Malignant pleural mesothelioma (MPM) is an aggressive lethal malignancy arising from the pleural lining. It is associated with a dismal prognosis and presents a major unmet therapeutic need, especially in the developing world as the incidence of MPM increases because of continued use and mining of asbestos. Platinum doublet chemotherapy, with or without antiangiogenesis therapy, is the current first-line approach to management of metastatic unresectable disease. MPM can be broadly divided into three different histologies that are prognostically different (sarcomatoid histology with the worst prognosis); however, current guidelines do not necessarily dictate a change in therapeutic management on the basis of histology alone. Following the success story in nonsmall cell lung cancer, where biomarker-based identification of targetable driver mutations has resulted in dramatic therapeutic successes, there has been interest to identify similar targetable mutations in MPM. One of the largest reports of comprehensive genomic profiling of MPM (n = 216 patient samples) was conducted by Bueno and colleagues (1). Using RNA sequencing, they demonstrated four distinct molecular subtypes, and through whole-exome sequencing (WES), they found that BAP1, NF2, TP53, SETD2, DDX3X, ULK2, RYR2, CFAFP45, SETDB1, and DDX51 were significantly mutated (q-score ≥ 0.8) in MPMs. Additionally, recurrent gene fusions and splice alterations were noted to be frequent mechanisms for inactivation of NF2, BAPI, and SETD2, defining a disease that is predominantly driven by inactivation of tumor suppressor genes.

In this issue of Cancer Discovery, Hmeljak and colleagues report on integrative genomic characterization of 74 patients with MPM and present significant findings with potential therapeutic implications (2). One interesting finding relates to the observation that, using WES, the authors report that all but one sample had low tumor mutational burden (TMB), with <2 nonsynonymous mutations per megabase. TMB is an emerging biomarker of responsiveness to anti–PD-1 therapy in other solid tumors such as non–small cell lung cancer and melanoma, where it has been correlated to improvements in overall survival and progression-free survival with the use of checkpoint inhibitor therapy, including dual PD-1/CTLA4 blockade (3). However, it is unknown whether TMB serves as a useful biomarker for predicting response to other forms of immunotherapy and to PD-1/PD-L1 blockade in other tumor histologies, including MPM. These are novel findings that raise interesting questions. First, this observation places MPM toward the low spectrum of tumor mutational signature in human cancer (4), and second, it is counterintuitive to clinical observations of a meaningful response with anti–PD-1 therapies in MPM (5). The low TMB finding is surprising, because most environmentally induced cancers (i.e., due to smoking or UV light) have a high TMB, and thus mesotheliomas (induced by asbestos) would be expected to show similar high TMB. One potential explanation for these TMB findings is that the approaches used in this analysis from The Cancer Genome Atlas (TCGA) may underestimate the neoantigen load that could be present due to innumerable microdeletions and DNA breaks that frequently occur in MPM. Indeed, in a recent study using mate-pair, RNA, and T-cell receptor sequencing along with in silico predictions, Mansfield and colleagues observed that chromosomal rearrangements occurred in every specimen, many of which resulted in neoantigens that were predicted to bind patient-specific HLA molecules. They also identified T cells reactive to these predicted neoantigens (6). In MPM, clinical responses seen with anti–PD-1 therapies are possibly being driven by other tumor and tumor microenvironment factors. High PD-L1 expression is seen in ~16% of patients with MPM and is independently associated with a poor prognosis. Only patients with high PD-L1
expression were included in the phase II study of pembrolizumab, and thus this study potentially selected specific patients slated to respond to immunotherapy. Additionally, gene-expression analyses suggest that MPM is an inflamed tumor type, and there may be certain subsets of MPM that may be better suited to cancer immunotherapy, independent of the TMB score.

V-domain immunoglobulin suppressor of T-cell activation (VISTA) is a novel immune checkpoint that suppresses T-cell activation (7). VISTA is constitutively expressed within the hematopoietic compartment, with the highest expression level on myeloid cells and a lower level on T cells. Its expression on antigen-presenting cells acts as a ligand to suppress T-cell proliferation and cytokine production. In addition, VISTA might function as an inhibitory receptor on T cells to suppress their activation. In this report, the authors reported strong expression of VISTA in MPM cells, the highest expression seen in any other cancer type studied by TCGA. This was particularly seen in the more differentiated epithelioid subtype and correlated highly with mesothelin expression. Antibodies against VISTA are being explored as potential checkpoint inhibitors. It remains to be seen if the high level of VISTA will translate into a meaningful clinical target in MPM. Nevertheless, these are provocative findings, as the high level of VISTA expression may contribute to the immune-suppressive environment of MPM. It has already been demonstrated to be a compensatory inhibitory pathway in the setting of ipilimumab therapy in prostate cancer. These findings point to a strategy of combination blockade of VISTA with PD-1/PD-L1/CTLA4, which may be essential in a subset of patients with MPM to provide substantial clinical benefit.

BRCA1-associated protein 1 (BAP1), a tumor suppressor gene that encodes a deubiquitinating enzyme, is an important regulator of proliferation, cellular differentiation, and DNA damage repair. Germline BAP1 mutations result in a novel cancer syndrome with increased risk of uveal and cutaneous melanoma, mesothelioma, renal cell carcinoma, and other malignancies (8). Somatic mutations in BAP1 have also been observed in an increasing number of MPMs. This study is the one of the most comprehensive studies to evaluate BAP1 alterations, which were found in 57% of all samples, and has potential implications for treatment. Therapeutically, BAP1 loss in mice has been shown to result in increased activity of enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) expression, an epigenetic regulator (9). This observation signaled the way for development of novel drugs that inhibit the EZH2 pathway, such as tazemetostat, specifically for patients with recurrent, platinum-refractory MPM. Additionally, similar to BRCA1/2-deficient cancers, mutation in the BAP1 gene leads to a deficient homologous recombinant pathway and increases the reliance on other DNA-repair pathways. Based on these observations, PARP inhibitors, alone or in combination with PI3K inhibitors, are currently being evaluated in patients with BAP1-mutant MPM.

This study confirmed early studies highlighting that MPMs, unlike non-small cell lung cancer, appeared to have very few targetable driver mutations in RTKs, MAPK pathway or PI3/AKT signaling pathway genes. No fusions involving EWSR1 or receptor tyrosine kinases were observed. Mutations were not related to smoking history or asbestos exposure. Deletions (deep, homozygous) in CDKN2A were confirmed in ~49% of the patients. This study once again highlighted that MPM is a disease driven primarily by inactivation of tumor suppressor genes; in addition to BAP1, numerous recurrent inactivating alterations in CDK N2A, NF2, TP53, LAT52, and SETD2 were confirmed.

The highlight of this work lies in the integrative multi-platform analysis undertaken by the authors. Using iCluster and PARADIGM, four distinct novel prognostic subsets of MPM were identified. iCluster 1 was found to have the best prognosis. This group enriched for epithelioid tumors, low rate of mutations and copy-number alterations, and relatively few CDKN2A homozygous deletions (11%), and the majority of patients had BAP1 alterations. Conversely, the poorest-prognosis iCluster 4 had a high score of epithelial-mesenchymal transition based on gene expression, low expression of mesothelin, enrichment for LAT52 mutation, and a high rate of CDKN2A homozygous deletions (66%). Interestingly, this cluster showed higher AURKA mRNA expression and elevated mRNA expression of DNA damage response genes. These results were identical in the epithelioid-only analysis, i.e., AURKA mRNA expression was upregulated in the poor-prognosis iCluster 4, corroborating the results from the overall histology agnostic MPM analyses. Moreover, these prognostically relevant molecular profiles were reproducible in samples from other cohorts and can be potentially used to improve risk stratification of patients with MPM.

MPM is a heterogeneous disease, with different histologies and genomic characteristics, which have been well outlined in the study in the current issue of Cancer Discovery. We have embarked on an era where we can move beyond empiric combinations in unslected patients and apply these scientific observations to rational therapeutic combinations for MPM. Although this study cannot clearly differentiate genomic characteristics based on gender (10) or smoking history, it does offer some novel pathways that can be explored, including AURKA inhibitors, dual checkpoint immunotherapy, and VISTA inhibition.

Disclosure of Potential Conflicts of Interest
C. Aggarwal is a consultant/advisory board member for Bristol-Myers Squibb, Genentech, Celgene, and MedImmune. No potential conflicts of interest were disclosed by the other author.

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