



## INTERVIEW

### Neil L Spector, MD

Dr Spector is Co-Director of the Experimental Therapeutics Program at Duke Cancer Institute in Durham, North Carolina.

#### Tracks 1-17

- Track 1** Determinants of the efficacy of HER2-targeted therapies
- Track 2** Distinct biologic characteristics of inflammatory breast cancer (IBC)
- Track 3** Activity of lapatinib in heavily pretreated, HER2-positive IBC versus non-IBC
- Track 4** Mechanisms of action of trastuzumab: Focus on antibody-dependent cell-mediated cytotoxicity
- Track 5** Mode of action of trastuzumab-DM1 (T-DM1)
- Track 6** Biological hypothesis for the observed clinical benefits of adjuvant trastuzumab in patients with HER2-normal early breast cancer (BC) in the NSABP-B-31 study
- Track 7** Modulating the inhibitory capabilities of heregulin on anti-HER2 therapies with pertuzumab
- Track 8** Selectivity of the EGFR/HER2 tyrosine kinase inhibitor (TKI) lapatinib
- Track 9** Effects of inhibiting HER2 phosphorylation with lapatinib
- Track 10** Acquired resistance to trastuzumab in HER2-overexpressing BC
- Track 11** Truncated HER2 receptors, p95HER2 and response to trastuzumab versus HER2 TKIs
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- Track 16** Redefining the paradigm of drug discovery and development via increased collaboration between industry and academia
- Track 17** Personal reflection on undergoing a heart transplant for Lyme disease-related cardiomyopathy

#### Select Excerpts from the Interview

##### Track 5

► **DR LOVE:** What are your thoughts on some of the new agents being investigated for HER2-positive breast cancer?

► **DR SPECTOR:** I find the T-DM1 story interesting. This agent uses the “magic bullet” approach by essentially capitalizing on the specificity and ability of an

antibody like trastuzumab to selectively seek out only those cells that overexpress HER2 on the tumor cell surface. A mechanism internalizes the antibody and protein into the cell. That internalization then leads to the release of maytansine, which is a poison that blocks protein synthesis.

Having only a few molecules of maytansine in a cell is highly toxic. T-DM1 is killing breast cancer cells that overexpress HER2, not necessarily through an immune-mediated response but by delivering a poison directly into the tumor cell. If we can deliver poison specifically to tumor cells and not normal tissue, then that's the "Holy Grail" of therapeutics (Hurwitz 2011; [1.1]).

**1.1**

**Randomized Phase II Study of T-DM1 versus Trastuzumab and Docetaxel as First-Line Therapy for HER2-Positive Metastatic Breast Cancer**

|                                  | T-DM1<br>(n = 67) | Trastuzumab/docetaxel<br>(n = 70) | Hazard<br>ratio | p-value |
|----------------------------------|-------------------|-----------------------------------|-----------------|---------|
| Median progression-free survival | 14.2 mo           | 9.2 mo                            | 0.594           | 0.0353  |

**Conclusion:** This is the first study to evaluate an antibody-drug conjugate for HER2-positive metastatic breast cancer compared to standard therapy. These results validate the hypothesis that the unique targeted delivery of chemotherapy through T-DM1 may lead to an improved therapeutic index.

Hurwitz S et al. European Multidisciplinary Cancer Congress 2011; **Abstract 5001**.

 **Track 6**

▶ **DR LOVE:** What are your thoughts about the NSABP trial evaluating adjuvant trastuzumab in HER2-low breast cancer (1.2), which is based on data from Soon Paik (Paik 2008)?

▶ **DR SPECTOR:** I believe it's an intriguing observation that a subpopulation of women whose tumors do not overexpress HER2 still respond to trastuzumab. This points to the fact that patients may have HER2 expressed on their tumor cells that may not meet the definition of overexpression but may still be functionally relevant to those cells.

Is it because the HER2 that is not overexpressed in tumors that still may respond to trastuzumab is heavily phosphorylated? Perhaps this indicates that although the gene is not amplified, it's still being activated through some mechanism that we don't fully understand. Maybe it's being activated through its association with HER3 or EGFR.

 **Tracks 10-11**

▶ **DR LOVE:** Would you discuss the issues of acquired resistance to trastuzumab and why patients who clinically become resistant to trastuzumab often still have HER2 overexpression?

## NSABP-B-47: A Phase III Trial of Adjuvant Chemotherapy with or without Trastuzumab for Patients with Node-Positive or High-Risk Node-Negative, HER2-Normal Invasive Breast Cancer

Protocol IDs: CDR0000692574; NCT01275677 Target Accrual: 3,260 (Open)

### Eligibility

- Resected unilateral invasive adenocarcinoma
- HER2 IHC 1+ or 2+
- <4 HER2 copies per nucleus or HER2:CEP17 ratio <2 by FISH
- ECOG PS 0 to 1

R

Chemotherapy\* alone

Chemotherapy\* +  
trastuzumab

\* Investigator preference: Docetaxel/cyclophosphamide OR doxorubicin/cyclophosphamide → paclitaxel

[www.clinicaltrials.gov](http://www.clinicaltrials.gov), November 2011.

► **DR SPECTOR:** Changes may be occurring in the immune response because trastuzumab relies heavily on an immune effect, and changes may affect the ability of the immune system to respond to those cells that are bound by trastuzumab. In addition, other receptors such as insulin-like growth factor 1 receptor (IGF1R) on the surface of HER2-positive breast cancer cells may be involved in mediating the development of resistance. Several therapeutic strategies involving IGF1R are now in clinical development.

Some evidence exists that IGF1R may take over some of the survival regulation in HER2-positive breast cancer cells that have been treated with trastuzumab. My analogy is when you shut down one light switch, another switch keeps the room lit. So we are interested in an approach that combines trastuzumab with inhibitors of IGF1R.

Evidence suggests that PI3 kinase mutations, which are prevalent in breast cancer, mediate resistance to trastuzumab and potentially to lapatinib as well (Wang 2011). That is a downstream event, not something on the cell surface and not another light switch that you haven't shut down. It's essentially a screwup in the wiring within the wall, which makes the cell independent of the receptor. It doesn't matter whether you turn the switch off or on — you need to go in and cut the wiring. Therefore, combining trastuzumab with small molecule inhibitors of PI3 kinase and mTOR is of interest.

Another hypothesis surrounding response to trastuzumab centers on truncation of the HER2 receptor. A truncated HER2 receptor is missing the extracellular domain — the part of the receptor that “flaps in the breeze” in the bloodstream. This is part of the receptor that is the target for trastuzumab and likely also for pertuzumab and T-DM1. You can imagine that in a patient with breast cancer whose tumor has a lot of truncated HER2 the antibody is no longer going to be effective. But that truncated receptor is still signaling and promoting the growth, survival and metastatic progression of that tumor.

Women with HER2-positive breast cancer with evidence of truncated HER2 may have a completely different clinical outcome than women who have no evidence of truncated HER2 (Scaltriti 2007). It has been suggested that small molecule tyrosine kinase inhibitors (TKIs), which get into the cell and affect the portion of the truncated HER2 receptor that is still active, may be more beneficial for women who have evidence of truncated HER2.

I believe that this will be a discriminating factor when recommending that women receive an antibody-based HER2-targeted therapy or potentially a TKI HER2-targeted therapy. That approach is now being tested in clinical trials. We've been limited to date in that we do not have good assays for truncated HER2 receptors. I hope that in the next 5 years we'll have that capability.

## Tracks 12-13

► **DR LOVE:** What is your perspective on the use of anti-HER2 therapies in other solid tumors?

► **DR SPECTOR:** I believe some people have a tendency to say, “We did FISH and IHC and this tumor overexpresses HER2, and therefore we need to jump right in with HER2-targeted therapies without understanding the full milieu of what that tumor is.” HER2-positive inflammatory breast cancer (IBC) is different from HER2-positive noninflammatory breast cancer, so even within breast cancer, factors make one type of HER2-positive breast cancer much more sensitive to HER2-targeted therapies than another.

We also need to understand some of these other tumor types. I'd hate to see clinical trials evaluating trastuzumab, lapatinib and other HER2-targeted therapies come up with less than impressive data and lead to a decision that this approach will never have an impact on nonbreast and nongastric HER2-overexpressing cancer. It would be wise to try to understand the biology and use these combinations more judiciously.

I would propose that we should be moving more toward a molecular phenotype denominator. I don't care whether it's proteomic, genomic, metabolomic or combinations of all of the above. I find it unconscionable that we'll spend 25 years going through each tumor type individually when, in fact, maybe what we need is to spend more time understanding the biology, then perform clinical trials based on a signature and have an approval based on a molecular type as opposed to a tumor type. ■

## SELECT PUBLICATIONS

Paik S et al. **HER2 status and benefit from adjuvant trastuzumab in breast cancer.** *N Engl J Med* 2008;358(13):1409-11.

Scaltriti M et al. **Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer.** *J Natl Cancer Inst* 2007;99(8):628-38.

Wang L et al. **PI3K pathway activation results in low efficacy of both trastuzumab and lapatinib.** *BMC Cancer* 2011;11:248.