INTERVIEW

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Select Excerpts from the Interview

Tracks 2, 4-5

DR LOVE: What is the typical duration of response in patients with ALK-positive non-small cell lung cancer (NSCLC) receiving crizotinib?

DR CAMIDGE: The median progression-free survival (PFS) is between 9 and 10 months, but "the devil's very much in the details." We reported at ASCO 2012 that in about 46% of patients with ALK-positive NSCLC when crizotinib stops working, it does so due to disease progression within the brain.

Of note, in about 85% of cases, the brain was the only site of progression. The brain is standing out as the Achilles heel for crizotinib. When we administered radiation therapy to patients with CNS-only progression and continued crizotinib, it took an average of 7 months before patients experienced another progression outside of the brain (Weickhardt 2012a).

DR LOVE: Would you discuss the recent data your group has reported on crizotinib-related visual and gonadal effects?

DR CAMIDGE: Visual effects can manifest within days of a patient receiving crizotinib. They are classically at the edges of the patient's vision, usually in low-light conditions. Patients see either flashing lights or smearing of lights (Salgia 2012). Occasionally, patients see high-contrast images, such as banisters on the staircase, invert their registrations of dark and light. These issues improve over time, and that may be because the visual system slowly adapts. These visual effects are not harmful in any way. They don't prohibit people from driving or watching TV. However, I warn patients about them because otherwise they are concerned that it may be a more serious problem.

The hypogonadism story goes back to a 35-year-old patient of mine who was faring fantastically on crizotinib and whose cancer had melted away. He came in for a follow-up visit feeling absolutely exhausted. Patients typically get a bit of fatigue on crizotinib but not to this extent. We ended up checking his testosterone level and it was low. We're aware that testosterone levels can drop with advanced cancer if you've been through chemotherapy, so we began evaluating testosterone levels in both the patients receiving crizotinib and in a "control group" of my other patients with advanced NSCLC who were receiving standard therapies.

Consistent with the literature, we found low testosterone levels in about 30% of patients receiving standard therapy, but levels were low in 100% of the men who were receiving crizotinib. When we tracked the levels longitudinally, they were generally normal before patients began receiving crizotinib but would drop to below the lower limit of normal within about 3 weeks of initiating crizotinib (Weickhardt 2012b). I send these patients receiving crizotinib to the endocrinologist, where they discuss the pros and cons of testosterone replacement.

Track 6

DR LOVE: Would you comment on another major story that has evolved recently with evidence that crizotinib has clinical activity in patients with advanced NSCLC harboring ROS1 gene rearrangement?

DR CAMIDGE: This year at ASCO we saw a report of crizotinib for patients with ROS1 gene rearrangements, which are similar to ALK translocations. Although ROS1 rearrangements occur in fewer than 1% of lung cancer cases, patients with these mutations respond as well to crizotinib as do the patients with ALK positivity. I believe that will probably lead to a slight label expansion for crizotinib.

DR LOVE: Have you administered crizotinib to any patients with ROS1 rearrangements?

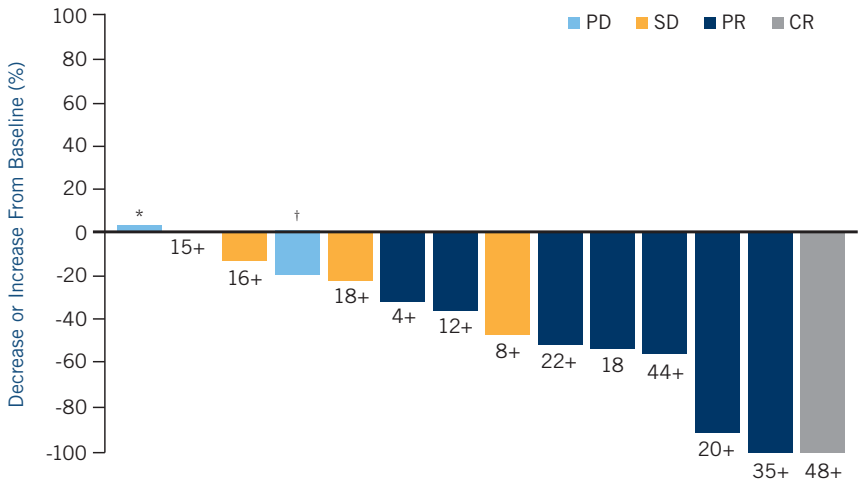
DR CAMIDGE: I had a patient, a medical oncologist actually, who had me test him for everything, all of which was negative. The ROS1 story had only broken a few months prior. We developed our own assay, and his was the first positive result.

He'd experienced a minimal response to carboplatin/pemetrexed/bevacizumab, and we placed him on our crizotinib study. He experienced a rapid, excellent response. We had to discontinue crizotinib about 6 weeks later for an unrelated bowel perforation. He was unwell and in intensive care.

Afterward, per study protocol, his first CT scan indicated progression. He'd been off crizotinib for many weeks, and if you look at the waterfall plot that Dr Alice Shaw presented at ASCO 2012, he is one of the patients who experienced progression (Shaw 2012; [1.1]). We were able to rechallenge with crizotinib when he'd recovered from his bowel operation, and he experienced another 6 to 7 months of disease control on crizotinib.

1.1

Clinical Activity of Crizotinib in Advanced Non-Small Cell Lung Cancer Harboring ROS1 Gene Rearrangement



Overall response rate	Median duration of treatment	Disease control rate at 8 weeks
57.1%	25.7 weeks	79.0%

* Tumor ROS1 FISH-positive but negative for ROS1 gene fusion expression; † Crizotinib held >6 weeks prior to first scans that indicated PD; + Treatment ongoing (in weeks)
PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response

With permission from Camidge DR, Shaw AT et al. *Proc ASCO* 2012;**Abstract 7508**.

Track 8

DR LOVE: What are your thoughts on the recently reported results from the LUX-Lung 3 study evaluating the irreversible EGFR tyrosine kinase inhibitor (TKI) afatinib versus cisplatin/pemetrexed as first-line therapy for advanced EGFR-mutant NSCLC?

DR CAMIDGE: These results appear to corroborate the existing data that patients with EGFR mutation benefit from up-front targeted therapy with an EGFR TKI. Patients who received afatinib on the LUX-Lung 3 study experienced a PFS benefit compared to those who received standard therapy (Yang 2012; [1.2]). Because the study included patients with other rare, less responsive types of EGFR mutations, not just the classic L858R and exon 19 deletions, the authors performed a subset analysis in which they analyzed patients with only those common mutations. In the afatinib arm, the PFS was a little more than 13 months in patients with L858R/del 19 mutations, although that may be mild massaging of the data.

Now we ask, what does that mean? If and when afatinib receives an FDA license, will it be the first to be mutation specific in the EGFR category? What will cause somebody to use afatinib rather than erlotinib in that setting, even though erlotinib doesn't technically have a mutation-specific license? Some people are worried that the toxicity with afatinib appears to be greater than that with erlotinib. The Grade 3 rates of diarrhea, rash and paronychia are in the 10% to 20% range. These are severely toxic agents in some individuals and may require dose reductions. An ongoing head-to-head study in the Far East of afatinib versus gefitinib will help toward ascertaining the side effects and finding out whether afatinib is any better or worse than the traditional reversible EGFR TKIs. ■

1.2

LUX-Lung 3: A Phase III Trial of Afatinib versus Cisplatin/Pemetrexed (Cis/Pem) as First-Line Therapy in Advanced EGFR-Mutant Non-Small Cell Lung Cancer

Efficacy	Afatinib (n = 230)	Cis/pem (n = 115)	Hazard ratio	*p*-value
Median progression-free survival	11.1 mo	6.9 mo	0.58	0.0004
Objective response rate	56.1%	22.6%	—	<0.001
	Afatinib (n = 229)		**Cis/pem** (n = 111)	
Select adverse events	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhea	95.2%	14.4%	15.3%	0%
Rash/ache	89.1%	16.2%	6.3%	0%
Paronychia	56.8%	11.4%	0%	0%

Yang JC et al. *Proc ASCO* 2012;**Abstract LBA7500**.

SELECT PUBLICATIONS

Salgia R et al. **Visual effects in anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) patients treated with crizotinib.** *Proc ASCO* 2012;**Abstract 7596**.

Weickhardt AJ et al. **Continuation of EGFR/ALK inhibition after local therapy of oligoprogressive disease in EGFR mutant (Mt) and ALK+ non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012a;**Abstract 7526**.

Weickhardt AJ et al. **Rapid-onset hypogonadism secondary to crizotinib use in men with metastatic nonsmall cell lung cancer.** *Cancer* 2012b;[Epub ahead of print].