ASSESSMENT OF ADDED ACTIVITY OF AN ANTITUMOR AGENT

Zhiping Sun, Eric Rubín, David Weinstock, Emmett Schmidt, Cong Chen*. Merck and Co., Inc., Rahway, NJ, USA

Background Growing clinical evidence shows that treatment effect of most approved combination therapies can be largely explained by the independent drug action model (IDA), i.e., the benefit a patient receives from a combination therapy is driven by the drug component his or her tumor is most sensitive to. IDA has been successfully used to predict objective response rate (ORR), progression-free-survival (PFS), and duration of response (DoR) for many combination therapies.1-5

Methods When IDA is applied to ORR (aka Bliss model6), the ORR of the combination therapy is expected to be the sum of ORRs from Drug 1 and Drug 2 minus the product of the two (figure 1). When IDA model is applied to DoR, those who potentially respond to both drugs will have the best duration to a drug component. ORR or DoR alone is not adequate to capture the overall antitumor activity but jointly may.7-8 Integrating results from the two, the added activity from Drug 2 to combination is:

\[ \text{ORR}_{\text{Drug2}} \times \text{DoR}_{\text{Drug2}} \times (1 - \text{ORR}_{\text{Drug1}} \times \text{DoR}_{\text{Drug1}}) / \text{Sum of DoRs of Drug1 and Drug2} \]

Clearly, any new drug with single-agent ORR too low or DoR too short is unlikely to add much activity to the combination.

Results Further inspection of the index suggests that DoR of Drug 2 is more impactful than ORR. It also reveals that it is more impacted by ORR than by DoR of Drug 1, implying that there is more room for improvement over standard-of-care with lower ORR (but longer DoR) than with shorter DoR (but higher ORR). When Drug 2 has a superior DoR than Drug 1, the benefit of Drug 2 is largely retained after combination, which explains why some immune checkpoint inhibitors are successful after combining with chemotherapies. Conversely, when Drug 1 has a superior DoR than Drug 2, the benefit of Drug 2 is largely derived from those who do not respond to Drug 1, predicting the challenges in developing new drugs with short DoR for combining with established immune checkpoint inhibitors.

Conclusions We have derived a simple index to help researchers make early Go-No Go decisions on combination therapies. It is insightful, and, assisted with proper analysis method [9-10], it can potentially play a critical role in executing FDA's forthcoming Project FrontRunner.

REFERENCES