Am J Transl Res 2021;13(11):12386-12394
www.ajtr.org /ISSN:1943-8141/AJTR0136594

Original Article

Integrin signaling gene alterations and outcomes of cancer patients receiving immune checkpoint inhibitors

Panagiotis J Vlachostergios

Division of Hematology and Medical Oncology, Department of Medicine, Weill Cornell Medicine, New York 10021, NY, USA

Received June 21, 2021; Accepted September 24, 2021; Epub November 15, 2021; Published November 30, 2021

Abstract: Background: Immune evasion is a hallmark of cancer and is associated with resistance to PD-1/PD-L1 and CTLA-4 inhibitors. Several interactions between tumor and immune cells within the tumor microenvironment are effected through integrin signaling; however the latter has been underrecognized as a pathway that could have an impact on oncological outcomes after treatment with immune checkpoint inhibitors (ICIs). This study aimed to assess the clinical relevance of genomic alterations in the integrin signaling pathway in ICI-treated patients with advanced cancers. Methods: Next generation sequencing (NGS) data from tumor samples of patients with advanced cancers treated with ICIs (anti-PD-1/PD-L1, anti-CTLA4 or both) were queried from four independent publicly available cohorts for mutations and structural variations in 72 integrin signaling pathway genes (Gene Set: GOBP_CELL_ADHESION_MEDIATED_BY_INTEGRIN). The Kaplan Meier method was used to assess the association between mutated and unmutated genes with overall (OS) and progression-free survival (PFS). All results were reported at the 0.05 significance level. Results: The largest cohort included 1662 patients (discovery set) and comprised 350 non-small cell lung cancer (NSCLC), 321 melanoma, 214 bladder, 151 renal cell carcinoma (RCC), 138 head neck (HN), 126 esophageal/gastric (EG), 117 glioma, 110 colorectal (CRC), 90 cancer of unknown primary (CUP), and 45 breast cancer patients. ICI treatments included PD-1 or PD-L1 inhibitors (n=1256), anti-CTLA4 inhibitors (n=146) or both (n=260). 170 patients (10% of the entire cohort) harbored mutations in PIK3CG (6%), RET (3%), SYK (1.4%), LYN (1.4%), PTPN11 (1.3%), and CRKL (0.1%) genes. Presence of these mutations was more frequent in melanoma (18%), followed by CRC (14.5%), CUP (11%), and NSCLC (11%). Patients with mutated tumors experienced a significantly longer median OS (41 months) compared to those without alterations (16 months, log-rank P<0.001). The favorable prognostic value of PIK3CG, RET, SYK, LYN, PTPN11, and CRKL alterations was confirmed in three melanoma cohorts (validation set, n=212, P=0.024). Assessment of mutation status of these genes in a fourth cohort of NSCLC patients (n=75) revealed a predictive significance as well, with regard to PFS after treatment with ipilimumab and nivolumab combination (P=0.048). Conclusion: Mutations and/or structural variations in integrin signaling genes may have prognostic and predictive value in patients with metastatic malignancies who receive ICIs. Although confirmation in larger studies with concurrent investigation of underlying immunologic mechanisms is needed, these findings pose therapeutic implications for co-targeted approaches to overcome immune evasion and resistance.

Keywords: Integrin signaling, cancer immunotherapy, prognostic, predictive, overall survival, progression-free survival, genomics, mutations, copy number alterations, immune checkpoint inhibitors, PD-1, PD-L1, CTLA-4

Introduction

Immunotherapy with use of immune checkpoint inhibitors (ICIs) is currently an established treatment option for patients with various cancer types [1]. While surrogate biomarkers such as tissue-based programmed death ligand 1 (PD-L1) have been developed to guide the use of PD-1/PD-L1 inhibitors [2], there are multiple shortcomings that limit their use unanimously and thus more robust tools are needed [3]. Other examples of imperfect biomarkers for predicting immune response include the load of DNA mutations, tumor neoantigens and mRNA expression signatures from immune cells within the tumor microenvironment [4, 5].

Integrins are an integral part of the stromal microenvironment and comprise a family of heterodimeric α/β integrin receptors, which facili-

Table 1. GOBP_CELL_ADHESION_MEDIATED_BY_INTEGRIN gene set and properties

Genes	Gene Family
CCL21, CCL5, CCN3, CXCL13, LIF, PLAU, TGFB2	Cytokines and growth factors
FOXC2, SNAI2	Transcription factors
ADAM17, CD3E, DPP4, ICAM1, ITGA2, ITGA4, ITGA5, ITGAV, ITGB1, ITGB2, ITGB3, ITGB4, MUC1*	Cell differentiation markers
EPHA2, EPHA8, LYN, PTK2, RET*, SYK*, WNK1	Protein kinases
PTPN11, MUC1*, RET*, SYK*	Oncogenes
EXT1	Tumor suppressors
ACER2, ADA, ADAM9, CIB1, COL16A1, CRK, CRKL, CYP1B1, EFNA1, FBN1, FERMT1, ERMT3, FOXC2, FYB2, HRG, IFT74, ITGA11, ITGB1BP1, ITGB5, ITGB6, ITGB7, ITGB8, ITGBL1, JAM3, LPXN, NCKAP1L, NEXMIF, NPNT, P2RY12, PDE3B, PIEZO1, PIK3CG, PLPP3, PODXL, PTK2, PTPN11, PTPN6, RAC3, SERPINE1, SFRP2, SKAP1, SNAI2, SWAP70, TESC, TGFB2, VTN, WNK1	Rest

*Integrin signaling genes that belong to multiple gene families.

tates contacts with components of the extracellular matrix (ECM) and in some cases with adhesion receptors on other cells. Tumor cell interactions with platelets, neutrophils, monocytes, endothelial cells are key mediators of cancer progression and facilitate hallmarks of cancer including immune evasion and metastatic dissemination [6, 7]. Further to these direct effects, integrin cell adhesion pathways may promote several immunosuppressive signals, including integrin-dependent activation of tumor growth factor beta (TGFβ), and PD-L1 expression in human and murine cancerous cells [8, 9]. Several lines of evidence indicate this across various primary tumors. Overexpression of integrins ITGB1, ITGB5 and ITGB6 correlated with an immune suppressive gene expression signature characterized by abundance of tumor-associated macrophages, T-regs and depletion of CD8 T cells in pancreatic cancer [10]. Integrin-mediated TGF-β activation promotes an immune suppressive microenvironment in glioblastoma multiforme via direct cell-to-cell contact between glioblastoma stem cells and natural killer (NK) cells, which is reversible with allogeneic NK cells in combination with integrin inhibitors [11]. A similar immunosuppressive signal has been described in triple negative breast cancer (TNBC), whereby the integrin αvβ6 receptor on the surface of tumor cells upregulates expression of the transcription factor SOX2 via TGFβ signaling [12]. Inhibition of SOX2 expression by an integrin blocking monoclonal antibody resulted in a substantial survival benefit in metastatic murine TNBC models poorly responsive to PD-1 blockade [12]. The integrin-TGFβ axis is also involved in inducing intratumoral immunosuppression in murine melanoma through recruitment of FoxP3+ T-regs, myeloid-derived suppressor cells (MDSC), and M2 macrophages [13].

However, the clinical significance of these observations in cancer patients treated with ICIs remains elusive. This study tested the hypothesis that somatic gene alterations affecting integrin signaling could have an impact on the clinical outcomes of cancer patients after treatment with anti-PD-1/PD-L1 or/and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) ICIs.

Materials and methods

This study analyzed next generation sequencing (NGS) data corresponding to a variety of tumor types from patients who were treated with at least one dose of ICI, available at cBioportal for Cancer Genomics (www.cbioportal.org) [14]. NGS data from the discovery cohort [15] consisting of 1662 patients were queried for mutations and fusions in integrin signaling genes. The GOBP_CELL_ADHESION_MEDIATED_BY_INTEGRIN gene set from the Gene Set Enrichment Analysis (GSEA) molecular signatures database (http://www.gsea-msigdb.org/gsea/msigdb/index.jsp) [16] was used as a reference to include the most important integrin-related genes in the analyses (**Table 1**).

Altered integrin genes from the discovery cohort were queried in validation cohorts. For validation, three additional cohorts from patients with melanoma treated with ICIs with available NGS data were used [17-19] and were combined into one meta-dataset for analysis.

Additionally, one non-small cell lung cancer (NSCLC) cohort was analyzed for association

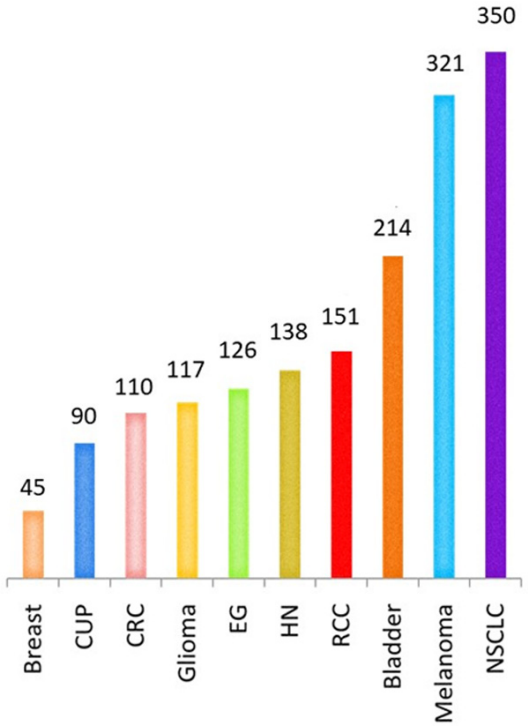

Figure 1. Patient distribution per tumor type (discovery set).

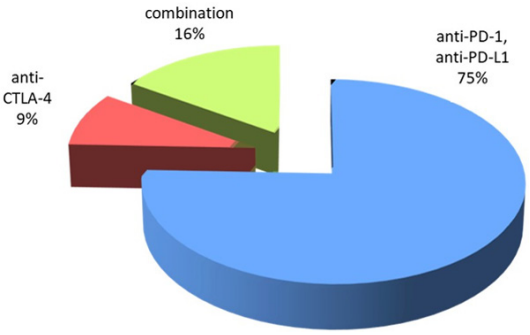

Figure 2. Patient distribution per treatment (discovery set).

between integrin gene alterations and progression-free survival after treatment with ICIs [20].

The Kaplan Meier method was used to assess the association between altered and unaltered integrin pathway genes with overall survival (OS) and progression-free survival (PFS). OS was measured from the date of first ICI treatment to time of death or last follow-up. PFS was defined as the time of first ICI dose to the date of first disease progression or death, if death occurred within 100 days of the final dose of ICI, as previously described [20]. All results were reported at the 0.05 significance level.

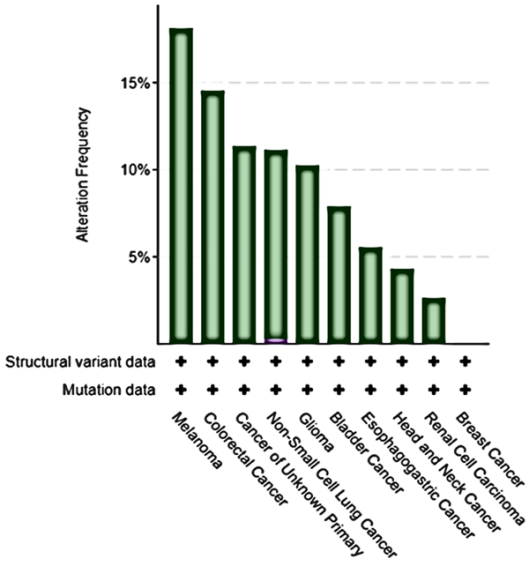

Figure 3. Frequency of alterations in GOBP_CELL_ADHESION_MEDIATED_BY_INTEGRIN genes per tumor type (discovery set).

Results

One thousand six hundred sixty-two patients were examined in the discovery set, most of whom had metastatic disease (94%). The majority of patients had a diagnosis of NSCLC (n=350) or melanoma (n=321). The distribution of different primaries is illustrated in **Figure 1**.

The majority of patients were treated with an anti-PD-1 or anti-PD-L1 ICI, including pembrolizumab, atezolizumab, nivolumab, durvalumab, or avelumab (n=1256). A minority of patients (n=146) received a CTLA-4 inhibitor, ipilimumab or tremelimumab, or combinations of anti-PD-1/PD-L1 and anti-CTLA-4 (n=260) (**Figure 2**).

Interrogation of the discovery cohort for mutations and copy number variations using the GOBP_CELL_ADHESION_MEDIATED_BY_INTEGRIN gene set revealed that a subset of tumors corresponding to 170 patients (10% of total cohort) harbored mutations in PIK3CG (6%), RET (3%), SYK (1.4%), LYN (1.4%), PTPN11 (1.3%), and CRKL (0.1%) genes (Supplementary Table 1). These mutations were more frequent in melanoma (18%), followed by CRC (14.5%), CUP (11%), NSCLC (11%), glioma (10%), bladder (8%), EG (5.5%), HN (4.3%), and RCC (2.7%) (**Figure 3**). Alteration in one gene frequently co-occurred with alteration in another, within this

Table 2. Molecular alterations in integrin signaling genes in tumor samples of patients treated with ICIs (discovery set)

Gene A	Gene B	Log2 Odds Ratio	*P*-Value	q-Value	Tendency
PIK3CG	SYK	2.981	<0.001	0.002	Co-occurrence
PIK3CG	RET	2.028	<0.001	0.004	Co-occurrence
RET	SYK	>3	<0.001	0.004	Co-occurrence
PIK3CG	PTPN11	2.462	0.005	0.018	Co-occurrence

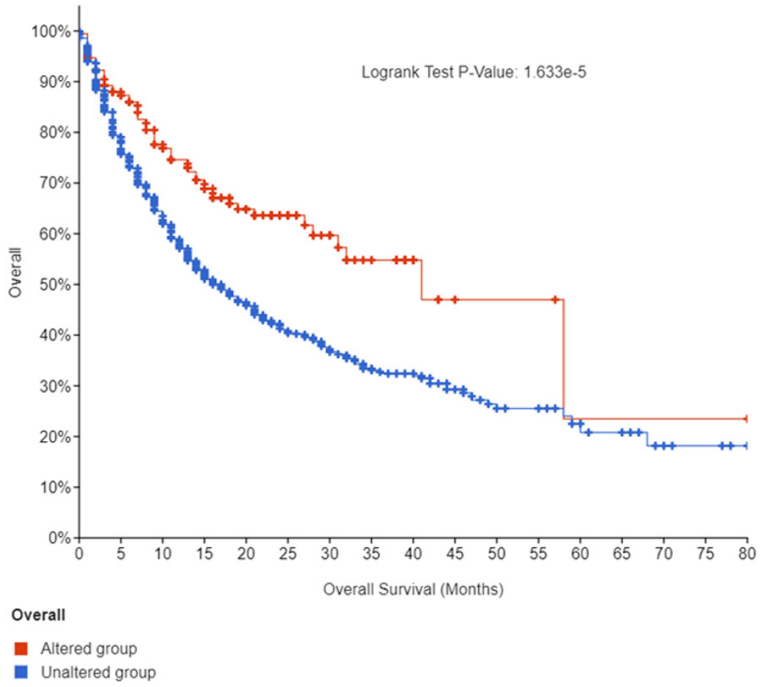

Figure 4. Kaplan-Meier overall survival plot of patients according to alterations in integrin signaling genes (discovery set).

subset of six integrin signaling pathway genes (**Table 2**).

After a median follow-up of 19 months (range 0-80), patients carrying somatic mutations in one or more of these integrin signaling genes experienced a significantly longer median OS (41 months) compared to those without tumor alterations (16 months, log-rank P<0.001) (**Figure 4**).

To validate these findings on OS, three additional cohorts of patients with melanoma (total n=212) who received ICIs were interrogated [17-19]. Mutations and/or copy number variations occurred at a frequency of 15% in PI3KG and RET genes, 11% in LYN, 8% in PTPN11, and 7% in SYK and CTRL genes (**Figure 5**). Patients with somatic alterations in these integrin signaling genes (n=93) experienced a significantly longer median OS of 26.7 months (20.4-49.3) compared to the median OS of 12.6 months (9.6-20.1) in the unaltered group (n=118), P= 0.024 (**Figure 6**).

Additionally, to assess the clinical significance of integrin signaling mutations with respect to PFS after treatment with ICIs, a cohort of 75 NSCLC patients who received combination of PD-1 and CTLA-4 inhibitors was interrogated [20]. The majority of tumors were of non-squamous histology and were characterized by mutations in PI3KG (9%), RET (7%), SYK (2.7%), LYN (1.3%) whereas there were no mutations found in PTPN11 and CRKL genes (**Figure 7**). Patients with tumors harboring these mutations (n=13) demonstrated a longer median PFS after treatment with ICI combination, 23 months (7.9-NA) as opposed to patients (n=62) without mutations who experienced a shorter median PFS of only 6.5 months (3.6-8.1), P=0.048 (**Figure 8**).

Discussion

In the present study, the clinical utility of molecular alterations in the integrin signaling pathway was examined in patients with advanced cancer treated with ICIs across various studies. Mutations in a subset of genes, including PIK3CG, RET, SYK, LYN, PTPN11, and CRKL were associated with favorable outcomes, including PFS and OS in those patients.

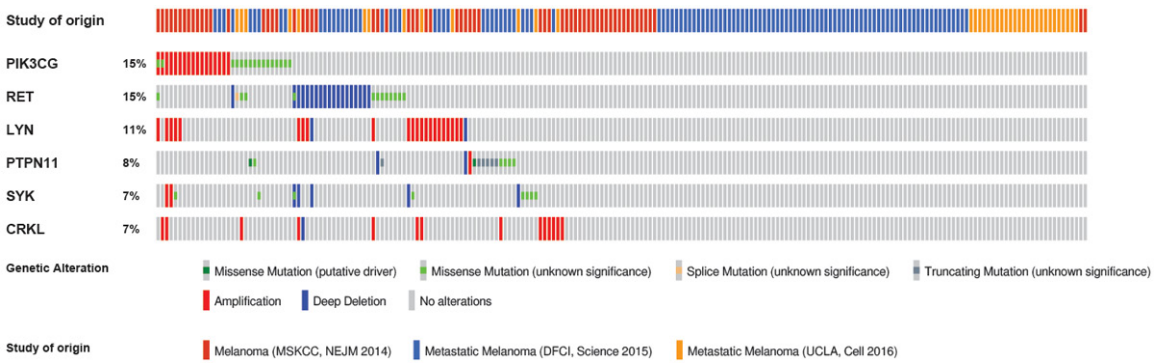

Figure 5. Oncoplot of mutations and copy number alterations in integrin signaling genes in melanoma (validation set, n=212).

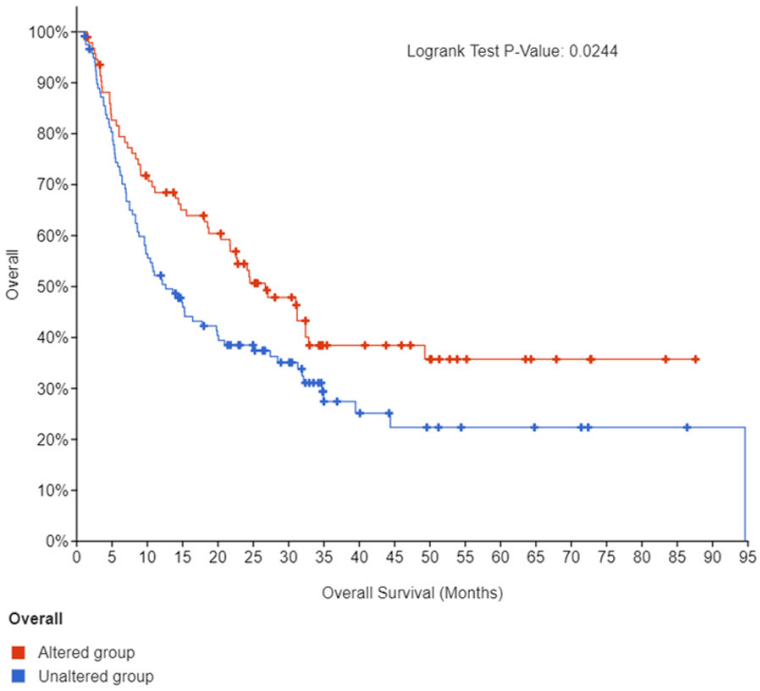

Figure 6. Kaplan-Meier overall survival plot of patients according to alterations in integrin signaling genes in melanoma (validation set).

There are several mechanistic implications posed by this study that are in line with previous *in vitro* and *in vivo* observations. First, the immune response of tumor-bearing PIK3CG-/- mice in an orthotopic HN squamous cell carcinoma model was found to be marked by increased anti-tumor cytotoxic molecules IFN-γ, IL-17 from T-cells and immune checkpoint marker (PD-L1, PD-1) expression by myeloid cells and T-cells compared to tumor-bearing wild-type mice [21]. This suggests that inactivation of PI3KCG might be beneficial for response to ICIs. This is not surprising given that the PIK3CG gene product, PI3Kγ, is a key regulator of T-cell signaling. For example, PI3Kγ is responsible for acute rejection of allogenic transplants and this is reversible in PI3Kγ-null mice receiving heart allografts or after specific PI3Kγ inhibition [22]. Furthermore, PI3K inhibitors or genetic deletions of PI3Kγ in TNBC enhance antitumor immunity, and sensitize cancer cells to PD-1 inhibitors [23].

Second, RET-rearranged NSCLC tumors are less responsive to immunotherapy whereas RET inhibitors can lead to induction of HLA expression and appearance of new tumor neoantigens [24, 25]. This is also logical in view of RET function, best evidenced in RET transgenic mouse models of spontaneous skin melanoma, which are enriched in highly immunosuppressive regulatory T-cells [26].

Third, blockade of the SYK kinase, which is of key importance for the function of B-cells, results in downmodulation of pSTAT3 immune suppressive signaling, as well as reversal of PD-1-associated T-cell exhaustion in chronic lymphocytic leukemia [27]. Likewise, inhibition of the PTPN11 gene product SHP-2 reverses the suppressive effects of PD-1 on Th1 immunity and T-cell activation at tumor sites [28].

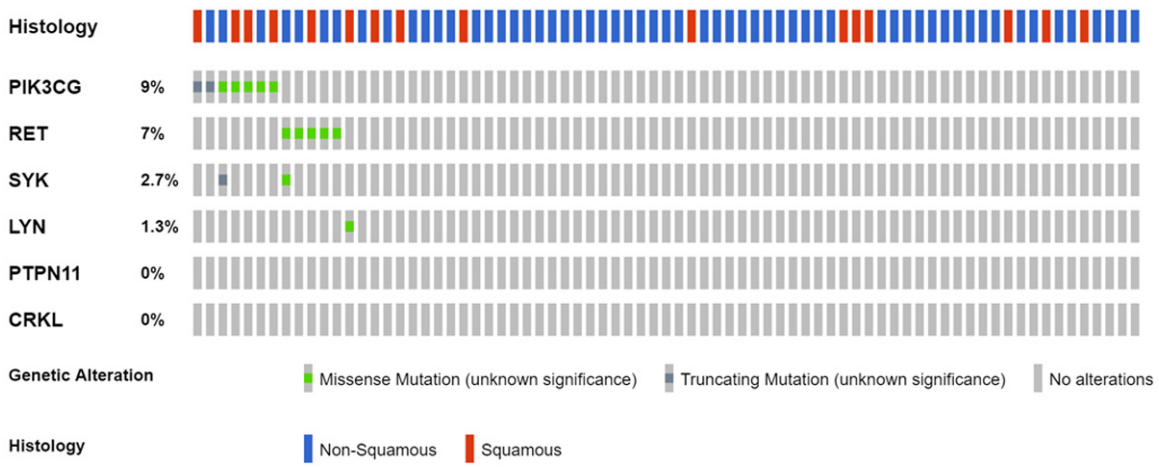

Figure 7. Oncoplot of mutations in integrin signaling genes in NSCLC (n=75).

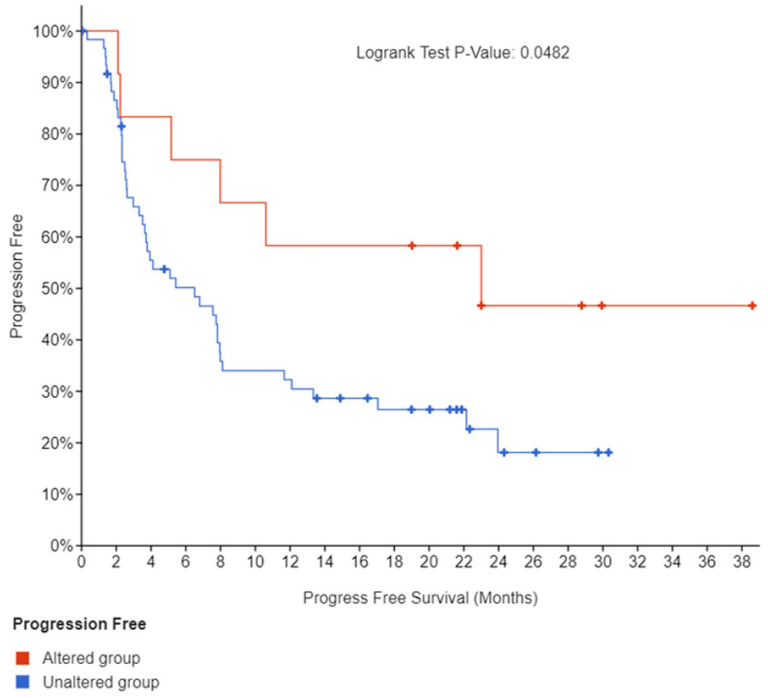

Figure 8. Kaplan-Meier progression-free survival plot of patients according to alterations in integrin signaling genes in NSCLC.

Collectively, placing this study's results in the above-described mechanistic context, it is tempting to speculate that mutations and/or structural variations in the afore-mentioned integrin signaling genes may cause a net-effect of attenuated function of corresponding gene products and integrin signaling overall that could translate into improved OS and response of patients treated with ICIs compared to those with unaltered tumors. While prospective confirmation of this study's results is warranted, it is conceivable that integrin mutations could serve as surrogate markers to guide ICI treatment decisions if further investigation of the underlying immunologic mechanisms confirms such a role.

Reversely, overexpression of a T-cell exhaustion gene signature, including LYN, was associated with worse prognosis of lung adenocarcinoma patients [29]. Along the same lines, Crk adaptor protein encoded by CRKL gene promotes PD-L1 expression on tumor cells of murine breast adenocarcinoma to induce immune evasion which is reversible upon genetic ablation [30].

Taken together, the results of this study pose important therapeutic implications for the use of integrin signaling modulation as a tool to sensitize patients to anti-PD-L1 ICIs. While functional integrin antagonism does not contribute significantly to efficacy, combining an engineered mouse serum albumin/IL-2 fusion with an Fc fusion to an integrin-binding peptide (2.5F-Fc) recruits both an innate and adaptive

immune response such that administration of this integrin-targeted immunotherapy together with an anti-PD-1 antibody further improves responses in syngeneic mouse models [31]. Additionally, integrin αvβ3-targeted radionuclide therapy combined with anti-PD-L1 immunotherapy synergistically enhanced anti-tumor efficacy in a murine colon cancer model [32].

This study was limited by heterogeneity of patient cohorts with regard to different primaries, number of prior therapies, and timing of NGS testing relative to ICI initiation, as well as different platforms of NGS used by different research groups [15, 17-20]. Additionally, because this was a hypothesis-generating analysis of previously reported genomic data through the lens of integrin signaling on efficacy of immunotherapy, it underscores the effects of other genomic and/or epigenomic alterations on OS and PFS, focusing merely on mutations and fusions of integrin-related cell adhesion genes.

Future studies that integrate other genomic and/or histopathologic biomarkers may allow for the development of an optimized predictive tool to inform clinical decisions on the use of ICIs. Taking a step further, modulating expression of integrin pathway gene products could improve antitumor responses elicited by anti-PD-1 or/and anti-CTLA-4 therapy. Different groups of anti-integrin drugs have been developed, including monoclonal antibodies (e.g., abituzumab) and others such as cilengitide, E7820 and MK-0429 [33]. These drugs have been evaluated in various cancer types. However, they have shown modest efficacy, and none of them have yet been approved for cancer treatment [34]. Correlative studies on genomic and epigenomic surrogates of response and resistance, wherever available, will be of key importance to better target specific subpopulations and improve the efficacy of ICIs, particularly in combination with anti-integrin signaling therapies, including inhibitors of most relevant members within this pathway, namely PI3Kγ, RET, SYK, SHP-2, LYN, and CRK adaptor protein.

Disclosure of conflict of interest

None.

Address correspondence to: Panagiotis J Vlachostergios, Weill Cornell Medicine, 520 East 70th Street, New York, NY 10021, USA. Tel: 1-646-962-2072; Fax: 1-646-962-1603; E-mail: pjv9003@med.cornell.edu

References

[1] Gong J, Chehrazi-Raffle A, Reddi S and Salgia R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. J Immunother Cancer 2018; 6: 8.

[2] Doroshow DB, Bhalla S, Beasley MB, Sholl LM, Kerr KM, Gnjatic S, Wistuba II, Rimm DL, Tsao MS and Hirsch FR. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. Nat Rev Clin Oncol 2021; 18: 345-362.

[3] Vlachostergios PJ and Faltas BM. The molecular limitations of biomarker research in bladder cancer. World J Urol 2019; 37: 837-848.

[4] Xiao Q, Nobre A, Piñeiro P, Berciano-Guerrero MÁ, Alba E, Cobo M, Lauschke VM and Barragán I. Genetic and epigenetic biomarkers of immune checkpoint blockade response. J Clin Med 2020; 9: 286.

[5] Gibney GT, Weiner LM and Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol 2016; 17: e542-e551.

[6] Läubli H and Borsig L. Altered cell adhesion and glycosylation promote cancer immune suppression and metastasis. Front Immunol 2019; 10: 2120.

[7] Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646-674.

[8] Nolte M and Margadant C. Controlling immunity and inflammation through integrin-dependent regulation of TGF-β. Trends Cell Biol 2020; 30: 49-59.

[9] Vannini A, Leoni V, Barboni C, Sanapo M, Zaghini A, Malatesta P, Campadelli-Fiume G and Gianni T. αvβ3-integrin regulates PD-L1 expression and is involved in cancer immune evasion. Proc Natl Acad Sci U S A 2019; 116: 20141-20150.

[10] Zhuang H, Zhou Z, Ma Z, Li Z, Liu C, Huang S, Zhang C and Hou B. Characterization of the prognostic and oncologic values of ITGB superfamily members in pancreatic cancer. J Cell Mol Med 2020; 24: 13481-13493.

[11] Shaim H, Shanley M, Basar R, Daher M, Gumin J, Zamler DB, Uprety N, Wang F, Huang Y, Gabrusiewicz K, Miao Q, Dou J, Alsuliman A, Kerbauy LN, Acharya S, Mohanty V, Mendt M, Li S, Lu J, Wei J, Fowlkes NW, Gokdemir E, Ensley EL, Kaplan M, Kassab C, Li L, Ozcan G, Banerjee PP, Shen Y, Gilbert AL, Jones CM, Bdiwi M, Nunez-Cortes AK, Liu E, Yu J, Imahashi N, Muniz-Feliciano L, Li Y, Hu J, Draetta G, Marin D,

Yu D, Mielke S, Eyrich M, Champlin RE, Chen K, Lang FF, Shpall EJ, Heimberger AB and Rezvani K. Targeting the αv integrin/TGF-β axis improves natural killer cell function against glioblastoma stem cells. J Clin Invest 2021; 131: e142116.

[12] Bagati A, Kumar S, Jiang P, Pyrdol J, Zou AE, Godicelj A, Mathewson ND, Cartwright ANR, Cejas P, Brown M, Giobbie-Hurder A, Dillon D, Agudo J, Mittendorf EA, Liu XS and Wucherpfennig KW. Integrin αvβ6-TGFβ-SOX4 pathway drives immune evasion in triple-negative breast cancer. Cancer Cell 2021; 39: 54-67. e9.

[13] Shidal C, Singh NP, Nagarkatti P and Nagarkatti M. MicroRNA-92 expression in CD133+ melanoma stem cells regulates immunosuppression in the tumor microenvironment via integrin-dependent activation of TGFβ. Cancer Res 2019; 79: 3622-3635.

[14] http://www.cbioportal.org. Accessed August 7, 2021.

[15] Samstein RM, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, Barron DA, Zehir A, Jordan EJ, Omuro A, Kaley TJ, Kendall SM, Motzer RJ, Hakimi AA, Voss MH, Russo P, Rosenberg J, Iyer G, Bochner BH, Bajorin DF, Al-Ahmadie HA, Chaft JE, Rudin CM, Riely GJ, Baxi S, Ho AL, Wong RJ, Pfister DG, Wolchok JD, Barker CA, Gutin PH, Brennan CW, Tabar V, Mellinghoff IK, DeAngelis LM, Ariyan CE, Lee N, Tap WD, Gounder MM, D'Angelo SP, Saltz L, Stadler ZK, Scher HI, Baselga J, Razavi P, Klebanoff CA, Yaeger R, Segal NH, Ku GY, DeMatteo RP, Ladanyi M, Rizvi NA, Berger MF, Riaz N, Solit DB, Chan TA and Morris LGT. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet 2019; 51: 202-206.

[16] http://www.gsea-msigdb.org/gsea/msigdb/index.jsp. Accessed August 7, 2021.

[17] Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, Sucker A, Hillen U, Foppen MHG, Goldinger SM, Utikal J, Hassel JC, Weide B, Kaehler KC, Loquai C, Mohr P, Gutzmer R, Dummer R, Gabriel S, Wu CJ, Schadendorf D and Garraway LA. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science 2015; 350: 207-211.

[18] Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, Walsh LA, Postow MA, Wong P, Ho TS, Hollmann TJ, Bruggeman C, Kannan K, Li Y, Elipenahli C, Liu C, Harbison CT, Wang L, Ribas A, Wolchok JD and Chan TA. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014; 371: 2189-2199.

[19] Hugo W, Zaretsky JM, Sun L, Song C, Moreno BH, Hu-Lieskovan S, Berent-Maoz B, Pang J, Chmielowski B, Cherry G, Seja E, Lomeli S, Kong X, Kelley MC, Sosman JA, Johnson DB, Ribas A and Lo RS. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. Cell 2016; 165: 35-44.

[20] Hellmann MD, Nathanson T, Rizvi H, Creelan BC, Sanchez-Vega F, Ahuja A, Ni A, Novik JB, Mangarin LMB, Abu-Akeel M, Liu C, Sauter JL, Rekhtman N, Chang E, Callahan MK, Chaft JE, Voss MH, Tenet M, Li XM, Covello K, Renninger A, Vitazka P, Geese WJ, Borghaei H, Rudin CM, Antonia SJ, Swanton C, Hammerbacher J, Merghoub T, McGranahan N, Snyder A and Wolchok JD. Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung cancer. Cancer Cell 2018; 33: 843-852, e4.

[21] Anderson K, Ryan N, Alkhimovitch A, Siddiqui A and Oghumu S. Inhibition of PI3K isoform p110γ increases both anti-tumor and immunosuppressive responses to aggressive murine head and neck squamous cell carcinoma with low immunogenicity. Cancers (Basel) 2021; 13: 953.

[22] Uehara M, McGrath MM, Ohori S, Solhjou Z, Banouni N, Routray S, Evans C, DiNitto JP, Elkhal A, Turka LA, Strom TB, Tullius SG, Winkler DG, Azzi J and Abdi R. Regulation of T cell alloimmunity by PI3Kγ and PI3Kδ. Nat Commun 2017; 8: 951.

[23] Sai J, Owens P, Novitskiy SV, Hawkins OE, Vilgelm AE, Yang J, Sobolik T, Lavender N, Johnson AC, McClain C, Ayers GD, Kelley MC, Sanders M, Mayer IA, Moses HL, Boothby M and Richmond A. PI3K inhibition reduces mammary tumor growth and facilitates antitumor immunity and anti-PD1 responses. Clin Cancer Res 2017; 23: 3371-3384.

[24] Baglivo S, Ludovini V, Moretti R, Bellezza G, Sidoni A, Roila F and Metro G. RET Rearrangement as a predictor of unresponsiveness to immunotherapy in non-small cell lung cancer: report of two cases with review of the literature. Oncol Ther 2020; 8: 333-339.

[25] Oh CY, Klatt MG, Bourne C, Dao T, Dacek MM, Brea EJ, Mun SS, Chang AY, Korontsvit T and Scheinberg DA. ALK and RET inhibitors promote HLA class I antigen presentation and unmask new antigens within the tumor immunopeptidome. Cancer Immunol Res 2019; 7: 1984-1997.

[26] Umansky V and Sevko A. Ret transgenic mouse model of spontaneous skin melanoma: focus on regulatory T cells. Pigment Cell Melanoma Res 2013; 26: 457-63.

[27] Lam V, Best S, Kittai A, Orand K, Spurgeon SE, Liu T and Danilov AV. Proapoptotic and immunomodulatory effects of SYK inhibitor entospletinib in combination with obinutuzumab in

patients with chronic lymphocytic leukaemia. Br J Clin Pharmacol 2021; [Epub ahead of print].

[28] Marasco M, Berteotti A, Weyershaeuser J, Thorausch N, Sikorska J, Krausze J, Brandt HJ, Kirkpatrick J, Rios P, Schamel WW, Köhn M and Carlomagno T. Molecular mechanism of SHP2 activation by PD-1 stimulation. Sci Adv 2020; 6: eaay4458.

[29] Ahluwalia P, Ahluwalia M, Mondal AK, Sahajpal N, Kota V, Rojiani MV, Rojiani AM and Kolhe R. Immunogenomic gene signature of cell-death associated genes with prognostic implications in lung cancer. Cancers (Basel) 2021; 13: 155.

[30] Kumar S, Davra V, Obr AE, Geng K, Wood TL, De Lorenzo MS and Birge RB. Crk adaptor protein promotes PD-L1 expression, EMT and immune evasion in a murine model of triple-negative breast cancer. Oncoimmunology 2017; 7: e1376155.

[31] Kwan BH, Zhu EF, Tzeng A, Sugito HR, Eltahir AA, Ma B, Delaney MK, Murphy PA, Kauke MJ, Angelini A, Momin N, Mehta NK, Maragh AM, Hynes RO, Dranoff G, Cochran JR and Wittrup KD. Integrin-targeted cancer immunotherapy elicits protective adaptive immune responses. J Exp Med 2017; 214: 1679-1690.

[32] Chen H, Zhao L, Fu K, Lin Q, Wen X, Jacobson O, Sun L, Wu H, Zhang X, Guo Z, Lin Q and Chen X. Integrin αvβ3-targeted radionuclide therapy combined with immune checkpoint blockade immunotherapy synergistically enhances anti-tumor efficacy. Theranostics 2019; 9: 7948-7960.

[33] Łasiñska I and Mackiewicz J. Integrins as a new target for cancer treatment. Anticancer Agents Med Chem 2019; 19: 580-586.

[34] Lorusso G, Rüegg C and Kuonen F. Targeting the extra-cellular matrix-tumor cell crosstalk for anti-cancer therapy: emerging alternatives to integrin inhibitors. Front Oncol 2020; 10: 1231.

Supplementary Table 1. Mutation characteristics by affected gene within the GOBP_CELL_ADHESION_MEDIATED_BY_INTEGRIN group of genes (discovery set)

Integrin pathway Gene	Sample ID	Cancer Type	Protein Change	Mutation Type	Allele Frequency
PIK3CG	P-0004693-T01-IM5	Lung Adenocarcinoma	D946N	Missense	0.06
	P-0010241-T01-IM5	Nasopharyngeal Carcinoma	R191H	Missense	0.06
	P-0007121-T01-IM5	Lung Adenocarcinoma	V994L	Missense	0.06
	P-0022952-T01-IM6	Esophageal Adenocarcinoma	S449Y	Missense	0.06
	P-0005851-T01-IM5	Poorly Differentiated Non-Smal...	H834Y	Missense	0.06
	P-0007310-T01-IM5	Renal Clear Cell Carcinoma	K103N	Missense	0.06
	P-0006177-T01-IM5	Cutaneous Melanoma	Q134*	Nonsense	0.06
	P-0002855-T01-IM3	Colon Adenocarcinoma	D819N	Missense	0.06
	P-0003368-T01-IM5	Lung Adenocarcinoma	G1038*	Nonsense	0.07
	P-0011357-T01-IM5	Colon Adenocarcinoma	V162I	Missense	0.08
	P-0008874-T01-IM5	Lung Adenocarcinoma	G790L	Missense	0.08
	P-0001808-T01-IM3	Colon Adenocarcinoma	E573*	Nonsense	0.08
	P-0008874-T01-IM5	Lung Adenocarcinoma	G436C	Missense	0.08
	P-0013826-T01-IM5	Desmoplastic Melanoma	P208S	Missense	0.08
	P-0009924-T01-IM5	Lung Adenocarcinoma	Q1007R	Missense	0.08
	P-0007493-T02-IM5	Lung Adenocarcinoma	S504P	Missense	0.08
	P-0009189-T01-IM5	Cutaneous Melanoma	V11M	Missense	0.08
	P-0005954-T01-IM5	Renal Clear Cell Carcinoma	T733S	Missense	0.09
	P-0009950-T01-IM5	Melanoma of Unknown Primary	S761F	Missense	0.09
	P-0007619-T01-IM5	Lung Adenocarcinoma	V115G	Missense	0.09
	P-0010499-T01-IM5	Colon Adenocarcinoma	E209K	Missense	0.1
	P-0001710-T01-IM3	Cutaneous Melanoma	E267K	Missense	0.1
	P-0015177-T01-IM6	Pleomorphic Carcinoma of the L...	V882E	Missense	0.1
	P-0019428-T01-IM6	Colon Adenocarcinoma	Q391*	Nonsense	0.1
	P-0012729-T01-IM5	Lung Adenocarcinoma	T886R	Missense	0.11
	P-0002151-T01-IM3	Lung Adenocarcinoma	N289S	Missense	0.11
	P-0004189-T01-IM5	Lung Adenocarcinoma	H60R	Missense	0.11
	P-0024824-T01-IM6	Colorectal Adenocarcinoma	E415G	Missense	0.11
	P-0009950-T01-IM5	Melanoma of Unknown Primary	W410*	Nonsense	0.12
	P-0012999-T01-IM5	Cutaneous Melanoma	K920*	Nonsense	0.12
	P-0026723-T01-IM6	Bladder Urothelial Carcinoma	D358N	Missense	0.12
	P-0009950-T01-IM5	Melanoma of Unknown Primary	T155R	Missense	0.13
	P-0001808-T01-IM3	Colon Adenocarcinoma	D950Y	Missense	0.13
	P-0007119-T01-IM5	Lung Adenocarcinoma	P508T	Missense	0.13
	P-0003728-T01-IM5	Melanoma of Unknown Primary	E41K	Missense	0.14
	P-0007916-T01-IM5	Lung Adenocarcinoma	S650I	Missense	0.15
	P-0010587-T01-IM5	Colon Adenocarcinoma	A676T	Missense	0.15
	P-0015512-T01-IM6	Cutaneous Melanoma	W201*	Nonsense	0.15
	P-0010499-T01-IM5	Colon Adenocarcinoma	R1021H	Missense	0.15
	P-0010736-T01-IM5	Lung Adenocarcinoma	P241A	Missense	0.15
	P-0004783-T01-IM5	Rectal Adenocarcinoma	M804I	Missense	0.16
	P-0007101-T02-IM5	Lung Adenocarcinoma	P206H	Missense	0.16
	P-0013232-T01-IM5	Cutaneous Melanoma	P193S	Missense	0.16
	P-0003524-T01-IM5	Upper Tract Urothelial Carcinoma	R472H	Missense	0.16
	P-0014451-T01-IM6	Lung Adenocarcinoma	D120H	Missense	0.16
	P-0012188-T01-IM5	Cancer of Unknown Primary	S53I	Missense	0.16
	P-0007916-T01-IM5	Lung Adenocarcinoma	V10L	Missense	0.16
	P-0006281-T01-IM5	Bladder Urothelial Carcinoma	E880*	Nonsense	0.16
	P-0013089-T01-IM5	Renal Clear Cell Carcinoma	Y6_K7delins*	Nonsense	0.17
	P-0019101-T01-IM6	Upper Tract Urothelial Carcinoma	E41D	Missense	0.18
	P-0010115-T01-IM5	Melanoma of Unknown Primary	P526S	Missense	0.18
	P-0015512-T01-IM6	Cutaneous Melanoma	E337K	Missense	0.19
	P-0015512-T01-IM6	Cutaneous Melanoma	V763G	Missense	0.2

	P-0015928-T01-IM6	Squamous Cell Carcinoma, NOS	S82N	Missense	0.2
	P-0001733-T01-IM3	Esophageal Adenocarcinoma	G334S	Missense	0.2
	P-0004051-T01-IM5	Colon Adenocarcinoma	R687K	Missense	0.21
	P-0017658-T01-IM5	Small Cell Bladder Cancer	Q1071*	Nonsense	0.22
	P-0021503-T01-IM6	Bladder Urothelial Carcinoma	D654N	Missense	0.23
	P-0021774-T01-IM6	Cancer of Unknown Primary	E511K	Missense	0.23
	P-0002351-T01-IM3	Lung Squamous Cell Carcinoma	R184S	Missense	0.23
	P-0012860-T01-IM5	Cutaneous Melanoma	W617*	Nonsense	0.24
	P-0015923-T01-IM6	Bladder Urothelial Carcinoma	D493N	Missense	0.25
	P-0019475-T01-IM6	Colon Adenocarcinoma	L555S	Missense	0.25
	P-0000697-T01-IM3	Cutaneous Melanoma	V202M	Missense	0.26
	P-0012860-T01-IM5	Cutaneous Melanoma	G300E	Missense	0.27
	P-0010317-T01-IM5	Adenocarcinoma of the Gastroes...	V43M	Missense	0.28
	P-0014159-T01-IM5	Melanoma of Unknown Primary	N167S	Missense	0.28
	P-0005823-T01-IM5	Colon Adenocarcinoma	R184C	Missense	0.28
	P-0024731-T01-IM6	Cutaneous Squamous Cell Carcin...	K809Nfs*68	Frameshift deletion	0.29
	P-0002392-T01-IM3	Desmoplastic Melanoma	R1021C	Missense	0.29
	P-0009311-T01-IM5	Cutaneous Melanoma	P780L	Missense	0.29
	P-0020986-T01-IM6	Cancer of Unknown Primary, NOS	F965L	Missense	0.29
	P-0010613-T01-IM5	Glioblastoma Multiforme	R477H	Missense	0.29
	P-0010004-T01-IM5	Glioblastoma Multiforme	R359H	Missense	0.3
	P-0000235-T01-IM3	Lung Squamous Cell Carcinoma	A676S	Missense	0.3
	P-0015438-T01-IM6	Melanoma of Unknown Primary	P780S	Missense	0.3
	P-0009918-T01-IM5	Stomach Adenocarcinoma	V165I	Missense	0.3
	P-0005583-T01-IM5	Cutaneous Melanoma	R849Q	Missense	0.31
	P-0004442-T01-IM5	Lung Adenocarcinoma	L119M	Missense	0.31
	P-0015923-T01-IM6	Bladder Urothelial Carcinoma	N949Y	Missense	0.32
	P-0019003-T01-IM6	Small Cell Carcinoma of Unknow...	G65S	Missense	0.32
	P-0002490-T01-IM3	Melanoma of Unknown Primary	S264N	Missense	0.32
	P-0002380-T01-IM3	Cutaneous Melanoma	G300R	Missense	0.32
	P-0024731-T01-IM6	Cutaneous Squamous Cell Carcin...	P401L	Missense	0.32
	P-0015501-T01-IM6	Bladder Urothelial Carcinoma	Q533E	Missense	0.32
	P-0009017-T01-IM5	Lung Adenocarcinoma	E279*	Nonsense	0.32
	P-0014599-T01-IM6	Non-Small Cell Lung Cancer	T607I	Missense	0.33
	P-0006034-T01-IM5	Cutaneous Melanoma	G540E	Missense	0.33
	P-0010340-T01-IM5	Melanoma of Unknown Primary	S915F	Missense	0.33
	P-0005851-T01-IM5	Poorly Differentiated Non-Smal...	A156E	Missense	0.34
	P-0001560-T01-IM3	Cutaneous Melanoma	D674N	Missense	0.35
	P-0002874-T01-IM3	Lung Adenocarcinoma	T176Sfs*6	Frameshift deletion	0.36
	P-0007918-T01-IM5	Cutaneous Melanoma	P786S	Missense	0.38
	P-0009349-T01-IM5	Cutaneous Melanoma	X920_splice	Splice	0.38
	P-0009245-T01-IM5	Cutaneous Melanoma	F694Y	Missense	0.39
	P-0009349-T01-IM5	Cutaneous Melanoma	R690K	Missense	0.39
	P-0009833-T01-IM5	Lung Adenocarcinoma	S454Y	Missense	0.39
	P-0006724-T01-IM5	Poorly Differentiated Non-Smal...	R226G	Missense	0.39
	P-0026350-T01-IM6	Undifferentiated Malignant Neo...	D308N	Missense	0.39
	P-0010613-T01-IM5	Glioblastoma Multiforme	A243T	Missense	0.39
	P-0015415-T01-IM6	Melanoma of Unknown Primary	G1097E	Missense	0.4
	P-0008942-T01-IM5	Cutaneous Melanoma	E615K	Missense	0.42
	P-0004142-T01-IM5	Cutaneous Melanoma	D674N	Missense	0.42
	P-0005792-T01-IM5	Lung Squamous Cell Carcinoma	D328E	Missense	0.44
	P-0014786-T01-IM6	Poorly Differentiated Non-Smal...	L1069V	Missense	0.47
	P-0005366-T01-IM5	Cutaneous Melanoma	W410*	Nonsense	0.48
	P-0015438-T01-IM6	Melanoma of Unknown Primary	G900R	Missense	0.48
	P-0023966-T01-IM6	Undifferentiated Malignant Neo...	D356N	Missense	0.56
RET	P-0000208-T01-IM3	Lung Adenocarcinoma	RET-KIF5B fusion	Fusion	
	P-0012188-T01-IM5	Cancer of Unknown Primary	M848I	Missense	0.32

	P-0001081-T01-IM3	Cutaneous Melanoma	E1058K	Missense	0.38
	P-0000082-T01-IM3	Lung Adenocarcinoma	K124*	Nonsense	0.28
	P-0008997-T01-IM5	Cutaneous Melanoma	R873W	Missense	0.22
	P-0001578-T01-IM3	Bladder Urothelial Carcinoma	R348Q	Missense	0.53
	P-0015344-T01-IM6	Bladder Urothelial Carcinoma	D489N	Missense	0.25
	P-0008718-T01-IM5	Bladder Urothelial Carcinoma	M1009I	Missense	0.15
	P-0003555-T01-IM5	Bladder Urothelial Carcinoma	G949Efs*16	Frameshift deletion	0.12
	P-0003650-T01-IM5	Stomach Adenocarcinoma	R287W	Missense	0.17
	P-0002049-T01-IM3	Mucinous Adenocarcinoma of the...	S339L	Missense	0.32
	P-0005228-T01-IM5	Cutaneous Melanoma	D839N	Missense	0.28
	P-0002826-T01-IM3	Lung Adenocarcinoma	R817H	Missense	0.14
	P-0003009-T01-IM3	Larynx Squamous Cell Carcinoma	Y809*	Nonsense	0.21
	P-0003869-T01-IM5	Lung Adenocarcinoma	E251Q	Missense	0.15
	P-0003871-T01-IM5	Cutaneous Melanoma	P841S	Missense	0.65
	P-0005146-T01-IM5	Cutaneous Melanoma	E1036Q	Missense	0.05
	P-0005159-T01-IM5	Cutaneous Melanoma	R897P	Missense	0.15
	P-0005783-T01-IM5	Cancer of Unknown Primary	D627Y	Missense	0.11
	P-0005783-T01-IM5	Cancer of Unknown Primary	S829I	Missense	0.12
	P-0006510-T01-IM5	Renal Clear Cell Carcinoma	S836N	Missense	0.22
	P-0006713-T01-IM5	Lung Adenocarcinoma	H352P	Missense	0.31
	P-0007561-T01-IM5	Cutaneous Melanoma	R67C	Missense	0.93
	P-0008434-T01-IM5	Cutaneous Melanoma	R67C	Missense	0.24
	P-0007997-T01-IM5	Colon Adenocarcinoma	T754M	Missense	0.21
	P-0007810-T02-IM5	Melanoma of Unknown Primary	T317R	Missense	0.07
	P-0010581-T01-IM5	Colon Adenocarcinoma	A306V	Missense	0.09
	P-0009256-T01-IM5	Lung Adenocarcinoma	P720L	Missense	0.3
	P-0009833-T01-IM5	Lung Adenocarcinoma	H103N	Missense	0.33
	P-0009833-T01-IM5	Lung Adenocarcinoma	L109I	Missense	0.33
	P-0009918-T01-IM5	Stomach Adenocarcinoma	A279T	Missense	0.23
	P-0010115-T01-IM5	Melanoma of Unknown Primary	R897Q	Missense	0.22
	P-0010587-T01-IM5	Colon Adenocarcinoma	T1055A	Missense	0.18
	P-0010736-T01-IM5	Lung Adenocarcinoma	E428G	Missense	0.15
	P-0010736-T01-IM5	Lung Adenocarcinoma	D567Y	Missense	0.11
	P-0012049-T01-IM5	Lung Adenocarcinoma	G593R	Missense	0.27
	P-0012080-T01-IM5	Cutaneous Melanoma	W717*	Nonsense	0.22
	P-0012361-T01-IM5	Cutaneous Melanoma	A55V	Missense	0.63
	P-0015904-T01-IM6	Stomach Adenocarcinoma	H403Q	Missense	0.18
	P-0019351-T01-IM6	Stomach Adenocarcinoma	K662R	Missense	0.07
	P-0019475-T01-IM6	Colon Adenocarcinoma	I88V	Missense	0.24
	P-0026892-T01-IM6	Bladder Urothelial Carcinoma	C137Y	Missense	0.23
	P-0026350-T01-IM6	Undifferentiated Malignant Neo...	R1050*	Nonsense	0.25
	P-0015512-T01-IM6	Cutaneous Melanoma	Q497*	Nonsense	0.19
	P-0015791-T01-IM6	Cutaneous Melanoma	P785T	Missense	0.12
	P-0015830-T01-IM6	Cutaneous Melanoma	S411F	Missense	0.1
	P-0015937-T01-IM6	Lung Adenocarcinoma	A479P	Missense	0.08
	P-0016025-T01-IM6	Oral Cavity Squamous Cell Carc...	E818K	Missense	0.08
	P-0016175-T01-IM6	Lung Adenocarcinoma	R820C	Missense	0.16
	P-0016314-T01-IM6	Colon Adenocarcinoma	G607C	Missense	0.33
	P-0013525-T01-IM5	Cutaneous Melanoma	S128L	Missense	0.06
	P-0021774-T01-IM6	Cancer of Unknown Primary	E979Y	Missense	0.37
	P-0021622-T01-IM6	Upper Tract Urothelial Carcinoma	Y52C	Missense	0.17
	P-0021255-T01-IM6	Bladder Urothelial Carcinoma	E574D	Missense	0.1
	P-0013596-T01-IM5	Cutaneous Melanoma	R635C	Missense	0.31
	P-0014910-T01-IM6	Melanoma of Unknown Primary	T130P	Missense	0.42
	P-0014242-T01-IM6	Melanoma of Unknown Primary	Q341*	Nonsense	0.37
	P-0014137-T01-IM5	Cutaneous Melanoma	R415K	Missense	0.2
PTPN11	P-0010744-T01-IM5	Anaplastic Oligodendroglioma	G115E	Missense	0.3

	P-0004140-T01-IM5	Colon Adenocarcinoma	R351*	Nonsense	0.24
	P-0001808-T01-IM3	Colon Adenocarcinoma	K91N	Missense	0.16
	P-0005823-T01-IM5	Colon Adenocarcinoma	R465W	Missense	0.32
	P-0010499-T01-IM5	Colon Adenocarcinoma	T356A	Missense	0.06
	P-0015407-T01-IM6	Cutaneous Melanoma	A461T	Missense	0.44
	P-0001603-T01-IM3	Cutaneous Melanoma	A122T	Missense	0.27
	P-0009747-T01-IM5	Cutaneous Melanoma	P107F	Missense	0.05
	P-0015407-T01-IM6	Cutaneous Melanoma	S150Lfs*18	Frameshift deletion	0.35
	P-0013204-T01-IM5	Glioblastoma Multiforme	E69K	Missense	0.3
	P-0006672-T01-IM5	Glioblastoma Multiforme	E76G	Missense	0.09
	P-0007504-T01-IM5	Glioblastoma Multiforme	F285S	Missense	0.4
	P-0014677-T01-IM6	Glioblastoma Multiforme	F285S	Missense	0.12
	P-0005361-T01-IM5	High-Grade Glioma, NOS	E76K	Missense	0.02
	P-0002620-T01-IM3	High-Grade Glioma, NOS	E76G	Missense	0.12
	P-0002620-T01-IM3	High-Grade Glioma, NOS	A72V	Missense	0.16
	P-0013603-T01-IM5	High-Grade Glioma, NOS	A72G	Missense	0.05
	P-0003229-T01-IM5	Lung Adenocarcinoma	I309M	Missense	0.09
	P-0003229-T01-IM5	Lung Adenocarcinoma	R46G	Missense	0.08
	P-0003869-T01-IM5	Lung Adenocarcinoma	S321*	Nonsense	0.42
	P-0002490-T01-IM3	Melanoma of Unknown Primary	H426Y	Missense	0.64
	P-0009950-T01-IM5	Melanoma of Unknown Primary	P33S	Missense	0.12
	P-0009950-T01-IM5	Melanoma of Unknown Primary	H443Y	Missense	0.05
	P-0013652-T01-IM5	Oropharynx Squamous Cell Carci...	G24R	Missense	0.15
	P-0022520-T01-IM6	Upper Tract Urothelial Carcinoma	R421W	Missense	0.06
SYK	P-0013347-T01-IM5	Glioblastoma Multiforme	A52T	Missense	0.41
	P-0019475-T01-IM6	Colon Adenocarcinoma	G33Afs*2	Frameshift deletion	0.23
	P-0000686-T01-IM3	Cutaneous Melanoma	D603N	Missense	0.51
	P-0010670-T01-IM5	Melanoma of Unknown Primary	D603N	Missense	0.64
	P-0009245-T01-IM5	Cutaneous Melanoma	E210K	Missense	0.39
	P-0003728-T01-IM5	Melanoma of Unknown Primary	G231E	Missense	0.15
	P-0003347-T01-IM5	Lung Squamous Cell Carcinoma	G201C	Missense	0.54
	P-0012678-T01-IM5	Lung Squamous Cell Carcinoma	E26K	Missense	0.08
	P-0015415-T01-IM6	Melanoma of Unknown Primary	G231R	Missense	0.26
	P-0010587-T01-IM5	Colon Adenocarcinoma	E442K	Missense	0.21
	P-0001560-T01-IM3	Cutaneous Melanoma	M435I	Missense	0.13
	P-0004214-T01-IM5	Cutaneous Melanoma	G272S	Missense	0.46
	P-0005783-T01-IM5	Cancer of Unknown Primary	D554Y	Missense	0.28
	P-0005823-T01-IM5	Colon Adenocarcinoma	S84T	Missense	0.26
	P-0009108-T01-IM5	Melanoma of Unknown Primary	F16I	Missense	0.53
	P-0009747-T01-IM5	Cutaneous Melanoma	G37R	Missense	0.07
	P-0010174-T01-IM5	Head and Neck Squamous Cell Ca...	Y539*	Nonsense	0.08
	P-0010581-T01-IM5	Colon Adenocarcinoma	E144G	Missense	0.19
	P-0011047-T01-IM5	Cutaneous Melanoma	G224E	Missense	0.32
	P-0021915-T01-IM6	Oropharynx Squamous Cell Carci...	L29V	Missense	0.27
	P-0015603-T01-IM6	Glioblastoma Multiforme	X575_splice	Splice	0.38
	P-0016314-T01-IM6	Colon Adenocarcinoma	Q265H	Missense	0.18
	P-0012550-T01-IM5	Melanoma of Unknown Primary	G190R	Missense	0.25
LYN	P-0021651-T01-IM6	Small Cell Carcinoma of Unknown Primary	E359K	Missense	0.28
	P-0016720-T01-IM6	Upper Tract Urothelial Carcinoma	L302F	Missense	0.06
	P-0015438-T01-IM6	Melanoma of Unknown Primary	G97E	Missense	0.26
	P-0015512-T01-IM6	Cutaneous Melanoma	X325_splice	Splice	0.19
	P-0015612-T01-IM6	Cutaneous Melanoma	P512H	Missense	0.43
	P-0020770-T01-IM6	Poorly Differentiated Carcinoma, NOS	K332N	Missense	0.25
CRKL	P-0011357-T01-IM5	Colon Adenocarcinoma	R282H	Missense	0.1
	P-0002018-T01-IM3	Melanoma of Unknown Primary	P176S	Missense	0.61