonged SD (no *KRAS* alterations) and the other had PD (no *KRAS* alterations).

Due to the pragmatic nature of the TAPUR Study, minimal data collection was required to minimize the burden on patients, clinical sites, and treating physicians. Thus, we do not have access to patient scans and only collect the three most recent treatments before TAPUR enrollment. While the results of this study are encouraging and align with prior studies, large clinical trials of afatinib in these patient populations are needed to solidify these findings, despite the challenges due to the rarity of *NRG1* fusions.

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DISCLOSURE

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