INTERVIEW

## Ronald B Natale, MD

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### Tracks 1-8

Track 1 **Case discussion:** A 52-year-old man and never smoker with EGFR L858R mutation-positive Stage IIIA adenocarcinoma of the lung receives adjuvant erlotinib on the RADIANT trial

Track 2 Use of next-generation sequencing in patients with recurrent adenocarcinoma of the lung

Track 3 Clinical trial of carboplatin/gemcitabine in combination with the PARP inhibitor iniparib

Track 4 Activity of third-generation EGFR TKIs in patients with T790M-mutant NSCLC

Track 5 Dose, schedule and activity of nanoparticle albumin-bound (*nab*) paclitaxel with carboplatin for untreated locally advanced or metastatic NSCLC

Track 6 Use of gemcitabine as second-line therapy for pan-wild-type adenocarcinoma of the lung

Track 7 Therapeutic options for patients with advanced adenocarcinoma of the lung who are eligible to receive bevacizumab

Track 8 Perspective on the activity of ramucirumab with docetaxel as second-line therapy for Stage IV NSCLC

## Select Excerpts from the Interview

### Track 5

**CASE DISCUSSION:** A 62-year-old woman with advanced adenocarcinoma of the lung achieves a good response with carboplatin/paclitaxel/bevacizumab but experiences severe paclitaxel-associated side effects

**DR NATALE:** This was a fairly healthy patient who stopped smoking about 20 years ago. Her tumor had no detectable mutations. A medical oncologist in the community administered induction therapy with carboplatin/paclitaxel/bevacizumab, and the patient experienced a terrific response.

She came to see me during treatment because she was extraordinarily sensitive to paclitaxel and developed significant problems with peripheral neuropathy. This patient also had severe hematologic toxicity, which was more than what is usually observed with carboplatin/paclitaxel. She developed thrombocytopenia and had been hospitalized because of febrile neutropenia. I talked with her oncologist regarding trying different schedules of administration and alternating with docetaxel.

**DR LOVE:** *Nab* paclitaxel is approved in lung cancer in combination with carboplatin for patients with untreated locally advanced or metastatic NSCLC. What is your view on its efficacy and tolerability?

**DR NATALE:** *Nab* paclitaxel is well tolerated when it's administered on a weekly basis. It is an available option, but I don't administer it often. A study by Belani and colleagues comparing carboplatin/paclitaxel every 3 weeks to a weekly schedule in patients with advanced NSCLC showed no significant difference in efficacy between the 2 arms. Less neuropathy but more anemia was evident on the weekly carboplatin/paclitaxel arm (Belani 2008).

A subsequent study comparing weekly *nab* paclitaxel with carboplatin to every 3-week carboplatin/paclitaxel demonstrated a higher response rate and an insignificant improvement in PFS with *nab* paclitaxel/carboplatin and no difference in overall survival. The differences in toxicity included less neuropathy with *nab* paclitaxel but a higher incidence of anemia requiring erythropoietic growth factors or blood transfusions (4.1). The results were similar to the earlier study by Belani and colleagues.

From my perspective, weekly *nab* paclitaxel, despite good efficacy, is not attractive because of its cost. I'm an outlier in this respect. For many oncologists, *nab* paclitaxel is the go-to agent, especially for elderly patients. I understand their rationale. It is FDA approved and effective.

**4.1**

**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 |
| Anemia | 22% | 5% | 6% | <1% | <0.001 |
| Thrombocytopenia | 13% | 5% | 7% | 2% | <0.001 |
| Sensory neuropathy | 3% | 0% | 11% | <1% | <0.001 |

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.

## Tracks 7-8

**DR LOVE:** What's your usual up-front induction treatment for metastatic wild-type adenocarcinoma, and how do you approach maintenance therapy?

**DR NATALE:** My choice for first-line therapy for patients with nonsquamous histology is carboplatin/pemetrexed, usually without bevacizumab. However, for younger patients I add bevacizumab to carboplatin/pemetrexed to maximize benefit. More importantly, in younger patients the adverse effects of adding bevacizumab would be less than in an older patient population. When I administer carboplatin/pemetrexed in the first-line setting, I usually continue maintenance therapy with pemetrexed.

The NCCN Guidelines allow the addition of bevacizumab to any platinum doublet as induction therapy. Unfortunately, the only studies showing a positive outcome with bevacizumab in the first-line setting are those combining it with carboplatin/paclitaxel (Zhou 2015). So in the absence of data that show that adding bevacizumab to carboplatin/pemetrexed in the first-line setting improves outcome, I prefer not to add bevacizumab.

**DR LOVE:** What is your preference for therapy for these patients in the second-line setting outside a clinical trial?

**DR NATALE:** Docetaxel is FDA approved and is the gold standard against which all other regimens in the second-line setting are compared. So outside a protocol setting, docetaxel remains my first choice for patients who previously received carboplatin and pemetrexed.

**DR LOVE:** Would you comment on the findings from the Phase III REVEL trial evaluating docetaxel with or without the addition of ramucirumab in the second-line treatment of Stage IV NSCLC after disease progression on 1 platinum-based chemotherapy regimen?

**DR NATALE:** The REVEL trial demonstrated a small benefit with the addition of ramucirumab to docetaxel as second-line therapy for metastatic NSCLC (Garon 2014). My experience with adding ramucirumab to docetaxel in this setting has been limited to a few patients. I administer docetaxel to most of my patients. But for young, healthy patients who have a good performance status, adding ramucirumab to docetaxel is a good option. ■

## SELECT PUBLICATIONS


Belani C et al. **Randomized, Phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer.** *J Clin Oncol* 2008;26(3):468-73.

Garon EB et al. **Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial.** *Lancet* 2014;384(9944):665-73.

Patel JD et al. **PointBreak: A randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2013;31(34):4349-57.

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.

Socinski MA et al. **Safety and efficacy of weekly *nab*-paclitaxel in combination with carboplatin as first-line therapy in elderly patients with advanced non-small-cell lung cancer.** *Ann Oncol* 2013;24(2):314-21.

Zhou C et al. **BEYOND: A randomized, double-blind, placebo-controlled, multicenter, Phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2015;33(19):2197-204.