A Pan-cancer Analysis of Impact of MDM2/MDM4 on Immune Checkpoint Blockade (ICB).

[1]Wafik S. El-Deiry, [2]Taylor Arnoff, [3]Ilyas Sahin, [4]Hossein Borghaei, [5]Vivek Subbiah, [2]Hina Khan, [2]Benedito A. Carneiro, [2]Howard Safran, [2]Stephanie L. Graff, [2]Don S. Dizon, [6]Elisabeth I. Heath, [2]Eric T. Wong, [2]Abbas Abbas, [2]Christopher G. Azzoli, [7]Michael J. Demeure, [8]Jim Abraham,[9] Razelle Kurzrock, [8]Joanne Xiu, [10]Emil Lou, [11]Stephen V. Liu

[1]Cancer Center at Brown University, Providence, RI; [2]Brown University, The Warren Alpert Medical School, Providence, RI; [3]Rhode Island Hospital, Providence, RI; [4]Fox Chase Cancer Center, Philadelphia, PA; [5] The University of Texas MD Anderson Cancer Center, Houston, TX; [6] Karmanos Cancer Institute, Department of Oncology, Detroit, MI; [7] Hoag Family Cancer Institute, Hoag Memorial Hospital Presbyterian, Newport Beach, CA; [8]Caris Life Sciences, Phoenix, AZ; [9] University of California, San Diego, San Diego, CA, [10]University of Minnesota School of Medicine, Minneapolis, MN; [11]Georgetown University, Department of Hematology and Oncology, School of Medicine, Washington, DC

Background

- *MDM2/MDM4* are implicated in hyperprogression after immune checkpoint blockade (ICB or IO).
- Our preclinical studies showed reduced T-cell killing of *MDM2*-amplified tumor cells that was overcome by an MDM2 antagonist or gene knockdown, and we observed additional tumor killing by T-cells with MDM2 inhibition plus anti-PD1.
- We hypothesized that *MDM2/4* gene amplification/overexpression correlates with resistance to ICB and investigated the association of MDM2/4 alterations to overall survival (OS) following ICB across multiple solid tumors.

Methods

- Solid tumors tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (NGS) were analyzed.
- *MDM2/4* amplification (amp) was tested by NGS and determined as either amp4 (cutoff of >=4.0 copies) or amp6 (>=6.0) or amp8 (>=8.0).
- Real-world OS was obtained from insurance claims data and calculated from treatment start or tissue collection to last contact.
- Kaplan-Meier estimates were calculated for molecularly defined groups. X^2/Fisher-Exact were used and significance determined as P-value adjusted for multiple comparisons (q<0.05).

Results

Table 1: Patient cohort characteristics

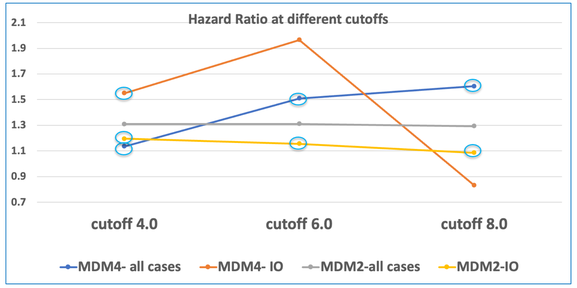
Number of patients included for the study						
	MDM4			MDM2		
All cases	**MDM4> 4.0**	**MDM4> 6.0**	**MDM4> 8.0**	**MDM2> 4.0**	**MDM2> 6.0**	**MDM2> 8.0**
Total N	1669	380	266	4053	2745	2115
Treated with IO (pembro, nivo, atezo)	100	13	7	373	248	185
TP53-WT tumors	**MDM4> 4.0**	**MDM4> 6.0**	**MDM4> 8.0**	**MDM2> 4.0**	**MDM2> 6.0**	**MDM2> 8.0**
Total N	1040	293	217	2785	**2108**	1721
Treated with IO (pembro, nivo, atezo)	59	8	4	262	**192**	149

Results

Table 2: Cancer type break down in TP53 Wild type cohort

TP53 WT, MDM4>4.0, total =1040, top 12 cancer types	n
Breast Carcinoma	302
Glioblastoma	212
Uterine Neoplasms	115
Lung Non-small cell lung cancer NSCLC	75
Ovarian Surface Epithelial Carcinomas	55
Prostatic Adenocarcinoma	53
Melanoma	40
Cholangiocarcinoma	24
Cancer of Unknown Primary	23
Neuroendocrine tumors	16
Soft Tissue Tumors	13
Pancreatic Adenocarcinoma	12
TP53 WT, MDM2>6.0, top 12 cancer types	**n**
Lung Non-small cell lung cancer NSCLC	423
Glioblastoma	270
Breast Carcinoma	249
Bladder cancer - urothelial	235
Soft Tissue Sarcoma - Well-Differentiated_Dedifferentiated Liposarcoma WD-DDLS for Retroperitoneal Sarcomas	171
Soft Tissue Tumors	121
Esophageal and Esophagogastric Junction Carcinoma	81
Cholangiocarcinoma	78
Melanoma	65
Gastric Adenocarcinoma	64
Uterine Neoplasms	56
Cancer of Unknown Primary	46

Figure 1: MDM2/4 clinical behavior in all solid tumors. Y-axis: Hazard ratios calculated from KM based on either overall survival (calculated from tissue collection to last day of contact) or post-IO survival (calculated from start of IO treatment to last day of contact)



- Detrimental effects of MDM2/4 amplification for prognosis seen at all cutoffs tested
- Increased MDM4 cutoff associated with higher HR (more detrimental effects on prognosis)
- Largely unchanged HR with increased MDM2 cutoff

Results

Figure 2: example Kaplan Meier curves in all solid tumors

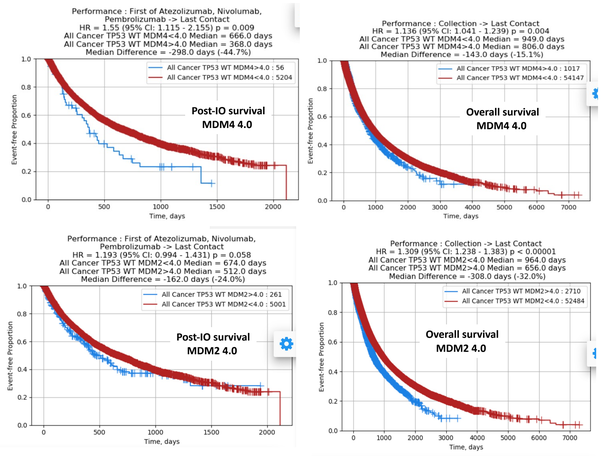
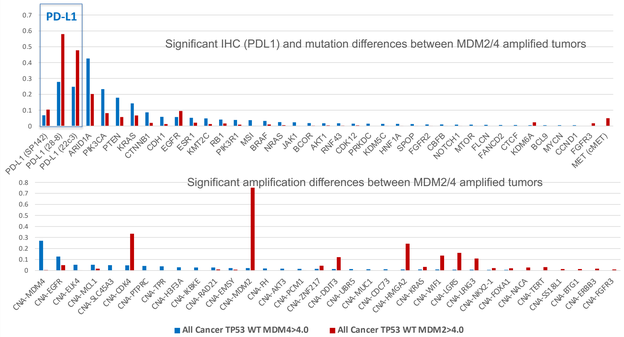


Figure 3: Significant molecular differences between MDM2 amp vs. MDM4 amp in all solid tumors. Y axis: prevalence of alterations in MDM2/4 amp cases



- MDM4 amplification co-occurs with more mutations
- PDL1 expression significantly higher in MDM2 amp tumors

Results

Figure 4: MDM4 amplification (at 4.0 cutoff) associated with decreased survival after IO treatment in NSCLC

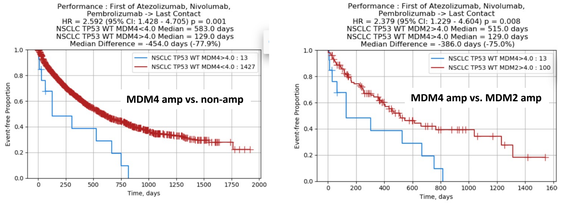
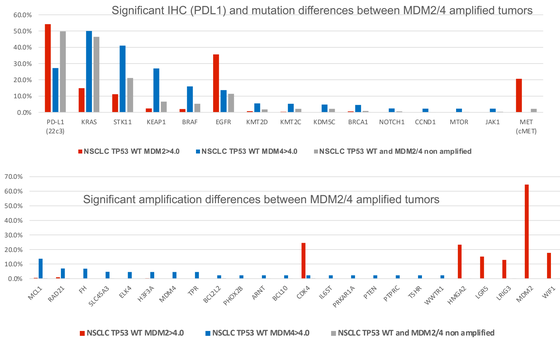


Figure 5: Significant molecular differences between MDM2 amp vs. MDM4 amp in NSCLC. Y axis: prevalence of alterations in MDM2/4 amp cases



- MDM2 and MDM4 amplification occur with different molecular drivers in NSCLC
- PDL1 expression significantly higher in MDM2 amp tumors

Conclusions

- *MDM2* and *MDM4* amplification are negative prognostic factors in TP53-WT breast cancer while *MDM4* amp is associated with reduced survival in ICB-treated NSCLC.