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Precision Medicine Clinic: Molecular Tumor Board

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Molecular tumor board–guided osimertinib therapy in EGFR L858R/Q701L–mutant lung adenocarcinoma supported by functional validation

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Abstract

Background: **Rare or compound EGFR variants in non–small-cell lung cancer (NSCLC) can create substantial therapeutic uncertainty, particularly when accompanied by additional co-alterations with potential resistance implications. In such settings, molecular tumor boards (MTBs) may integrate genomic, functional, and clinical data to guide treatment selection.**

Case presentation: **A 59-year-old Caucasian woman was diagnosed with metastatic lung adenocarcinoma involving the lungs, bones, and lymph nodes. Histopathology showed a TTF-1 positive pulmonary adenocarcinoma with low PD-L1 expression.**

Molecular findings: **Next-generation sequencing identified a compound *EGFR* alteration consisting of L858R and Q701L, along with additional alterations in *PIK3CA*, *ATM*, and *CTNNB1* and loss of *CDKN2A/B*, *MLH1,* and *BAP1*.**

Functional and molecular tumor board assessment: **To resolve this uncertainty, the EGFR mutations were recreated in vitro and characterized within national Network Genomic Medicine (nNGM) preclinical platform. In Ba/F3 models, the EGFR L858R/Q701L co-mutation showed sensitivity to first-, second-, and third-generation EGFR tyrosine kinase inhibitors. After integrating the molecular profile, functional data, and clinical context, the institutional MTB recommended in-label therapy with Osimertinib.**

Outcome: **Treatment resulted in rapid clinical improvement and a radiologically confirmed partial remission followed by durable disease control for 18 months. Disease progression occurred thereafter, and the patient died 23.4 months after initial diagnosis.**

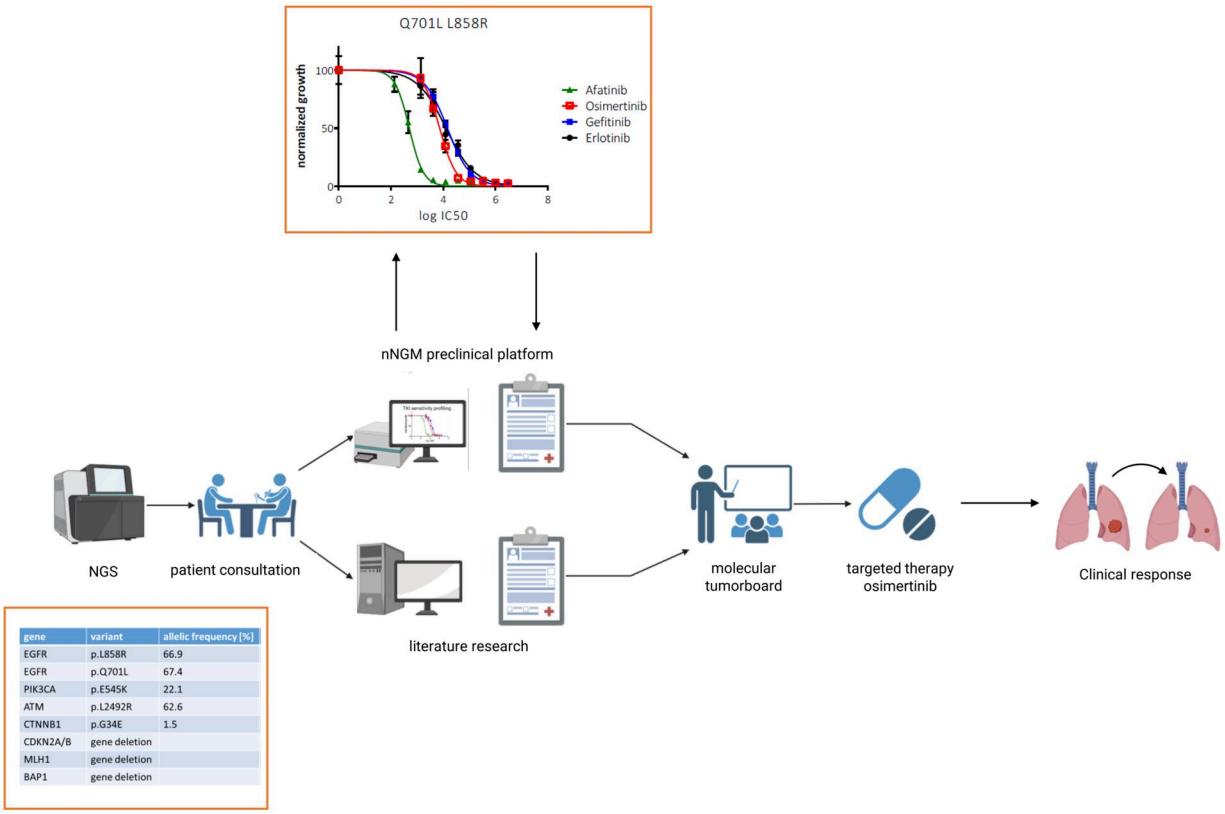
Conclusion: **This case highlights the importance of functional validation and multidisciplinary tumor board discussion in interpreting complex genomic profiles and guiding personalized therapy in NSCLC.**

Key words: EGFR compound mutation; predictive oncology

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Graphical abstract



Key Points

- The rare EGFR L858R/Q701L compound alteration created molecular uncertainty because EGFR Q701L is a variant, classified as variant of uncertain significance and had previously been observed after osimertinib exposure in an EGFR L858R-mutant NSCLC case, raising the hypothesis that L858R/Q701L may represent a potentially resistance-associated compound EGFR alteration; however, functional evidence had been lacking.
- Functional in vitro testing demonstrated preserved sensitivity of the L858R/Q701L co-mutated receptor to first-, second-, and third-generation EGFR tyrosine kinase inhibitors, including osimertinib, resolving therapeutic uncertainty in the context of very limited clinical data.
- This case involved 2 distinct layers of molecular uncertainty: besides the rare EGFR L858R/Q701L compound alteration additional co-alterations in PIK3CA, CTNNB1, ATM, and CDKN2A/B have been detected, that could also potentially modify EGFR TKI response.
- The observed clinical response and the parallel in vitro sensitivity data support the interpretation that the tumor remained therapeutically targetable through EGFR inhibition in this specific context.
- This case illustrates how functional validation of rare and compound EGFR mutations can critically inform therapeutic decision-making when clinical evidence is limited.
- The subsequent durable clinical response illustrates the value of a precision oncology workflow linking sequencing, preclinical validation, and MTB-guided therapy selection.

Introduction

Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, and molecular stratification has become central to the management of advanced disease.[1] Activating alterations in EGFR occur in around 10% of patients with NSCLC and define a therapeutically actionable subset of NSCLC and have enabled the development of increasingly effective tyrosine kinase inhibitors (TKIs), culminating in substantial survival gains for patients with classical sensitizing

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mutations.[2–4] However, the clinical interpretation of uncommon or compound EGFR variants remains challenging, particularly when these occur in the context of additional genomic alterations that may modify therapeutic response.

The development of EGFR-targeted TKIs began with first-generation agents like gefitinib and erlotinib, followed by second- and third-generation inhibitors including afatinib and osimertinib. These therapies have substantially improved response rates and survival in patients with classical activating EGFR mutations compared to chemotherapy, establishing EGFR-directed TKIs as a cornerstone of precision therapy in this patient population.[5]

However, the spectrum of EGFR alterations is heterogeneous, and clinical responses vary across different variants.[6,7] While classical mutations like exon19 deletions and the L858R substitution in exon 21 are well established as sensitizing alterations and serve as the molecular basis for current treatment guidelines,[8,9] uncommon mutations and especially compound variants remain difficult to interpret, both biologically and clinically. While some rare variants confer sensitivity to TKIs, others are associated with primary resistance or only partial responsiveness.[6,10–12] Moreover, the co-occurrence of additional genetic alterations in other genes, for example, in PIK3CA or CTNNB1, or loss of CDKN2A/B—may modulate signaling output and impact treatment efficacy, further complicating therapeutic decision-making.[13]

Molecular tumor boards (MTBs) provide a structured framework to resolve such ambiguity by integrating genomic findings with pathology, clinical context, and—where available—functional evidence. By bringing together the expertise from oncology, pathology, molecular biology, bioinformatics and clinical pharmacology, MTBs support the development of individualized treatment strategies, particularly in cases involving rare or complex genomic alterations.[14,15] In this setting, preclinical data can complement existing clinical evidence or, when clinical data are limited due to the rarity of a given alteration, play a central role in guiding personalized therapeutic decisions. Preclinical models, including Ba/F3 transformation and drug-sensitivity assays, are particularly informative, as they allow direct assessment of oncogenic potential and responsiveness to targeted therapies.[11,12,16] Functional validation may complement clinical and genomic evidence in rare or compound EGFR variants, particularly when performed in parallel with standard treatment and interpreted within an MTB framework.

Here, we describe a patient with metastatic lung adenocarcinoma harboring a rare EGFR L858R/Q701L co-mutation in the presence of additional alterations in *PIK3CA*, *ATM*, and *CTNNB1*. Functional characterization through the national Network Genomic Medicine nNGM preclinical platform demonstrated sensitivity of the co-mutant receptor to first-, second-, and third-generation EGFR TKIs. These data were incorporated into MTB deliberation and directly informed the recommendation for osimertinib. The patient experienced a rapid and durable clinical response, with ongoing disease control for more 18 months. This case highlights the clinical relevance of systematic integration of genomic diagnostics, preclinical validation, and MTB-based decision making for the personalized management of NSCLC with rare or compound EGFR mutations.

Case presentation

Clinical history and diagnosis

A 59-year-old Caucasian woman presented with progressive cough and dyspnea. Imaging demonstrated a lung mass with bilateral pulmonary, osseous, and lymphatic metastases (Figure 1). The disease was staged as advanced NSCLC (cT4, M2, M1c, UICC8).

Pathology

Histological analysis of a biopsy specimen revealed a TTF-1-positive pulmonary adenocarcinoma. PD-L1 testing showed an

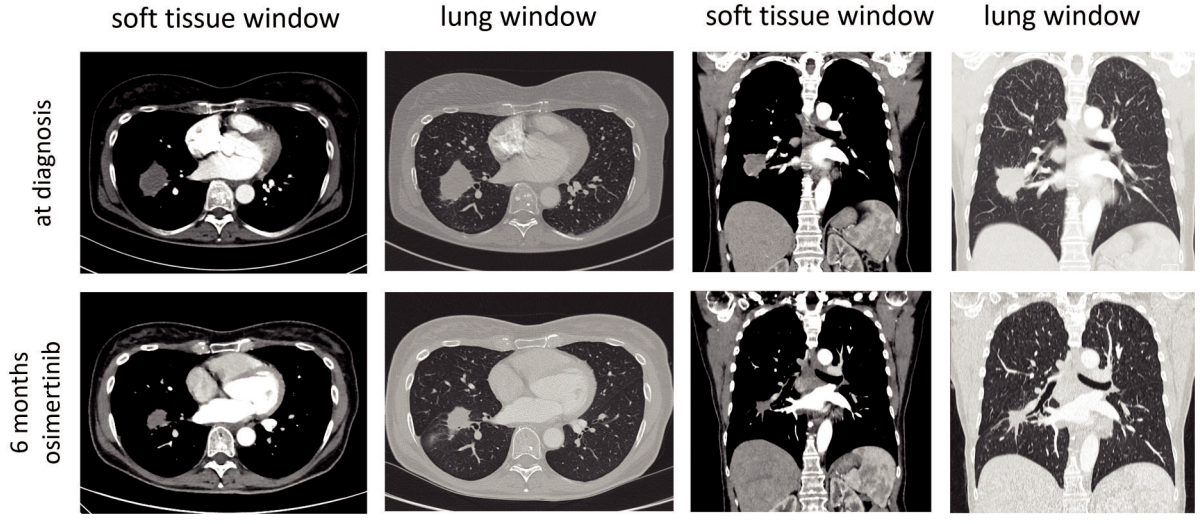


Figure 1. CT scans in initial staging and follow-up. Initial CT after malignancy confirmation revealed advanced-stage disease with primary tumor localization in the right lobe and bilateral pulmonary, osseous, lymphatic metastases. After 6 months of osimertinib treatment corresponding to 8 months after initial NSCLC diagnosis, a partial response (PR) was achieved.

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Table 1. NGS results (VAFs, classification of variants).

Gene	Variant	Allelic frequency (%)	Classification
EGFR	p.L858R	66.9	Activating
EGFR	p.Q701L	67.4	VUS
PIK3CA	p.E545K	22.1	Activating
ATM	p.L2492R	62.6	VUS
CTNNB1	p.G34E	1.5	Activating
CDKN2A/B	Gene deletion		
MLH1	Gene deletion		
BAP1	Gene deletion		

Overview of the results from molecular diagnostics. Panel sequencing of tissue material from initial diagnosis. Two missense mutations in the EGFR gene leading to p. L858R and p. Q701L with similar allelic frequencies were detected. In addition, an activating PIK3CA p. E545K mutation (allelic frequency 22.1%) and an ATM p. L2492R variant of uncertain significance (allelic frequency 62.6%) were identified. A further activating mutation, CTNNB1 p. G34E, was present at a low allelic frequency (1.5%). Copy-number analysis revealed homozygous deletions of CDKN2A/B, MLH1, and BAP1.

immune cell score of 5%, a tumor proportion score of <1%, and a combined positive score of 6.

Molecular findings

Next-generation sequencing revealed the established sensitizing EGFR mutation L858R (allele frequency 66.9%) together with the rare EGFR Q701L variant (67.4%), which was classified as a variant of uncertain significance in the diagnostic report. Additional variants were detected in *PIK3CA* (E545K, 22.1%), *ATM* (L2492R, 62.6%), and *CTNNB1* (G34E, 1.5%), along with loss of *CDKN2A/B, MLH1*, and *BAP1* (Table 1).

Functional assessment

The *EGFR* L858R mutation is a well-known sensitizing variant,[9,11] whereas the clinical significance of EGFR Q701L remains uncertain. EGFR Q701L has previously been detected in the post-treatment tumor specimen of an EGFR L858R-mutant NSCLC patient after osimertinib exposure, while the pretreatment specimen showed EGFR L858R without Q701L.[17] This raised the hypothesis that L858R/Q701L may represent a potentially resistance-associated compound EGFR alteration. Given this uncertainty, the EGFR L858R/Q701L alteration was functionally assessed in vitro within the framework of the national network genomic medicine lung cancer (nNGM) preclinical platform for clinical testing. Experimental details are provided in the Supplementary Material and methods. Our functional data support oncogenic activity of EGFR L858R, L858R/Q701L as well as Q701L alone. Besides, the in vitro assays demonstrated high sensitivity of the dual *EGFR* mutation to first-, second-, and third-generation TKIs (Figure 2; Figure S1) comparable to established sensitizing EGFR mutations.

EGFR mutation	IC50 in Ba/F3 cells [nM]			
	Erlotinib	Gefitinib	Osimertinib	Afatinib
E746_A750del	15	11	7	1
S768I	385	222	139	3
T790M	>3000	>3000	90	111
Q701L	111	37	52	2
L858R	26	26	11	1
Q701L L858R	13	14	7	1

	Erlotinib	Gefitinib	Osimertinib	Afatinib
sensitive	<100 nM	<100 nM	<100 nM	<20 nM
intermediate sensitive	100-300 nM	100-300 nM	100-300 nM	20-50 nM
resistant	>300	>300	>300	>50

Figure 2. EGFR TKI sensitivity of Q701L L858R mutation in Ba/F3 (summarized, with full IC50 curves in Figure S1). Analysis of the EGFR L858R Q701L mutation in the Ba/F3 cell model. Cells were retrovirally transduced with overexpression vectors encoding the indicated EGFR mutations. Cells were deprived of IL-3 and treated with increasing concentrations of EGFR TKIs erlotinib, gefitinib, afatinib or osimertinib and proliferation was measured after 48 h using WST-1 reagent. Proportional proliferation compared to the DMSO control and half maximal inhibitory concentration (IC50) are provided.

Molecular tumor board assessment

The case was discussed at the molecular tumor board of the Center for Personalized Medicine, University Medical Center Hamburg-Eppendorf, with participation from thoracic oncology, molecular pathology, bioinformatics, and translational oncology. The key question was whether the detected EGFR L858R/Q701L co-mutation represented a targetable driver constellation despite the presence of additional alterations with possible resistance implications. Available clinical evidence for Q701L was extremely limited and included concern for potential resistance in a different clinical context. Functional results from the nNGM preclinical platform, however, demonstrated preserved sensitivity of the co-mutant receptor to EGFR TKIs, including osimertinib. Based on the totality of evidence, the MTB concluded that the tumor remained primarily EGFR-driven and recommended in-label treatment with osimertinib.

Importantly, initiation of osimertinib was not delayed while awaiting functional results, as EGFR L858R represented an approved and guideline-concordant therapeutic indication. The rationale for functional testing was therefore not to replace standard first-line decision-making, but to clarify the biological relevance of the additional EGFR Q701L variant in the

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Figure 3. Clinical timeline of diagnosis, molecular work-up, treatment, and response. The figure summarizes the clinical course from initial presentation to the initiation of targeted therapy and subsequent response. It includes the time of diagnosis, results from molecular profiling, referral to the molecular tumor board, functional validation of the EGFR L858R/Q701L co-mutation, start of osimertinib treatment, and radiologically confirmed partial remission, followed by the duration of disease control and eventual progression.

compound setting and to support subsequent therapeutic interpretation should the patient show insufficient response or early progression.

Treatment and outcome

The treatment was well tolerated, with no severe adverse events. Disease stability was confirmed again at 11 months after initial diagnosis, and osimertinib therapy was continued. At 14 months, an urelated secondary malignancy, a malignant melanoma of the right forearm was diagnosed; the stage remained undetermined, and sentinel lymph node biopsy was not performed. Imaging studies at 15 months showed persistent disease stability under ongoing osimertinib treatment. However, at 18 months, progressive disease was documented. The patient was informed about the option of palliative radiotherapy and requested time to consider this approach. Radiotherapy was initiated at 20 months. At 22 months, multiple CNS metastases were detected. The patient died 23.4 months after initial diagnosis corresponding to 21.4 months after treatment initiation (Figure 3).

Discussion

This case highlights several key challenges in modern thoracic oncology. First, although *EGFR* mutations are among the best-studied oncogenic drivers in NSCLC, a substantial proportion of cases involve rare, compound, or complex variants for which clinical evidence is sparse.[7,12,18] In these scenarios, therapeutic uncertainty often arises, particularly when additional co-mutations with potential resistance implications are present.

In our patient, the combination of L858R, a well-established sensitizing mutation,[7,9] with the much rarer Q701L variant raised the question of whether standard EGFR-directed therapy would be effective. An additional point of uncertainty concerns the allelic configuration of the 2 EGFR variants. It cannot be determined from the available data whether L858R and Q701L occurred in cu sir in trans. However, the nearly identical variant allele frequencies make a cis configuration appear more likely, although this remains speculative.

While prior reports have described resistance associated with certain EGFR compound mutations,[18,19] EGFR Q701L has specifically been observed after osimertinib exposure in an EGFR L858R-mutant NSCLC case.[17] This clinical observation suggested, but did not prove, that Q701L might contribute to osimertinib resistance in a compound setting. In contrast, our in vitro functional assays demonstrated preserved sensitivity of the EGFR L858R/Q701L co-mutant receptor to EGFR tyrosine kinase inhibition, including osimertinib. These in vitro data supported MTB-based interpretation of genomic uncertainty during ongoing treatment and may inform early therapeutic reassessment or subsequent treatment adaptation if clinical benefit is insufficient. Beyond the individual case, functional characterization of rare or compound EGFR variants with limited clinical evidence can generate transferable evidence for future patients with similar molecular profiles. This approach is intended to accompany, rather than delay, initiation of an approved standard therapy when such therapy is indicated. This illustrates the value of integrating preclinical evidence into clinical decision-making, especially for uncommon variants.

The presence of additional alterations in *PIK3CA*, *CTNNB1*, and *CDKN2A/B* added a second layer of uncertainty, as such alterations may contribute to bypass signaling or modify EGFR TKI response in selected contexts.[20] We do not intend to imply that these co-alterations are generally overridden by EGFR dependence. Rather, in this individual case, the clinical response together with the functional sensitivity of the EGFR L858R/Q701L

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receptor supports the interpretation that EGFR inhibition remained therapeutically effective despite the complex genomic background. Importantly, such findings emphasize the need for continued real-world documentation of clinical outcomes in patients with complex mutational profiles, as these observations expand the evidence base beyond controlled clinical trials.[21]

Finally, this case underscores the critical role of molecular tumor boards in guiding personalized therapy. By combining genomic profiling, preclinical functional data, and multidisciplinary expertise, the MTB provided a high level of confidence in recommending targeted therapy. This collaborative framework is particularly essential as next-generation sequencing increasingly identifies rare or previously uncharacterized variants in clinical practice. The nNGM network exemplifies how national initiatives can systematically integrate molecular diagnostics and translational research into routine oncology care.[22]

In summary, this case supports 3 conclusions: (1) rare EGFR co-variants should be interpreted according to the strength of available evidence and not overclassified based on limited observations; (2) parallel functional validation can clarify the biological relevance of rare compound EGFR alterations without delaying standard therapy; and (3) MTB-based integration of clinical, genomic, and experimental data can generate clinically useful evidence for future patients with similar molecular profiles.

Conclusion

This case demonstrates how combining molecular diagnostics, functional validation, and multidisciplinary tumor board expertise can directly influence patient care. Osimertinib proved highly effective in an NSCLC patient with concurrent *EGFR* L858R and Q701L mutations, achieving a durable remission despite additional potentially resistance-associated alterations.

Author contributions

Corinna Albers-Leischner (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing), Matthias Ritgen (Data curation, Formal analysis), Finn-Ole Paulsen (Conceptualization, Formal analysis, Investigation), Benjamin Schmidt (Data curation, Validation), Nikolas von Bubnoff (Resources), Sivahari Prasad Gorantla (Methodology, Resources), Anne Letsch (Resources), Melanie Janning (Resources), Sonja Loges (Funding acquisition, Resources), Carsten Bokemeyer (Funding acquisition), and Maximilian Christopeit (Conceptualization, Data curation, Writing—review & editing)

Supplementary material

Supplementary material is available at *The Oncologist* online.

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Conflicts of interest

M.C. received honoraria, travel and research support from BeOne/BeiGene, JAZZ, GSK, Roche, Tillotts, AstraZeneca, AbbVie, Janssen Cilag, Ciba Geigy, Boehringer Ingelheim, Pfizer, MSD, Takeda, Medac, Servier, and BMS. He is the co-holder of US-Patent (PCT/US2014/72474) “EPIGENETIC STEM CELL COMMITMENT ASSOCIATED SIGNATURE.” S.L. received honoraria, travel and research support from Eli Lilly, BerGenBio, AS, Novartis, Boehringer Ingelheim, BMS, Roche, Astra Zeneca, MSD, Merck, Novartis, Janssen, Takeda, Pfizer, Amgen, Bayer, Daiichi-Sankyo, Beigene, Apontis Pharma, Mirati.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author. Figure 3 visualization was generated using ChatGPT.

Statement of patient publication consent

The investigators obtained informed consent to publish information and/or images from the participant. Written informed consent included the collection of the clinical data and scientific use of biopsy material as well as comprehensive genomic analysis.

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