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 article¹, 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 colleagues⁶ 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 benefits⁷.

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 treatment⁸ and recommends against the use of active anticancer treatments near the end of life⁹. 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, CicleMed, 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