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

1969P

Targeting *NRG1*-fusions in multiple tumour types: Afatinib as a novel potential treatment option

Stephen V. Liu,[1]* Michaël Duruisseaux,[2] Khaled Tolba,[3] Eva Branden,[4] Yasushi Goto,[5] Benjamin A. Weinberg,[6] Daniel J. Renouf,[7] Robert C. Doebele,[8] Christoph Heining,[9] Richard F. Schlenk,[10] Parneet Cheema,[11] Jacques Cadranel,[12] Martin R. Jones,[13] Alexander E. Drilon,[14] Domenico Trombetta,[15] Lucia A. Muscarella,[15] Agnieszka Cseh,[16] Flavio Solca,[17] Janessa J. Laskin[7]

[1]Division of Medical Oncology, Georgetown University, Washington, DC, USA; [2]Department of Respiratory Medicine, Hospices Civils de Lyon Cancer Institute, Université Claude Bernard Lyon 1, Lyon, France; [3]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [4]Department of Respiratory Medicine, Gävle Hospital, Gävle, Sweden; [5]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; [6]Division of Hematology and Oncology, Georgetown University Medical Center, Washington, DC, USA; [7]Division of Medical Oncology, Department of Medicine, University of British Columbia, BC Cancer, Vancouver, BC, Canada; [8]Department of Medicine, University of Colorado Cancer Center, Aurora, CO, USA; [9]Department of Translational Medical Oncology, National Center for Tumor Diseases Dresden, Dresden, Germany; [10]NCT Trial Center, National Center of Tumor Diseases Heidelberg, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany; [11]Faculty of Medicine, William Osler Health System, University of Toronto, Toronto, ON, Canada; [12]Department of Pneumology, Assistance Publique Hôpitaux de Paris, Hôpital Tenon and Sorbonne Université, Paris, France; [13]Precision Oncology, Bioinformatic Business Area, QIAGEN Inc., Redwood City, CA, USA; [14]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [15]Laboratory of Oncology, Fondazione IRCCS Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Foggia, Italy; [16]Department of Medical Affairs, Boehringer Ingelheim RCV GmbH & Co. KG, Vienna, Austria; [17]Department of PharMacology, Boehringer Ingelheim RCV GmbH & Co. KG, Vienna, Austria

Introduction

***NRG1* gene fusions**

- NRG1 is a growth factor that contains an EGF-like domain that binds to HER3 or HER4, 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[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

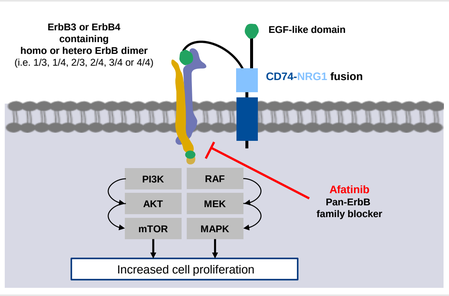
- Afatinib is an irreversible pan-ErbB family blocker[6]
- Due to the involvement of ErbB-signalling pathways in tumours harbouring *NRG1* fusions, afatinib may represent a viable therapeutic option for patients with *NRG1* fusion-positive solid tumours
- This theory is supported by published case reports (Table 1)

Table 1. Published case reports of afatinib used to treat patients with *NRG1*-fusion positive tumours

Patient	Tumour type	*NRG1* fusion partner	Best response	Duration of best response (months)
1[7]	Non-mucinous lung adenocarcinoma	SLC3A2	PR	12
2[8]	Lung adenocarcinoma	SDC4	PR	12
3[7]	IMA	CD74	PR	10
4[9]	IMA	CD74	PR	6.5
5[8]	Cholangiocarcinoma	ATP1B1	PR	8
6[10]	PDAC	ATP1B1	PR	3
7[11]	Ovarian cancer	CLU	SD	-

- Here we present an additional seven cases of *NRG1* fusion-positive tumours treated with afatinib

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



AKT, protein kinase B; ATP1B1, ATPase Na+/K+ transporting subunit beta 1; CD74, cluster of differentiation 74; CLU, clusterin; EGF, epidermal growth factor; IMA, invasive mucinous adenocarcinoma; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; NRG1, neuregulin 1; PDAC, pancreatic ductal adenocarcinoma; PI3K, phosphoinositide 3-kinase; PR, partial response; RAF, rapidly accelerated fibrosarcoma; SD, stable disease; SDC4, syndecan-4; SLC3A2, solute carrier family 3 member 2

Patient 1: Pan-wild type, non-mucinous, lung adenocarcinoma

- 70-year-old female never-smoker, diagnosed in 2004
- Received 14 lines of therapy prior to afatinib, which included chemotherapy, and erlotinib + gefitinib

Afatinib 40 mg/day
- Initiated in February 2015
- Rapid initial response; best response: PR
- Discontinued after 24 months in March 2017 due to PD

- CT (pemetrexed + gemcitabine) initiated in March 2017
- Discontinued in August 2017 due to PD

***NRG1* fusion identified by NanoString™ analysis in September 2017**

Afatinib 30 mg/day*
- Afatinib reinitiated in October 2017, at 30 mg/day
- Regression of lung condensations and improvement in cough
- Discontinued after 3 months due to cough/fever
- Afatinib reinitiated in April 2018
- Discontinued in August 2018 due to PD

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

- Atezolizumab initiated in August 2018 (best response: PD)

*14 days after afatinib 30 mg/day was initiated in October 2017, the dose was increased to 40 mg/day; 7 days after afatinib 30 mg/day was reinitiated in April 2018, the dose was increased to 40 mg/day; CT, chemotherapy; PD progressive disease

Patient 2: Metastatic non-mucinous lung adenocarcinoma

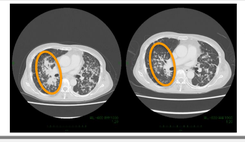
- 66-year-old female non-smoker with low body weight (<40 kg) and multiple lung and lymph node metastases at diagnosis (June 2015)
- Received four lines of treatment prior to afatinib (cisplatin + pemetrexed; nivolumab; docetaxel + ramucirumab; nivolumab); best response: SD

***CD74-NRG1* fusion identified by Oncomine™ Comprehensive Assay in December 2017**

Afatinib 40 mg/day 30 mg/day 20 mg/day
- Afatinib 40 mg/day initiated in December 2017; best response: PR
- Several dose adjustments due to diarrhoea and malaise symptoms
- After 19 months (July 2019) afatinib treatment is ongoing (20 mg/day), with PR

Best overall response on afatinib: PR | **Duration of best response, months:** 19+

Pre-treatment (Dec 2017)



+11 months afatinib (Nov 2018) → PR

Patient 3: Non-mucinous invasive lung adenocarcinoma

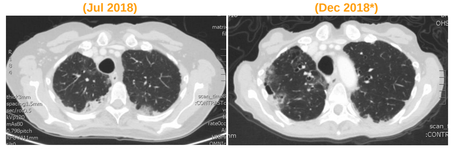
- 68-year-old male with a 20+ pack-year smoking history, diagnosed in January 2016
- Received two lines of treatment prior to afatinib (cisplatin + pemetrexed, best response: PD; nivolumab, best response: PR)

***SDC4-NRG1* fusion identified by RNA-sequencing in March 2018**

Afatinib 30 mg/day
- Initiated in August 2018 (SD for 4 months)
- Afatinib treatment discontinued due to PD
- The patient opted to receive no further treatment, and died shortly after in a hospice

Best overall response on afatinib: SD | **Duration of best response, months:** 4

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



*Scans were taken early December, before PD

Patient 4: Invasive mucinous lung adenocarcinoma

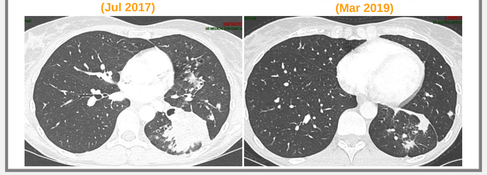
- 43-year-old female non-smoker, diagnosed with lung IMA in August 2016
- Received three lines of treatment prior to afatinib (pemetrexed/cisplatin + bevacizumab; maintenance bevacizumab/pemetrexed; nivolumab)

***CD47-NRG1* fusion identified by RNA-sequencing in September 2017**

Afatinib 40 mg/day
- Initiated in September 2017
- After 18 months (March 2019), afatinib treatment is ongoing, with a major PR

Best overall response on afatinib: PR | **Duration of best response, months:** 18+

Pre-treatment (Jul 2017) | +18 months afatinib (Mar 2019)



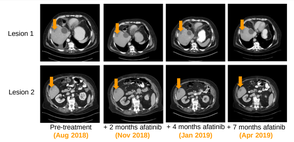
Patient 5: *KRAS*-mutated metastatic colorectal cancer

- 69-year-old male ex-smoker presented with GI bleeding, and had multiple liver/lung metastases at diagnosis (June 2017)
- Received two lines of treatment prior to afatinib (FOLFOX and irinotecan); neither treatment was tolerated; best response: PD
- Patient underwent a right hemicolectomy, and liver and lung metastasectomies

Novel *POMK-NRG1* fusion identified by Caris® profiling* in May 2018

Afatinib 30 mg/day
- Initiated in September 2018
- Initial SD with some CEA level response
- Metastatic progression after 4 months; treated with localised RT
- After 9 months (June 2019), afatinib treatment is ongoing, with SD

Best overall response on afatinib: SD | **Duration of best response, months:** 9+



*Biomarker analysis of tumour proteins, RNA and DNA; CEA, carcinoembryonic antigen; FOLFOX, folinic acid, fluorouracil and oxaliplatin; GI, gastrointestinal; POMK, protein-o-mannose kinase; RT, radiotherapy

Patient 6: *KRAS* wild-type metastatic pancreatic cancer[12]

- 54-year-old male, presented with abdominal pain in 2016, and had stage IV pancreatic ductal adenocarcinoma with metastasis to the liver at diagnosis (March 2018)
- Received one line of treatment prior to afatinib (gemcitabine + nab-paclitaxel, discontinued after one cycle due to toxicity)

***APP-NRG1* fusion identified by WGTA after intolerance to first-line therapy in May 2018**

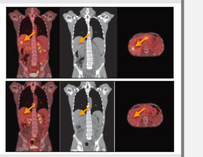
Afatinib 30 mg/day
- Initiated in October 2018
- Significant radiological response after 4 weeks, and PR for 8 months
- Imaging after 9 months (July 2019) suggestive of mild PD

Best overall response on afatinib: PR | **Duration of best response, months:** 8

Pre-treatment (Sep 2018)
- FDG-avidity in pancreatic head mass
- Multiple metastatic lymph nodes and liver metastases

+4 weeks afatinib (Nov 2018)
- Improvement in pancreatic head mass FDG-avidity
- Resolution of hepatic metastases

Afatinib-related AEs:
- Minor facial rash/paronychia



AE, adverse event; APP, amyloid precursor protein; FDG, fludeoxyglucose; WGTA, whole genome and transcriptome analysis

Patient 7: *KRAS* wild-type metastatic pancreatic cancer[12]

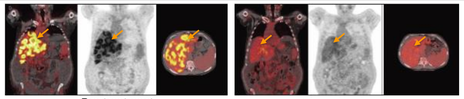
- 59-year-old male, presented with abdominal pain and weight loss in 2017, and had stage IV PDAC with multiple liver metastases at diagnosis (February 2017)
- Received two lines of treatment prior to afatinib (FOLFIRINOX + gemcitabine); best response: PR

***ATP1B1-NRG1* fusion identified by WGTA after progression on first-line therapy in February 2018**

Afatinib 40 mg/day
- Initiated in March 2018
- Significant radiological response after 4 weeks

Afatinib 30 mg/day
- Dose reduced to 30 mg/day due to diarrhoea
- Afatinib treatment discontinued after 5.5 months due to PD
- Patient died from PD in early 2019

Best overall response on afatinib: PR | **Duration of best response, months:** 5.5



Pre-treatment (Mar 2018) | +4 weeks afatinib (Apr 2018)

ATP1B1, ATPase sodium/potassium transporting subunit beta-1; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin

Key findings and conclusions

- These findings add to a growing body of evidence that afatinib is a potential treatment option for patients with *NRG1* fusion-positive tumours across multiple cancer types
  - This is particularly important in patients for whom targeted therapies are not available, such as patients with *KRAS* wild-type PDAC and 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
- 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

1. Drilon A, et al. Cancer Discov 2018;8:686–95
2. Fernandez-Cuesta L, Thomas RK. Clin Cancer Res 2014;21:1989–94
3. Duruisseaux M, et al. J Clin Oncol 2019;37(suppl 15): abstract 9081
4. Jonna S, et al. Clin Cancer Res 2019;25:4966–72
5. Trombetta D, et al. Oncotarget 2018;9:9661–71
6. Solca F, et al. J Pharmacol Exp Ther 2012;343:342–50
7. Gay N, et al. J Thoracic Oncol 2017;12:e107–10
8. Jones M, et al. Ann Oncol 2017;28:3092–97
9. Cheema P, et al. J Thoracic Oncol 2017;12:e200–2
10. Heining C, et al. Cancer Discov 2018;8:1087–95
11. Murumagi A, et al. Cancer Res 2019;79(suppl 13):abstract 2945
12. Jones MR, et al. Clin Cancer Res 2019; 25:4674–81

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

http://tqr.bz/qJQ

Presented at the 2019 European Society for Medical Oncology (ESMO) congress, Barcelona, Spain, 27 September–1 October 2019

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.

SVL reports: advisory councils/committees (Apollomics, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, G1 Therapeutics, Genentech/Roche, Heron, Ignyta, Inivata, Janssen, Lilly, Regeneron, Takeda/Ariad, Tempus); consulting fees (AstraZeneca, Celgene, Genentech/Roche, Lilly, Merck, Pfizer, Taiho, Takeda/Ariad) and grants/ funds (AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Clovis, Corvus, Esanex, Genentech/Roche, Ignyta, Lilly, Lycera, Merck, Molecular Partners, OncoMed, Pfizer, Rain Therapeutics, Threshold); co-author disclosure statements can be found in the published abstract. *Corresponding author email address: Stephen.V.Liu@gunet.georgetown.edu