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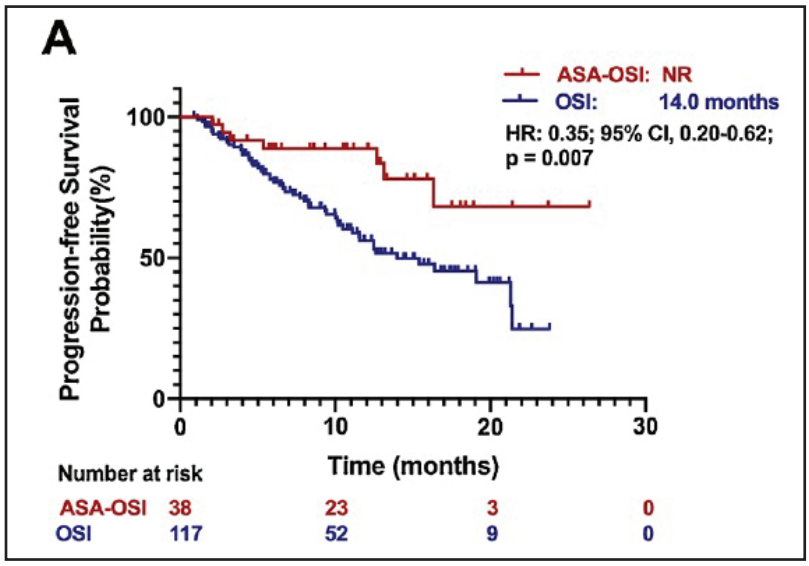
77-Year-Old female with metastatic EGFR-mutated lung cancer

In this patient with an EGFR exon 21 L858R mutated lung adenocarcinoma, the identified co-mutations and PD-L1 expression drive nuanced therapeutic decisions.

At age 77, a simple cancer treatment with an oral EGFR TKI or single-agent immune checkpoint blockade with PD-L1 > 50% would appear ideally kind and gentle. However, the co-mutations of the TP53 exon 5 and KDR Q472H greatly impact the benefit of simple EGFR TKI therapy alone. KDR Q472H co-mutations have been associated with primary resistance to an EGFR TKI. Even when responsive, TP53 mutations portend a much shorter PFS and OS. However, this adverse prognostic and predictive clinical behavior of these co-mutations may be clinically mitigated. TP53 mutations are associated with elevated VEGFA levels, which can be a resistance pathway in EGFR-mutated lung cancers. The kinase insert domain receptor (KDR) mutation encodes VEGFR-2 function, and these mutations are also associated with elevated VEGFA levels. Studies have shown dual EGFR and VEGF blockade can reverse secondary and overcome primary EGFR TKI resistance. Given these co-mutations and tumor biology, a dual EGFR and VEGF blockade with either bevacizumab or ramucirumab is a very compelling best-treatment approach in this setting.



The PD-L1 expression also carries a treatment decision impact—not with immune checkpoint blockade but with the choice of the EGFR TKI. In the FLAURA trial, osimertinib was associated with an unchanged 18.9/18.4-month PFS irrespective of PD-L1 expression of ≥ 1% or < 1%. However, in the comparator arm of either gefitinib or erlotinib, the PFS was impacted and decreased from 10.9 months to 6.9 months with PD-L1 expression.

Another emphasis with this case is the importance of knowing EGFR and ALK status before embarking upon immune-based therapies in lung cancer. These two targetable driver mutations do not benefit from immune checkpoint blockade, with FDA indications for first-line immune-based therapy mandating negative EGFR and ALK findings. Charging forward with immune-based therapies without knowing these molecular findings can lead to missing very effective targeted therapy and stepping forward with ineffective therapy with heightened pulmonary toxicity. The right treatment matters and time matters. Plasma and tissue molecular findings are complementary and can achieve the right treatment at the right time. Tissue NGS alone will miss one-third of targetable driver mutations. Both are needed to completely identify potential driver mutations/fusions. Drawing the plasma NGS at the time of tissue diagnosis and sending tissue for NGS immediately after the pathologist confirms a malignant diagnosis is the approach CIRCULOGENE advocates to ensure your patient is getting the right treatment in the quickest possible time from their cancer diagnosis.

IMMUNOTHERAPY TEST RESULTS		FDA GUIDANCE	RNA TEST RESULTS	
PD-L1 EXPRESSION	Positive (≥50%)	Pembrolizumab	ALK GENE FUSION	Not Detected
			ROS1 GENE FUSION	Not Detected

bPCR TEST RESULTS EGFR mutation: (+L858R) KRAS mutation: Not detected BRAF mutation: Not detected

TP53	p.V157I; c.469G>A Exon 5	5.7%
KDR	p.Q472H; c.1416A>T	4.1%

Another intriguing clinical tidbit is a recent study showing improved PFS with concurrent use of aspirin with osimertinib independent of TP53 mutation and PD-L1 status.

Case Study Prepared by Doctor Paul Walker
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