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Prevalence of High Tumor Mutational Burden (TMB-H) and Association with Survival in Patients with Less Common Solid Tumors

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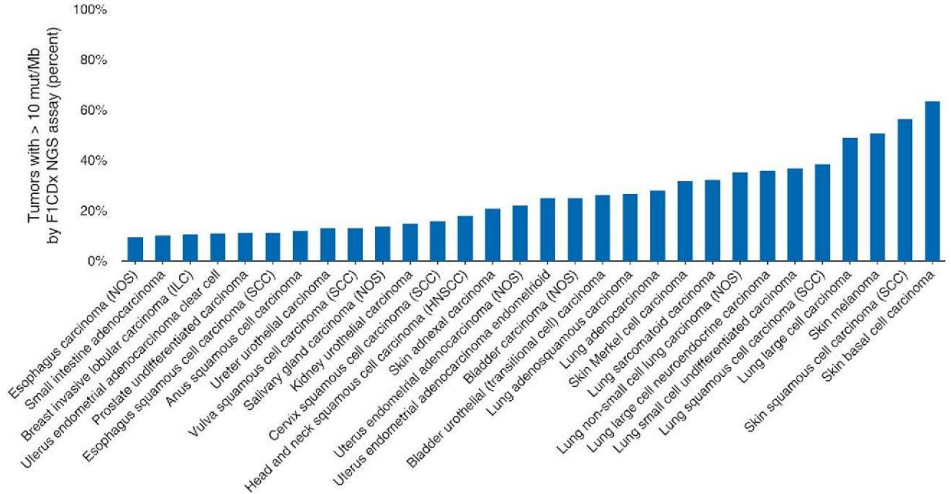
Research X - Mar 23, 2021

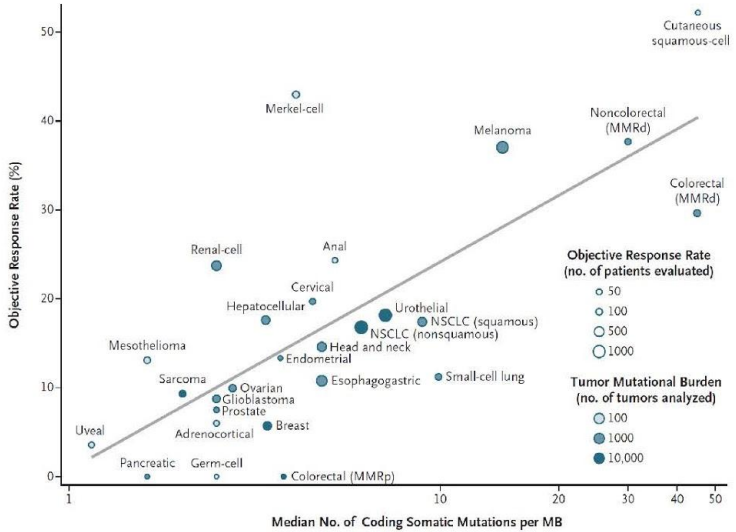
Conflict of interest

Chelsea Shao reports employment at Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and stock ownership in Merck & Co., Inc., Kenilworth, NJ, USA

Background

- Tumor mutational burden (TMB), defined as the number of non-driver somatic coding mutations per megabase of genome sequenced, is an emerging clinical biomarker of response to immune checkpoint inhibitor therapy
- TMB has been shown to vary markedly between tumor types as well as between patients within tumor types[1]
- High tumor mutational burden (TMB-H) has been associated with higher overall response rate (ORR) to PD-(L)1 inhibitors across various tumor types evaluated in multiple clinical trials[2]

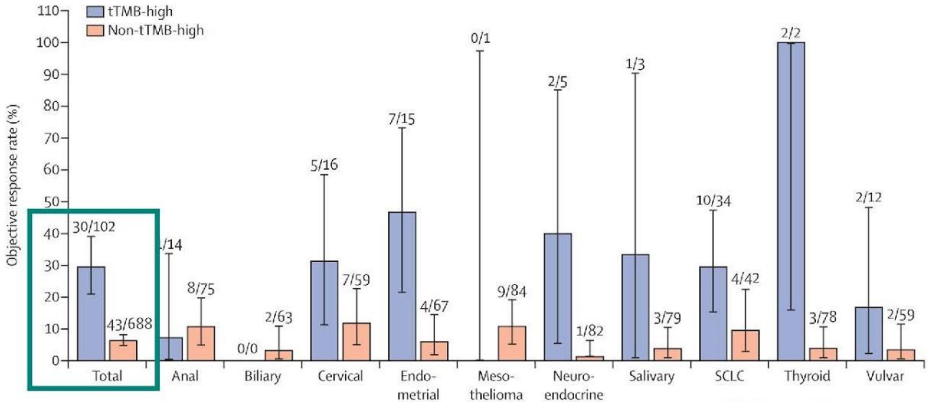




1. Chan et al. Ann Oncol. 2019;30(1):44; 2. Yarchoan et al. N Engl J Med. 2017;377(25):2500

Background

- The phase 2, multi-cohort KEYNOTE (KN)-158 study is evaluating multiple biomarkers including pre-specified TMB as predictive biomarkers for pembrolizumab across 10 advanced less common tumors[3]
- According to KN158, among 790 patients that had evaluable TMB and were included in efficacy analyses, 102 (13%) were TMB-H [≥10 mutations/megabase (mut/Mb)]. Objective responses were 29% in the TMB-H group and 6% in the non-TMB-H group[3]
- On June 16, 2020, FDA approved pembrolizumab to treat patients with TMB-H (≥10 mut/Mb) solid tumors who have progressed following prior treatment and who have no satisfactory alternative treatment options[4]
- There are limited real-world data available to describe the prevalence of TMB-H among patients with these 10 less common cancers
- Little is known about the prognostic effect of TMB-H among patients with these less common cancers who did not receive an immunotherapy (IO)



3. Marabelle et al. Lancet Oncol, 2020;21(10):1353
4. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors

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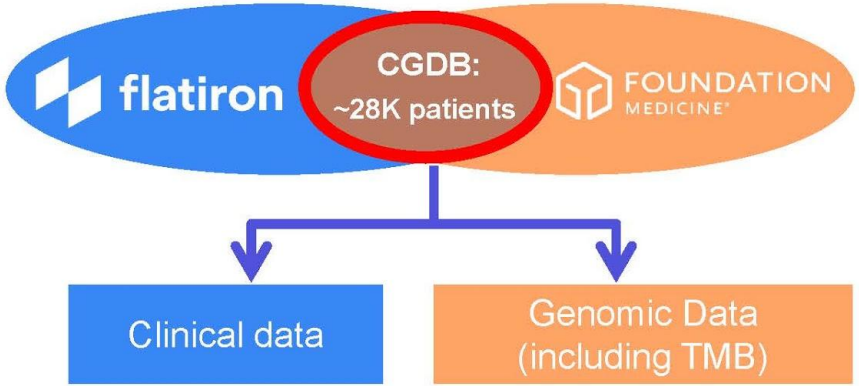
Objectives

- To evaluate the prevalence of TMB-H across the 10 tumor types included in KN158 based on pre-defined TMB-H cut-point(s) in a real-world dataset
- To evaluate the association between TMB status and real-world overall survival (rwOS) across the 10 tumor types who did not receive IO

Methods

The Flatiron and Foundation Medicine Clinico-genomic Dataset (FH-FMI CGDB) was used to select patients diagnosed with any of 10 solid cancers up to Jul 31, 2018



Study population

- aged 18 years or older as of FMI report date
- had a valid measurement of TMB based on a comprehensive genomic profiling test run by FMI
- had at least 1 documented clinic visit observed in the CGDB after January 1, 2011
- had a pathologist-confirmed solid tumor of 1 of the following types
  - anal carcinoma, biliary adenocarcinoma, cervical carcinoma, endometrial carcinoma, mesothelioma (meso), neuroendocrine tumor (NET), salivary gland carcinoma, small cell lung cancer (SCLC), thyroid carcinoma, or vulvar carcinoma.

Methods

- TMB-H was defined as ≥10 Mut/Mb assessed by FMI
- The primary analysis was descriptive and combined all tumor types included in the analysis
- Prevalence of TMB-H was reported with corresponding 95%CIs
- Patients with confirmed MSI-H cancers (by NGS, n=109) were excluded from primary analysis based on prespecified analysis plan
- rwOS from FMI report date (the primary index date) to the date of death of any cause or censor date was analyzed with the Kaplan-Meier method, stratified by TMB status (TMB-H vs non–TMB-H) with corresponding 95%CIs
- Cox proportional hazard model was performed to compare rwOS by TMB status (TMB-H vs non–TMB-H) adjusting for age, gender, cancer types, practice type and albumin
  - Patients with IO were excluded if start of IO earlier than or equal to FMI report date (69 pts), or censored if start of IO later than FMI report date (243 pts)

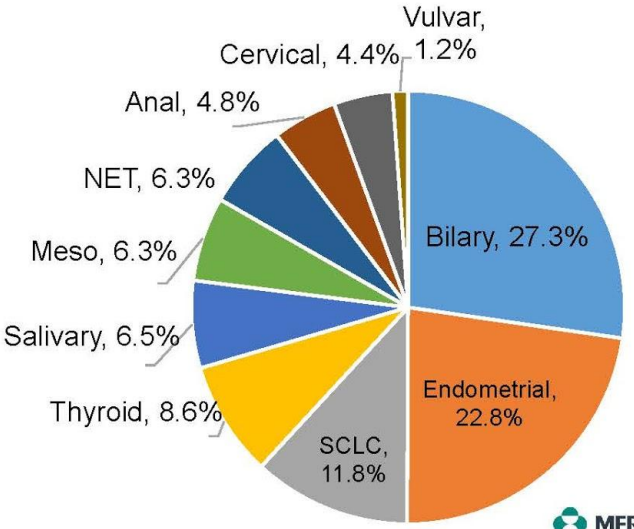
Results: Baseline Characteristics*

		n	%
Gender *	Female	1671	64.5%
	Male	917	35.4%
Age	Mean (Sd)	63.7 (11.7)	
	<65	1262	48.7%
	65+	1327	51.3%
Race	White	1803	69.6%
	Black	146	5.6%
	Asian	60	2.3%
	Other/Missing	580	22.4%
Practice type	Academic	451	17.4%
	Community	2138	82.6%
Last albumin within 90 days to FMI report date	>=3 g/dL	1289	49.8%
	<3 g/dL	88	3.4%
	Missing	1212	46.8%
Ever received antineoplastic drug	No	712	27.5%
	Yes	1877	72.5%
MSI status#	Non-MSI-H	1710	66.0%
	MSI unknown	879	34.0%
Follow up from FMI report date (m)	Mean (Sd)	8.1 (8.8)	
	Median (IQR)	5.4 (1.5, 11.3)	
Follow up from 1st antineoplastic date (m)	Mean (Sd)	18.2 (18)	
	Median (IQR)	13 (6, 24.6)	

* Missing 1 patient; # 109 pts with confirmed MSI-H cancers (by NGS) were excluded, 101 of whom had endometrial cancer
MSI-H: microsatellite instability-high; Meso: Mesothelioma; NET: Neuroendocrine tumor; SCLC: small cell lung cancer

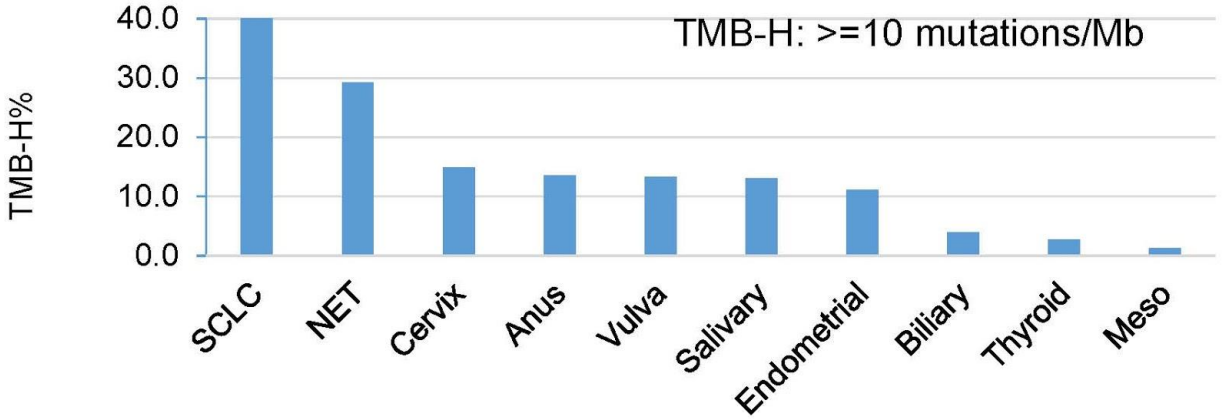
Of the ~28K patients in the pan-tumor CGDB, a total of 2,589 patients with TMB status and any of the 10 tumor types were included in the primary analysis

Distribution of Tumor Types



Results: TMB-H Prevalence

Using ≥10 Mut/Mb as the TMB cut-point, 12.8% of patients (332/2,589) were TMB-H*



n	305	164	114	125	30	169	590	706	223	163
#>=10	122	48	17	17	4	22	66	28	6	2

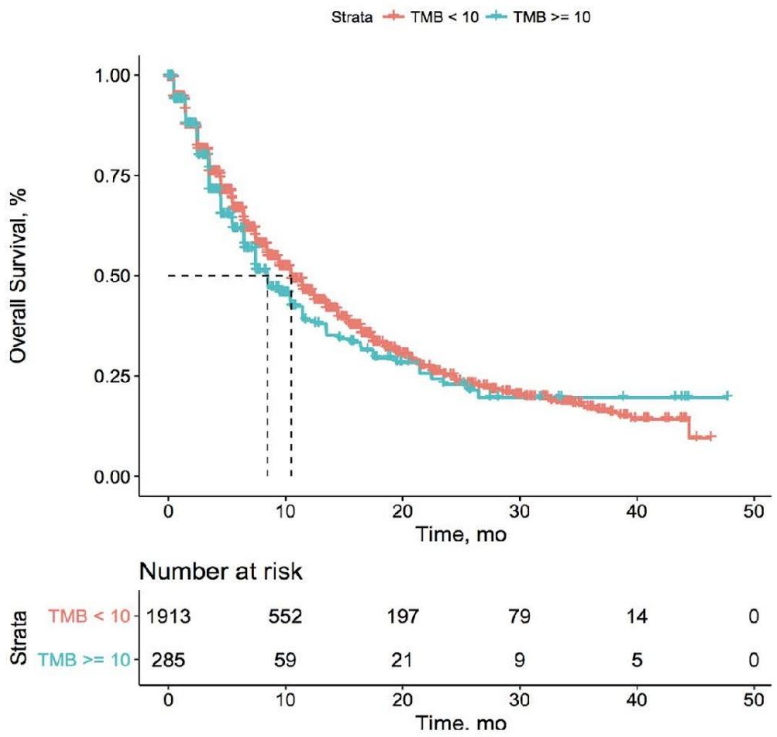
*109 pts with confirmed MSI-H cancers (by NGS) were excluded based on prespecified analysis plan, 101 of whom had endometrial cancer

Results: rwOS Analysis

- Patients with TMB-H tumors had rwOS that did not differ from that observed with non–TMB-H tumors when receiving non-immunotherapy treatments
- The adjusted hazard ratio (aHR)* of TMB-H vs. non-TMB-H was 0.94 (95% CI: 0.77-1.13) for rwOS from FMI report date

		rwOS (Mo, 95% CI)		HR (95% CI)	
	No	TMB-H	Non-TMB-H	Unadjusted	Adjusted
Total	2517	8.4 (7.4-11.4)	10.5 (9.5-11.5)	1.11 (0.93-1.33)	0.94 (0.77-1.13)

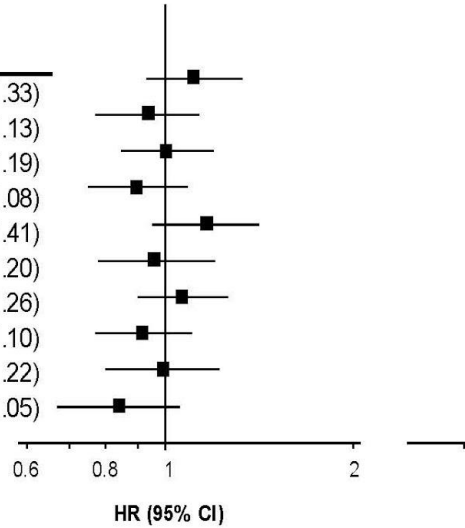
* Adjusting for age, gender, cancer type, practice type and albumin



Sensitivity analyses

Consistent results were observed in different sensitivity analyses, including patients with MSI-H cancers (n=109) and an analysis calculating rwOS from 1st observed antineoplastic treatment date

Analysis	TMB-H Cutpoint (≥10 / ≥13)	Study Population (F1 + F1CDx / CGDB eligible)[a]	MSI-H (Excluded / Included)	Index date for OS (FMI report / 1st antineoplastic)[b]	Hazard Ratio (Adjusted / Unadjusted)	N	HR (95% CI)
Primary	≥10	F1CDx	Excluded	FMI report	Unadjusted	2517	1.11 (0.93–1.33)
Primary	≥10	F1CDx	Excluded	FMI report	Adjusted	2516	0.94 (0.77–1.13)
Sensitivity 1	≥10	F1CDx	Included	FMI report	Unadjusted	2623	1.00 (0.85–1.19)
Sensitivity 2	≥10	F1CDx	Included	FMI report	Adjusted	2622	0.90 (0.75–1.08)
Sensitivity 3	≥10	F1CDx	Excluded	1st antineoplastic	Unadjusted	1822	1.16 (0.95–1.41)
Sensitivity 4	≥10	F1CDx	Excluded	1st antineoplastic	Adjusted	1822	0.96 (0.78–1.20)
Sensitivity 5	≥10	CGDB	Excluded	FMI report	Unadjusted	2811	1.06 (0.90–1.26)
Sensitivity 6	≥10	CGDB	Excluded	FMI report	Adjusted	2810	0.92 (0.77–1.10)
Sensitivity 7	≥13	F1CDx	Excluded	FMI report	Unadjusted	2517	0.99 (0.80–1.22)
Sensitivity 8	≥13	F1CDx	Excluded	FMI report	Adjusted	2516	0.84 (0.67–1.05)



Conclusion

- Overall, prevalence of TMB-H (assessed by FMI) in the real-world dataset was 12.8% using the cut-point of ≥10 Mut/Mb across the 10 solid tumor types evaluated excluding MSI-H tumors
- Prevalence of TMB-H varied widely across a range of solid tumors
- There was no association between TMB-H status and rwOS across the evaluated tumor types
- These findings indicate that TMB-H does not have a prognostic association among patients with these tumor types in the absence of immunotherapy

Shao et al. JAMA Netw Open . 2020 Oct 1;3(10):e2025109

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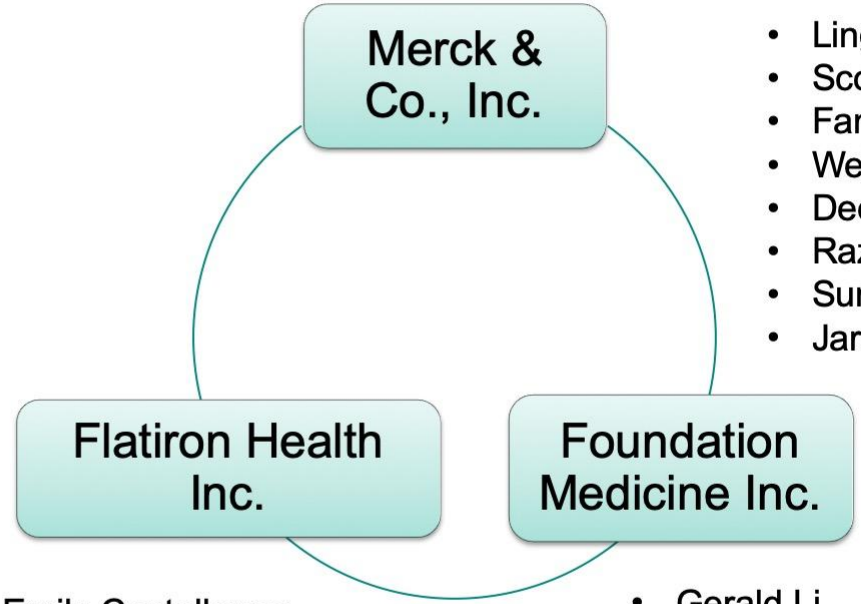
Thank you



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