Genetic and molecular analysis of solid tumors with immunotherapy associated hyperprogressive disease

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Background

- Immune checkpoint inhibitor use is common in oncology care
- A rare paradoxical rapid progression in tumor growth after initiation of immunotherapy (Figure 1) has been described and termed Hyperprogressive Disease (HPD)
- Frequency of HPD has been reported from 6% to 29%, with highest frequency in HNSCC and NSCLC
- EGFR mutations and MDM2/4 amplifications have been implicated in HPD, but underlying molecular mechanism remains unclear necessitating further study
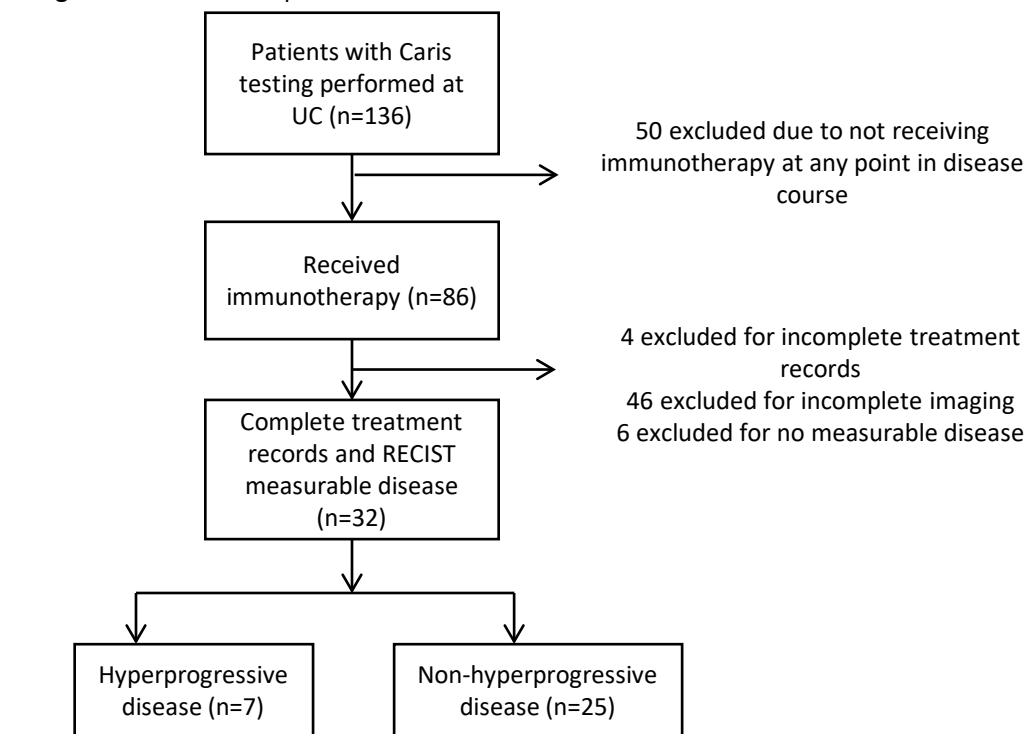

Before (-8 weeks) | Baseline | 1st Evaluation (+8 weeks)

Figure 1: Example CT images of hyperprogressive disease. Source: Champiat et al. Clin Cancer Res 2017;23:1920-1928

- *We hypothesized that distinct molecular pathways would be detected between HPD and non-HPD groups*

Methods

- This is a single center retrospective cohort study
- Inclusion criteria:
  - Completed Caris testing, received at least one dose of immunotherapy, complete records with pre-treatment, treatment initiation, and post-treatment scans, measurable disease by RECIST
- Exclusion criteria:
  - Age<18, incomplete treatment records, incomplete or inadequate imaging (non-diagnostic PET scans)
- Clinical data was manually extracted from the electronic medical record and was stored in REDCap
- HPD was defined as doubling of the Tumor Growth Rate (TGR) across 3 imaging studies
- Caris molecular profiles between HPD and non-HPD were compared using student's t-test, chi-squared test, and Fisher's exact test
- Secondary analysis was performed to compare patients who were refractory to immunotherapy treatment defined as time-to–treatment-failure (TTF) < 3 months.

Figure 2: Flowsheet of patient selection.

Patients with Caris testing performed at UC (n=136)
→ 50 excluded due to not receiving immunotherapy at any point in disease course
Received immunotherapy (n=86)
→ 4 excluded for incomplete treatment records
→ 46 excluded for incomplete imaging
→ 6 excluded for no measurable disease
Complete treatment records and RECIST measurable disease (n=32)
Hyperprogressive disease (n=7) | Non-hyperprogressive disease (n=25)

Results

HPD is associated with advanced age, female gender and adverse clinical outcomes

Table 1: Clinical characteristics between HPD and non-HPD groups. *Fischer's exact test performed .

	HPD	Non-HPD	p-value (2-tailed)
Total (n)	7	25	
Age at diagnosis (years)	63.53	59.29	0.444296356
Female	71%	24%	0.0318*
BMI	26.69	28.32	0.559354653
Prior Tobacco Use	86%	84%	1*
Head and neck	43%	28%	0.649
Lung	29%	40%	0.683
Other	29%	32%	1
Nivolumab	57%	36%	0.401
Pembrolizumab	14%	36%	0.387
Durvalumab	29%	32%	14
Other	0%	12%	
Median ECOG at diagnosis	1	1	
Previous treatment lines	1.71	1.5	0.180324826
Prior surgery	43%	44%	1*
Prior radiation	71%	72%	1*
Overall survival (mo)	3.8	5.5	0.524199154
Time to progression (mo)	7.82	10.15	0.651737282

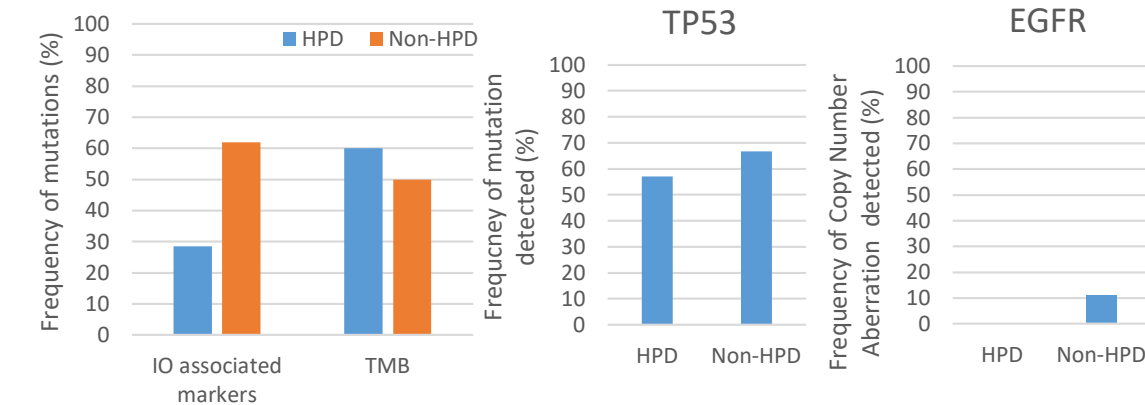## Frequency of mutations were similar in HPD and non-HPD groups

Figure 3: Comparison of selected pathways and individual genes between HPD and non-HPD.

TTF <3mo was associated with mutations in the notch pathway and absence of DNA damage repair (DDR) deficiency

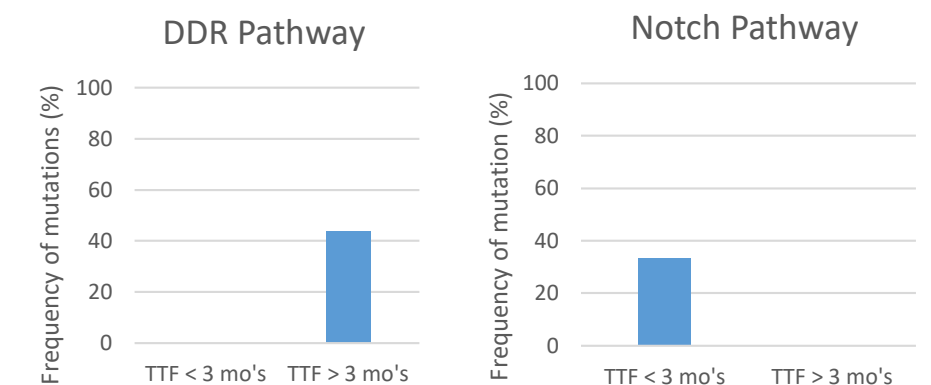- Of patients with complete records, 12/32 (37.5%) had TTF < 3 months

Figure 4: Comparison of selected pathways between patients with TTF < or > 3 months.

Conclusions

- HPD was associated with female gender and trends to a correlation with adverse clinical outcomes.
- There were no statistically significant differences in oncogenic mutations between HPD and non-HPD groups.
- Analysis of DDR and Notch pathways may be predictive of clinical response to IO.
- This study is limited by small sample size, but may support the hypothesis that HPD represents the natural disease course of some patients with aggressive cancers.
- Further studies will require larger sample size to further understand this phenomenon and help delineate between tumor types.

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