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Adherence to the Food and Drug Administration (FDA) guidance for the co-development of two or more investigational new drugs in phase 1/2 cancer trials

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Background

Combinations of cancer therapeutics (combo) have potential to improve antitumor efficacy over monotherapies, but their development remains challenging. To improve likelihood for success, the FDA issued guidance for the co-development of ≥2 INDs in 2013.

Methods

We reviewed all combo protocols in the MD Anderson Phase I Program between 2015-2020 for adherence to 4 key criteria: (1) intention to treat serious illness, (2) biological rationale, (3) full non-clinical characterization of combo, (4) compelling reason to not develop each drug independently. Parameters studied also included drug pharmacology, preclinical data, trial design, sponsor and biomarker use. Categorical variables are shown as percentages and compared by Chi-Square method.

Results

Of 470 protocols, 188 included combos [phase 1 (n=113), phase 1/2 (n=62), and phase 2 (n=13)], and 30 included multiple treatment arms. 166 combos included ≥1 approved drug, while 72 comprised only investigational agents. 54% of combos (n=128/238) met all 4 criteria. Industry-sponsored trials (51%, n=101/204) adhered to FDA guidance less often than non-Industry sponsored (74%, n= 25/34 Investigator and NCI sponsored) trials (p=0.01). Of 72 investigational agent-only combos, All treated a serious illness, 96% (n=69) had biological rationale, 79% (n=57) had full non-clinical characterization, 64% (n=46) had compelling reasons to not develop each drug independently; and 57% of these studies (n=41) met all 4 guidance criteria. Between immunotherapy only combos (IO) and targeted therapy only combos (TT): 98% (n=83/85) IO had biological rationale vs 89% (n=73/82) TT (p=0.03). 84% (n=69/82) TT had full non-clinical characterization vs 69% (n=59/85) IO combos (p=0.02). TT and IO combos had similar rates to not develop each drug independently (68% vs 60%; p=0.26) and to meet all 4 FDA criteria (60% vs 52%; p=0.30). Interestingly, IO combos incorporated patient selection biomarkers less often (15% vs 60%; p<0.001).

Conclusions

The FDA guidance for co-development provides a useful framework to evaluate combos, but only 57% of combos met all criteria. There are differences in adherence to the FDA guidance and use of biomarkers between IO and TT combos.

Legal entity responsible for the study

The Authors.

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