NRG1 fusion-positive (NRG1+) tumors: Afatinib as a novel potential treatment option

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Introduction

**NRG1 gene fusions**

- NRG1 is a growth factor that contains an EGF-like domain that binds to ErbB3 or ErbB4, activating ErbB signaling pathways\(^1,2\) (Figure 1)
- Clinically actionable *NRG1* gene fusions, which increase cell proliferation through ErbB signaling and may function as oncogenic drivers, have been identified in multiple tumors, including NSCLC\(^2-4\)
  - *NRG1* fusions have an estimated overall frequency of ~0.2% across solid tumors\(^4\) and have a reported prevalence of up to 31% in lung IMA\(^5\)
- In a study of Chinese patients, *NRG1* fusions occurred in 0.36% of all lung adenocarcinoma cases\(^6\)
  - This included four *CD74-NRG1* fusion-positive cases, one *RBPMS-NRG1* fusion-positive case, and one novel *ITGB1-NRG1* fusion-positive case

CD74, cluster of differentiation 74; EGF, epidermal growth factor; IMA, invasive mucinous adenocarcinoma; ITGB1, integrin subunit beta 1; NRG1, neuregulin 1; RBPMS, RNA-binding protein with multiple splicing
Afatinib as a novel potential treatment option

- Afatinib is an irreversible pan-ErbB family blocker\(^7\)
- Due to the involvement of ErbB-signaling pathways in NSCLC tumors harboring \(NRG1\) fusions, afatinib may represent a viable therapeutic option in this setting
- This theory is supported by case reports for:
  - One patient with \(SLC3A2-NRG1\) fusion-positive non-mucinous lung adenocarcinoma\(^8\)
  - One patient with \(SDC4-NRG1\) fusion-positive lung adenocarcinoma\(^9\)
  - Two patients with \(CD74-NRG1\) fusion-positive lung IMA\(^8,10\)
  - One patient with \(ATP1B1-NRG1\) fusion-positive pancreatic adenocarcinoma\(^11\)
  - One patient with \(ATP1B1-NRG1\) fusion-positive cholangiocarcinoma\(^12\)
  - One patient with \(CLU-NRG1\) fusion-positive metastatic low-grade serious ovarian carcinoma\(^13\)
  - Two patients with \(APP-NRG1\) and \(ATP1B1-NRG1\) fusion-positive pancreatic ductal adenocarcinoma\(^14\)
- Here we present five new cases of \(NRG1\) fusion-positive tumors treated with afatinib

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APP, Amyloid Beta Precursor Protein; ATP1B1, ATPase Na+/K+ transporting subunit beta 1; CLU, clusterin; RAF, rapidly accelerated fibrosarcoma; SDC4, syndecan 4; SLC3A2, solute carrier family 3 member 2
Figure 1. Downstream signaling pathways associated with \textit{NRG1} fusions, and mechanism of action of afatinib

ErbB3 or ErbB4 containing homo or hetero ErbB dimer (i.e. 1/3, 1/4, 2/3, 2/4, 3/4 or 4/4)

\textbf{CD74-NRG1 fusion}

- PI3K
- RAF
- AKT
- MEK
- mTOR
- MAPK
- Increased cell proliferation

\textbf{Afatinib}

Pan-ErbB Family Blocker

\textbf{EGF-like domain}

AKT, protein kinase B; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase
Patient 1: Pan-wild type, non-mucinous, lung adenocarcinoma

- 70-year-old Caucasian female never-smoker, diagnosed in 2004
- Received 14 lines of therapy prior to afatinib, which included chemotherapy, and erlotinib + gefitinib
- Afatinib treatment (40 mg/day) was initiated in February 2015; the patient showed a rapid initial response and continued treatment for 24 months before discontinuation in March 2017 due to PD
- NRG1 fusion was identified in September 2017 by NanoString™ analysis
- Afatinib treatment (30 mg/day) was reinitiated in October 2017, leading to regression in lung condensations
- Discontinued after 3 months due to cough/fever
- Reinitiated in April 2018
- Afatinib discontinued in August 2018 due to PD

Best overall response on afatinib: PR
Duration of response, months: 24

PD, progressive disease; PR, partial response
Patient 2: Metastatic non-mucinous lung adenocarcinoma

- 66-year-old Asian female non-smoker with low body weight (<40 kg), with multiple lung and lymph node metastases at diagnosis (June 2015)
- Received four lines of treatment (cisplatin + pemetrexed; nivolumab; docetaxel + ramucirumab; nivolumab)
- CD74-NRG1 fusion identified, and afatinib treatment (40 mg/day) initiated in December 2017
- The patient had several dose adjustments to a minimum of 20 mg/day due to diarrhea and malaise symptoms
- After 19 months (July 2019), the patient remains on afatinib treatment (20 mg/day) with ongoing PR
Patient 2: Metastatic non-mucinous lung adenocarcinoma (cont’d)

CT imaging of Patient 2

Pre-treatment (Dec 2017)

+11 months afatinib (Nov 2018)

Best overall response on afatinib: PR
Duration of response, months: 19+
Patient 3: Non-mucinous invasive lung adenocarcinoma

- 68-year-old Caucasian male with a 20+ pack-year smoking history, diagnosed in January 2016
- Received two lines of treatment prior to afatinib (cisplatin + pemetrexed, best response: PD; nivolumab, best response: PR)
- SDC4-NRG1 fusion identified in March 2018, and afatinib treatment (30 mg/day) initiated in August 2018
- The patient had SD for 4 months
- Following this, afatinib was discontinued due to PD
- The patient opted to receive no further treatment and died shortly after in a hospice

SD, stable disease
Patient 3: Non-mucinous invasive lung adenocarcinoma (cont’d)

CT imaging of Patient 3

Pre-afatinib treatment (Jul 2018)  
+4 months afatinib (Dec 2018*)

Best overall response on afatinib  
SD

Duration of response, months  
4

*Scans were taken early December, before PD
Patient 4: Invasive mucinous lung adenocarcinoma

- 43-year-old Caucasian female non-smoker, diagnosed with lung IMA in August 2016
- Prior to afatinib, she received pemetrexed/cisplatin + bevacizumab, then bevacizumab/pemetrexed in maintenance until July 2017; finally, she received nivolumab until September 2017
- **CD74-NRG1** fusion detected by RNA sequencing
- Afatinib treatment (40 mg/day) initiated
- Treatment is ongoing, and the patient has had a major PR
Patient 4: Invasive mucinous lung adenocarcinoma (cont’d)

CT imaging of Patient 4

Pre-treatment (Jul 2017)

Best overall response on afatinib

Duration of response, months

+18 months afatinib (Mar 2019)
Patient 5: Metastatic colorectal cancer

- 69-year-old Caucasian male ex-smoker with KRAS-mutated metastatic colorectal cancer initially presented with GI bleeding in June 2017
- He underwent a right hemicolecotomy, and liver and lung metastasectomies after intolerance of FOLFOX and single-agent irinotecan
- Caris® profiling revealed a novel POMK-NRG1 fusion not previously seen in colorectal cancer
- Afatinib treatment (30 mg/day) was initiated in September 2018
- There was metastatic progression after 4 months, treated with localized RT
- Patient remains on afatinib with SD, 9 months from initiation (June 2019)
Patient 5: Metastatic colorectal cancer (cont’d)

CT imaging of Patient 5

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<tr>
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<th>+4 months afatinib (January 2019)</th>
<th>+7 months afatinib (April 2019)</th>
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<tr>
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<td>PD</td>
<td>SD</td>
<td>Increase in metastatic lesion size; treated with RT</td>
<td>SD</td>
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<tr>
<td>Lesion 2</td>
<td>PD</td>
<td>SD</td>
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Best overall response on afatinib: SD
Duration of response, months: 9+
Key findings and conclusions

- These findings add to a growing body of evidence suggesting afatinib activity in NRG1 fusion-positive tumors across multiple cancer types.
- Mutational testing of patients with solid tumors may help to identify potentially targetable genomic aberrations, such as NRG1 fusions.
- Prospective study is ongoing in the Drug Rediscovery Protocol trial (DRUP; NCT02925234); in addition, the Targeted Agent and Profiling Utilization Registry study (TAPUR; NCT02693535) NRG1 cohort is in preparation (not yet recruiting).
References

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