Title: A pan-cancer analysis of PD-L1 immunohistochemistry and gene amplification, tumor mutation burden and microsatellite instability in 48,782 cases.

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要旨：Program death-ligand 1(PD-L1)免疫染色は特定の腫瘍において、免疫治療に対するコンパニオン診断薬として最も認知されている。しかしながらその他の免疫治療の指標となるバイオマーカーも多数存在する（microsatellite instability (MSI), tumor mutational burden (TMB), and CD274 (PD-L1) gene amplification）。今回、多種類の腫瘍のPD-L1免疫染色の状態を検討し、先に述べたバイオマーカーとの関係を調べた。2016年1月から2019年11月までの間、PD-L1免疫染色(using the DAKO 22C3 IHC　assay with either tumor proportion score (TPS) or combined positive score (CPS); or the VENTANA SP142 assay with infiltrating immune cell score (IC))とFoundation Medicineで施行された包括的な遺伝子異常プロファイリングの両方のデータを持っている全ての症例の後方視的検討を行った。PD-L1免疫染色陽性の定義としては、コンパニオン診断基準として定義されている（肺癌、頭頸部癌、乳癌など）腫瘍に関してはその基準で、定義されていない腫瘍に関してはTPS≥1を陽性とした。TMB陽性は≥10 mutations/Mbと定義した。トータル48782症例が

検討された。

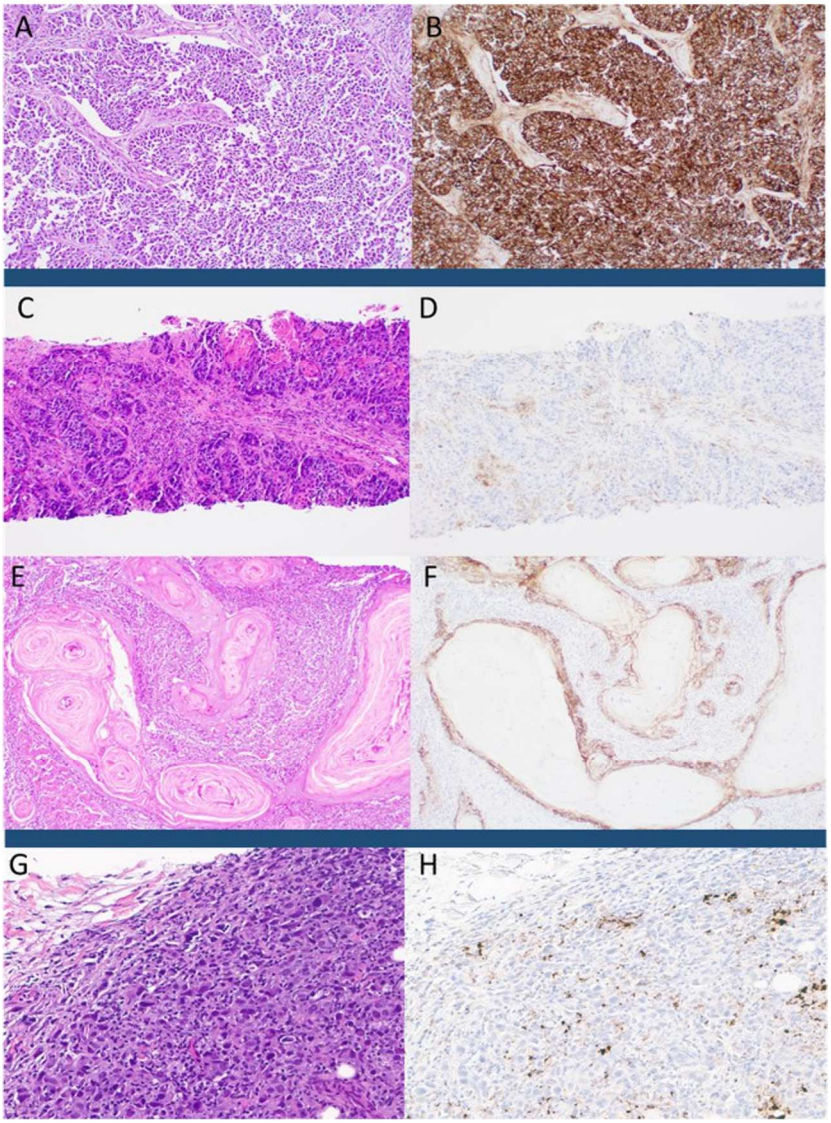


Fig. 1 Examples of a PD-L1 expression in different tumor types using different PD-L1 immunohistochemistry (IHC) assay. a Hematoxylin and Eosin (H&E) stain of a non-small cell lung carcinoma (NSCLC) case with all tumor cells staining in the corresponding. b DAKO 22C3 IHC giving it a tumor proportion score (TPS) of 100. Next are examples of two head and neck squamous cell carcinoma (HNSCC) with different biomarker status based on a tumor proportion score (TPS) cutoff of 1 and combined positive score (CPS) cutoff of 1. c H&E stain of a HNSCC case with no tumor cells but with immune staining in the corresponding. d DAKO 22C3 IHC giving it a negative status with the TPS score (TPS < 1) but positive status with the CPS score (CPS ≥ 1). e H&E stain of a HNSCC case with no immune cell but with tumor cell staining in the corresponding. f DAKO 22C3 IHC giving it a positive status for both the CPS score (CPS ≥ 1) and the TPS score (TPS ≥ 1). g The last H&E is of a triple negative breast carcinoma case that was stained with a (h) SP142 CDx IHC and shows the immune cells staining with a dark, granular punctate pattern. This case had a tumor-infiltrating immune cell (IC) score ≥ 1, which is considered positive with the SP142 CDx assay for TNBC. All digital images are at ×200 magnification.

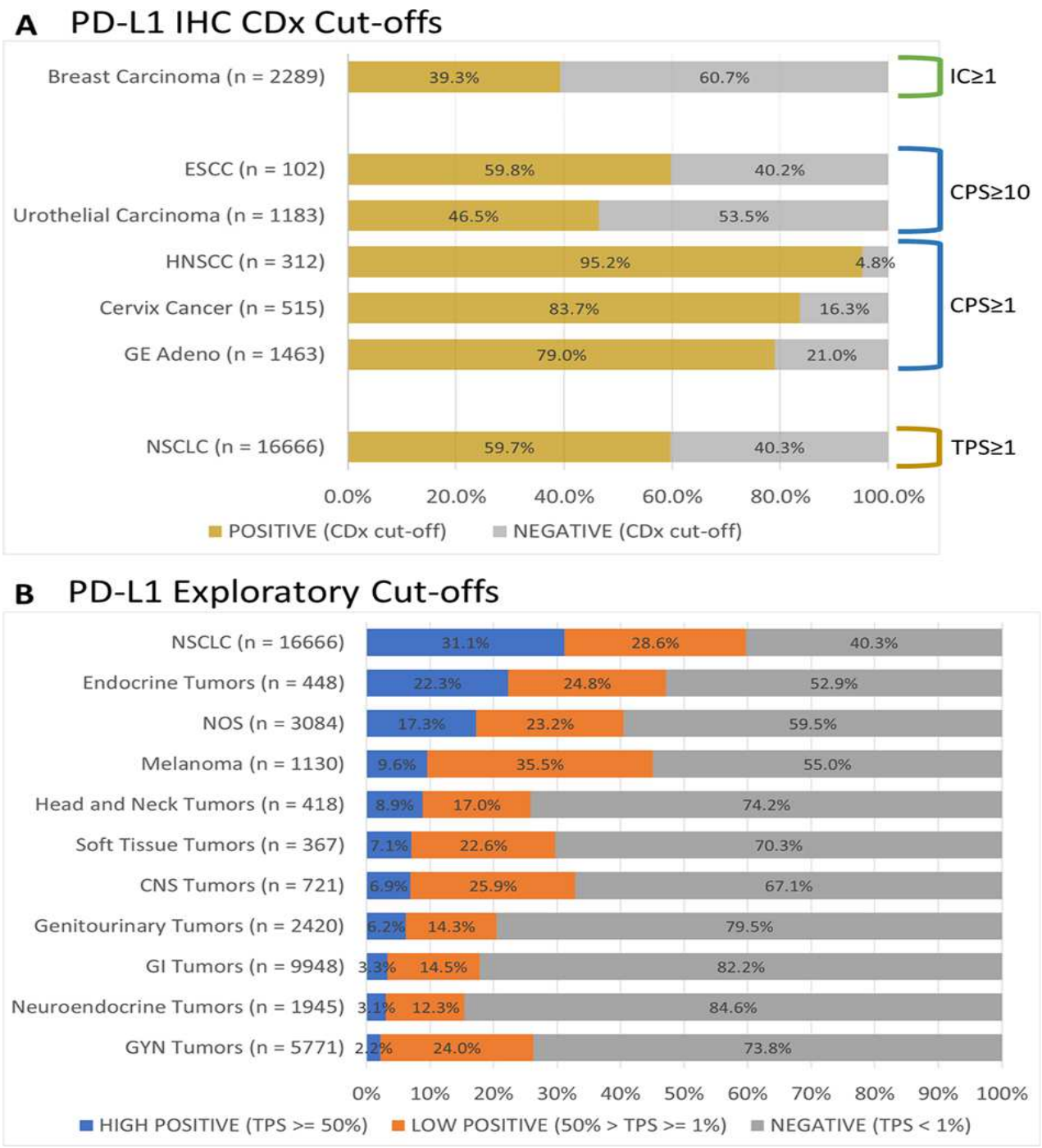


Fig. 2 Prevalence rates of various tumor types. a Shows all the prevalence rates based on the CDx cutoffs: DAKO 22C3 assay and tumor proportion scoring (TPS) method were used for NSCLC with a TPS cutoff of 1; DAKO 22C3 assay with combined positive scoring (CPS) method were used for gastric or gastroesophageal junction adenocarcinoma, cervical cancer, urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), and esophageal squamous cell carcinoma with a CDx cutoff of CPS ≥ 1%, CPS ≥ 1%, CPS ≥ 10%, CPS ≥ 1%, and CPS ≥ 10%, respectively; and SP142 CDx assay with tumor-infiltrating immune cell (IC) scoring method was used for breast carcinoma cases. b Shows the prevalence of all the tumor types without a CDx cutoff (except for NSCLC which has a CDx). DAKO 22C3 with the TPS scoring method was used for these cases and the results were stratified into a negative (<1%), low positive (1–49%), or high positive (≥50%) category for all the exploratory indications.

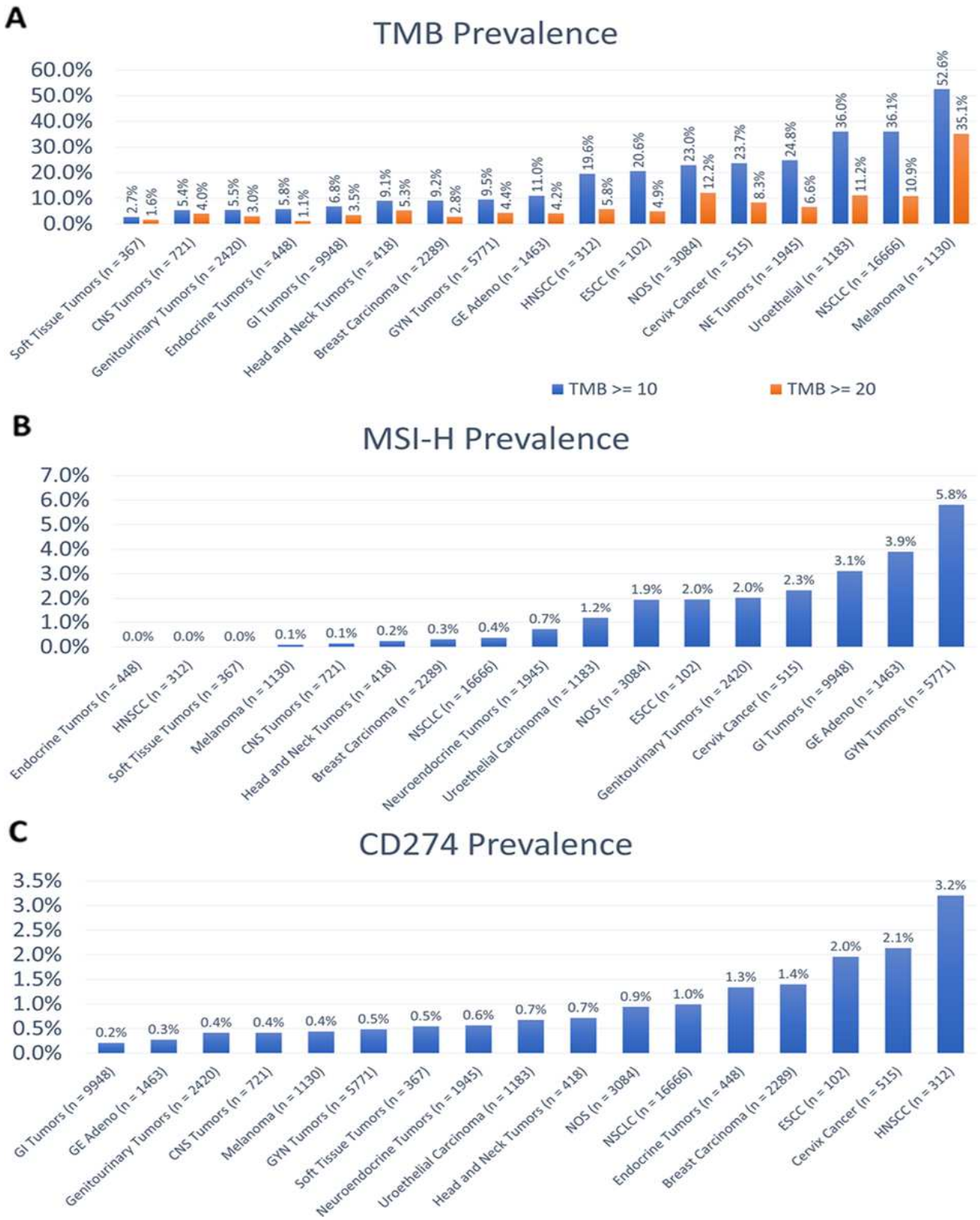
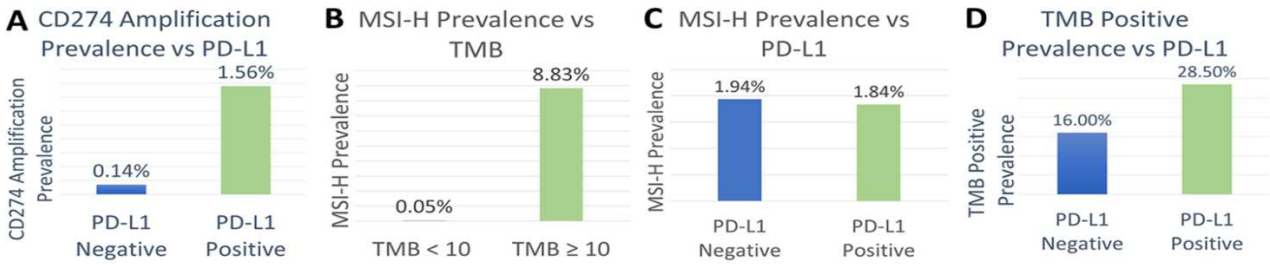
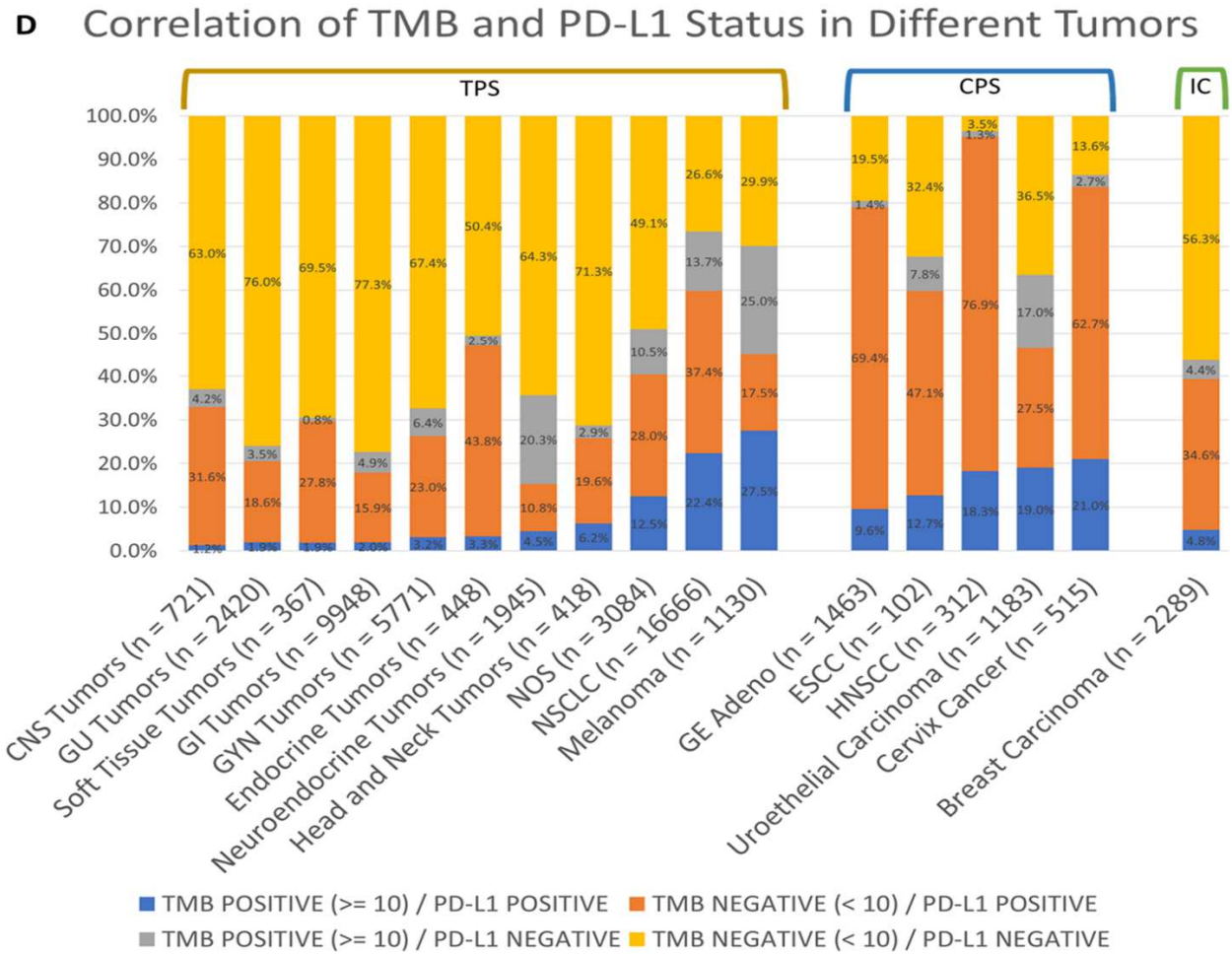


Fig. 3 The prevalence of rates of TMB, MSI-H, and CD274 gene amplification in individual tumor types. a In the overall cohort TMB ≥ 10 mutations/Mb was 21.1% (10273/48,782), and TMB ≥ 20 mutations/Mb was 7.7% (3767/48,782). b Overall, for MSI, 1.9% (925/48,782) were MSI-H, 88.6% (43217/48,782) of cases were MSS, and 9.5% (4640/48,782) were MSI-unknown. c The overall prevalence of CD274 amplification in the pan-tumor cohort is 0.72% (350/48,782).





PD-L1発現とCD274遺伝子増幅(p<0.001)、MSIとTMB(<0.001)、PD-L1発現とTMB(p<0.001)で有意差がみられた。次にPD-L1発現とTMBのコンビネーションで各種腫瘍と検討したところ、腫瘍間で違いが見られた(double positiveはMelanoma, NSCLC, cervixで20%以上）。著者らは今後、免疫チェックポイント阻害薬が実際に投与された症例の治療効果を確認する必要があり、特にPD-L1+/TMB+であった症例は特に効果があったか調べる必要があると述べている。

Take Home Message

PD-L1の発現状態は今後診断する機会が増加することが予想されるが、各腫瘍間における頻度を知っておいてもらいたい。また以下のFactorについても知っておいてもらいたい。

・TMB高頻度(Melanoma, NSCLC, Urothelial carcinoma)，低頻度(Soft tissue tumors, CNS tumors, Genitourinary tumors)

・MSI高頻度(Gynecological tumors, Gastroesophageal adenocarcinoma, Gastrointestinal tumors)，低頻度(Endocrine tumor, HNSCC, Soft tissue tumors)

・CD274遺伝子増幅高頻度(HNSCC, cervix cancer, ESCC)，低頻度(GI tumors, Gastroesophageal adenocarcinoma, Genitourinary tumors)

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