Correcting the ASCO position on phase I clinical trials in cancer

Howard A. Burris III

In a Comment article published on 30 August 2019 in *Nature Reviews Clinical Oncology* (Kimmelman, J. Phase I trials as therapeutic options: (usually) a betrayal of evidence-based medicine. *Nat. Rev. Clin. Oncol.* **16**, 719–720 (2019)), Jonathan Kimmelman questioned the therapeutic value of phase I trials in the treatment of cancer. In his arguments, he inaccurately portrays the perspective of the American Society of Clinical Oncology (ASCO). This letter clarifies and corrects ASCO's position.

In his article[1], Kimmelman conflates therapeutic intent with therapeutic benefit. ASCO's position is that phase I trials have the potential to provide patients with clinical benefit; the goal of participation is to attempt to treat the cancer (meaning that these trials are offered to patients with therapeutic intent) as well as to achieve the scientific objectives of the study[2,3]. This characterization is consistent with the National Cancer Institute Investigator Handbook, which states that "therapeutic intent is always present in phase I trials"[4]. This position is also aligned with US FDA policy, which acknowledges that a primary aim of phase I trials is "to gain early evidence of effectiveness."[5] Therapeutic intent does not mean that all investigational agents tested will be efficacious, nor does it mean that all phase I trials are likely to provide clinical benefit. Furthermore, Kimmelman's analogy between pharmacies and phase I trials ignores the additional patient protections provided by trials, such as institutional review board review, informed consent and protocol-specified monitoring and reporting procedures.

ASCO has repeatedly highlighted developments in the design and conduct of phase I trials that increase the likelihood of participants deriving benefit. These include innovative trial designs that limit the risk of patients receiving a dose of a drug that is too low to be effective, biomarker selection strategies that enable researchers to enrich the cohorts with participants most likely to obtain clinical benefit and the inclusion of efficacy end points and expansion cohorts that can be used to provide evidence for FDA approval[2,3]. Adashek and colleagues[6] identified a similar paradigm change in phase I trials in a manuscript published in this journal on 2 September 2019. Moreover, these developments are not diminished by the use of the objective response rate as a surrogate end point. The FDA has accepted this end point as a reasonable indication of clinical benefit and uses it to support accelerated approval; however, post-approval studies are necessary to confirm such clinical benefits[7].

Kimmelman posits that ASCO's position on phase I trials encourages patient recruitment and postpones painful discussions regarding the limitations of medicine. However, ASCO encourages improvements in the informed consent process and patient education to ensure that phase I trial participants understand the uncertainties regarding the potential for benefit and the risks involved, as well as the research objectives of these studies[2,3]. ASCO also supports the early initiation of supportive care as a fundamental part of cancer treatment[8] and recommends against the use of active anticancer treatments near the end of life[9]. The goal of these positions is to ensure that patients for whom continued cancer-directed therapy is medically appropriate are offered the opportunity to participate in clinical trials of all phases, not to unnecessarily prolong treatment.

In summary, ASCO believes that phase I trials have a crucial role in the treatment of patients with cancer as well as in research, and that sponsors and investigators should design trials that maximize the potential for clinical benefit.

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Competing interests

H.B. has acted as a consultant or advisor of AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eisai, FORMA Therapeutics, Incyte, Janssen, MedImmune, Mersana, Novartis, Roche/Genentech, Tolero Pharmaceuticals, and has provided Expert Testimony for Novartis. All funds for these activities were paid to H.B.'s institution. H.B.'s institution has received research funding from Agios, Arch, Arvinas, AstraZeneca, BioAtla, BioMed Valley Discoveries, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, CicloMed, CytomX Therapeutics, eFFECTOR Therapeutics, Gilead Sciences, GlaxoSmithKline, Harpoon therapeutics, Immunocore, Incyte, Janssen, Jiangsu Hengrui Medicine, Jounce Therapeutics, Kyocera, Lilly, Loxo, Macrogenics, Merck, Millennium, MedImmune, Moderna Therapeutics, Novartis, Roche/Genentech, Revolution Medicines, Seattle Genetics, Takeda, Tesaro, TG Therapeutics, Verastem and Vertex. H.B. is employed in a leadership role and owns stock in the for-profit health-care company HCA Healthcare/Sarah Cannon. H.B. is the current president of ASCO.

Reply to 'Correcting the ASCO position on phase I clinical trials in cancer'

Jonathan Kimmelman

I thank Dr. Burris for his letter. My article (Kimmelman, J. Phase I trials as therapeutic options: (usually) a betrayal of evidence-based medicine. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-019-0264-7 (2019))[1] concerns an ethical question: are oncologists and others justified in presenting phase I trial participation as a therapeutic option for patients meeting the eligibility criteria? My view is that, generally speaking, they are not. For as long as physicians do not yet know how to use a drug, much less whether it works under near-optimum conditions, presenting phase I trials as a therapeutic option betrays the spirit of evidence-based medicine. It also fails to alert clinicians to the fact that their

patients are, in fact, making personal sacrifices in the name of medical advances.

Dr Burris suggests (Burris, H.A. Correcting the ASCO position on phase I clinical trials in cancer. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-019-0311-4 (2019))[2] that I confuse ASCO's position (that phase I trials have 'therapeutic intent') with the position that phase I trials actually have 'therapeutic benefit.' Au contraire. My published response to ASCO's phase I position statement makes clear that a declaration of 'therapeutic intent' has practically no bearing on the ethical question I am concerned with[3]. Intent is merely a mental state. Physicians who offer quack treatments such as caesium chloride outside of the context of a clinical trial might do so with therapeutic intent. This intent, however, does not justify recommending such treatments, much less asking patients to endure their disruptive effects. By contrast, claiming that something is therapeutic is a substantive claim about the relationship between the risks and benefits of a particular treatment in a specific population of patients. From reading ASCO's and Dr Burris's statements, it is nearly impossible to come away with the view that both regard phase I trials not merely as therapeutically intended, but substantively therapeutic.

Dr. Burris also faults my pharmacy analogy for failing to note the existence of oversight mechanisms, like institutional review boards (IRBs), in clinical research. I challenge this by asking for a single example where an IRB, or the FDA for that matter[4], refused to allow a phase I trial to proceed owing to a lack of preclinical evidence of efficacy. Moreover, such bodies often acquiesce to the use of outdated study designs and evasive descriptions of the likelihood of clinical benefit, such as 'we do not know if you will receive medical benefit from taking part in this study.' Respectfully, I believe that ASCO's phase I trial policy statement can do better for patients, researchers and oversight bodies. Firstly, ASCO might explicitly urge researchers to explain to prospective trial participants that phase I trials are primarily aimed at eliminating unsafe and ineffective treatments. Second, it might endorse the use of the more forthright language recommended by the US National Cancer Institute: "it is unlikely this intervention will help you live longer"[5]. Lastly, ASCO might seek to remind oncologists that phase I trials are, first and foremost, scientific undertakings. The ultimate moral justification for exposing patients to an unproven intervention within a trial is to evaluate the effects of the intervention. Accordingly, investigators and IRBs should address the continuing challenges regarding the preclinical rationale, feasibility and design, integrity of the analysis, and the completeness of reporting of data from phase I trials involving patients with cancer.

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