INTERVIEW

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Tracks 1-10

Track 1 Utility of the 21-gene Recurrence Score versus other genomic assays for ER-positive, HER2-negative BC

Track 2 Ongoing Phase II feasibility study of dose-dense AC followed by eribulin with or without prophylactic growth factors as adjuvant therapy for early-stage, HER2-negative BC

Track 3 Results of an FDA-led meta-analysis evaluating trials of neoadjuvant systemic therapy for BC

Track 4 Perspective on the recent FDA approval of neoadjuvant pertuzumab

Track 5 FDA label indication and the NCCN guidelines on the use of (neo)adjuvant pertuzumab

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Track 9 CALGB-40101: Results of a Phase III trial comparing AC to single-agent paclitaxel as adjuvant therapy for patients with BC and 0 to 3 positive axillary nodes

Track 10 Dose-dense versus nondose-dense chemotherapy in BC

Select Excerpts from the Interview

Tracks 3-5

DR LOVE: The FDA recently granted accelerated approval to pertuzumab in combination with trastuzumab and docetaxel for the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory or early-stage breast cancer. What is your perspective on this approval?

DR HUDIS: Pertuzumab is an exciting new drug that demonstrated a dramatic improvement in progression-free and overall survival in CLEOPATRA, the first randomized trial of this agent in the metastatic setting. With the paucity of drugs that have been shown to improve survival in metastatic disease, optimism was high.

The adjuvant Phase III APHINITY trial evaluating the addition of pertuzumab to chemotherapy and trastuzumab for patients with HER2-positive primary breast cancer is now ongoing. The target accrual is approximately 5,000 patients, and the trial is powered to determine whether pertuzumab is beneficial in the adjuvant setting

(NCT01358877). I predict the results will be positive because the CLEOPATRA trial demonstrated such a significant benefit with pertuzumab.

Studies in the neoadjuvant setting, like the NEOSPHERE trial, reported a dramatic improvement in pathologic complete response (pCR) with the addition of pertuzumab (Gianni 2012). The question that arose was, does this improvement in pCR accurately predict long-term benefit? If it does, we will have a tremendous motivation to conduct a larger proportion of drug development studies in the neoadjuvant setting. The FDA weighed in on this, and a meta-analysis of clinical trials on neoadjuvant treatment for breast cancer was published. This study reported that an improvement in pCR does not correlate with an improvement in event-free and overall survival (Cortazar 2014).

The FDA has approved pertuzumab in the neoadjuvant setting for 3 to 6 cycles for patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer who have tumors larger than 2 centimeters or positive nodes. The problem is that by labeling the drug for the neoadjuvant setting and administering it for 3 to 6 cycles, we may only increase the pCR rate.

Shrinkage of the tumor to diminish the extent of surgery would be a benefit, but that would account for less than 10% of the cases. My passionate point of view is that if you're going to take a public health gamble with all the expense that's involved, you may as well gamble with what the APHINITY trial is testing in the adjuvant setting and administer the pertuzumab for a year.

DR LOVE: The NCCN considers it reasonable to incorporate pertuzumab as part of an adjuvant regimen even though we do not have any data to support that practice and pertuzumab has not been approved by the FDA in that setting. Would you comment on this?

DR HUDIS: I'm espousing the point of view of the NCCN, which is that if you were eligible to receive neoadjuvant pertuzumab, why should you be denied the agent simply because you saw a surgeon first? The vagaries of the referral pattern bother me. Only certain patients would receive neoadjuvant pertuzumab, depending on which specialist saw them first. They could not be offered the drug in the adjuvant setting off label. I would consider pertuzumab in the adjuvant setting for a year for patients who would be eligible for the drug preoperatively.

If the FDA wanted to grant pertuzumab accelerated approval, this approval should have included its use in the adjuvant setting also. If the APHINITY trial is negative, the approval could be withdrawn — the accelerated approval of pertuzumab in the neoadjuvant setting is contingent on APHINITY being positive.

Track 6

DR LOVE: What are your thoughts on the joint analysis of the SOFT and TEXT trials comparing adjuvant exemestane with ovarian function suppression to tamoxifen with ovarian function suppression for premenopausal women with ER-positive early breast cancer?

DR HUDIS: The results of the SOFT and TEXT trials demonstrated statistically significant improvements in disease-free survival and the rate of freedom from breast cancer with exemestane and ovarian suppression compared to tamoxifen and ovarian suppression (Pagani 2014; [2.1]). This could motivate a change in practice, although the differ-

ence in overall survival between the 2 arms was not statistically significant. The big question as to whether the addition of ovarian function suppression to hormone therapy is beneficial has still not been answered definitively with this analysis. The results from the control arm of tamoxifen alone were not included in this study.

2.1

Joint Analysis of the TEXT and SOFT Trials: Adjuvant Exemestane with Ovarian Function Suppression (OFS) versus Tamoxifen with OFS for Premenopausal Women with ER-Positive Early Breast Cancer (BC)

Efficacy*	Exemestane + OFS (n = 2,346)	Tamoxifen + OFS (n = 2,344)	Hazard ratio	*p*-value
Five-year disease-free survival	91.1%	87.3%	0.72	<0.001
Rate of freedom from BC at 5 years	92.8%	88.8%	0.66	<0.001
Overall survival	95.9%	96.9%	1.14	0.37

Adverse events

- Select adverse events of Grade 3 or 4 were reported for 30.6% of the patients in the exemestane + OFS group and 29.4% of those in the tamoxifen + OFS group, with profiles similar to those for postmenopausal women.
- Patients in the exemestane + OFS arm reported significantly more detrimental effects of bone or joint pain and vaginal dryness and a greater loss of sexual interest, whereas those in the tamoxifen + OFS group were significantly more affected by hot flashes and vaginal discharge.

* Median follow-up = 68 months

Pagani O et al. *N Engl J Med* 2014;371(2):107–18.

Track 8

DR LOVE: Would you discuss the Phase III POEMS/SWOG-S0230 study of goserelin and chemotherapy for early-stage, hormone receptor–negative breast cancer to reduce the risk of infertility from chemotherapy?

DR HUDIS: I believe that this study was, from a practical perspective, one of the most high-impact presentations at ASCO 2014. It asked an important lifestyle question: Do we have safe ways to preserve fertility for young patients whom we're trying to cure of breast cancer? Patients with hormone receptor–negative breast cancer were randomly assigned to receive standard chemotherapy with or without goserelin. The ovarian failure rate at 2 years and pregnancy outcomes for women in the 2 groups were compared.

The results clearly indicated that goserelin preserved ovarian function. The group that received goserelin had approximately twice as many pregnancies. Because the study size was small, one can't be sure that this result was related to the drug. Interestingly, a trend toward better clinical outcomes was also evident among the patients who were randomly assigned to receive goserelin (Moore 2014).

This is the first time that this approach has demonstrated consistent beneficial effects across multiple endpoints. We can now offer patients ovarian rest to maintain the premenopausal state. These results are practice changing for me. I believe that this study has implications well beyond breast cancer. It will provoke young people receiving chemotherapy to consider these agents.

Track 2

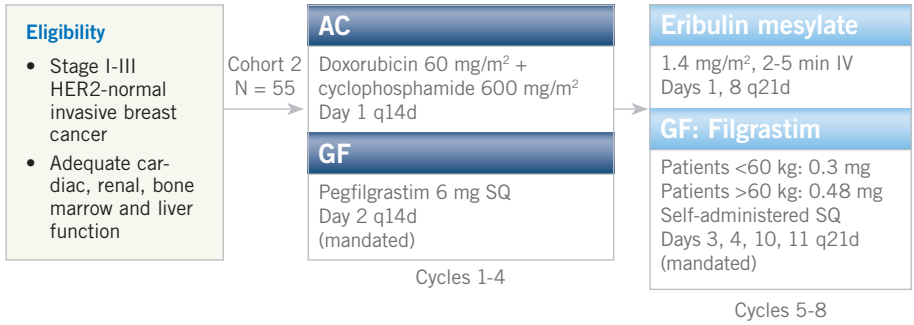
DR LOVE: Would you discuss the rationale for the ongoing Phase II study you're involved with evaluating dose-dense AC followed by eribulin as adjuvant therapy for early-stage HER2-negative breast cancer?

DR HUDIS: Eribulin was approved for previously treated metastatic breast cancer on the basis of its superiority to treatment of physician's choice. Although the difference in survival was modest, it was important because the primary endpoint was overall survival (Cortes 2011). Because eribulin improved survival in the metastatic setting, the hope was that it would be beneficial in the adjuvant setting. It is one of the few agents to have improved survival in metastatic disease, so it is worth investigating in the curative setting. The Phase II trial of AC followed by eribulin as adjuvant therapy for early breast cancer is a pilot study to move eribulin in that direction (Traina 2014; [2.2]). ■

2.2

Ongoing Phase II Study of Dose-Dense Doxorubicin and Cyclophosphamide (AC) Followed by Eribulin with or without Prophylactic Growth Factor (GF) as Adjuvant Treatment for Early-Stage Breast Cancer

Protocol ID: NCT01328249



SQ = subcutaneous

Primary objective: Determine feasibility of adjuvant AC for 4 cycles followed by eribulin for 4 cycles

- Cohort 1 with 55 enrolled patients who received treatment was closed. Without a prophylactic GF, the regimen was approaching nonfeasibility due to neutropenic events.
- Study was amended (cohort 2), and a prophylactic GF was required with eribulin.

Traina TA et al. *Proc ASCO* 2014;**Abstract TPS670**; **www.clinicaltrials.gov**. Accessed September 2014.

SELECT PUBLICATIONS

Cortazar P et al. **Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis.** *Lancet* 2014;384(9938):164-72.

Cortes J et al. **Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label randomized study.** *Lancet* 2011;377(9769):914-23.

Gianni L et al. **Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial.** *Lancet Oncol* 2012;13(1):25-32.

Moore HCF et al. **Phase III trial (Prevention of Early Menopause Study [POEMS]-SWOG S0230) of LHRH analog during chemotherapy (CT) to reduce ovarian failure in early-stage, hormone receptor-negative breast cancer: An international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance).** *Proc ASCO* 2014;**Abstract LBA505**.