Scan the QR code for an electronic copy of the poster and supplementary material

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

#P-291
Category: Clinical
Topic: Other

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. Laskin[2]

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

Introduction

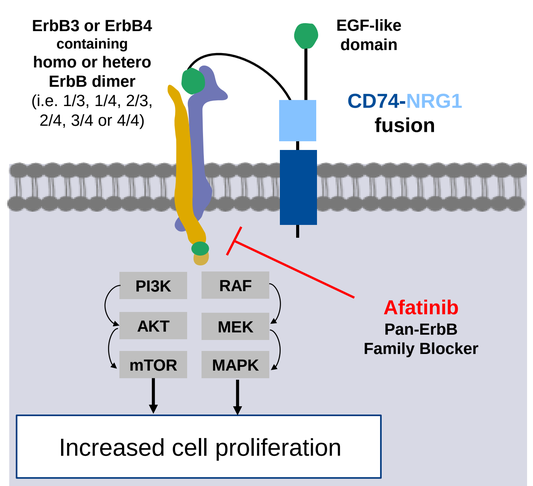
***NRG1* gene fusions**

- Neuregulin 1 (NRG1) is a growth factor that contains an epidermal growth factor (EGF)-like domain, which binds ErbB3 and ErbB4 and activates downstream ErbB family signalling pathways, leading to increased cell proliferation (**Figure 1**)[1–3]
- Oncogenic *NRG1* gene fusions have been identified in various cancer subtypes including pancreatic ductal adenocarcinoma (PDAC), colorectal cancer, and cholangiocarcinoma[1]
- 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[1–3]

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 (**Figure 1**)[1–3]
- This theory is supported by preclinical evidence[2] and published case reports for:
  - One patient with *ATP1B1-NRG1* fusion-positive cholangiocarcinoma, who achieved a partial response (PR) with afatinib, lasting 8 months[4]
  - One patient with *ATP1B1-NRG1* fusion-positive pancreatic adenocarcinoma, who achieved a PR of 3 months with afatinib[5]
  - Two patients with *APP-NRG1* and *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 *NRG1* fusion-positive colorectal cancer, and updated reports for two patients with *NRG1* fusion-positive PDAC[6]

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

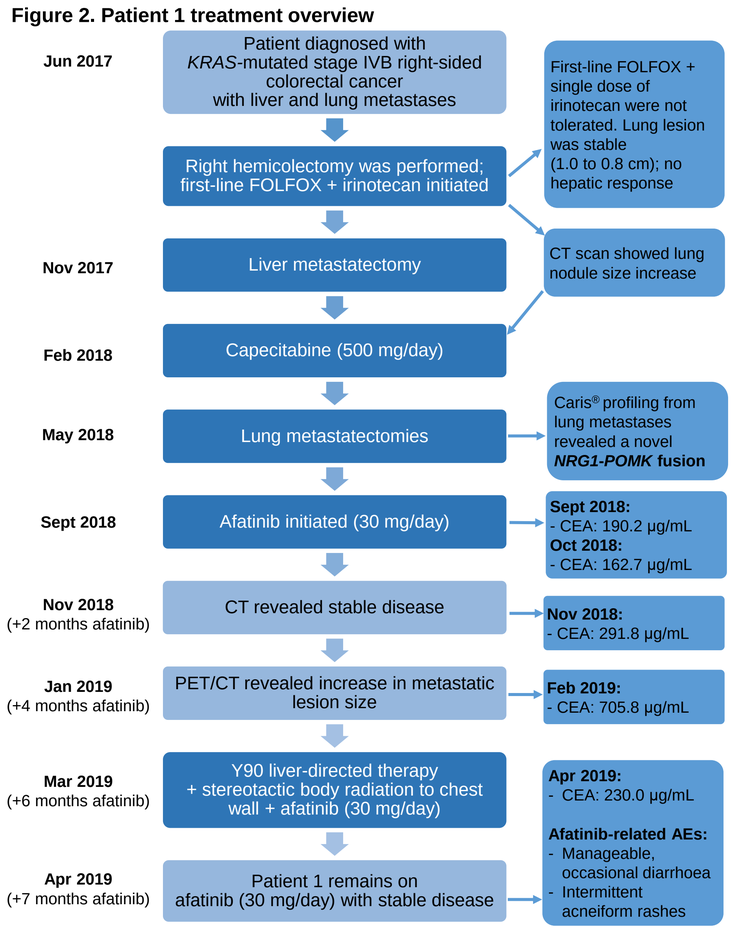


Patient 1: Colorectal cancer

Patient 1: *KRAS*-mutated, right-sided metastatic colorectal cancer

- Patient 1, a 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

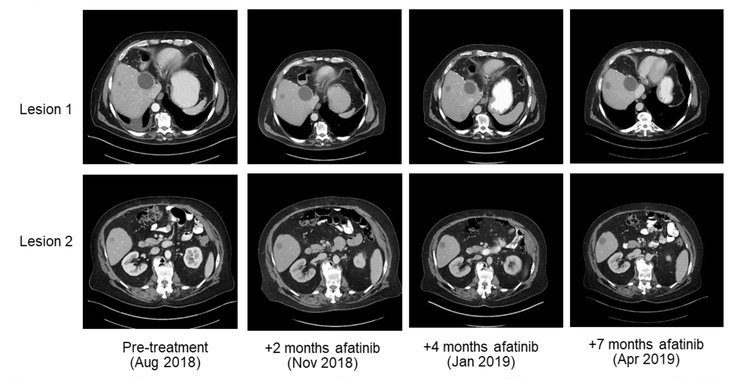
Figure 2. Patient 1 treatment overview



Patient 1: response to afatinib (Figure 3)

- 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

Figure 3. Patient 1 radiological response to afatinib treatment



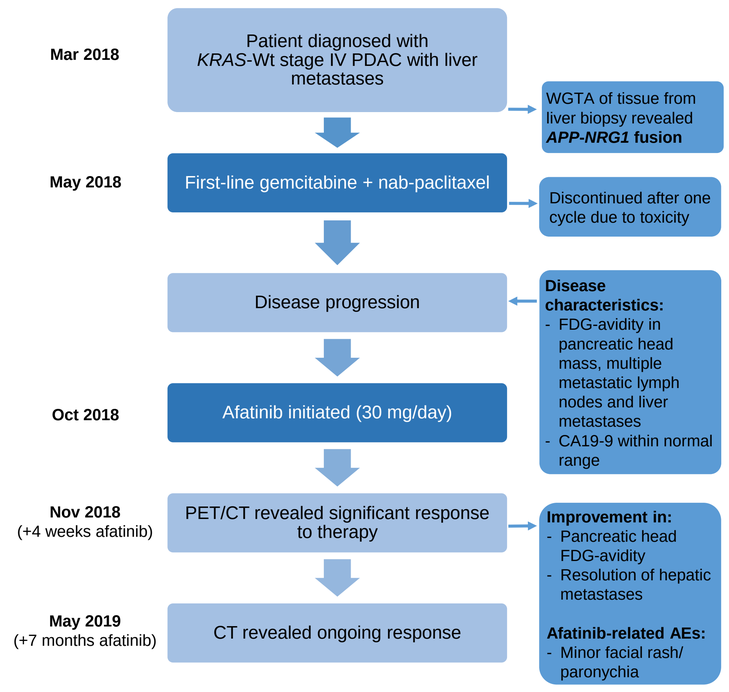
AE, adverse event; CEA, carcinoembryonic antigen; CT, computed tomography; FDG, fluorodeoxyglucose; FOLFOX, fluorouracil, leucovorin, oxaliplatin; PET, positron emission tomography; POMK, protein O-mannose kinase

Patient 2: Pancreatic cancer

Patient 2: *KRAS*-wild-type metastatic pancreatic cancer[6]

- 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 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

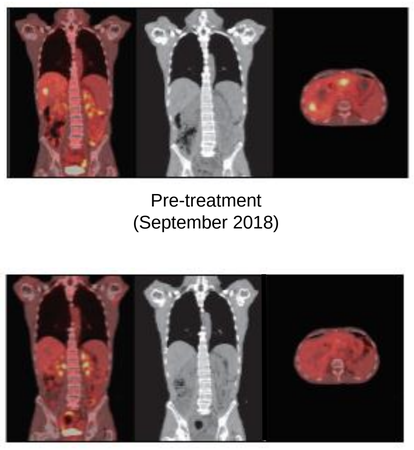
Figure 4. Patient 2 treatment overview



Patient 2: response to afatinib (Figure 5)

- 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 **(Figure 5)**
  - Response is ongoing over 7 months post-afatinib initiation, and the patient remains on afatinib treatment

Figure 5. Patient 2 radiological response to afatinib treatment



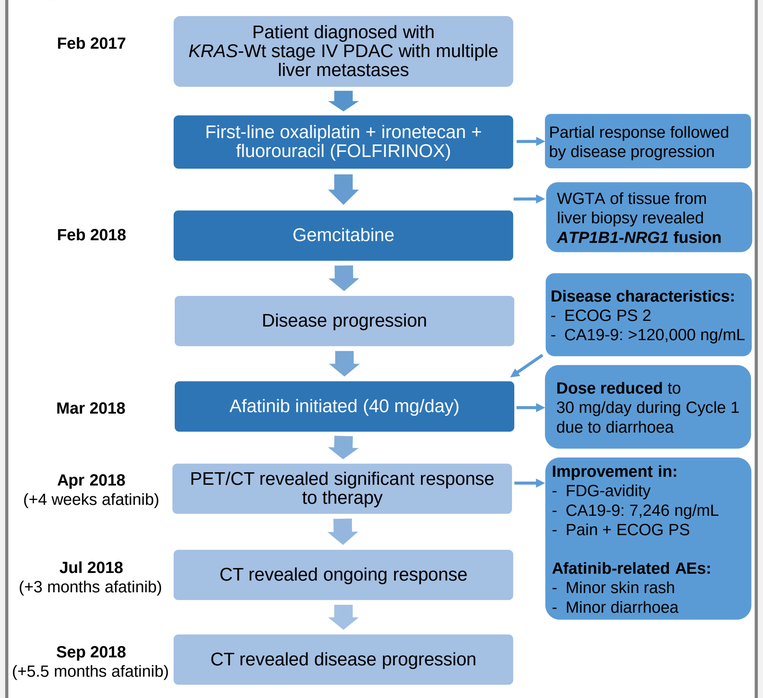
APP, amyloid precursor protein; CA19-9, carbohydrate antigen 19-9; WGTA, whole-genome and transcriptome analysis; Wt, wild-type

Patient 3: Pancreatic cancer

Patient 3: *KRAS*-wild-type metastatic pancreatic cancer[6]

- Patient 2, 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
- WGTA revealed *ATP1B1-NRG1* fusion (exon 3 of *ATP1B1* with exon 2 of *NRG1*), leading to increased *NRG1* expression and potential susceptibility to afatinib

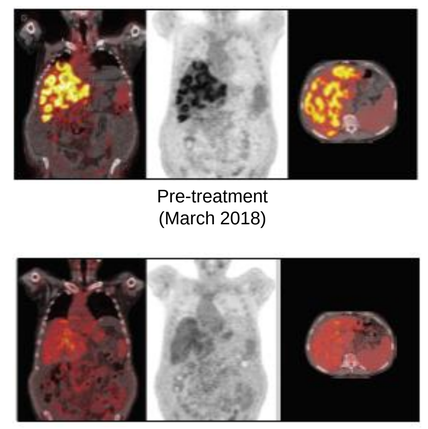
Figure 6. Patient 3 treatment overview



Patient 3: response 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 at 4 weeks (**Figure 7**)
  - 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

Figure 7. Patient 3 radiological response to afatinib treatment



ATP1B1, ATPase Na+/K+ Transporting Subunit Beta 1; ECOG PS, Eastern Cooperative Oncology Group performance status

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

1. Jonna S, et al. Clin Cancer Res 2019 [Epub ahead of print]; **2.** Drilon A, et al. Cancer Discov 2018;8:686–95; **3.** Fernandez-Cuesta and Thomas. Clin Cancer Res 2014;21:1989–94; **4.** Jones MR, et al. Ann Oncol 2017;28:3092–97; **5.** Heining C, et al. Cancer Discov 2018;8:1087–95; **6.** Jones MR, et al. Clin Cancer Res 2019 [Epub ahead of print]

Scan the QR code for an electronic copy of the poster and supplementary content†

http://tago.ca/RUZ

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.
Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Lucinda Sinclair, of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the development of this poster.
*Corresponding author email address: Benjamin.A.Weinberg@gunet.georgetown.edu

21WCGIC 291--P
Clinical Other
Benjamin Weinberg
DOI: 10.3252/pso.eu.21wcgic.2019
Poster presented at: ESMO WORLD CONGRESS ON Gastrointestinal Cancer
PosterSessionOnline.com