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Are We Ready to Include Organ-Impaired Patients in Oncology Trials? A Clinical Pharmacology Perspective on Recent Recommendations

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Recent recommendations have been published, following a working group initiative, that advise patients with renal and hepatic impairment be enrolled into oncology clinical trials.[1] The recommendations stem largely from the concern that once approved, new drugs are prescribed to patient populations for which established safety and efficacy data to support proper use are lacking.[1,2] In a collaboration between the American Society of Clinical Oncology (ASCO), Friends of Cancer Research (FOCR), and the US Food and Drug Administration (FDA), expert panels assessed multiple areas, including age, HIV status, brain metastases, prior or concurrent malignancies, comorbidities, and organ dysfunction, in which trial eligibility criteria could be expanded to increase patient participation in and real-world extrapolation of results from oncology studies. This American College of Clinical Pharmacology (ACCP) policy statement focuses on the last item: inclusion in oncology trials of patients with cancer who have renal or hepatic dysfunction. The advantages of expanding enrollment to such patients include, most importantly, increased information for providers to properly dose therapies and to understand the expected benefit-risk profile in these special populations.[3] Other advantages of expanding enrollment include (theoretically) faster recruitment and trial completion due to expanded inclusion criteria and a trial population that more closely resembles the real-world scenario in its diversity and generalizability.[4,5]

The ASCO/FOCR/FDA recommendations, however, fail to adequately address the barriers to including patients with organ impairment in oncology trials, particularly in pivotal and registration trials. In clinical trials, the first and fundamental rule is to protect the safety of the patient—and a major challenge to enrolling renally or hepatically impaired patients is concern for their safety. Particularly in oncology, where asset development often accelerates almost overnight, definitive information on risks to these patients may not be available when a registration trial begins or, from the perspectives of the sponsor, regulators, and scientific or ethics review boards, the data available may translate to different levels of perceived safety risk. In some malignancies, the risk of serious adverse events among patients with renal or hepatic impairment is higher simply due to physiological processes stemming from the disease itself. For example, in leukemia, liver or kidney infiltration may itself cause organ dysfunction. As a result, understanding the full safety risk requires more than mere identification of drug disposition pathway(s). Finally, there are operational hurdles to the inclusion of organ-impaired patients in clinical trials, such as identifying investigators able to tailor monitoring for these patients, attaining alignment on the protocol design, and ensuring the willingness of investigators to recruit organ-impaired patients even though their participation may necessitate increased resources relative to healthier patients.

Further, the question of the proper and acceptable study design is crucial and must be debated openly. Sponsors need designs that are reasonable and minimize any "penalty" for expanding pivotal protocols

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to include organ-impaired patients. Instead of simply expanding overall eligibility, it may be preferable to consider a parallel study in which these special populations are enrolled, which would not delay or impact the efficacy and/or safety reporting of the registration trial. It may be more efficient and resource-effective to obtain information on the safety of a medication or combination therapy in these patients outside of the clinical trial setting, such as through registries or other databases. There are multiple ways to gather additional data, and therefore provide more guidance, on the effects of new treatments in patients with cancer who are organ-impaired.

Call to Action

First and foremost, the current ASCO/FoCR/FDA working group behind this initiative must include expert clinical pharmacologists in its leadership to help shape its recommendations. Clinical pharmacologists and their close counterparts, clinical pharmacists, must serve as leaders on these panels alongside scientists, oncologists, statisticians, and others, if the working group is to be truly an interdisciplinary one. In addition, as the FDA is supporting and distributing these recommendations, it therefore should work toward alignment between its offices and divisions on what is acceptable in terms of eligibility criteria, trial design, and analysis methods for safety and efficacy.[2] Further, the FDA needs to determine what level of data sponsors must provide to appropriately anticipate approval of a protocol that allows organ-impaired patients. Prior to a sponsor embarking on a study with broader eligibility criteria, issues including the robustness of supportive data (and how robust the data must be in order to be informative), sufficiency of the nonclinical data package, appropriateness of preliminary pharmacokinetic (PK) analyses with hepatic and renal function covariates, and the requirement for a dedicated human mass balance study prior to enrolling organ-impaired patients should be resolved. Looking forward to a new drug submission after such a study is complete, the FDA will also need to address whether particular strategies for assessment in organ-impaired patients can support labeling language and/or may impact the regulatory requirement for dedicated renal or hepatic impairment studies. The FDA should engage other regulators around the globe to promote acceptance of this approach to minimize risk to an entire protocol when including organ-impaired patients, as these pivotal trials will likely be global studies. Sponsors will be hesitant to embark on expanding enrollment until these details have been addressed and investigators will be hesitant to perform the study unless they are convinced that patient safety and end point interpretation will not be compromised by the effort to include these patients.

Sponsors must be willing to be creative and diligently engage the FDA early and frequently (through processes already expected and/or recommended by the FDA as part of standard drug development)[6,7]; close collaboration among medical, statistical, and clinical pharmacology experts is crucial during study design and data analysis plan authorship, as both require enhanced clarity surrounding group and subgroup analyses for end points. The need to obtain and subsequently use early data to inform study eligibility criteria, such as in vitro and in vivo nonclinical data, available physiologically-based PK modeling or population PK or pharmacodynamic (PD) modeling, is heightened, as is the argument for running earlier human mass balance studies to determine metabolism and elimination pathways. As data accumulate, the eligibility criteria must be updated and evolutions in the benefit-risk profile must be communicated clearly to investigators. Sponsors must also select the appropriate clinical sites for organ-impaired patients; while pivotal studies may be at global phase 2 or 3 sites, these patients will require increased monitoring and sample collection for safety labs as well as PK and/or PD and, thus, may need to be enrolled into phase 1 sites more attuned to handling frequent assessments.

Investigators in oncology clinical trials should understand the risks of enrolling patients with renal and hepatic impairment, be discerning in their clinical judgement of which patients should remain excluded from studies, have a keen understanding of the particular drug(s) and specific monitoring required, and consciously commit to ensuring increased oversight with resources necessary to support additional assessments. Investigators must remain highly engaged, and a candid, real-time sharing of outcomes with the sponsor and co-investigators is needed.

Clinical pharmacologists occupy a unique position to weigh the evidence for and against these recommendations and how they may rationally be implemented in clinical studies; their contribution to the overall discussion is essential. Clinical pharmacologists in industry have a great opportunity to guide study or asset teams and provide recommendations in clinical practice, starting with promoting rational eligibility criteria supported by available data on the compound even in early-phase clinical protocols, and updating them as more data become available. Working alongside nonclinical pharmacologists, clinical pharmacologists can leverage their unique expertise in modeling and simulation, including physiologically based PK, population PK, and PKPD, to support study design and future labeling instructions for these special populations. By collecting appropriate PK and PKPD data in

early patient studies or in select subgroups with varying organ function and conducting human mass balance studies earlier in development to inform drug disposition (when appropriate), the clinical pharmacologist can drive decisions regarding dosing and safety risks for these patients and establish rational, clinically-relevant, fit-for-purpose dose modification recommendations in special populations. It is also an opportunity to demonstrate value to peers in medical, statistical, and other fields and advocate for a greater voice and permanent place at the discussion table for overall clinical strategy and decision making. The clinical pharmacology community should take seriously the partnership with clinical colleagues to ensure the safety of organ-impaired patients within and outside of clinical trials, as well as the quality and applicability of the clinical data that are collected to form dosing decisions.

The ACCP and its associated journals, as well as other clinical pharmacology organizations, should aid in this process by encouraging submission of presentations and publications on studies that incorporate organ-impaired patients, regardless of positive or negative trial outcome. This will promote sharing of clinical experience on study design, regulatory challenges (both in the United States and abroad), and data analysis and interpretation and will facilitate progress in this field. Rational design of future oncology trials will benefit from a comprehensive understanding of what has worked well and what needs further guidance or refinement. Lastly, the ACCP and other organizations are positioned to hold symposia specifically to promote discussion among sponsors, scientists, investigators, and regulators to address the current state of and progress made in dosing of patients with cancer who are renally or hepatically impaired. These discussions are necessary prior to widespread adoption by stakeholders of expanded eligibility criteria across oncology trials.

Disclosures and Conflicts of Interest

JCM is a full-time employee of Pfizer Inc., and holds Pfizer stock. PW has nothing to disclose.

References

1. Lichtman SM, Harvey RD, Damiette Smit MA, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group. *J Clin Oncol*. 2017;35(33):3753-3759.
2. Kim ES, Bruinooge SS, Roberts S, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research statement. *J Clin Oncol*. 2017;35(33):3737-3744.
3. Statler A, Radivoyevitch T, Siebenaller C, et al. The relationship between eligibility criteria and adverse events in randomized controlled trials of hematologic malignancies. *Leukemia*. 2017;31(8):1808-1815.
4. Garcia S, Bisen A, Yan J, et al. Thoracic oncology clinical trial eligibility criteria and requirements continue to increase in number and complexity. *J Thorac Oncol*. 2017;12(10):1489-1495.
5. Srikanthan A, Vera-Badillo F, Ethier J, et al. Evolution in the eligibility criteria of randomized controlled trials for systemic cancer therapies. *Cancer Treat Rev*. 2016;43:67-73.
6. Food and Drug Administration Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Guidance for Industry DRAFT: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products. Silver Spring, MD: Food and Drug Administration; 2017.
7. Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry: End-of-Phase 2A Meetings. Silver Spring, MD: Food and Drug Administration; 2009.