INTERVIEW

Ann H Partridge, MD, MPH

Dr Partridge is Director of the Adult Survivorship Program and Founder and Director of the Program for Young Women with Breast Cancer at Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: Would you discuss the Phase II APT trial that your group presented at the 2013 San Antonio Breast Cancer Symposium evaluating adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer (Tolaney 2013)?

DR PARTRIDGE: The APT trial was designed to ascertain the potential value of trastuzumab for women with lower-risk HER2-positive breast cancer. Much thought went into the design of this trial. We never would have been able to perform a prospective randomized trial of trastuzumab-based therapy in this setting because it would take 20 years to obtain all the data. So the main considerations were to design a study that

would be able to accrue patients while providing some information to inform care. In the end this study accrued more than 400 patients, and the results turned out to be a boon for the whole cancer community. The rate of recurrence overall was extremely small. A total of 10 recurrence events occurred, and only 2 distant recurrence events were reported at a median follow-up of approximately 3 years. Most of the events were contralateral or a recurrence in the ipsilateral breast. We need to continue to observe these patients over time.

DR LOVE: How does the tolerability of this regimen compare to other regimens that are typically used in this setting?

DR PARTRIDGE: I've administered all of the various anti-HER2 regimens to numerous patients, and the toxicities are like night and day. We're all familiar with the low but serious risk of cardiotoxicity and the secondary leukemia risk associated with anthracyclines and the AC regimen. Docetaxel/carboplatin and trastuzumab (TCH) is a good alternative but is extraordinarily toxic in terms of quality of life because of the neutropenia, fatigue, nausea and neuropathy that many women experience.

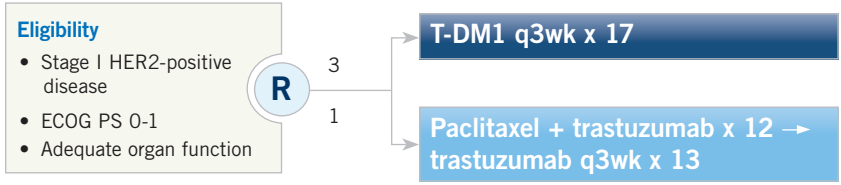
We did not observe the same levels of risk in terms of long-term, late side effects with paclitaxel/trastuzumab. Some neuropathy was observed, in addition to other quality-of-life side effects such as fatigue, but in my clinical experience the incidence was not remotely as high as one would anticipate with one of the more standard, "kitchen-sink regimens" as I like to call them.

A follow-up study to the APT trial called ATEMPT is evaluating T-DM1 versus paclitaxel/trastuzumab for patients with Stage I HER2-positive breast cancer (1.1). This exciting trial was designed to further reduce toxicity and potentially improve efficacy for patients with low-risk HER2-positive disease. I believe T-DM1 is the beginning of what I hope to be an explosion of therapies that will allow us to have excellent disease control in the adjuvant setting while not wreaking havoc on the rest of the body.

1.1

ATEMPT: A Phase II Trial of T-DM1 versus Paclitaxel and Trastuzumab for Stage I HER2-Positive Breast Cancer

Protocol ID: NCT01853748 **Target Accrual:** 500



Adjuvant endocrine therapy (if applicable) may be initiated after completion of 12 weeks of therapy. Adjuvant radiation therapy may be administered concurrently with study treatment.

Tolaney SM et al. San Antonio Breast Cancer Symposium 2013;**Abstract S1-04**.

Track 6

DR LOVE: You are very involved in programs targeting young women with breast cancer. What is known about the safety of anti-HER2 directed therapies during pregnancy?

DR PARTRIDGE: A registry called MotHER is currently tracking all in-utero exposures to trastuzumab and pertuzumab, and a poster on this program was presented at ASCO 2013 (Brown 2013).

Currently trastuzumab includes a black box warning, as does pertuzumab, which contraindicates use during pregnancy because of reports of oligohydramnios, which is less fluid than you'd like in the amniotic sac. This phenomenon can lead to poor fetal outcomes, including fetal demise, so avoidance of those antibody therapies is prudent at this time (Sarno 2013; [1.2]).

Does that mean that exposure to trastuzumab in utero is a guaranteed cause of oligohydramnios? No, and some reports demonstrate that babies are being delivered safely after exposure to trastuzumab. However, in general we would not want to expose a fetus to it at this point. I am not aware of any reports of T-DM1 exposure in utero, but it sounds like a bad idea and not one I'd want to test.

1.2

Use of Trastuzumab as Breast Cancer Therapy During Pregnancy

"Monoclonal antibodies are the cornerstone of the treatment of several types of tumors, but their use in pregnant women is not clearly defined … Trastuzumab administration has been associated with an elevated incidence of oligohydramnios and poor neonatal outcomes, particularly when prescribed after the first trimester for repeated infusions, and therefore it is not recommended … Few data are available about other [monoclonal antibodies], and hence their use during pregnancy remains discouraged."

Sarno MA et al. *Immunotherapy* 2013;5(7):733–41.

Track 10

DR LOVE: The 21-gene Recurrence Score is now widely used for patients with ER-positive, HER2-negative, node-negative tumors. In what situations, if any, do you employ this assay in patients with positive nodes?

DR PARTRIDGE: I consider ordering the assay for an older patient with a few positive nodes — à la the SWOG trial reported by Dr Kathy Albain, which analyzed the use of the 21-gene Recurrence Score assay for patients with 1 to 3 positive nodes (Albain 2010). Above that level of nodal involvement the risks are higher and it's much harder to justify not administering chemotherapy. However, some uncertainty persists. We await the ultimate RxPONDER trial results (NCT01272037).

My threshold for administering chemotherapy is probably a little lower for younger patients, although I try not to base treatments on age. Such patients will have ovarian function for a long time, so I consider that. But more important is how chemotherapy averse the person is and how much benefit I believe it will add. I order a 21-gene Recurrence Score only when I'm ambivalent about the decision.

In terms of patients with negative nodes, if a patient presents with a T1a tumor, I do not administer chemotherapy as a rule, with rare exceptions, no matter how big the tumor is, so I don't order a 21-gene Recurrence Score. If a person comes in with an 8-cm tumor, unless the patient is older or it's a low-grade tumor and there is some reason not to administer chemotherapy, or multiple positive lymph nodes are detected, I don't order a Recurrence Score assay because I will be administering chemotherapy in that setting.

The assay comes into play in the in-between situations, and what I tell patients is, I'm ordering this assay because I believe you have a "sheep" and I'm trying to see if it's a "wolf in sheep's clothing." So I don't order a Recurrence Score if I believe you have a "wolf" and I don't order it if I know you have a "sheep." I order it only when I believe you have a "sheep" and I want to make sure it's not a "wolf."

Track 11

DR LOVE: How do you approach the issue today in your practice of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years for patients with ER-positive early breast cancer?

DR PARTRIDGE: I believe it's not quite the knee-jerk, "no-brainer" that many interpreted from the data (Davies 2013; Gray 2013). The problem of whether to extend endocrine therapy beyond 5 years is driven by the original risk of the disease, so anybody who was at higher risk of recurrence in the first 5 years is generally at higher risk of recurrence in the second 5 years and beyond. Then it's driven by how well they tolerate the therapy, what stage of life they they are at and how much additional risk reduction they want compared to tolerating the side effects, if any.

It's a highly individual decision based on all of those factors. It is also dependent on age because as women age their risk of serious adverse events from tamoxifen, such as blood clots and cancer of the uterus, increases. When I consult with younger patients, I say, "We'll talk about it. Right now the standard is 5, but we could consider 10." Notice my semantics. I say the standard is 5 years. Can the standard be 10 years right now? Sure. We have 2 randomized trials that say 10 is better, but I find clinically that when I tell patients they are to receive 10 years of hormonal therapy, some feel as though I've sentenced them to a 10-year jail sentence. I don't find that this works emotionally.

So I say, "We're going to treat for 5 years at a minimum and then let's talk about whether or not it makes sense for you to do more." I find that much easier to swallow for those patients, and it's the reality because some of these patients will stop therapy earlier because of intolerance, and some may change their mind over time about how they feel about tamoxifen. I believe some women view tamoxifen as their power pill and some women view it as a jail sentence, and that can have huge implications for whether they even take it and how well they tolerate it. ■

SELECT PUBLICATIONS

Albain KS et al. **Prognostic and predictive value of the 21-gene Recurrence Score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomised trial.** *Lancet Oncol* 2010;11(1):55-65.

Brown V et al. **MotHER: A registry for women with breast cancer who received trastuzumab (T) with or without pertuzumab (P) during pregnancy or within 6 months prior to conception.** *Proc ASCO* 2013;**Abstract TPS658**.

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**.

Sarno MA et al. **Are monoclonal antibodies a safe treatment for cancer during pregnancy?** *Immunotherapy* 2013;5(7):733-41.

Zagouri F et al. **Trastuzumab administration during pregnancy: A systematic review and meta-analysis.** *Breast Cancer Res Treat* 2013;137(2):349-57.