848PD Impact of zumor mutation burden on nivolumab efficacy in second-line urothelial carcinoma patients: Exploratory analysis of the phase ii checkmate 275 study

M.D. Galsky[1], A. Saci[2], P.M. Szabo[2], A. Azrilevich[3], C. Horak[2], A. Lambert[4], A. Siefker-Radtke[5], A. Necchi[6], P. Sharma[7]

[1]Department of Medicine, Icahn School of Medicine at Mount Sinai/Tisch Cancer Institute, New York, NY, USA, [2]Oncology, Bristol-Myers Squibb, Princeton, NJ, USA, [3]Global Clinical Research/Oncology, Bristol-Myers Squibb, Princeton, NJ, USA, [4]Oncology, Bristol-Myers Squibb, Braine-l'Alleud, Belgium, [5]Medicine, MD Anderson Cancer Center, University of Texas, Houston, TX, USA, [6]Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, [7]Genitourinary Medical Oncology, MD Anderson Cancer Center, University of Texas, Houston, TX, USA

Background: Nivolumab, a programmed death (PD)-1 inhibitor, demonstrated efficacy in a single-arm phase II study in patients (pts) with metastatic or surgically unresectable urothelial carcinoma (UC) (CheckMate 275; Sharma et al. 2017). The current analysis explores the potential association between pretreatment tumor mutation burden (TMB) and response to nivolumab.

Methods: Tumor DNA from pretreatment archival tumor tissue and matched whole blood samples was profiled by whole exome sequencing. TMB was defined as the total number of missense somatic mutations per tumor, and was evaluated as a continuous variable and by tertiles (missense count: high ≥167, medium 85–166, low <85). Cox models were used to explore the association between TMB and progression-free survival (PFS) and overall survival (OS); and logistic regression for objective response rate (ORR). Tumor PD-ligand 1 (PD-L1) expression was assessed by Dako PD-L1 immunohistochemistry 28-8 assay and was categorized as </≥1%.

Results: 139 (51%) of 270 pts had evaluable TMB. Baseline characteristics, ORR, PFS, and OS were similar between all treated pts and the TMB subgroup. ORR, PFS and OS in all pts and TMB/PD-L1 subgroups are shown in the Table. TMB showed a statistically significant positive association with ORR (P=0.002) and PFS (P=0.005), and a strong association with OS (P=0.067), even when adjusted for baseline tumor PD-L1 expression, liver metastasis status, and serum hemoglobin. High TMB had the greatest impact on survival in pts with <1% PD-L1 expression (Table).

Conclusions: These exploratory findings suggest that TMB may enrich for response to nivolumab and may provide complementary prognostic/predictive information beyond PD-L1. Further analyses in randomized trials are warranted to define the prognostic/predictive value of TMB in the context of other biomarkers in UC pts treated with immunotherapy.

Clinical trial identification: NCT02387996

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: M.D. Galsky: Received research funding from Bristol-Myers Squib, Novartis, and Merck and has served on advisory boards for Genentech, Merck, EMD-Serono, and AstraZeneca. A. Saci: Reports being an employee of Bristol-Myers Squibb during the conduct of the study. A. Azrilevich: Reports being an employee of the sponsor, Bristol-Myers Squibb. C. Horak: Reports being an employee and stockholder of Bristol-Myers Squibb A. Lambert: Reports employment and stock owner from Bristol-

Table: 848PD ORR, PFS and OS: All patients and TMB/PD-L1 subgroups

	All pts N = 270		TMB subgroup N = 139		TMB high N = 47		TMB medium N = 46		TMB low N = 46	
ORR, %	20.0		20.1		31.9		17.4		10.9	
PFS, months median	2.00		2.00		3.02		1.87		1.91	
(95% CI)	(1.87–2.63)		(1.87–3.02)		(1.87–NR)		(1.68–3.65)		(1.84–3.15)	
OS, months median	8.57		7.23		11.63		9.66		5.72	
(95% CI)	(6.05–11.27)		(5.72–11.63)		(5.82–NR)		(4.76–NR)		(4.21–11.30)	
	PD-L1 <1% N = 146	PD-L1 ≥1% N = 124	PD-L1 <1% N = 69	PD-L1 ≥1% N = 70	PD-L1 <1% N = 23	PD-L1 ≥1% N = 24	PD-L1 <1% N = 21	PD-L1 ≥1% N = 25	PD-L1 <1% N = 25	PD-L1 ≥1% N = 21
ORR, %	15.8	25.0	17.4	22.9	30.4	33.3	23.8	12.0	0	23.8
PFS, months median	1.87	3.53	1.87	2.30	3.02	3.52	1.77	1.94	1.77	3.12
(95% CI)	(1.77–2.04)	(1.94–3.71)	(1.71–3.02)	(1.87–3.71)	(1.81–NR)	(1.87–NR)	(1.54–5.78)	(1.68–3.71)	(1.68–2.10)	(1.87–7.23)
OS, months median	5.95	11.63	5.68	10.28	NR	10.60	4.53	11.30	4.96	8.57
(95% CI)	(4.37–8.08)	(9.10–NR)	(4.40–NR)	(6.05–NR)	(4.70–NR)	(5.82–NR)	(2.23–NR)	(5.85–NR)	(2.92–NR)	(4.21–NR)

ORR based on blinded independent review committee assessment CI = confidence interval; NR = not reached

Myers Squibb, outside the submitted work. A. Siefker-Radtke: Reports being on the Scientific advisory board for AstraZeneca, Bristol-Myers Squibb, Eisai, EMD Serono, Genentech, Inovio, Janssen, and Merck, outside the submitted work. A. Necchi: Reports consulting or advisory role from AstraZeneca, Bayer, Roche, Merck & Co. Inc., and Pfizer; Reports research funding from Amgen, AstraZeneca, and Merck & Co. Inc., outside the submitted work. P. Sharma: Reports being a consultant for Bristol-Myers Squibb, Glaxo Smith Kline, AstraZeneca, Amgen, Constellation, Jounce, Kite Pharma, Neon, Evelo, EMD Sereno, Astellas; stock from Jounce, Kite Pharma, Evelo, Constellation, Neon, outside the submitted work. All other authors have declared no conflicts of interest.