and North America, where squamous neoplasia is common in Asia. One key limitation of this study is that the pathology incorporated was limited to the Chinese population and hence cannot be generalised to other countries. Nevertheless, this is an important step towards use of artificial intelligence in real-time gastrointestinal endoscopy.

There is a lot of excitement in the medical community; however, uncertainty and anxiety about artificial intelligence in medicine is also evident.[5] A global unified approach is necessary for the development of such artificial intelligence systems develop and validate artificial intelligence platforms, so that all ethnicities and pathologies are represented and tested. The level of intelligence that can be achieved by artificial intelligence ultimately depends on our enthusiasm in perfecting these systems before announcing victory.

*Krish Ragunath*
Curtin Medical School, Faculty of Health Sciences Curtin University, and Department of Gastroenterology, Royal Perth Hospital, Perth 6000, Australia
krish.ragunath@curtin.edu.au

I declare no competing interests.

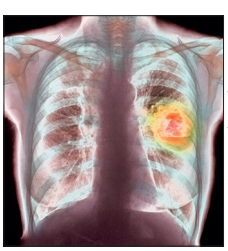


1 [No authors listed]. Olympus launches endoscope software "EndoBRAIN" based on AI data. Nikkei Biotech news release, March 4, 2019. https://window-to-japan.eu/2019/03/04/olympus-launches-endoscope-software-endobrain-based-on-ai-data/ (accessed Oct 2, 2019).
2 Mori Y, Kudo SE, Misawa M, et al. Real-time use of artificial intelligence in identification of diminutive polyps during colonoscopy: a prospective study. *Ann Intern Med* 2018; **169:** 357–66.
3 Beg S, Wilson A, Ragunath K. The use of optical imaging techniques in the gastrointestinal tract. *Frontline Gastroenterol* 2016; **7:** 207–15.
4 Luo H, Xu G, Li C, et al. Real-time artificial intelligence for detection of upper gastrointestinal cancer by endoscopy: a multicentre, case-control, diagnostic study. *Lancet Oncol* 2019; published online Oct 4. **20:** 1645–54.
5 Sarwar S, Dent A, Faust K, et al. Physician perspectives on integration of artificial intelligence into diagnostic pathology. *NPJ Digit Med* 2019; **2:** 28.

# Are neutralising anti-VEGF or VEGFR2 antibodies necessary in the treatment of *EGFR*-mutated non-small-cell lung cancer?

The NEJ026 study[1] in patients with *EGFR*-positive non-small-cell lung cancer (NSCLC) showed that the combination of erlotinib (150 mg/day) plus intravenous bevacizumab (15 mg/kg once every 21 days) yields a median progression-free survival of 16·9 months (95% CI 14·2–21·0) compared with 13·3 months (11·1–15·3) in patients treated with erlotinib alone (p=0·016). The trial was permissive, allowing patients with CNS metastases (32% in each group) and an Eastern Cooperative Oncology Group performance status of 2 or lower to enroll. Median progression-free survival was also longer in patients with Leu858Arg mutations in the erlotinib and bevacizumab group (17·4 months [95% CI 12·6–not estimable]) than in the erlotinib group (13·7 months [8·8–15·5]). However, no significant differences were found between treatment groups in patients with *EGFR* exon 19 deletions.[1] In *The Lancet Oncology*, Kazuhiko Nakagawa and colleagues[2] report the results of a phase 3 trial (RELAY) assessing the combination of erlotinib 150 mg/day plus ramucirumab (an anti-VEGFR2 antibody) 10 mg/kg intravenously every 2 weeks versus erlotinib 150 mg/day plus intravenous placebo every 2 weeks. Median progression-free survival was 19·4 months (95% CI 15·4–21·6) in the erlotinib plus ramucirumab group versus 12·4 months (11·0 –13·5) in the erlotinib plus placebo group (hazard ratio 0·59 [95% CI 0·46–0·76], p<0·0001). Grade 3 hypertension occurred in 52 (24%) of the 221 patients in the erlotinib plus ramucirumab group safety population. In the previous NEJ026 study,[1] in the erlotinib plus bevacizumab group, grade 3 hypertension also occurred in 23% of the patients. Both trials shed light on the convenience of combining EGFR tyrosine kinase inhibitors with other drugs. However, several questions arise, because in both trials, the proportion of patients attaining a complete response was very low in the combination group: three (1%) of 224 in RELAY and eight (7%) of 112 in NEJ026.

Notably, invasion and metastases increase after the inhibition of VEGF signalling in preclinical tumour models of glioblastoma and pancreatic neuroendocrine tumours. Treatment with a neutralising anti-VEGF antibody reduces tumour burden, but also augments tumour hypoxia, hypoxia-inducible


Simon Fraser/Science Photo Library

Published **Online** October 4, 2019 https://doi.org/10.1016/S1470-2045(19)30636-9

See **Articles** page 1655

factor-1α, c-Met activation, invasion, and metastases, making a complete response less likely. The preclinical models indicate that invasion and metastases are simultaneous, via VEGF and c-Met.[3] The triple inhibition of EGFR, Met, and VEGF with erlotinib, crizotinib, and bevacizumab suppresses tumour growth in erlotinib-resistant, *EGFR*-mutant cell lines.[4] Treatment with foretinib, which blocks VEGFR, c-Met, and several other receptor tyrosine kinases, including AXL, was effective in preclinical models, as was cabozantinib, a receptor tyrosine kinase inhibitor that blocks VEGFRs, c-Met, and other kinases.[3] It is tempting to postulate that multitargeted receptor tyrosine kinases, such as foretinib or cabozantinib, could be superior to neutralising anti-VEGF or anti-VEGFR2 antibodies in the treatment of *EGFR*-positive NSCLC.

Combinatory therapies of drugs that inhibit STAT3 and YAP1 with EGFR tyrosine kinase inhibitors are warranted in order to limit the unavoidable rapid resistance that occurs almost immediately after starting treatment with an EGFR tyrosine kinase inhibitor that triggers STAT3 and Src-YES-associated protein YAP1 signalling, such as repotrectinib or dasatinib.[5] Several receptor tyrosine kinases are co-expressed in *EGFR*-mutant cell lines and tumour samples of patients with *EGFR* mutations, commonly with co-activation of AXL and CDCP1.[6] Gefitinib and osimertinib both activate STAT3 and YAP1. The combination of either of these drugs with STAT3 and Src inhibition abrogates tumour growth in culture and in vivo.[5] Although the combination of erlotinib with bevacizumab or ramucirumab has shown a longer progression-free survival than erlotinib alone, it might activate Met, as has been seen in cancer cell lines, the consequences of which are invasion and metastases. Unfortunately, this hypothesis is not easily proven.

Neratinib, an EGFR2, HER2, and HER4 inhibitor, compared with other EGFR inhibitors, such as gefitinib, erlotinib, lapatinib, or afatinib, has been shown to cause increased EGFR internalisation and degradation. Neratinib can also downregulate c-Met and reduce the expression of MCL-1.[7] MCL-1 is a frequent cause of resistance to EGFR inhibitors.[8] The combination of neratinib and sildenafil, a phosphodiesterase-5 inhibitor, causes notable activation of the Hippo pathway, via Rubicon, with downregulation of YAP1.[7] Neratinib is approved by the US Food and Drug Administration as a component of adjuvant therapy in breast cancer. The potent action of neratinib in autophagy (Beclin1 and Rubicon complexes) adds further interest in the drug, since *EGFR* mutations induce Beclin1 phosphorylation and autophagy suppression, leading to tumour progression and resistance.[9]

In conclusion, future clinical trials should be based on accumulated, preclinical data, rather than on empirical design. Multiple layers of evidence indicate that, although lung cancer biology is not yet fully understood, the complexities of interdigitated signalling pathways could be reasonably manageable and translated to available combinatory therapies.[5,6,10]

**Rafael Rosell, Carlos Pedraz-Valdunciel*
Germans Trias i Pujol Research Institute and Hospital, Badalona 08916, Spain (RR, CP-V); and Universitat Autónoma de Barcelona, Barcelona, Spain (RR, CP-V)
rrosell@iconcologia.net

We declare no competing interests.

1 Saito H, Fukuhara T, Furuya N, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol* 2019; **20:** 625–35.
2 Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; published online Oct 3. https://doi.org/10.1016/S1470-2045(19)30634-5.
3 Sennino B, Ishiguro-Oonuma T, Wei Y, et al. Suppression of tumor invasion and metastasis by concurrent inhibition of c-Met and VEGF signaling in pancreatic neuroendocrine tumors. *Cancer Discov* 2012; **2:** 270–87.
4 Nakade J, Takeuchi S, Nakagawa T, et al. Triple inhibition of EGFR, Met, and VEGF suppresses regrowth of HGF-triggered, erlotinib-resistant lung cancer harboring an EGFR mutation. *J Thorac Oncol* 2014; **9:** 775–83.
5 Chaib I, Karachaliou N, Pilotto S, et al. Co-activation of STAT3 and YES-associated protein 1 (YAP1) pathway in EGFR-mutant NSCLC. *J Natl Cancer Inst* 2017; **109:** 1–12.
6 Karachaliou N, Chaib I, Cardona AF, et al. Common co-activation of AXL and CDCP1 in EGFR-mutation-positive non-small cell lung cancer associated with poor prognosis. *EBioMedicine* 2018; **29**: 112–27.
7 Dent P, Booth L, Roberts JL, et al. Neratinib inhibits hippo/YAP signaling, reduces mutant K-RAS expression, and kills pancreatic and blood cancer cells. *Oncogene* 2019; **38:** 5890–904.
8 Song K-A, Hosono Y, Turner C, et al. Increased synthesis of MCL-1 protein underlies initial survival of *EGFR*-mutant lung cancer to EGFR inhibitors and provides a novel drug target. *Clin Cancer Res* 2018; **24:** 5658.
9 Wei Y, Zou Z, Becker N, et al. EGFR-mediated beclin 1 phosphorylation in autophagy suppression, tumor progression, and tumor chemoresistance. *Cell* 2013; **154:** 1269–84.
10 Rosell R, Bivona TG, Karachaliou N. Genetics and biomarkers in personalisation of lung cancer treatment. *Lancet* 2013; **382:** 720–31.