current article [1]. However, these limitations of our study were already mentioned in the discussion where we described that we could not perform re-meta-analyses according to gender, smoking status or ethnicity, which should therefore be interpreted based on the summary of the umbrella review summarized in the supplementary Table S1, available at *Annals of Oncology* online [4].

Finally, Markozannes et al. pointed out that we used a *P*-value threshold of 0.05 for Egger's regression asymmetry test as evidence for small-study effects, but this test is known to be underpowered and 0.10 is the widely accepted threshold [1]. We are sympathetic to this opinion, but already described that the application of prediction interval (PI), heterogeneity and publication bias may not be definitive criteria in limitation section. When we applied a *P*-value threshold of 0.1 for Egger's regression asymmetry test to all our results, the results almost did not change.

In conclusion, the evidence for the associations of BMI with each cancer should be interpreted with caution and the evidence grading for each comparison should be done according to the obesity parameter used, which could change the evidence grading for the same cancer type. The methods for the evidence grading deserve further attention and discussion.

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ESCAT: a step in the right direction

We applaud the effort by Mateo and colleagues to create the recently published ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) [1]. There is an unmet need for standardizing this knowledge. Unlike the parallel world of germline variation, there has been no consistent ranking system for somatic variants due to the fact that: (1) the field is relatively young; (2) the biological implications of variants are incompletely understood; (3) inter-tumor and intra-tumor heterogeneity [2] affects the clinical implication of variants; (4) interactions between coexisting variants remains poorly understood; and (5) variants only tell part of the story of why a drug may or may not be efficacious.

Given the importance of standardizing the language used in precision cancer medicine, ESCAT is a very good attempt that overcomes some of the ambiguities of earlier schemes. Its explicit consideration of study rigor and tumor context in deciding the evidence level of a drug moves precision-medicine classification nearer to the goal of facilitating clinical decision-making.

As presented, ESCAT is driven entirely by efficacy considerations. Efficacy is important, but considerations of toxicity, quality of life, and cost are equally so. Many current genome-directed therapies are oral home medications with a tolerable side-effect profile, whereas comparators are often infused chemotherapies, given in a clinic, which cause the predictable side effects of nausea, hair loss, and fatigue.

Furthermore, the only efficacy considered is *sensitivity* (i.e. does a drug work and to what extent?). There appears to be no accommodation for variants that predict *resistance* (e.g. EGFR p.T790M and resistance to gefitinib [3]). This omission fails to provide clinicians with all of the information needed for treatment decisions and may dampen drug resistance research by allowing consequential facts to remain latent.

Apart from the categories themselves, it is also important to think about how evidence will be classified within them. Though a tier should ostensibly consist of recommendations based on equivalent evidence, considerable variation in the quality of the evidence and the magnitude of clinical benefit may remain. As an example, of the nine trials cited as Tier 1-A evidence by Mateo et al., only four had a statistically significant overall survival end point and one [4] was of marginal statistical significance ($P = 0.046$).

As the authors mention, Tier II-A evidence, such as the retrospective identification of PTEN loss in prostate cancer, often leads to Tier I trials. One unanswered question is whether Tier II-A evidence should be changed if confirmatory Tier I testing is negative. Since there is a considerable chance that a negative RCT is negative due to power issues (e.g. from low accrual), it would

probably be hasty to dispose of a Tier II-A recommendation completely, on that development alone.

Finally, we think the authors may have avoided the elephant in the room—how to handle the case where there are multiple alterations that map to Tier I evidence. In this case, which will become increasingly common with more available therapies and broader sequencing, how should someone using the ESCAT scale pick and choose therapies?

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