Title

The last word to new FDA draft guidance for cancer clinical trial eligibility criteria for patients with incurable cancer

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The US Food and Drug Administration (FDA) issued new draft guidance on June 25th 2021, to permit patients with incurable cancer (when there is no potential for cure or prolonged/near normal survival) to enroll in oncology clinical trials regardless of whether they have received existing alternative treatment options, when patients have been provided adequate information to make an informed decision on clinical trial participation [1]. Implementation of this guidance may cause a significant shift in oncology trial design and conduct globally, and the FDA invited comments to this draft guidance [2].

The FDA received six comments from various organizations, including medical associations, patient advocacy organizations and commercial companies. To ensure the opinions of the wider community are given due consideration we have collated, summarized, and analyzed these responses.

1. Association for Clinical Oncology (ASCO) and Friends of Cancer Research (Friends)

A joint statement from both organizations expressed support for the FDA's ongoing efforts to expand clinical trial options by modernized eligibility criteria for cancer clinical trials. Overall, they deemed 'the inclusion of patients with non-curable cancers essential' and with appropriate informed consent, patients in the non-curative setting should be eligible for trials of investigational cancer drugs regardless of having received available therapy [3]. However, they noted reducing potential therapeutic options to curative versus non-curative may neglect other important factors patients may consider when seeking a therapy(ies) that extend beyond the potential for a 'cure', such as delayed progression or improved quality of life and suggest addressing these factors would provide further clarity to this issue.

Comments from the ASCO-Friends Prior Therapies Work Group include that there are justifiable scenarios in which receipt of prior therapy(ies) may be necessary to 'maintain patient safety and ensure treatment efficacy'. As per the group's recommendations, 'patients should be eligible for clinical trials regardless of the number or type of prior therapies and without a requirement to have received a specific prior therapy, unless a scientific or clinical rationale is provided as justification', in both the curative and non-curative settings [3,4].

2. *American Society of Hematology (ASH)*

Comments made by ASH in response to the draft guidance were positive, stating 'Overall, the society is supportive of this document and the Agency's goal of increasing the inclusion of cancer patients (especially those with incurable cancers or individuals with hematologic malignancies with unfavourable long-term overall survival) in clinical trials', with the caveat that patients have been provided with appropriate informed consent that clearly states other treatment options might be clinically beneficial to them, and understand the possible benefits, risks, and uncertainties associated with the drug being studied and agree with the Agency's recommendation 'that if and when, such patients are enrolled into a study, they could be evaluated as a separate cohort to effectively interpret the efficacy of the drug being studied' [5].

Further comments state that 'ASH is supportive of these proposed recommendations because they will allow hematologists to recommend the best possible treatment path for their patients, which could be participating in a clinical trial rather than being required to first use existing treatments that might be suboptimal for them' [5]. ASH conclude their comments with the hope that 'the FDA will consider developing a similar guidance for non-malignant diseases' [5].

3. *Oncology Nursing Society (ONS)*

The ONS statement is supportive and 'encourages the FDA to finalize this draft guidance.' They fully support the efforts to reduce barriers to clinical trial enrolment and participation and further state that 'not all effective therapies are listed as "curative intent." We maintain that clinical trials may offer feasible options for prolonging disease-free survival or quality of life, outcomes that are just as important for patients living with a non-curable cancer' [6]. Overall, they hope that expanding access and eligibility will help with the extrapolation of clinical trial data.

4. *SHEPHERD Foundation*

The SHEPHERD Foundation is a patient advocacy focused on discovering, developing, and connecting lifesaving cures for patients with rare cancer. The response to this draft guidance was positive, stating 'The SHEPHERD Foundation is excited about the potential of new therapies and supports the science and research into the potential of effective treatments that can be gained with this change' [7]. Overall, they view this guidance as a 'step toward reducing the percentage of patients that lack effective treatment options' [7].

5. *Comments from industry*

Comments were also received from Bristol-Myers Squibb (BMS), a global BioPharma company and Syneos Health, a biopharmaceutical solutions organization. Both organizations recommended some modifications or adaptions to the draft guidance, rather than endorsement or support of the draft guidance.

Syneos Health provided various comments about modifying the

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background section, including referencing examples of solid tumors in the non-curative setting where studies should require patients to have received established therapy, such as ovarian cancer and BRAF-mutated metastatic melanoma. BMS had only one specific comment about the draft guidance. They state 'the recommendation to evaluate separately patients who have received certain prior available therapy(ies) and those who have not for the purpose of efficacy assessment is clear. However, we propose that it may that it may often be appropriate for the assessment of safety, such as in a Phase 1 dose escalation study, to evaluate patients with heterogeneous prior therapy history together. The small size of dose escalation cohorts renders subgroup analysis impractical' [8].

6. Discussion and concluding remarks

The FDA has taken recent strides to provide additional recommendations to expand the eligibility of cancer trials to include patients with organ dysfunction, prior or concurrent malignancies, brain metastasis or central nervous system involvement, and concurrent infection with human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus. This new guidance represents the next step in expanding clinical trials eligibility further to include more cancer patients.

The proposed broader inclusion of treatment-naïve patients with incurable cancer would be more appropriate for some cancer types, especially those malignancies with poor first-line treatment options and promising investigation therapies with biomarkers predictive of clinical response. Experience drawn from the development of molecularly directed therapies, such as anaplastic lymphoma kinase rearrangements in non-small cell lung cancer, have shown these therapies are highly preferable compared to the prior standard of care, cytotoxic chemotherapy, and earlier accessibility would be highly desirable [9]. However, in cancer with first-line options demonstrate good overall efficacy, then this new guidance would be less appropriate. For example, in the case of a newly diagnosed patient with HER2+ metastatic breast cancer, they could receive the CLEOPATRA regimen (combination of trastuzumab, pertuzumab and docetaxel) followed by subsequent lines of therapy to give a projected median overall survival of 56 months [10]. Despite this significant overall survival, this would be unlikely to give a 'normal or near normal life expectancy', and this guidance would permit this patient to enrol in a Phase 1 trial of an unproven therapy in lieu of receiving this highly effective regimen. In a drug development environment prone to hype and exaggeration of benefits patients who are eligible to receive highly effective, evidence-based options may. elect to enrol in early phase clinical trials of unproven therapies [11]. This view is echoed by one respondent, citing ovarian cancer and BRAF+ metastatic melanoma as similar examples of when this guidance may not be appropriate [8].

Implementation of this guidance will have significant global consequences. Many oncology trials, particularly larger phase III studies are run globally, and regulatory harmonisation between other medicines regulators is essential for studies to be conducted internationally. If other large global regulators, such as the European Medicines Agency, fail to endorse or implement this new guidance, this may limit clinical studies to the US, which may significantly slow down recruitment and ultimately study reporting. The overall reaction from industry to this guidance was muted, and comments did not provide any specific endorsement, focusing more on the modification or adaption of specific content. Furthermore, the absence of comments from many large pharmaceutical and biopharmaceutical companies is notable and could be interpreted as the industry viewing the draft guidance as having only modest impact due to the global nature of cancer clinical trials.

Overall, organizations, with the notable exception of industry, who provided comments to the draft guidance have been wholly supportive, with the caveat of providing more specific guidance and detail to scenario's when this guidance may not be appropriate. ASH goes one step further, calling on the FDA to consider developing similar draft guidance for patients with non-malignant hematological conditions [5].

This draft FDA guidance is now closed for comment, however considering the overall positive nature of the comments received, it is highly likely this will be adopted. This will permit patients with incurable cancer(s) to enrol in oncology clinical trials regardless of receiving standard or prior therapy with appropriate informed consent and has the potentially to significantly transform cancer clinical trial conduct in the US and globally.

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Competing Interest

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