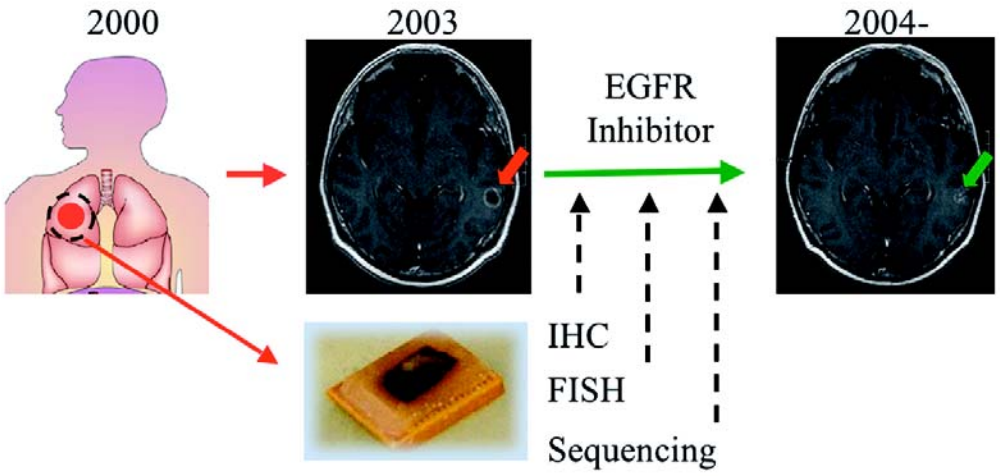
Supplementary information S1

Box S1 | **Case study of an EGFR-TKI treated lung cancer patient**

Our first clinical experience with EGFR inhibitors was a 63-year-old, female non-smoker, who was diagnosed with NSCLC adenocarcinoma in 2000 (REF. 1) **(Box figure).** In 2003, MRI scans revealed multiple brain metastases in both hemispheres with the associated signs and symptoms of elevated intracranial pressure. Her clinical status rapidly deteriorated despite 12 cycles of 3 Gy whole brain radiotherapy (WBRT). The relatives of the patient consulted with our medical team if we would recommend taking one of the experimental drugs such as the EGFR-inhibitors gefitinib or erlotinib. At this time, the results of the Phase III trials of both drugs were available and were disappointing, as neither provided a significant survival advantage in an unselected NSCLC population[2–4]. However, a few cases of major responses were also reported in non-smokers and women. Since this clinical profile fitted our patient, we examined her archived tissue sample taken from her primary tumor and found that in addition to staining positive for EGFR, gene amplification by FISH analysis was also detectable. At that time nor preclinical or clinical data was available that would have directly proven the predictive significance of *EGFR* gene amplification in response to gefitinib or erlotinib in NSCLC. However, gene amplification of *EGFR* is rare in NSCLC (only 5-10%)[5]. We hypothesized that although these drugs failed to achieve significant survival benefit in an unselected patient population, those few who benefited from the EGFR inhibitor therapy may have had gene amplification. Previous experience with successful targeted therapies indicated the genetic alterations of target genes are often reliable predictors of response. The local drug administration agency accepted our reasoning and permitted the treatment of the patient with gefitinib. After only two months of treatment, her condition rapidly improved and the control MRI pictures of her brain showed complete response of all the metastasis, and after four years of therapy she is still in complete remission.

When the first reports of positive correlation between *EGFR* activating mutations and response to EGFR inhibitors were published, we also sequenced this sample and identified one of these mutations[6–8]. In response to these reports, we started to optimized these molecular diagnostics methods and from the beginning of 2005 to be ready for routine clinical testing. We have published recently the results of prospective analysis of more than hundred lung adenocarcinomas. We found that standardized EGFR immunohistochemistry can be negative in *EGFR*-mutant or FISH-positive tumors. Several patients with *EGFR*-mutant, but immunohistochemistry-negative tumours, had major clinical responses, which further emphasize the importance of molecular diagnostics[9].



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