Editorial Commentary

Hyperprogressive disease with immunotherapy: new directions

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The phenomenon of hyperprogression and its association with the use of immune checkpoint inhibitors (ICIs) has been increasingly described in recent literature. However, hyperprogressive disease (HPD) as a unique growth pattern remains controversial. HPD can be defined as the sudden acceleration of tumor growth kinetics above its baseline growth rate. The tumor genome is inherently unstable and changes affecting crucial mechanisms of cell growth can result in unexpeted changes in growth patterns. Small cell transformation in oncogene addicted cancers is an example of such sudden change. The point of contention with HPD is whether it is truly acceleration of growth caused by ICI exposure or simply a failure of antitumor efficacy (i.e., the tumor's natural history). As ICIs move into the frontline treatment of several different cancer types, it is important to understand this phenomenon in order to avoid causing harm.

HPD was first described by Champiat *et al.* in a retrospective study documenting tumor growth kinetics, suggesting an increased incidence after ICI exposure compared to chemotherapy (1). The reported incidence of HPD in retrospective studies ranged from 7–29% (1-5). Ferrara *et al.* focused on patients with advanced non-small cell lung cancer (NSCLC), thus avoiding the heterogeneity of tumor subtypes in response to ICI, and used a retrospective cohort treated with chemotherapy as a control (2). Using a definition of a change in tumor growth rate (TGR) of greater than 50% at first evaluation compared to before treatment, the incidence of HPD was 13.8% in the ICI treated group compared to 5% in the chemotherapy treated group. Significantly worse overall survival (OS) was seen in those with HPD compared to those with slower rates of progression (3.4 *vs.* 6.2 months). However, the current retrospective HPD literature are limited by selection bias, small sample sizes and patient heterogeneity.

Data from prospective studies may provide us with further insight into whether HPD is a true phenomenon. A post-hoc analysis of the phase III OAK study comparing atezolizumab to docetaxel in patients with pre-treated advanced NSCLC attempted to address the issue of HPD (6). The incidence of rapid progression was defined as a ≥50% increase in the sum of the longest diameters (SLD) of lesions at first assessment compared to baseline, and was similar in both groups, (45% *vs.* 29%). Critics maintain that this may still simply represent failure of efficacy rather than true HPD. The ARCTIC study compared durvalumab ± tremelimumab to chemotherapy and included patients who had progressed on 2 prior lines of therapy (7). The standard of care chemotherapy included single agent gemcitabine, vinorelbine or erlotinib in epidermal growth factor receptor (EGFR) wild type patients with low response rates, similar to that of placebo, in this setting. Interestingly, there was no significant difference between progression-free survival (PFS) and OS among ICI and chemotherapy-treated groups. Thus, the prospective evidence raises questions of whether HPD does exist. In fairness, a small population of patients could be easily missed, and closer examination of TGRs pre- and post-treatment initiation would be required.

Several attempts have been made to identify clinicopathologic characteristics that define this group of

HPD patients. The post hoc analysis of the OAK study identified 3 factors to be associated with fast progression: high lactate dehydrogenase (LDH), high SLD and ≥3 metastatic sites (6). Subsequent retrospective studies have tried to establish similar relationships. Unfortunately, each study identified different factors, and all had weak associations. For example, Champiat *et al.* reported that older age was associated with an increased risk of HPD (1). Kanjanapan *et al.* reported that sex, not age, was associated with HPD (3). Ferrara and colleagues reported that neither factor was a significant predictor of HPD (2). Where Ferrara *et al.* reported that the presence of driver mutations such as EGFR and anaplastic lymphoma kinase (ALK) were not associated with HPD, Kato *et al.* found them to be significant predictors (4). Unfortunately, information on PD-L1 expression, which enriches for response in NSCLC, is often unavailable and has not been studied in this setting. The lack of distinctive clinical factors supports the theory that patients with HPD are inconsistently included in clinical trials and suggests that other unmeasured factors are at play.

It is important to recognize that reports of HPD occur almost exclusively in patients receiving checkpoint inhibitors as monotherapy (1-5). This is likely a function of publication and investigator bias, as previously this phenomenon would have been dismissed as lack of efficacy of other treatments such as chemotherapy. However, increasing pre-clinical evidence suggest that the underlying mechanisms behind HPD with PD-1 inhibition lie in the tumor microenvironment (TME). The TME is composed of a highly complex system of tumor cells, effector T cells and regulatory T cells that normally exist in an equilibrium. The goal of PD-1 inhibition is to reinvigorate effector T cells and turn the equilibrium towards tumor killing. However, PD-1 receptors are also expressed on T regulatory cells and under certain conditions, monotherapy with PD-1 inhibition may tip the balance in the opposite direction, creating a pro-tumor environment. Other immune subpopulations, such as myeloid derived suppressor cells (MDSC), may also play a role in maintaining the fine balance between immune activation and suppression in the TME and is affected by PD-1 axis inhibition (8). Recently, Lo Russo *et al.* reported that the presence of M2 macrophages with immune suppressive activity in the TME was associated with HPD (9). Chemotherapy has been associated with a reduction of MDSCs and T regulatory cells, and despite its overall myelosuppressive effects, may offer synergistic effects when combined with PD-1 inhibitors (10,11). Reassuringly, the survival outcomes are improved compared to monotherapy alone and an excess of early deaths have not been observed in prospective clinical trials combining chemotherapy with ICIs (12). While these mechanisms need to be further elucidated, they provide a biologic explanation and a basis for designing rational drug combinations to avoid HPD.

Additional pathways through which tumors facilitate immune escape are also being discovered. Due to the widespread use of extended molecular profiling, astute investigators have observed that a subgroup of STK11 and KEAP1 mutant lung cancers derive little benefit from PD-1 inhibition (13,14). Mutations in STK11 results in silencing of stimulator of interferon genes (STING), which, by impairing a variety of processes such as poor T cell recruitment, results in an immunologically "cold" TME. In this instance, PD-1 inhibition, whether alone or in combination with chemotherapy have little effect on tumor growth and alternative therapeutic strategies are needed. The mechanisms through which KEAP1 mutations affect response to PD-1 inhibitors are less well understood. KEAP1 modulates response to oxidative stress by regulating nuclear translocation of the transcription factor NRF2 (15). The KEAP1-NRF2 pathway is considered an important player in tumor progression where expression of NRF2 associated antioxidant genes confers protection of tumor from environmental stress and contributes to chemoresistance and radioresistance (16). KEAP1 mutants likely represent a distinct subgroup of non-responders to PD-1 inhibition and its impact on the immune populations in the TME warrant further study.

Advances in molecular sequencing technologies may also be harnessed to address some of the crucial limitations in relying solely on radiographic measurements to determine response. While RECIST 1.1 and iRECIST are important tools to standardize radiographic response reporting, it is only a limited assessment of the overall tumor burden (17,18). Despite stringent criteria using TGR, in the study by Ferrara *et al.*, six patients were initially misclassified as hyperprogression (2). These six patients subsequently achieved stable disease for at least 6 months, a prognosis that is much better than those in the HPD group. Quantification of plasma circulating tumor DNA (ctDNA) maybe helpful in the scenario. Early clearance of plasma ctDNA in NSCLC treated with targeted therapy have demonstrated prognostic value and is being explored as a tool for personalized treatments (19,20). Incorporation of plasma ctDNA assessments in ongoing clinical studies

of ICIs can more clearly identify patients with early progression so that they can be further studied to determine pathways leading to resistance.

While HPD is a phenomenon that is likely not exclusive to ICI, it may be more prevalent. As scientists become more attuned to the checks and balances of the immune system and the various pathways of tumor immune escape, we are sure to find new drug combinations and biomarkers to improve clinical outcome in those patients that do not respond to ICI therapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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