Introducing the Semi-Quantitative Index (SQI) Reporting Tool

SQI Reporting tool not available in the U.S.

cobas®

Life needs answers

Tyrosine kinase inhibitors (TKIs), such as erlotinib and gefitinib, target the epidermal growth factor receptor (EGFR) and are effective anti-cancer drugs in patients with non-small cell lung cancer (NSCLC). Mutations in the ATP-binding pocket of EGFR enhance the binding of the TKI at the expense of ATP and confer sensitivity to these agents.[1]

Subsequent resistance to TKIs develops in 90% of patients. In many, this is associated with the T790M resistance mutation in exon 20. Identifying patients with this mutation is important as this population may benefit from third-generation TKIs.

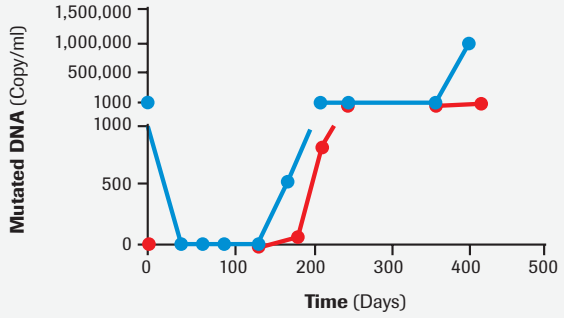
Historically, testing patients for mutations has been conducted with tissue samples. However, biopsy is an invasive procedure that is not always possible to perform in severely ill patients. In patients with NSCLC, obtaining sufficient tissue can be difficult due to the location and size of the tumour. Plasma from these patients contains cell-free DNA (cfDNA) from the original tumour, and analysis of the plasma allows more frequent assessment of disease state.

ADVANTAGES OF PLASMA-BASED ANALYSES

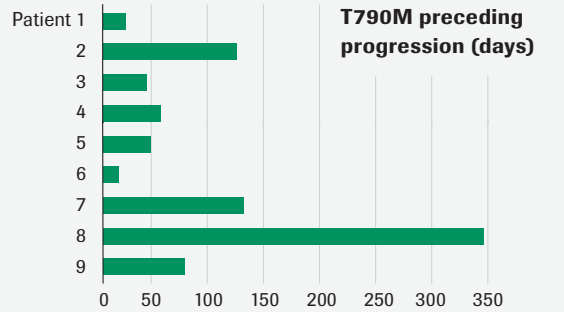
- Non-invasive compared with biopsy
- Increased sampling frequency possible
- Testing possible in the critically ill
- Allows testing at diagnosis when no tumour material is available
- Reflects overall tumour burden

The **cobas**® EGFR Mutation Test v2 uses real-time PCR technology to detect and identify 42 mutations in exons 18, 19, 20 and 21 in the *EGFR* gene using plasma samples.* Serial testing of plasma from 23 NSCLC patients with TKI-sensitizing EGFR mutations found that the amount of plasma DNA containing these mutations was reduced in 96% of patients treated with erlotinib.[2] At the time of disease progression, nine patients had the T790M resistance mutation, accompanied in every case by an increase in the amount of the original sensitizing mutation (Fig. 1). The most interesting finding from this study was that the initial sensitizing mutation and the T790M mutation appeared prior to evidence of clinical disease progression. In the case of T790M, this was up to 344 days (range 15–344 days) before disease progression according to established RECIST criteria.

Fig. 1. Amount of mutated EGFR plasma DNA in a patient treated with erlotinib. Red line: T790M mutation; Blue line: EGFR exon 19 deletion.



The value of molecular monitoring in detecting mutations before disease progression by CT scans.



The Semi-Quantitative Index (SQI) is a new feature included in the analysis report of the **cobas**® EGFR Mutation Test v2. The SQI is a measure of the amount of

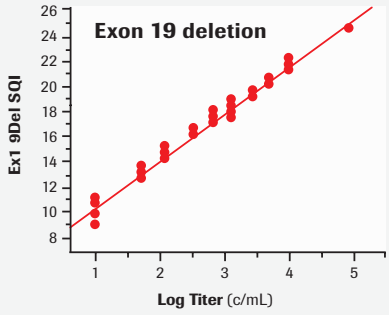
SERIAL TESTING FOR EGFR MUTATIONS AND TRACKING THE SQI VALUE CAN HELP THE TREATING PHYSICIAN UNDERSTAND TUMOUR PROGRESSION IN THE INDIVIDUAL PATIENT, FACILITATING CONFIDENT TREATMENT DECISIONS

*__cobas__® EGFR Mutation Test v2 can be used on tissue samples.

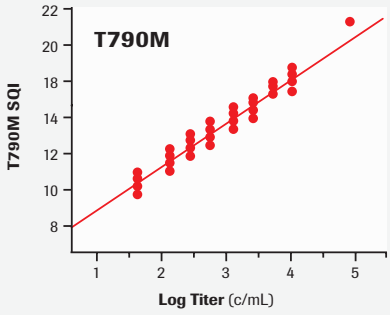
mutant cfDNA in a sample and can be used to measure differences in mutation load over time. An increase or decrease in the SQI value indicates a respective change in the amount of corresponding target mutation in an individual patient.

Linearity studies have demonstrated a clear correlation between SQI and the mutation copy number across a linear range of $10-10^5$ copies for exon 19 deletions and L858R and $50-10^5$ for T790M (Fig. 2). In repeatability studies, the **cobas**® EGFR Test had a correct call rate of 99.92%, and results were highly reproducible (Table 1).

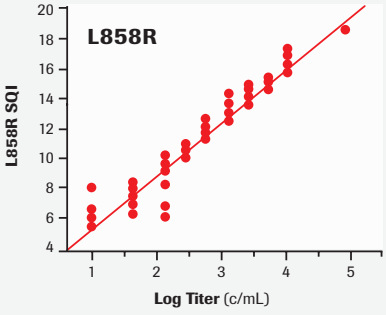
Fig. 2. Positive correlation between SQI and mutation copy number.



SQI=7.042+3.507 * Log Copies per mL R^2=0.981



SQI=3.593+3.352 * Log Copies per mL R^2=0.973



SQI2.543+3.283 * Log Copies per mL R^2=0.933

The clinical utility of the SQI was evaluated by serial monitoring of EGFR mutations at initiation of therapy with TKIs.[3] A progressive decline in SQI was apparent from day 4 in 95% of patients.

Table 1. ***cobas***® *had a correct call rate of 99.92% (381/384).* ***Repeatability*** *four samples, tested in duplicate by two operators, using two different reagent lots and two cobas z480 analyzers over 4 days.*

Exon	Mutation	Mean SQI	SD SQI
18	G719A	4.53	0.41
		6.86	0.38
		11.81	0.67
19	Ex19Del	13.42	0.46
		16.85	0.42
		22.31	0.55
20	S7681	5.99	0.45
		8.49	0.43
		14.13	0.43
20	T790M	9.00	1.03
		13.28	0.43
		19.52	0.57
20	Ex20Ins	4.92	0.43
		6.77	0.40
		12.61	0.60
21	L858R	9.81	0.47
		12.91	0.28
		17.21	0.81
21	L861Q	3.58	0.73
		7.91	0.45
		10.06	0.60

70% of patients demonstrated a decrease of >50% and were considered 'rapid responders' (Fig. 3). The rate of decrease correlated with percent tumour shrinkage (PTS) at 2 months as assessed by RECIST criteria. The mean PTS was significantly greater in the rapid responders ($P < 0.0001$; Fig. 4).

This strong correlation between SQI and clinical response early in TKI makes the SQI a powerful new tool in the management of NSCLC patients.

Fig. 3. SQI correlation for Rapid Responders (A) and Slow Responders (B).

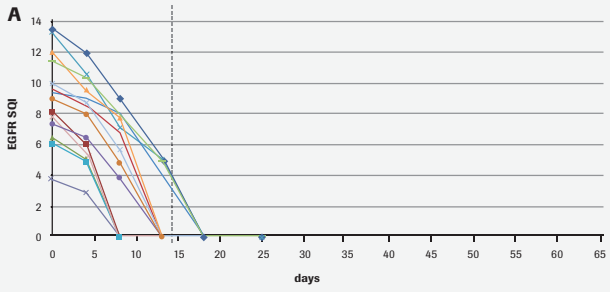
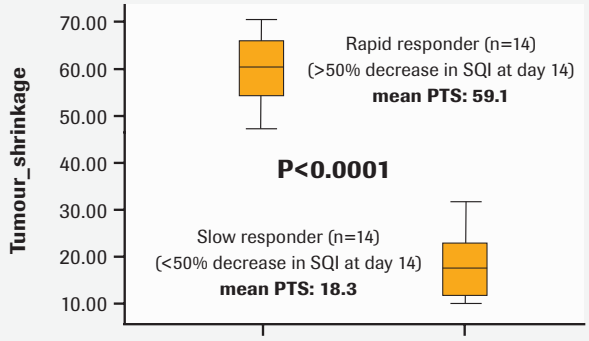


Fig. 4. PTS in rapid and slow responders.



COMPONENTS AND PART NUMBERS

Product/component	Quantity	Part number
cobas® EGFR Mutation Test v2 (CE-IVD)	24 Tests	07248563190
cobas® cfDNA Sample Preparation Kit (IVD)	24 Isolations	07247737190
cobas® DNA Sample Preparation Kit (IVD)	24 Isolations	05985536190

SQI: IMPLICATIONS FOR CLINICAL PRACTICE

- Serial measurements using the SQI can assist in the management of NSCLC patients based on EGFR mutation status
- The SQI correlates with clinical disease progression
- The SQI identifies trends in EGFR mutations and may:
  - Allow early prediction of clinical response to TKIs
  - Identify resistance mutations months before clinical progression is evident
  - Identify patients less likely to respond to first-generation TKIs
  - Allow early triage of patients more likely to respond to third-generation TKIs early
- The SQI may represent a new tool to facilitate drug efficacy comparisons in clinical trials

REFERENCES

[1] Pao W, et al. *Proc Natl Acad Sci USA* 2004;101(36):13306–11.

[2] Sorensen BS, et al. *Cancer* 2014;120:3896–901.

[3] Marchetti A, et al. *J Thorac Oncol* 2015;10:1437–43.

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