Editorial

# Can we cure metastatic *EGFR*-mutated lung cancer today?

**Petros Christopoulos**[1,2]^

[1]Department of Medical Oncology, Thoraxklinik and National Center for Tumor Diseases at Heidelberg University Hospital, Heidelberg, Germany; [2]Translational Lung Research Center at Heidelberg University Hospital, Member of the German Center for Lung Research (DZL), Heidelberg, Germany

*Correspondence to:* Petros Christopoulos. Department of Oncology, Thoraxklinik at Heidelberg University Hospital, Röntgenstr. 1, Heidelberg 691269, Germany. Email: petros.christopoulos@med.uni-heidelberg.de.

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Ever since the availability of tyrosine kinase inhibitors (TKI) against the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and other oncoproteins with superior efficacy and tolerability than cytotoxic chemotherapy for non-small cell lung cancer (NSCLC), first priority of management has been the precise identification of patients able to benefit from targeted drugs (1). Upfront use of EGFR inhibitors has pushed the median overall survival (OS) for *EGFR*-mutant metastatic lung cancer beyond 3 years (2). However, the possibility and requisites for cure of these patients remain unclear.

In the this issue of *Translational Cancer Research*, Wan *et al.* describe a very interesting case of lung cancer with ongoing long-term benefit over 8 years under EGFR inhibitors and contribute valuable evidence about the potential circumstances of such extraordinarily favorable courses (3). Owing to the detailed profiling of this patient by the authors, several interesting characteristics can be noted: (I) the primary driver alteration was an *EGFR* exon 19 deletion (del19), which has been associated with higher TKI sensitivity, as well as longer progression-free (PFS) and OS than *EGFR* p.L858R or "rare" *EGFR* mutations (4); (II) female sex (5), Asian ethnicity (6), and secondary stage IV following relapse of an early-stage tumor after surgery (7) have all been described as favorable, as well; (III) she was a never-smoker, which is also linked to longer survival (8), possibly due to the correlation with a lower tumor mutational burden (9); (IV) she presented with brain-only oligometastatic disease, which is indicative of less aggressive NSCLC biology (10); (V) at the time of gefitinib failure in the first line, she developed oligoprogression in the brain, which is known to occur later and correlate with longer OS compared to diffuse disease progression in NSCLC under any systemic treatment, in particular when local ablative therapies are additionally applied (11,12); (VI) the authors managed to perform multiple rebiopsies and deliver 4 successive lines of treatment, which is an indication of very careful and close managements, since approximately 30–40% of patients are lost and die without subsequent systemic therapy after each disease progression in EGFR+ NSCLC according to retrospective studies (2). Simultaneous presence of multiple good prognostic features explains the long-lasting clinical benefit in the current patient despite the *per se* unfavorable brain involvement (4), and may help predict exceptional responses in other similar patients the future (*Table 1*). That being said, this case was diagnosed several years ago, in April 2014, which poses the important question: what else could have been done today?

One essential issue is the method and extent of molecular profiling: while the *EGFR* mutation in the described patient was detected using real-time PCR (ADx-ARMs) back in 2014 (3), combined DNA and RNA next-generation

^ ORCID: 0000-0002-7966-8980.

**Table 1** Available biomarkers of long-lasting responses to EGFR inhibitors in NSCLC

| Parameter | Value | Reference |
|---|---|---|
| Molecular | | |
| *EGFR* mutation type | Exon 19 deletion | (4) |
| *TP53* status | Wild-type | (4,13) |
| Tumor mutational burden | Low | (9) |
| Clinical | | |
| Sex | Female | (5) |
| Ethnicity | Asian | (6) |
| Smoking status | Never smoker | (8) |
| Presentation | Secondary stage IV (disputed) | (7) |
| | Oligometastatic | (10) |
| | Lack of brain metastases | (4) |
| On-treatment | | |
| Progression pattern | Oligoprogression | (12) |
| ctDNA monitoring | ctDNA clearance under therapy | (13) |

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ctDNA, circulating tumor DNA.

sequencing (NGS) is meanwhile the recommended standard at initial diagnosis of advanced NSCLC regardless of histology for the timely, i.e., within 10 working days, parallel testing of all potentially actionable genetic alterations (1,14). One special advantage from such a broader approach is the additional coverage of genes with prognostic and predictive importance, like *TP53*, the wild-type status of which has been linked to durable responses under EGFR and ALK inhibitors (4,15). While no *TP53* sequencing was performed here, as *TP53* was not included in the 23-gene NGS panel used in April 2022 (3), it is reasonable to assume that this particular patient with >62-month-long response to late-line osimertinib lacked *TP53* mutations, since these are strongly associated with shorter PFS and OS in this situation, with a hazard ratio >2.5 compared to *TP53* wild-type in retrospective analyses (16). One additional possibility to further refine patient stratification are longitudinal circulating tumor DNA (ctDNA) assays under treatment, as clearance under EGFR TKI (13) and/or undetectable ctDNA at the time of oligoprogression (17) are associated with better outcomes in oncogene-driven NSCLC (*Table 1*). In fact, the detectability of *EGFR* del19 in the last plasma analysis performed by the authors in April 2022, during the ongoing radiological response to osimertinib (3), suggests that the described patient is actually not cured, but destined to experience another disease progression, which highlights the need for additional and more potent therapies.

What can we offer today? Unfortunately, not much. The combination of osimertinib with bevacizumab given by the authors as fourth-line treatment for a "progressive" brain lesion under osimertinib may have facilitated a >40-month-long radiologic response here, but cannot be generally recommended: two randomized phase 2 trials have shown no benefit from the addition of bevacizumab to osimertinib, neither in the first-line setting, nor in T790M+ patients, despite the positive results of the erlotinib/bevacizumab and erlotinib/ramucirumab studies, as well as the preclinical evidence of VEGF induction by oncogenic signaling (18-20). Actually, it is quite possible that the growing lesion under osimertinib successfully treated by bevacizumab may in fact have been a manifestation of radionecrosis (RN), which is rare (1–2%), but possible after whole-brain radiotherapy and responds very well to angiogenics (21), contrary to what would be expected for osimertinib-resistant cancer cells. In case of further disease progression without actionable drivers, the first option would currently be the chemoimmunotherapy with carboplatin/paclitaxel/atezolizumab/bevacizumab (IMpower150 regime), which can achieve a response rate of approximately 80% and a median PFS of 10 months in TKI-resistant EGFR+ NSCLC patients (22). In the near future, recent progresses in deciphering the immunologic tumor microenvironment of EGFR+ NSCLC (23) may facilitate successful application of more effective, next-generation immunotherapies for these patients, such as multispecific antibodies and T-cell receptor transgenic T (TCR-T) cells (24,25), which currently hold a justified hope for the cure of lung cancer and other solid tumors (20).

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## References

1. Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol 2022;40:1231-58.
2. Magios N, Bozorgmehr F, Volckmar AL, et al. Real-world implementation of sequential targeted therapies for EGFR-mutated lung cancer. Ther Adv Med Oncol 2021;13:1758835921996509.
3. Wan Y, Xu F, Wang J. Long-term survival of a non-small cell lung cancer patient with EGFR-mutated brain metastases: a case report. Transl Cancer Res 2022;11:4448-54.
4. Christopoulos P, Kirchner M, Roeper J, et al. Risk stratification of EGFR(+) lung cancer diagnosed with panel-based next-generation sequencing. Lung Cancer 2020;148:105-12.
5. Xiao J, Zhou L, He B, et al. Impact of Sex and Smoking on the Efficacy of EGFR-TKIs in Terms of Overall Survival in Non-small-Cell Lung Cancer: A Meta-Analysis. Front Oncol 2020;10:1531.
6. Gibson AJW, D'Silva A, Elegbede AA, et al. Impact of Asian ethnicity on outcome in metastatic EGFR-mutant non-small cell lung cancer. Asia Pac J Clin Oncol 2019;15:343-52.
7. Bozorgmehr F, Kazdal D, Chung I, et al. De Novo Versus Secondary Metastatic EGFR-Mutated Non-Small-Cell Lung Cancer. Front Oncol 2021;11:640048.
8. Zhang Y, Kang S, Fang W, et al. Impact of smoking status on EGFR-TKI efficacy for advanced non-small-cell lung cancer in EGFR mutants: a meta-analysis. Clin Lung Cancer 2015;16:144-151.e1.
9. Offin M, Rizvi H, Tenet M, et al. Tumor Mutation Burden and Efficacy of EGFR-Tyrosine Kinase Inhibitors in Patients with EGFR-Mutant Lung Cancers. Clin Cancer Res 2019;25:1063-9.
10. Mentink JF, Paats MS, Dumoulin DW, et al. Defining oligometastatic non-small cell lung cancer: concept versus biology, a literature review. Transl Lung Cancer Res 2021;10:3329-38.
11. Rheinheimer S, Heussel CP, Mayer P, et al. Oligoprogressive Non-Small-Cell Lung Cancer under Treatment with PD-(L)1 Inhibitors. Cancers (Basel) 2020;12:1046.
12. Weickhardt AJ, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J Thorac Oncol 2012;7:1807-14.
13. Boysen Fynboe Ebert E, McCulloch T, Holmskov Hansen K, et al. Clearing of circulating tumour DNA predicts clinical response to osimertinib in EGFR mutated lung cancer patients. Lung Cancer 2020;143:67-72.
14. Volckmar AL, Leichsenring J, Kirchner M, et al. Combined targeted DNA and RNA sequencing of advanced NSCLC in routine molecular diagnostics: Analysis of the first 3,000 Heidelberg cases. Int J Cancer 2019;145:649-61.
15. Elsayed M, Christopoulos P. Therapeutic Sequencing in ALK(+) NSCLC. Pharmaceuticals (Basel) 2021;14:80.
16. Roeper J, Christopoulos P, Falk M, et al. TP53 co-mutations as an independent prognostic factor in 2nd and further line therapy-EGFR mutated non-small cell lung cancer IV patients treated with osimertinib. Transl Lung Cancer Res 2022;11:4-13.
17. Christopoulos P, Dietz S, Angeles AK, et al. Earlier extracranial progression and shorter survival in ALK-

 

rearranged lung cancer with positive liquid rebiopsies. Transl Lung Cancer Res 2021;10:2118-31.
18. Soo RA, Han JY, Dafni U, et al. A randomised phase II study of osimertinib and bevacizumab versus osimertinib alone as second-line targeted treatment in advanced NSCLC with confirmed EGFR and acquired T790M mutations: the European Thoracic Oncology Platform (ETOP 10-16) BOOSTER trial. Ann Oncol 2022;33:181-92.
19. Kenmotsu H, Wakuda K, Mori K, et al. LBA44 Primary results of a randomized phase II study of osimertinib plus bevacizumab versus osimertinib monotherapy for untreated patients with non-squamous non-small cell lung cancer harboring EGFR mutations: WJOG9717L study. Ann Oncol 2021;32:S1322-3.
20. Gaissmaier L, Christopoulos P. Immune Modulation in Lung Cancer: Current Concepts and Future Strategies. Respiration 2020. [Epub ahead of print]. doi: 10.1159/000510385.
21. Gondi V, Bauman G, Bradfield L, et al. Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2022;12:265-82.
22. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir Med 2019;7:387-401.
23. Budczies J, Kirchner M, Kluck K, et al. Deciphering the immunosuppressive tumor microenvironment in ALK- and EGFR-positive lung adenocarcinoma. Cancer Immunol Immunother 2022;71:251-65.
24. Elshiaty M, Schindler H, Christopoulos P. Principles and Current Clinical Landscape of Multispecific Antibodies against Cancer. Int J Mol Sci 2021;22:5632.
25. Gaissmaier L, Elshiaty M, Christopoulos P. Breaking Bottlenecks for the TCR Therapy of Cancer. Cells 2020;9:2095.

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