Dear ODAC Committee,

The Society for Immunotherapy of Cancer (SITC) appreciates the opportunity to provide public comment to this Oncologic Drug Advisory Committee (ODAC) meeting. Prior to providing comments, SITC would like to state that our interest in this meeting concerns the implications of the discussion regarding clinical trial design and implementation. Our following comments are not intended to advocate for regulatory decisions pertaining to the treatments being discussed during this meeting.

SITC is the world’s leading member-driven organization specifically dedicated to improving cancer patient outcomes by advancing the science, development and application of cancer immunology and immunotherapy. For decades, SITC members have been at the forefront of cancer immunotherapy research working to develop and advance novel therapeutics into the clinic for the treatment of various cancers, including the design and execution of numerous Immunotherapy clinical trials.

In recent years the US Food and Drug administration has approved cancer therapies – including immunotherapies – based on improved progression free survival (PFS) in the context of well-controlled randomized trials. This has translated into prompt patient access to novel treatments that provide significant benefits while maintaining safety standards. However, despite support for the use of PFS in some cancer settings, its value as a primary endpoint for registrational clinical trials remains a point of debate across the field of oncology. Some experts argue that overall survival (OS) is the only time-to-event endpoint that shows “true” benefit to patients while others believe that PFS should be accepted if trials are held to rigorous standards. This is particularly important in settings of advanced/metastatic disease where measuring OS can be confounded by effective post-progression treatments and, most importantly, by crossover to the experimental arm either within the trial or if the treatment is approved and becomes available on the market.

SITC is highly interested in the ODAC conversation concerning the assessment and necessity of statistically significant OS benefit for a treatment to gain full regulatory approval when the measurement of OS is confounded by trial designs that allow for unidirectional crossover (e.g. from the control arm to the experimental arm). Please find below several points we ask the committee to consider while evaluating this important topic:

- The allowance for crossover of the control arm is ethically desirable when anti-tumor activity of the experimental treatment has been previously observed (e.g. in a later line of therapy for the same tumor type and/or similar class of drugs)

- We find it important for the committee to recognize that in some cases the benefit of the treatment may have an impact on the statistical significance between PFS and OS when allowing crossover of the control arm. If participants of the crossover benefit from the treatment, the crossover will impact the overall OS ratio and potentially limit statistical significance. As such, the specifics of how crossover of the control arm was conducted with a given trial should be taken into consideration when evaluating efficacy of an experimental treatment
In settings for which there is effective post-trial therapy or when crossover within the trial is allowed, PFS could generally be used as the primary endpoint, especially if the magnitude of the PFS effect is clinically meaningful and post-progression survival is expected to be long. As more trials implement crossover of the control arm, it will be incumbent on both trialists and reviewers to consider how best to allow for crossover while clearly assessing efficacy. In this regard, using composite endpoints (e.g. associating PFS with improvement of quality of life/symptom control endpoints) is an approach that could be further investigated.

Drugs that have a marked PFS benefit but unclear OS benefit in randomized trials, because of the challenges described above, may still prove to be valuable options in improving patient care. Specifically in earlier lines of treatment, when an agent is shown to provide a clinically significant treatment free interval with acceptable safety profile and no detriment in OS, these therapies offer patients and physicians options to consider as they develop their unique treatment plan (e.g. prolonged treatment free interval versus alternative treatments with more involved dosed regimens).

The discussion and outcomes related to control arm crossovers at this ODAC meeting will have an impact on future trial design. The feedback given by the committee will help to set a precedent for future Immunotherapy trials, even beyond CAR-T therapies. As novel therapies come through the pipeline, it will be crucial for trialists to have the tools to conduct efficient trials that allow for rapid patient access to safe and effective treatments.

SITC is happy to further elaborate or assist on any of the above discussion points. We see this as a critical topic for the field and encourage all points and perspectives to be expressed. We again state that we are in no way advocating for the recommendation or non-recommendation of any individual therapy and/or treatment.

We thank the committee for providing an opportunity to comment on this important topic. Should you have any questions, please do not hesitate to contact me at mdean@sitcancer.org. We look forward to collaborating in the future on all efforts focused on providing cancer patients with safe and effective treatment options.

Sincerely,

Mary Dean, JD, CAE
Executive Director
Society for Immunotherapy of Cancer