Assessing oncologic benefit in clinical trials of immunotherapy agents

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Background: USA Food and Drug Administration approval for cancer therapy requires demonstration of patient benefit as a marker of clinical efficacy. Prolonged survival is the gold standard for demonstration of efficacy, but other end points such as antitumor response, progression-free survival, quality of life, or surrogate end points may be used.

Design: This study was developed based on discussion during a roundtable meeting of experts in the field of immunotherapy.

Results: In most clinical trials involving cytotoxic agents, response end points use RECIST based on the premise that 'effective' therapy causes tumor destruction, target lesion shrinkage, and prevention of new lesions. However, RECIST may not be appropriate in trials of immunotherapy. Like other targeted agents, immunotherapies may mediate cytostatic rather than direct cytotoxic effects, and these may be difficult to quantify with RECIST. Furthermore, significant time may elapse before clinical effects are quantifiable because of complex response pathways. Effective immunotherapy may even mediate transient lesion growth secondary to immune cell infiltration.

Conclusions: RECIST may not be an optimal indicator of clinical benefit in immunotherapy trials. This article discusses alternative clinical trial designs and end points that may be more relevant for immunotherapy trials and may offer more effective prediction of survival in pivotal phase III studies.

Key words: cancer, clinical benefit, immunotherapy, mixed response, RECIST, response evaluation

introduction

Overall survival (OS) has been a gold standard for ascertaining the clinical benefit of anticancer treatment. In the era before targeted therapy, approximately one-third of oncologic agents were approved by USA Food and Drug Administration (FDA) because of a documented survival advantage (Table 1) [1]. The major challenge with a survival end point in oncology trials is the fact that many patients, especially at academic medical centers, may be treated with a long series of subsequent agents, confounding the OS benefit that can accurately be attributed to any single agent. Furthermore, OS may be a reasonable end point in some malignancies, but in more slowly progressing cancers such end points may be unrealistic. A randomized phase III trial for such patients could take decades to complete, and this constitutes an impractical and frustrating situation.

In early FDA approvals for cancer therapy, end points were rooted in safety and efficacy as defined by tumor response to therapy [1]. Classic systemic therapies were cytotoxic and therefore were likely to meet this end point if they had activity against the cancer. Response rate was judged to be an appropriate surrogate for improved patient outcome in part because of the assumption that tumor shrinkage was likely to predict real clinical benefit such as improved survival. However, in the 1980s the Oncologic Drugs Advisory Committee recommended that oncologic trials meet a defined clinical end point, such as improved survival or an improvement in quality of life (QoL) [2], and suggested that objective response rate alone would be insufficient for approval. The change was ratified by the FDA because of a new focus on use of patient-centered outcomes such as survival and/or QoL to compare therapies. Additionally, it was noted that possible benefits associated with tumor shrinkage did not necessarily justify the side-effects typically associated with treatment using toxic anticancer drugs [1]. Thus, the second generation of chemotherapies subject to regulatory approval was evaluated in a setting in which toxicity would play a more defined role in determining whether approval would be granted. In 1992, the FDA added accelerated approval mechanisms for diseases classified as serious or life threatening. Accelerated approval, also known as Subpart H (21 CFR 314) was ratified for use with the understanding that defined clinical outcomes such as OS...
**Table 1.** Registrational trial end points used to support USA FDA approval of 57 drugs (1 January 1990 to 1 November 2002)

<table>
<thead>
<tr>
<th>End Point</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>18</td>
</tr>
<tr>
<td>RR and/or TtP alone</td>
<td>18</td>
</tr>
<tr>
<td>Tumor-related signs and symptoms</td>
<td>13</td>
</tr>
<tr>
<td>Alone</td>
<td>4</td>
</tr>
<tr>
<td>+RR</td>
<td>9</td>
</tr>
<tr>
<td>DFS (adjuvant setting)</td>
<td>2</td>
</tr>
<tr>
<td>Recurrence of malignant pleural effusion</td>
<td>2</td>
</tr>
<tr>
<td>Decreased incidence of new BC occurrence</td>
<td>2</td>
</tr>
<tr>
<td>Decreased impairment of creatinine clearance</td>
<td>1</td>
</tr>
<tr>
<td>Decreased xerostomia</td>
<td>1</td>
</tr>
</tbody>
</table>

Adapted from Williams et al. [1].

*Predominantly hormone treatment of BC or hematologic malignancies. USA FDA, USA Food and Drug Administration; RR, response rate; TtP, time to progression; DFS, disease-free survival; BC, breast cancer.

may take many years to measure in tumors with an indolent natural history [3]. Additionally, subsequent therapies after failure of the study agent could affect survival and, hence, confound data regarding the survival benefit of a given agent. Accelerated approval requires postmarketing commitments from the sponsor in the form of mature data grounded in defined end points such as response rate, response duration, and survival [4].

RECIST criteria were born out of the notion that an objective, uniform, and reliable method of assessing tumor response was needed to validate the surrogate results in clinical trials between international research organizations [5]. The use of RECIST response criteria as a surrogate for patient outcomes relies on the assumption that (i) agent activity results in the shrinkage of disease and that (ii) enlargement of disease is the result of growth of the tumor refractory to the agent (i.e. the tumor is agent resistant). The original RECIST criteria, published in 2000 by a consortium of the European Organization for Research and Treatment of Cancer, National Cancer Institute, and National Cancer Institute of Canada, were validated from an analysis of response in >4000 patients [5].

Key features of RECIST criteria include the independent evaluation of response at target tumor sites, screening for new lesions, and evaluation of response in nontarget lesions (Table 2) [6]. A composite evaluation of response is made on the basis of scored measures of each subcomponent. For complete response (CR) or partial response (PR) to therapy per RECIST 1.0 criteria, favorable tumor response must be seen in all of the subvariables. RECIST 1.1 criteria were modified to include lymph node sites and simplify the evaluation of target lesions, but fundamentally rely on a similar definition of response as in RECIST 1.0. An objective response is achieved when target lesions exhibit a complete regression or show a defined reduction for a specified time period. Stable tumors are excluded from response rate determinations [7]. Approximately one-third of oncologic therapies approved between 1990 and 2002 were approved on the basis of a positive response rate (Table 1) [1].

Aside from their difficulties with stable disease, RECIST criteria have been criticized based on their inability to reliably predict clinical benefit [8]. Specifically, objective response does not uniformly translate into improved progression-free survival (PFS) or OS. To assess the presumed correlation between RECIST response rates and OS, Chen et al. [9] compared phase II trial response rates with the subsequent phase III trial survival data using patients treated with experimental regimens for extensive-stage small-cell lung cancer. They found a poor Pearson correlation coefficient ($P = 0.67$) between phase II response rate and phase III OS. In other tumor types (i.e. metastatic colorectal cancer), a more reasonable correlation between RECIST response rate and OS has been documented, suggesting that the utility of response rate as a surrogate for OS might depend to some degree on the disease or treatment regimen in question [10].

Targeted therapies have several theoretical advantages, including the potential to induce fewer adverse effects via activity on normal cells. Many, but not all, targeted therapies exhibit antitumor activity in the form of a cytostatic, rather than a cytotoxic effect [11]. Thus, cytostatic agents slow or stop tumor growth and the development of metastasis without shrinking existing tumors [12]. Response trajectories for targeted agents may include disease stabilization, delayed tumor response, or transient tumor swelling followed by tumor response. Using strict RECIST criteria applied at typical follow-up points in a clinical trial, such responses are not ‘counted’, and patients with delayed response, or who experience a response after initial tumor growth, may be classified as nonresponders.

Consequently, the ability of any particular agent to induce a response may not be required for improved survival. For example, bevacizumab, a monoclonal antibody (mAb) specific for vascular endothelial growth factor, was recently approved for the first-line treatment of metastatic colorectal cancer. In a phase I testing of bevacizumab, no patient experienced an objective PR or CR [13]. Although this phase I trial was a dose escalation study, nearly half of the patients were treated with

**Table 2.** RECIST 1.1 criteria

<table>
<thead>
<tr>
<th>Target lesions</th>
<th>Nontarget lesions</th>
<th>New lesions</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD or not all evaluated</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD or not all evaluated</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>Non-PD</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or no</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or no</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

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CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.
a therapeutic dose of the agent. Notwithstanding, the subsequent phase II trial showed a longer median survival with bevacizumab when given with 5-fluorouracil (5-FU)/leucovorin (LV) in comparison to 5-FU/LV alone [14]. If the development of bevacizumab as an agent for colorectal cancer was driven solely by RECIST criteria, this clinical approval might have never been achieved.

While the response to a potent cytostatic agent may manifest itself simply as a cessation of tumor growth, immunotherapeutic agents such antibodies directed against the immune checkpoint molecule cytotoxic T lymphocyte-associated antigen 4 (CTLA4) may induce responses with a variety of kinetic patterns [15]. Some tumors may respond rapidly, meeting criteria for a RECIST response. Other tumors may respond late in the course of treatment, wherein standard 2- and 3-month evaluations of these patients would classify them as nonresponders. In rare cases, tumors may actually increase in diameter before eventually regressing. Using RECIST criteria, such patients would be classified as having disease progression and generally would be removed from a trial before late response might be documented [15]. Because of the unique patterns of clinical response that arise with immune-modulating therapies, alternative clinical trial design and end points are necessary to properly evaluate these targeted agents.

**rationale: immunotherapy and alternative end points**

Traditional targeted agents are preferentially directed against molecules that are novel or are overexpressed in tumor cells. These agents include antiangiogenic agents, protein kinase inhibitors, histone deacetylase inhibitors, and agents that enhance apoptosis. These drugs have moved forward clinically because of the selective nature of their action and the generally low toxicity associated with their clinical use. In contrast, cancer immunotherapy broadly refers to approaches that attempt to treat cancer by activating an immune response directed against malignant tissue [16]. A number of different approaches fall under this category, including dendritic cell vaccination, DNA vaccination, peptide vaccination, viral vaccine vectors, and cell-based approaches in which irradiated cancer cells are either transduced to produce proinflammatory cytokines or coadministered with granulocyte–macrophage colony-stimulating factor-secreting ‘bystander’ cells. Such agents are commonly referred to as ‘vaccines’, although this term is misleading since vaccination is more appropriately applied to preventive immunization.

A second evolving approach to cancer immunotherapy involves the blockade of immune checkpoints, molecules expressed on T cells that inhibit their ability to mediate an antitumor T-cell response [17]. Among such molecules, CTLA4 is of particular interest as blockade of CTLA4 using mAbs augments a T-cell response in a number of tumor as well as infectious disease models [18]. Typically, two signals are required for full T-cell activation; these include (i) binding of the T-cell receptor to the antigen-bound major histocompatibility complex on the antigen-presenting cell (APC) and (ii) CD28 on the T cell binding to B7 on the APC (Figure 1). Following T-cell activation, CTLA4 translocates to the T-cell surface and outcompetes CD28 for binding to B7, thus down-regulating T-cell activation. Other checkpoints of interest include programmed-death 1, which serves as a marker of CD8 T-cell exhaustion in models of chronic viral infection [19] as well the immune-activating molecule 4-1BB (CD137) [20]. Tumor-infiltrating lymphocytes appear to express these checkpoint molecules at higher levels than their peripheral counterparts; in an appropriate host, checkpoint blockade might serve to unleash a preexisting immune response, even in the absence of specific vaccination. Among these various immune checkpoints of interest, blockade of CTLA4 with specific mAbs is furthest along in clinical development.

Ipilimumab (formerly MDX-010; Medarex, New York, NY and Bristol-Myers Squibb, New York, NY) and tremelimumab (formerly CP-675,206 and ticilimumab; Pfizer Inc., New York, NY) are both fully human anti-CTLA4 mAbs that have been studied in phase I, II, and III trials, in patients with metastatic melanoma and in a range of other malignancies. Ipilimumab has induced durable responses in metastatic melanoma as first-line therapy with chemotherapy and in second line as either monotherapy or combination with vaccination. As described above, the kinetics of ipilimumab responses differ from standard chemotherapy [15]. Responses may take time to develop and follow periods of stable disease or progression [21–23]. As may be the case for a number of immunotherapy regimens, analysis of the long-term survival benefit of patients participating in phase I trials of tremelimumab showed long-term survival benefit in the absence of RECIST responses [24, 25]. Further, in an analysis of responses to ipilimumab, the majority (61%) of objective responses occurred after 3 months of treatment, and several patients with apparent progressive disease were later assessed as having an objective response without additional anticancer treatment off study [26].

The initial appearance of progressive disease may occur during immunologic therapy for at least two reasons. First, immunotherapy may induce lymphocytic tumor infiltration and inflammation of the tumor, and the associated increase in tumor diameter scored as progression on radiographic imaging (i.e. ‘tumor flare’). Second, the appearance of new lesions or growth of primary lesions may occur after immunotherapy has been administered, since the process of immune activation is
complex and delayed. During this period of activation, the tumor may be able to transiently grow even when effective therapy is priming an immune system versus tumor response. As described above, the use of standard response rate criteria may erroneously result in the declaration of treatment-resistant disease.

**alternative end points for clinical benefit**

A typical development pathway for cytotoxic agents involves phase II trials that are conducted as single-arm studies comparing a primary end point of response rate against historical controls. Subsequent development in phase III trials is based upon antitumor activity observed in phase II trials [27]. Goffin et al. [28] found that in cytotoxic chemotherapy, phase I and phase II study response rate accurately predicted the probability of FDA approval in most solid tumor types. Interestingly, this correlation was not observed in studies of melanoma and renal cell carcinoma, the two tumor types typically felt to be ‘immunogenic’. If a phase II response rate does not predict phase III success, then what other end points might be considered?

**composite end points and biomarkers**

Composite end points and biomarkers may be helpful in phase II studies to predict efficacy in subsequent phase III studies. For example, in multiple myeloma, the FDA has identified response rate with substantial duration as a valid composite end point for accelerated approval (overall response rate ≥28%, CR ≥3%, and median response duration of 12 months) [29]. In an analysis by Chen et al. [9], a statistical model was devised to predict the efficacy of an agent in phase III studies when the response rate and survival were established in the preceding phase II study. Hence, response was used in conjunction with the power of the response rate (given sample size and degree of response) to predict phase III efficacy. This composite end point may be helpful in preventing agents with borderline efficacy in phase II studies from being tested in phase III studies when the probability of efficacy and eventual FDA approval is low. Appropriate biomarkers may be especially important in phase II studies of targeted agents. For example, in an interesting *post hoc* analysis, Comin-Anduix et al. [30] found that peripheral blood markers such as T-cell activation and increase in T-cell memory markers were predictive of long-lasting response to CTLA4 blockade in patients who received tremelimumab. Other biomarkers that may predict efficacy with biologic agents include Her-2/neu expression and herceptin response in breast cancer [31], and EGFR (epidermal growth factor receptor) gene status, K-ras mutation, and phosphatase and tensin homolog expression in predicting efficacy to cetuximab response [32].

**time to progression and PFS**

Time to progression (TtP) or ‘time to symptomatic progression’ has been suggested by the FDA as an alternative end point. Although a variety of definitions for time to symptomatic progression have been used, to date no cancer drugs have been approved using such an end point. Still, TtP in randomized phase II trials may provide a means to predict which agents are likely to be efficacious in phase III clinical studies. The obstacle with a PFS end point in an unblinded study is the potential for bias between the treatment arms given the subjective nature of scan interpretation. Freidlin et al. [33] advocates for central review of scans when PFS is the end point of interest, to minimize the probability of observer bias. Additional scans at multiple predefined time points after progression may be required to confirm the presence or absence of true disease progression [33].

**quality of life**

QoL, or improvement in tumor-related symptoms, is theoretically acceptable by the FDA as an end point for oncologic agent approval. However, only four agents were approved based on such ‘signs and symptoms’ (patient-reported outcomes) between 1990 and 2002 [1]. Mitoxantrone plus prednisone was approved for castration-resistant prostate cancer after a QoL benefit, as defined at the study onset, was demonstrated [34, 35]. Specifically, the combination therapy was shown to decrease pain intensity by ~2 points on an intensity scale and to provide relief persisting for at least 6 weeks. Although QoL and PROs have not been formally evaluated as surrogate end points in immunotherapy trials, several case reports show objective tumor progression (tumor flare) in the first months of immunogenic therapy associated with paradoxical subjective improvement in tumor-related symptoms by patient reporting [15, 36]. Withdrawal of investigational immunologic therapy in patients with subjective improvement may limit the perceived efficacy of the therapy and diminish the possibility of observing objective responses in preplanned subsequent imaging studies.

**objective response criteria**

Objective response criteria with modifications have not yet been accepted by the FDA as a demonstration of clinical efficacy, but may be appropriate end points in phase II studies evaluating the efficacy of targeted and immunogenic agents. The biologic basis for evaluation with modified response rate criteria rests on the premise that the time required to establish an effective cellular immune response to active immunotherapy may exceed either the observation period designed into the study or the average TtP for many patients with advanced disease. Once progression has been detected with conventional criteria such as RECIST, patients usually are taken off treatment and are frequently also taken off study, with a high likelihood of missing a late biologic effect induced by the immunotherapy [27]. Formal modifications of World Health Organization (WHO) criteria have been proposed to account for the unique patterns of tumor response that arise with immunotherapy [37]. In the proposed immune-related response criteria (irRC), total tumor burden is considered only for measurable lesions ≥1 cm, total tumor burden is defined as the sum of index lesions identified at baseline and new lesions detected after baseline, and follows patients after progression to detect late activity. In addition to patients who have a PR or CR to therapy, objective response defined by irRC includes patients achieving stable
disease and a slow decline in tumor volume (≥25%) [37]. irRC have been applied retrospectively to a group of melanoma patients treated with immunotherapy in three phase II trials, showing a response rate to therapy of 25.8%, 15.3%, and 30.9%. In contrast, the response rate in the same group of patients defined by modified WHO (mWHO) criteria shows inferior response (5.8%, 11.1%, and 15.8%) and may erroneously misclassify patients who derive clinical benefit from the therapy [37].

**additional end points**

In a recent meta-analysis of phase II trials carried out by cooperative groups in 2100 patients with metastatic melanoma, Korn et al. [38] established historic 1-year OS curves that make use of the distribution of prognostic factors of the patients. These benchmarks serve as a reference to compare future data and gain early insights on the likelihood of efficacy in future phase II trials [38]. While these data indicate that clinical trial development could potentially be accelerated with an early end point, prospective validation of such an end point is most likely required before widespread adoption in the clinical trials realm.

**clinical trial design for immunotherapy agents**

Classic drug development consists of a series of developmental milestones. The selection of appropriate phase II end points and clinical trial design can be guided by preclinical and early phase findings. Additionally, primary end points can inform the optimal design of phase II clinical trials (see Figure 2). The goal of phase III clinical trials is to confirm the findings of clinical activity discovered in earlier stage studies. However, phase II studies in oncology are poorly predictive of positive phase III results and eventual FDA approval (Table 3) [39]. Classic end points such as response rate in early phase trials are even less predictive in immunotherapy trials, making phase III trials less confirmatory and more exploratory in nature. Interestingly, negative phase II trials in oncology are a significant predictor of negative phase III trials in oncology, begging the question as to why subsequent phase III trials were initiated.

**randomized phase II trials**

Randomized phase II trials are typically not employed in oncology drug development because a sample size sufficient for statistically significant interarm differences is deemed too large at early stages in drug development [40]. However, larger patient populations may provide a higher likelihood of observing substantive antitumor activity, and might add predictive value important in initiating phase III trials. Although randomized phase II survival trials in oncology are usually highly underpowered, 12-month survival or 6-month PFS rates can aid in selection of drugs or regimens for further study in phase III trials. Incorporation of a comparison arm into study design may be particularly useful because there is a high probability of selecting the treatment that is more effective or at least equally effective as the comparator. Additionally, randomized phase II oncologic trials with alternative end points such as composite biologic end points or modified objective response rate criteria may further improve the sensitivity of immunologic phase II trials to screen out agents appropriate for phase III evaluation.

**randomized discontinuation trials**

Randomized discontinuation trials are designed to evaluate the ability of a therapy to produce longitudinal stable disease [41]. Discontinuation trials are designed on the premise that newer

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**Figure 2.** Factors influencing clinical trial design in immunotherapy agents.
agents, especially those with specific molecular targets, may not be cytotoxic and may, therefore, require new study designs to address the questions of whether maintenance therapy is useful. In these randomized studies, patients with progressive disease are taken off study and patients who meet traditional objective response criteria continue on therapy. Patients with overall stable disease after therapy are randomly assigned to either continue on the experimental agent or receive no therapy. The randomization arms use end points to evaluate the cytostatic ability of the agent of interest [41]. In a randomized discontinuation trial of the kinase inhibitor sorafenib in patients with metastatic renal cell cancer, the objective response rate by mWHO criteria was 4% [42]. However, when patients with stable disease were randomly assigned to continue sorafenib versus no additional therapy, there was an obvious and highly significant difference in failure-free survival, which was confirmed in subsequent phase III trials [39, 43]. If this drug was developed with classic phase II designs regarding objective response rate end point, it might not have moved forward to phase III testing in an expeditious manner. However, results of such discontinuation trials should be interpreted with caution—the duration of drug administration needed to induce disease stability and the carryover effect of the drug into the placebo group after discontinuation are difficult to predict. Hence, interpreting results of such studies is not always straightforward [44].

conclusions

For approval of new oncology agents, the FDA accepts improved survival as well as surrogates that predict clinical benefit: RECIST response rates, composite end points, and occasionally QoL-related data. RECIST response rates are an established end point in cytotoxic therapy, but it should be understood that RECIST represents a surrogate marker for clinical benefit. In trials of immunotherapy agents, RECIST response rates measured at predefined intervals of follow-up while on study drug may be confounded by the delayed time required to mount a response or by apparent radiographic progression. Late responders may be classified erroneously as nonresponders on protocol, leading to aberrant conclusions regarding therapeutic efficacy. Thus, the use of traditional RECIST response rates may underestimate the efficacy of targeted therapies. If RECIST criteria are used in phase II immunotherapy trials, it seems that imaging studies for tumor evaluation should be obtained after appropriate time has elapsed for an immune response to be initiated. Estimating this time precisely is difficult, given the wide variation in tumor progression rates, and in patients’ individual immune responses. A delay in initial tumor evaluation might also permit the resolution of tumor flare. Delaying restaging scans will also provide the necessary time for complex pathways intrinsic to immunotherapy to engage, eventually resulting in migration of effector lymphocytes to tumor sites and immune-mediated cytotoxicity. Lastly, smaller deposits of tumor may continue to grow in the first few months of effective immunotherapy and appear as progressive disease on restaging scans. RECIST or WHO criteria modified and applied to immunotherapy should allow for the appearance of new lesions that arise during this period of immune priming. These areas of apparent pseudoprogression should be carefully followed to distinguish nonresponding patients with progressive disease from those with delayed but defined immune-modulated activity. Future phase II trials in immunogenic oncologic therapies will need to focus on appropriate end points in well-designed experimental trials. If patient numbers permit, randomized phase II trials might be considered. A randomized discontinuation trial design might also be considered when stable disease is the expected end point. The use of appropriate biomarkers may serve to guide dosing and patient selection, with the ultimate goal of improving the quality and quantity of life for patients suffering from cancer.

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conflict of interest

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