INTERVIEW

Pasi A Jänne, MD, PhD

Dr Jänne is Director of the Lowe Center for Thoracic Oncology at the Dana-Farber Cancer Institute, Professor of Medicine at Harvard Medical School and Scientific Director at the Belfer Institute for Applied Cancer Science in Boston, Massachusetts.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What is the rationale behind using serologic assays to detect and monitor tumor mutations in patients with advanced non-small cell lung cancer (NSCLC)?

DR JÄNNE: As cancer cells grow and divide, they shed their DNA, and when you're dealing with cancer that has a mutation you can find that DNA in the patient's blood. The DNA is certainly coming from the cancer because these mutations are cancer

specific. This can potentially be used as a tool not only to diagnose noninvasively with a so-called liquid biopsy but also, ultimately, to perhaps monitor the disease.

This procedure is easier to perform than multiple serial biopsies. I believe we have technologies now that weren't available even a couple of years ago. When a patient's disease acquires resistance to targeted therapy, often biopsies may not be feasible or the results may take too long to obtain. Being able to obtain the same information from a blood sample and receive a rapid answer has real clinical importance and value.

DR LOVE: Recently it seems that the paradigm has shifted toward the use of biopsies, when possible, for patients receiving first-line EGFR tyrosine kinase inhibitor (TKI) therapy who then experience disease progression. At this point, do you consider that standard, even in the community setting?

DR JÄNNE: We now know that the third-generation EGFR inhibitors, such as osimertinib (AZD9291) or rociletinib (CO-1686), work much better in individuals who have the T790M EGFR mutation compared to those who do not. Mutation status is important to know because that would dictate which direction to go with treatment if you have access to these agents or, through a clinical trial, to many of the others that are currently under clinical development. Once these agents become commercially available, then biopsy does become a standard practice.

DR LOVE: Do you believe we may experience a transient phase in which biopsies will be indicated and that these kinds of serum assays will soon rapidly replace repeat biopsies?

DR JÄNNE: We are able to perform these serum tests more rapidly than next-generation sequencing (NGS), and this ability is a real game changer in the management of lung cancer and many other solid tumors. That said, many of the technologies can't capture the gene rearrangements. For that you need a sequencing-based technology. Some emerging technologies are able to do this. We haven't seen them yet in clinical applications, but the hope is that we will also have access to these.

Tracks 3-4

DR LOVE: What have your group and others reported on the efficacy and side effects of osimertinib?

DR JÄNNE: Osimertinib is clearly an effective agent with efficacy at multiple dose levels, from 20 to 240 mg daily. In our study for patients with NSCLC and acquired resistance to EGFR TKIs, patients with T790M-mutation positive disease had a higher objective response rate (ORR, 59% versus 29%) and progression-free survival (PFS, 13.1 months versus 5.6 months) than those without that mutation (Jänne 2015; [1.1]).

Although this class of agents is more selective for the mutant form than the wild-type form of EGFR, as we increased the dose we started to see some inhibitory effects on wild-type EGFR. However, at high doses osimertinib causes Grade 3 or higher rash and diarrhea, so 80 mg daily is the recommended Phase II dose.

The ORR is 21% with osimertinib in the population of patients without the T790M mutation. Some of that could be attributed to a re-treatment effect in patients who had previously received an EGFR TKI. If you specifically evaluate the individuals who immediately came off an EGFR TKI before trial entry, the ORR was only 11%. The median PFS for patients with T790M-negative NSCLC was 2.8 months.

DR LOVE: Would you discuss the data your group presented evaluating this agent as first-line therapy for advanced EGFR mutation-positive NSCLC and the other avenues being explored with this agent currently?

DR JÄNNE: The question is, for a patient with NSCLC previously untreated with an EGFR TKI, what is the response rate or PFS with osimertinib? The results of the AURA study of osimertinib as first-line therapy were presented at the 2015 ASCO meeting (Ramalingam 2015; [1.1]). Interestingly, the ORR was about 70%. Although the PFS rates were promising, it's too early to determine the median PFS.

The ongoing Phase III AURA 3 trial is evaluating osimertinib versus chemotherapy for patients with EGFR T790M mutation-positive advanced NSCLC after disease progression on an EGFR TKI (NCT02151981). Also, the randomized Phase III FLAURA trial evaluating osimertinib versus gefitinib or erlotinib as initial therapy for EGFR-mutant lung cancer is ongoing (NCT02296125).

1.1 **Phase I/II AURA Trial: Efficacy and Safety Results with Osimertinib (AZD9291) in Patients with EGFR Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer**

	Dose-escalation and expansion cohorts[1]			First-line cohort[2]
Response	**All patients** (n = 239)	**T790M-positive** (n = 127)	**T790M-negative** (n = 61)	**All patients** (n = 60)
ORR (evaluable)	51%	61%	21%	73%
DCR (evaluable)	84%	95%	61%	97%
Survival	**n = 222**	**n = 138**	**n = 62**	**n = 60**
Median PFS	8.2 months	9.6 months	2.8 months	Not reached
Select AEs (Grade ≥3)	**20 mg daily** (n = 21)	**80 mg daily** (n = 90)	**160 mg daily** (n = 63)	**All patients** (n = 60)
Rash	0%	0%	3%	2%
Diarrhea	0%	1%	2%	3%
Nausea	5%	0%	0%	2%
Decreased appetite	5%	1%	0%	0%
Fatigue	5%	0%	0%	0%

ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival; AEs = adverse events

[1] Jänne PA et al. *N Engl J Med* 2015;372(18):1689-99; [2] Ramalingam SS et al. *Proc ASCO* 2015;**Abstract 8000**.

Track 5

DR LOVE: What is known about the efficacy and safety of rociletinib in NSCLC?

DR JÄNNE: In the Phase I/II trial presented by Dr Sequist at ASCO 2015, the response rate with rociletinib in patients with T790M-positive disease was about 60% (Sequist 2015; [1.2]). This is similar to the response rate observed in the Phase I/II AURA trial. Finding the right dose for this agent has been challenging. Treatment-related toxicities include hyperglycemia and QTc prolongation, which have forced the use of lower doses. Reasonable activity was observed in patients with T790M-negative NSCLC. Whether this is due to the effect of the agent or to heterogeneity among the tumor cells is unknown.

1.2

Efficacy and Safety Results from a Phase I/II Trial of Rociletinib (CO-1686) for Patients with EGFR-Mutated Non-Small Cell Lung Cancer After Failure of an EGFR Inhibitor

Outcome (any dose)	**T790M-positive** (n = 46)	**T790M-negative** (n = 17)
ORR	59%	29%
DCR	93%	59%
Median PFS	13.1 months	5.6 months
Select adverse events (n = 92)*	**Any grade**	**Grade 3**
Hyperglycemia	47%	22%
Nausea	35%	2%
Fatigue	24%	4%
Diarrhea	22%	0%
Vomiting	14%	2%
QTc prolongation	12%	5%

* Therapeutic dose of rociletinib (500, 625, 750, 900 and 1,000 mg BID)

ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival; QTc = QT interval corrected for heart rate

Sequist LV et al. *N Engl J Med* 2015;372(18):1700–9.

Track 11

DR LOVE: What is your perspective on the results of the Phase III PROCLAIM trial evaluating pemetrexed/cisplatin and thoracic radiation therapy (TRT) versus etoposide/cisplatin/TRT followed by consolidation chemotherapy for patients with previously untreated locally advanced NSCLC (Senan 2015; [1.3])?

DR JÄNNE: Oncologists have been administering etoposide/cisplatin with TRT for a long time. These data supported the use of pemetrexed/cisplatin/TRT but did not demonstrate superiority with etoposide/cisplatin/TRT. Some differences are apparent in the toxicity profile. No Grade 3 or higher alopecia occurred with pemetrexed/cisplatin. Another advantage with pemetrexed/cisplatin is that it can be administered once every 3 weeks, whereas etoposide is administered for 5 consecutive days every 4 weeks. After seeing these data, I will certainly start to use pemetrexed/cisplatin/TRT in my practice.

Tracks 15-17

DR LOVE: Would you discuss the differential effect of afatinib based on the presence of deletion 19 mutations versus the L858R EGFR mutation?

DR JÄNNE: In a pooled analysis, it seemed as if the patients who had an exon 19 deletion mutation had a greater survival advantage with afatinib compared to chemotherapy than did those with the L858R mutation (Yang 2015). Whether this is a class effect of EGFR TKIs is unknown. Two ongoing trials are addressing this question: LUX-Lung 7 (NCT01466660) and ARCHER-1050 (NCT01774721).

1.3

Phase III PROCLAIM Trial: Efficacy and Safety of Pemetrexed (Pem)/ Cisplatin (Cis)/Thoracic Radiation Therapy (TRT) versus Etoposide (Eto)/Cis/ TRT Followed by Consolidation Chemotherapy in Patients with Previously Untreated Locally Advanced Nonsquamous Non-Small Cell Lung Cancer

Outcome	Pem/cis/TRT (n = 301)	Eto/cis/TRT (n = 297)	Hazard ratio	*p*-value
Median OS	26.8 mo	25.0 mo	0.98	0.831
Median PFS	11.4 mo	9.8 mo	0.86	0.130
ORR	35.9%	33.0%	NR	0.458
DCR	80.7%	70.7%	NR	0.004
	Pem/cis/TRT (n = 283)		Eto/cis/TRT (n = 272)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Esophagitis	48.1%	15.5%	50.7%	20.6%
Abnormal neutrophil/granulocyte counts	42.8%	24.4%	54.8%	44.5%
Alopecia	8.1%	0%	36.0%	0.4%
Febrile neutropenia	5.7%	5.3%	10.3%	9.6%

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; NR = not reported; DCR = disease control rate

Senan S et al. *Proc ASCO* 2015;**Abstract 7506**.

DR LOVE: Outside of a protocol setting, how do you select between afatinib and erlotinib?

DR JÄNNE: I typically use erlotinib. I believe afatinib is more toxic than erlotinib when used as initial therapy. It is not yet clear if afatinib will be better than erlotinib for patients with exon 19 deletion mutations. Until the results from the LUX-Lung 7 study are presented, I will continue to favor erlotinib.

DR LOVE: Do you believe afatinib/cetuximab has a role in EGFR T790M mutation-negative disease?

DR JÄNNE: Yes. In the initial study the ORR was approximately 25% for patients with T790M-negative disease and a bit more for those with T790M-positive NSCLC, with an overall PFS of about 4.7 months (Janjigian 2014). So this combination could potentially be used in T790M-negative disease. The challenge with this regimen is toxicity. The randomized Phase II/III SWOG-S1403 trial of first-line cetuximab/afatinib versus afatinib in advanced EGFR-mutant NSCLC (NCT02438722) is still ongoing. Whether that trial will be completed given the emergence of the third-generation EGFR TKIs remains to be determined. ■

SELECT PUBLICATIONS

Janjigian YY et al. **Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations.** *Cancer Discov* 2014;4(9):1036–45.

Yang JC et al. **Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of overall survival data from two randomised, phase 3 trials.** *Lancet Oncol* 2015;16(2):141–51.