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Detection of microsatellite instability-high (MSI-H) by liquid biopsy predicts robust and durable response to immunotherapy in patients with pancreatic cancer

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ABSTRACT

Clinical trials reporting the robust antitumor activity of immune checkpoint inhibitors (ICIs) in microsatellite instability-high (MSI-H) solid tumors have used tissue-based testing to determine the MSI-H status. This study assessed if MSI-H detected by a plasma-based circulating tumor DNA liquid biopsy test predicts robust response to ICI in patients with pancreatic ductal adenocarcinoma (PDAC). Retrospective analysis of patients with PDAC and MSI-H identified on Guardant360 from October 2018 to April 2021 was performed; clinical outcomes were submitted by treating providers. From 52 patients with PDAC +MSI-H, outcomes were available for 10 (19%) with a median age of 68 years (range: 56–82 years); the majority were male (80%) and had metastatic disease (80%). Nine of 10 patients were treated with ICI. Eight out of nine patients received single-agent pembrolizumab (8/9), while one received ipilimumab plus nivolumab. The overall response rate by Response Evaluation Criteria in Solid Tumors was 77% (7/9). The median progression-free survival and overall survival were not reached in this cohort. The median duration of treatment with ICI was 8 months (range: 1–24), and six out of seven responders continued to show response at the time of data cut-off after a median follow-up of 21 months (range: 11–33). Tissue-based MSI results were concordant with plasma-based G360 results in five of six patients (83%) who had tissue-based test results available, with G360 identifying one more patient with MSI-H than tissue testing. These results suggest that detecting MSI-H by a well-validated liquid biopsy test could predict a robust response to ICI in patients with PDAC. The use of liquid biopsy may expand the identification of PDAC patients with MSI-H tumors and enable treatment with ICI resulting in improved outcomes.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a 5-year overall survival rate of less than 10%.[1] In the USA, approximately 60,000 patients are diagnosed with PDAC annually, most presenting with metastatic disease.[2] While there has been a rapid increase in the development of targeted therapies in other cancer types, PDAC generally lacks a targetable alteration.[2] Recent literature reported remarkable antitumor activity of immune checkpoint inhibitor (ICI), irrespective of tumor type and checkpoint inhibitor used, in patients harboring tumors with a high level of microsatellite instability (MSI-H) as a result of deficient mismatch repair (dMMR).[3] The detection of MSI-H status in patients with pancreatic tumors may provide a unique opportunity for treatment with ICI, although the prevalence of MSI-H signature in patients with PDAC is quite low (<1%).[4]

MSI-H status can be assessed in cancer patients by genomic profiling and has historically been performed on tissue specimens. However, several well-known barriers to genomic profiling of tumor tissue exist, including tissue insufficiency or the inability to perform a tissue biopsy. Additionally, the invasive procedure involved in obtaining a tissue biopsy often poses challenges and may add to patient morbidity. A high degree of concordance between circulating tumor DNA (ctDNA)-based tumor genomic profiling and tissue-based tumor genomic profiling has been reported.[5] As a result, the use of liquid biopsy for genomic profiling is rapidly gaining popularity[6] and may be used to assess tumor genomic profiles in a low risk, timely fashion.

The use of well-validated liquid biopsies can not only help with the completion of genotyping, it can also rapidly identify MSI-H,[6] which may offer expanded treatment opportunities in patients with a diverse group of tumor types, including pancreatic cancer,

given tumor agnostic approvals. Previous studies reported significant antitumor activity of ICI in MSI-H gastric[7] and patients with prostate cancer[8] whose MSI-H status was detected by liquid biopsy testing. Here, we investigated the prevalence of MSI-H/dMMR tumors in a large cohort of patients with PDAC using a well-validated liquid biopsy assay and assessed if the dMMR/MSI-H signature detected by a plasma-based testing predicts robust and durable response to ICI.

METHODS

Patients and samples

The Guardant central database was searched for patients with PDAC who had MSI-H tumors detected by a plasma-based liquid biopsy that assesses ctDNA, Guardant360 (G360), performed as a part of routine clinical care between October 1, 2018 and April 15, 2021. Clinicians providing care to the patients with MSI-H PDAC detected by G360 were contacted to obtain clinical data that included patient and tumor characteristics, treatment details, and outcomes. The data cut-off date was September 1, 2021.

Sequencing and analysis

G360 (Guardant Health, Redwood City, California, USA) is a commercially available 74-gene panel plasma-based tumor genomic profiling assay validated to detect a variety of genomic alterations, including MSI-H signature,[7] single-nucleotide variants, indels, copy number alterations (amplifications and fusions)[9] in cell-free DNA (cfDNA) from plasma of patients with solid tumors, including PDAC. G360 determines MSI-H status by sequencing 90 pan-cancer informative microsatellite loci in cfDNA and reports MSI-H status based on the number of unstable sites relative to a predetermined cut-off, as previously described.[7] Reporting of MSI-H status was included in the G360 test result beginning September 27, 2018.

RESULTS

During the study period, over 6000 patients with PDAC had G360 as part of clinical care, 52 of whom had MSI-H identified for a prevalence of 0.8%. Clinical outcome data available for 10 of 52 (19%) patients were included in the final analysis. The cohort had a median age of 68 years (range: 56–82); 80% were male, and 80% of patients had metastatic disease (table 1).

The diagnosis of MSI-H was made by G360 in 7 of 10 (70%) patients. Most patients had KRAS or GNAS alterations, while more than half also had alterations related to homologous recombination repair identified by G360 testing in addition to the identification of MSI-H (table 2). Tissue analysis of MSI-H status by IHC was performed in 6 of 10 (60%) cases. All but one result was concordant; in the discordant case, immunohistochemistry (IHC) testing on the pancreatic body mass biopsy tissue failed to identify dMMR status, but G360 obtained 2 weeks before starting immunotherapy identified MSI-H. This patient received neoadjuvant therapy with an ICI combination (ipilimumab plus nivolumab) followed by surgery; the resected specimen confirmed complete pathological response.

Table 1 Characteristics of patients with MSI-H pancreatic cancer

Characteristic	n=10
Age at diagnosis, median (range), years	68 (65–82)
Sex	
Male	8 (80%)
Female	2 (20%)
Race	
Caucasian	10 (100%)
Site of the primary tumor	
Head	4 (40%)
Body	3 (30%)
Tail	2 (20%)
Stage at diagnosis	
Metastatic	8 (80%)
Locally advanced	2 (20%)
Line in which immunotherapy received	
First line	3 (30%)
Second line	3 (30%)
Third line	3 (30%)
Not received	1 (10%)
Prior therapy	6 (60%)

MSI-H, microsatellite instability-high.

ICI was administered in 9 of 10 patients, 7 of whom received ICI following the identification of MSI-H status by G360. The only patient who did not receive ICI passed away before being able to receive ICI, therefore, outcome analysis included 9 patients. Nearly all patients who received ICI received single-agent pembrolizumab (8/9), while one received ipilimumab plus nivolumab; however, patients received ICI across various lines of therapy . At the time of data cut-off, the overall response rate (ORR) by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 77% (7/9) and 6 of 7 responders continued to show response at the time of data cut-off after a median follow-up of 21 months (range: 11–33) (figure 1). The median progression-free survival and overall survival were not reached in this cohort, where the median duration of ICI therapy was 8 months (range: 1–24). Among the nine patients treated with ICI, 7/9 (78%) were alive at the time of data cut-off.

Table 2 Co-occurring deleterious alterations and concordance of MSI-H identification between tissue immunohistochemistry and Guardant360 in patients with pancreatic ductal adenocarcinoma

	Guardant360 findings				Tissue concordance	
Patient ID	RAS findings	RAF findings	HRR gene-related findings	Other findings	Tissue assessed ?	G360/Tissue MSI-H concordant?
Responders (CR/PR)						
2	KRAS	none	BRCA1 K654fs	EGFR amp	No—QNS	N/A
	G12D		BRCA2 K585fs			
	KRAS amp		BRCA2 T3085fs			
3	KRAS	none	ATM K1773fs	TP53 E339*	Yes	Concordant
	Q61H				(MLH1, PMS2)	
5	KRAS	none	none	none	Yes	Discordant.
	G12D					G360-MSI-H
						IHC-proficient MMR
6	GNAS R201H	BRAF K483E	none	none	No—QNS	N/A
7	GNASR201H	BRAFV600E	ATM Y2019C	PIK3CA A1066V,	No—QNS	N/A
			CDK12 R882Q	PIK3CA E545D,		
			CDK12 splice	PIK3CA H1047R,		
			ARID1A T294fs	CTNNB1 T41A,		
			BRCA2 I605fs	APC S587fs,		
				PTEN K267fs,		
				TP53 Y126C,		
				TP53 S215G,		
				TP53 K382fs,		
				TP53 R273H		
8	KRASG12D	none	none	TP53 R213L	Yes (MLH1, PMS2	Concordant
9	Wild-type	none	BRCA1 K339fs	NOTCH1 splice	Yes	Concordant
				TP53 E258G	(MLH1, PMS2)	
Non-responders (PD)						
1	KRASG12D	none	ARID1A P1575fs	TP53 R175H	Yes	Concordant
			ARID1A D1850fs	TP53R283P		
			ARID1A F2141fs			
4	KRAS G12V	none	ARID1A K1072fs	TP53 C242F	Yes (MSH6)	Concordant
				MLH1 splice		
Not given ICI						
10	KRAS G12V,	none	ATM R3008H	PIK3CA amp	No—QNS	N/A
	KRAS amp		BRCA2 T3033fs	TP53P278S		

CR, complete response; EGFR, epidermal growth factor receptor; HRR, homologous recombination repair; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; N/A, not available; PD, progressive disease; PR, partial response; QNS, quantity not sufficient; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus gene.

DISCUSSION

The present retrospective cohort study investigated if the detection of MSI-H with a liquid biopsy test (G360) in patients with PDAC predicts a robust response to ICI. In this study, PDAC patients who had MSI-H tumors detected by G360 showed a robust response to ICI, evidenced by an ORR of 77%. The responses were durable, with six out of seven responders experiencing disease control for a prolonged period. Additionally, the study demonstrated a high degree of concordance (83%) between the plasma-based and the tissue-based detection of MSI-H, with liquid biopsy able to identify MSI-H not identified on IHC testing in one patient. This is the first study to our knowledge reporting a robust response to ICI in patients

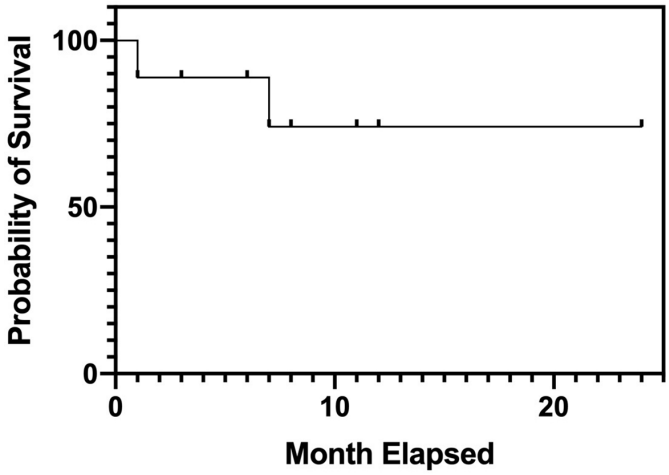

Figure 1 Progression-free survival of nine evaluable patients with microsatellite instability-high pancreatic cancer treated with immune checkpoint inhibitor.

with MSI-H PDAC in which MSI-H was detected by liquid biopsy.

MSI-H has emerged as a tumor-agnostic predictive biomarker for response to ICI, supported by several large prospective studies.[3 10–12] The high antitumor activity of ICI in patients harboring MSI-H tumors irrespective of tissue of origin led to accelerated tissue-agnostic approval of pembrolizumab, an ICI that acts by blocking programmed death 1 (PD-1) receptor on the lymphocytes, by the Food and Drug Administration (FDA) of the USA for adult and pediatric patients with unresectable or metastatic MSI-H/dMMR solid tumors resistant to standard therapies. Subsequently, FDA approved pembrolizumab in treatment naïve patients with MSI-H metastatic colorectal cancer based on the KEYNOTE-177 trial data.[10] However, a large data set confirming ICI activity in dMMR/MSI-H PDAC patients are unavailable. Although the immunosuppressive tumor microenvironment of pancreatic cancer characterized by a lack of T cells, an abundance of immune-suppressive myeloid cells, and dense desmoplasia is a cause for concern,[13] preliminary data suggest that ICI has significant activity in dMMR/MSI-H PDAC patients. The pivotal study by Le *et al* investigating the antitumor activity of pembrolizumab in patients (n=86) with 12 different types of MSI-H/dMMR solid tumors had 8 patients of PDAC.[11] In this study, the reported ORR was 62% (5/8) in patients with PDAC and 53% in the whole group.[11] The remarkable activity of ICIs in MSI-H/dMMR pancreatic tumors has been reported in several case reports.[14 15] Furthermore, the successful utilization of ICI as neoadjuvant therapy has been reported in several small studies and a case report in patients with localized or locally advanced dMMR/MSI-H tumors.[14 16 17] Consequently, detecting MSI-H/dMMR in patients with PDAC can enable treatment with IO that often results in an improved outcome. The high response rate observed in this study is consistent with the previously reported studies with pancreatic and non-pancreatic tumors, supporting the feasibility of MSI-H status determination with plasma-based testing. It is important to mention that phase II KEYNOTE-158 study in which patients with chemotherapy-refractory MSI-H/dMMR advanced noncolorectal cancer received pembrolizumab reported a rather low response rate of 18%,[18] a result discordant with most studies. The underlying cause of this discordance is unknown, although one might speculate if the prior therapies influenced the response rate.

It is unclear why some patients with MSI-H tumors do not respond to ICI. Two patients in the current cohort did not respond to ICI. Patient 1 had MSI-H confirmed on both G360 and tissue-based testing. However, this patient was tested for MSI late at progression and had worsening clinical status, ultimately leading to death after an early round of ICI. Patient 4 had MSI-H confirmed on tissue as well as G360 and was initially treated with single-agent pembrolizumab for 6 months with a mixed response but overall progressive disease by RECIST. At the time of data cut-off, the patient had received one dose of ipilimumab plus nivolumab, and early markers continued to be concerning for progression. Of note, his ctDNA was not cleared on subsequent G360 tests, showing active disease evolution even when actively treated with ICI. Concurrent alterations on G360 were identified in KRAS, ARID1A, MLH1, and TP53 (table 2); tissue NGS testing identified the same ARID1A, KRAS, and MLH1 alterations. Potential explanations for this patient's non-response may include tumor heterogeneity, or an altered microenvironment, among others.

The prevalence of MSI-H/dMMR tumors in patients with PDAC appears to be low, around 1%,[4] as seen in this study and others. Hu *et al* evaluated the mismatch repair status in 833 patients of PDAC using a next-generation sequencing assay where MSI-H tumor was detected in only 0.8% of patients.[19] Another study analyzed 445 tumor specimens from patients with PDAC with an IHC-based assay and reported the presence of dMMR tumor in 1.6% of cases.[20] Conversely, a single institution study reported dMMR tumors in 22% (24/109) of pancreatic tumor biopsies.[21] The range of reported prevalence of MSI-H/dMMR tumors in PDAC patients is likely related to patient selection criteria in different studies. Overall, it appears that the prevalence of MSI-H/dMMR signature is low in patients with PDAC. Although the possibility of finding MSI-H tumors in PDAC patients is low, as it was in this study cohort, it is reasonable to test for MSI-H/dMMR status in all patients with PDAC as the identification of the MSI-H/dMMR status provides a unique opportunity for treatment with ICI that often leads to a robust response.

Insufficient tumor tissue in the biopsy for genomic profiling is a well-recognized barrier to genomic profiling and is frequently encountered in localized PDAC in which tissue collected by endoscopic ultrasound-guided fine-needle biopsy and aspiration yields inadequate samples in as high as 29% of cases.[22] A recent trial showed that liquid biopsy might be able to overcome tissue-based genomic profiling challenges in advanced GI cancers, including

PDAC, due to higher rates of successful genomic profiling, faster sample acquisition, and quicker result availability.[22] Furthermore, IHC-based tests occasionally misclassify dMMR/MSI-H status[23 24] as 5%–11% of MSI-H tumors may demonstrate intact MMR protein expression, likely related to retained antigenicity in otherwise nonfunctional MMR proteins.[23] A well-validated liquid biopsy test can effectively fill these critical gaps as observed in one patient described in this study where an IHC-based test reported proficient MMR, but G360 identified MSI-H. This patient received neoadjuvant therapy with an ICI combination (ipilimumab plus nivolumab) followed by surgery, and the resected specimen confirmed complete pathological response. The intratumoral heterogeneity[25] or retained antigenicity of the nonfunctional MMR proteins as described above[23] may have contributed to the observed discordance in this patient. Such discordance between IHC and G360 has been described in a previous study in which G360 accurately identified MSI-H with IHC providing an incorrect result,[6] highlighting the importance of using multiple methodologies to maximize the identification of patients with MSI-H tumors. Validation studies of G360 to determine the MSI-H status reported an overall accuracy of 98.4% and a positive predictive value of 95%,[7] as well as multiple cohorts showing robust response to ICI, supports the utility of G360 to be used concurrently with comprehensive genomic profiling on tissue specimens and/or where tissue is insufficient or inaccessible. Communication with the coauthors revealed that payers agreed to pay for the prescribed ICI in patients who had MSI-H detected by liquid biopsy alone.

This study has several limitations, including the retrospective nature of this analysis, a small sample size, and the non-availability of treatment outcome information in a significant number of patients who had MSI-H tumors detected by G360. However, the robust and durable responses to ICI observed in this study among the patients with MSI-H PDAC provide confidence that prescribing ICI guided by plasma-based identification of MSI-H signature is appropriate.

CONCLUSION

In this small cohort of patients with PDAC, the detection of MSI-H by ctDNA testing was highly concordant to tissue-based testing and correlated with robust and durable responses to ICI. The use of a well-validated liquid biopsy assay may expand the identification of MSI-H tumors in patients with PDAC and enable treatment with ICI resulting in improved outcomes.

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REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7–30.
2 Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. *JAMA* 2021;326:851–62.
3 Petrelli F, Ghidini M, Ghidini A, *et al*. Outcomes following immune checkpoint inhibitor treatment of patients with microsatellite Instability-High cancers: a systematic review and meta-analysis. *JAMA Oncol* 2020;6:1068–71.
4 Luchini C, Brosens LAA, Wood LD, *et al*. Comprehensive characterisation of pancreatic ductal adenocarcinoma with microsatellite instability: histology, molecular pathology and clinical implications. *Gut* 2021;70:148–56.
5 Cescon DW, Bratman SV, Chan SM, *et al*. Circulating tumor DNA and liquid biopsy in oncology. *Nat Cancer* 2020;1:276–90.
6 Keller L, Belloum Y, Wikman H, *et al*. Clinical relevance of blood-based ctDNA analysis: mutation detection and beyond. *Br J Cancer* 2021;124:345–58.
7 Willis J, Lefterova MI, Artyomenko A, *et al*. Validation of microsatellite instability detection using a comprehensive plasma-based genotyping panel. *Clin Cancer Res* 2019;25:7035–45.
8 Barata P, Agarwal N, Nussenzveig R, *et al*. Clinical activity of pembrolizumab in metastatic prostate cancer with microsatellite instability high (MSI-H) detected by circulating tumor DNA. *J Immunother Cancer* 2020;8:e001065.
9 Odegaard JI, Vincent JJ, Mortimer S, *et al*. Validation of a plasma-based comprehensive cancer genotyping assay utilizing orthogonal tissue- and plasma-based methodologies. *Clin Cancer Res* 2018;24:3539–49.
10 André T, Shiu K-K, Kim TW, *et al*. Pembrolizumab in Microsatellite-Instability-High advanced colorectal cancer. *N Engl J Med* 2020;383:2207–18.
11 Le DT, Durham JN, Smith KN, *et al*. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;357:409–13.
12 Overman MJ, Lonardi S, Wong KYM, *et al*. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch Repair-Deficient/

Microsatellite Instability-High metastatic colorectal cancer. *J Clin Oncol* 2018;36:773–9.
13 Karamitopoulou E. Tumour microenvironment of pancreatic cancer: immune landscape is dictated by molecular and histopathological features. *Br J Cancer* 2019;121:5–14.
14 Cox RE, Mahipal A, Chakrabarti S. A patient with locally advanced mismatch-repair-deficient pancreatic ductal adenocarcinoma successfully treated with neoadjuvant immunotherapy. *Cureus* 2021;13:e14640.
15 Kamatham S, Shahjehan F, Kasi PM. Circulating tumor DNA-based detection of microsatellite instability and response to immunotherapy in pancreatic cancer. *Front Pharmacol* 2020;11:23.
16 Chalabi M, Fanchi LF, Dijkstra KK, *et al*. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med* 2020;26:566–76.
17 Ludford1 KR K, Blum Murphy MA, Fleming ND. 1758O - Neoadjuvant pembrolizumab in localized/locally advanced solid tumors with mismatch repair deficiency. *ESMO Congress* 2021;32 (suppl_5):S1211–26.
18 Marabelle A, Le DT, Ascierto PA, *et al*. Efficacy of pembrolizumab in patients with Noncolorectal high microsatellite Instability/Mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol* 2020;38:1–10.
19 Hu ZI, Shia J, Stadler ZK, *et al*. Evaluating mismatch repair deficiency in pancreatic adenocarcinoma: challenges and recommendations. *Clin Cancer Res* 2018;24:1326–36.
20 Lupinacci RM, Goloudina A, Buhard O, *et al*. Prevalence of microsatellite instability in intraductal papillary mucinous neoplasms of the pancreas. *Gastroenterology* 2018;154:1061–5.
21 Eatrides JM, Coppola D, Al Diffalha S, *et al*. Microsatellite instability in pancreatic cancer. *JCO* 2016;34:e15753
22 Larson BK, Tuli R, Jamil LH, *et al*. Utility of endoscopic ultrasound-guided biopsy for next-generation sequencing of pancreatic exocrine malignancies. *Pancreas* 2018;47:990–5.
23 Dudley JC, Lin M-T, Le DT, *et al*. Microsatellite instability as a biomarker for PD-1 blockade. *Clin Cancer Res* 2016;22:813–20.
24 Guyot D'Asnières De Salins A, Tachon G, Cohen R. Discordance between immunochemistry of mismatch repair proteins and molecular testing of microsatellite instability in colorectal cancer. *ESMO Open* 2021;6:100120.
25 Kim ST, Cristescu R, Bass AJ, *et al*. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *Nat Med* 2018;24:1449–58.