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NCI to Implement More Transparent Formula For Calculating Cancer Center Support Grants

By Paul Goldberg and Will Craft

NCI took another step toward adopting a new formula for determining the size of cancer center support grants, with the National Cancer Advisory Board accepting a report from a working group that has been working on the problem since the fall of 2012.

The schema proposed by the working group was accepted by the advisory board at its meeting June 23. It recommends broad organizing principles rather than specific numbers.

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After the Plenary

Don Berry: In NeoALTTO & ALTTO Trials, Neoadjuvant Response Predicts Adjuvant

By Donald Berry

An article in the June 6 issue of *The Cancer Letter* described plenary presentations at ASCO 2014. One presentation was the adjuvant breast cancer clinical trial ALTTO in HER2-positive disease, which "was chosen [for the plenary session] because it addressed the reliability of pathological complete response as a surrogate for patient benefit."

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In Brief

Three Named to Leadership Posts at St. Jude; Weiss Appointed Chair of Hematology

ST. JUDE CHILDREN'S RESEARCH HOSPITAL announced the appointment of three physician-scientists to leadership positions.

Mitchell Weiss was named chair of the St. Jude Department of Hematology.

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NCI Staff Starts Work On Implementation Plan

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It's now up to NCI officials to put together the funding formula and make plans for implementation.

Under the new approach, the size of the P30 Cancer Center Support Grants would be calculated based on the following components:

• **Base award:** At renewal, a predetermined base award applicable to all centers of the same type would be the starting point. All basic, clinical and comprehensive centers would receive preset base awards. This component would use up 50 percent of the direct cost budget of the NCI Centers Program.

• **Merit funding:** This would be calculated on a linear scale, as a percent multiplier of base award, using impact score. If a center is underperforming, it may end up with a reduction of its base award. This component would use up 30 percent of the direct cost budget of the centers program.

• **Size:** This would be calculated as a percent multiplier of the base award, using figures for total peer-reviewed funding reported by the center. This component would use up to 15 percent of the direct cost budget.

• **Supplements:** This would be based on review of proposed innovative and impactful programs, cores, new initiatives and consistency with NCI priorities. This would use up to 5 percent of the direct cost budget.

The text of the draft report is available on The Cancer Letter website.

NCI officials started to rethink their approach to determining the size of P30 grants after a group of directors of emerging and smaller centers argued that the existing funding system funnels larger amounts of money to more established and larger centers.

As it stands, just being in the centers program for many cycles can build up an institution's funding base. This favors the older centers.

The problem has been decades in the making, but it became more urgent in 2012, when NCI capped the grant sizes, in effect cementing inequity into place, critics said at the time.

NCI Director Harold Varmus sanctioned the reinvention of the formula for funding centers.

"The conclusions of the working group were that, in fact, significant disparities do exist in the size of CCSG awards, often due to factors other than merit," said Kevin Cullen, director of the University of Maryland Greenebaum Cancer Center, one of the center directors who brought the problem to the attention of NCI and later joined the NCAB working group.

"These [factors] included longevity, size of NCI budget, competitors in the year of application," said Cullen, presenting the report to NCAB June 23. "There was significant variability about the budget available in a given year dependent on when a center was renewing and what other centers were renewing in that fiscal year. Prior performance and prior size of the grant were major determinants of future awards. Point of fact, the awards changed relatively little from one grant cycle to the next."

The new system will become rational and transparent, said Linda Weiss, director of the NCI Office of Cancer Centers.

"What we anticipate going forward—although models are not finalized, and mode of implementation are not finalized—is that this will be a much more standardized, formulaic approach to center funding, which in fact will be clearer to all the centers involved," Weiss said at the NCAB meeting. "Much more consistent, and we hope fairer. So you should be able, once we have arrived at a final model, to anticipate, to some extent at least, how the award will be calculated, which is not actually the case at this point."

Varmus said he supports the new approach: "We are trying to make it a more numerically-based competition."

"You are still competing for a bigger budget, but you are not really competing against those particular co-competing institutions in the same year," he said.

The working group that produced the report included officials from the variety of centers—large, small, established, and emerging—and was headed by

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William Hait, global head of research and development at Janssen, a unit of Johnson & Johnson and a former director of The Cancer Institute of New Jersey.

The group recommended that the cancer center administrators be engaged in the planning for implementation of the new approach. The timeline and implementation strategies for this far-reaching change remain to be determined, the report's authors and NCI officials said.

Varmus: "It's striking that CCSGs are so small"

Varmus said he is a "big supporter" of the report's recommendations, which, he said lay the groundwork for correcting a problem that has developed over many decades.

"To take a larger perspective on this, it's striking to me that the CCSGs are small," Varmus said at the meeting. "They are the size of large R01s, in many cases, and P01s, and considering what we ask the centers to do, in my view, and considering the incredible productivity of the centers, they are the engines of new developments throughout cancer research.

"Eighty percent of our cancer research goes on at our cancer centers. We underfund these. Compared to other centers around, those supported by NIH institutes including CTSAs, I think the budgets are too small.

"It would be a lot easier to fix the system and penalize no one, and advantage several, by making these adjustments with a rise in our budget. But I don't have the money, and that makes things difficult.

"Kevin points out a number of things that have determined the current situation, and I think a lot of it is unfair and not merit based. I am a big supporter of what has been done here. There is clearly a big influence of history and in some cases of politics, and some of that political negotiation is not crazy, because I want to see the fruits of NCI supported research felt everywhere in the country, and we do make an effort to make sure there is some geographical distribution to the centers.

"Unlike other funding mechanisms where there is a tremendous dynamic, that is, even though people applying for renewal have an advantage over those applying for a new grant, even there the success rate is in the 30-40 percent range, whereas success rates for reapplication of your cancer center is well over 95 percent. That decreases the dynamics of funding and restricts our freedom of motion.

"But, that's a good thing, because I think centers should be stable, and I'd like to think they are all reasonably high performing and worth continuing. It limits the ability to make the kind of adjustments the committee is recommending.

"We are wrestling with the question of how to implement these changes, how to get the ratios right—the ratio of base score, priority, the quality of the priority score, and the size as elements—and still save some money for supplementary activity. I'd like to avoid any precipitous loss of revenue, which is very difficult, especially for some of the smaller centers to put their budgets for the whole center together. If there are corrected reductions, I'd like the pace of change to be relatively gradual.

"We are doing several things:

"We have already started to use supplements more actively, as recommended by the committee. As some of you know, we have had supplements given for activities in global health, and a couple of other things over the past year or two.

"We are doing a lot of modeling to see how we can best produce an equitable set of changes with variations of the ratio and other aspects of the funding plan that we are still trying to work out. We think implementation has got to be gradual over several years. We are trying to figure out how to do that in a way that is coordinated with review, because clearly once a review occurs, your budget is going to change in one way or the other.

"Nothing has happened as yet, we are still mulling this over. We will develop a plan, we'll bring it to the BSA. And of course we are always hoping for some relief from appropriations, but I don't see that happening in the near future. We will try to begin to implement a plan based on the principles that have been very well enunciated by this committee as we examine these models and their impact on current budgets."

NCAB member William Sellers, global head of oncology at the Novartis Institute for BioMedical Research, said the institute should now review its programs and find a way to increase funding for CCSG.

"I'd like to second something I said in the past, which is I think more money should be in the cancer centers," Sellers said at the meeting. "I know you don't have more money, and I am talking about redirecting money within the current budget to what I've consistently heard is the top performing mechanism we have. I'd like to see that as an agenda item: which ways within the existing budget could we increase CCSG funding."

Discussion of the way NCI determines CCSGs started in April 2012, when NCI announced a plan to cap the growth of awards to cancer centers while also tightening the requirements for review (The Cancer Letter, May 11, 2012).

Maryland's Cullen objected to the funding restrictions in a letter to Linda Weiss, director of the NCI Office of Cancer Centers. Separately, a group of 11 center directors expressed similar objections in a letter to Weiss.

"I believe that the current proposal effectively legislates an inequitable system, which is largely based on history, and effectively excludes consideration of a change in populations and demographics or changing national needs in future times," Cullen wrote at the time.

NCI responded by setting up a 10-member committee that produced the current report. An earlier version of the proposal was presented to the Board of Scientific Advisors last June (The Cancer Letter, July 3, 2013).

At the meeting Feb. 27, NCAB was asked to comment on the proposed formula, but no action was expected (The Cancer Letter, March 14).

Insiders say that the plan would benefit smaller and newer centers while potentially brining about cuts

When the plan was first aired at the BSA meeting last June, Varmus cautioned the board members about potential political problems.

"There is another factor, as I look out on the landscape here, and that is a political factor," Varmus said at the meeting. "Centers are not only important for the NCI, because they are the backbone of the NCI. But members of Congress, mayors, and governors, and others are very focused—as they should be—on the success of their centers.

"When centers are perceived to be losing money unfairly or not getting the money that people perceive they should be getting, that is one of the most common causes of a call to the NCI director. There is the opportunity for us to say, 'Let's just erase the blackboard and start over,' and, believe me, political pandemonium will result, and I don't think anybody would survive in this seat in that atmosphere.

"Before you all get exorcised about wiping the slate clean and starting over, let's keep that in mind."

A year after these words were uttered, no signs of a political backlash are known to have materialized. In fact, working group members have said repeatedly that larger and older centers on the board have been supportive of the overall plan.

It remains to be seen whether this will change after NCI puts specific implementation plans on the table.

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After the Plenary

Berry: What Does ALTTO Tell Us About the Neoadjuvant Approach?

(Continued from page 1)

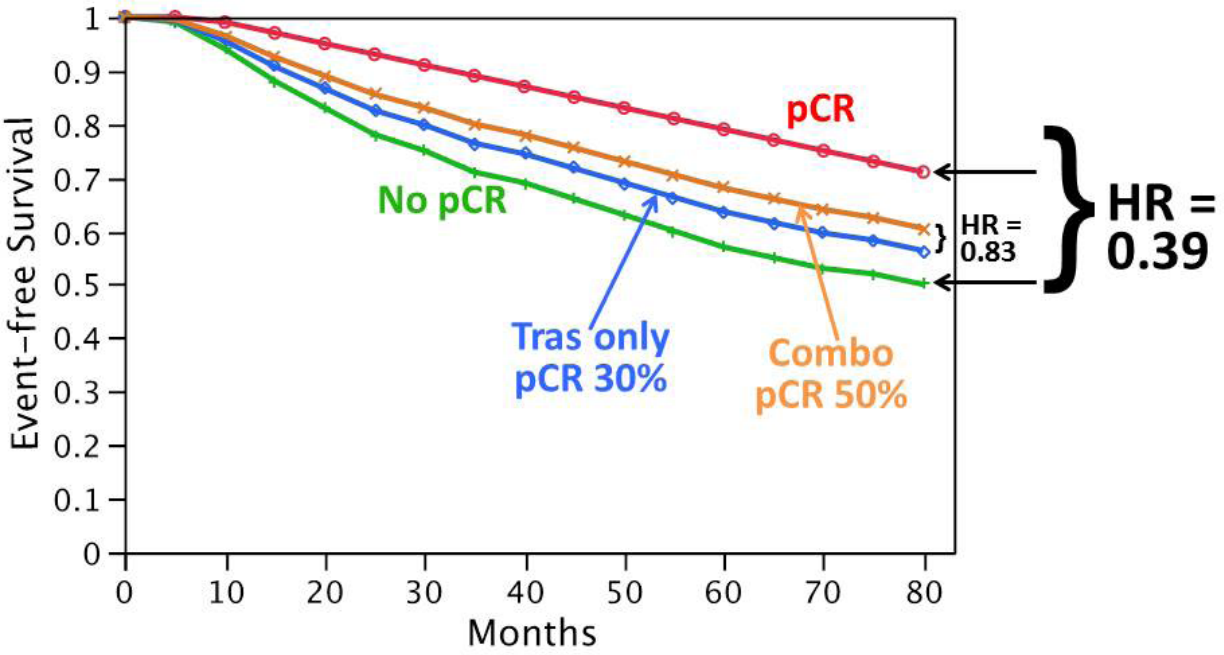
The article and much ASCO and post-ASCO rhetoric in the breast cancer community focused on the conclusion that ALTTO failed to show a statistically significant benefit in disease-free survival (DFS) for combination lapatinib/trastuzumab in comparison with trastuzumab, both on a backbone of chemotherapy. This was despite a statistically significant benefit in pathological complete response (pCR) in NeoALTTO, the neoadjuvant version of ALTTO.

Statistical significance in one trial on one endpoint does not imply statistical significance in another trial on another endpoint. Moreover, lack of significance in the second trial is irrelevant as regards the predictability of the latter endpoint from the former. Contrary to the rhetoric, the best available and generally accepted evidence regarding the relationship between DFS and pCR actually perfectly predicts ALTTO from NeoALTTO.

The best available evidence is the FDA-led meta-analysis showing the relationship between pCR and EFS (event-free survival, the FDA's version of DFS). This meta-analysis was presented at the 2012 San Antonio Breast Cancer Symposium and published by Cortazar, et al. in *Lancet*, 2014. It showed that the EFS hazard ratio of achieving a pCR as opposed to less than a complete response in HER2-positive breast cancer was 0.39 (95% confidence interval 0.31-0.50).

This comparison was across the various therapies used in the meta-analysis, including standard therapies and experimental therapies that showed no benefit in pCR rate beyond control therapy. An obvious and quite reasonable concern is that the relationship evinced by the HR of 0.39 in the meta-analysis would not apply for a particular experimental therapy. For example, perhaps adding lapatinib to trastuzumab changes some non-responders to having pCRs but without improving those patients' EFS.

The DFS HR of the combination versus trastuzumab in ALTTO was 0.84 (97.5% confidence interval 0.70 to 1.02) on the basis of about 2100 patients in each of the two groups. The two-sided p-value was 0.048, which was not statistically significant because the investigators added another comparison, the non-inferiority of trastuzumab followed by lapatinib versus trastuzumab, both for a total of one year. So the usual alpha-level of



0.05 was split in two with the targeted two-sided p-value for each comparison being 0.025.

So what value of HR would the FDA's meta-analysis have predicted for ALTTO based on the pCR improvement in NeoALTTO? The principal endpoint in NeoALTTO was pCR in the breast, with the combination improving the rate by 22%. But the FDA's meta-analysis was based on pCR in the axilla as well as in the breast, with the corresponding improvement in NeoALTTO of 20% (49% versus 29%).

The "pCR" and "No pCR" curves in the attached figure are smoothed versions of the EFS curves in the FDA's metaanalysis of patients with HER2-positive tumors. The HR is 0.39, as indicated in the figure, which is a 61% reduction in hazard. A 20% improvement in pCR would mean moving an extra 1 in 5 patients from the No pCR curve to the pCR curve. Such a shift would obviously evince a reduction in EFS hazard for the combination that is smaller than 61%, although it would not be as small as one-fifth of this quantity. The resulting HR for the treatment comparison is shown in the figure: 0.83. This is almost exactly the value 0.84 that was observed in ALTTO.

Neoadjuvant trials other than NeoALTTO addressed the same question, albeit in somewhat different populations and in the context of different backbone chemotherapies. These trials were mentioned by Martine Piccart who presented ALTTO at ASCO and also by George Sledge who discussed her presentation.

The following table gives the results of these trials where pCR includes axilla as well as breast:

Trial	Sample size	Combo improves pCR rate
NeoALTTO	277	20%
CALGB 40601	233	9%
CHERLOB	119	22%
NSABP B-41	529	11%
TRIO US B-07	92	5%
Total	1250	13%

The overall advantage in pCR of the combination in these five trials was 13%. Based on the FDA metaanalysis the EFS hazard ratio corresponding to a 13% pCR advantage in HER2-positive disease is 0.88. So using all the relevant neoadjuvant data, the results of ALTTO with its hazard ratio of 0.84 are actually somewhat more positive than the FDA's metaanalysis would predict.

These observations support the relationship between pCR and EFS in the FDA's metaanalysis. The pCR and EFS results in NeoALTTO and ALTTO certainly provide no evidence to challenge that relationship. Although the ALTTO trial does not validate the role of pCR rate in predicting EFS it is a comforting addition to the corpus of information regarding the validity of the neoadjuvant approach to drug development.

In his discussion of ALTTO at ASCO, Dr. Sledge lamented, "If we cannot trust neoadjuvant and metastatic results to predict adjuvant results, how will we move forward?" The implication is that there is no alternative but to carry out large adjuvant trials. Happily, the neoadjuvant approach and the FDA's leadership in establishing pCR as an accelerated approval endpoint are alive and well.

But even if pCR couldn't be trusted, large adjuvant trials will soon be out of the question. We can't afford them and patients can't afford to wait many years to get answers. Moreover, cancer biologists are changing our understanding of the disease at least monthly, with no signs of slowing advances. Waiting 5 and even 10 years for the results of a clinical trial means the results will then be passé. (ALTTO was announced 7 years after the first patient accrued. Even though it accrued over 8300 patients it achieved only 555 DFS events for the comparison of the combination versus trastuzumab, one-third fewer than the planned total of 850 events required for 80% power.) Moreover, given the ever increasing narrowing of disease subtypes, clinical trials addressing the benefits of targeted therapies—including combinations of targeted therapies—cannot require thousands of patients because that would be orders of magnitude larger than the entire eligible patient population!

All of this means that we have to make improvements in clinical trial design to attempt to keep pace with the amazing advances in cancer biology. The neoadjuvant approach is one step, and the good news is that there is no evidence that it is a faux pas. But clinical trialists must make additional advances, including building on the neoadjuvant approach as a foundation.

The author is a professor of biostatistics at MD Anderson Cancer Center.

Financial Disclosure: The author is co-owner and statistical consultant for Berry Consultants, LLC. Berry Consultants designs adaptive clinical trials for many pharmaceutical and medical device companies and academic consortia, including NIH cooperative groups.

Counterpoint

Sledge: Neoadjuvant Doesn't Predict Adjuvant in Breast Cancer

By George Sledge

As always, I both enjoyed and learned something interesting from Dr. Don Berry, one of the great biostatisticians of our era. I find, reading his analysis of ALTTO and NeoALTTO, much that I agree with. I am certainly no statistician, and must bow to his statistical analysis of ALTTO and NeoALTTO. And yet at the same time I think it misses the point. So I will beg to differ.

Let us begin with the use of pCR as a predictor of adjuvant benefit. The Cortazar analysis suggests, as does virtually every analysis of neoadjuvant therapy, that having a pathologic complete response is a very good thing for an individual. The great majority of patients with a pCR go on to have prolonged disease-free survival. There is no question but that, *for an individual*, pCR is a powerful predictor of benefit. This is true in all breast cancer subgroups, and the 0.39 EFS hazard ratio quoted by Dr. Berry refers to this striking relationship.

But that is not the real question for a clinical trialist. The question is, rather (at least in part), what difference in pCR rate must one see between two arms of a neoadjuvant trial for one to see an improvement in event-free survival rates for the overall trial population. The Cortazar meta-analysis was quite clear in this regard: there was no obvious relationship between a delta in pCR and a delta if EFS hazard ratio. This was true even after excluding low-grade, hormone-receptor positive tumors that would be expected not to benefit from chemotherapy. To quote the *Lancet* paper: "the results of the analyses by breast cancer subtype were consistent with findings in the overall population: no correlation between improvement in frequency of pathological complete response and the treatment's effect on EFS or OS was recorded."

A reasonable criticism of the Cortazar analysis was the relative lack of data involving combinations of chemotherapy and trastuzumab: in essence, a single trial (the NOAH trial), which suggested a relationship between pCR and EFS. But I am uncomfortable with applying the results of a single trial to the overall question, just as I am uncomfortable about applying the FDA metaanalysis results (which, to repeat the *Lancet* paper, show "no correlation between improvement in frequency of pathological complete response and the treatment's effect on EFS or OS") to a different drug than what was used in the metaanalysis.

I believe this to be an important point going

forward. If we look at a well-defined biologic subset, such as HER2-positive breast cancer, will past outcomes with one drug confidently predict the results with another novel agent? Dr. Berry's analysis assumes that this is the case. But will this always be a rational biologic assumption? For instance, neoadjuvant bevacizumab improves pCR rates in triple negative breast cancer; adjuvant bevacizumab does not improve DFS rates. We cannot always safely assume that what happens in a primary tumor will be reflected in a metastatic site, even (as in the bevacizumab case) when we analyze similar biologic subsets. Nor can we assume that two agents targeting the same biologic process (e.g., HER2) will always perform equally with regard to the relationship between pCR and EFS. It may be a reasonable hypothesis, but until tested it is just that: a hypothesis.

Dr. Berry, in his table, shows what he considers compelling support for the relationship between pCR rates and the ALTTO outcome. We look at the same data and come to somewhat different conclusions, perhaps because of where we start, as statistician and clinician. The differences in pCR rates with the addition of lapatinib are, quite frankly, all over the map, ranging from 5% to 22%. With lapatinib we were quite fortunate, in that we had numerous neoadjuvant trials (and therefore a relatively large number of events) to call on. The average pCR rate seen is therefore a reasonable point estimate. I doubt that we will always have such good fortune with future agents. We certainly lack many large neoadjuvant trials for most agents. I am concerned that we could either toss away an active agent, or embrace an ineffective one, if the roll of the dice in a smaller trial betrayed us.

Dr. Berry properly stated that I lamented the results of the ALTTO trial. He is correct. His retrospective analysis notwithstanding, there was general enthusiasm for the ALTTO trial, and a widespread belief that the preoperative data suggested that ALTTO would be an impressively positive trial. One could not go to a breast cancer meeting in recent years without hearing the confident prediction that ALTTO would be a positive trial. Perhaps the speakers (this one included) should have paid heed to Dr. Berry's analysis; perhaps the trialists involved in the trial design should have as well. But I heard no investigator suggest that the trial was not worth performing.

In retrospect, ALTTO was a seriously underpowered trial. We were no doubt led astray by the startling success of trastuzumab, which shattered all expectations. We might well have performed a lapatinib trial with fewer arms, and more patients per arm. And perhaps, had we done so, the p values might well have crossed the boundaries for statistical significance. But this brings us to our other problem with ALTTO. Clinicians and patients do not only look at differences in event-free survival when analyzing a trial. A deeper dive into the ALTTO results suggests why clinicians, collectively, lamented the results of ALTTO.

One routinely hears a question at ODAC meetings: what is the clinical benefit of this new agent? Clinical benefit is, and always has been, something more than a positive p value. It is a compilation of DFS, OS, toxicity (short-term and long-term), quality of life and (true in 2014, though rarely mentioned at ODAC) cost. And clinical benefit was certainly on the mind of many looking at the ALTTO data.

First, the small (non-significant) improvement in DFS seen in ALTTO was not accompanied by an improvement in overall survival. Perhaps we have not followed the patients out far enough, but as of 2014 we cannot tell any woman that she would live a day longer if she received adjuvant lapatinib. This is a very real issue in the clinic when offering adjuvant therapy to a healthy woman, and often a crucial decision point for a patient.

Secondly, the experimental arm was quite toxic compared to the control arm, to the extent that a significant percentage of patients did not complete their assigned duration of adjuvant lapatinib. Indeed, it is possible (though impossible to prove) that this affected the results. Regardless, this diminishes enthusiasm for this agent. Women will often accept significant toxicity if they know they will receive benefit, but in the absence of defined clinical benefit toxicity represents a major barrier to adopting a drug for routine, standard-of-care therapy.

Third, ALTTO was interesting in that it allowed patients to receive HER2-targeted therapy either in combination with chemotherapy (an approach utilized in the original North American trastuzumab trials) or following chemotherapy (similar to the HERA adjuvant trastuzumab trial). Though non-randomized, and subject to all the constraints associated with retrospective subset analyses, patients receiving the concurrent approach appeared to receive absolutely no benefit from lapatinib (hazard ratio=0.94, p=0.68). If this is this is the case, then adding lapatinib might only have been a way of making up for the failure to perform concurrent therapy. Is this just a chance finding of the sort one sees in underpowered subset analyses? Perhaps, perhaps not.

This, by the way, is another potential issue with extrapolating pooled neoadjuvant data to an adjuvant trial. In the case mentioned above (concurrent versus sequential therapy) there was certainly the strong suggestion from the N9831 adjuvant trastuzumab trial that the concurrent approach might prove superior to

sequential therapy. A pooled analysis of neoadjuvant trials, some using a combination approach and some using a sequence, might well muddy the waters.

Dance partners may well matter. Imagine a drug that has a low single agent pCR rate, and which when combined with chemotherapy appears to diminish the effectiveness of chemotherapy (as suggested by SWOG 8814). Would such an agent cross over from a neoadjuvant trial to an adjuvant trial? Probably not, but fortunately we didn't have to find out: the drug is called tamoxifen, and it saves more lives than any other drug in all of cancer medicine on a worldwide basis. One can argue that we are smarter about cancer biology than we were in 1974, but in truth we frequently learn a great deal about biology in the clinic.

Neoadjuvant trial results offer other concerns for practicing oncologists. Duration of therapy is certainly one of them. We were exceptionally fortunate with trastuzumab: a year of adjuvant trastuzumab, by some miracle, appears to have been exactly the right duration. Shorter durations appear worse, and longer durations no better, than a year of adjuvant trastuzumab. And yet, when Don Berry and I and the leaders of the cooperative groups planning N9831 decided on a year for that trial, it wasn't even a guess.

A neoadjuvant trial's pCR endpoints are reached fairly quickly, in a matter of months. How long should we administer an agent in the adjuvant setting? For the same length as the neoadjuvant trial? For a year? For 5 years? And yet, duration matters: consider ER-positive disease. And remember the suggestion made by NSABP investigators that adjuvant bevacizumab failed in colorectal cancer due to inadequate duration. A neoadjuvant trial gives us no clue whatsoever to appropriate duration. And yet one could easily imagine a scenario in which early discontinuation of a biologic might result in a deleterious rebound.

Dr. Berry laments that stodgy medical oncologists remain wed to large Phase III trials. He appropriately mentions a looming crisis: the progressive sub-segmentation of virtually every cancer type in the genomic era makes the old-style, cast of thousands trial almost impossible to conceive. I share this concern: indeed, it formed a major part of my ASCO Presidential address in 2011. It will be very, very difficult to perform well-powered adjuvant trials if we are addressing a kinase mutation present in 2% of breast or lung or colon cancer. But I regret to say that I remain unconvinced that neoadjuvant trials represent a solution to this very real problem.

The good news in HER2 positive disease is that we have other active agents in the adjuvant pipeline, drugs such as the FDA-approved pertuzumab and T-DM1. There is reason to hope that these will add significantly to the care of early stage HER2-positive disease. Indeed, the FDA approved pertuzumab in the neoadjuvant setting based upon a positive preoperative trial. The FDA, in it press release associated with pertuzumab's neoadjuvant approval, emphasized that this approval was based on the totality of the data, particularly the demonstrable survival benefit in the metastatic setting. Certainly this interesting approach will continue to evolve.

The author is chief of oncology at Stanford University.

Conflict of Interest: An honorarium from Genentech ($500) for speaking at their annual research scientist's scientific retreat.

Berry's Rejoinder

By Donald Berry

As a long-time and ardent admirer of George Sledge as a clinician and as a scientist, I expected insightful and erudite comments from him regarding translating benefits from the neoadjuvant to the adjuvant setting. I was not disappointed. Those readers seeking controversy will be disappointed because there is little difference between us, even less difference than Dr. Sledge may think.

An example of our agreement where Dr. Sledge points to a difference is the issue of translating the benefits of pCR to EFS in clinical trials, as in NeoALTTO vs. ALTTO. He notes the lack of correlation between treatment benefit on pCR and treatment benefit on EFS in the Cortazar et al. meta-analysis where the clinical trial is taken to be the fundamental unit. I consider the patient-level data. The data are the same and therefore it is not surprising that our conclusions are the same. I prefer focusing on the results of individual patients because it mitigates the problems associated with the heterogeneity of and variability across the particular clinical trials in the meta-analysis and it does not rely on having treatment benefits in the trials considered. With the individual patient data in hand one can easily simulate clinical trials. For example, by conditioning on the actual pCR rates in the two treatment arms of each trial involved in the meta-analysis and generating EFS data using the patient-level Kaplan-Meier curves, one would get correlations between pCR and EFS effects very similar to the ones in the Cortazar et al. article.

The major advantage of using the patient-level

data is that it lets me construct a trial that is not one of the trials in the meta-analysis, one such as ALTTO.

In this regard Dr. Sledge says, "If we look at a well-defined biologic subset, such as HER2-positive breast cancer, will past outcomes with one drug confidently predict the results with another novel agent? Dr. Berry's analysis assumes that this is the case. But will this always be a rational biologic assumption?" My answer is no. I should have said it better, but this is what I meant by "An obvious and quite reasonable concern is that the relationship evinced by the HR of 0.39 in the meta-analysis would not apply for a particular experimental therapy. For example, perhaps adding lapatinib to trastuzumab changes some non-responders to having pCRs but without improving those patients' EFS." When I design neoadjuvant trials with EFS as a primary endpoint in line with the FDA's draft guidance, I very specifically consider relationships between pCR and EFS that are different from those in the meta-analysis, and the relationship may be differ for the two arms in the trial. I may include the meta-analysis as a prior distribution of the relationship but using a statistical model I update that distribution based on the actual pCR/EFS results accruing in the trial.

The reason I assumed the meta-analysis relationship between pCR and EFS for NeoALTTO and ALTTO was to make the point that this assumption perfectly predicted ALTTO. This does not mean the meta-analysis will always apply. It doesn't even mean the meta-analysis will apply in predicting a clone of ALTTO. A sample of size 1 cannot lend strong support to any hypothesis, but the NeoALTTO/ALTTO pairing lends some support to the applicability of the Cortazar et al. meta-analysis in drug development. And this pairing should not be viewed as "blocking the rapid path" to development of breast cancer drugs, as claimed by some reports out of ASCO.

For reasons I mentioned in my commentary, the neoadjuvant approach is critical for developing breast cancer drugs. But like the young, vibrant child who has great potential, the approach needs nurturing and encouragement. Biology is the key to building effective oncology drugs and combination therapies, and to eventually curing cancer. But the clinical trial continues to be the final barrier to getting the fruits of biology to market. The neoadjuvant approach enables building sleeker and more informative clinical trials that will play a critical role in getting therapies to the right patients, and to getting them to patients faster.

AACR Changes Its Logo—For the Fifth Time Since 2000

By Tessa Vellek

The American Association for Cancer Research ushered in the year 2000 with a round logo that combined the lamp of knowledge with a map of the Americas and an aspirational slogan in Latin.

The 26-year-old logo gave way to one that looked more corporate. However, AACR didn't stop at just one redesign. It changed the logo four more times.

On July 1, the AACR released its Redesign No. 5, which features blocky letters and bright green accents, and adds a tagline: "Finding Cures Together."

"Our new awareness campaign positions the AACR as a major fundraising and grant-giving organization for highly meritorious, innovative cancer science and medicine," AACR Chief Executive Officer Margaret Foti said in a statement. "The AACR is changing the way it presents itself to both the scientific community and the public, and is providing a visual 'shorthand' message that more clearly and boldly tells the story and the amazing impact of our organization. This is not just a new logo. It is the mark of a new—more public-facing—direction for the AACR."

According to the AACR press office, a small boutique design firm, Allemann Almquist & Jones in Philadelphia, in conjunction with the AACR's communications and marketing departments, designed the newest logo. Officials declined to disclose the cost.

"There is a visual narrative, a connection between the 'R' and the 'C' that reflects the inextricable link between research and the goal of eradicating cancer," Foti's statement continues. "The green color of the logo implies hope, life, and growth. The tagline 'Finding Cures Together' conveys the essential collaboration between the AACR, its research partners around the world, the AACR Foundation, and the funding public as they all work together urgently to address this complex disease."

An AACR spokesman said Foti would be unavailable to discuss the rationale for the redesigns with The Cancer Letter.

Multiple redesigns are unusual for any organization, marketing experts say.

"Unless there's a clear and compelling reason why a logo change is necessary (such as the group changing its name), it should be done sparingly, because it has the potential to confuse constituents," said Dorie Clark, adjunct professor of business administration at Duke University's Fuqua School of Business.

"Logo changes are usually 'fun' projects for boards or marketing committees because everyone has an opinion about what colors and fonts to use. But the real work of marketing an organization takes place at a far deeper level."

The original AACR logo was designed by Bernette Bohen, a medical illustrator and wife of former AACR President Lloyd Law, said James Holland, a professor of medicine, hematology and medical oncology at Mount Sinai Hospital.

The lantern in the center of the logo is Aladdin's lamp, "from which magic could come," Holland said, describing the design. The symbol was overlaid onto an outline of the Americas with a slogan in Latin, *"Ut cancrum vincamus,"* meaning, "That we may conquer cancer."

The redesign in 2000 departed from the round seal, featuring red accents and the acronym AACR with overlapping "A's" and connecting "C" and "R" in italic lettering.

The next three designs kept the basic structure of this 2000 logo, varying the red and gold accents and adding the slogan "Saving lives through research" in 2005, and then a round design to celebrate its centennial in 2007.

During the same time, the American Society of Clinical Oncology changed its logo twice, in 2000 and 2007.

According to tax documents, the AACR revenues were at $68.5 million in 2012, the most recent year for which data are publicly available. This represents a $25 million increase over the 2010 level. The society's gross took a $17 million dip that occurred between 2009 and 2010.

The AACR Foundation's revenues, reported as $38 million in 2012, revealed a similar pattern, dipping $22 million between 2009 and 2010 and then rising again by $21 million by 2012.

NIH Funding Opportunity

Outstanding Investigator Award In Cancer Research Available

NIH has published a funding opportunity announcement for the Outstanding Investigator Award in any area of cancer research.

The objective of the NCI Outstanding Investigator Award is to provide long-term support to experienced investigators with outstanding records of cancer research productivity who propose to conduct exceptional research. The award would allow an institution to nominate a program director or principal investigator for a seven-year R35 grant.

According to the summary, the award is intended to "allow investigators the opportunity to take greater risks, be more adventurous in their lines of inquiry, or take the time to develop new techniques."

"The research projects should break new ground or extend previous discoveries toward new directions or applications that may lead to a breakthrough that will advance biomedical, behavioral, or clinical cancer research," the announcement states.

The earliest application submission date is Sept. 20.

In Brief

Three Physicians Appointed To Leadership Posts at St. Jude

(Continued from page 1)

Weiss was recruited to the institution from the University of Pennsylvania Perelman School of Medicine and the Children's Hospital of Philadelphia, where he was professor of pediatrics and held an endowed chair.

J. Paul Taylor, who joined the St. Jude Department of Developmental Neurobiology in 2008, was appointed chair of the new St. Jude Department of Cell and Molecular Biology. He will also hold the Edward F. Barry Endowed Chair in Cell and Molecular Biology.

Kim Nichols was selected to launch the new Division of Hereditary Cancer Predisposition in the St. Jude Department of Oncology. She currently directs the CHOP Pediatric Hereditary Cancer Predisposition Program. She is also an associate professor of pediatrics at the UPenn Perelman School of Medicine.

AMY ABERNETHY was named chief medical officer and senior vice president of oncology at **Flatiron Health**.

Abernethy is the co-director of both the Duke Center for Learning Health Care and the Duke Cancer Care Research Program.

At Flatiron, Abernethy will collaborate with cancer care providers, life science companies and data partners to solve practical data and analytic problems. She will lead the clinical and oncology data teams. She will be on a leave of absence from the majority of her responsibilities at Duke University.

WILLIAM HOGAN joined the **University of Florida College of Medicine**'s department of health outcomes and policy and will serve as director of biomedical informatics at UF's Clinical and Translational Science Institute.

Hogan will lead the development of a medical informatics training program and support services for researchers who need assistance with managing and analyzing large medical data sets.

He previously served as the chief of the University of Arkansas for Medical Sciences' division of biomedical informatics.

J. ALAN DIEHL joined the **Medical University of South Carolina** as associate director for basic sciences at Hollings Cancer Center. He will also serve as professor in the MUSC Department of Biochemistry & Molecular Biology.

Prior to joining MUSC, Diehl held the position of director of the Cancer Cell Biology Program at the University of Pennsylvania within the Abramson Family Cancer Research Institute and co-director of the Tumor Biology Program in the Abramson Cancer Center.

Diehl's research interests focus on neoplastic growth. He has made seminal contributions to the understanding of how dysregulation of cell division, specifically D-type cyclins, directly contributes to cancerous growth.

His additional research efforts focus on how

tumor cells survive in a harsh tumor environment with a specific interest in how alterations in lipid biosynthesis and signaling contribute to tumor growth and development.

VINCENT O'NEILL was appointed as chief medical officer of **Exosome Diagnostics**.

O'Neill most recently served as global head personalized medicine and companion diagnostics at Sanofi.

Prior to working at Sanofi, he managed the clinical development programs of several oncology therapeutic candidates, including biomarker development, at both Genentech and GlaxoSmithkline. At GlaxoSmithkline, he managed the signal transduction discovery unit from which the first Investigative New Drug application and clinical trial, including patient selection strategy, of an MEK inhibitor (Mekinist) was conducted.

JOSEPH HAYWOOD was named president of the **Federation of American Societies for Experimental Biology**.

In 2012, Haywood served as FASEB vice president for science policy and has also served as chair of FASEB's Animal Care and Experimentation and Public Affairs Committees. Haywood is an active member of two FASEB societies: the American Physiological Society, where he served on its council; and the American Society for Pharmacology and Experimental Therapeutics.

Haywood is professor of pharmacology and toxicology and assistant vice president for regulatory affairs at Michigan State University.

Haywood's research interests are in the area of neurohumoral control of arterial pressure, especially in experimental models of hypertension. He has focused on the action of circulating hormones and diet on neurotransmitter control of the paraventricular nucleus of the hypothalamus in regulating the sympathetic nervous system.

Other appointed FASEB officers include president-elect Parker Antin; vice president for science policy Hudson Freeze; and vice president-elect for science policy Thomas Baldwin.

Antin is professor of cellular and molecular medicine at the University of Arizona and has served as chair of FASEB's NIH Subcommittee. He is a member of the Society for Developmental Biology.

Freeze is a professor of glycobiology and director of the Genetic Disease Program at the Sanford-Burnham Medical Research Institute. He is a member of the Society for Glycobiology.

Baldwin is professor of biochemistry at the University of California, Riverside and represents the American Society for Biochemistry and Molecular Biology on the FASEB Board of Directors.

THOMAS JEFFERSON UNIVERSITY received a $110 million gift from the **Sidney Kimmel Foundation**. The gift will benefit Jefferson Medical College, which was renamed the Sidney Kimmel Medical College at Thomas Jefferson University.

The gift, the largest in the university's history, will create the Caroline Kimmel Endowment Fund for Scholarships, the Sidney Kimmel Capital Fund, the Sidney Kimmel Innovation and Research Fund, and the Sidney Kimmel Presidential Endowment Fund.

STAND UP TO CANCER CANADA was announced by EIF Canada and members of the cancer research community.

They were joined by actors Dan Aykroyd, Jesse Tyler Ferguson and Kyle MacLachlan.

The announcement was made by Calvin Stiller, co-founder of the MaRS Centre in Toronto; Tom Hudson, president and scientific director of the Ontario Institute for Cancer Research; Michael Taylor, of The Hospital for Sick Children and a member of the SU2C-St. Baldrick's Pediatric Dream Team; Pamela Fralick, president and CEO of the Canadian Cancer Society; Sandra Palmaro, co-CEO of the Canadian Breast Cancer Foundation; and Lisa Paulsen, EIF Canada Board Member and president and CEO of The Entertainment Industry Foundation.

The initiative plans to raise funds to support collaborative research teams and education and awareness programs conducted in Canada.

All four of Canada's English language network broadcasters—CBC, City, CTV and Global—will simultaneously air a Canadian-inclusive Stand Up To Cancer Canada special this September.

BRISTOL-MYERS SQUIBB announced a collaboration with Duke University through the Duke Clinical Research Institute focused on clinical trial transparency.

Bristol-Myers Squibb will expand access to a broader set of clinical trial information from in-scope company-sponsored studies and enable an independent scientific review through DCRI of requests from researchers that meet pre-specified requirements.

Clinical trial information being made available for scientific research will include protocols, full clinical study reports and de-identified patient-level data and study-level data for medicines and indications approved in the U.S. and/or Europe for trials completed after January 2008. Information from terminated programs will be available two years after discontinuation.

Bristol-Myers Squibb will also publish CSR synopses athttp://bms.com/clinical_trials/Pages/home.aspx for studies that support a product's marketing authorization application to FDA or the European Medicines Agency shortly after the regulatory approval of the product has been granted.

THE PEW CHARITABLE TRUSTS and the Alexander and Margaret Stewart Trust announced the inaugural class of Pew-Stewart Scholars for Cancer Research.

Five early-career scientists will receive funding for research aimed at finding cures for cancer using approaches that include genetics, pharmacology, and structural biology. They will receive funding over four years and will have the opportunity to collaborate with Pew biomedical scholars and Latin American fellows at Pew's annual biomedical meeting.

The 2014 Pew-Stewart Scholars for Cancer Research are:

Arvin Dar, assistant professor at Mount Sinai School of Medicine, Icahn School of Medicine

Shawn Douglas, assistant professor at the University of California, San Francisco

Andrew Holland, assistant professor at the Johns Hopkins University School of Medicine

Agnel Sfeir, assistant professor at the New York University Langone School of Medicine

Roberto Zoncu, assistant professor at the University of California, Berkeley

Their full abstracts and more information about the program is available on the Pew website.

STEVEN BANGERT, of CoBiz Financial, was named CEO of the Year at the **American Cancer Society Corporate Impact Conference**.

All of the company's 530 employees participating in the company-sponsored health plan have 100 percent coverage of all cancer prevention and early detection screenings, and are reminded to do so with a special email on their birthdays.

Employees receive a paid day off to get a physical, with 95 percent employee participation. Employees also have access to a 100 percent tobacco-free work place and cover Nicotine Replacement Therapy for employees and dependents. The company has also committed to donating more than $120,000 in sponsorship to the American Cancer Society.

The society also recognized several companies for their efforts to reduce employee cancer risk.

CoBiz Financial received the Excellence in Cancer Control award for their promotion of employee health and wellness benefits, policies, and programs.

Delta Air Lines received the Excellence in Employee Engagement and Excellence in Philanthropy award.

IBM Corporation received the Excellence in Employee Giving award for their outstanding employee giving contribution campaign and involvement in Society activities where their employees live and work.

Express Scripts received the Excellence in Tobacco Control award for major improvements to their tobacco policy.

Twenty companies were also presented with the American Cancer Society Excellence in Philanthropy award for their generous support of the society's efforts. The honor is given to corporations that have provided $1 million or more to the society during the previous calendar year through a combination of corporate contributions, in-kind support, cause marketing and sponsorship, employee giving, and/or event fundraising.

This year's winning corporations collectively contributed more than $47 million. They include: Abbott Laboratories, Bank of America, Curves International, Delta Air Lines, Extended Stay America Hotels, General Motors Corporation and Chevrolet, Humble Bundle, IBM Corporation, Kohl's Department Stores and Kohl's Cares, Kroger Company, Lee Jeans, Maurice's, Dressbarn & Lane Bryant, the National Football League, Nucor Corporation, New York State United Teachers, Procter & Gamble, The Walgreen Company, Walmart, WellPoint, and Wells Fargo.

Drug Development

FDA Grants Breakthrough Designation to CTL019 in ALL

FDA granted Breakthrough Therapy status to CTL019, an investigational chimeric antigen receptor therapy for the treatment of pediatric and adult patients with relapsed/refractory acute lymphoblastic leukemia.

The filing was submitted by the University of Pennsylvania's Perelman School of Medicine, which has an exclusive global agreement with Novartis to research, develop and commercialize personalized CAR T cell therapies for the treatment of cancers.

According to the FDA, the designation is intended to expedite the development and review of new medicines that treat serious or life-threatening conditions if the therapy has demonstrated substantial improvement over an available therapy on at least one clinically significant endpoint. The designation includes all of the fast track program features, as well as more intensive FDA guidance.

It is a distinct status from both accelerated approval and priority review, which can also be granted to the same drug if relevant criteria are met.

The European Commission issued marketing authorization approval for Halaven (eribulin) for locally advanced or metastatic breast cancer that has progressed after at least one chemotherapeutic regimen for advanced disease.

Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting, unless patients were not suitable for these treatments.

The authorization for eribulin is based on clinical evidence from two global Phase III trials; EMBRACE and study 301. These studies involved more than 1,800 women.

EMBRACE showed eribulin can prolong median overall survival in heavily pre-treated women with MBC compared to women receiving an alternative treatment of physician's choice by 2.7 months (13.2 vs 10.5 HR 0.81 (95% CI 0.67, 0.96) nominal p=0.014).

Study 301, a head-to-head trial of eribulin vs. capecitabine, had a co-primary endpoint of overall survival and progression-free survival. The study demonstrated a trend favoring improved overall survival with eribulin compared to capecitabine in the intention-to-treat population, although the improvement was not statistically significant.

Women treated with eribulin had a median overall survival of 15.9 months versus 14.5 months with capecitabine (HR 0.879; 95% CI: 0.770-1.003; p=0.056). For women with human epidermal growth factor receptor 2 negative metastatic breast cancer, overall survival was 15.9 months for eribulin vs. 13.5 months for capecitabine (HR 0.838; 95% CI: 0.715-0.983).

Eribulin is a non-taxane, microtubule dynamics inhibitor.Eribulin belongs to a class of antineoplastic agents, the halichondrins, which are natural products, isolated from the marine sponge Halichondria okadai. It is believed to work by inhibiting the growth phase of microtubule dynamics which prevents cell division.

FDA granted Breakthrough Therapy designation to investigational bispecific T cell engager antibody **blinatumomab**, for adults with Philadelphia-negative (Ph-) relapsed/refractory B-precursor acute lymphoblastic leukemia.

The designation was based on the results of a phase II trial of 189 adult patients with Ph- relapsed/refractory B-precursor ALL treated with blinatumomab. Data from the trial were most recently presented at the annual meeting of the American Society of Clinical Oncology and the Congress of the European Hematology Association.

Blinatumomab is an investigational antibody designed to direct the body's cell-destroying T cells against target cells expressing CD19, a protein found on the surface of B-cell derived leukemias and lymphomas.

Bispecific T cell engager antibodies are a type of immunotherapy using modified antibodies designed to engage two different targets simultaneously, thereby juxtaposing T cells to cancer cells. The antibodies help place the T cells within reach of the targeted cell, with the intent of allowing it to inject toxins and trigger apoptosis.

Mylan Inc. launched Carboplatin Injection, 50 mg/5 ml, in multi-dose vials—the generic version of Bristol-Myers Squibb's Paraplatin Injection.

Mylan received final approval from FDA for its Abbreviated New Drug Application for this product, which is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents.

Mylan also received final approval for Carboplatin Injection, 150 mg/15 ml, 450 mg/45 ml, 600 mg/60 ml, in multi-dose vials, and intends to launch them subsequently.