

Table S1: Clinical and genetic characteristics of the MSKCC colorectal c

Legend: All data was extracted from the electronic medical record with verification of 3% of patient data by licensed physicians. MMR/*pol-d* status classification was assigned per Supplementary methods. Calculations were performed with R statistical software. "NE" indicates not evaluable

Covariate	All patients (N=4283)	TMB<10 mut/Mb (N=3464)	TMB≥10 mut/Mb (N=793)
Fraction of total population (%)	100%	81%	18%
Median age (range) -yr	58 (14-90)	57 (14-90)	63 (19-90)
Sex- no. (%)			
Male:	2333 (54%)	1912 (55%)	404 (51%)
Female	1942 (45%)	1546 (45%)	387 (49%)
Unknown	8 (0%)	6 (0%)	2 (0%)
Race- no. (%)			
White	3286 (77%)	2622 (76%)	642 (81%)
Black	307 (7%)	260 (8%)	47 (6%)
Asian	348 (8%)	299 (9%)	46 (6%)
Other	342 (8%)	283 (8%)	58 (7%)
Tumor Sidedness-no. (%)			
Left-sided	2208 (52%)	1873 (54%)	318 (40%)
Right-sided	438 (10%)	275 (8%)	163 (21%)
Unknown	1636 (38%)	1315 (38%)	312 (39%)
Histological Subtype -no. (%)			
Adenocarcinoma	4168 (97%)	3400 (98%)	744 (94%)
Mucinous adenocarcinoma	115 (3%)	64 (2%)	49 (6%)
Median TMB (range)	6.1 (0-415)	5.6 (0-9.8)	37.7 (10-415)
MMR/<i>pol-d</i> status			
MMRp	3787 (88%)	3461 (100%)	326 (41%)
MMRd	431 (10%)	3 (0%)	428 (54%)
<i>pol-d</i>	39 (1%)	0 (0%)	39 (5%)
Indeterminate	26 (1%)	0 (0%)	0 (0%)

Cancer patient cohort according to TMB status

Unknown

(N=26)

1%

54.5 (22-88)

17 (65%)

9 (35%)

0 (0%)

22 (85%)

0 (0%)

3 (12%)

1 (4%)

17 (65%)

0 (0%)

9 (35%)

24 (92%)

2 (8%)

NE

0 (0%)

0 (0%)

0 (0%)

26 (100%)

Table S2: Clinical and genetic characteristics of advanced colore

Legend: All data was manually abstracted from the electronic medical record and verified by licensed physicians. Mutational characteristics are reported from MSKCC IMPACT Next Generation Sequencing panel results. MMR/*pol-d* status classification was assigned per Supplementary Methods. Calculations were performed with R statistical software.

Covariate	All patients (N=137)
Median Age (range) -yr	52.5 (18.8-86)
Sex- no. (%)	
Male:	75 (55%)
Female	62 (45%)
Race- no. (%)	
White	104 (76%)
Black	9 (7%)
Asian	15 (11%)
Other	6 (4%)
Tumor Sidedness-no. (%)	
Left-sided	79 (58%)
Right-sided	57 (42%)
Unknown	1 (1%)
Histological Subtype -no. (%)	
Adenocarcinoma	116 (85%)
Mucinous adenocarcinoma	14 (10%)
Medullary carcinoma	2 (1%)
Signet ring	5 (4%)
Median TMB (range)	7.9 (0-369)
TMB \geq 10	52 (38%)
TMB<10	85 (62%)
Mutation Characteristics-no. (%)	
KRAS driver mutation	71 (52%)
No KRAS driver mutation	66 (48%)
NRAS driver mutation	6 (4%)
No NRAS driver mutation	131 (96%)
BRAF driver mutation	9 (7%)
No BRAF driver mutation	128 (93%)
Treatment Characteristics-no. (%)	
Single immune checkpoint Inhibitor	71 (52%)
Combination immune checkpoint inhibitors	24 (17%)
Combination immune checkpoint inhibitor and other agent	42 (31%)
Median number of previous treatment lines (range)	2 (0-5)

rectal cancer patients exposed to immune checkpoint inhibitors

MMRp TMB<10 (N= 84)	MMRp TMB≥10 (N= 13)	MMRd (N=36)	<i>pol-d</i> (N=4)
50.8 (18.8-80.2)	62.7 (43.8-80.4)	58.9 (23.6-86)	61.5 (52.8-65.4)
42 (50.0%)	9 (69.2%)	20 (55.6%)	4 (100.0%)
42 (50.0%)	4 (30.8%)	16 (44.4%)	0 (0.0%)
67 (79.8%)	11 (84.6%)	25 (69.4%)	1 (25.0%)
5 (6.0%)	1 (7.7%)	2 (5.6%)	1 (25.0%)
6 (7.1%)	1 (7.7%)	7 (19.4%)	1 (25.0%)
6 (7.1%)	0 (0.0%)	2 (5.6%)	1 (25.0%)
60 (71.4%)	4 (30.8%)	15 (41.7%)	0 (0.0%)
23 (27.4%)	9 (69.2%)	21 (58.3%)	4 (100.0%)
1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
79 (94.0%)	11 (84.6%)	22 (61.1%)	4 (100.0%)
4 (4.8%)	2 (15.4%)	8 (22.2%)	0 (0.0%)
0 (0.0%)	0 (0.0%)	2 (5.6%)	0 (0.0%)
1 (1.2%)	0 (0.0%)	4 (11.1%)	0 (0.0%)
5.4 (0-9.8)	166 (65-204)	58 (8.8-369)	166 (64.9-204)
0 (0.0%)	13 (100.0%)	35 (97.2%)	4 (100.0%)
84 (100.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)
45 (53.6%)	8 (61.5%)	15 (41.7%)	3 (75.0%)
39 (46.4%)	5 (38.5%)	21 (58.3%)	1 (25.0%)
6 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
78 (92.9%)	13 (100.0%)	36 (100.0%)	4 (100.0%)
1 (1.2%)	2 (15.4%)	6 (16.7%)	0 (0.0%)
83 (98.8%)	11 (84.6%)	30 (83.3%)	4 (100.0%)
30 (35.7%)	8 (61.5%)	29 (80.6%)	4 (100.0%)
16 (19.0%)	1 (7.7%)	7 (19.4%)	0 (0.0%)
38 (45.2%)	4 (30.8%)	0 (0.0%)	0 (0.0%)
3 (0-5)	3 (0-5)	1 (0-4)	3 (2-4)

Table S3: Univariate and multivariate analyses of overall survival

Legend: Survival rates and median overall survival were calculated for all patients with advanced colorectal cancer using Kaplan-Meier analysis. Hazard ratios (HR) for death were calculated using Cox Proportional Hazards Regression. Covariates with HR showing an association (95% CI not overlapping 1.0) between overall survival or progression free survival (Table S6) were placed into a multivariate Cox proportional hazards regression model together. Patients with combination checkpoint inhibitor and non-checkpoint inhibitor therapy were not included in the univariate checkpoint inhibitor treatment analysis. "NR" indicates

Covariate	Number of patients
DNA Repair Status	
MMRp TMB<10	84
MMRp TMB≥10	13
MMRd	36
<i>pol-d</i>	4
Age (continuous)	
Sex	
Female	62
Male	75
Race	
Non-Caucasian	33
Caucasian	104
Tumor Sidedness	
Left-sided	79
Right-sided	57
Mutational Status	
No KRAS driver mutation	66
KRAS driver mutation	71
No BRAF driver mutation	128
BRAF driver mutation	9
Checkpoint Inhibitor Treatment	
Single immune checkpoint inhibitor	71
Combination immune checkpoint inhibitors	24

Survival of advanced colorectal cancer patients exposed to i

Univariate Analysis		
Median OS in months (95% CI)	1 year OS (95% CI)	2 year OS (95% CI)
12.1 (9.61-15.3)	52.2% (40.8%-62.5%)	21.8% (12.8%-32.3%)
10.6 (4.41-22.2)	41.0% (13.8%-66.9%)	15.4% (1.1%-46.2%)
NR (34.28-NE)	69.4% (51.7%-81.8%)	69.4% (51.7%-81.8%)
NR (1.68-NE)	75% (12.8%-96.1%)	75% (12.8%-96.1%)
18.2 (12.0-31.2)	50.3% (37.1%-62.2%)	31.8% (20.1%-44.0%)
12.0 (7.76-14.6)	62.1% (50.0%-72.1%)	41.7% (29.7%-53.2%)
18.6 (7.76-NE)	54.4% (36.1%-69.5%)	44.3% (26.8%-60.4%)
14.1 (11.18-18.2)	57.7% (47.5%-66.7%)	34.7% (25.0%-44.6%)
13.4 (9.90-34.3)	57.5% (45.7%-67.6%)	33.1% (21.9%-44.7%)
15.3 (9.67-22.2)	57.1% (43.1%-68.9%)	42.3% (29.1%-54.8%)
14.1 (7.76-20.9)	56.1% (43.3%-67.0%)	31.0% (19.8%-42.8%)
14.2 (10.76-33.6)	57.2% (44.5%-68.1%)	43.6% (31.2%-55.4%)
14.2 (10.9-18.6)	56.1% (46.9%-64.3%)	36.8% (27.9% -45.6%)
22.2 (0.72-NE)	66.7% (28.2%-87.8%)	41.7% (10.9%-70.8%)
16.4 (8.81-31.2)	55.7% (43.3%-66.4%)	43.9% (31.7%-55.5%)
16.2 (11.9-34.3)	70.8% (48.4%-84.9%)	33.3% (15.9%-51.9%)

immune checkpoint inhibitors

Multivariate Analysis	
HR for death (95% CI)	HR for death (95% CI)
(ref)	(ref)
1.17 (0.60-2.28)	1.17 (0.59-2.32)
0.29 (0.15-0.53)	0.29 (0.15-0.54)
0.18 (0.02-1.35)	0.18 (0.02-1.37)
1.00 (0.99-1.02)	
(ref)	
0.74 (0.49-1.13)	
(ref)	
1.31 (0.78-2.17)	
(ref)	(ref)
0.87 (0.53-1.22)	1.13 (0.72-1.78)
(ref)	
0.80 (0.53-1.22)	
(ref)	(ref)
0.89 (0.39-2.04)	0.77 (0.34-1.72)
(ref)	
1.07 (0.61-1.87)	

Table S4: Hazard ratio for death in cancer patients with tumors treated with immunotherapy

Legend: Univariate Cox proportional hazards regression was performed to establish HRs for an association between DNA-repair subgroup status and death in each respective tumor type. HRs are represented visually in Figure 1C. An aggregated model was made for patients with breast, kidney, neuroendocrine, uveal melanoma and mucosal melanoma cancers. Patients were aggregated into two models depending on the presence (TMB sensitive) or absence (TMB insensitive) of a positive association of TMB ≥ 10 mut/Mb with survival in the respective tumor types. "NE" indicates not evaluable

TMB Sensitive Primary Tumor Type	Number of patients
Head and Neck	
MMRp TMB<10	118
MMRp TMB ≥ 10	26
MMRd or <i>pol-d</i>	2
Melanoma	
MMRp TMB<10	108
MMRp TMB ≥ 10	148
MMRd or <i>pol-d</i>	2
NSCLC	
MMRp TMB<10	236
MMRp TMB ≥ 10	111
MMRd or <i>pol-d</i>	7
Combined TMB sensitive tumors	
MMRp TMB<10	462
MMRp TMB ≥ 10	285
MMRd or <i>pol-d</i>	11

TMB Insensitive Primary Tumor Type	Number of patients
Urinary tract carcinoma	
MMRp TMB<10	126
MMRp TMB ≥ 10	77
MMRd or <i>pol-d</i>	10
CUP	
MMRp TMB<10	44
MMRp TMB ≥ 10	19

MMRd or <i>pol-d</i>	3
CRC	
MMRp TMB<10	65
MMRp TMB≥10	13
MMRd or <i>pol-d</i>	35
EG	
MMRp TMB<10	107
MMRp TMB≥10	9
MMRd or <i>pol-d</i>	10
Brain	
MMRp TMB<10	108
MMRp TMB≥10	9
MMRd or <i>pol-d</i>	0
Kidney*	
MMRp TMB<10	149
MMRp TMB≥10	2
MMRd or <i>pol-d</i>	0
Breast*	
MMRp TMB<10	43
MMRp TMB≥10	3
MMRd or <i>pol-d</i>	0
Mucosal Melanoma*	
MMRp TMB<10	34
MMRp TMB≥10	2
MMRd or <i>pol-d</i>	0
Uveal Melanoma*	
MMRp TMB<10	20
MMRp TMB≥10	0
MMRd or <i>pol-d</i>	0
Neuroendocrine*	
MMRp TMB<10	13
MMRp TMB≥10	4
MMRd or <i>pol-d</i>	0
Combined Kidney, Breast, Mucosal Melanoma, Uveal Melanoma, Neuroendocrine*	
MMRp TMB<10	259
MMRp TMB≥10	11
MMRd or <i>pol-d</i>	0
Combined TMB insensitive tumors	
MMRp TMB<10	709
MMRp TMB≥10	138
MMRd or <i>pol-d</i>	56

ated with immune checkpoint inhibitors classified according to tumor type a

**Hazard Ratio for death
(95% Confidence Interval)**

(ref)
0.46 (0.22-0.95)
0.82 (0.11-6.00)

(ref)
0.62 (0.41-0.94)
NE

(ref)
0.70 (0.52-0.95)
0.69 (0.25-1.85)

(ref)
0.52 (0.41-0.64)
0.81 (0.34-1.97)

**Hazard Ratio for death
(95% Confidence Interval)**

(ref)
0.77 (0.50-1.18)
0.13 (0.02-0.91)

(ref)
0.72 (0.28-1.81)

0.90 (0.12-6.76)

(ref)

0.87 (0.34-2.25)

0.26 (0.11-0.62)

(ref)

0.97 (0.07-1.29)

0.31 (0.38-2.47)

(ref)

0.74 (0.30-1.85)

NE

(ref)

NE

NE

(ref)

0.27 (0.04-2.05)

NE

(ref)

NE

NE

(ref)

NE

NE

(ref)

0.38 (0.05-3.11)

NE

(ref)

0.40 (0.10-1.62)

NE

(ref)

0.84 (0.63-1.11)

0.34 (0.18-0.61)

nd stratified by TMB and DNA-repair defect status

Table S5: TMB and DNA-repair status of patients with multiple cancer

Legend: Data was obtained from a publicly-available validation cohort of patients with metastatic cancer of different primary tumors treated with immune checkpoint inhibitors from 2015 to 2019. Similar tumor types were consolidated into larger categories according to tumor primary site and pathological results. Mutational and DNA-repair status information was identified using an internal MSKCC institutional database. *Indicates tumor type combined into "Other Tumors combined" category

Primary Tumor Type

	Number of patients
Brain -no. (% tumor type)	117 (7%)
Breast*-no. (% tumor type)	46 (3%)
CRC -no. (% tumor type)	111 (7%)
CUP -no. (% tumor type)	66 (4%)
EG -no. (% tumor type)	126 (7%)
Head and Neck -no. (% tumor type)	146 (9%)
Kidney* -no. (% tumor type)	151 (9%)
Melanoma -no. (% tumor type)	258 (15%)
Mucosal Melanoma* -no. (% tumor type)	36 (2%)
NSCLC -no. (% tumor type)	354 (22%)
Urinary Tract Carcinoma -no. (% tumor type)	213 (13%)
Uveal Melanoma* -no. (% tumor type)	20 (1%)
Neuroendocrine* -no. (% tumor type)	17 (1%)
Other Tumors* combined - no. (% tumor type)	270 (16%)
Total Number -no. (% total number patients)	1661 (100%)

r types exposed to immune checkpoints inhibitors

Mutational and DNA-repair status			
MMRp TMB<10	MMRp TMB ≥ 10	MMRd	<i>pol</i>
108 (92%)	9 (8%)	0 (0%)	0 (0%)
43 (93%)	3 (7%)	0 (0%)	0 (0%)
65 (59%)	13 (12%)	29 (26%)	4 (4%)
44 (67%)	19 (29%)	3 (5%)	0 (0%)
107 (85%)	9 (7%)	10 (8%)	0 (0%)
118 (81%)	26 (18%)	2 (1%)	0 (0%)
149 (99%)	2 (1%)	0 (0%)	0 (0%)
108 (42%)	148 (57%)	0 (0%)	2 (1%)
34 (94%)	2 (6%)	0 (0%)	0 (0%)
236 (67%)	111 (31%)	3 (1%)	4 (1%)
126 (59%)	77 (36%)	7 (3%)	3 (1%)
20 (100%)	0 (0%)	0 (0%)	0 (0%)
13 (76%)	4 (24%)	0 (0%)	0 (0%)
259 (96%)	11 (4%)	0 (0%)	0 (0%)
1171 (70%)	423 (25%)	54 (3%)	13 (1%)

Total DNA Repair-defect

0 (0%)
0 (0%)
33 (30%)
3 (5%)
10 (8%)
2 (1%)
0 (0%)
2 (1%)
0 (0%)
7 (2%)
10 (5%)
0 (0%)
0 (0%)
0 (0%)
67 (4%)

Immune Checkpoint Inhibitor Therapy

PD-1/PDL-1	CTLA4	Combo
114 (97%)	0 (0%)	3 (3%)
22 (48%)	20 (43%)	4 (9%)
100 (90%)	1 (1%)	10 (9%)
60 (91%)	0 (0%)	6 (9%)
93 (74%)	2 (2%)	31 (25%)
134 (92%)	0 (0%)	12 (8%)
122 (81%)	0 (0%)	29 (19%)
106 (41%)	59 (23%)	93 (36%)
13 (36%)	12 (33%)	11 (31%)
333 (94%)	0 (0%)	21 (6%)
190 (89%)	0 (0%)	23 (11%)
9 (45%)	4 (20%)	7 (35%)
11 (65%)	1 (6%)	5 (29%)
177 (66%)	37 (14%)	56 (21%)
1296 (79%)	98 (6%)	250 (15%)

Table S6: Univariate and multivariate analyses of progres

Legend: Survival rates and median progression-free survival were calculated for all patients with advanced colorectal cancer using Kaplan-Meier analysis. Hazard ratios (HR) for death were calculated using Cox Proportional Hazards Regression. Covariates with a positive association between MMRp TMB \geq 10 status and either progression free survival or overall survival (HR 95% CI not overlapping 1.0) were placed into a multivariate model together. Patients with combination checkpoint inhibitor and non-checkpoint inhibitor therapy were not included in the univariate checkpoint inhibitor treatment analysis. "NE" indicates non evaluable

Covariate	Number of patients
DNA Repair Status	
MMRp TMB<10	84
MMRp TMB \geq 10	13
MMRd	36
<i>pol-d</i>	4
Age (continuous)	
Sex	
Female	62
Male	75
Race	
Non-Caucasian	33
Caucasian	104
Primary Tumor Laterality	
Left-sided	79
Right-sided	57
Mutational Status	
No KRAS driver mutation	66
KRAS driver mutation	71
No BRAF driver mutation	128
BRAF driver mutation	9
Checkpoint Inhibitor Treatment	
Single immune checkpoint inhibitor	71
Combination immune checkpoint inhibitors	24

ission-free-survival of advanced colorectal cancer patients exposec

Univariate Analysis		
Median PFS in months (95% CI)	1 year PFS (95% CI)	2 year PFS (95% CI)
1.81 (1.64-2.01)	1.2% (0.0%-5.8%)	0%
2.37 (1.84-4.18)	7.7% (0.4%-29.2%)	0%
27.01 (9.70-NE)	62.6% (44.3%-76.3%)	56.6% (38.6%-71.2%)
3.68 (1.68-NE)	50% (5.8%-84.5%)	50% (5.8%-84.5%)
2.04 (1.68-3.49)	15.6% (7.8%-25.8%)	15.6% (7.8%-25.8%)
2.73 (1.84-4.18)	21.9% (13.3%-32.0%)	16.5% (9.0%-25.8%)
3.68 (1.84-5.30)	23.3% (10.6%-38.9%)	20.0% (8.3%-35.3%)
2.01 (1.81-3.26)	17.7% (11.0%-25.6%)	14.7% (8.7%-22.3%)
1.92 (1.78-3.26)	12.8% (6.6%-21.2%)	11.5% (5.7%-19.7%)
3.65 (1.97-5.30)	28.3% (17.2%-40.5%)	22.7% (12.7%-34.4%)
2.73 (1.84-4.14)	21.5% (12.3%-32.3%)	19.8% (11.1%-30.5%)
2.01 (1.74-3.65)	16.9% (9.3%-26.4%)	12.7% (6.2%-21.5%)
2.04 (1.84-3.26)	17.3% (11.2%-24.4%)	14.0% (8.6%-20.7%)
8.49 (0.07-NE)	44.4% (13.6%-71.9%)	44.4% (13.6%-71.9%)
3.26 (2.04-4.44)	28.3% (18.3%-39.1%)	25.3% (15.8%-36.0%)
1.81 (1.61-5.69)	21.8% (8.0%-40.0%)	17.5% (5.0%-35.1%)

l to immune checkpoint inhibitors

Multivariate Analysis	
HR for progression or death (95% CI)	HR for progression or death (95% CI)
(ref)	(ref)
0.66 (0.37-1.20)	0.72 (0.40-1.30)
0.13 (0.07-0.23)	0.13 (0.07-0.24)
0.13 (0.03-0.56)	0.16 (0.04-0.71)
0.99 (0.98-1.01)	
(ref)	
0.85 (0.59-1.23)	
(ref)	
1.34 (0.86-2.07)	
(ref)	(ref)
0.64 (0.44-0.94)	0.92 (0.61-1.36)
(ref)	
1.28 (0.88-1.84)	
(ref)	(ref)
0.39 (0.16-0.95)	0.41 (0.18-0.90)
(ref)	
1.29 (0.77-2.15)	

Table S7: Survival from time of advanced cancer diagnosis in patients

Legend: Median survival from date of metastatic diagnosis to either documented date of patient death or last follow-up (censored at that moment) was performed using Kaplan-Meier analysis for patients with advanced colorectal cancer who were or were not treated with immune checkpoint inhibitors (ICI). The median time from metastatic diagnosis to date of first ICI treatment was also similarly calculated for patients with advanced CRC who were treated with ICI. "NR" indicates not reached and "NE" indicates not evaluable

TMB subgroup	Number of patients
Non-ICI treated patients	
TMB<10	1086
TMB≥10	143
ICI-Treated Patients	
TMB<10	85
TMB≥10	42

DNA-Repair Status Subgroup	Number of patients
Non-ICI treated patients	
MMRp TMB<10	1085
MMRp TMB≥10	117
MMRd	25
<i>pol-d</i>	2
ICI-Treated Patients	
MMRp TMB<10	84
MMRp TMB≥10	11
MMRd	29
<i>pol-d</i>	3

nts with colorectal cancer treated with and without ICI

Patients without precise stage IV diagnosis date	Median survival (from stage IV diagnosis) in months (95% CI)
0	38.9 (33.8-49.3)
0	24.0 (14.4-35)
0	51 (45-59)
10	52 (27-NR)

Patients without precise stage IV diagnosis date	Median survival (from stage IV diagnosis) in months (95% CI)
0	38.9 (33.3-49.3)
0	17.6 (13-27.5)
0	NR (28.8-NE)
0	14.4 (14.4-NE)
0	51 (45-60)
2	51 (15-87)
7	NR (23-NE)
1	NR (6-NE)

Median time from metastatic diagnosis to ICI in months (95% CI)

N/A
N/A

29 (23-36)
13 (7-20)

Median time from metastatic diagnosis to ICI in months (95% CI)

N/A
N/A
N/A
N/A

29 (24-36)
30 (11-45)
25 (5-14)
59 (4-NE)

|

Table S8: Median follow-up time per treatment arm in each study

Legend: Median time from immune checkpoint inhibitor treatment to follow-up was performed using Kaplan-Meier analysis for both the advanced annotated colorectal cohort and larger validation cohort of patients with multiple malignancy types.

Advanced Colorectal Cohort

TMB Subgroups

TMB<10

TMB≥10

DNA-repair status Subgroup

MMRp TMB<10

MMRp TMB≥10

MMRd

pol-d

Expanded Cancer Type Cohort

TMB Sensitive Primary Tumor Type

Head and Neck

MMRp TMB<10

MMRp TMB≥10

MMRd or *pol-d*

Melanoma

MMRp TMB<10

MMRp TMB≥10

MMRd or *pol-d*

NSCLC

MMRp TMB<10

MMRp TMB≥10

MMRd or *pol-d*

Combined TMB sensitive tumors

MMRp TMB<10

MMRp TMB≥10

MMRd or *pol-d*

TMB Insensitive Primary Tumor Type

Urinary tract carcinoma

MMRp TMB<10

MMRp TMB≥10

MMRd or *pol-d*

CUP

MMRp TMB<10

MMRp TMB \geq 10
MMRd or *pol*-d

CRC

MMRp TMB<10
MMRp TMB \geq 10
MMRd or *pol*-d

EG

MMRp TMB<10
MMRp TMB \geq 10
MMRd or *pol*-d

Brain

MMRp TMB<10
MMRp TMB \geq 10
MMRd or *pol*-d

Kidney*

MMRp TMB<10
MMRp TMB \geq 10
MMRd or *pol*-d

Breast*

MMRp TMB<10
MMRp TMB \geq 10
MMRd or *pol*-d

Mucosal Melanoma*

MMRp TMB<10
MMRp TMB \geq 10
MMRd or *pol*-d

Uveal Melanoma*

MMRp TMB<10
MMRp TMB \geq 10
MMRd or *pol*-d

Neuroendocrine*

MMRp TMB<10
MMRp TMB \geq 10
MMRd or *pol*-d

Combined Kidney, Breast, Mucosal Melanoma, Uveal Melanoma, Neuroendocrine*

MMRp TMB<10
MMRp TMB \geq 10
MMRd or *pol*-d

Combined TMB insensitive tumors

MMRp TMB<10
MMRp TMB \geq 10
MMRd or *pol*-d

cohort

Number of patients	Median Follow-up in months (95% CI)
85	26.3 (21.5-38.9)
52	33.5 (28.8-38.1)
84	26.3 (22.5-NR)
13	17.7 (17.7-NR)
36	33.3 (29.7-49.5)
4	33.8 (33.5-NR)

Number of patients	Median Follow-Up in months (95% CI)
118	14 (12-24)
26	15 (8-21)
2	16 (NE)
108	29 (24-32)
148	25 (23-30)
2	5.5 (1-NR)
236	25 (23-29)
111	19 (17-22)
7	22 (15-NR)
462	24 (22-27)
285	21 (20-24)
11	16 (15-NR)

Number patients	Median Follow-Up in months (95% CI)
126	14 (10-20)
77	17 (15-27)
10	25 (6-NR)
44	9 (5-16)

19	8 (4-NR)
3	4 (2-NR)

65	16 (10-27)
13	10 (5-NR)
35	26 (10-28)

107	9 (8-12)
9	12 (6-NR)
10	8 (2-NR)

108	23 (21-NR)
9	23 (8-NR)
0	NE

149	29 (25-33)
2	34.5 (26-NR)
0	NE

43	18 (14-NR)
3	23.5 (19-NR)
0	NE

34	29 (20-55)
2	24 (17-NR)
0	NE

20	23 (19-NR)
0	NE
0	NE

13	16 (2-NR)
4	3 (2-NR)
0	NE

259	19 (15-NR)
11	26 (24-30)
0	NE

709	21 (19-23)
138	15 (12-20)
56	12 (9-23)

Table S9: Restricted Mean Survival Time analysis of patients with

Legend: Mean survival time and between-group ratios were determined for patients with advanced colorectal cancer treated with immune checkpoint inhibitors (ICI) using a restricted mean survival time analysis at various time intervals between TMB subgroups (using data represented in Figure 1A) and DNA-Repair Status Subgroups (using data represented in Figure 1B). Between group ratios were determined in relation to the labeled "ref" group.

TMB Subgroups

TMB<10

TMB≥10

DNA-Repair Status Subgroup

MMRp TMB<10

MMRp TMB≥10

MMRd

pol-d

1 advanced colorectal cancer treated with ICI

6 month truncated timepoint

Restricted Mean Survival Time in months (95% CI)	Between-group ratio (95% CI)
5.40 (5.15-5.65)	(ref)
5.21 (4.74-5.67)	0.97 (0.87-1.07)
5.39 (5.14-5.64)	(ref)
5.40 (4.76-6.04)	1.00 (0.88-1.14)
5.19 (4.80-5.79)	0.96 (0.85-1.10)
4.92 (3.09-6.75)	0.91 (0.63-1.33)

12 month truncated timepoint

Restricted Mean Survival Time in months (95% CI)	Between-group ratio (95% CI)
9.13 (8.35-9.90)	(ref)
9.41 (8.31-10.51)	1.031 (0.89-1.19)
9.15 (8.37-9.94)	(ref)
8.86 (6.95-10.77)	0.97 (0.77-1.22)
9.52 (8.18-10.86)	1.04 (0.88-1.23)
9.42 (5.04-13.80)	1.03 (0.64-1.65)

18 month truncated timepoint

Restricted Mean Survival Time in months (95% CI)	Between-group ratio (95% CI)
11.54 (10.27-12.81)	(ref)
13.23 (11.42-15.05)	1.15 (0.96-1.37)
11.6 (10.32-12.87)	(ref)
10.92 (7.71-14.14)	0.94 (0.69-1.29)
13.69 (11.48-15.88)	1.18 (0.97-1.43)
13.92 (6.99-20.85)	1.20 (0.72-2.00)

24 month truncated timepoint

Restricted Mean Survival Time in months (95% CI)	Between-group ratio (95% CI)
13.16 (11.45-14.88)	(ref)
16.97 (14.41-19.53)	1.29 (1.06-1.57)
13.24 (11.51-14.97)	(ref)
12.49 (8.01-16.97)	0.94 (0.63-1.38)
17.85 (14.78-20.93)	1.35 (1.09-1.67)
18.42 (8.95-27.89)	1.39 (0.82-2.37)

30 month truncated timepoint

Restricted Mean Survival Time in months (95% CI)	Between-group ratio (95% CI)
14.32 (12.20-16.43)	(ref)
20.61 (17.28-23.93)	1.44 (1.16-1.79)
14.41 (12.28-16.54)	(ref)
13.41 (7.92-18.91)	0.93 (0.60-1.44)
22.0 (18.05-25.99)	7.61 (3.11-12.11)
22.92 (10.90-34.94)	1.59 (0.92-2.74)