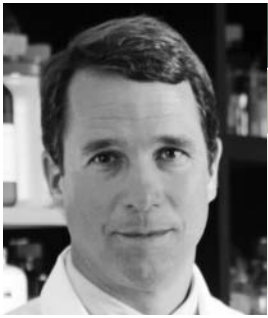

INTERVIEW

Matthew Kulke, MD, MMSc

Dr Kulke is Director of the Program in Neuroendocrine and Carcinoid Tumors at Dana-Farber/Brigham and Women's Cancer Center and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-12

Track 1 **Case discussion:** A 60-year-old patient with a history of progressive diarrhea and intermittent flushing episodes is diagnosed with a carcinoid neuroendocrine tumor (NET)

Track 2 Therapeutic options for low-grade carcinoid NETs

Track 3 Results of the PROMID study: Effect of the somatostatin analog octreotide on tumor growth in patients with metastatic neuroendocrine midgut tumors

Track 4 Role of surgical resection and radiofrequency ablation in the treatment of carcinoid NET

Track 5 Differential management of carcinoid and pancreatic NET

Track 6 Clinical experience with and tolerability of octreotide for carcinoid NET

Track 7 **Case discussion:** A 42-year-old patient with low-grade, progressive pancreatic NET

Track 8 Efficacy and side effects of everolimus and sunitinib for progressive advanced pancreatic NET

Track 9 Clinical experience with everolimus-associated mucositis and pneumonitis

Track 10 Early study results and ongoing clinical trials of bevacizumab-based therapies for patients with pancreatic NET

Track 11 Chemotherapy options for high-grade, poorly differentiated NET

Track 12 Novel agents under investigation in advanced NET

Select Excerpts from the Interview

Track 5

DR LOVE: What is known in terms of the spectrum of drug activity in pancreatic neuroendocrine tumors (NET) as opposed to carcinoid NET? If an agent is effective in one, will it be effective in the other?

DR KULKE: We don't know the answer to that question yet, though ongoing trials are attempting to address it. We know that the somatostatin analog octreotide can slow tumor progression in carcinoid NET, but we are not as sure about that in pancreatic neuroendocrine tumors. An ongoing trial called the CLARINET study is evaluating another somatostatin analog called lanreotide in gastroenteropancreatic NET, so we hope to have an answer soon. (Editor's note: Subsequent to this interview the results of the CLARINET study were presented at ESMO [2.1].)

DR LOVE: What about chemotherapy in carcinoid NET?

2.1

CLARINET: A Phase III Study of Lanreotide versus Placebo for Gastroenteropancreatic Neuroendocrine Tumors (NET)

	Lanreotide (n = 101)	Placebo (n = 103)	Hazard ratio (HR)	*p*-value
Median progression-free survival	Not reached	18 mo	0.47	0.0002

- After 2 years, 62% of patients who received lanreotide versus 22% of patients who received placebo had not experienced disease progression or died.
- A subgroup analysis showed a statistically significant benefit for patients with midgut NET (HR = 0.35; $p = 0.009$) and a benefit, though not statistically significant, for patients with pancreatic NET (HR = 0.58; $p = 0.064$).*

Caplin M et al. *Proc ECCO* 2013;**Abstract LBA3**. * Available at: **http://www.ipsen.com/wp-content/uploads/2013/09/PR-Results-Clarinet-ESMO.pdf**.

DR KULKE: Traditional chemotherapy — streptozocin or temozolomide — is not highly effective for most carcinoid tumors. Those agents, however, are effective in pancreatic neuroendocrine tumors.

DR LOVE: In a patient with progressive disease, what systemic therapies do you use in carcinoid NET other than octreotide, if any?

DR KULKE: Beyond octreotide we arrive rapidly in a fairly data-free zone, but methods that we talk about for a patient with hepatic-predominant disease, such as chemoembolization, can be effective in this setting. We also know that alpha interferon can be helpful and slow tumor progression in some cases. Everolimus, which is known to be effective in pancreatic NET, has also been evaluated in carcinoid tumors. The RADIANT-2 study suggested activity there (Pavel 2011), and a follow-up Phase III study called RADIANT-4 is now evaluating everolimus versus placebo in carcinoid NET to try to confirm the hints of activity that were observed in the first study (NCT01524783).

Tracks 3, 6

DR LOVE: Would you discuss the design and results of the PROMID study, which evaluated the effect of octreotide on tumor growth in patients with metastatic midgut NET?

DR KULKE: PROMID was a randomized study involving patients with locally inoperable or metastatic midgut NET. Patients were randomly assigned to receive either octreotide using the long-acting formulation at a dose of 30 mg or placebo. The trial reported a clear benefit in terms of time to tumor progression on the order of 14 months versus 6 months favoring octreotide, so octreotide seemed to slow tumor progression (Rinke 2009).

DR LOVE: Do any other somatostatin analogs have potential advantages compared to octreotide?

DR KULKE: Lanreotide is approved right now in Europe for carcinoid syndrome. It is a similar agent, although it is administered slightly differently. Octreotide LAR is administered using an IM injection in the gluteus muscle, which works but can be painful sometimes. Lanreotide can be self-administered as a deep subcutaneous injection. Efficacy is probably similar between the 2 agents.

DR LOVE: Do you observe any toxicity or side effects with octreotide?

DR KULKE: We typically see few side effects with octreotide. Patients sometimes develop a borderline elevated glucose level. It is fairly unusual that you need to institute treatment for that. You must watch out for biliary sludge. If the patient still has a gallbladder, a slightly higher risk of gallstones exists. If a patient already has borderline diabetes and they start octreotide, you do need to watch the blood glucose, and not uncommonly you'll need to start an oral hypoglycemic.

Track 8

DR LOVE: What are the options for treatment for progressive pancreatic NET?

DR KULKE: The classic situation in which you should consider a targeted therapy is in a patient with fairly low-volume disease who is feeling well but clearly has evidence of tumor growth within 1 year. The 2 targeted therapies that have recently been approved for use in progressive advanced pancreatic neuroendocrine tumors are everolimus and sunitinib.

DR LOVE: Would you discuss the data supporting those 2 agents and how you weigh them in a situation like this?

DR KULKE: The data for both agents come from randomized placebo-controlled trials, and in both cases a clear improvement in progression-free survival was evident for patients who received the targeted agent versus patients who received placebo. Interestingly enough, the numbers were extremely close — approximately an 11-month progression-free survival for patients receiving the targeted agent and on the order of 5 months for patients who received placebo (2.2, 2.3).

The flip side of that is that objective responses with either agent are fairly low. The response rate in the sunitinib trial was 9%, and on the everolimus trial it was 5%. Realistically you will not see a great rate of tumor shrinkage if you are using these drugs.

2.2

RADIANT-3: Results from the Phase III Study of Everolimus for Advanced Pancreatic Neuroendocrine Tumors

Efficacy	**Everolimus** (n = 207)	**Placebo** (n = 203)	Hazard ratio	*p*-value
Median progression-free survival	11.0 mo	4.6 mo	0.35	<0.001
Median overall survival	Not reached	Not reached	1.05	0.59
	Everolimus (n = 204)		**Placebo** (n = 203)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Stomatitis	64%	7%	17%	0%
Fatigue	31%	2%	14%	<1%
Anemia	17%	6%	3%	0%
Pneumonitis	17%	2%	0%	0%
Hyperglycemia	13%	5%	4%	2%
Thrombocytopenia	13%	4%	<1%	0%

Yao JC et al. *N Engl J Med* 2011;364(6):514-23.

2.3

Results from a Phase III Trial of Sunitinib Malate for Patients with Advanced or Metastatic, Well-Differentiated Pancreatic Neuroendocrine Tumors

Efficacy	**Sunitinib** (n = 86)	**Placebo** (n = 85)	Hazard ratio	*p*-value
Median progression-free survival	11.4 mo	5.5 mo	0.42	<0.001
Median overall survival	Not reached	Not reached	0.41	0.02
Objective response rate	9.3%	0%	—	0.007
	Sunitinib (n = 83)		**Placebo** (n = 82)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Diarrhea	59%	5%	39%	2%
Nausea	45%	1%	29%	1%
Fatigue	32%	5%	27%	8%
Neutropenia	29%	12%	4%	0%
Hypertension	26%	10%	5%	1%
Hand-foot syndrome	23%	6%	2%	0%

Raymond E et al. *N Engl J Med* 2011;364(6):501-13.

In deciding between the 2 agents, probably one of the biggest factors is simply evaluating the patient, considering some of the comorbidities and seeing which one might be a better fit for that specific patient.

The side effects for both agents have been well described because they are both used for other indications also. Sunitinib is a tyrosine kinase inhibitor, so expect to see some of the classic side effects, such as hypertension, perhaps a slightly higher bleeding risk and in rare cases some hepatic toxicity.

With everolimus, patients may have side effects like mild mucositis. One of the rare but potentially more concerning side effects is pulmonary toxicity and infiltrates. So if the patient has any underlying lung disease, you might not want to start with everolimus.

One of the great things about having both of these available, at least in comparison to the more traditional chemotherapy, is how well tolerated they are. We have observed some quality-of-life issues in patients with renal cell carcinoma receiving sunitinib, which initially had been administered on a different dosing schedule. The dosing schedule that was used previously was 50 mg per day for 4 weeks, followed by 2 weeks off. We observed some fatigue associated with that. The dosing schedule that was used in the neuroendocrine trial was 37.5 mg continuously, which seemed to be much better tolerated without nearly as much fatigue (Raymond 2011; [2.3]). ■

SELECT PUBLICATIONS

Pavel ME et al. **Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): A randomised, placebo-controlled, phase 3 study.** *Lancet* 2011;378(9808):2005-12.

Rinke A et al; PROMID Study Group. **Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID Study Group.** *J Clin Oncol* 2009;27(28):4656-63.