March 12, 2020

TO: U.S. Food and Drug Administration

RE: Docket ID: FDA-2019-D-4964
Draft Guidance for Industry Entitled "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products"

The Chris Elliott Fund DBA the EndBrainCancer Initiative (EBCI) supports FDA's efforts to create guidelines that take into consideration clinical circumstances where additional flexibility may be warranted while ensuring substantial evidence of effectiveness such as the severity of the disease, unmet medical need, rarity of the disease, and whether it is feasible and ethical to conduct a randomized concurrently controlled superiority trial.

As a brain tumor patient services and advocacy organization who works directly and daily with patients, we can tell you that from the "patient perspective and voice" the goal of the brain cancer patient as it relates to clinical trials is IMMEDIATE ACCESS to ALL treatment options, including clinical trials, as for this disease and patient population, there currently is no effective Standard of Care (SOC) under the NCCN Guidelines. Additionally, current SOC for this population often disqualifies these patients from clinical trial enrollment due to restrictive enrollment eligibility requirements.

Somatic genomic testing in clinical trial design and enrollment is especially critical for patients with an aggressive brain cancer diagnosis such as glioblastoma multiforme.

> *Novel trial approaches to explore antitumor efficacy in rare molecular subtypes and novel trial access mechanisms such as just-in-time trial access activating genomically matched trials appropriate for individual patient genotype are needed.* [1.] page 2762

EBCI strongly supports the following wording found in Section V.B.3. and V.B.4. on pages 17 and 18 with recommended edits in red below.

658 3. *Number of trials*
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660 A second trial may be infeasible in certain rare disease settings where the limited patient
661 populations preclude the conduct of a second trial. A similar situation may also arise when a
662 drug is developed to target, for example, a low-frequency, molecularly defined subset of a more
663 common disease and it may not be possible to screen and enroll enough patients within a
664 reasonable period of time to conduct the second trial.[34] In these cases, the substantial evidence
665 of effectiveness would typically be provided by a single trial plus confirmatory evidence.
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667 4. Statistical considerations

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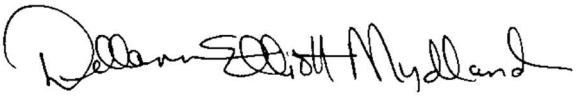
As noted above, treatments for rare diseases often are intended to address unmet needs, and the considerations of balancing the harmful consequences of false positive and false negative results will often apply In addition, the amount of evidence that can practically be acquired may be limited by the number of patients who can be recruited for trials. FDA may interpret the substantial evidence standard flexibly considering the harmful consequences of false negative and false positive results and the amount of evidence that can practically be acquired. Statistical approaches to evaluating treatments for rare diseases should consider the feasibility of trial design, sample size, and endpoints, using methods and thresholds for demonstrating substantial evidence that are appropriate to these setting, including molecularly defined subset analyses of trial data.

[34] Guidance for industry *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease* (October 2018)

Thank you for this great step forward to make more treatment options available for patients with brain cancer and other rare diseases.

Blessings,



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1. Meric-Bernstam F, Brusco L, Shaw K, Horombe C, Kopetz S, Davies MA, Routbort M, Piha-Paul SA, Janku F, Ueno N, Hong D, De Groot J, Ravi V, Li Y, Luthra R, Patel K, Broaddus R, Mendelsohn J, Mills GB. Feasibility of Large-Scale Genomic Testing to Facilitate Enrollment Onto Genomically Matched Clinical Trials. J Clin Oncol. 2015 Sep 1;33(25):2753-62. doi: 10.1200/JCO.2014.60.4165. Epub 2015 May 26.