INTERVIEW

Stephen Chia, MD

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Tracks 1-10

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Track 4

DR LOVE: Will you review the issue of the use of extended adjuvant endocrine therapy for patients with hormone-dependent breast cancer?

DR CHIA: The aTTom and ATLAS trial data demonstrated a couple of points. First, 10 years of tamoxifen is better than 5 years, although I believe that the relative risk reduction is fairly modest (4.1). It has not yet been proven that 10 years of an AI is better than 5 years, but a lot of people are trying to make extrapolations.

Studies evaluating that approach have been fully accrued, and we're awaiting those results. In terms of how to select patients, however, we don't yet have a verified or validated predictive profile that says this tumor is more sensitive to 10 years versus 5 years of tamoxifen.

DR LOVE: In what situations do you generally continue tamoxifen beyond 5 years for premenopausal women?

4.1

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

	10 y TAM vs 5 y: **aTTom trial** (n = 6,934 ER+/UK)	10 y TAM vs 5 y: **ATLAS trial*** (n = 10,543 ER+/UK)	10 y TAM vs 5 y: **aTTom and ATLAS combined** (n = 17,477 ER+/UK)
Years 5-9	1.08 (0.85-1.38)	0.92 (0.77-1.09)	0.97 (0.84-1.15)
Years 10+	0.75 (0.63-0.90) $p = 0.007$	0.75 (0.63-0.90) $p = 0.002$	0.75 (0.65-0.86) $p = 0.00004$
All years	0.88 (0.74-1.03) $p = 0.1$	0.83 (0.73-0.94) $p = 0.004$	0.85 (0.77-0.94) $p = 0.001$

* Inverse variance-weighted estimate of the effect in ER-positive disease

- aTTom and ATLAS together provide "proof beyond reasonable doubt" that continuing TAM beyond 5 years reduces recurrence over the following years: No effect in years 5-6, benefit mainly after year 7
- Continuing TAM beyond 5 years also reduces breast cancer mortality: No effect in years 5-9, 25% reduction after year 10
- Main risk: Endometrial cancers (10 y vs 5 y TAM: 2.9% vs 1.3%, $p < 0.0001$)

Gray R et al. *Proc ASCO* 2013;**Abstract 5**; Davies C et al. *Lancet* 2013;381(9869):805-16.

DR CHIA: Where I practice within British Columbia we have our own large clinical outcomes database with which we've evaluated residual risk in premenopausal women with breast cancer after 5 years of tamoxifen. It appears that patients with Stage II disease or greater have a residual risk that would probably warrant an absolute risk reduction of at least 2% if they were to take tamoxifen.

DR LOVE: Are there any situations in which you would consider going beyond 5 years of an AI in the postmenopausal setting?

DR CHIA: I struggle with this. I do believe that the concept of longer hormonal therapy has been proven with the ATLAS and aTTom trials, albeit with tamoxifen. It's difficult to fathom that that wouldn't also be the case with AIs.

The way I approach it is to ask, what is the residual risk for that woman at 5 years? Has she been compliant with her hormonal therapy? What toxicities has she experienced so far? If the patient has experienced few toxicities, her bone mineral density is good and the risk of osteoporosis is low, I would consider continuing the AI. But I'm frank and honest in telling patients that we do not yet have Level 1 evidence in this setting. That could change in a couple of years when the results from the Phase III NSABP-B-42 and MA17R trials of extended use of AIs are reported.

Track 5

DR LOVE: Would you discuss some of the key points of your group's recent publication entitled, "A prospective clinical utility and pharmacoeconomic study of the impact of the 21-gene Recurrence Score (RS) assay in ER-positive, node-negative breast cancer" (Davidson 2013)?

DR CHIA: We've been practicing for many years with the only predictive markers being ER and HER2. But I'm a big fan of predictive assays, and the Onco*type* DX assay is the first but it clearly won't be the last. The aspect about the Onco*type* DX assay

that I believe is positive is that many of the prospective clinical utility studies have had consistent results.

Our clinical utility and pharmacoeconomic study showed a 30% change in the recommendation of chemotherapy by physicians. For 20% of patients we removed the delivery of chemotherapy and for 10% we added it, based on the Onco*type* DX RS (Davidson 2013; [4.2]). Basically this type of proportion was replicated across multiple countries, whether it was in Spain, Germany, Israel, the United States or Australia. So I believe the consistency of that finding is strong.

We also performed a prospective analysis of cost and demonstrated that it was cost effective to add the 21-gene RS to your clinical algorithm. The cost-effectiveness ratio was in the range of about 7,000 Canadian dollars per quality-adjusted life-year gained. And remember, a life-years gain is associated with this. This means that if a high RS is returned for a patient for whom you were not suspecting that or considering chemotherapy, you can prevent a distant metastasis by administering adjuvant chemotherapy.

The treatment of breast cancer recurrence in the metastatic setting is expensive, and clearly it would be great to prevent having to treat in that setting if possible. We see a number of patients and families in our clinic for whom it's extremely difficult to decide whether to proceed with chemotherapy or not. The studies that have been conducted with the 21-gene assay have shown that it reduces decisional conflict. Having the RS result increases the confidence of both the physician and the patient.

4.2

Changes in Physicians' Treatment Recommendations Based on the Onco*type* DX Assay Recurrence Score (RS)

	Chemotherapy + hormonal therapy		Change in recommendation
	Preassay (n)	Postassay (n)	
High RS (n = 36)	24	34	+28%
Intermediate RS (n = 45)	18	13	-11%
Low RS (n = 69)	20	0	-29%
Total (n = 150)	62	47	-10%

- Physicians changed their adjuvant chemotherapy recommendation after receiving the RS result for 45 patients, or 30% of all cases.
  - In two thirds of these situations (20%), chemotherapy was omitted in favor of endocrine therapy alone.
  - In one third of these situations (10%), chemotherapy was added after the oncologist had initially planned to proceed only with endocrine therapy.

Davidson JA et al. *Eur J Cancer* 2013;49(11):2469-75.

Track 8

DR LOVE: What are your thoughts on the meta-analysis presented at SABCS 2013 on the effects of bisphosphonate treatment on recurrence in women with early breast cancer (Coleman 2013)?

DR CHIA: This presentation by Dr Rob Coleman was a surprise in that it showed a reduction in the incidence of bone metastases for postmenopausal women who received adjuvant bisphosphonates regardless of type of bisphosphonate used or treatment

schedule. A benefit also was seen in terms of breast cancer-specific survival (Coleman 2013; [4.3]). I'm hesitant because you're merging all the data and evaluating a subgroup that wasn't initially under consideration and didn't have the biology to support that. This was an afterthought after a couple of the more recent trials suggested that it is the postmenopausal patients who seem to benefit from adjuvant bisphosphonate therapy.

I'm not arguing what this meta-analysis demonstrated, but I would have loved to see a confirmatory trial. One that may come out with time is evaluating denosumab versus placebo (NCT01077154).

So if you have a reason to administer a bisphosphonate — in other words, if you have a postmenopausal woman to whom you're administering at least 5 years of an AI, she has a low bone mineral density and you'll prescribe it to her for bone strength anyway — then, sure, why not? I'm not sure it's a given that you administer it to all postmenopausal women — for instance, in someone with normal bone mineral density without a high risk of recurrence. ■

4.3

Meta-Analysis of the Effects of Bisphosphonate Treatment in Women with Early Breast Cancer

	Number of events	Rate ratio	10-year gain	*p*-value
All women (n = 17,016)				
Breast cancer mortality	2,049	0.91	1.7%	0.04
Breast cancer recurrence	3,284	0.94	1.0%	0.13
Distant recurrence	2,751	0.92	1.3%	0.05
Bone recurrence	825	0.79	1.4%	0.002
Postmenopausal women (n = 10,540)				
Breast cancer mortality	1,107	0.83	3.1%	0.004
Breast cancer recurrence	1,809	0.86	3.0%	0.002
Distant recurrence	1,503	0.83	3.3%	0.0007
Bone recurrence	445	0.65	2.9%	0.00001

Conclusions: Adjuvant bisphosphonate therapy reduces bone recurrences and improves survival for postmenopausal women. Benefits in postmenopausal women were independent of bisphosphonate type, treatment schedule, ER status, nodal involvement or use of concomitant chemotherapy. However, no effects are apparent on disease outcomes for premenopausal women, and no effects on nonbone recurrence were observed regardless of menopausal status.

Coleman R et al. San Antonio Breast Cancer Symposium 2013;**Abstract S4-07**.

SELECT PUBLICATIONS

Coleman R et al. **Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer: A meta-analysis of individual patient data from randomised trials.** San Antonio Breast Cancer Symposium 2013;**Abstract S4-07**.

Davidson JA et al. **A prospective clinical utility and pharmacoeconomic study of the impact of the 21-gene Recurrence Score assay in oestrogen receptor positive node negative breast cancer.** *Eur J Cancer* 2013;49(11):2469-75.

Davies C et al. **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.

Gray R et al. **aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer.** *Proc ASCO* 2013;**Abstract 5**.