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Hyperprogression and Immune Checkpoint Inhibitors:

Hype or Progress?

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Abstract

There are currently seven approved immune checkpoint inhibitors (ICI) for the treatment of various cancers. These drugs are associated with profound, durable responses in a subset of patients with advanced cancers. Unfortunately, in addition to individuals whose tumors show resistance, there is a minority subgroup treated with ICIs who demonstrate a paradoxical acceleration in the rate of growth or their tumors – hyperprogressive disease. Hyperprogressive disease is associated with significantly worse outcomes in these patients. This phenomenon, though still a matter of dispute, has been recognized by multiple groups of investigators across the globe and in diverse types of cancers. There are not yet consensus standardized criteria for defining hyperprogressive disease, but most commonly time-to-treatment failure less than two months and an increase in pace of progression of at least two-fold between pre-immunotherapy and on-treatment imaging has been used. In some patients, the change in rate of progression can be especially dramatic – up to 35- to 40-fold. *MDM2* amplification and *EGFR* mutations have been suggested as genomic correlates of increased risk of hyperprogression, but these correlates require validation. The underlying mechanism for hyperprogression is not known, but warrants urgent investigation.

Key Points

- Hyperprogressive disease, reflecting a marked acceleration in tumor progression, after immune checkpoint blockade can occur in diverse cancer types and is associated with ~3-month overall survival
- Relative frequency of hyperprogressive disease after immune checkpoint blockade ranges from <5% to 29%
- *MDM2* amplification and *EGFR* alterations have been associated with hyperprogressive disease, but these genomic markers and their mechanism of action require validation in larger datasets.
- A change in pace of progression between pre-immunotherapy and on-treatment imaging is important to differentiate between patients who have accelerated progression on immunotherapy versus those who have an aggressive disease regardless of treatment.

Immunotherapy in the form of checkpoint blockade has resulted in impressive responses for several previously refractory tumor types. Indeed, the Food and Drug Administration (FDA) has now approved seven checkpoint inhibitors: pembrolizumab, nivolumab, durvalumab, avelumab, atezolizumab, cemiplimab, and ipilimumab.[1-7] Immune checkpoint inhibitors (ICIs) mediate responses by reactivating the immune system. Reactivation occurs because these antibodies interfere with checkpoints such as programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) that have been exploited by tumor cells to evade the immune response, a necessity if the cancer is going to survive.[8] The FDA approvals

notwithstanding, there are now multiple groups who have reported that a minority of patients (albeit encompassing diverse cancers), experience a dramatic acceleration in the rate of tumor progression after starting checkpoint blockade, -- a phenomenon designated hyperprogressive disease (HPD) (**Table 1**).[9-20] Unfortunately, in the patients who are deemed to have HPD, their median overall survival (OS) is estimated to be roughly three months.[21]

The phenomenon of enhanced progression after checkpoint blockade has been described with different checkpoint blockade agents and in numerous tumor types including, but not limited to, non-small cell lung, head and neck, breast, gastric, and genitourinary cancers.[9-16,18-23] The fact that various histologies that can be afflicted by HPD suggests that there could be common, histology-agnostic biologic/molecular mechanism(s). A final reason for the controversy around the existence of HPD may be the reluctance of physicians and other stakeholders to acknowledge that therapies like checkpoint blockade could make some patients worse. Indeed, despite HPD, our impression remains that immune checkpoint inhibitors are some of the most effective drugs ever brought into the clinical cancer arena, with transformative activity in a broad range of lethal malignancies, including long-term complete remissions in some individuals with highly refractory disease and heavy disease burden. For this reason, HPD should be considered “a toxicity,” or an immune-related adverse event (irAE) similar to other potential side effects, and should not restrict the use of these important agents. Even so, there is an urgent imperative to inform patients

of the risk of HPD, to determine the predictors of this phenomenon, and to unravel its underlying biology.

The frequency of HPD after immunotherapy varies depending on the publication, ranging from <5% to 29% (the latter reported in one study of head and neck squamous cell carcinoma). [9-16,21-23] One question that arises is whether or not HPD is unique to immunotherapy. One report suggests that HPD after chemotherapy can occur, albeit at a much lower rate of 5.1% (3/59) (versus ~14% after checkpoint blockade in that study).[15]

A key debate regarding the existence of HPD is whether or not the cancer was an aggressive one in the first place, with the thought being that rather than an induced immunologic effect, the aggressive growth is merely a lack of effective therapy (**Figure 1**). In this regard, there are varying criteria that have been proposed to define HPD (**Table 1**). For instance, Champiat and colleagues[9] define HPD as RECIST progression after first evaluation and ≥2-fold increase of the tumor growth rate between the reference (prior) and the experimental periods; Kato et al[10] defined HPD as >50% increase in tumor burden while on checkpoint blockade compared with pre-immunotherapy, with a <2-month time-to-treatment failure (TTF) and a >2-fold increase progression pace.[10] Importantly, the latter requires scans approximately two months before starting immunotherapy to be compared to pre-immunotherapyscans, to exclude the possibility that the tumor had an aggressive pace of growth even before starting immunotherapy. Virtually all other research groups have almost identical definitions for HPD (**Table 1**) except for Matos Garcia et al[13] and Lo Russo et

al.[18] The first group used the following definition: TTF <2 months and increase in measurable lesions of ≥10 mm plus the following: (i) increase of ≥40% in target tumor burden compared to pre-immunotherapy; or (ii) increase of ≥20% in target tumor burden plus multiple new lesions. The second group used a similar definition, and patients with HPD had to fulfill at least three of the following clinical/radiological criteria: (i) TTF < 2 months (ii) increase ≥50% in the sum of target lesions major diameters between baseline and first radiologic evaluation; (iii) appearance of at least two new lesions in an organ already involved between pre-immunotherapy and first radiologic evaluation; (iv) spread of the disease to a new organ between pre-immunotherapyand first radiologic evaluation; (v) clinical deterioration with decrease in Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 during the first 2 months of treatment. To avoid attributing rapid progression to immunotherapy when it simply reflects aggressive disease, some have argued that criteria that identifying HPD include a comparison to a pre-baseline time period (perhaps ~2 months) to demonstrate a substantial change in pace of tumor growth. Even this may not be valid, as patients are often on therapy during the period preceding initiation of immunotherapy. Further, this strategy could be difficult to apply when immunotherapy is administered in first line; therefore, validation of surrogate criteria that do not include a pre-baseline scan will be an important future effort.

Despite the controversy around the existence of HPD, unique response patterns after checkpoint blockade are not new.[24,25] For instance, a

phenomenon termed pseudoprogression has been well established after checkpoint blockade, albeit in a small subgroup of patients.[25-27] Pseudoprogression is defined by the appearance of progression on scans, probably because of immune infiltration, but the patient is asymptomatic or feels better (in contrast to hyperprogression where the patient, in our experience, feels worse) (**Figure 1**). Furthermore, with pseudoprogression, scans ultimately show tumor response. Forms of pseudoprogression have also been previously described, albeit rarely, with agents outside of immunotherapy, e.g. after glioblastoma treatment and with some targeted therapeutics.[28-30] The relatively unique response patterns after checkpoint blockade have resulted in development of modified RECIST criteria for immunotherapy—i.e., iRECIST.[31,32] Importantly, with iRECIST, new lesions are assessed as per RECIST 1.1[17], but are recorded separately (and not included in the sum of target lesions identified at baseline). This type of evaluation results in a new category of unconfirmed progression (iUPD). Confirmed progression (iCPD) is only assigned if, at the next imaging, an increase in the size of new lesions is seen or additional new lesions appear.

Because of the urgency associated with the rapid progression that is the hallmark of HPD, it is crucial to differentiate between hyperprogression and pseudoprogression as early as possible, even before re-imaging. With the former, checkpoint blockade should be immediately stopped; in contrast, with the latter, treatment should be continued. Liquid biopsies that interrogate serial blood-derived circulating cell-free DNA (cfDNA) may be useful in this regard. It appears, at least based on one small study, that the

genome instability number in cfDNA rises precipitously with hyperprogression, but falls with pseudoprogression, when measured at about three to six weeks after starting immunotherapy.[33]

Another key question in HPD is whether there are clinical or molecular features that are associated with an increased risk of accelerated growth after checkpoint blockade. Predictors of HPD have included age ≥65 years old, female gender, regional recurrence of disease, having more than two sites of metastases, low baseline highly differentiated CD4+ T cells or effector memory CD8+ T cells, high severely exhausted T cells or proliferating T regulatory cells , clustered $CD163^{+}$ PD-$L1^{+}$ $CD33^{+}$ macrophages with epithelioid morphology as well as genomic markers (mainly *MDM2*/*MDM4* alterations and *EGFR* alterations) (**Table 1**).[9-16,18-20,22] There are inconsistencies between studies in that some have not shown age or sex to be predictors. Further, while described by several groups including ours, [10,12,19,34] the putative genomic correlates (e.g., *MDM2/MDM4* and *EGFR* alterations) require larger sample size validation, and an understanding of potential mechanisms by which these alterations could mediate or facilitate accelerated tumor growth after checkpoint blockade.

Despite the current uncertainty regarding molecular markers such as *MDM2* amplification and *EGFR* alterations that may predict HPD[9,12,34], the use of genomic aberrations as biomarkers for immunotherapy response pattern has been previously established.[35-41] Indeed, although genomics and immunotherapy are often considered as separate fields, in reality, they are tightly linked.[42] There are various genomic aberrations that correlate with

immunotherapy response include (but are not limited to): (i) mismatch repair gene defects that result in microsatellite instability high (MSI-H); (ii) high tumor mutational burden (TMB-high); (iii) *PBRM1 and CDK12* mutations; and (iv) *PD-L1* amplification.[35-41] Other biomarkers such as high PD-L1 protein expression, gut microbiome, as well as *POLE*[43], *ATM*[44] *(TMB-mediated)*, *ATR*[45] *(TMB-mediated)*, and *CDK12*[46] mutations which have been shown to predict response to immunotherapy.[33,47-49] Of interest in this regard, pembrolizumab was granted the first tissue-agnostic approval by the FDA in patients with mismatch repair gene-altered/MSI-H solid tumors of any type, based on response rates of ~40%.[1] The reasons that MSI-H and TMB-high predict response to immunotherapy are probably related, since MSI-H almost inevitably leads to a high TMB.[50] TMB-high means that there are likely many neo-antigens produced by the tumor mutational genome and, hence, a greater chance that the reactivated immune system post-checkpoint blockade will be able to differentiate the neoplasm from normal tissue elements and target it for eradication.[51,52] In certain tumor types, such as clear cell renal cell carcinoma, *PBRM1* mutations have been associated with response to immunotherapy.[35,40] *PBRM1* encodes a subunit of the PBAF switch-sucrose nonfermentable (SWI/SNF) chromatin remodeling complex, which regulates how tightly DNA is packaged in cells; its loss may increase expression of T cell cytotoxicity.[35,40] Similarly *PD-L1* amplification in Hodgkin lymphoma and various solid tumors also associates with immunotherapy benefit.[39,53,54] There are also several markers of tumor resistance, again of genomic origin: (i) *STK11* and *KRAS* co-mutations in lung cancer[55]; (ii) loss-of-function mutations in the genes encoding interferon-receptor–associated

Janus kinase 1 or Janus kinase 2, concurrent with deletion of the wild-type allele[56]; and (iii) truncating mutations in the gene encoding the antigen-presenting protein beta-2-microglobulin (which leads to loss of surface expression of major histocompatibility complex class I resulting in attenuated neo-antigen presentation)[56]. These observations suggest that genomic markers can predict response pattern after checkpoint blockade, and that their mechanism of action is not always fully understood, at least initially.

In summary, despite the numerous research teams that have documented HPD[9-16,18,20-22], the existence of this phenomenon remains a matter of dispute. Indeed, an analysis of the OAK trial[57], which was a randomized study of checkpoint blockade versus chemotherapy in lung cancer, did not show a difference in the number of “fast progressors” between the arms. However, this trial had no pre-immunotherapy evaluation to demonstrate whether or not the pace of progression had increased. Patients with rapid progression who do not have pre-immunotherapy imaging available may be currently difficult to designate as having HPD. Important to note however, using pre-immunotherapy imaging may not always be feasible for all treatment settings; for example, in the first-line setting not all cancer patients have available pre-immunotherapy scans. Therefore some groups (**Table 1**)[13,18] have suggested criteria for HPD that do not require pre-immunotherapy scans; these criteria will need to be validated in patients with existing pre-immunotherapy scans. Recent data has shown that HPD can be recapitulated in preclinical models.[18] As physicians make immunotherapy a mainstay of treatment in more cancer types, it will be

imperative to develop predictive markers for HPD and to understand the biology that underlies this devastating irAE.

Figure 1. Potential outcomes after initiation of immunotherapy for the treatment of various cancers

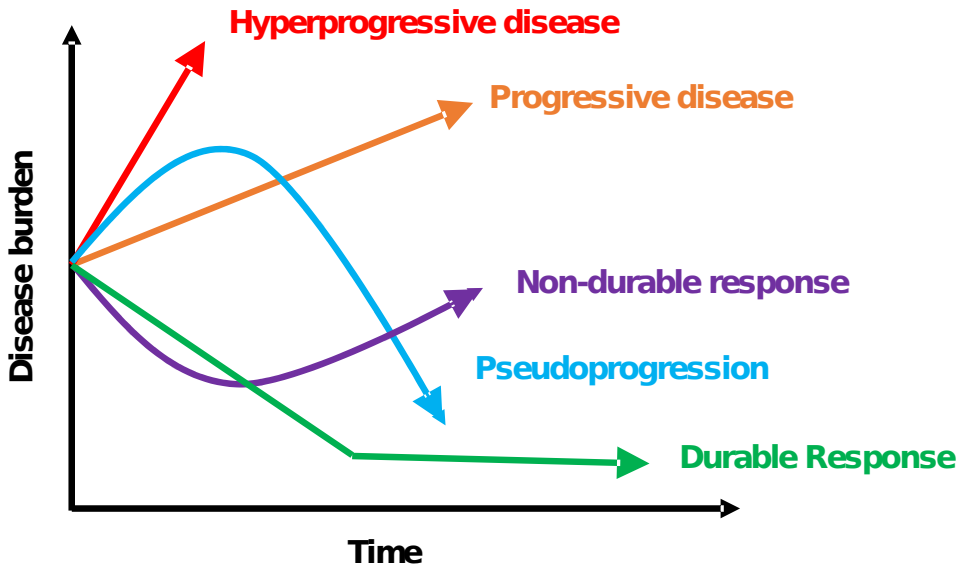

Figure Legend: Possible outcomes of treatment with immune checkpoint inhibitors over time. Durable response to treatment where target lesions shrink on imaging and remain attenuated (green), non-durable response where lesions initially response to therapy, but on subsequent surveillance imaging, lesions become resistant and increase in size (purple), disease progression where target lesions grow >20% from previous imaging (orange_, pseudoprogression where tumors enlarge on imaging initially followed by decrease in size seen (blue), and hyperprogressive disease where rapid growth occurs after initiating immune checkpoint inhibitors (red).

Table 1. Criteria for and predictors of hyperprogressive disease (HPD) according to different research groups

Author	Criteria for HPD	Predictors of HPD
Peer-Reviewed Manuscript		
Champiat S et al[9]	RECIST progression after first evaluation and ≥2-fold increase of the TGR between pre-immunotherapy imaging and on-treatment	≥65 years old
Kato S et al[10]	TTF <2 months, >50% increase in tumor burden compared with baseline pre-immunotherapy imaging, and >2-fold increase in progression pace	*MDM2/MDM4* and *EGFR* alterations Poor TTF (defined as TTF <2 months) was not associated with age, tumor type, Royal Marsden or MD Anderson score, or type of checkpoint blockade *DNMT3A* alterations also significantly associated with poor TTF in multivariate analysis
Saada-Bouzid E et al[11]	TGK_R calculated as ratio of the slope of tumor growth pre-immunotherapy and the slope of tumor growth on-treatment.. HPD was defined as a $TGK_R \geq 2$	HPD seen in 39% of patients with at least a locoregional recurrence and 9% of patients with exclusively distant metastases.
Ferrara R et al[15]	Disease progression at the first evaluation with change in TGR exceeding 50%	More than two metastatic sites prior to immunotherapy
Kanjanapan Y et al[16]	RECIST 1.1[17] progression at the first on-treatment scan and ≥2-fold increase in TGR between pre-immunotherapy and on-treatment	Female gender–
Lo Russo G et al[18]	TTF <2 months, increase ≥50% in the sum of target lesions major diameters, appearance of at least two new lesions in an organ already involved, spread of the disease to a new organ, ECOG performance status worse ≥ 2 during the first 2 mos. HPD on the basis of 3 concomitant out of the 5 possible criteria	Clustered macrophages with epithelioid morphology and co-localization of CD163, PD-L1, and CD33 markers (defined as complete phenotype) in HPD cases
Kamada T et al[19]	TTF <2 months; >50% increase in tumor burden compared with pre-immunotherapy imaging, and >2-fold increase in progression speed (same as per reference 10)	PD-1 blockade facilitated the proliferation of highly suppressive PD-1^+ effector (CD4+) T regulatory cells 1 of 3 patients with HPD had *MDM2* amplification versus 0 of 18 without HPD
Kim CG et al[20]	TTF <2 months or ≥2-fold increase of the TGR between pre-immunotherapy and on-treatment (same as per reference 9)	HPD was associated with lower frequency of effector/ memory ($CCR7^-CD45RA^-$) circulating CD8+ T cells, and higher frequency of severely exhausted ($TIGIT^+PD1^+$) circulating CD8+ T cells
Abstract Only		
Singavi A et al[12]	Progression at first restaging on-treatment with increase in tumor size >50%, >2-fold increase in TGR	*MDM2/MDM4, EGFR,* amplifications on 11q13 *(CCND1*, *FGF3*, *FGF4*, *FGF19*)

Matos Garcia I et al[13]	TTF <2 months and minimum increase in measurable lesions of 10mm plus: 1) increase of ≥40% in target tumor burden compared to baseline or 2) increase ≥20% in target tumor burden plus multiple new lesions	HPD was not associated with age, tumor type, checkpoint inhibitor regimens, previous checkpoint inhibitor or metastatic site
Kim Y et al[14]	Defined by TGK pre-immunotherapy versus on-treatment (details not provided)	No associations found.

Abbreviations: HPD = hyperprogressive disease; IO = immunotherapy; $TGK_{(R)}$ = tumor growth kinetic (ratio)

TGR, tumor growth rate; TTF = time to treatment failure;

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