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

Benjamin A. Weinberg, Daniel Renouf, Howard Lim, Christoph Heining, Richard F. Schlenk, Martin R. Jones, Stephen V. Liu, Agnieszka Casz, Flavio Solca, Janessa L. Laskin

Introduction

NRG1 gene fusions

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

Afatinib as a novel potential treatment option

- Afatinib is a 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 (Figure 1-1)
- This theory is supported by preclinical evidence2 and published case reports for:
  - One patient with ATP7B-NRG1 fusion-positive cholangiocarcinoma, who achieved a partial response (PR) with afatinib, lasting 8 months
  - One patient with ATP7B-NRG1 fusion-positive pancreatic adenocarcinoma, who achieved a PR of 3 months with afatinib
  - Two patients with ARK-NRG1 and ATP1B1-NRG1 fusion-positive PDAC, for whom primary reports have been published
- Here, we present a new case of afatinib treatment in a patient with NRG1 fusion-positive colorectal cancer, and updated reports for two patients with NRG1 fusion-positive PDAC

Patient 1: Colorectal cancer

Patient 1 treatment overview

Jan 2017
- Initial diagnosis was KRAS-mutated stage IVB right-sided colorectal cancer with liver and lung metastases
- Attributable was irreversible ErbB family blocker
- Prior to the initiation of NRG1 FISH, patient was treated with line of mTOR inhibitor (mg/day during Cycle 1)

Mar 2017
- PET/CT revealed significant response to afatinib

May 2017
- PET/CT revealed ongoing response to afatinib

Patient 2: KRAS wild-type metastatic pancreatic cancer

- Patient 2, a 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 metastases to the liver
- Following response to frontline treatment (gemcitabine + nab-paclitaxel), WGA of tissue from the liver biopsy revealed a complex structural rearrangement leading to fusion of NRG1 ( exon 15 and 16), indicating potential susceptibility to afatinib

Patient 3: Pancreatic cancer

- Patient 3, a 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
- WGA revealed ATP1B1-NRG1 fusion ( exon 3 and 4 at ATP1B1) with exon 2 of NRG1, leading to increased NRG1 expression and potential susceptibility to afatinib

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


Figure 6. Patient 3 treatment overview

Patient 3 was a 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. WGA revealed ATP1B1-NRG1 fusion ( exon 3 and 4 at ATP1B1) with exon 2 of NRG1, leading to increased NRG1 expression and potential susceptibility to afatinib.

Figure 7. Patient 3 radiological response to afatinib treatment

Patient 3 responded to afatinib (Figure 7)

- Afatinib treatment (40 mg/day, reduced to 30 mg/day due to toxicity) was initiated in March 2018.
- Significant radiological response was observed in 4 weeks (Figure 7).
- Significant improvements were observed in laboratory performance status.
- CT at 5.5 months from afatinib initiation showed disease progression in early 2019.
- Patient 3 subsequently stopped treatment and died from progressive disease in early 2019.

Figure 8. Patient 2 radiological response to afatinib treatment

Patient 2 responded to afatinib (Figure 5)

- Afatinib treatment (20 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 
  FOG-avidity (Figure 5).
- Response is ongoing over 7 months post-afatinib initiation, and the patient remains on afatinib treatment.

Figure 1. Oncogenic overexpression of NRG1 fusions: mechanism of action

EGF or NRG1 in G1/S cells in tissues or blood: increased EGR activity

Increased cell proliferation

Patient 1: response to afatinib (Figure 3)

- Afatinib treatment (20 mg/day) was initiated in September 2018.
- Four months later, after initial stable disease, PET/CT revealed increased FOG 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, NR2C1/POMK fusion was still present in tissue from the liver biopsy.
- At the end of June 2019, 3 months from initiation, Patient 1 remained on afatinib treatment; CEA levels on 5 June 2019 were 246.8 μg/mL.

Figure 3. Patient 1 radiological response to afatinib treatment

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.

Patient 2: response to afatinib (Figure 5)

- Afatinib treatment (20 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 
  FOG-avidity (Figure 5).
- Response is ongoing over 7 months post-afatinib initiation, and the patient remains on afatinib treatment.

Figure 3. NRG1 fusion-positive gastrointestinal tumours: Afatinib as a novel potential treatment option

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.

Presented at the ESMO 21st World Congress on Gastrointestinal Cancer, Barcelona, Spain, 3-6 July 2019

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.

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

*These materials are for personal use only and may not be reproduced without prior written permission from NRG1 FUSION-positive tumors: Afatinib as a novel potential treatment option.