

## American Society of Clinical Oncology Policy Statement Update: The Critical Role of Phase I Trials in Cancer Research and Treatment

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### INTRODUCTION

The American Society of Clinical Oncology (ASCO) represents more than 35,000 oncologists and other health care professionals who care for people with cancer and conduct research to improve cancer treatment. ASCO approved a policy statement on the importance of phase I trials in cancer treatment in 1996 and published it in 1997.<sup>1</sup> ASCO and its member clinicians have repeatedly used this statement as evidence that phase I trials have therapeutic intent (ie, potential to provide patients with clinical benefit) and to argue for insurance coverage of routine patient costs in these trials.

Since the 1997 statement was published, there have been significant developments in cancer care and research. The Patient Protection and Affordable Care Act (ACA) of 2010<sup>2</sup> has led to enormous changes in the health care delivery system by increasing the number of individuals with health insurance and improving patients' access to many high-quality and preventive care services. The number of people diagnosed with cancer<sup>3</sup> and surviving cancer<sup>4</sup> is also rapidly increasing. Thus, there is an increase in the number of patients in need of cancer care, and these patients are more likely than in the past to have health insurance that covers the cost of their treatment. The ACA requires payers to cover routine patient costs in phase I to IV trials.

Simultaneously, the biopharmaceutical industry has been investing in molecularly targeted agents and immunotherapies for cancer, leading to an increase in the number of promising new agents that need testing in phase I trials.<sup>5</sup> Researchers are also exploring innovative trial designs, which may decrease patient risk, expose fewer patients to less-than-optimal drug doses, increase patients' potential for clinical benefit from trial participation, better identify subpopulations of patients likely to benefit from an agent, and reduce the chance of ineffective agents continuing through the development process.<sup>6-14</sup> The result is that phase I trials in cancer

have greater potential as a treatment option for many patients with cancer than they did in 1997.

To address this changing landscape in cancer, ASCO convened a working group of the Cancer Research Committee to review and update the ASCO policy statement on phase I trials. This update reaffirms the critical importance of phase I trials in cancer research and treatment and emphasizes their therapeutic intent. The first section of the statement defines phase I trials in cancer and underscores the importance of trial design in the drug development process. Subsequent sections review the evidence that phase I trials provide patients with clinical benefit and make a series of recommendations on how to increase participation in these trials. The statement concludes with a section on special issues in pediatric phase I trials.

### DEFINING PHASE I TRIALS

Phase I trials are an important step in translating basic research into clinical practice and are generally the first-in-human studies of new agents. These studies are used by researchers to determine the recommended dose and schedule of an investigational agent, as well as to provide initial observations of the clinical effect of an agent and an assessment of its safety profile. Trials often include pharmacokinetic and pharmacodynamic studies of the investigational agent and, increasingly, explore development of relevant biomarkers.

Subsequent phase I studies (phase IB) may evaluate new schedules of existing agents or combinations of new agents with established agents or radiation therapy. They may also assess toxicity, tolerability, and biologic end points in patient populations that were excluded in prior phase I studies. In addition, researchers are increasingly conducting phase I/II studies that accrue hundreds of patients with both dose escalation and cohort expansions and that include an assessment of efficacy. For example, the approvals by the US Food and Drug

Administration (FDA) of the combination of dabrafenib and trametinib and the use of pembrolizumab for metastatic melanoma were based on phase I/II studies.<sup>15,16</sup>

Traditional phase I study designs treat cohorts of patients with increasing doses of an agent, with the goal of determining the maximum-tolerated dose.<sup>17,18</sup> In the era of molecularly targeted agents and immunotherapies, factors other than toxicity influence researchers' determination of dosage to take forward to future studies. Researchers have developed study designs that focus on the detection of signals of activity, while monitoring for toxicity.<sup>6-14</sup> These designs allow researchers to more efficiently escalate the dosage of the agent patients are receiving to levels that are more likely to result in a therapeutic effect. If the target of an agent is well defined, these new designs also permit researchers to enrich the research participants with molecularly selected patients who are most likely to have disease driven by the targeted pathway. This has the potential to promote drug development by ensuring that the subset of patients most likely to benefit from the agent are participating in the trial, which optimizes the chance of patient benefit and provides drug developers with early information about the efficacy of the new agent.

## EVIDENCE OF CLINICAL BENEFIT

Both patients and clinicians participate in phase I trials because they believe these trials have the potential to provide clinical benefit.<sup>19-22</sup> The National Cancer Institute (NCI) Investigator Handbook states that "therapeutic intent is always present in phase I trials."<sup>19p13</sup> Similarly, the FDA acknowledges that one of the primary aims of phase I trials is "to gain early evidence of effectiveness."<sup>23</sup> This section reviews the evidence that patients who participate in phase I trials may experience improved quality of life, psychological benefit, and direct medical benefit, as well as examines a number of factors in phase I trials in cancer that are reducing research participants' risk.

### Improved Quality of Life and Psychological Benefit

Participation in phase I trials in cancer is likely to provide patients with improved quality of life and psychological benefit.<sup>24-28</sup> Patients who participate in these trials receive a defined treatment plan,<sup>29</sup> which ensures that patients have routine contact with clinicians and are treated following a strict treatment protocol.<sup>29-31</sup> Participation also gives patients the opportunity to exercise control over their disease by trying a novel therapy and contributing to generalizable knowledge about their disease.<sup>29,31,32</sup> Many participants are empowered by knowing they are helping to inform the treatment of future patients.<sup>21,30,31</sup>

In addition, participants in phase I trials have access to palliative care to manage their pain or cancer-related symptoms and may also be referred to hospice for care at the end of life.<sup>33</sup> Thus, patients participating in phase I trials do not need to make a painful choice between receiving these critical services and participating in a trial. In multiple surveys, phase I trial participants have reported maintaining a high quality of life throughout the duration of the studies and have not reported physical or mental decline.<sup>34-36</sup>

### Direct Medical Benefit

Many participants in phase I trials in cancer have the "prospect of a direct medical benefit."<sup>37p617</sup> There are instances in phase I trials in

cancer where the agents being tested have had a significant therapeutic impact on large numbers of patients. Imatinib mesylate, for example, led to a complete hematologic response in 53 of 54 enrolled patients with chronic myeloid leukemia, and 96% of patients experienced a benefit beyond 1 year.<sup>38,39</sup> More recent examples include pembrolizumab for metastatic melanoma, which produced an objective anti-tumor response in 38% of patients; 6% of patients experienced a complete response at or after 12 weeks.<sup>40</sup> Similarly, more than 60% of patients with ALK-positive non-small-cell lung cancer achieved an objective response to crizotinib, and the estimated overall survival at 1 year was 75%.<sup>41</sup>

Several older meta-analyses of phase I trials in cancer found that approximately 5% of patients experience an objective response.<sup>42-46</sup> Agrawal and Emanuel,<sup>29</sup> in addition to other researchers, have identified a number of reasons why objective response rates in more recent phase I trials of anticancer therapies may be higher than 5%.<sup>47</sup> Most of the original meta-analyses included studies published from 1970 to 1991 that did not include molecularly targeted agents or immunotherapies. These studies often did not measure disease stabilization, which is problematic, because prolonged disease stabilization is becoming an increasingly important end point for a range of new agents.<sup>48</sup> They also do not reflect improvements in clinicians' provision of palliative care in recent years<sup>49</sup> or the implementation of better staging tests, which may lead to better patient outcomes.<sup>26</sup>

Data from these meta-analyses mask important instances of phase I trial participants experiencing a direct medical benefit. More than 60% of the agents evaluated in the original meta-analyses, for example, had at least one patient whose tumor shrunk more than 50%. Plus, more than 30% of the agents tested in these studies had objective response rates greater than 5%.<sup>29</sup>

Newer meta-analyses of patients' response rates in phase I trials in cancer have found higher rates of effectiveness. Horstmann et al<sup>50</sup> analyzed NCI-funded phase I trials of both single and combination agents in 2005. Of the 12,000 individuals who participated in these trials, almost 11% experienced an objective response. This number increased to almost 18% of patients when a phase I trial of a combination regimen included an FDA-approved drug. Similarly, Italiano et al<sup>47</sup> conducted a systematic review of phase I cancer studies conducted by the Adult Phase I Unit of the Institut Gustave Roussy from 2003 to 2006. Of the 180 patients participating in 10 phase I trials, 13 had either a complete or partial response (7%). Stable disease was reported in 75 patients (41%).

Response rates between 5% and 18% in phase I trials in cancer are equivalent to the response rates for many FDA-approved drugs.<sup>29</sup> For example, topotecan for ovarian cancer has a 10% response rate,<sup>51,52</sup> gemcitabine for pancreatic cancer has a 5.4% response rate,<sup>53</sup> and ipilimumab for melanoma has a response rate slightly more than 10%.<sup>54</sup>

### Reduced Risk

Roberts et al<sup>55</sup> found that the risk-benefit ratio for patients in phase I trials in cancer has improved over time. Their analysis reviewed the proceedings of the ASCO annual meetings between 1991 and 2002 and identified 213 published phase I trials involving almost 6,500 patients. The overall objective response rate in these trials was approximately 4%, and the overall rate of death related to toxicity was 0.5%. However, treatment-related death rates decreased significantly from more than 1% between 1991 and 1994 to 0.06% between 1999

and 2002. The odds of a patient dying as a result of an experimental treatment in the earlier time period were more than 10× those in the later time period.

The advent of molecularly targeted agents in cancer care may explain some of the improvement in the risk-benefit ratio for patients with cancer participating in phase I trials.<sup>56</sup> These agents have the potential to allow researchers and clinicians to better identify which patients are likely to respond to a specific agent.<sup>57</sup> Researchers at MD Anderson Cancer Center, for example, evaluated 460 patients with molecular alterations who participated in phase I trials and found that patients whose therapy was matched to their molecular profile had a response rate of 27%, compared with a response rate of 5% in patients whose therapy was not matched.<sup>58</sup> In addition, phase I trials of molecularly targeted agents may not require exposing patients to the maximum-tolerated dose, as is done with traditional cytotoxic drugs, because patients may respond at lower doses.<sup>31,32,59,60</sup>

New trial designs are also helping researchers minimize exposing patients to subtherapeutic doses in phase I trials.<sup>54,57,58,61</sup> Agrawal and Emanuel<sup>29</sup> noted that providing participants with low doses of the agent in early cohorts “ironically ensures that the majority of participants are treated at doses that cannot produce responses in human tumors.”<sup>29p1075</sup> When researchers use accelerated and adaptive trial designs, more patients can be treated at biologically active doses; thus, the risk of patients being exposed to toxic drug doses is reduced, and researchers’ identification of recommended phase II doses is facilitated.<sup>16,61-67</sup>

## RECOMMENDATIONS

It is critical that patients have the opportunity to make informed decisions about participating in phase I trials as part of their cancer treatment, given the potential for these trials to provide clinical benefit, as we have reviewed. ASCO targets five main stakeholders in its recommendations for improving patients’ understanding of and access to phase I trials in cancer<sup>1</sup>: payers,<sup>2</sup> professional societies and patient advocacy organizations,<sup>3</sup> clinicians,<sup>4</sup> researchers, and<sup>5</sup> the biopharmaceutical industry and other trial sponsors. Table 1 provides an overview of the ASCO recommendations.

### Improve Coverage of Phase I Trials

Because patients with cancer regularly benefit from phase I trials, it is critical that payers provide insurance coverage for these trials. The current uneven application of laws and regulations, however, does not require all payers to cover routine patient costs in phase I trials. The ACA requires many private payers to cover these costs for phase I to IV

trials, but the coverage rules for Medicare are unclear. Medicaid and plans that are grandfathered under the ACA are not required to provide coverage.

In Medicare, the National Coverage Determination for routine patient costs in clinical trials does not mention the phases of trials that are covered; Medicare defers to regional contractors regarding coverage of individual trials. The three basic requirements for Medicare coverage are as follows<sup>68</sup>:

- The subject or purpose of the trial must be an evaluation of an item or service that falls within a Medicare benefit category (eg, physicians’ service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (eg, cosmetic surgery, hearing aids).
- The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent.
- Trials of therapeutic interventions must enroll sufficient patients to have a proper control group.

Medicare contractors may use the therapeutic intent language to deny coverage for phase I trials. However, the Medicare policy does not require therapeutic intent to be the primary end point of a trial for the trial to qualify for coverage. Therapeutic intent only needs to be a component of the trial and, as reviewed under Evidence of Clinical Benefit, phase I trials in cancer meet this standard. Thus, these trials should be covered by Medicare.

Similarly, some health care plans are grandfathered under the ACA and do not need to comply with the ACA provision on clinical trial coverage. Grandfathered plans include group health plans or health insurance coverage in existence on March 23, 2010 (ie, date of ACA enactment). The number of these plans will decrease over time, because a plan loses its grandfathered status if it either decreases benefits or increases costs for plan members.

The coverage gap in Medicaid program is more significant than the gap for grandfathered plans, because it will not be fixed over time. Federal laws do not require state Medicaid plans (whether fee for service or managed care) to cover routine patient costs in clinical trials. Requirements for Medicaid to cover these costs are governed by state law. Inconsistencies among state laws create disparities in patients’ access to phase I trials. Some states guarantee coverage of routine patient costs, whereas others do not.<sup>69-71</sup> This is problematic, given the potential clinical benefit patients may receive from participating in these trials.

#### Recommendation 1

- The Centers for Medicare and Medicaid Services should recognize that phase I cancer clinical trials meet the therapeutic intent requirement of the National Coverage Determination for routine patient costs in clinical trials.
- State Medicaid programs should reimburse for routine patient costs associated with clinical trials, including phase I trials.

### Improve Patients’ Understanding of Goals of Phase I Trials

Patients may have misconceptions about the potential for clinical benefit from participating in phase I trials in cancer.<sup>72-76</sup> This situation is magnified when clinicians and researchers inadequately communicate issues that are central to patients’ informed decision making

**Table 1.** Goals of Recommendations

Goal
Improve payers’ coverage of routine patient costs in phase I trials
Improve patients’ and clinicians’ understanding of goals of phase I trials
Increase number of patients who enroll onto phase I trials
Increase researcher and trial sponsor compliance with best practices for phase I trials
Increase biopharmaceutical industry support of pediatric phase I trials

about trial participation.<sup>77</sup> For example, one study found that clinicians explained that the goals of a phase I trial include safety in only 23% of conversations with patients and include determining the appropriate dose of the treatment in 52% of conversations with patients.<sup>78</sup> Another study found that clinicians spent limited time with their patients discussing the fact that the primary purposes of these trials are dosing and safety or that the agents are early in testing and may never come to market.<sup>79</sup>

Despite these challenges, there is evidence that intervening in the informed consent process can improve patients' comprehension of the goals of phase I trials. Kass et al<sup>80</sup> showed that patients who watched a video about trial participation were more likely to correctly state the purpose of early-phase trials than patients in the control group. Similarly, Fallowfield et al<sup>81</sup> demonstrated that clinician participation in a workshop on recruitment for early-phase trials led to improvements in clinicians' confidence and ability to communicate key information to patients about the risks and benefits of phase I trial participation. Other changes to the informed consent process, such as using interactive electronic formats that can be shared with family members and primary care clinicians, could also improve patient comprehension.

*Recommendation 2*

- The educational efforts of professional societies should target improving clinicians' and researchers' abilities to discuss the purposes and risk-benefit assessment of patients' participation in phase I trials in cancer.
- Professional societies and patient advocacy organizations should develop enhanced educational materials for patients to explain the goals of phase I trials in cancer.

**Increase Enrollment Onto Phase I Clinical Trials**

Clinicians and researchers may be reluctant to recommend phase I trials to patients because routine patient costs incurred during the trial may not be reimbursed. As we have mentioned, however, coverage of phase I trials was improved by the ACA and should be further enhanced to address the remaining gaps in coverage for phase I trials in cancer (Recommendation 1).

Clinicians and researchers may also be reluctant to recommend phase I trials because they consider these trials a last resort for patients with advanced disease. However, the evidence cited under Evidence of Clinical Benefit suggests that this belief is unfounded. In some malignancies and in some scenarios, a phase I trial may provide the most promising treatment option. Moreover, clinical practice guidelines from ASCO<sup>82</sup> and the National Comprehensive Cancer Network<sup>83</sup> stipulate that patients should have the choice of participation in a clinical trial at each stage of their treatment, including phase I trials. Similarly, the 2013 Institute of Medicine report on the quality of cancer care highlights the importance of clinicians providing patients with cancer with care that is consistent with their needs, values, and preferences.<sup>84</sup> Determining a patient's needs, values, and preferences requires that the clinician present the option of participating in a trial during initial care planning, rather than after all other treatment options have failed.

*Recommendation 3*

- Professional societies should enhance educational materials for clinicians and researchers to help overcome challenges to phase I trial enrollment, such as incomplete understanding

of insurance coverage and attitudes that phase I trials should be considered only after other treatment options fail.

**Improve Phase I Trial Research Process**

The NCI recently modified its template for phase I trial protocols to include a secondary objective about the therapeutic intent of these trials. The model language states that "although the clinical benefit of this/these drugs has not been established yet, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability."<sup>85p8</sup> Researchers' and trial sponsors' inclusion of this language in phase I trial protocols would clarify that phase I trials meet the requirement for coverage of routine patient costs by Medicare (ie, these trials have therapeutic intent). Researchers should also clearly discuss with potential trial participants, and include in the consent form, information about the objectives of the trial and potential benefits and risks (Recommendation 2).

In addition, as noted under Defining Phase I Trials and Reduced Risk, new phase I trial designs (eg, accelerated titration designs, continual reassessment methods, and 3 + 3 + 3 designs)<sup>86</sup> are allowing researchers to more efficiently escalate the dosage of the agent being tested to levels that are more likely to result in therapeutic effect. Researchers' use of these designs may make it easier to accrue patients to phase I trials.

Researchers' use of these trial designs is also important for the drug development process. Many phase I studies proceed directly into randomized phase II or III studies. Thus, it is crucial to identify the optimal dose of an agent to bring forward to future studies and any biologic activity that may help researchers identify the subpopulation of patients most likely to benefit from an agent. Traditional study designs that rely on dose escalation to toxicity (eg, 3 + 3 design) may over- or underestimate toxicity and may miss biologic activity.<sup>14</sup> This may lead to failure of the agents in phase II or III studies. In contrast, newer study designs may be better able to identify an optimal dose and use larger cohorts of patients, which helps researchers define biologic end points.<sup>62,87</sup> Despite these advantages, most phase I studies in adults still use traditional study designs.<sup>63,83-85</sup>

*Recommendation 4*

- Researchers and trial sponsors should include language on therapeutic intent in phase I trial protocols.
- Researchers and trial sponsors should use phase I trial designs that minimize the number of patients exposed to potentially subtherapeutic doses of the agent being tested.

**Special Issues in Pediatrics**

The development of new agents for children with cancer is urgently needed. Cancer is the leading cause of death resulting from disease in children,<sup>88</sup> and large numbers of childhood cancer survivors experience long-term or late effects from their treatment.<sup>89-95</sup>

There are a number of challenges, however, to rapid development of new anticancer agents for children.<sup>96,97</sup> Childhood cancers are a collection of rare and ultra-rare diseases, which means the biopharmaceutical industry has few incentives to conduct pediatric phase I trials. The incentives that do exist, such as the pediatric patent extension in the Best Pharmaceuticals for Children Act<sup>98</sup>, are inadequate to encourage early research and development in pediatric populations.<sup>99</sup>



As a result, almost no drug development programs are primarily focused on childhood cancers. Companies too frequently delay the development of pediatric agents until adult phase III trials are under way or completed or until regulatory approval for an adult indication is received. In addition, companies may halt clinical testing of new agents in children if pivotal trials in adults prove negative.

The concern of the biopharmaceutical industry that adverse events observed in pediatric phase I trials could delay the development of a drug for adults is unfounded. Phase I trials in pediatrics provide drug developers with an enormous opportunity to test the safety and efficacy of their products alongside the ability to gain further scientific insight into fundamental biologic pathways the study of childhood cancer may afford. Given that upward of 60% of children and adolescents participate in clinical trials when such trials are available,<sup>100</sup> pediatric phase I trials can be conducted in a timely and efficient manner. Industry should leverage the high level of clinical trial participation in pediatric populations and start phase I trials in children earlier.

#### Recommendation 5

- The biopharmaceutical industry should initiate pediatric phase I trials for agents directly relevant to childhood cancers during the late phase I or early phase II adult drug development program timeframe.

## DISCUSSION

Phase I trials simultaneously generate new knowledge about novel agents and combinations of agents and, by virtue of having a therapeutic intent, can provide patients with clinical and psychological

benefits. This statement documents the importance of phase I trials in cancer treatment and research, emphasizes the importance of phase I trial design in the development of new agents, and makes several recommendations to improve patients' access to and understanding of these trials. All participants and stakeholders, including clinicians, researchers, patients, payers, drug and biologic manufacturers, professional societies, and patient advocacy organizations, should work together to create a health care delivery and payment system that supports patients' decisions to participate in these trials. By working toward this shared goal, patients with cancer can take full advantage of basic scientific discoveries that have the potential to improve their clinical outcomes and quality of life.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

### American Society of Clinical Oncology Policy Statement Update: The Critical Role of Phase I Trials in Cancer Research and Treatment

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