NRG1 fusion-positive gastrointestinal tumours: Afatinib as a novel potential treatment option

Benjamin A. Weinberg,1 Daniel Renouf,2 Howard Lim,2 Christoph Heining,3 Richard F. Schlenk,4 Martin R. Jones,5 Stephen V. Liu,1 Agnieszka Cseh,6 Flavio Solca,6 Janessa J. Laskin2

1Georgetown University Medical Center, Washington, DC, USA; 2Division of Medical Oncology, Department of Medicine, University of British Columbia, BC Cancer, Vancouver, BC, Canada; 3National Center for Tumor Diseases Dresden, Dresden, Germany; 4National Center of Tumor Diseases Heidelberg, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany; 5Bioinformatic Business Area, QIAGEN Inc., Redwood City, CA, USA; 6Boehringer Ingelheim RCV GmbH & Co KG, Vienna, Austria

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Introduction: *NRG1* gene fusions

- NRG1 is a growth factor that contains an EGF-like domain, which binds ErbB3 and ErbB4 and activates downstream ErbB family signalling pathways, leading to increased cell proliferation\(^1\)–\(^3\)
- Oncogenic *NRG1* gene fusions have been identified in various cancer subtypes including PDAC, colorectal cancer, and cholangiocarcinoma\(^1\)
- Although only thought to be present in around 0.1–0.5% of GI cancers,\(^1\) there is mounting evidence that these *NRG1* fusions are clinically actionable\(^1\)–\(^3\)

GI, gastrointestinal; NRG1, neuregulin 1; PDAC, pancreatic ductal adenocarcinoma
Introduction: Afatinib as a novel potential treatment option

- Afatinib is an irreversible ErbB family blocker
- Due to the involvement of ErbB-signalling pathways in GI tumours harbouring *NRG1* fusions, afatinib may represent a viable therapeutic option in this setting\(^1\)–\(^3\)

**Oncogenic overexpression of NRG1 fusions: mechanism of action**

- *ErbB3* or *ErbB4* containing homo or hetero *ErbB* dimer (i.e. 1/3, 1/4, 2/3, 2/4, 3/4 or 4/4)
- CD74-*NRG1* fusion
- EGF-like domain

**Afatinib**

- **PI3K**
- **RAF**
- **AKT**
- **mTOR**
- **MEK**
- **MAPK**

**Increased cell proliferation**
Introduction: Afatinib as a novel potential treatment option

- This theory is supported by preclinical evidence\(^2\) and published case reports for:
  - One patient with \textit{ATP1B1-NRG1} fusion-positive cholangiocarcinoma, who achieved a PR with afatinib, lasting 8 months\(^4\)
  - One patient with \textit{ATP1B1-NRG1} fusion-positive pancreatic adenocarcinoma, who achieved a PR of 3 months with afatinib\(^5\)
  - Two patients with \textit{APP-NRG1} and \textit{ATP1B1-NRG1} fusion-positive PDAC, for whom primary reports have been published\(^6\)

- Here, we present a new case of afatinib treatment in a patient with \textit{NRG1} fusion-positive colorectal cancer, and updated reports for two patients with \textit{NRG1} fusion-positive PDAC\(^6\)

PR, partial response
Patient 1: *KRAS*-mutated colorectal cancer

- 69-year-old male ex-smoker
  - presented with GI bleeding in June 2017
- His initial diagnosis was *KRAS*-mutated stage IVB right-sided colorectal cancer with liver and lung metastases
- Following progression on first-line treatment, Caris® profiling revealed a novel *NRG1-POMK* fusion not previously seen in colorectal cancer; indicating potential susceptibility to afatinib

POMK, protein O-mannose kinase
Patient diagnosed with KRAS-mutated stage IVB right-sided colorectal cancer with liver and lung metastases

First-line FOLFOX + single dose of irinotecan were not tolerated. Lung lesion was stable (1.0 to 0.8 cm); no hepatic response

Right hemicolecetomy was performed; first-line FOLFOX + irinotecan initiated

CT scan showed lung nodule size increase

Liver metastatectomy

Capecitabine (500 mg/day)

Caris® profiling from lung metastases revealed a novel NRG1-POMK fusion

Lung metastatectomies

Afatinib initiated (30 mg/day)

Sept 2018:
- CEA: 190.2 μg/mL
Oct 2018:
- CEA: 162.7 μg/mL

CEA, carcinoembryonic antigen; CT, computed tomography; FOLFOX, fluorouracil, leucovorin, oxaliplatin;
Patient 1: Treatment overview (cont’d)

- **Sept 2018**: Afatinib initiated (30 mg/day)
  - Sept 2018: CEA: 291.8 μg/mL
  - Oct 2018: CEA: 190.2 μg/mL

- **Nov 2018** (+2 months afatinib): CT revealed stable disease
  - Nov 2018: CEA: 291.8 μg/mL

- **Jan 2019** (+4 months afatinib): PET/CT revealed increase in metastatic lesion size
  - Feb 2019: CEA: 705.8 μg/mL

- **Mar 2019** (+6 months afatinib): Y90 liver-directed therapy + stereotactic body radiation to chest wall + afatinib (30 mg/day)
  - Apr 2019: CEA: 230.0 μg/mL
  - Afatinib-related AEs:
    - Manageable, occasional diarrhoea
    - Intermittent acneiform rashes

- **Apr 2019** (+7 months afatinib): Patient 1 remains on afatinib (30 mg/day) with stable disease
Patient 1: Response to afatinib

- Afatinib treatment (30 mg/day) was initiated in September 2018
  - Four months later, after initial stable disease, PET/CT revealed increased FDG-avidity in the chest wall and liver, consistent with metastatic disease
  - CEA levels increased to 705.8 μg/mL
- In March 2019, after local radiotherapy to chest wall and hepatic metastases, CT showed stable disease
  - CEA levels reduced to 230.0 μg/mL
  - *NRG1-POMK* fusion was still present in tissue from the liver biopsy
- As of June 2019, 9 months from afatinib initiation, Patient 1 remains on afatinib treatment
  - CEA levels on 5 June 2019 were 249.6 μg/mL

FDG, fluorodeoxyglucose
Patient 1: Radiological response to afatinib

Lesion 1

Pre-treatment (Aug 2018)  +2 months afatinib (Nov 2018)  +4 months afatinib (Jan 2019)  +7 months afatinib (Apr 2019)

Lesion 2
Patient 2: KRAS-wild-type metastatic PDAC

- 54-year-old male with a limited family history of cancer
  - presented with abdominal pain
- In March 2018, he was diagnosed with stage IV PDAC with metastasis to the liver
- Following intolerance to first-line treatment (gemcitabine + nab-paclitaxel), WGTA of tissue from a liver biopsy revealed a complex structural rearrangement leading to fusion of NRG1 (exons 6/7) and APP (between exons 15 and 16), indicating potential susceptibility to afatinib

*APP*, amyloid precursor protein; *WGTA*, whole-genome and transcriptome analysis
Patient 2: Treatment overview

Mar 2018
- Patient diagnosed with KRAS-Wt stage IV PDAC with liver metastases

May 2018
- First-line gemcitabine + nab-paclitaxel
- Disease progression

Oct 2018
- Afatinib initiated (30 mg/day)

Nov 2018
(+4 weeks afatinib)
- PET/CT revealed significant response to therapy

May 2019
(+7 months afatinib)
- CT revealed ongoing response

WGTA of tissue from liver biopsy revealed **APP-NRG1 fusion**

Discontinued after one cycle due to toxicity

**Disease characteristics:**
- FDG-avidity in pancreatic head mass, multiple metastatic lymph nodes and liver metastases
- CA19-9 within normal range

**Improvement in:**
- Pancreatic head FDG-avidity
- Resolution of hepatic metastases

**Afatinib-related AEs:**
- Minor facial rash/paronychia

CA19-9, carbohydrate antigen 19-9; Wt, wild-type
Patient 2: Response to afatinib

- Afatinib treatment (30 mg/day) was initiated in October 2018
  - After 4 weeks he had a significant radiological response, with resolution of multiple hepatic metastases and reduction in pancreatic head FDG-avidity
  - Response is ongoing over 7 months post-afatinib initiation, and the patient remains on afatinib treatment
Patient 2: Radiological response to afatinib

Pre-treatment (September 2018)

+4 weeks afatinib (November 2018)
Patient 3: *KRAS*-wild-type metastatic PDAC$^6$

- 59-year-old male with a family history of prostate and colon cancer
  - presented in 2017 with abdominal pain and weight loss
- His initial diagnosis was *KRAS*-Wt stage IV PDAC with multiple liver metastases
- WGTA revealed *ATP1B1*-*NRG1* fusion (exon 3 of *ATP1B1* with exon 2 of *NRG1*), leading to increased *NRG1* expression and potential susceptibility to afatinib
Patient 3: Treatment overview

Feb 2017
- Patient diagnosed with KRAS-Wt stage IV PDAC with multiple liver metastases
- First-line oxaliplatin + irinotecan + fluorouracil (FOLFIRINOX)
- Gemcitabine

Feb 2018
- Disease progression

Mar 2018
- Afatinib initiated (40 mg/day)

Apr 2018
- (+4 weeks afatinib)
- PET/CT revealed significant response to therapy

Jul 2018
- (+3 months afatinib)
- CT revealed ongoing response

Sep 2018
- (+5.5 months afatinib)
- CT revealed disease progression

Partial response followed by disease progression
- WGTA of tissue from liver biopsy revealed ATP1B1-NRG1 fusion
- Disease characteristics:
  - ECOG PS 2
  - CA19-9: >120,000 ng/mL
- Dose reduced to 30 mg/day during Cycle 1 due to diarrhea
- Improvement in:
  - FDG-avidity
  - CA19-9: 7,246 ng/mL
  - Pain + ECOG PS
- Afatinib-related AEs:
  - Minor skin rash
  - Minor diarrhea

ECOG PS, Eastern Cooperative Oncology Group performance status
Patient 3: Response to afatinib

- Afatinib treatment (40 mg/day, reduced to 30 mg/day due to toxicity) was initiated in March 2018
  - Significant radiological response was observed at 4 weeks
  - Significant improvements were observed in pain and performance status
- CT at 5.5 months from afatinib initiation showed disease progression
  - Patient 3 subsequently stopped treatment and died from progressive disease in early 2019
Patient 3: Radiological response to afatinib

Pre-treatment (March 2018)

+4 weeks afatinib (April 2018)
Key findings and conclusions

• These findings show anti-tumour activity of afatinib in patients with *NRG1* fusion-positive GI tumours, suggesting that afatinib is a potential treatment option in this setting.

• Mutational testing of patients with GI tumours, particularly in patients with *KRAS*-Wt pancreatic adenocarcinoma for whom there is a high unmet clinical need, may help to identify potentially targetable genomic aberrations, e.g. *NRG1* fusions.

• Further investigation of the therapeutic benefit of afatinib in GI and other cancer types is warranted.
References

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• Corresponding author email address: Benjamin.A.Weinberg@gunet.georgetown.edu