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The FDA's latest move to expand eligibility for oncology trials — a double-edged sword?

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Recent FDA draft guidance for sponsors of oncology clinical trials encourages enrolment of patients with incurable cancer and no potential for prolonged and/or near-normal survival, regardless of whether they have received existing treatment options. This guidance constitutes a substantial departure from current standards, with potentially profound implications for trial participants as well as drug regulation and reimbursement.

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On 25 June 2021, the FDA issued draft guidance proposing that patients with incurable cancer ("when there is no potential for cure or prolonged/near normal survival")[1] might reasonably be permitted to enrol in oncology clinical trials regardless of whether they have received existing alternative treatment options. If accepted and finalized, this guidance would mean that, with "appropriate informed consent"[1], sponsors could arguably target almost any patient with an advanced-stage cancer for inclusion in trials of investigational drugs, including first-in-human and other phase I studies, even if those patients have not received available evidence-based therapy, including agents proven to increase overall survival (OS) or quality of life. This departure would constitute a substantial shift from current standards and has profound implications for both patients participating in clinical trials and drug approval and reimbursement.

The FDA's draft proposal

Given that most advanced-stage cancers are incurable, patients are usually treated with a series of therapies, often called lines, intended to prolong life for as long as possible. Typically, novel anticancer drugs are tested initially in uncontrolled clinical trials involving patients who have exhausted available treatment options — which might consist of one to more than three prior lines of therapy, depending on the type of cancer. Indeed, the FDA has traditionally discouraged sponsors from enrolling patients in such studies unless the patients have already received all therapies with proven efficacy or the investigational agents are given in combination with a proven therapy. Phase I dose-escalation trials, including first-in-human trials, are a subset of these studies and are associated with a low likelihood of tumour response and much less clinical benefit, with systematic reviews indicating objective response rates of only ~5%[2]. The proposed FDA guidance would arguably permit sponsors of not only uncontrolled phase II trials of novel cancer drugs but potentially also such phase I studies to enrol any patient diagnosed with an advanced-stage and incurable cancer, with the exception of a small number of malignancies for which current treatments are associated with a near-normal life expectancy (for example, chronic myeloid leukaemia), even before exhausting effective treatment options. If finalized, this guidance means patients with many common types of cancer might forgo 1–3 lines of therapy, which are likely to include drugs with proven OS benefits.

Limited engagement of patients in oncology clinical trials is an important public health issue; <5% of adult patients with cancer are reported to enrol in a trial, and >20% of trials fail to accrue sufficient patient numbers[3]. This draft guidance forms part of the FDA's broader initiative to encourage rational expansion of eligibility for oncology clinical trials, such as inclusion of both elderly and paediatric patients and those with HIV, brain metastases, prior malignancies or substantial co-morbidities[4]. While these steps are commendable and needed, expanding this list to potentially include patients with incurable cancer who have not received any prior therapy in trials of agents with no known efficacy presents a considerable increase in risk for patients and disrupts the current landscape of drug development.

Risk for patients

Novelty is alluring in cancer treatment, and many investigational drugs are hailed as 'miracles', 'revolutions', 'game-changers' or 'cures', sometimes based only on results in mice[5]. In a drug development environment prone to hype and exaggeration, one immediate risk is that more patients who are eligible to receive existing, evidence-based, potentially highly effective therapies will instead choose to enrol in early phase trials of ultimately disappointing agents. Consider the case of a woman newly diagnosed with HER2$^+$ metastatic breast cancer at 61 years of age

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(the median age of diagnosis). This patient would probably be eligible for the CLEOPATRA regimen, a combination of FDA-approved drugs (pertuzumab, trastuzumab and docetaxel) followed by subsequent lines of therapy, a strategy proven to provide a median OS duration of 56 months[6]; however, such treatment is unlikely to result in normal or near-normal life expectancy. On the basis of the draft guidance, the patient could potentially enrol in a phase I trial in lieu of receiving this highly effective regimen. Hopefully, the discussion between patients and their physicians constituting 'appropriate informed consent' would lead most patients to avoid this possibility and opt for the lower-risk, existing treatment option. Nevertheless, if such a choice was made en masse, a serious erosion in cancer outcomes might occur, as the odds are that most investigational agents in phase I trials will not provide meaningful clinical benefit. Thus, deferring proven drugs for the opportunity to participate in trials of novel agents might result in losses in both quantity and quality of life[7]. Investigators might also feel pressure to shift patients from standard therapy to clinical trials, particularly given that financial and professional incentives at many cancer centres encourage trial enrolment[8]. Furthermore, this guidance could potentially lead to an entrenchment of existing inequalities in US health care, given that existing treatments are generally very expensive whereas clinical trial costs are predominantly covered by the sponsor.

Risk for drug development

The current rules around clinical trials encourage sponsors to initially seek drug approval in later lines of therapy, which many do on the basis of uncontrolled surrogate radiological end points (for example, objective response rates). After approval, companies then move to conduct randomized controlled trials of the agents in earlier lines of therapy, potentially opening the treatment to a larger pool of patients. This two-step model ensures that drugs tested in the frontline already have established antitumour activity or proven survival gains in later lines, suggesting a stronger likelihood of benefit for patients with previously untreated disease.

The FDA's draft guidance might change these incentives. If allowed to enrol patients who have not exhausted available treatment options, companies might be incentivized to pursue marketing authorization across all lines of therapy through a single, nonrandomized study based on radiological measures of activity against a particular cancer type. In such a case, the company would have little or nothing to gain from conducting any rigorous randomized trials in larger cohorts of patients with the same disease. Even if post-market commitments are made, reviews show that delays in completing confirmatory studies are common, and the FDA and its expert advisory committees have been reluctant to recommend revoking approved indications even when the post-market trials are negative[9]. If, as a result of the draft guidance, post-approval trials also become unnecessary for manufacturers to gain market share, the net incentive will be not to conduct them and instead to seek to influence prescribing through marketing and circumstantial data, for example, from nonrandomized, single-arm, open-label studies.

A paradigm shift

With this proposed guidance, the FDA is trying to catalyse a new paradigm in cancer drug development, and many of its proposals are intended to encourage broader enrolment in oncology trials. The proposed broader inclusion of treatment-naive patients with incurable cancer in clinical trials might be appropriate for some cancer types, especially those malignancies for which frontline treatment options are poor and investigational agents have promising preclinical efficacy and/or biomarkers that are predictive of response. Indeed, experience drawn from the development of certain molecularly directed therapies, such as tyrosine kinase inhibitors for patients with non-small-cell lung cancer harbouring *ALK* rearrangements, has shown us that receiving targeted therapy in a trial setting can be favourable to receiving standard cytotoxic chemotherapy. Nevertheless, we believe that allowing patients with incurable cancer to forgo established treatments and enrol in trials of untested new products will lead some patients — particularly those drawn to innovation — to defer effective therapy, with potentially deleterious consequences, and will decrease incentives for companies to rigorously test their products in broader populations after approval.

Clinical trials need to be more accessible for patients who have exhausted proven medical therapy. Relaxation of strict eligibility criteria, the growth of expanded access or even large, pragmatic trials (such as the RECOVERY trial[10]) might better balance the wishes of patients and the need to generate robust scientific knowledge. The FDA should work with patient groups, clinical trial investigators and drug manufacturers to implement these changes without disrupting the current rules that protect patients with incurable cancer from omission of well-proven treatments.

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Competing interests

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