August 20th, 2015

American Society of Clinical Oncology
2318 Mill Road
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To: The American Society of Clinical Oncology
From: Friends of Cancer Research
Re: Comments on the ASCO Value Framework

We appreciate the opportunity to comment on ASCO's *Conceptual Framework to Assess the Value of Cancer Treatment Options*. At Friends of Cancer Research, our mission is to ensure that patients have access to the best treatment options available to them. Fortunately, advances in basic and medical applied sciences have led to the development of several innovative and highly effective new options for cancer within the last few years, as well as the ability to identify those patients most likely to benefit from a particular drug. However, the high costs associated with some of these new drugs have prompted attempts to assess their "value".

The ASCO value framework attempts to do this through the use of an equation weighing the relative efficacy and toxicity of drugs compared within a single clinical trial.[1] We agree that the high costs of drugs are unsustainable, and we commend ASCO for attempting to address this important issue. However, we believe the initial approach in this "value framework" is flawed, does not resolve the underlying problem, and could have unintended negative consequences for patients.

"Value" is a highly contextual as well as personal concept, meaning different things to different patients in different situations. This personal, subjective component is absent from the value framework, and even objective information regarding what is known about the relative risks and benefits of cancer drugs is vastly oversimplified with this tool. Unfortunately, this tool provides little if any value to the decision-making process and could potentially lead to inaccurate assessments of the relative merits of different treatment options.

Methodological Limitations:

Initially, there are several methodological limitations within the ASCO framework.

Efficacy Component: The tool overemphasizes the endpoint of overall survival, thereby penalizing some of the most effective and transformative drugs currently available to cancer patients. Many of these drugs have demonstrated unprecedented effects on overall response rates and disease control rates in

[1] Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. *J Clin Oncol*. 2015 Jun 22.

settings of high unmet need, such that a randomized trial to assess the overall survival benefit might not be possible or even ethical.

Although the tool allows response rates in the formula when overall survival or progression-free survival have not been reported, the weights given to the different endpoints are arbitrary and may result in scores that do not reflect a drug's benefit.

It also does not assess either duration of response or disease control. This choice ignores the value that prolonged disease control and reduction of tumor burden may have for many patients in terms of one of the most important metrics - quality of life.

Example: Crizotinib in ALK-positive metastatic non-small cell lung cancer[2]: The initial accelerated approval of crizotinib was based on a response rate of approximately 50-60%. This merits a benefit score of only 24 using the ASCO framework.

However, the confirmatory trial, on which full FDA approval was based, demonstrated a greater than double improvement in progression-free survival, which would merit a benefit score of 55.

For many breakthrough therapies initially approved based on response rates, their full benefit wouldn't be captured by the value framework immediately, or even for some time following the initial approval, and this could have significant implications for patient care and utilization.

Toxicity Component: Only the relative sums of grade 3 – 5 toxicities are compared, while the rates of these toxicities are not. If two drugs produce the same toxicity, but one produces it in only 5% of patients whereas the other produces it in 30% of patients, this is information that is clearly important to decision-making but not captured in the value framework.

Further, summing all grade 3-5 toxicities is misleading because the grades vary in severity. It also neglects toxicities that may be low-grade but chronic and have a greater impact on overall quality of life than a more serious, but acute and rapidly resolving adverse event. Finally, the tool also does not reflect whether or not there are mitigating strategies for management of a particular toxicity, or what might be known about long-term treatment effects.

Cost Component: Drug acquisition costs, while substantial, are only a fraction of the overall cost of care or financial burden for an individual patient. The method of drug delivery has significant impact on both the overall cost of care as well as other costs to patients. These costs can include burden of family caretaker time, time lost at work, transportation and parking costs – among others.

Costs associated with emergency medical care, extended hospital stays, toxicity management, or additional interventions that may be needed as a result of choosing one drug over another are also not captured. As mentioned above, the tool does not capture long-term effects of treatment which, in some cases, are significant enough to prevent survivors from maintaining employment –a substantial potential financial concern for patients.

Scoring Component: The value framework's scoring is entirely dependent on data obtained from a single clinical trial, rather than being representative of the full body of knowledge that exists to support a drug. This has two important implications.

[2] http://www.cancer.gov/about-cancer/treatment/drugs/fda-crizotinib#Anchor-Reg

The first is that the scores are not comparable between different drugs. The framework can only compare two drugs against each other, while treatment decisions often involve choosing between more than two options. The second implication is that, depending on the source of trial data and how it is interpreted, the tool could easily be misused.

Example: Pemetrexed in first-line treatment of metastatic lung cancer. The original publication of the framework described a net health benefit of zero for pemetrexed in first-line treatment of metastatic lung cancer based on results obtained in both squamous and non-squamous non-small cell lung cancer[3]. However, that same clinical trial and associated publication demonstrated an overall survival benefit and less toxicity in the non-squamous subset, the specific population for which the drug is approved. Although ASCO has since updated pemetrexed's score to reflect the benefit it provides to the indicated population[4], this demonstrates how easily the tool may be misleading.

Many of the limitations discussed above are acknowledged in the framework, but collectively they result in a tool that, at best, presents an incomplete assessment of what professionals, patients, caregivers and payers should consider in their decision-making. At worst, this framework could be used out of context to deny a patient an effective treatment that might be the medically optimal choice for that individual, and which might even be the most cost-effective based on a variety of factors not captured in this framework tool.

We respect the intent of prompting dialogue in this area, and yet we wish to call attention to the fact that an oversimplified answer is potentially worse than the current state. It could also easily detract from a more fruitful dialogue to find public policy answers that will allow society to develop better therapeutics at costs and prices which will be sustainable and realistic. The current "value framework" does not fulfill that goal, and we wish to emphasize the limitations of this first-generation assay.

We appreciate the opportunity to comment on the framework and look forward to a continued dialogue on this vital issue.

Sincerely,

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[3] Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008 Jul 20;26(21):3543-51.
[4] Kelly, C. Alimta Value Revisited: ASCO Raises Score In Framework Update. *The Pink Sheet*. 2015 Jul 14.