INTERVIEW

Rowan T Chlebowski, MD, PhD

Dr Chlebowski is Professor of Medicine at David Geffen School of Medicine at UCLA and Chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center in Torrance, California.

Tracks 1-10

Select Excerpts from the Interview

Tracks 1, 3-4

DR LOVE: What are your thoughts on the results of the ATLAS trial evaluating 5 versus 10 years of adjuvant therapy with tamoxifen for women with early breast cancer?

DR CHLEBOWSKI: In this large trial of continuing adjuvant tamoxifen versus stopping it after 5 years, we observed little effect in years 5 to 10, during the extended tamoxifen administration period — the recurrence rate ratio was 0.90. In years 10 to 15, however, we observed an approximately 30% reduction in risk, resulting in a net statistically significant reduction in breast cancer incidence, breast cancer mortality and overall mortality (Davies 2013; [4.1, 4.2]). This is a spectacular result.

The activity in years 10 to 15 suggests to me that we're not killing cancer cells with hormonal therapy, we're simply controlling them. The disease might require long-term therapy. That's a challenging concept.

DR LOVE: What are the clinical implications of longer-duration adjuvant tamoxifen?

DR CHLEBOWSKI: Significantly fewer coronary heart disease events are reported and no increase in the incidence of strokes is observed, but clinicians should regard the

4.1

ATLAS Trial: Effect of Continuing Adjuvant Tamoxifen (TAM) to 10 Years versus Stopping at 5 Years on Breast Cancer Recurrence and Mortality

	Continue TAM to 10 y (n = 3,428)	Stop TAM at 5 y (n = 3,418)
Recurrence rate		
10 y (treatment end)	13.1%	14.5%
15 y (10 y since study entry)	21.4%	25.1%
Breast cancer mortality		
10 y (treatment end)	5.8%	6.0%
15 y (10 y since study entry)	12.2%	15.0%

Continuing TAM to 10 years reduced the risk of breast cancer recurrence compared to stopping TAM (617 versus 711 recurrences; $p = 0.002$), reduced breast cancer mortality (331 versus 397 deaths; $p = 0.01$) and reduced overall mortality (639 versus 722 deaths; $p = 0.01$).

Davies C et al. *Lancet* 2013;381(9869):805-16.

4.2

Event Rate Ratios in ER-Positive Disease by Time Period from Diagnosis in Meta-Analyses of Trials of 5 Years of Tamoxifen (TAM) versus None and in the ATLAS Trial

	A. 5-y TAM vs 0: Meta-analyses (n = 10,645)	B. 10-y vs 5-y TAM: ATLAS (n = 6,846)	Estimated effects in a trial of 10-y TAM vs 0 (product of **A** and **B**)
Recurrence			
0-4 y	0.53*	1	0.53*
5-9 y	0.68*	0.9	0.61*
≥10 y	0.94	0.75†	0.7†
Breast cancer mortality			
0-4 y	0.71*	1	0.71*
5-9 y	0.66*	0.97	0.64‡
≥10 y	0.73‡	0.71§	**0.52***

* $p < 0.00001$; † $p < 0.01$; ‡ $p = 0.0001$; § $p = 0.0016$

"Taken together with the results from trials of 5 years of tamoxifen versus none, the results from ATLAS show that 10 years of effective endocrine therapy can approximately halve breast cancer mortality during years 10-14 after diagnosis."

Davies C et al. *Lancet* 2013;381(9869):805-16.

data cautiously. Patients who would have been sensitive and more disposed to developing these conditions perhaps would not come forward after 5 years of tamoxifen. In addition, the increased risk of mortality from endometrial cancer was only two tenths of a percent, and we noted a reduction of 3% in the risk of breast cancer mortality. So longer-duration tamoxifen came out ahead with nearly a 3% absolute benefit in terms of survival, which is surprising.

DR LOVE: How are you applying these data in your own practice, and are you administering adjuvant endocrine therapy beyond 10 years?

DR CHLEBOWSKI: We haven't used such an approach. I've been tracking the ATLAS trial for a number of years now, so I've been continuing aromatase inhibitors for at least a couple of years, and the decision of what to do after 7 years or so has not often come

up. But it is a puzzle what one should do if one is to stick strictly to guidelines. It will take years and years to obtain a definitive answer.

Track 5

DR LOVE: It's been 8 years since you presented the data at ASCO from the WINS study evaluating dietary fat and its relation to breast cancer progression in the adjuvant setting (Chlebowski 2006). Where are we today with this concept?

DR CHLEBOWSKI: The LISA (Lifestyle Intervention Study in Adjuvant treatment of early breast cancer) trial in Canada studied dietary fat intake, weight loss and physical activity. The investigators demonstrated the feasibility of successfully encouraging weight loss and increased physical activity with a central approach using telephone calls to patients, and I believe that's moving forward in the cooperative group setting. They hope to accrue about 2,000 patients (NCT00463489).

The ENERGY trial will enroll 800 patients with resected breast cancer, and this trial also will include centrally based intervention for weight loss and increased physical activity (NCT01112839). A similar trial in Germany, the SUCCESS-C trial, has already accrued about 1,000 patients, and DIANA-5 in Italy also targeted weight loss with a Mediterranean diet and physical activity among approximately 1,200 patients. So 2 trials are ongoing and have completed accrual, and 2 are planned studies.

Finally, a meta-analysis that included 107 studies demonstrated a reduction in the risk of recurrence with moderate physical activity — walking 3 to 4 hours a week (Hardefeldt 2012; [4.3]). I tell patients that they should do this. When you study overall patient populations, you see that 50% to 60% of women in the United States report that they are not engaging in any recreational physical activity. We should at least be able to get people to walk 3 or 4 hours a week. ■

4.3

Meta-Analysis of the Effect of Physical Activity and Weight Loss on the Risk of Breast Cancer in Pre- and Postmenopausal Women

Variable (107 studies)	Odds ratio
Physical activity	
Postmenopausal women	0.75
Premenopausal women	0.80
Low-intensity activity	0.82
High-intensity activity	0.78
Weight loss	0.81

Conclusion: "Physical activity and weight loss significantly reduce the risk of breast cancer in both pre- and postmenopausal women. However, the intensity and timing of the physical activity do not affect the protective effect."

Hardefeldt P et al. San Antonio Breast Cancer Symposium 2012;**Abstract P1-11-01**.

SELECT PUBLICATIONS

Chlebowski RT et al. **Dietary fat reduction and breast cancer outcome: Interim efficacy results from the Women's Intervention Nutrition Study.** *J Natl Cancer Inst* 2006;98(24):1767-76.

Cuzick J et al. **Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial.** *Lancet Oncol* 2010;11(12):1135-41.

Davies C et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. **Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial.** *Lancet* 2013;381(9869):805-16.

Hardefeldt P et al. **Physical activity reduces the risk of breast cancer.** San Antonio Breast Cancer Symposium 2012;**Abstract P1-11-01**.

Van Horn L, Manson J. **The Women's Health Initiative: Implications for clinicians.** *Cleve Clin J Med* 2008;75(5):385-90.