Targeting *NRG1*-fusions in lung adenocarcinoma: afatinib as a novel potential treatment strategy

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Presented at the 2019 World Conference on Lung Cancer (WCLC), Barcelona, Spain, 7–10 September 2019

Introduction

NRG1 gene fusions

- NRG1 is a growth factor that contains an EGF-like domain that binds to ErbB3 or ErbB4, activating ErbB signalling pathways[1,2] (Figure 1)
- Clinically actionable *NRG1* gene fusions, which increase cell proliferation through ErbB signalling and may function as oncogenic drivers, have been identified in multiple tumours, including NSCLC[2–4]
  - NRG1 fusions have an estimated overall frequency of ~0.2% across solid tumours[4] and have a reported prevalence of up to 31% in lung IMA[5]

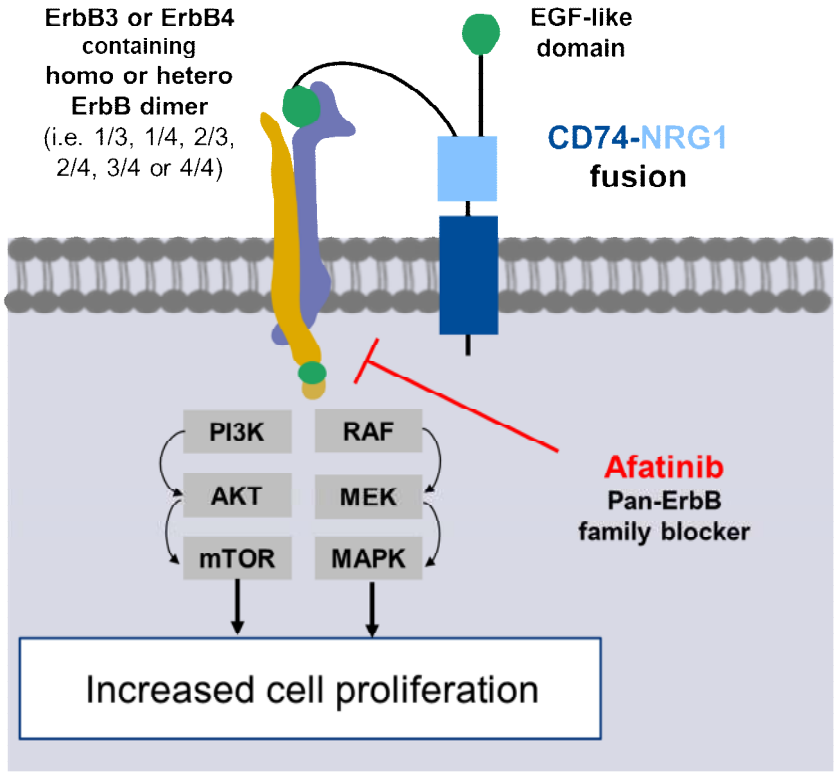
Afatinib as a novel potential treatment option

- Afatinib is an irreversible pan-ErbB family blocker[6]
- Due to the involvement of ErbB-signalling pathways in NSCLC tumours harbouring *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[7]
  - One patient with *SDC4-NRG1* fusion-positive lung adenocarcinoma[8]
  - Two patients with *CD74-NRG1* fusion-positive lung IMA[7,9]
- Here we present four new cases of *NRG1* fusion-positive lung adenocarcinoma treated with afatinib

EGF, epidermal growth factor; IMA, invasive mucinous adenocarcinoma; NRG1, neuregulin 1; SDC4, syndecan 4; SLC3A2, solute carrier family 3 member 2

Introduction (cont'd)

Figure 1. Downstream signalling pathways associated with *NRG1* fusions, and mechanism of action of afatinib



AKT, protein kinase B; CD74, cluster of differentiation 74; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma

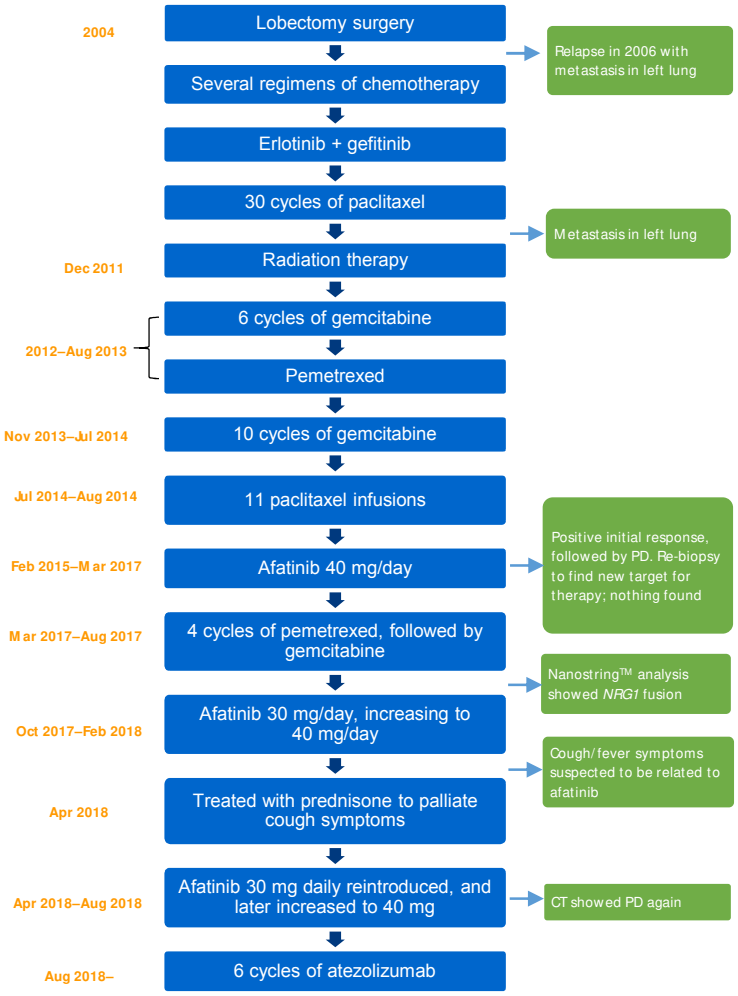
Patient 1: Pan-wildtype, non-mucinous, lung adenocarcinoma

- 70-year-old Caucasian female non-smoker, diagnosed in 2004
- Received 14 lines of therapy prior to afatinib, which included chemotherapy, and erlotinib + gefitinib (Figure 2)
- 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 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

CT, computerised tomography; PD, progressive disease; PR, partial response

Patient 1: Pan-wildtype, non-mucinous, lung adenocarcinoma (cont'd)

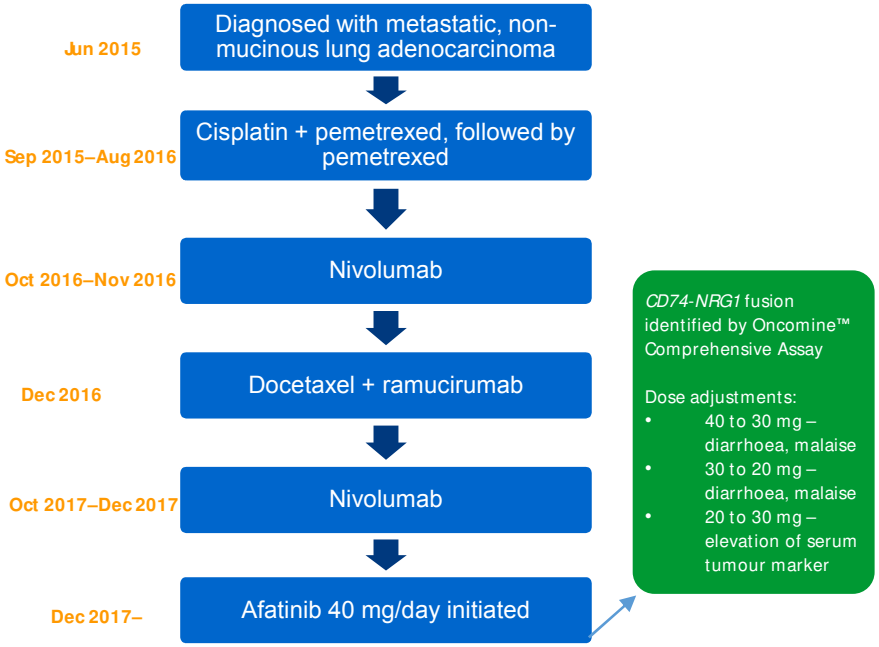
Figure 2. Patient 1 treatment overview



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 in June 2015
- Received four lines of treatment prior to afatinib (cisplatin + pemetrexed; nivolumab; docetaxel + ramucirumab; nivolumab; Figure 3)

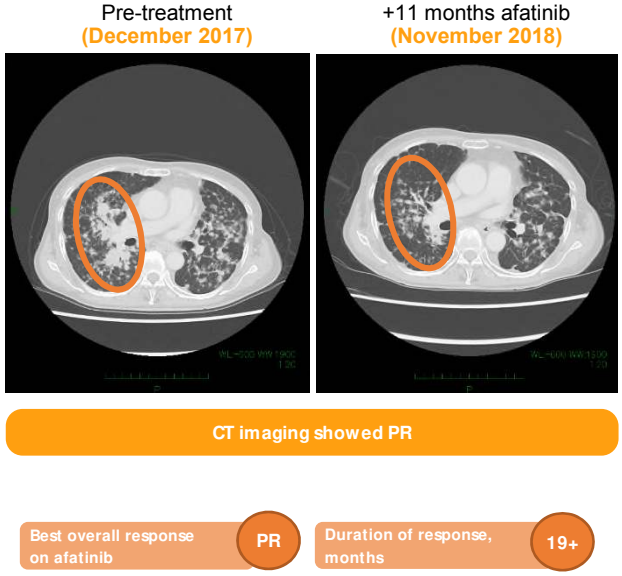
Figure 3. Patient 2 treatment overview



Patient 2: Metastatic non-mucinous lung adenocarcinoma (cont'd)

- Afatinib treatment (40 mg/day) was initiated in December 2017
- The patient had several dose adjustments to a minimum of 20 mg/day due to diarrhoea and malaise symptoms
- After 19 months (July 2019), the patient remains on afatinib treatment (20 mg/day) with ongoing PR (Figure 4)

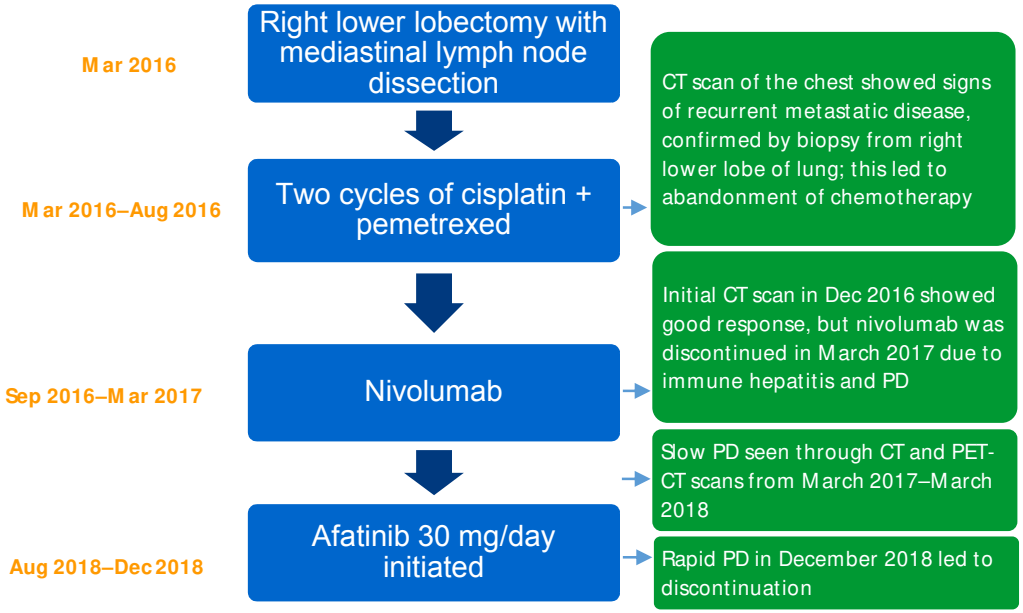
Figure 4. CT imaging of Patient 2



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; Figure 5)

Figure 5. Patient 3 treatment overview



PET, positron emission tomography; RNA, ribonucleic acid; SD, stable disease

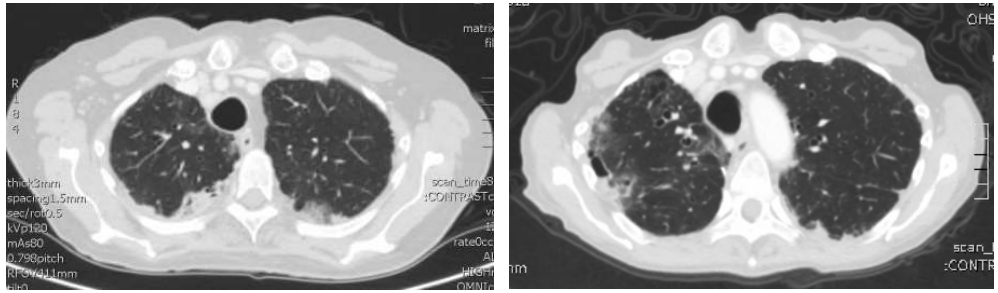
Patient 3: Non-mucinous invasive lung adenocarcinoma (cont'd)

- *SDC4-NRG1* fusion identified by RNA-sequencing in March 2018
- Afatinib treatment (30 mg/day) was initiated in August 2018
- The patient had SD for 4 months (Figure 6)
- Following this, afatinib was discontinued due to PD
- The patient opted to receive no further treatment and died shortly after in a hospice

Figure 6. CT imaging of Patient 3

Pre-afatinib treatment
(July 2018)

+4 months afatinib
(December 2018*)



*Scans were taken early December, before PD

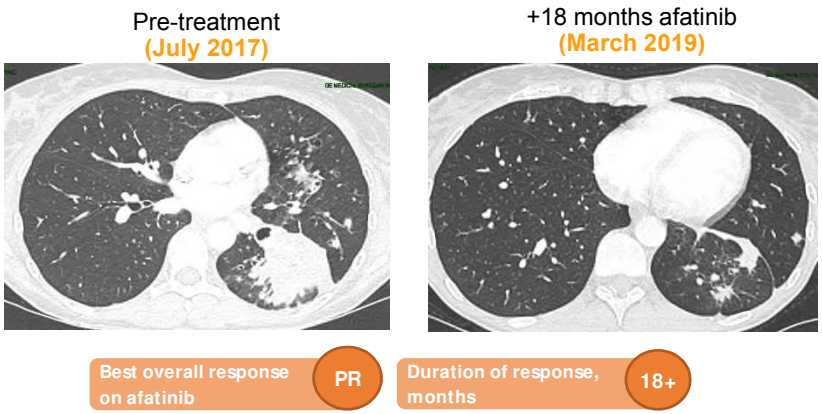
Best overall response on afatinib SD

Duration of response, months 4

Patient 4: Invasive mucinous adenocarcinoma of the lung

- 43-year-old Caucasian female non-smoker, diagnosed with lung IMA in August 2016
- Prior to afatinib, she received pemetrexed/cisplatin plus bevacizumab, then bevacizumab/pemetrexed as maintenance therapy 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 (Figure 7)

Figure 7. CT imaging of Patient 4



Key findings and conclusions

- These findings add to a growing body of evidence suggesting afatinib activity in *NRG1* fusion-positive NSCLC
- Mutational testing of patients with solid tumours may help to identify potentially targetable genomic aberrations, such as *NRG1* fusions
  - This may be particularly important in lung IMA, where *NRG1* fusion prevalence is relatively high
- A prospective study of a larger cohort of patients with *NRG1* fusion-positive NSCLC treated with afatinib is warranted to better evaluate its potential activity

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Acknowledgments

- This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version
- Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Steven Kirkham, of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the development of this poster