Sequential, Multiple Assignment, Randomized Trial Designs in Immuno-oncology Research

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Abstract

Clinical trials investigating immune checkpoint inhibitors have led to the approval of anti–CTLA-4 (cytotoxic T-lymphocyte antigen-4), anti–PD-1 (programmed death-1), and anti–PD-L1 (PD-ligand 1) drugs by the FDA for numerous tumor types. Immune checkpoint inhibitors are a novel class of immunotherapy agents that block normally negative regulatory proteins on T cells and enable immune system activation. By activating the immune system rather than directly attacking the cancer, immunotherapy drugs differ from cytotoxic chemotherapy and oncolytics. Immune checkpoint inhibitors are an effective treatment for metastatic melanoma. The anti–CTLA-4 drug ipilimumab was approved for the treatment of metastatic melanoma in 2011 and as adjuvant therapy for resected stage III melanoma in 2015. Combination therapy is also being tested in other malignancies. In melanoma, ipilimumab improves overall survival but is associated with 20% grade 3/4 immune related adverse events (1–6). Agents that inhibit PD-1 and PD-L1 have less immune-related adverse events than CTLA-4–blocking agents (7). PD-1 and PD-L1 agents have been approved by the FDA for use in multiple malignancies including, but not limited to, melanoma (nivolumab and pembrolizumab), non–small cell lung cancer (NSCLC; nivolumab, pembrolizumab, and atezolizumab), renal cell carcinoma (nivolumab), and urothelial carcinoma (atezolizumab; refs. 8–10). Combinations of checkpoint inhibitors that block both CTLA-4 and PD-1 are more effective than CTLA-4 blockade alone (ipilimumab) in patients with melanoma, but combination immunotherapy is associated with increased frequency and severity of toxicity. Although we build our framework on the FDA-approved combination of anti–PD-1 therapy and ipilimumab, as this reflects the current landscape, one could replace the anti–PD-1 and ipilimumab combination with anti–PD-1 and any drug to reflect novel combination agents that may become available downstream. The SMART (sequential, multiple assignment, randomized trial) design to evaluate immune checkpoint inhibitors to find treatment regimens that adapt within an individual based on intermediate response and lead to the longest overall survival. We provide a hypothetical example SMART design for BRAF wild-type metastatic melanoma as a framework for investigating immunotherapy treatment regimens. We compare implementing a SMART design to implementing multiple traditional randomized clinical trials. We illustrate the benefits of a SMART over traditional trial designs and acknowledge the complexity of a SMART. SMART designs may be an optimal way to find treatment strategies that yield durable response, longer survival, and lower toxicity. Clin Cancer Res; 24(4): 730–6. ©2017 AACR.

Introduction

Clinical trials investigating immune checkpoint inhibitors have led to the approval of anti–CTLA-4 (cytotoxic T-lymphocyte antigen-4), anti–PD-1 (programmed death-1), and anti–PD-L1 (PD-ligand 1) drugs by the FDA for numerous tumor types. Combination therapy is an effective treatment for metastatic melanoma. Some individuals may not need combination therapy because they may respond to a single agent, and these individuals should not be subjected to increased toxicities associated with combination therapy. Defining this group of individuals, however, is difficult. Many trials are being proposed to evaluate combinations or sequences of immunotherapy drugs alone in combination with other treatments such as chemotherapy, radiation, and targeted therapies, or with varied doses and schedules (sequential versus concurrent). The goal of these trials is to increase efficacy and decrease toxicity (11).

The long-term effect of immune activation by these drugs is unknown. It is also unknown whether individuals need continued treatment. Oncologists must optimize a balance in the clinic, incorporating observed efficacy and toxicity, and informally implement treatment pathways so that treatment may change for an individual depending on the individual’s status. Many of these treatment pathways are ad hoc, based on the physician’s experience and judgement or information pieced together from several randomized clinical trials. Formalized, evidence-based treatment pathways to inform decision-making over the course of care are needed. Formal, evidence-based treatment guidelines

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that adapt treatment based on a patient's outcomes, including efficacy and toxicity, are known as treatment pathways, dynamic treatment regimens (12), or adaptive interventions (13). Specifically, a treatment pathway is a sequence of treatment guidelines or decisions that indicate if, when, and how to modify the dosage or duration of interventions at decision stages throughout clinical care (14). For example, in treating individuals with stage III or stage IV Hodgkin lymphoma, one treatment pathway is as follows: "Treat with two cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). At the end of therapy (6 to 8 weeks), perform positron emission tomography/computed tomography (PET/CT) imaging. Treat with an additional 4 cycles of ABVD if the scan scores 1–3 on the Deauville scale (considered a negative scan). Otherwise, if the scan scores 4–5 on the Deauville scale (considered a positive scan), switch treatment to escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (eBEACOPP) for 6 cycles (15)." Note that one treatment pathway includes an initial treatment followed by subsequent treatment that depends on an intermediate outcome for all possibilities of that intermediate outcome.

Treatment pathways are difficult to develop in traditional randomized clinical trial settings because they specify adapting treatments over time for an individual based on response and/or toxicity. Treatments may have delayed effects such that the best initial treatment is not a part of the best overall treatment regimen. For example, one treatment may initially produce the best response rate, but that treatment may also be so aggressive that for those who did not have a response, they cannot tolerate additional treatment whereas another treatment may produce a lower proportion of responders initially but can be followed by an additional treatment to rescue more nonresponders and lead to a better overall response rate and longer survival. Thus, treatments in combination or sequence do not necessarily result in overall best outcomes. The sequential, multiple assignment, randomized trial (SMART; refs. 16, 17) is a multistage trial that is designed to develop and investigate treatment pathways. SMART designs can investigate delayed effects as well as treatment synergies and antagonisms, and provide robust evidence about the timing, sequences, and combinations of immunotherapies. Furthermore, treatment pathways may be individualized to find baseline and time-varying clinical and pathologic characteristics associated with optimal response.

In this article, we describe a novel use of SMART design to evaluate immuno-oncologic agents. We provide a hypothetical example SMART design for metastatic melanoma as a framework for investigating immunotherapy treatment. We compare implementation of a SMART design with implementation of multiple traditional randomized clinical trials. We illustrate the benefits of a SMART over traditional trial designs and acknowledge the complexity of a SMART. SMART designs may be an optimal way to find treatment strategies that yield durable response, longer survival, and lower toxicity.

**SMART Design**

A SMART is a multistage, randomized trial in which each stage corresponds to an important treatment decision point. Participants are enrolled in a SMART and followed throughout the trial, but each participant may be randomized more than once. Subsequent randomizations allow for unbiased comparisons of post-initial randomization treatments and comparisons of treatment pathways. The goal of a SMART is to develop and find evidence of effective treatment pathways that mimic clinical practice.

In a generic two-stage SMART, participants are randomized between several treatments (usually 2–3; Fig. 1). Participants are followed, and an intermediate outcome is assessed over time or at a specific time. On the basis of the intermediate outcome, participants may be classified into groups, and they may be re-randomized to subsequent treatment. The intermediate outcome is a measure of early success or failure that allows the identification of those who may benefit from a treatment change. This intermediate outcome, also known as a tailoring variable, should have only a few categories so that it is a low-dimensional summary that is well defined, agreed upon, implementable in practice and gives early information about the overall endpoint. This intermediate outcome does not need to be defined as response/nonresponse, or more specifically as tumor response, but rather, it may be defined differently, such as adherence to treatment, a composite of efficacy measures, or efficacy and toxicity measures. It is imperative that the intermediate outcome is validated and replicable. Although the two-stage design is most commonly used, SMARTs are not limited to two stages, such as a SMART that investigated treatment strategies in prostate cancer (18).

A SMART is similar to other commonly used trial designs but has unique features that enable the development of robust evidence of effective treatment strategies. The SMART design is a type of sequential factorial trial design in which the second-stage treatment is restricted based on the previous response. A SMART design is similar to a crossover trial in that the same participants are followed throughout the trial and participants may receive multiple treatments. However, in a SMART, subsequent treatment is based on the response to the previous treatment, and a SMART design takes advantage of treatment interactions as opposed to washing out treatment effects (i.e., a SMART does not require time in between treatments to eliminate carryover effects from the initial treatment on the assessment of the second-stage treatment).

We focus this overview on SMART designs that are nonadaptive. In a nonadaptive SMART, the operating characteristics of the trial, including randomization probabilities and eligibility criteria, are predetermined and fixed throughout the trial. Treatment may adapt within a participant based on intermediate response, but randomization probabilities or other trial-operating characteristics do not change for future participants based on previous participants’ results. By following the same participants over the trial, a SMART enables the development of evidence for treatment pathways that specify an initial treatment, followed by a maintenance treatment for responders and rescue treatment for nonresponders. These treatment pathways are embedded within a SMART design, but within the trial, participants are randomized to treatments based on the intermediate outcome to enable unbiased comparisons and valid causal inference. The end goal of the trial is to provide definitive evidence for treatment pathways to be used in practice. The SMART design has been used in oncology (19, 20), mental health (21), and other areas (22), but to our knowledge, this is the first description of using a SMART in immuno-oncology.

**Hypothetical Melanoma SMART**

Ipilimumab and anti–PD-1 therapy currently are approved to treat metastatic melanoma. However, combinations of these and
other immunotherapy drugs may cause toxic events, and it remains unclear whether patients should start with these combinations or start with single agent anti–PD-1 therapy and receive these additional treatments upon disease progression. There are also questions about the number of doses required to sustain a response for single-agent or combination therapy. The best treatment strategy that may provide enough therapy for sustained response and limit toxicities is unknown. A SMART design may address these questions to provide rigorous evidence for the best immunotherapy treatment pathway for individuals. Our proposed example focuses on patients with BRAF wild-type metastatic melanoma to avoid complexities of additionally considering incorporation of BRAF and MEK inhibitors into the treatment regimen of patients with BRAF-mutant melanoma.

In a hypothetical SMART design to investigate treatment strategies, including anti–PD-1 therapy and ipilimumab, participants may be randomized in the first stage to receive four doses of single-agent anti–PD-1 therapy (pembrolizumab 2 mg/kg or nivolumab 240 mg) or combination nivolumab (1 mg/kg), and ipilimumab (3 mg/kg; Fig. 2, note these drugs could be replaced with any novel immunotherapy or approved drug). During follow-up, participants would be evaluated for their tumor response; the intermediate outcome in this SMART would be defined by disease response after four doses of immunotherapy (week 12). Although Response Evaluation Criteria in Solid Tumors (RECIST) could be used to define disease response, favorable response could also be defined as any decline in total tumor burden, even in the presence of new lesions, as specified by principles related to immune-related response criteria (23).

In the second stage of the trial, responders to either initial treatment would be re-randomized to continue versus discontinue their initial treatment. Specifically, participants who responded to single agent anti–PD-1 would be re-randomized to continue current treatment for additional doses up to 2 years or to discontinue treatment, and participants who responded to the combination of anti–PD-1 + ipilimumab would be re-randomized to continue anti–PD-1 maintenance or discontinue treatment. Participants who did not respond to single-agent anti–PD-1 by 12 weeks would be re-randomized to receive ipilimumab or the combination of anti–PD-1 and ipilimumab. Participants who did not respond to the combination therapy would receive the standard of care (e.g., oncogene-directed targeted therapy if appropriate, chemotherapy, or considered for clinical trials; Fig. 2). As newer drugs become available and are promising for nonresponders to combination therapy, we anticipate that there could be an additional randomization for these nonresponders to explore additional treatment pathways. All participants would be followed for at least 28 months. The overall outcome of the trial would be overall survival. Any participant who experienced major toxicity at any time or progressive disease in the second stage would be removed from the study and treated as directed by the treating physician.

Participants belong to one subgroup (Fig. 2) in a SMART. Two subgroups make up one treatment pathway, since a treatment pathway describes the clinical guidelines for initial treatment and subsequent treatment for both responders and nonresponders (Fig. 2). Although there are seven subgroups that a participant may belong to, there are six embedded treatment pathways in this SMART design. The six treatment pathways include the following:

1. First begin with single-agent anti–PD-1 therapy. If no response to single-agent anti–PD-1 therapy, then switch to single-agent ipilimumab. If response to single-agent anti–PD-1, then continue treatment (subgroups 1 and 3);
(2) First begin with single-agent anti–PD-1 therapy. If no response to single-agent anti–PD-1 therapy, then switch to single-agent ipilimumab. If response to single-agent anti–PD-1 therapy, then continue treatment (subgroups 1 and 2).

(3) First begin with single-agent anti–PD-1 therapy. If no response to single-agent anti–PD-1 therapy, then add ipilimumab to anti–PD-1 therapy. If response to single-agent anti–PD-1 therapy, then discontinue treatment (subgroups 2 and 3).

(4) First begin with single-agent anti–PD-1 therapy. If no response to single-agent anti–PD-1 therapy, then add ipilimumab to anti–PD-1 therapy. If response to single-agent anti–PD-1 therapy, then continue treatment (subgroups 2 and 3).

(5) First begin with combination anti–PD-1 therapy + ipilimumab. If no response to combination anti–PD-1 therapy + ipilimumab, then receive standard of care. If response to combination anti–PD-1 therapy + ipilimumab, then continue treatment (subgroups 5 and 6).

(6) First begin with combination anti–PD-1 therapy + ipilimumab. If no response to combination anti–PD-1 therapy + ipilimumab, then receive standard of care. If response to combination anti–PD-1 therapy + ipilimumab, then discontinue treatment (subgroups 5 and 7).

A SMART may have several scientific aims, some of which may resemble those of traditional trials and some pertaining to the treatment pathways, differ. It is important, as in standard trials, to identify and power on a primary aim. Subsequent aims and multiple comparisons may be additionally powered for using any type I error-control method (24). In metastatic melanoma, the SMART may be interested in answering one of following four questions:

(1) Does a treatment strategy that begins with single-agent anti–PD-1 or combination anti–PD-1 and ipilimumab therapy lead to the longest overall survival?
(2) For responders to initial therapy, does continuing or discontinuing treatment provide the longest overall survival?
(3) For nonresponders to single-agent anti–PD-1 therapy, does ipilimumab or the combination of ipilimumab and anti–PD-1 therapy provide the longest overall survival?
(4) Is there a difference in the overall survival between the six embedded treatment pathways?

Questions similar to numbers 1, 2, and 3 could be answered in three separate, traditional, parallel-arm clinical trials. The traditional paradigm would run a single-stage trial (e.g., single-agent anti–PD-1 therapy or a combination of anti–PD-1 therapy + ipilimumab) followed by a confirmatory single-stage trial in responders. SMARTs, however, provide an opportunity to answer these questions in a single-stage trial design, thereby reducing the required sample size and providing more efficient and accurate answers.

A hypothetical two-stage SMART design in the setting of BRAF wild-type metastatic melanoma. Participants are initially randomized to either single-agent anti–PD-1 therapy or to a combination of anti–PD-1 therapy + ipilimumab (Ipi). Note that Ipi may be replaced by any novel combination agent. After four doses or approximately 12 weeks, response is measured. Those who did not respond to the single agent are re-randomized to receive Ipi or the combination. Those who did respond to single-agent anti–PD-1 are re-randomized to continue the single agent or discontinue therapy. Those who did not respond initially to the combination receive standard of care and those who did respond are re-randomized to continue the combination or discontinue therapy. Subgroups 1 to 7 denote the subgroups that any one participant may fall into. There are six embedded treatment pathways in this SMART, and each one is made up of 2 subgroups: (1,3), (1,4), (2,3), (2,4), (5,6), and (5,7).
vs. combination therapy) to determine the most effective therapy. A first trial may investigate single agent anti–PD-1 versus the combination of anti–PD-1 and ipilimumab. Another trial with a randomized discontinuation design could identify if continuing or discontinuing treatment leads to longer overall survival for individuals who received the most effective therapy (e.g., anti–PD-1 alone or in combination with ipilimumab). And a third trial could determine for those refractory to anti–PD-1 therapy, if ipilimumab or the combination of ipilimumab and anti–PD-1 therapy results in longer survival. For each of these three traditional trials, power and analyses are standard in terms of powering for and analyzing a two-group comparison with a survival outcome.

If question 1, 2, or 3 is the primary aim of a SMART, the sample size and analysis plan is also standard; however, for questions 2 and 3, the calculated sample size must be inflated. For question 2, the sample size must be inflated on the basis of the assumed response rates to first-stage therapies. Specifically, if 40% respond to single-agent therapy and 55% to combination therapy, the calculated two-group comparison sample size must be increased by these amounts to ensure that in the SMART there will be sufficient responders in the second stage. For question 3, the sample size must also be inflated for the expected percentage of nonresponders to anti–PD-1 therapy. Similarly, in a standard one-stage trial to address question 2 (or 3), more patients would need to be screened to account for the response status, but unlike a SMART, the nonresponders (responders) would not be followed. Furthermore, implementing three separate trials may not provide robust evidence for entire treatment pathways and instead provide evidence for only the best treatments at specific time points.

For a SMART powered on question number 1, 2, or 3, the analysis of treatment pathways would be exploratory and hypothesis generating to be confirmed in a follow-up trial. Instead, the SMART may be powered to compare the embedded treatment pathways (question 4) in contrast with the stage-specific differences. Comparisons of pathways require power calculations and analytic methods specific to SMART designs. Currently, the only sample-size calculator available for a SMART design with a survival outcome compares two specific treatment pathways using a weighted log-rank test. This calculator is only applicable for designs similar to the hypothetical melanoma SMART if the non-responders to anti–PD-1 therapy were not re-randomized (i.e., if there were only 4 embedded treatment pathways instead of 6; ref. 25). Any other SMART design (e.g., our hypothetical design in Fig. 2) or any other test (e.g., a global test of equality across all treatment pathways or finding the best set of treatment pathways using multiple comparisons with the best) requires statistical simulation. Other sample size calculations exist for survival outcomes but do not have an easy-to-implement calculator (26, 27).

Methods are available to estimate survival (28, 29) and compare (25, 26, 30–32) treatment pathways with survival outcomes, and R packages (33) can aid in the analysis.

In this example, we calculate sample sizes of implementing three single trials versus implementing one trial using a SMART design. For the first single-stage trial, we assume a log-rank test, survival rates of 80% and 68%, respectively, at 1 year for combination and single agent anti–PD-1, exponential survival distributions, 1 year for accrual, and an additional 2.5 years of follow-up. The same assumptions were applied for continuing initial treatment versus discontinuing the initial (this is a conservative sample size for this trial, since the survival rates at 1 year would likely be closer together and require more patients). To have the same assumptions across the single-stage trials and SMART design, the survival rate at 1 year for those who did not respond to single agent anti–PD-1 therapy and received ipilimumab was set at 68% and for those who received the combination anti–PD-1 and ipilimumab was set to 74%. Parameters for the SMART were specified to mimic the single-stage settings with the additional assumptions of a response rate to initial therapy being 40% and 1-year survival rates of 69%, 68%, 75%, 74%, 80%, and 74% for the treatment pathways 1 through 6, respectively. For the SMART, a weighted log-rank test of any difference in the six treatment pathways was used for power via simulation (30, 33). With these assumptions, 570 participants are required to observe any difference in the six embedded treatment pathways within 1 SMART (Table 1). This sample size is less than the 1,142 participants that are required by summing the sample sizes with the same assumptions using three traditional single-stage trials. We note that using a global test in the SMART allows for less participants, and that potentially, one of the trials in the single-stage trial setting may be dropped on the basis of previous trial results. However, a SMART allows us to answer many questions simultaneously and find optimal treatment pathways potentially ignored in the single-stage setting.

A SMART would most likely require less time from start to finish than the single-stage trials because it is unlikely that the single-stage trials would run simultaneously (because the trials based on response to initial treatment would require an actionable result from the first trial; ref. 34). Furthermore, because participants are followed throughout the trial and offered follow-up treatment, individuals may be more likely to enroll in the SMART (i.e., the sample of participants in a SMART may be more generalizable) and adhere to treatment (34).

Beyond the sequences of treatments in a SMART design that are tailored to an individual based on intermediate outcome, additional analyses (like subgroup analyses in traditional trials) may evaluate more individualized treatment pathways. Information, including demographic, clinical, and pathologic data collected at baseline and between baseline and the measurement of the

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NOTE: The trials in approach 1 would require a total of 1,142 participants versus 570 total participants from one SMART.
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Discussion

This article has focused on an example SMART in BRAF wild-type metastatic melanoma to answer questions about the best treatment pathways, including ipilimumab and anti–PD-1 therapy. As new immunotherapies are available for trials, ipilimumab may ultimately be replaced in this type of design by one of the more novel drugs (e.g., inhibitors of the immunosuppressive enzyme IDO or other checkpoint inhibitors such as drugs targeting lymphocyte-activation gene 3, “LAG-3”). Our proposed SMART design could be considered as a template for testing any number of these potential future possible combinations.

A SMART design may be a more efficient trial design to understand which immunotherapy treatment pathways in BRAF wild-type metastatic melanoma lead to the longest overall survival. SMARTs can definitively evaluate the treatment pathways that many physicians use in practice, leading to the recommendation of treatments over time based on individual response. A single SMART can enroll and continue to follow participants throughout the course of care to provide evidence for beginning treatment with single-agent anti–PD-1 or combination therapy and the optimal number of doses needed to sustain a response while limiting toxicity.

Of course, a SMART design is not limited to providing robust evidence for treatment pathways in BRAF wild-type metastatic melanoma but can help develop and test treatment pathways that lead to optimal outcomes in other melanomas, cancers, and diseases. We acknowledge our SMART proposal is inherently limited by heterogeneity in some of the treatment pathways, such as in the “Standard-of-care” box in subgroup 5. In our melanoma example, this box could include diverse treatments such as chemotherapy, inhibitors of other molecular drivers such as imatinib for patients with KIT mutations, and other potentially effective immunotherapy agents. How the various treatments within this pathway affect overall outcomes remains unknown in our proposed design.

A SMART requires less overall participants and can be implemented and analyzed in a shorter period of time than executing several single-stage, standard two-arm trial designs (34). However, a commitment to more participants at the initiation of the trial for a SMART is needed than for individual standard trials, and logistics may be more complex in a SMART by re-randomizing participants at an intermediate time point (34). With current technology that can handle multiple interim randomizations or the ability to randomize participants upfront to follow particular treatment pathways, the increased logistics should not outweigh the benefits of finding optimal immunotherapy treatment pathways from SMART designs.

The SMART design, even when powered on questions regarding the best initial treatment in a pathway or best strategy for responders or nonresponders (i.e., question 1, 2, or 3 from the previous section), may be more beneficial than multiple traditional single-stage designs. A SMART can conclusively answer one question with additional analyses to address questions concerning treatment pathways that may be relevant to clinical practice, such as how long to remain on immunotherapy. Furthermore, SMART designs can identify treatment interactions when treatments differ in the first and second stages (i.e., a SMART design that differs from that in Fig. 2 by re-randomizing to different treatments in the second stage as opposed to continuing or discontinuing initial treatment), and there may be delayed effects of initial treatments that modify the effects of follow-up treatments. Single-stage trials cannot evaluate these interactions between first and second-stage treatments dependent on intermediate outcomes.

More novel trial designs, including the SMART, may be needed to answer pertinent treatment questions and provide robust evidence for effective treatment regimes, especially in immuno-oncology research where novel combinations are frequently being proposed. A SMART can examine treatment sequences and combinations of immunotherapies and other drugs that lead to the longest overall survival with decreased toxicities. SMART designs may be able to verify potential optimal treatment pathways identified from dynamic mathematical modeling (38). SMARTs may require a paradigm shift for practicing physicians, pharmaceutical companies, and guidance agencies to begin to test and approve treatment regimens that may adapt within an individual along the course of care, as opposed to testing and approving agents at particular snapshots in time and piecing these snapshots together trusting that these pieces tell the full story.

Disclosure of Potential Conflicts of Interest

M.A. Postow reports receiving commercial research grants from Bristol-Myers Squibb, speakers bureau honoraria from Bristol-Myers Squibb and Merck, and is a consultant/advisory board member for Array BioPharma, Bristol-Myers Squibb, Merck, and Novartis. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.M. Kidwell, K.S. Panageas

Writing, review, and/or revision of the manuscript: K.M. Kidwell, M.A. Postow, K.S. Panageas

Study supervision: K.S. Panageas

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References


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