Real Patients, Real Results

60-Year-Old female with metastatic EGFR-mutated lung cancer

EGFR p.T790M; c.2369C>T (Exon 20) 10.9% Osimertinib

GENE	ALTERATION	MUTANT FRACTION	FDA TARGETED THERAPIES (lung cancer)	FDA TARGETED THERAPIES (for other indications)	CLINICAL TRIALS (DETAILS BELOW)
RB1	p.R455*; c.1363C>T	7.2%	None		3
TP53	p.I254T; c.761T>C (Exon 7)	5.3%	None		6
TP53	p.R156C; c.466C>T (Exon 5)	4.2%	None		6

ADDITIONAL THERAPEUTIC INFORMATION (see pg 4)
Chemotherapy

RB1 DESCRIPTION
The protein encoded by this gene is a negative regulator of the cell cycle and was the first tumor suppressor gene found. The encoded protein also stabilizes constitutive heterochromatin to maintain the overall chromatin structure. The active, hypophosphorylated form of the protein binds transcription factor E2F1. Defects in this gene are a cause of childhood cancer retinoblastoma (RB), bladder cancer, and osteogenic sarcoma. [provided by RefSeq, Jul 2008]

TP53 DESCRIPTION
This gene encodes a tumor suppressor protein containing transcriptional activation, DNA binding, and oligomerization domains. The encoded protein responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Mutations in this gene are associated with a variety of human cancers, including hereditary cancers such as Li-Fraumeni syndrome. Alternative splicing of this gene and the use of alternate promoters result in multiple transcript variants and isoforms. Additional isoforms have also been shown to result from the use of alternate translation initiation codons from identical transcript variants (PMIDs: 12032546, 20937277). [provided by RefSeq, Dec 2016]

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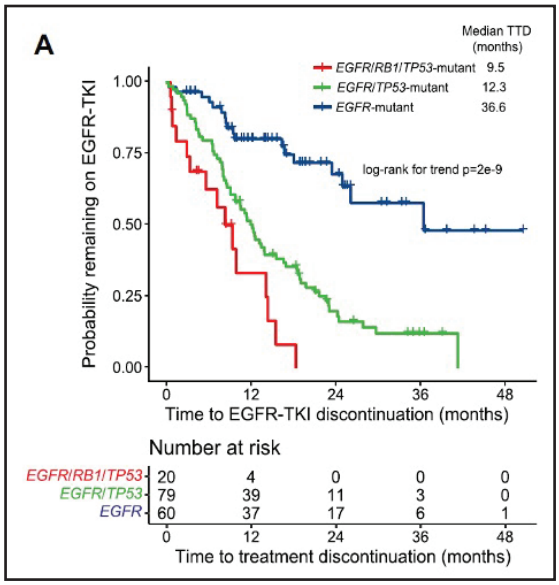
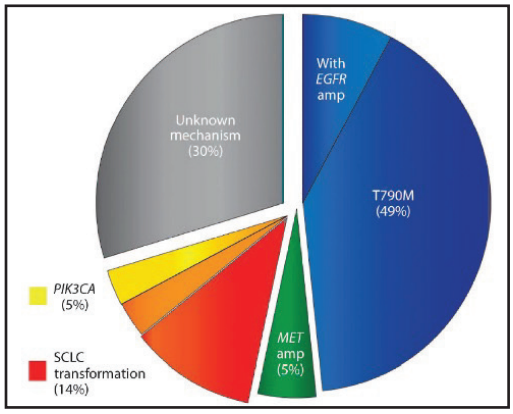
The plasma ctDNA in this patient identifies an EGFR T790M mutation but also RB1 and TP53 co-mutations. These co-mutations provide guidance for a treatment decision today but also direct a heightened clinical awareness of potential evolving tumor biology changes tomorrow.

An unexpected oncologic finding treating EGFR-mutated lung adenocarcinomas with an EGFR TKI has been a 10-15% clonal small cell transformation upon progression. The radiographic presentation is often classic bulky small cell lung cancer with CNS metastasis but can be an isolated recurrence. This appears consistent irrespective of the TKI used, including second- or first-line osimertinib. The EGFR mutation often persists but is no longer the driver oncogene in this setting. Aggressive chemotherapy is forced with transformed small cell median survivals of 10.9 months. De novo small cell histologies with an EGFR mutation have also been reported and appear different, with potential retained EGFR driver and TKI sensitivity.

There is now data to indicate that the finding of RB1 and TP53 co-mutations at the time of diagnosis can portend this aggressive transformation. In a study of 863 patients with EGFR-mutated lung adenocarcinomas evaluated by NGS molecular testing, 5% were EGFR/RB1/TP53 triple mutated. Small cell histology was ultimately seen in 25% of that molecular subset, either de novo or upon progression. Notably, none of the patients without baseline RB1 and TP53 co-mutations had small cell transformation. However, even in those without small cell transformation, the presence of RB1 and TP53 mutations had a much shorter time until progression and discontinuation of the EGFR TKI of only 9.5 months compared to 36.6 months in patients without these two co-mutations.





When RB1 and TP53 co-mutations are present at baseline, a heightened awareness of this small cell transformation potential is needed. PIK3CA mutations also frequently evolve. When present, T790M ctDNA mutations have cleared on osimertinib with SCLC progression, whereas other EGFR mutations persist. Although yet to be known, this shortened benefit of an EGFR TKI alone and the aggressive small cell transformation potential is very compelling for a combinatorial approach of upfront systemic chemotherapy with the EGFR TKI, clearly osimertinib in this setting.

Only with broad NGS testing would this be known. Narrow molecular testing, just looking at targetable driver mutations, would miss clinically impactful co-mutations. A liquid biopsy plasma NGS provides insight into a cancer's aggressive tumor biology that can make a difference for your patient.

Case Study Prepared by Doctor Paul Walker
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Sources:
- 2019 Published by Elsevier Inc. on behalf of the International Association for the Study of Lung Cancer
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