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special articles

Updated Standardized Definitions for Efficacy End Points (STEEP) in Adjuvant Breast Cancer Clinical Trials: STEEP Version 2.0

Sara M. Tolaney, MD, MPH[1,2]; Elizabeth Garrett-Mayer, PhD[3]; Julia White, MD[4]; Victoria S. Blinder, MD[5]; Jared C. Foster, PhD[6]; Laleh Amiri-Kordestani, MD[7]; E. Shelley Hwang, MD, MPH[8]; Judith M. Bliss, MSc[9]; Eileen Rakovitch, MD[10]; Jane Perlmutter, PhD, MBA[11]; Patricia A. Spears, BS[12]; Elizabeth Frank, EdM[1]; Nadine M. Tung, MD[13]; Anthony D. Elias, MD[14]; David Cameron, MD[15]; Neelima Denduluri, MD[16]; Ana F. Best, PhD[6]; Angelo DiLeo, MD, PhD[17]; Lawrence Baizer, PhD[18]; Lynn Pearson Butler, MS[19]; Elena Schwartz, PhD[18]; Eric P. Winer, MD[1,2]; and Larissa A. Korde, MD[20]

abstract

PURPOSE The Standardized Definitions for Efficacy End Points (STEEP) criteria, established in 2007, provide standardized definitions of adjuvant breast cancer clinical trial end points. Given the evolution of breast cancer clinical trials and improvements in outcomes, a panel of experts reviewed the STEEP criteria to determine whether modifications are needed.

METHODS We conducted systematic searches of ClinicalTrials.gov for adjuvant systemic and local-regional therapy trials for breast cancer to investigate if the primary end points reported met STEEP criteria. On the basis of common STEEP deviations, we performed a series of simulations to evaluate the effect of excluding non–breast cancer deaths and new nonbreast primary cancers from the invasive disease–free survival end point.

RESULTS Among 11 phase III breast cancer trials with primary efficacy end points, three had primary end points that followed STEEP criteria, four used STEEP definitions but not the corresponding end point names, and four used end points that were not included in the original STEEP manuscript. Simulation modeling demonstrated that inclusion of second nonbreast primary cancer can increase the probability of incorrect inferences, can decrease power to detect clinically relevant efficacy effects, and may mask differences in recurrence rates, especially when recurrence rates are low.

CONCLUSION We recommend an additional end point, invasive breast cancer–free survival, which includes all invasive disease–free survival events except second nonbreast primary cancers. This end point should be considered for trials in which the toxicities of agents are well-known and where the risk of second primary cancer is small. Additionally, we provide end point recommendations for local therapy trials, low-risk populations, noninferiority trials, and trials incorporating patient-reported outcomes.

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INTRODUCTION

In 2007, a group of breast cancer experts from the National Cancer Institute (NCI) and the National Clinical Trials Network proposed standardized definitions for efficacy end points in adjuvant breast cancer therapeutic trials, widely known as the Standardized Definitions for Efficacy End Points (STEEP). Their proposed end point definitions are summarized in Table 1.[1] The STEEP criteria have since been used and referred to broadly in breast cancer clinical trials. The expert panel that proposed the original STEEP criteria endorsed invasive disease–free survival (IDFS) as a less ambiguous end point than disease-free survival (DFS), which had historically varied significantly across trials in terms of the events included. The definition for IDFS included invasive local, regional, and distant recurrences; contralateral breast cancer; second nonbreast primary cancer; and death from any cause. IDFS was meant to specifically exclude in situ cancer events (ipsilateral and/or contralateral ductal carcinoma in situ [DCIS], lobular carcinoma in situ [not deemed a preinvasive cancer], and all in situ cancers of nonbreast sites). A separate end point termed IDFS-DCIS was proposed for trials in which inclusion of DCIS events was deemed appropriate.[1]

Breast cancer clinical trials and treatments have evolved substantially since the STEEP criteria were established. Advances include improved sensitivity of diagnostic imaging, development of multiple immunohistochemistry markers that distinguish disease origin, and clinical acknowledgment of the need for pathologic confirmation of recurrence. In addition, improvements in breast cancer management have decreased the risk of recurrence, leading to a relatively higher likelihood of death from non–breast cancer causes in adjuvant trial participants.[2,3] Moreover, because of the improvements in managing treatment-related toxicities and a commitment to enrolling a group of patients more representative of the actual affected population, patients enrolled in clinical trials increasingly include older patients. These patients have a higher risk of dying from causes

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Given the evolution of breast cancer clinical trials and improvements in outcomes, are modifications to the STEEP criteria needed?

Knowledge Generated

An additional endpoint, invasive breast cancer-free survival, which includes all invasive disease-free survival events except second nonbreast primary cancers, can be considered for trials in which the toxicities are well known and where risk of second primary cancer is small. Additional end points for local therapy trials, low-risk populations, noninferiority trials, and trials incorporating patient-reported outcomes are also included.

Relevance

The choice of a primary end point is critical for detecting a treatment effect and including events that have similar rates in the treatment groups may dilute treatment differences and can increase the likelihood of a false inference of noninferiority.

unrelated to their breast cancer or treatment. This evolution in breast cancer treatment and outcomes led the NCI and National Clinical Trials Network Breast Cancer Steering Committee to convene an international group of experts to reassess the STEEP criteria and to determine whether modifications were needed. The panel focused on end points for the adjuvant setting.

STEEP Adherence

We assessed utilization of STEEP criteria in phase III adjuvant trials published after January 1, 2008 (after the original STEEP publication) with a completion date for the primary analysis before January 1, 2020. Deviations from STEEP definitions were discussed by the panel and these deviations and discussions were used to inform the proposed updated recommendations. The review was conducted in ClinicalTrials.gov using the following search criteria:

1. Breast cancer (for Condition);
2. Adjuvant (for Other terms);
3. Active, not recruiting, Suspended, Terminated, or Completed (for Status); and
4. Phase 3 (for Study phase).

Of the resulting 83 trials, nonadjuvant trials, those without primary efficacy end points, and those without a full manuscript publication (because of inability to fully assess end point definition) were excluded. The search yielded 11 adjuvant phase III breast cancer trials with primary efficacy end points (Table 2).[4-14] Of these, three had primary end points that fully complied with the STEEP criteria, four used STEEP definitions but not the corresponding end point names (eg, used STEEP IDFS but called it DFS), and four used definitions not included in the original STEEP manuscript.

Since the initial search did not produce a comprehensive list, we broadened our search to include all phase III adjuvant trials that had a primary efficacy end point, listed results, and had a primary completion date between January 1, 2010 and January 1, 2020 (Data Supplement, online only).[4-6,9,12,15-37] The resulting list is still not comprehensive but adequately reflects variability in end points across trials and deviations from end point definitions. Trials were divided into five categories: superiority, local therapy, endocrine, low-risk population, and noninferiority trials.

Superiority Trials

Most superiority trials either used or referenced a STEEP definition and stated which events were not included (Data Supplement). In trials that deviated from STEEP, the most common deviation was exclusion of second nonbreast primary cancers. While developing the original STEEP guidelines, inclusion of second nonbreast primary cancer in the IDFS definition was strongly debated, given the potential disadvantage of including events that are not related to the cancer or the treatment being studied, which might dilute the efficacy effect. However, IDFS can identify events that may be related to treatment, such as uterine cancer from tamoxifen. Additionally, it avoids the potential problem of missing distant recurrences that were erroneously diagnosed as new primary cancers. Because second cancers are usually serious, often affect overall survival (OS), and might not be distinguishable from breast cancer or treatment-related events, the original STEEP panel favored including them in the IDFS definition. The three trials in our review that excluded second nonbreast primary cancers all examined the addition of new targeted therapies to standard chemotherapy and trastuzumab-based therapy for early-stage breast cancer,[5,6,9] and all three led to US Food and Drug Administration (FDA) approval of the agents in early-stage breast cancer.

Modeling the limitations of IDFS. Common wisdom suggests that for time-to-event end points, such as IDFS or recurrence-free interval (RFI), more events means more power. However, having more events does not necessarily translate to increased power and may decrease power

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TABLE 1. Standardized Definitions for Breast Cancer Clinical Trial End Points in the Adjuvant Setting and New Definitions Proposed for STEEP 2.0

Adjuvant Trials

End Point	Invasive IBTR	Local-Regional Invasive Recurrence	Distant Recurrence[a]	Death From Breast Cancer	Death From Non–Breast Cancer Cause	Death From Unknown Cause	Invasive Contralateral Breast Cancer[b]	Ipsilateral DCIS	Contralateral DCIS	Second Primary Invasive Cancer (nonbreast)[c]
OS				X	X	X				
DFS-DCIS	X	X	X	X	X	X	X	X	X	X
IDFS	X	X	X	X	X	X	X			X
DDFS			X	X	X	X				X
DRFS			X	X	X	X				
RFS	X	X	X	X	X	X				
RFI[d]	X	X	X	X						
Breast cancer–free interval	X	X	X	X			X	X	X	
Distant RFI			X	X						
IBCFS	**X**	**X**	**X**	**X**	**X**	**X**	**X**			

Local-Regional Therapy Trials

End Point	Invasive Ipsilateral Tumor Recurrence in Breast or Chest Wall[e]	Ipsilateral DCIS	Nodal Recurrence in Ipsilateral Axilla, SCL, or Internal Mammary Regions	Contralateral Invasive Cancer or DCIS
LRR	**X**	**X**	**X**	
IBR	**X**	**X**		
IBR-invasive	**X**			
IBR-DCIS		**X**		
Regional nodal recurrence			**X**	
New contralateral primary				**X**

NOTE. Lobular carcinoma in situ is not included as an event in these definitions as it is not generally considered to be a direct precursor of breast cancer. New definitions are shown in bold: (1) adjuvant trial end points were proposed in original STEEP, except for IBCFS; (2) local-regional therapy trial end points were not proposed in the original STEEP. Adapted from original STEEP paper.[1]

Abbreviations: DCIS, ductal carcinoma in situ; DDFS, distant disease–free survival; DFS-DCIS, disease-free survival-ductal carcinoma in situ; DRFS, distant relapse–free survival; IBCFS, invasive breast cancer–free survival; IBR, ipsilateral breast recurrence; IBR-DCIS, ipsilateral breast recurrence-ductal carcinoma in situ; IBTR, ipsilateral breast tumor recurrence; IDFS, invasive disease–free survival; LRR, locoregional recurrence; OS, overall survival; RFI, recurrence-free interval; RFS, recurrence-free survival; SCL, supraclavicular; STEEP, Standardized Definitions for Efficacy End Points.

[a]Site of first metastasis should be reported using the appropriate common data element term.

[b]The term contralateral invasive breast cancer is preferred to second primary breast cancer as it is less ambiguous. Ipsilateral invasive breast cancers are presumed to be a recurrence.

[c]Second nonbreast primary cancers should not include squamous or basal cell skin cancers or new in situ carcinomas of any site.

[d]Interval signifies time from random assignment or registration to event.

[e]Can include in-breast recurrence or new primary after lumpectomy, chest wall recurrence after mastectomy, or both, depending on the patient population specified in eligibility criteria.

when some events included in the outcome have the same rates in the two arms of the study and others have different rates. To understand the potential impact of including second nonbreast primary cancer diagnoses on the primary end point that may or may not be related to disease or treatment, simulations were performed that assumed a two-arm study, comparing a standard-of-care (SOC) therapy with an experimental therapy. Traditional IDFS was compared with IDFS with second nonbreast primary cancers excluded; we termed this modified end point invasive breast cancer–free survival (IBCFS). Figure 1 demonstrates a superiority trial that aims to detect a 95% 3-year IBCFS in the experimental arm versus 92% in the SOC arm (ie, detection of a hazard ratio [HR] of 0.615 [red points]). This trial has approximately 90% power with a sample size of 2,000 patients with a two-sided alpha of .05, assuming 3

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TABLE 2. Trials Identified in the Review of STEEP 1.0 Adherence

Trial	Type of Intervention	Study Arms	Primary End Point	Used STEEP Definition?	Referenced STEEP 1.0?
D-CARE[4]	Bone-targeted treatment	SOC ± denosumab	BMFS	No	No
APHINITY[5]	Targeted therapy	Chemotherapy + trastuzumab ± pertuzumab	IDFS[a]	No	Yes
KATHERINE[6]	Targeted therapy	Trastuzumab *v* T-DM1	IDFS[a]	No	Yes
PRESENT[7]	Vaccine	GM-CSF ± NP-S	Either DFS-DCIS or IDFS	Yes[b]	No
NSABP B47[8]	Targeted therapy	Chemotherapy ± trastuzumab	IDFS	Yes	No
ExteNET[9]	Targeted therapy	Trastuzumab ± neratinib	IDFS[a]	No	No
PlanB[10]	Chemotherapy	Epirubicin/cyclophosphamide/docetaxel (four cycles) *v* docetaxel/cyclophosphamide (six cycles)	IDFS (but they called it DFS)	Yes[b]	No
SOLD[11]	Targeted therapy (reduced duration)	Docetaxel + trastuzumab (9 weeks) → FEC *v* Docetaxel + trastuzumab (9 weeks) → FEC + trastuzumab (to complete 1 year)	IDFS (but they called it DFS)	Yes[b]	No
TITAN[12]	Chemotherapy	Doxorubicin + cyclophosphamide → ixabepilone *v* Doxorubicin + cyclophosphamide → paclitaxel	RFS	No[b]	No
DBCG-07-READ[13]	Chemotherapy	Cyclophosphamide + docetaxel ± epirubicin	IDFS	Yes	No
NSABP B-46-I[14]	Targeted therapy	TC6, TAC6, or TC6 plus bevacizumab	IDFS	Yes	No

Abbreviations: BMFS, bone metastasis–free survival; DFS, disease-free survival; DFS-DCIS, disease-free survival-ductal carcinoma in situ; FEC, fluorouracil, epirubicin, and cyclophosphamide; GM-CSF, granulocyte-macrophage colony-stimulating factor; IDFS, invasive disease–free survival; NP-S, nelipepimut-S; RFS, recurrence-free survival; SOC, standard of care; STEEP, Standardized Definitions for Efficacy End Points; TAC6, docetaxel + doxorubicin + cyclophosphamide ×6 cycles; TC6, docetaxel + cyclophosphamide ×6 cycles; T-DM1, trastuzumab emtansine.

[a]IDFS indicates IDFS with second nonbreast primary cancer excluded.

[b]Used the STEEP definition, but not the corresponding STEEP end point name.

years of enrollment and 3 years of follow-up after the last patient is enrolled.

To investigate the impact of second nonbreast cancers on the IDFS end point, an annual rate of 1% was assumed for this event in the SOC and 0.5%, 1%, and 2% in the experimental arms, respectively (Figs 1A-1C). Figure 1 shows that the estimated HR for IBCFS is insensitive to these events, even when the rates vary between the SOC and experimental arms because of censoring event times for these nonrecurrence events (ie, the HRs for the two scenarios are essentially the same for all three panels of Fig 1 for IBCFS). However, the HR for IDFS varies for different rates of second primary diagnosis. Even when the rate of second nonbreast cancers is the same in the SOC and experimental arms (1%; Fig 1B), the HR is higher (HR = 0.71) and power is lower (81%) compared with using IBCFS as the primary end point. Thus, adding events to an end point will not necessarily increase the power: if the event added has the same rate in the two treatment groups, the inclusion of the event will dilute the treatment effect, increasing the chance of a false-negative result. When the rate in the experimental arm is higher (2%) than in the SOC arm (1%), the power drops to 5% and the HR becomes 0.99 (Fig 1C). Conversely, when the rate in the experimental arm is lower (0.5%), the power increases and the HR moves further from 1 (power = 99%; HR = 0.58; Fig 1A). Thus, if the event rate of second nonbreast cancers differs in the two treatment groups (possibly because of chance imbalances), the HR and the power will both be affected, and IDFS will favor the arm with the lower rate.

This highlights the challenge of incorporating multiple events in the same end point: it is not possible to distinguish which events are driving the differences between arms. Figure 1 reveals that inclusion (or exclusion) of events from the primary end point can have a dramatic effect on inferences in the trial, depending on the relative rates of these events. When there is no difference in the event rates of second nonbreast cancers between the SOC and experimental arms, including them will dilute the observed efficacy effect of interest and decrease the power. However, excluding them could mask unanticipated toxicity effects, and if excluded, toxicity effects should be considered as a separate (secondary) end point to ensure differences in treatment arms are identified if they exist (see the Data Supplement regarding further implications on sample size).

Also shown in Figure 1 are analogous results to those described above; but when a superiority trial assumes a 3-year IBCFS of 72% versus 75% (blue points), the effects on

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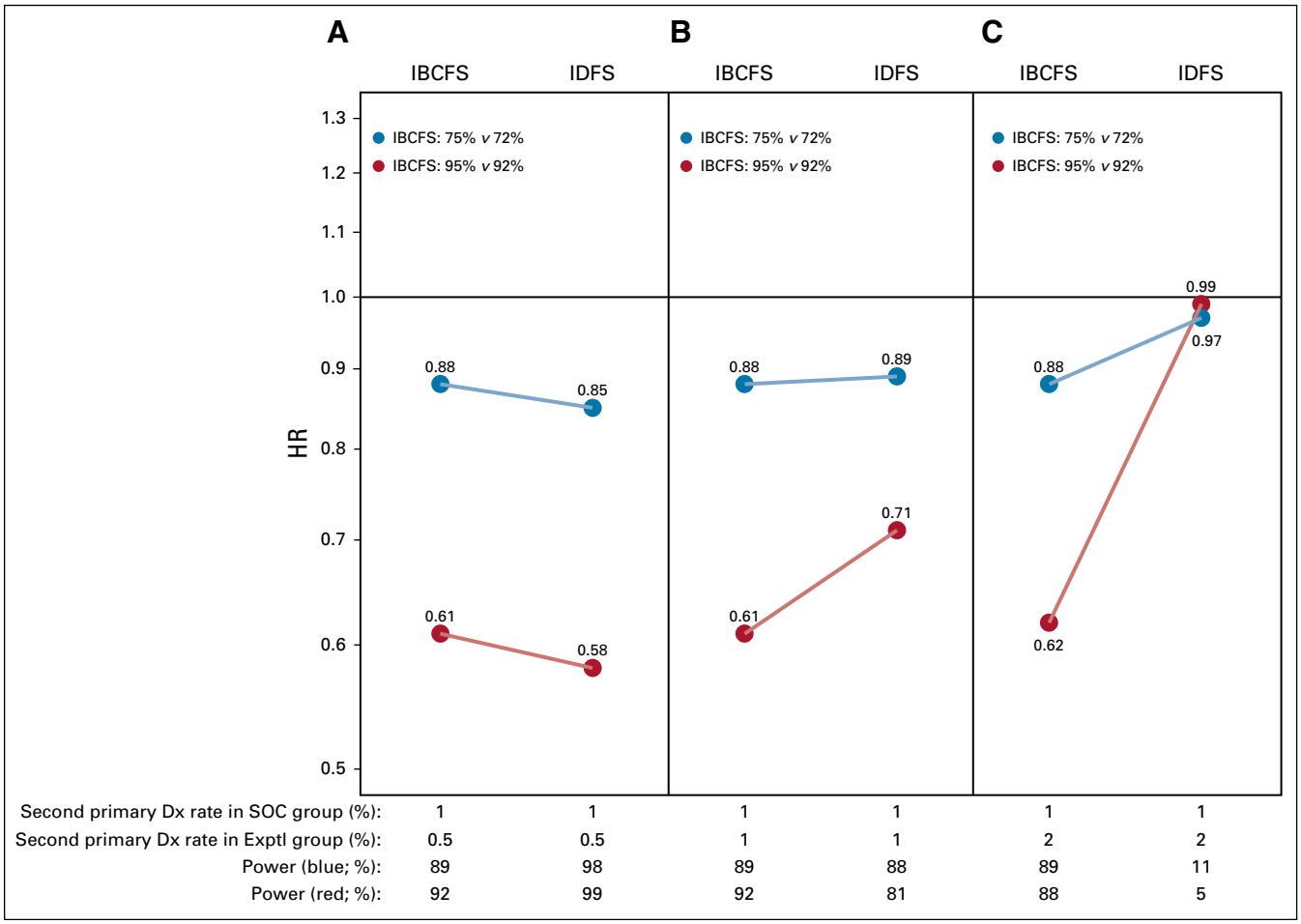

FIG 1. Comparison of IDFS versus IBCFS in the superiority design setting. Assumed new non-BC second primary cancer rate in the SOC arm is 0.01 annually and in the Exptl arm is (A) 0.005 (lower rate), (B) 0.01 (same rate), or (C) 0.02 (higher rate) annually. Two-sided α of .05 and 3 years of follow-up. Data simulated under the two models. Red: hypothesis of 92% 3-year IBCFS (SOC) versus 95% (Exptl) (HR = 0.615); sample size of 1,000 per arm. Blue: hypothesis of 72% 3-year IDFS without new non-BC second primary cancer events (SOC) versus 75% (Exptl) (HR = 0.876); sample size of 3,341 per arm. BC, breast cancer; Dx, diagnosis; Exptl, experimental; HR, hazard ratio; IBCFS, invasive breast cancer–free survival; IDFS, invasive disease–free survival; SOC, standard of care.

power and the estimated HRs trend in the same direction as those in the previous example. However, the effects of varying rates of second nonbreast cancers on the HR and power are substantially lower, demonstrated by the much smaller differences in IDFS versus IBCFS for the blue versus the red points. Thus, trials that have low event rates are particularly sensitive to the number and types of events that are included in the primary end point.

Figure 2 provides analogous results to Figure 1 in a noninferiority de-escalation setting, demonstrating that an event with a low rate can have a substantial effect on inferences when the rate of recurrence is low, leading to an increased chance of falsely inferring noninferiority when, in fact, inferior effects of treatment have been masked by inclusion of unrelated events (Data Supplement).

On the basis of our review and these results, IBCFS, which includes all events in IDFS except second nonbreast cancers, is proposed (Table 1). IBCFS has already been used in numerous trials that have led to FDA approval of drugs in the adjuvant setting and may be preferred over IDFS in superiority trials if the intervention being assessed has been well-studied in the population likely to be enrolled in the trial and is known not to cause second nonbreast cancers. Second nonbreast primary cancers should still be ascertained, and standard IDFS should be reported as a secondary outcome. The IBCFS end point should only be used in trials in which the events that contribute to the primary and secondary outcomes can be adequately adjudicated. If a trial is conducted in lower-resource settings where imaging and other diagnostics cannot distinguish metastases from second nonbreast cancers, this end point is not optimal. Additionally, it is important that long-term follow-up be conducted and reported to better understand late events and toxicities and that all STEEP end points be reported so that a better understanding of events and end points can be ascertained.

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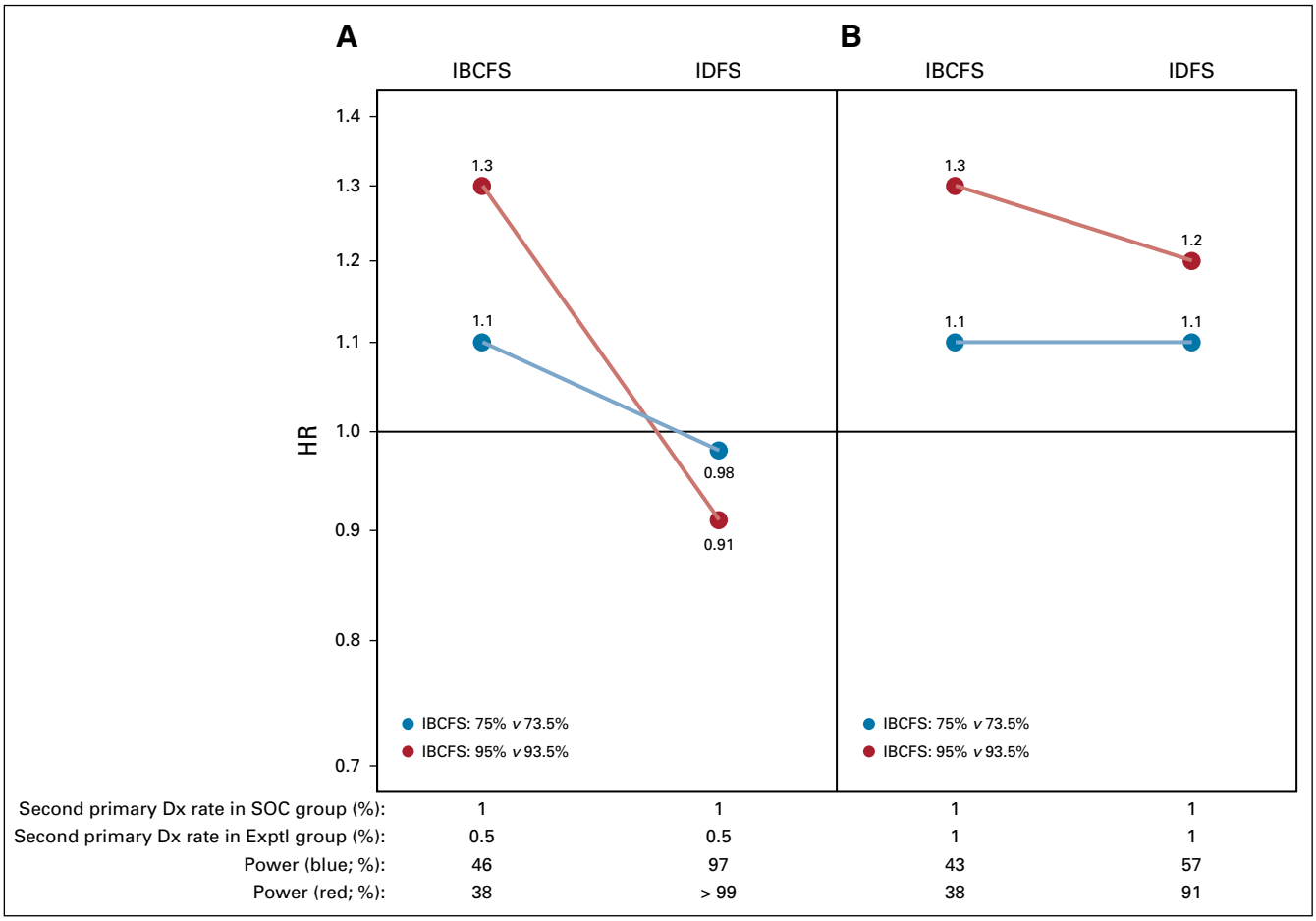

FIG 2. Comparison of IDFS versus IBCFS in the noninferiority, de-escalation design setting. Assumed new non-BC second primary cancer rate in the SOC arm is 0.01 annually and in the Exptl arm is (A) 0.005 (lower rate) or (B) 0.01 (same rate) annually. Five years of follow-up; inference on the basis of upper limit of 90% CI for HR. Data simulated under the two models. Red: hypothesis of 95% 5-year IBCFS (SOC) versus 93.5% (Exptl) (HR = 1.31); sample size of 1,000 per arm. Blue: hypothesis of 75% 5-year IDFS without new non-BC second primary cancer events (SOC) versus 73.5% (Exptl) (HR = 1.07); sample size of 2,750 per arm. BC, breast cancer; Dx, diagnosis; Exptl, experimental; HR, hazard ratio; IBCFS, invasive breast cancer–free survival; IDFS, invasive disease–free survival; SOC, standard of care.

Local Therapy Trials

To understand the typical end points used in adjuvant local therapy trials, we searched ClinicalTrials.gov for local therapy trials using the following search criteria:

1. Breast cancer (for Condition);
2. Adjuvant (for Other terms);
3. Active, not recruiting, Suspended, Terminated, or Completed (for Status); and
4. Phase 3 (for Study phase).

Since these types of trials and end points were not discussed in the original manuscript, we extended this search to trials that started on or after January 1, 1999 and had primary completion on or before January 1, 2020. Of the 181 trials identified, only three were local therapy trials: RTOG-9804,[38] ACOSOG-Z0011,[39] and APBI-IMRT-Florence.[40] The primary end points were ipsilateral breast tumor recurrence (IBTR), 10-year OS, and 5-year IBTR, respectively (Table 3).[38-40] As this search did not yield a comprehensive list, we reviewed a wider collection of adjuvant phase III local therapy trials in breast cancer (Data Supplement).[38,41-52]

Surgical and radiotherapy trials. As improvements in systemic therapy have reduced the risk of distant recurrence, many recent trials have focused on optimizing local therapy. These include randomized trials of whole-breast radiotherapy (RT) versus observation following breast-conserving therapy,[38,49] whole-breast versus partial-breast RT,[42,46,48] and local excision versus observation[41,43-45,47,50,51] (Data Supplement). For these trials, IBTR was the predominant primary end point. The composite end point IBTR does not allow discrimination of histologic type (invasive or DCIS) or location of in-breast recurrence. We, therefore, recommend alternative locoregional end points that differentiate these events (Table 1). These end points will provide more informative data on cancer progression and therapeutic effect (eg, comparison of in-field versus out-of-field recurrences).

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TABLE 3. Local Therapy Trials Identified in ClinicalTrials.gov

Trial	Type of Intervention	Study Arms	Primary End Point
RTOG-9804[38]	Radiation	Optional tamoxifen ± whole-breast RT	IBTR
ACOSOG-Z0011[39]	ALND	Whole-breast RT ± ALND	10-Year OS
APBI-IMRT-Florence[40]	Radiation	Whole-breast RT *v* accelerated partial-breast RT	5-Year IBTR

Abbreviations: ALND, axillary lymph node dissection; IBTR, ipsilateral breast tumor recurrence; OS, overall survival; RT, radiation therapy.

We recommend a new composite end point, ipsilateral breast recurrence (IBR), defined as the development of a subsequent invasive breast cancer (either a recurrent cancer or a new primary) or DCIS in the ipsilateral breast or on the chest wall (Table 1). The terms IBR-invasive and IBR-DCIS can be used in trials where distinguishing invasive from DCIS local recurrences is critical. The quadrant location of both the primary and recurrence should be recorded if feasible, to distinguish between recurrences within or outside of the tumor bed, or outside of the radiated field. Contralateral breast tumor recurrence, including invasive cancer and DCIS, should continue to be recorded as a separate locoregional end point, and a competing risks approach for analysis should be considered.

Regional nodal treatment. Randomized trials of regional nodal treatment include trials of nodal RT versus none and trials of axillary nodal dissection versus nodal RT, either in the adjuvant setting or following neoadjuvant treatment. Although some reported trials used end points contained within STEEP 1.0, the panel recommends including an additional end point: regional nodal recurrence, defined as tumor recurrence in lymph nodes in the ipsilateral axilla, supraclavicular fossa, or internal mammary region. We also recommend explicitly indicating the location of the nodal recurrence where possible. We propose the inclusive end point locoregional recurrence to include ipsilateral breast or chest wall recurrence of invasive cancer or DCIS and any ipsilateral recurrence in these nodal groups. These end points are particularly relevant for trials of de-escalation of axillary nodal surgery.

Endocrine Therapy Trials

Endocrine therapy trials were given special consideration in the original guidelines, which noted inconsistencies in the definition of DFS among adjuvant trials comparing aromatase inhibitors with tamoxifen. Since the incidence of contralateral breast primaries is altered by endocrine therapy, it is important to include these in the primary end point to adequately characterize the benefits of the treatment. However, these events may not be as important as distant recurrences to different groups of patients. For example, those who have had bilateral mastectomies are generally not considered to be at sufficient risk of a contralateral primary breast cancer for that benefit to justify therapy. Patients who experience symptomatic toxicities may decline to continue therapy if it does not prevent a distant recurrence. Thus, as was noted in the original guidelines,[1] publications should include a table detailing the prevalence of event type (ipsilateral, contralateral, and distant) by study arm. This allows for clinicians to individualize the discussion of risks and benefits of the intervention for a patient's clinical situation and treatment goals.

Low-Risk Populations

When the anticipated event rate in a treated population is low, a randomized trial may not be feasible given the large sample size that would be required to demonstrate a treatment effect. If historical data exist for the anticipated event rate with the standard of care, a single-arm trial that identifies a clinically acceptable event rate with a new treatment may be acceptable.

Two recent examples of single-arm trial designs that influenced the standard of care for early-stage breast cancer are the low-risk arm of TAILORx[53] and APT.[54,55] In TAILORx, on the basis of robust retrospective data that failed to demonstrate a benefit for adjuvant chemotherapy in patients with low Oncotype Dx recurrence score,[56] patients with a recurrence score of 0-10 were treated with endocrine therapy alone. These patients had a 5-year IDFS of 93.8% (95% CI, 92.4 to 94.9) and RFI of 99.3% (95% CI, 98.7 to 99.6),[53] confirming endocrine therapy alone as the preferred treatment and the dominance of non–breast cancer events in such a population.

Similarly, the APT trial prospectively assessed whether a systemic therapy regimen (paclitaxel and trastuzumab) was associated with a clinically acceptable event rate in patients with small, node-negative human epidermal growth factor receptor 2–positive breast cancers. This trial demonstrated a 7-year IDFS of 93% (95% CI, 90.4 to 96.2) and a 7-year RFI of 97.5% (95% CI, 95.9 to 99.1).[54,55] Although the APT study cannot conclude that treatment with paclitaxel and trastuzumab is better than no therapy, the low event rate suggests that escalating therapy by using more intensive regimens, such as those administered in the pivotal adjuvant studies, is unlikely to produce better outcomes.

When choosing an end point for a trial in patients at a relatively low risk of distant or local recurrence, it is important to acknowledge that IDFS captures events such as new contralateral primary breast cancers and deaths from other causes that do not reflect a recurrence of the initial breast cancer. With long follow-up, the frequency of these events increases, and their occurrence may dilute the

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effect of treatment on the end point. RFI, which includes invasive locoregional and distant recurrences and deaths as a result of breast cancer (but not contralateral breast cancer, second nonbreast primary cancers, and non–breast cancer death), may better describe the relevant event rate in this patient population and should be considered in these settings. However, we acknowledge that in older patient populations, a comparison of all-cause mortality may also be relevant, to provide context for cancer-specific mortality. To evaluate the impact of including non–breast cancer deaths in low-risk patient populations, simulations were performed similar to those shown in Figure 1 (Data Supplement).

If RFI is used as the primary end point, IDFS should still be presented as a secondary end point since it has the advantage of potentially uncovering previously unidentified treatment toxicities.

Noninferiority Trials

Noninferiority trials are designed to demonstrate that an alternative treatment is not less effective than a standard treatment by a prespecified amount (noninferiority margin). This trial design has been increasingly used to assess treatment de-escalation, either by using a new, less toxic agent or by assessing a shorter duration of therapy or omission of a treatment modality.

Critical to the design of noninferiority trials is the identification of a clinically acceptable noninferiority margin. Noninferiority trials should include careful adverse event reporting, especially if outcomes are similar in trial arms, as the adverse event profile may be essential for making treatment decisions. Historically, cross-trial comparison has been complicated by the use of different end point definitions and noninferiority thresholds in different trials conducted in similar populations. The MINDACT[57] trial and the randomized portion of TAILORx[22] both assessed whether chemotherapy could be omitted in patients defined by a genomic profile; however, the studies used different primary end points (5-year IDFS in TAILORx; distant metastasis–free survival in MINDACT) and different thresholds. Both trials achieved results well within the specified noninferiority thresholds, but it is difficult to compare results since different end points and noninferiority thresholds were used (Table 4).

Modeling the limitations of IDFS. As demonstrated in Figure 2 and described above, events with low rates can affect estimation of HRs and the effects are more dramatic in low-risk populations, leading to increased chance of falsely concluding noninferiority when unrelated events are included in end point definitions. Noninferiority trials are particularly relevant in low-risk populations as the avoidance of toxicity is more important when the expected risk of recurrence is low. Thus, as above, consideration of IBCFS or RFI as the primary end point may be warranted so that events captured are a true reflection of therapy administered. Comparisons of RFI and RFS in the noninferiority, de-escalation design setting are shown in the Data Supplement. The results are similar to those for comparing IDFS and IBCFS.

Patient-Reported Outcomes as a Trial End Point

An important goal in a randomized controlled trial of adjuvant therapy is to provide clinically relevant information that can inform shared decision making. Including patient-reported outcome (PRO) assessments in clinical trials can provide information about a patient's health that is important in discussions between patients and their clinicians. Validated PRO assessments that can help inform decision making should be included whenever possible. For example, PRO-Common Terminology Criteria for Adverse Events can be used to assess symptomatic adverse events to measure safety and tolerability from patients' perspectives.[58] Furthermore, if PROs are critical to the overall trial objectives, the study should be designed to accommodate them. For example, a PRO may be classified as a co-primary rather than secondary end point, with the type I error divided between primary end points. Importantly, PRO results should be reported concurrently with efficacy results so that both sets of results may be interpreted together to provide a balanced evaluation of advantages and disadvantages to each arm of a trial. This is particularly vital in noninferiority studies where patients and their clinicians will need to weigh the possible loss of efficacy against the potential gain in quality of life.

Regulatory Considerations

The primary end point of an oncology clinical trial can serve different regulatory purposes (eg, a clinical end point that represents clinical benefit for regular or traditional approval, such as OS; a surrogate end point to support traditional approval, such as IDFS; or a surrogate end point to support an accelerated approval, such as overall response rate). The determination is generally based on the specific disease and is dependent on factors such as effect size, available therapy, disease setting, and the risk-benefit relationship. Historically, the use of IDFS as the primary end point in adjuvant breast cancer trials has conferred advantages, but it is also subject to important disadvantages as discussed above. Furthermore, the definition of IDFS has varied among trials, and it includes non–breast cancer deaths and second nonbreast primary cancers. The FDA has released a guidance for sponsors to select appropriate end points for oncology trials that will support marketing applications.[59] It is recommended that sponsors meet with the FDA before submitting protocols intended to support a new drug or biologics license marketing application. The FDA has advised that they will ensure that these meetings include a multidisciplinary team of oncologists, statisticians, clinical pharmacologists, and external expert consultants as needed. Sponsors can request a special

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TABLE 4. Important Considerations by Type of Trial

Trial Type	Considerations
Superiority trials	IBCFS may be preferred over IDFS if the intervention being assessed has been well-studied in the population likely to be enrolled in the trial and is known not to cause second nonbreast cancers Second nonbreast primary cancers should still be ascertained, and standard IDFS should be reported as a secondary outcome The IBCFS end point should only be used in trials in which the events that contribute to the primary and secondary outcomes can be adequately adjudicated
Endocrine therapy trials	DFS is a reasonable end point, but it is critical to provide breakdown of the prevalence of each type of event (ipsilateral, contralateral, and distant) by study arm
Low-risk trials	RFI may better describe the relevant event rate in this patient population and should be considered, and IDFS should also be reported
Noninferiority trials	Consideration of IBCFS or RFI as the primary end point may be warranted so that the events captured are a true reflection of the therapy administered IDFS should also be reported
Breast surgery and radiation therapy trials	Consider IBR as the primary end point (see Table 1 for local-regional therapy end points)

Abbreviations: DFS, disease-free survival; IBCFS, invasive breast cancer–free survival; IBR, ipsilateral breast recurrence; IDFS, invasive disease–free survival; RFI, recurrence-free interval.

protocol assessment that provides confirmation of the acceptability of study design and end points to support drug marketing applications.

SUMMARY

The original STEEP criteria were established for adjuvant breast cancer trials, recognizing that it is critical to select the appropriate multievent end point to describe treatment benefits and risks and to allow for cross-trial comparisons. This article addresses end points for phase III trials of either adjuvant or local-regional therapy trials for patients with breast cancer. We did not consider end point selection for trials assessing neoadjuvant breast cancer therapies, or adjuvant therapy after neoadjuvant therapy, which were reviewed by Fumigalli et al[60] in an effort led by the Breast International Group and the NCI-sponsored North American Breast Cancer Group. However, we think our proposed revision of adjuvant trial end points could be applicable to longer-term end points of such studies.

The simulations described in this article illustrate that the choice of primary end point is critical for detecting a treatment effect and raise several important points to consider:

1. When choosing an end point that includes multiple events, it is often difficult to identify which events are driving the estimated HR. Even if the HR is close to 1, it cannot be inferred that the treatments have similar efficacy and toxicity effects—in fact, these could be offsetting each other, with one treatment having higher toxicity yet lower efficacy than the other.
2. Including events that have the same or similar rates in treatment groups will compromise power and may dilute other treatment differences in superiority trials. In noninferiority trials, it can increase the likelihood of false inference of noninferiority.
3. When events of interest are relatively rare, the impact of including events that are unaffected by treatment is more substantial. However, in situations when events are rare, it is risky to assume, rather than test, whether or not the events may be treatment related.

When agents being studied have well-known toxicity profiles and have been shown not to increase the risk of death, occurrence of second nonbreast primary cancers, or other serious adverse events, IBCFS and RFI should be considered as alternatives to IDFS. When choosing an appropriate end point, characteristics of the population being studied, including comorbidities and competing risks, should be considered. Regardless of the primary end point, data pertaining to both IDFS and IBCFS (or other relevant complementary end points) should be captured and reported in study results, with clear rationale of which end point was a priori selected as the primary end point. RFI, which includes invasive locoregional and distant recurrences and breast cancer–related deaths, may better describe the relevant event rate in low-risk patient populations and thus should be used in these settings. Inclusion of at least one other STEEP end point in a secondary objective is essential to understand how treatments affect different end points. Additionally, it is important for trials to have long-term follow-up not only to understand efficacy over time but also to evaluate late toxicities. Finally, inclusion of appropriately measured and powered PROs, and timely reporting of their results, ideally concurrently with the efficacy end points, is important to ensuring that study results may be used to best inform clinical decision making by patients and their doctors.

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AFFILIATIONS

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA
[2]Harvard Medical School, Boston, MA
[3]American Society of Clinical Oncology, Alexandria, VA
[4]The Ohio State University Comprehensive Cancer Center, Columbus, OH
[5]Memorial Sloan Kettering Cancer Center, New York, NY
[6]Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, MD
[7]US Food and Drug Administration, Silver Spring, MD
[8]Department of Surgery, Duke University Comprehensive Cancer Center, Durham, NC
[9]Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, United Kingdom
[10]Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada
[11]Gemini Group, Ann Arbor, MI
[12]University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC
[13]Beth Israel Deaconess Medical Center, Boston, MA
[14]University of Colorado School of Medicine, Aurora, CO
[15]University of Edinburgh Cancer Research Centre, Edinburgh, United Kingdom
[16]US Oncology Network, Virginia Cancer Specialists, Arlington, VA
[17]Hospital of Prato, Istituto Toscano Tumori, Prato, Italy
[18]Coordinating Center for Clinical Trials, National Cancer Institute, Rockville, MD
[19]The Emmes Corporation, Rockville, MD
[20]Cancer Therapy and Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, MD

CORRESPONDING AUTHOR

Sara M. Tolaney, MD, MPH, Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215; e-mail: sara_tolaney@dfci.harvard.edu.

DISCLAIMER

The views expressed in this article are the authors' views and do not necessarily represent the views, opinions, or positions of ASCO, the National Cancer Institute, and the FDA.

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AUTHOR CONTRIBUTIONS

Conception and design: Sara M. Tolaney, Elizabeth Garrett-Mayer, Julia White, Victoria S. Blinder, Jared C. Foster, Laleh Amiri-Kordestani, E. Shelley Hwang, Judith M. Bliss, Jane Perlmutter, Nadine M. Tung, David Cameron, Neelima Denduluri, Angelo DiLeo, Lawrence Baizer, Lynn Pearson Butler, Eric P. Winer, Larissa A. Korde
Provision of study materials or patients: Elena Schwartz
Collection and assembly of data: Jared C. Foster, Laleh Amiri-Kordestani, E. Shelley Hwang, Eileen Rakovitch, Anthony D. Elias, David Cameron, Neelima Denduluri, Ana F. Best, Lynn Pearson Butler, Larissa A. Korde
Data analysis and interpretation: Elizabeth Garrett-Mayer, Victoria S. Blinder, Jared C. Foster, Laleh Amiri-Kordestani, E. Shelley Hwang, Judith M. Bliss, Eileen Rakovitch, Patricia A. Spears, Elizabeth Frank, Anthony D. Elias, David Cameron, Neelima Denduluri, Angelo DiLeo, Elena Schwartz, Larissa A. Korde
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Updated Standardized Definitions for Efficacy End Points (STEEP) in Adjuvant Breast Cancer Clinical Trials: STEEP Version 2.0

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Sara M. Tolaney
Consulting or Advisory Role: Novartis, Pfizer, Merck, Lilly, Nektar, NanoString Technologies, AstraZeneca, Puma Biotechnology, Genentech, Eisai, Sanofi, Celldex, Bristol Myers Squibb, Paxman, Seattle Genetics, Odonate Therapeutics, AbbVie, Silverback Therapeutics, G1 Therapeutics, OncoPep, Kyowa Hakko Kirin, Samsung Bioepis, CytomX Therapeutics, Daiichi Sankyo, Athenex, Immunomedics/Gilead, Mersana, Certara
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Travel, Accommodations, Expenses: AstraZeneca, Lilly, Merck, Nektar, Novartis, Pfizer, Genentech/Roche, Immunomedics, Eisai, NanoString Technologies, Puma Biotechnology, Celldex

Elizabeth Garrett-Mayer
Consulting or Advisory Role: Deciphera, Tyme

Julia White
Research Funding: Intraop Medical

Judith M. Bliss
Research Funding: AstraZeneca, Merck Sharp & Dohme, Puma Biotechnology, Pfizer, Roche, GlaxoSmithKline/Novartis, Lilly, Janssen-Cilag, Clovis Oncology
Travel, Accommodations, Expenses: Pfizer

Eileen Rakovitch
Honoraria: AstraZeneca
Research Funding: Genomic Health International

Patricia A. Spears
Consulting or Advisory Role: Pfizer

Elizabeth Frank
Honoraria: AstraZeneca
Travel, Accommodations, Expenses: Roche

Nadine M. Tung
Research Funding: AstraZeneca

Anthony D. Elias
Stock and Other Ownership Interests: AbbVie, Merck, Gilead Sciences, Allergan, Pfizer, Abbott Laboratories, Amgen, Bristol Myers Squibb, United Health Group, Align Oncology, Illumina, Exact Sciences, Lilly, Agilent, Cigna, Alexion Pharmaceuticals, Biogenerix
Consulting or Advisory Role: Ayala Pharmaceuticals
Research Funding: Medivation, Astellas Pharma, Genentech, Deciphera, Xencor, Infinity Pharmaceuticals, Karyopharm Therapeutics, TopAlliance BioSciences Inc, Fosun Orinove, BioAtla
Uncompensated Relationships: Seiyax

David Cameron
Consulting or Advisory Role: Lilly, Novartis, Research Triangle Institute Health Solutions, Daiichi Sankyo, Prima BioMed, Merck Sharp & Dohme, Zymeworks, Eisai, Puma Biotechnology, Pfizer, Oncolytics, Roche, Samsung Bioepis, Seattle Genetics, Synthon, Clarity Pharmaceuticals
Research Funding: Roche, Novartis, AstraZeneca
Travel, Accommodations, Expenses: Novartis

Neelima Denduluri
Employment: AstraZeneca
Research Funding: Amgen, Novartis, Genentech, Lilly, Pfizer, Daiichi Sankyo, Immunomedics
Travel, Accommodations, Expenses: Seattle Genetics

Angelo DiLeo
Honoraria: Roche, Novartis, Pfizer, AstraZeneca, Eisai, Lilly, Celgene, Amgen
Consulting or Advisory Role: Roche, Novartis, Pfizer, AstraZeneca, Lilly, Celgene, Puma Biotechnology, Ipsen, Genentech, Amgen, Seattle Genetics, Genomic Health, Athenex, Daiichi Sankyo
Travel, Accommodations, Expenses: Roche, Pfizer, Celgene, Novartis

Eric P. Winer
Honoraria: Genentech/Roche, Genomic Health
Consulting or Advisory Role: Leap Therapeutics, Seattle Genetics, Jounce Therapeutics, GlaxoSmithKline, Carrick Therapeutics, Lilly, G1 Therapeutics, Syros Pharmaceuticals, Genentech/Roche, Gilead Sciences, Zymeworks
Research Funding: Genentech, AstraZeneca
Other Relationship: InfiniteMD

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