Urine Detection of EGFR T790M Mutation in non-small-cell lung cancer: an outcomes and total cost of care analysis

Introduction

Patients with EGFR mutation adenocarcinoma lung on first-line tyrosine kinase inhibitors (TKIs) eventually develop progression. About 70% develop an acquired secondary EGFR T790M mutation. Third-generation EGFR TKIs (2nd-gen TKIs) target 790M-positive tumors and improve outcomes. Standard approach for determining EGFR T790M mutation status after a 2nd- or 3rd generation TKI is molecular testing of a biopsied tumor tissue specimen. Biopsy includes complication risks, and the median cost of hospitalization for biopsy related complications ranges from $10,000 to $15,000 in 2015 USD. Current technology allows for the same molecular testing to be carried out in blood or urine samples. Circulating tumor DNA (ctDNA) fragments from cell lysis or apoptosis can be collected in urine. Investigators of the TIGER-X trial reported that patients with T790M-positive disease treated with a 3rd-generation TKI had similar response rates and overall survival (OS) regardless of whether positive status was detected with urine ctDNA or tissue.

The purpose of this study is to assess the clinical and total-cost of care implications of two different care pathways around detection of T790M status from a US third-party payer perspective.

Methods

**Urine Testing Strategy (UTS):** Testing 790M status via biopsy only and tissue molecular genotyping.

**Urine Testing Strategy (UTS):** Testing 790M mutation status initially by urine ctDNA. If negative, the TTS care pathway is then initiated.

Estimated 70% of patients that progress on first line EGFR therapy harbor 790M mutation. Probability of positive, negative, and indeterminate tests for patients with 790M-positive disease, stratified by urine ctDNA or tissue, was estimated from the TIGER-X trial data.

Median PFS with 790M-positive disease is 4 to 5 months when treated according to NCCN guidelines. Cost of biopsy based on analysis of electronic medical records and database of about 800 NSCLC patients on erlotinib undergoing biopsy. Mean cost of outpatient biopsy is between $1,212 and $1,524 in 2012-13 USD. Inpatient biopsies are much more expensive ($12,600 to $34,815 in 2013 USD). Costs adjusted to 2016 showed weighted cost of a biopsy $3,473 to $4,173.

From data, 79,518 biopsies was reported from a voluntary, fee-supported database. Pneumothorax occurred in 21.4% of inpatient and 12.2% of outpatient biopsies. Hospitalization due to biopsy occurred in 21.2% of inpatients and 2.3% of outpatients.

We estimated the proportion of outpatient biopsy to be 80.5%. Weighted average costs of managing hospitalization for pneumothorax across these three subsets of patients was $10,189.

We implemented the base case for molecular testing to be $942 and examined the implication of cost savings significantly depend on factors including the type of treatment for T790M-negative disease. The actual cost of care savings is likely higher.

**Test “positive” (“T790M+”)**

Average PFS 10.41 mos with TTS and 10.85 mos with UTS (difference, 0.44 months is due to improvement in detection of T790M with UTS).

**Test “negative” (“T790M-”)**

Among a cohort of 800 patients progressed after initial treatment, 880 biopsies would be performed with TTS. Between cohorts, higher utilization of more expensive 3rd-gen TKIs in UTS compared to TTS increases the cost of UTS treatment.

**Test “Indeterminate”**

UTS was cost saving over the range of input values (Figure 2). The most influential inputs on total cost of care savings were the probability of T790M positivity by tissue and the cost of treatment for tissue-negative patients.

Figure 4 shows the difference of UTS and TTS in total cost of care versus the difference in PFS presented in 1000 simulations where all parameters are varied across their pre-protocol distributions. PFS and total cost of care were highly correlated (ρ = 0.882), in which a higher difference in PFS was related to a higher difference in total cost of care. This is a consequence of total costs increasing when 3rd-gen TKIs are appropriately administered to patients with T790M-positive disease. In over 96% of 1000 simulations, UTS increased PFS compared with TTS (Quadrant ii and iv) and in more than 70% of simulations, UTS was both beneficial and cost-saving (Quadrant iv, Figure 4).

Results

UTS is expected to reduce biopsies and associated risk of complications by 55.6% compared to TTS.

Cost savings exceeding $1,300 are anticipated and may be 2 to 3-fold larger ($2700 per test ordered).

UTS increases the likelihood of detecting T790M and treating appropriately.

Savings significantly depend on factors including the type of treatment for T790M-negative disease. The actual cost of care is likely higher.

**Conclusions**

UTS is a dominant care pathway relative to TTS. It saves costs and improves the patient experience.

Figure 1. Schematic of care pathways (uring testing strategy versus testing strategy) for detecting T790M positive disease

(A) TTS care pathway

(B) UTS care pathway

Table 1. Urine testing strategy and comparator costs.

<table>
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<tr>
<th>Strategy</th>
<th>Test &quot;negative&quot; (T790M-)</th>
<th>Test &quot;positive&quot; (T790M+)</th>
<th>Test &quot;Indeterminate&quot;</th>
<th>Cost of biopsy inpatient</th>
<th>Cost of biopsy outpatient</th>
<th>Cost of management pneumothorax</th>
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</table>

Figure 2. Sensitivity analysis - cost savings of UTS based on the cost of molecular testing and the probability of patients with the somatic T790M mutation

Figure 3. Full variable involved in the model (base case)

Figure 4. Urine testing strategy analysis (UTS vs. TTS)