RWD110

Real-world outcomes in patients with advanced/metastatic solid tumors who are immuno-oncology-naïve and received second-line therapy: analysis by tumor mutational burden status

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Background

- Tumor mutational burden (TMB) measures the number of mutations within a tumor genome and represents an emerging prognostic and predictive biomarker of response to immuno-oncology (IO) therapy across multiple types of solid tumors[1-5]
- Despite extensive research into a possible role for TMB in patients with cancer receiving IO therapy, there has been limited focus on the predictive/prognostic utility of TMB among patients who are not treated with IO therapy
  - In a prior study of patients with metastatic cancers not receiving IO therapy, TMB assessed by next-generation sequencing was not associated with overall survival (OS)[1]
- Here, we conducted a retrospective observational study to evaluate the predictive impact of TMB on efficacy outcomes among patients who were IO-naïve and who received non-IO therapy in the second- or later-line setting for various advanced or metastatic solid tumors

Methods

- This study utilized the US-based, nationwide, de-identified Flatiron Health-Foundation Medicine, Inc. (FH-FMI) multi-tumor clinico-genomic database (CGDB)
  - Retrospective longitudinal clinical data were derived from electronic health record data, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, and were linked to genomic data derived from FMI comprehensive genomic profiling tests in the FH-FMI CGDB by de-identified, deterministic matching[6]
- Data originated from approximately 280 US cancer clinics, representing approximately 800 sites of care
- Study inclusion criteria were
  - Diagnosis between January 1, 2011, and November 30, 2020, with 1 of the following advanced or metastatic tumors: colorectal, breast, pancreatic, ovarian, gastric, prostate, endometrial, bladder, lung (small cell), head and neck, or liver (hepatocellular)
  - Age ≥ 18 years at the time of diagnosis of advanced or metastatic disease
  - IO-naïve and treated with non-IO therapy in the second- and later-line settings
  - A known tissue TMB score as determined by the FoundationOne CDx™ assay (Foundation Medicine, Cambridge, MA, USA)
- Patients were excluded if they had insufficient data after their advanced or metastatic cancer diagnosis; another cancer within the previous 2 years; treatment with any IO therapy either before or after the defined study treatment; only blood TMB data available; treatment with second- or later-line therapy for locoregional/nonmetastatic disease or study treatment prior to 14 days before their advanced or metastatic cancer diagnosis; or they were involved in a clinical trial
- The reported outcome measures were progression-free survival (PFS) and OS, estimated from an index date of the start of second-line therapy using Kaplan-Meier methodology
  - PFS data were only available for patients with colorectal, breast, gastric, bladder, lung (small cell), or liver (hepatocellular) cancers
- Cox proportional hazards models were used to assess the influence of the following factors on PFS and OS: TMB; age; sex; race; practice type; insurance type; initial tumor, nodes, metastasis (TNM) staging; and Eastern Cooperative Oncology Group performance status (ECOG PS)
- TMB analyses used a cutoff of 10 mutations per Mb
  - TMB-high (TMB-H) was defined as ≥ 10 mutations per Mb, TMB-low (TMB-L) as < 10 mutations per Mb

Results

Patients

- In total, 7465 patients met the inclusion criteria and were included in the study (**Table 1**)
  - Median age was 63 years, 63% were female, and 92% were treated at a community site
  - Most patients (72%) had an ECOG PS of 0 or 1
  - The most common tumor types were colorectal (34%) and breast (28%), and most patients received index treatment between 2016 and 2020
- Demographic and clinical characteristics were generally balanced between the TMB-H and TMB-L subgroups (**Table 1**)

Impact of TMB on PFS and OS

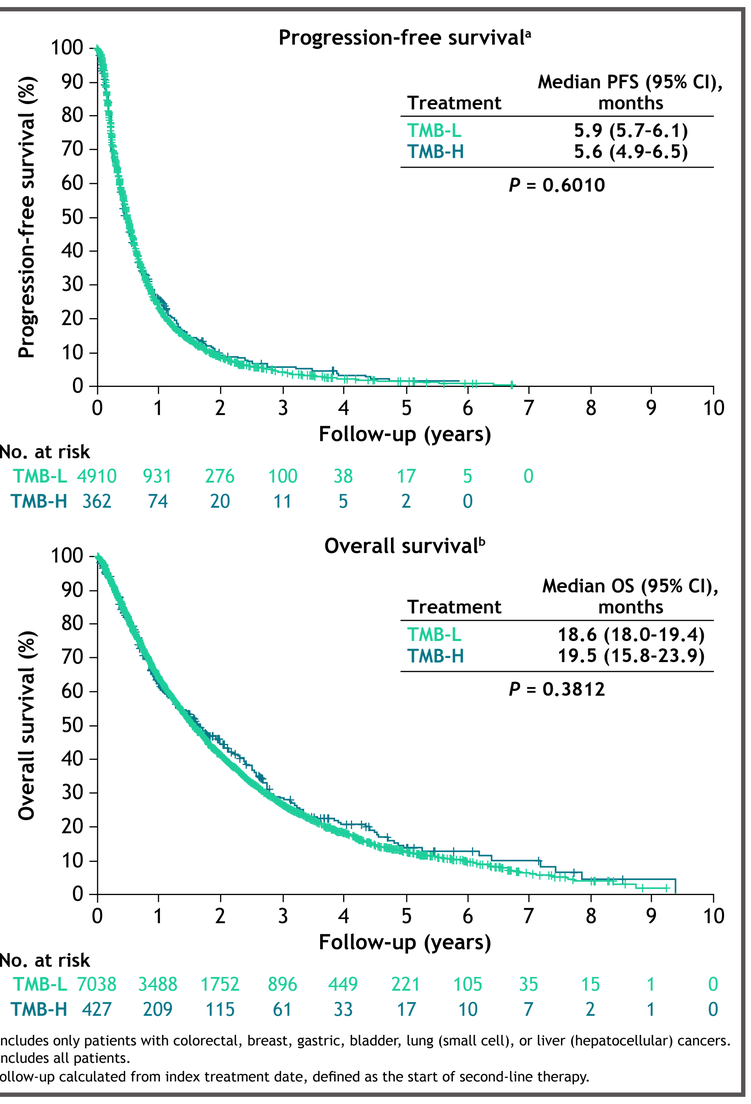
- Among all eligible patients (N = 7465), median PFS (95% confidence interval [CI]) was 5.9 (5.7-6.1) months and median OS (95% CI) was 18.7 (18.1-19.4) months
- When assessed according to TMB status, median PFS and OS were not significantly different between the TMB-H and TMB-L subgroups (**Figure 1**)
- TMB was not significantly associated with PFS or OS in both univariate (not shown) and adjusted Cox proportional hazards models (**Figure 2**)
  - The adjusted Cox proportional hazards models showed that sex and ECOG PS were significantly associated with both PFS and OS, and initial TNM staging was associated with OS only
  - In addition, some race and insurance type subcategories showed significant associations with PFS or OS

Table 1. Baseline demographic and clinical characteristics by TMB status

	All patients (N = 7465)	TMB-H (n = 427)	TMB-L (n = 7038)
Age, median (range), years[a]	63 (19-85)	64 (24-85)	63 (19-85)
Sex, n (%)			
Male	2785 (37)	139 (33)	2646 (38)
Female	4679 (63)	288 (67)	4391 (62)
Missing	1 (< 1)	0	1 (< 1)
Race, n (%)			
White	5092 (68)	284 (67)	4808 (68)
Black or African American	588 (8)	33 (8)	555 (8)
Asian	188 (3)	13 (3)	175 (2)
Other[b]	1162 (16)	67 (16)	1095 (16)
Missing	435 (6)	30 (7)	405 (6)
Practice type, n (%)			
Academic institution	584 (8)	30 (7)	554 (8)
Community site	6881 (92)	397 (93)	6484 (92)
Insurance type, n (%)			
Commercial health plan	3389 (45)	185 (43)	3204 (46)
Medicare	1745 (23)	107 (25)	1638 (23)
Medicaid	176 (2)	7 (2)	169 (2)
Other government program	169 (2)	7 (2)	162 (2)
Other payer[c]	1500 (20)	79 (19)	1421 (20)
Patient assistance program	351 (5)	20 (5)	331 (5)
Self-pay	52 (< 1)	4 (< 1)	48 (< 1)
Missing	1545 (21)	94 (22)	1451 (21)
ECOG PS, n (%)[a]			
0-1	5373 (72)	284 (67)	5089 (72)
≥ 2	765 (10)	63 (15)	702 (10)
Missing	1327 (18)	80 (19)	1247 (18)
Tumor type, n (%)			
Colorectal	2569 (34)	116 (27)	2453 (35)
Breast	2120 (28)	160 (37)	1960 (28)
Pancreatic	759 (10)	6 (1)	753 (11)
Ovarian	669 (9)	15 (4)	654 (9)
Gastric	478 (6)	43 (10)	435 (6)
Prostate	445 (6)	16 (4)	429 (6)
Endometrial	238 (3)	22 (5)	216 (3)
Bladder	82 (1)	27 (6)	55 (< 1)
Lung (small cell)	59 (< 1)	17 (4)	42 (< 1)
Head and neck	31 (< 1)	4 (< 1)	27 (< 1)
Liver (hepatocellular)	15 (< 1)	1 (< 1)	14 (< 1)
Year of index treatment date, n (%)			
2011	26 (< 1)	4 (< 1)	22 (< 1)
2012	106 (1)	8 (2)	98 (1)
2013	264 (4)	25 (6)	239 (3)
2014	513 (7)	41 (10)	472 (7)
2015	703 (9)	43 (10)	660 (9)
2016	902 (12)	58 (14)	844 (12)
2017	1081 (14)	59 (14)	1022 (15)
2018	1234 (17)	53 (12)	1181 (17)
2019	1303 (17)	65 (15)	1238 (18)
2020	1333 (18)	71 (17)	1262 (18)
Disease stage, n (%)[d]			
0	2 (< 1)	0	2 (< 1)
I	437 (6)	24 (6)	413 (6)
II	1091 (15)	72 (17)	1019 (14)
III	1585 (21)	90 (21)	1495 (21)
IV	3913 (52)	203 (48)	3710 (53)
Missing	437 (6)	38 (9)	399 (6)
Median (range) follow-up, months[e]	12 (0-113)	11 (0-113)	12 (0-111)
Median (SD) TMB, mutations/Mb	2.6 (8.8)	13.8 (29.7)	2.6 (2.3)

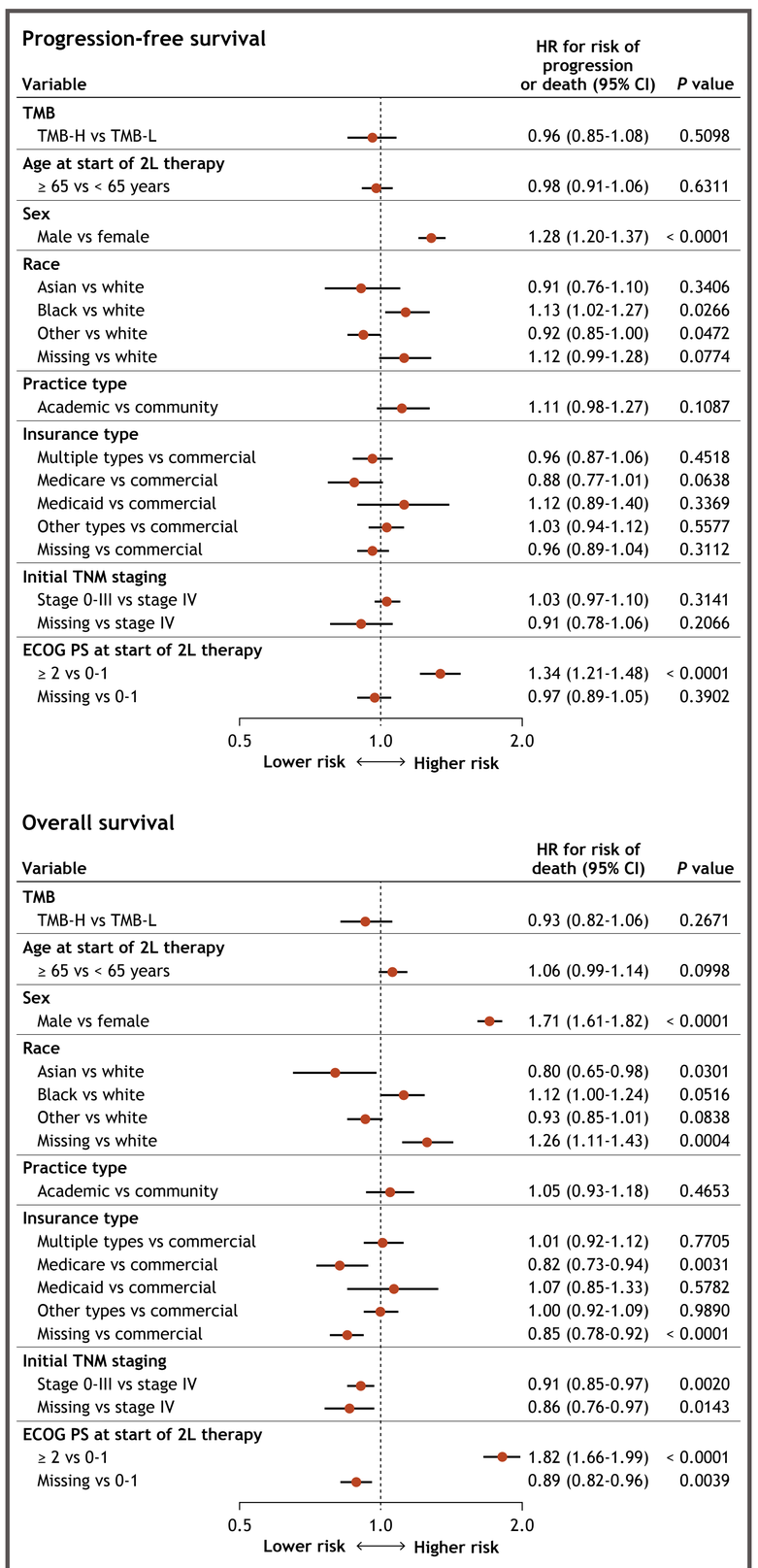
[a]Age and ECOG PS determined at index treatment date, defined as the start of second-line therapy. [b]Includes Hispanic/Latino and other racial minorities, such as Native American. [c]Includes "type unknown" and "workers compensation." [d]At initial diagnosis. [e]Follow-up calculated from index treatment date, defined as the start of second-line therapy; for patients who died, follow-up end date was the death date; for patients without evidence of death, follow-up end date was the last clinical activity date.
SD, standard deviation.

Figure 1. Survival outcomes by TMB status



[a]Includes only patients with colorectal, breast, gastric, bladder, lung (small cell), or liver (hepatocellular) cancers. [b]Includes all patients.
Follow-up calculated from index treatment date, defined as the start of second-line therapy.

Figure 2. Association of TMB and other variables with survival outcomes



2L, second line; HR, hazard ratio.

Limitations

- Limitations include the retrospective nature of the analysis, the potential for missing data or errors in data entry, variation in follow-up time, and no consistent assessment of disease progression
- The results may also have been influenced by the relative proportion of patients with certain tumor types (the population included an over-representation of patients with colorectal and breast cancers [> 60%]), as well as utilization of the 10 mutations per Mb TMB cutoff

Conclusions

- Results from this large-scale, real-world analysis suggest that TMB is not a generalizable predictive biomarker for patients receiving non-IO therapy for various advanced or metastatic solid tumors
- Additional analyses will be required to investigate possible alternative TMB cutoff values across patients with various solid tumor types receiving non-IO therapy

References

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Acknowledgments

- The patients and families who made this study possible
- Foundation Medicine for collaborative development of the FoundationOne CDx™ assay
- This study was supported by Bristol Myers Squibb
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Richard Daniel, PhD, of Parexel, funded by Bristol Myers Squibb

Presented at ISPOR Europe 2022; November 6-9, 2022; Vienna, Austria, and virtual

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