INTERVIEW

Vera Hirsh, MD

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Tracks 1-8

Select Excerpts from the Interview

Track 6

DR LOVE: Would you talk about your research involving bone-targeted therapies in general and specifically what's been going on recently in lung cancer?

DR HIRSH: We have known for many years that patients with NSCLC and bone metastases have poor prognoses. The reason for that is their performance status rapidly deteriorates because of pain and complications such as spinal cord compression, fractures and hypercalcemia. These complications are collectively known as skeletal-related events (SREs).

We've been involved in a number of trials in attempts to prevent SREs, and zoledronic acid was the first agent established to try to address them. When zoledronic acid was compared to placebo, it delayed SREs and the percent of patients who developed these events was smaller (Rosen 2004). Anticancer activity was also reported with zoledronic acid, as it produced a pro-apoptotic effect against the growth of cancer cells and stimulated the immune system against the cancer cells.

We now have a new agent, denosumab, which is a monoclonal antibody against RANKL, which also shows antiresorptive bone activity. We participated in a Phase

III trial that evaluated denosumab versus zoledronic acid in patients with advanced solid tumors — excluding breast and prostate cancer — or multiple myeloma and bone metastases, which reported superiority of denosumab compared to zoledronic acid.

We observed prolonged survival and improved pain control in patients who received denosumab. Noninferiority was reached in the overall patient population (Henry 2011). But when we excluded the patients with multiple myeloma and evaluated only those with solid tumors, we noted superiority with denosumab compared to zoledronic acid.

Also, a subgroup analysis we performed of patients with metastatic lung cancer in this Phase III trial reported superiority with denosumab compared to zoledronic acid not only for SREs but also for overall survival (Scagliotti 2012; [5.1]).

5.1

Overall Survival Improvement in Patients with Lung Cancer and Bone Metastases Treated with Denosumab versus Zoledronic Acid: Subgroup Analysis from a Phase III Trial

Efficacy	Denosumab (n = 411)	Zoledronic acid (n = 400)	Hazard ratio	*p*-value
Median overall survival	8.9 mo	7.7 mo	0.80	0.01
Adverse events (AEs)	**Denosumab** (n = 406)		**Zoledronic acid** (n = 395)	
Serious AEs	66.0%		72.9%	
Hypocalcemia	8.6%		3.8%	
Osteonecrosis of the jaw	0.7%		0.8%	

Scagliotti GV et al. *J Thorac Oncol* 2012;7(12):1823-9.

Tracks 7-8

DR LOVE: Nanoparticle albumin-bound (*nab*) paclitaxel, an agent already approved for breast cancer, was recently approved by the FDA in combination with carboplatin for patients with untreated locally advanced or metastatic NSCLC. What is known about this agent in lung cancer?

DR HIRSH: *Nab* paclitaxel is albumin-bound paclitaxel. It enables the drug to better penetrate the cancer cell, and we observe higher concentrations of the agent in the cancer cells (Desai 2006). Another advantage of *nab* paclitaxel is that steroid premedications are not required as they are with paclitaxel.

A Phase III trial that I was involved in evaluated paclitaxel/carboplatin versus *nab* paclitaxel/carboplatin as first-line therapy for advanced NSCLC. *Nab* paclitaxel was administered weekly with carboplatin as opposed to an every 3-week schedule for paclitaxel. The primary endpoint of the trial was overall response rate, and we reported an advantage for the patients who received *nab* paclitaxel/carboplatin. A trend for improved overall survival was also observed, but it was not statistically significant (Socinski 2012).

We noted a number of signals in certain subgroups of patients that I believe to be of importance. These groups seemed to benefit more from *nab* paclitaxel with regard to progression-free and overall survival than did the overall patient population. One

such group was elderly patients older than age 70, and another included patients with squamous cell histology (5.2).

Another big advantage with *nab* paclitaxel are the symptoms. Peripheral sensory neuropathy, which can be significant with paclitaxel, occurred less with *nab* paclitaxel and was faster to reverse once the agent was stopped. Another important aspect is that patients receiving paclitaxel can experience arthralgias or myalgias. These side effects also occurred with less frequency in patients receiving *nab* paclitaxel, as did edema and hearing loss. ■

5.2

Phase III Trial of *Nab* Paclitaxel/Carboplatin (*Nab*-PC) versus Solvent-Based Paclitaxel/Carboplatin (sb-PC) as First-Line Therapy for Patients with Advanced Non-Small Cell Lung Cancer

Efficacy	*Nab*-PC		sb-PC		*p*-value
Overall response rate					
All patients (n = 521, 531)	33%		25%		0.005
Squamous (n = 229, 221)	41%		24%		<0.001
Nonsquamous (n = 292, 310)	26%		25%		0.808
Patients aged ≥70 y (n = 74, 82)	34%		24%		0.196
Median progression-free survival					
All patients (n = 521, 531)	6.3 mo		5.8 mo		0.214
Squamous (n = 229, 221)	5.6 mo		5.7 mo		0.245
Nonsquamous (n = 292, 310)	6.9 mo		6.5 mo		0.532
Patients aged ≥70 y (n = 74, 82)	8.0 mo		6.8 mo		0.134
Median overall survival					
All patients (n = 521, 531)	12.1 mo		11.2 mo		0.271
Squamous (n = 229, 221)	10.7 mo		9.5 mo		0.284
Nonsquamous (n = 292, 310)	13.1 mo		13.0 mo		0.611
Patients aged ≥70 y (n = 74, 82)	19.9 mo		10.4 mo		0.009
Select adverse events	Grade 3	Grade 4	Grade 3	Grade 4	*p*-value
Neutropenia	33%	14%	32%	26%	<0.001
Thrombocytopenia	13%	5%	7%	2%	<0.001
Sensory neuropathy	3%	0%	11%	<1%	<0.001
Myalgia	<1%	0%	2%	0%	0.011
Arthralgia	0%	0%	2%	0%	0.008

Socinski MA et al. *Ann Oncol* 2013;24(9):2390-6; Socinski MA et al. *Ann Oncol* 2013;24(2):314-21; Socinski MA et al. *J Clin Oncol* 2012;30(17):2055-62.

SELECT PUBLICATIONS

Desai N et al. **Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of Cremophor-free, albumin-bound paclitaxel, ABI-007, compared with Cremophor-based paclitaxel.** *Clin Cancer Res* 2006;12(4):1317-24.

Henry DH et al. **Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma.** *J Clin Oncol* 2011;29(9):1125-32.

Rosen LS et al. **Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: A randomized, Phase III, double-blind, placebo-controlled trial.** *Cancer* 2004;100(12):2613-21.

Socinski MA et al. **Safety and efficacy analysis by histology of weekly *nab*-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer.** *Ann Oncol* 2013;24(9):2390-6.