INTERVIEW

D Ross Camidge, MD, PhD

Dr Camidge is Director of the Thoracic Oncology Clinical Program and Associate Director for Clinical Research at the University of Colorado Cancer Center in Aurora, Colorado.

Tracks 1-17

Track 1 **Case discussion:** A 53-year-old former smoker with EGFR-mutant metastatic adenocarcinoma of the lung previously treated with multiple lines of systemic therapy presents with progressive disease

Track 2 Therapeutic options for patients with EGFR-mutant tumors and asymptomatic disease progression on an EGFR tyrosine kinase inhibitor (TKI)

Track 3 Management of treatment-associated hyperglycemia with the third-generation, irreversible EGFR TKI rociletinib (CO-1686)

Track 4 Efficacy and toxicity of third-generation EGFR TKIs (rociletinib, AZD9291, HM61713)

Track 5 Dual inhibition of EGFR with afatinib/cetuximab in TKI-resistant, EGFR-mutant non-small cell lung cancer (NSCLC) with and without T790M mutations

Track 6 **Case discussion:** A 67-year-old never smoker with EML4-ALK-positive, crizotinib-resistant adenocarcinoma of the lung

Track 7 Sensitivity of diagnostic assays for identification of ALK-positive NSCLC

Track 8 Incidence and management of hypogonadism secondary to crizotinib use in men

Track 9 Dose reduction in the management of ceritinib-associated gastrointestinal toxicities

Track 10 Antitumor activity of crizotinib and ceritinib in patients with brain metastases

Track 11 Consideration of second-generation ALK inhibitor therapy for patients with asymptomatic ALK-positive NSCLC and multiple brain metastases

Track 12 Use of erlotinib for patients with asymptomatic EGFR-mutant NSCLC and multiple brain metastases

Track 13 Investigation of the second-generation ALK inhibitor alectinib as first-line therapy for ALK-positive NSCLC

Track 14 Use of stereotactic radiation therapy to control sites of extra-CNS oligoprogressive disease in patients receiving crizotinib for ALK-positive NSCLC

Track 15 **Case discussion:** A 64-year-old smoker with pan-negative squamous cell carcinoma (SCC) of the lung for whom a next-generation sequencing panel reveals a RET rearrangement

Track 16 Activity of the multitargeted TKI ponatinib in SCC of the lung

Track 17 Efficacy of crizotinib in patients with advanced c-MET-amplified NSCLC

Select Excerpts from the Interview

Track 2

DR LOVE: What is your approach to patients with EGFR-mutant non-small cell lung cancer (NSCLC) who develop acquired resistance to an EGFR tyrosine kinase inhibitor (TKI) such as erlotinib?

DR CAMIDGE: There is currently a debate as to whether patients with EGFR-mutant lung cancer who develop resistance to erlotinib should be taken off erlotinib. No one

has proven whether the re-treatment approach is better or worse than continuing TKI therapy and adding in chemotherapy. Patients who develop acquired resistance to TKIs respond well to chemotherapy. When they receive re-treatment with the TKI, they may have a good response. I believe that we should aim to suppress as many cancerous clones as possible. I have changed my approach in recent years. I continue to administer erlotinib to patients who develop disease progression while receiving the drug, and I add in chemotherapy.

The mechanisms of acquired resistance in cancer cells change, depending on the environment they're adapting to. The T790M resistance mutation in the EGFR tyrosine kinase cripples the kinase, resulting in a relatively indolent clone that does not survive well in the absence of erlotinib. Patients who have been off erlotinib for some time will rerespond well to erlotinib, though the duration of response is shorter.

Editor's note: Subsequent to this interview, data were presented by Dr Tony Mok and colleagues at ESMO 2014 on the Phase III IMPRESS trial evaluating gefitinib/chemotherapy versus chemotherapy for EGFR mutation-positive NSCLC after disease progression on first-line gefitinib. The authors concluded that continuation of gefitinib in addition to cisplatin/pemetrexed would be of no clinical benefit for patients with acquired resistance to gefitinib (Mok T et al. *Proc ESMO* 2014;**Abstract LBA2_PR**).

Tracks 3-4

DR LOVE: What do we know about the efficacy of the third-generation EGFR TKIs HM61713, AZD9291 and rociletinib (CO-1686) for EGFR TKI-resistant NSCLC?

DR CAMIDGE: Third-generation EGFR TKIs are designed to have activity against common EGFR activating mutations and the T790M mutation while sparing wild-type EGFR. HM61713 elicits a disappointingly low response rate of approximately 20% in patients who develop disease progression on EGFR TKIs (Kim 2014a).

I believe it's turning into a "2-horse race" between rociletinib and AZD9291, both of which have good activity. In patients who have the T790M mutation, AZD9291 demonstrated a 64% response rate. In the T790M-negative cohort, the response rate was 22% (Janne 2014). With rociletinib the response rate was 58% (Sequist 2014).

Rociletinib and AZD9291 have yielded impressive progression-free survival (PFS) curves. Although the data are not mature, the median PFS for rociletinib is more than 12 months. We have to await further data to determine if one is superior.

DR LOVE: What side effects are observed with rociletinib and AZD9291?

DR CAMIDGE: Hyperglycemia is a relatively common side effect of rociletinib. This is drug-induced diabetes, and it doesn't happen in all patients. In a study presented at the ASCO 2014 meeting, hyperglycemia and impaired glucose tolerance were reported in more than 50% of patients, with Grade 3 hyperglycemia occurring in approximately 20% of patients (Sequist 2014; [1.1]). Hyperglycemia can be managed with oral antihyperglycemic drugs, but some patients may require insulin.

Hyperglycemia doesn't appear to be a problem with AZD9291. Some patients experience rash. Grade 3 or higher adverse events were observed in approximately 20% of

patients at the 80-mg dose of AZD9291, which is the dose being used moving forward (Janne 2014; [1.1]).

1.1

Efficacy and Safety of Third-Generation EGFR Inhibitors AZD9291 and Rociletinib for EGFR-Resistant NSCLC

Efficacy	AZD9291*[1] (n = 61)	Rociletinib[2] (n = 40)
Overall response rate	54%	58%
Select adverse events (any grade)	**AZD9291*** **(n = 74)**	**Rociletinib** **(n = 72)**
Diarrhea	20%	23.6%
Rash	27%	4%
Nausea	14%	34.7%
Hyperglycemia	1%	52.7%†
QT prolongation	1%	15.3%

* At Phase II dose of 80 mg; † Including impaired glucose tolerance

[1] Janne P et al. *Proc ASCO* 2014;**Abstract 8009**; [2] Sequist L et al. *Proc ASCO* 2014;**Abstract 8010**.

Track 5

DR LOVE: Would you discuss the recent paper that you were part of that investigated the combination afatinib/cetuximab in patients with EGFR-mutant NSCLC with acquired resistance to EGFR TKIs (Janjigian 2014)?

DR CAMIDGE: Afatinib/cetuximab is an interesting combination that shuts off all EGFR signaling. In our study, 126 patients with EGFR-mutant NSCLC received the combination of afatinib and cetuximab. The overall response rate was 32% in patients harboring T790M-positive tumors and 25% in the T790M-negative cohort, with a duration of response of 5.7 months. The median PFS was 4.7 months (Janjigian 2014; [1.2]).

The side effects of the combination were significant. Approximately 40% of patients needed a dose reduction, mostly because of skin toxicity and diarrhea. The afatinib/cetuximab combination is being investigated by SWOG as an alternative to afatinib as first-line therapy. Though the combination is relatively toxic, it can offer a few additional months of disease control.

DR LOVE: Would you discuss your recent review titled "Acquired resistance to TKIs in solid tumors: Learning from lung cancer" (Camidge 2014a)?

DR CAMIDGE: The review discussed some of the approaches that can be used after the development of acquired resistance to TKI therapy. We discussed different options, including stopping the TKI and switching to chemotherapy, staying on the TKI and adding in chemotherapy or switching to a new agent, such as an immune checkpoint inhibitor. The emerging and still controversial role of focused radiation therapy for isolated areas of disease progression was also discussed. All of these strategies were presented so that you have a menu card of options that could be considered.

1.2

Phase Ib Trial of Afatinib/Cetuximab for Patients with EGFR-Mutant Non-Small Cell Lung Cancer and Acquired Resistance to Erlotinib or Gefitinib

Clinical outcome	T790M mutation status: T790M+ (n = 71)	T790M mutation status: T790M- (n = 53)	Total (n = 126)
Confirmed OR	32%	25%	29%
Median DoR	5.6 mo	9.5 mo	5.7 mo
Median PFS	4.8 mo	4.6 mo	4.7 mo
Adverse events (n = 126)	**All grades**		**Grade 3/4**
Rash	90%		20%
Diarrhea	71%		6%
Fatigue	47%		3%
Nausea	42%		2%
Xerosis	42%		2%
Stomatitis	56%		1%

OR = overall response; DoR = duration of response; PFS = progression-free survival

No significant difference in OR rate ($p = 0.341$) or PFS ($p = 0.643$) between patients with T790M-positive and T790M-negative tumors

Janjigian YY et al. *Cancer Discovery* 2014;4(9):1036–45.

Tracks 9-10, 13-14

DR LOVE: Moving on to patients with ALK gene rearrangements, what is known about the response to the recently approved TKI ceritinib in patients with ALK-rearranged NSCLC and brain metastases?

DR CAMIDGE: At ASCO 2014, Dr Kim presented the best available data from the Phase I ASCEND-1 trial on the activity of ceritinib at the 750-mg dose in patients who previously received ALK inhibitors and had brain metastases, but the sample size was only 10. In this relatively small data set a response rate of 40% was observed (Kim 2014b; [1.3]).

Ceritinib is not well tolerated at 750 mg. Approximately 60% of patients required a dose reduction. I had a patient who responded well to the 750-mg dose of ceritinib, but he found it difficult to tolerate because of gastrointestinal toxicities. The dose was reduced to 600 mg, which he tolerated much better. However, after 10 months of therapy he developed extensive brain metastases.

When you reduce the dose of an agent, it may still be effective systemically, but the exposure in the brain may be dramatically lower. The brain is emerging as the battleground that we have to watch out for even with the second-generation drugs.

DR LOVE: What is known about the efficacy of crizotinib in patients who have ALK-rearranged disease and brain metastases?

DR CAMIDGE: Retrospective data show that crizotinib has activity in the brain, but the intracranial response rate is much lower than that reported systemically. The duration of those responses is at least half that in the body. So it's not entering the brain in most patients.

DR LOVE: What is your approach to caring for patients with ALK-positive NSCLC who are receiving crizotinib and develop extra-CNS oligoprogressive disease?

DR CAMIDGE: Our data show that stereotactic radiation therapy can durably control sites of extra-CNS disease in patients with ALK-positive disease receiving crizotinib. A single course of local ablative therapy was associated with 4 months of PFS benefit. With longer follow-up, the median PFS extension with local ablative therapy was 5.5 months (Gan 2014).

DR LOVE: Besides ceritinib, what are the other promising second-generation ALK inhibitors?

DR CAMIDGE: Alectinib is another second-generation ALK inhibitor that is promising. A Phase II study investigating alectinib in patients with crizotinib-resistant ALK-positive NSCLC is nearing completion (NCT01801111). If that shows that alectinib is effective, it could lead to compassionate access for this agent relatively soon. ALEX is an ongoing Phase III study comparing alectinib to crizotinib in treatment-naïve, ALK-positive advanced NSCLC (NCT02075840). ■

1.3

Phase I ASCEND-1: Ceritinib in Advanced ALK-Rearranged Non-Small Cell Lung Cancer

Efficacy	ALK inhibitor treated	ALK inhibitor naïve	Overall
All patients (n = 163, 83, 246)			
Overall response rate	54.6%	66.3%	58.5%
Complete response	1.2%	1.2%	1.2%
Partial response	53.4%	65.1%	57.3%
Overall intracranial response rate in patients with brain metastases at baseline (n = 10, 4, 14)	40.0%	75.0%	50.0%

Select adverse events (n = 255)	Any grade	Grade 3/4
Diarrhea	86%	6%
Nausea	80%	4%
Vomiting	60%	4%
Fatigue	52%	5%
Elevated ALT	80%	27%
Elevated AST	75%	13%

Kim D et al. *Proc ASCO* 2014b;**Abstract 8003**.

SELECT PUBLICATIONS

Camidge RD et al. **Acquired resistance to TKIs in solid tumours: Learning from lung cancer.** *Nat Rev Clin Oncol* 2014a;11(8):473-81.

Camidge RD et al. **Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC).** *Proc ASCO* 2014b;**Abstract 8001**.

Gan GN et al. **Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib.** *Int J Radiat Oncol Biol Phys* 2014;88(4):892-8.

Kim DW et al. **Clinical activity and safety of HM61713, an EGFR-mutant selective inhibitor, in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations who had received EGFR tyrosine kinase inhibitors (TKIs).** *Proc ASCO* 2014a;**Abstract 8011**.