SUPPLEMENTARY MATERIALS

Supplementary Tables

Supplementary Table 1. Homologous recombination-related genes

No.	Gene	Relation
1	*BARD1*	Core
2	*BLM*	Core
3	*BRCA1*	Core
4	*BRCA2*	Core
5	*BRIP1*	Core
6	*MRE11*	Core
7	*NBN*	Core
8	*PALB2*	Core
9	*RAD50*	Core
10	*RAD51*	Core
11	*RAD51B*	Core
1	*ABL1*	Related
2	*ATM*	Related
3	*ATR*	Related
4	*BAP1*	Related
5	*CDK12*	Related
6	*CHEK1*	Related
7	*CHEK2*	Related
8	*DNMT3A*	Related
9	*ERCC1*	Related
10	*ERCC4*	Related
11	*FANCA*	Related
12	*FANCC*	Related
13	*FANCD2*	Related
14	*FANCE*	Related
15	*FANCF*	Related
16	*FANCG*	Related
17	*FANCL*	Related
18	*NONO*	Related
19	*RECQL4*	Related
20	*RMI2*	Related
21	*SFPQ*	Related
22	*WRN*	Related

Supplementary Table 2. Patients' characteristics based on homologous recombination machinery in the MSS/pMMR population

Characteristics	MSS/pMMR population	HRP	HRD with mutations in the "core" machinery	HRD with mutations in the "related" machinery	HRD with mutations in both "core" and "related" machinery	*P*[a]	q[a]	*P*[b]	q[b]	*P*[c]	q[c]
Total No. (%)	8702 (93.6)	7875 (90.5)	289 (3.3)	498 (5.7)	40 (0.5)						
Median age (range), y	60 (14-90)	60 (14-90)	60 (24-88)	60 (20-92)	52 (24-81)	0.32[d]	0.46[d]	0.70[d]	0.75[d]	0.0001[d]	<0.001[d]
Sex, No. (%)											
Male	4730 (54.4)	4299 (54.6)	159 (55.0)	240 (48.2)	32 (80.0)	0.89[e]	0.89[e]	0.01[e]	0.02[e]	0.001[e]	0.004[e]
Female	3972 (45.6)	3576 (45.4)	130 (45.0)	258 (51.8)	8 (20.0)						
Primary tumor location, No.	6280	5678	289	498	40						
Left and Rectum, No. (%)	4326 (68.9)	3932 (69.2)	145 (70.7)	231 (63.1)	18 (58.1)	0.65[e]	0.74[e]	0.01[e]	0.03[e]	0.18[e]	0.27[e]
Right, No. (%)	1954 (31.1)	1746 (30.8)	60 (29.3)	135 (36.9)	13 (41.9)						
NA, No.	2422	2197	84	132	9						
RAS mutational status, No.	8697	7870	289	498	40						
mut, No. (%)	4706 (54.1)	4245 (53.9)	152 (52.6)	290 (58.2)	21 (52.5)	0.65[e]	0.74[e]	0.06[e]	0.12[e]	0.42[e]	0.54[e]
wt, No. (%)	3991 (45.9)	3625 (46.1)	137 (47.4)	208 (41.8)	19 (47.5)						
NA, No.	5	5	0	0	0						
BRAF mutational status, No.	8695	7870	289	496	40						
mut, No. (%)	598(6.9)	532 (6.8)	22 (7.6)	44 (8.9)	0 (0.0)	0.57[e]	0.71[e]	0.07[e]	0.12[e]	0.09[e]	0.14[e]
wt, No. (%)	8097 (93.1)	7338 (93.8)	269 (92.4)	452 (91.1)	40 (100.0)						
NA, No.	7	5	0	2	0						
TMB-high (≥10 mut/Mb), No.	4838	4359	164	293	22						
Yes, No. (%)	136 (2.8)	97 (2.2)	11 (6.7)	12 (4.1)	16 (72.7)	<0.001[e]	0.001[e]	0.04[e]	0.08[e]	<0.001[e]	<0.001[e]
No, No. (%)	4702 (97.2)	4262 (97.8)	153 (93.3)	281 (95.9)	6 (27.3)						
NA, No.	3864	3516	125	205	18						
TMB (mut/Mb), No.	4838	4359	164	293	22						
Median (range)	4 (0-446)	4 (0-115)	5 (0-124)	5 (1-211)	111.5 (2-446)	<0.001[d]	<0.001[d]	0.008[d]	0.02[d]	<0.001[d]	<0.001[d]
PD-L1, No.	8348	7562	278	469	39						
Yes, No. (%)	217 (2.6)	178 (2.4)	15 (5.4)	20 (4.3)	4 (10.3)	0.001[e]	0.004[e]	0.01[e]	0.02[e]	0.001[e]	0.004[e]
No, No. (%)	8131 (97.4)	7384 (97.6)	263 (94.6)	449 (95.7)	35 (89.7)						
NA, No.	354	313	11	29	1						

CMS subtypes, No.	1436	1301	51	82	2						
CMS1, No. (%)	139 (9.7)	122 (9.4)	6 (11.8)	10 (12.2)	1 (50.0)	0.75[e]	0.78[e]	0.39[e]	0.54[e]	NA	NA
CMS2, No. (%)	448 (31.2)	415 (31.9)	14 (27.5)	19 (23.2)	0 (0.0)						
CMS3, No. (%)	153 (10.6)	138 (10.6)	4 (7.8)	10 (12.2)	1 (50.0)						
CMS4, No. (%)	696 (48.5)	626 (48.1)	27 (52.9)	43 (52.5)	0 (0.0)						
NA, No.	7266	6574	238	416	38						

[a] HRP *versus* HRD with mutations in the “core” machinery. NA = not available; mut = mutation; MSS = microsatellite stable; pMMR = proficient mismatch repair; TMB = Tumor Mutational Burden; Mb = Mega-base; CMS = Consensus Molecular Subtype. Q = Benjamini-Hochberg adjusted p value.

[b] HRP *versus* HRD with mutations in the “related” machinery

[c] HRP *versus* HRD with mutations in both “core” and “related” machinery

[d] Two-sided Mann-Whitney test.

[e] Two-sided Chi-square test.

Supplementary Table 3. Patients' characteristics based on homologous recombination-related genes alterations in the MSS/pMMR population

Characteristics	MSS/pMMR population	HRP	HRD with *ATM* mutations	HRD with *BRCA1/2* mutations	HRD with other mutations	*P*[a]	q[a]	*P*[b]	q[b]	*P*[c]	q[c]
Total No. (%)	8702 (93.6)	7875 (90.5)	275 (3.2)	129 (1.5)	378 (4.3)						
Median age (range), y	60 (14-90)	60 (14-90)	61 (20-90)	60 (24-86)	60 (27-92)	0.28[d]	0.42[d]	0.58[d]	0.71[d]	0.28[d]	0.42[d]
Sex, No. (%)											
Male	4730 (54.4)	4299 (54.6)	136 (49.5)	66 (51.2)	192 (50.8)	0.09[e]	0.28[e]	0.44[e]	0.62[e]	0.15[e]	0.29[e]
Female	3972 (45.6)	3576 (45.4)	139 (55.5)	63 (48.8)	186 (49.2)						
Primary tumor location, No.	6280	5678	275	129	378						
Left and Rectum, No. (%)	4326 (68.9)	3932 (69.2)	126 (63.6)	62 (66.7)	188 (67.9)	0.09[e]	0.28[e]	0.59[e]	0.71[e]	0.63[e]	0.71[e]
Right, No. (%)	1954 (31.1)	1746 (30.8)	72 (36.4)	31 (33.3)	89 (32.1)						
NA, No.	2422	2197	77	36	101						
RAS mutational status, No.	8697	7870	275	129	378						
mut, No. (%)	4706 (54.1)	4245 (53.9)	169 (61.5)	71 (55.0)	199 (52.6)	0.01[e]	0.06[e]	0.80[e]	0.83[e]	0.62[e]	0.71[e]
wt, No. (%)	3991 (45.9)	3625 (46.1)	106 (38.5)	58 (45.0)	179 (47.4)						
NA, No.	5	5	0	0	0						
BRAF mutational status, No.	8695	7870	275	129	378						
mut, No. (%)	598(6.9)	532 (6.8)	25 (9.1)	13 (10.1)	27 (7.2)	0.13[e]	0.29[e]	0.14[e]	0.28[e]	0.75[e]	0.81[e]
wt, No. (%)	8097 (93.1)	7338 (93.8)	250 (90.9)	116 (89.9)	349 (92.8)						
NA, No.	7	5	0	2	0						
TMB-high (≥10 mut/Mb), No.	4838	4359	168	76	208						
Yes, No. (%)	136 (2.8)	97 (2.2)	4 (2.4)	6 (7.9)	12 (5.8)	0.89[e]	0.89[e]	0.001[e]	0.007[e]	0.001[e]	0.007[e]
No, No. (%)	4702 (97.2)	4262 (97.8)	164 (97.6)	70 (92.1)	196 (94.2)						
NA, No.	3864	3516	107	53	170						
TMB (mut/Mb), No.	4838	4359	168	76	208						
Median (range)	4 (0-446)	4 (0-115)	5 (1-211)	6 (0-124)	5 (1-99)	0.07[d]	0.27[d]	<0.001[d]	0.007[d]	0.005[d]	0.03[d]
PD-L1, No.	8348	7562	261	124	357						
Yes, No. (%)	217 (2.6)	178 (2.4)	10 (3.8)	12 (9.7)	13 (3.6)	0.13[e]	0.28[e]	<0.001[e]	<0.001[e]	0.12[e]	0.28[e]
No, No. (%)	8131 (97.4)	7384 (97.6)	251 (96.2)	112 (90.3)	344 (96.4)						
NA, No.	354	313	14	5	19						
CMS subtypes, No.	1436	1301	45	22	63						
CMS1, No. (%)	139 (9.7)	122 (9.4)	5 (11.1)	1 (4.6)	8 (12.7)	0.26[e]	0.42[e]	0.186[e]	0.335[e]	0.58[e]	0.71[e]

CMS2, No. (%)	448 (31.2)	415 (31.9)	8 (17.8)	3 (13.6)	22 (34.9)
CMS3, No. (%)	153 (10.6)	138 (10.6)	6 (13.3)	3 (13.6)	4 (6.4)
CMS4, No. (%)	696 (48.5)	626 (48.1)	26 (57.8)	15 (68.2)	29 (46.0)
NA, No.	7266	6574	230	107	315

[a] HRP *versus* HRD with ATM mutations. NA: not available; N: number; mut: mutation; MSS: microsatellite stable; pMMR: proficient mismatch repair; TMB: Tumor Mutational Burden; Mb: Mega-base; CMS: Consensus Molecular Subtype. q: Benjamini-Hochberg adjusted p value. A total of 214 samples that harbored a combination of *ATM*, *BRCA1/2*, and other HRD mutations were excluded from this analysis.

[b] HRP *versus* HRD with BRCA1/2 mutations

[c] HRP *versus* HRD with other mutations

[d] Two-sided Mann-Whitney test.

[e] Two-sided Chi-square test.

Supplementary Table 4. MCP-counter analysis according to HR status

Cell population	MSS/pMMR (HRD n=135; HRP n=1283)			MSI-H/dMMR (HRD n=76; HRP n=16)		
	Fold-change (HRD/HRP)	*P*[a]	q	Fold-change (HRD/HRP)	*P*[a]	q
T cells	1.07	0.31	0.38	1.45	0.37	0.53
CD8 T cells	1.27	0.01	0.09	1.80	0.14	0.41
Cytotoxic lymphocytes	1.24	0.004	0.07	1.06	0.83	0.95
NK cells	1.05	0.46	0.46	1.42	0.18	0.41
B lineage	1.04	0.07	0.13	1.33	0.24	0.44
Monocytic lineage	1.16	0.02	0.09	1.38	0.12	0.41
Myeloid dendritic cells	1.11	0.03	0.09	1.47	0.25	0.44
Neutrophils	1.09	0.09	0.14	1.45	0.04	0.29
Endothelial cells	1.15	0.03	0.09	1.31	0.31	0.50
Fibroblasts	1.16	0.04	0.10	1.87	0.001	0.02
Immune checkpoint						
PD-1	1.16	0.03	0.39	1.07	0.42	0.56
PD-L1	1.19	0.08	0.13	1.06	0.70	0.87
PD-L2	1.02	0.14	0.18	1.74	0.16	0.41
CTLA-4	1.05	0.39	0.42	0.86	0.98	0.98
TIM-3	1.17	0.02	0.09	1.32	0.17	0.41
LAG-3	1.15	0.08	0.13	0.92	0.97	0.98

[a] The median gene expression levels were compared between each subgroup, and the fold change was calculated. To adjust P values for multiple hypothesis testing, the q values were calculated using the Benjamini–Hochberg method. Statistical tests are two-sided. HR: homologous recombination; HRD: homologous recombination deficiency; HRP: homologous recombination proficient; MSS: microsatellite stable; pMMR: mismatch repair proficient; MSI-H: microsatellite instability high; dMMR: mismatch repair deficient; q: Benjamini-Hochberg adjusted p value.

Supplementary Table 5. Patients' characteristics of the intention-to-treat and NGS cohorts of TRIBE2 population

Characteristics	Intention-to-treat cohort (N=679)	NGS cohort (N=296)	*P*
Age, No.	679	296	
Median (range), y	61 (29-75)	61 (29-75)	0.91[a]
Sex, No.	679	296	
Male, No. (%)	387 (57.0)	160 (54.1)	0.39[b]
Female, No. (%)	292 (43.0)	136 (45.9)	
ECOG-PS, No.	679	296	
0, No. (%)	582 (85.7)	267 (90.2)	0.06[b]
1-2, No. (%)	97 (14.3)	29 (9.8)	
Metastatic disease, No.	679	296	
Synchronous, No. (%)	604 (89.0)	265 (89.5)	0.79[b]
Metachronous, No. (%)	75 (11.0)	31 (10.5)	
Prior Adjuvant chemotherapy, No.	679	296	
Yes, No. (%)	15 (2.2)	5 (1.7)	0.60[b]
No, No. (%)	664 (97.8)	291 (98.3)	
Primary tumor location, No.	679	296	
Left and Rectum, No. (%)	420 (61.9)	168 (56.8)	0.13[b]
Right, No. (%)	259 (38.1)	128 (43.2)	
Mucinous histology, No.	675	294	
No, No. (%)	581 (86.1)	233 (79.3)	0.008[b]
Yes, No. (%)	94 (13.9)	61 (20.7)	
NA, No.	4	2	
Liver-only disease, No.	677	296	
Yes, No. (%)	201 (29.7)	83 (28.0)	0.60[b]
No, No. (%)	476 (70.3)	213 (72.0)	
NA, No.	2	-	
Resected primary tumor, No.	679	296	
Yes, No. (%)	346 (51.0)	234 (79.1)	<0.001[b]
No, No. (%)	333 (49.0)	62 (20.9)	
Mutational status, No.	646	289	
RAS mut, No. (%)	436 (67.5)	187 (64.7)	0.41[b]
BRAF mut, No. (%)	66 (10.2)	38 (13.1)	
RAS and *BRAF* wt, No. (%)	144 (22.3)	64 (22.2)	

NA, No.	33	7	
MS/MMR status, No.	554	287	
MSI-H/dMMR, No. (%)	26 (4.7)	16 (5.6)	0.58[b]
MSS/pMMR, No. (%)	528 (95.3)	271 (94.4)	
NA, No.	125	9	

[a] Two-sided Mann-Whitney test. ECOG-PS: Eastern Cooperative Oncology Group Performance Status; NA: not available; mut: mutated; wt: wild-type; MS: microsatellite; MMR: mismatch repair; MSI-H: microsatellite instability high; dMMR: deficient mismatch repair; MSS: microsatellite stable; pMMR: proficient mismatch repair; N: number.

[b] Two-sided Chi-square test.

Supplementary Table 6. Patients' characteristics in the TRIBE2 population

Characteristics	Overall population	MSS/pMMR population[a] (n=271)				MSI-H/dMMR population[a] (n=16)			
		HRD	HRP	*P*	q	HRD	HRP	*P*	q
Total, No. (%)	296 (100)	29 (10.7)	242 (89.3)			9 (56.3)	7 (43.7)		
Age, No.	296	29	242			9	7		
Median (range), y	61 (29-75)	64 (32-75)	61 (29-75)	0.33[c]	0.33[c]	66 (54-71)	55 (38-68)	0.081[c]	0.24[c]
Sex, No.	296	29	242			9	7		
Male, No. (%)	160 (54.1)	18 (62.1)	128 (52.9)	0.35[d]	1.0[d]	5 (55.6)	4 (57.1)	1.0[e]	1.0[e]
Female, No. (%)	136 (45.9)	11 (37.9)	114 (47.1)			4 (44.4)	3 (42.9)		
ECOG-PS, No.	296	29	242			9	7		
0, No. (%)	267 (90.2)	27 (93.1)	218 (90.1)	1.0[e]	1.0[e]	8 (88.9)	7 (100)	1.0[e]	1.0[e]
1-2, No. (%)	29 (9.8)	2 (6.9)	24 (9.9)			1 (11.1)	0 (0.0)		
Metastatic disease, No.	296	29	242			9	7		
Synchronous, No. (%)	265 (89.5)	28 (96.6)	215 (88.8)	0.33[e]	0.50[e]	8 (88.9)	7 (100)	1.0[e]	1.0[e]
Metachronous, No. (%)	31 (10.5)	1 (3.4)	27 (11.2)			1 (11.1)	0 (0.0)		
Prior Adjuvant chemotherapy, No.	296	29	242			9	7		
Yes, No. (%)	5 (1.7)	0 (0.0)	5 (2.1)	1.0[e]	1.0[e]	0 (0.0)	0 (0.0)	1.0[e]	1.0[e]
No, No. (%)	291 (98.3)	29 (100)	237 (97.9)			9 (100)	7 (100)		
Primary tumor location, No.	296	29	242			9	7		
Left and Rectum, No. (%)	168 (56.8)	16 (55.2)	143 (59.1)	0.69[d]	0.69[d]	1 (11.1)	3 (42.9)	0.26[e]	0.78[e]
Right, No. (%)	128 (43.2)	13 (44.8)	99 (40.9)			8 (88.9)	4 (57.1)		
Mucinous histology, No.	294	29	240			9	7		
No, No. (%)	233 (79.3)	20 (69.0)	194 (80.8)	0.14[d]	0.42[d]	7 (77.8)	5 (71.4)	1.0[e]	1.0[e]
Yes, No. (%)	61 (20.7)	9 (31.0)	46 (19.2)			2 (22.2)	2 (28.6)		
NA, No.	2	-	2			-	-		
Liver-only disease, No.	296	29	242			9	7		
Yes, No. (%)	83 (28.0)	8 (27.6)	68 (28.1)	0.95[d]	1.0[d]	3 (33.3)	3 (42.9)	1.0[e]	1.0[e]
No, No. (%)	213 (72.0)	21 (72.4)	174 (71.9)			6 (66.7)	4 (57.1)		
Resected primary tumor, No.	296	29	242			9	7		
Yes, No. (%)	234 (79.1)	24 (82.8)	191 (78.9)	0.81[e]	1.0[e]	7 (77.8)	6 (85.7)	1.0[e]	1.0[e]
No, No. (%)	62 (20.9)	5 (17.2)	51 (21.1)			2 (22.2)	1 (14.3)		
Mutational status[a], No.	289	28	237			9	7		
RAS mut, No. (%)	187 (64.7)	18 (64.2)	160 (67.5)	0.55[b]	0.55[b]	2 (22.2)	4 (57.1)	0.29[b]	0.43[b]
BRAF mut, No. (%)	38 (13.1)	5 (17.9)	26 (11.0)			4 (44.5)	1 (14.3)		
RAS and *BRAF* wt, No. (%)	64 (22.2)	5 (17.9)	51 (21.5)			3 (33.3)	2 (28.6)		
NA, No.	7	1	5			-	-		
TMB-high (≥10 mut/Mb)[b], No.	223	22	185			4	5		
Yes, No. (%)	19 (8.5)	3 (13.6)	7 (3.8)	0.08[e]	0.11[e]	4 (100)	4 (80.0)	1.0[e]	1.0[e]

No, No. (%)	204 (91.5)	19 (86.4)	178 (96.2)			0 (0.0)	1 (20.0)		
NA, No.	73	7	57			5	2		
TMB (mut/Mb)[b]	223	22	185			4	5		
Median (range)	6 (2 – 207)	6 (3 – 207)	5 (2 – 11)	0.008[c]	0.01[c]	37 (31 – 53)	30 (4 – 37)	0.07[c]	0.07[c]

[a] Local assessment. MSS: microsatellite stable; pMMR: proficient mismatch repair; MSI-H: microsatellite instability high; dMMR: deficient mismatch repair; HRD: homologous recombination deficiency; HRP: homologous recombination proficient; n: number; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; NA: not available; mut: mutated; wt: wild-type; TMB: Tumor Mutational Burden; Mb: Mega-base. q: Benjamini-Hochberg adjusted p value.

[b] Caris MI TumorSeek Panel.

[c] Two-sided Mann-Whitney test.

[d] Two-sided Chi-square test.

[e] Two-sided Fisher’s exact test.

Supplementary Table 7. Uni- and multivariate analyses for progression-free survival and overall survival in the MSS/pMMR* population of the TRIBE2 study

Characteristics	No. (%)	Progression-free survival					Overall survival				
		Median, months	Univariate analysis		Multivariate analysis		Median, months	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P*	HR (95% CI)	*P*		HR (95% CI)	*P*	HR (95% CI)	*P*
HR status											
HRP	242 (89)	10.4	1	0.08	1	0.07	23.8	1	0.04	1	0.07
HRD	29 (11)	13.5	0.72 (0.50 – 1.04)		0.67 (0.45 – 1.02)		40.2	0.66 (0.45 – 0.98)		0.64 (0.39 – 1.03)	
Arm											
FOLFOX+bev	147 (54)	9.6	1	0.03	1	0.001	22.3	1	0.09	1	0.11
FOLFOXIRI+bev	124 (46)	12.7	0.68 (0.53 – 0.88)		0.66 (0.51 – 0.85)		28.0	0.79 (0.60 – 1.03)		0.80 (0.60 – 1.05)	
ECOG PS											
0	245 (90)	11.2	1	0.10	1	0.16	25.2	1	0.01	1	0.03
1-2	26 (10)	8.0	1.50 (0.93 – 2.42)		1.35 (0.89 – 2.06)		17.5	1.97 (1.17 – 3.32)		1.61 (1.04 – 2.51)	
Previous Adjuvant Therapy											
No	266 (98)	10.6	1	0.97	-	-	24.1	1	0.77	-	-
Yes	5 (2)	10.4	1.02 (0.41 – 2.49)		-		29.5	0.87 (0.35 – 2.19)		-	
Time to Metastases											
Metachronous	28 (10)	11.0	1	0.58	-	-	25.5	1	0.98	-	-
Synchronous	243 (90)	10.6	1.12 (0.74 – 1.71)		-		24.1	1.01 (0.65 – 1.56)		-	
Resected Primary Tumor											
No	56 (21)	8.0	1	0.007	1	0.02	18.7	1	<0.001	1	0.001
Yes	215 (79)	11.4	0.62 (0.44 – 0.88)		0.69 (0.50 – 0.93)		26.6	0.51 (0.35 – 0.74)		0.58 (0.42 - 0.80)	0
Liver Only Disease											
No	195 (72)	9.8	1	0.08	1	0.04	21.3	1	0.006	1	0.01
Yes	76 (28)	11.9	0.79 (0.60 – 1.03)		0.74 (0.56 – 0.99)		30.1	0.67 (0.50 – 0.89)		0.66 (0.48 – 0.91)	
Site of Primary Tumor											
Right	112 (41)	9.4	1	0.11	-	-	22.5	1	0.11	-	-
Left and rectum	159 (59)	11.9	0.81 (0.62 – 1.05)		-		25.4	0.79 (0.60 – 1.05)		-	
RAS/BRAF mutational Status[b]											
All wt	56 (21)	11.3	1		-		34.0	1		1	
RAS mut	178 (67)	10.4	1.05 (0.77 – 1.44)	0.74	-	-	23.9	1.68 (1.29 – 2.30)	0.005	1.57 (1.08– 2.28)	0.02
BRAF mut	31 (12)	8.0	1.20 (0.75 – 1.93)	0.42	-	-	17.1	1.97 (1.17 – 3.34)	0.009	1.82 (1.06 – 3.12)	0.03
NA	6										
TMB-high (≥10 mutation/Mb)[b]											

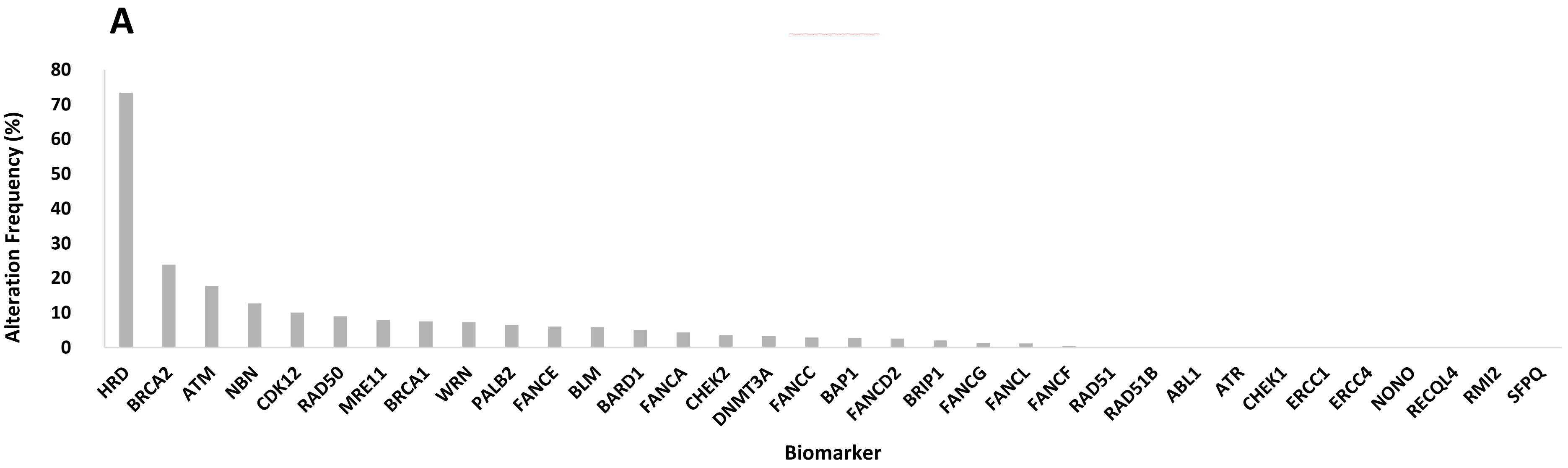
No	197 (95)	10.7	1	0.26	-	-	22.6	1	0.77	-	-
Yes	10 (5)	8.8	0.69 (0.37 – 1.31)		-		18.7	0.90 (0.44 – 1.85)		-	
NA	64										

[a] Local assessment. MSS: microsatellite stable; pMMR: proficient mismatch repair; n: number; HR: homologous recombination; HRD: homologous recombination deficiency; HRP: homologous recombination proficient; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; NA: not available; mut: mutated; wt: wild-type; TMB: Tumor Mutational Burden; Mb: Mega-base.

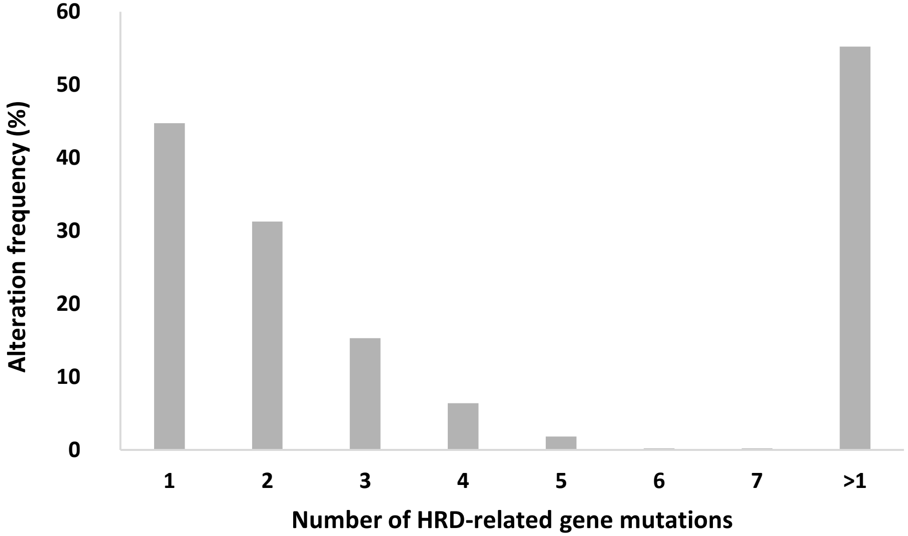
[b] Caris MI TumorSeek Panel

Supplementary Figures

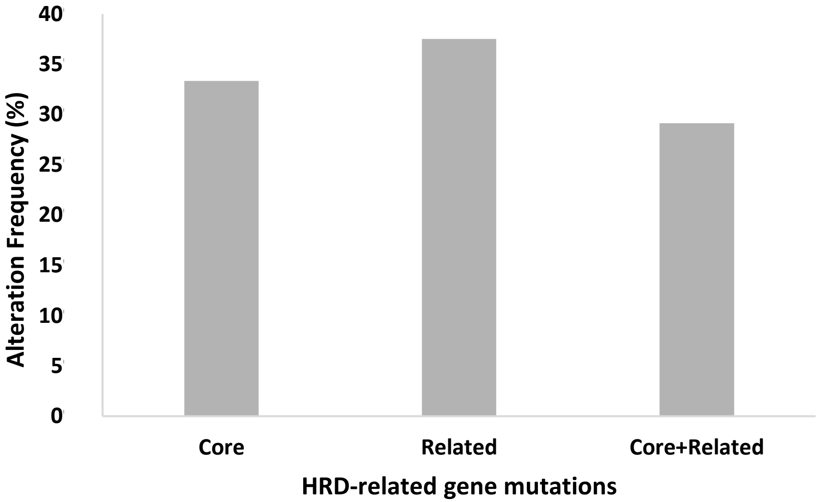
Supplementary Figure 1: Frequency of HR-related genes alterations in MSI-H/dMMR cohort of the overall population (Panel A); Frequency of tumors according to number of mutated HR-related genes in MSI-H/dMMR cohort of the overall population (Panel B); Frequency of tumors according to mutated HR-related genes belonging to “core” and “related” homologous recombination system in MSI-H/dMMR cohort of the overall population (Panel C). HR: homologous recombination; dMMR: deficient mismatch repair; MSI-H: microsatellite instability-high; MSS: microsatellite stable; pMMR: proficient mismatch repair.



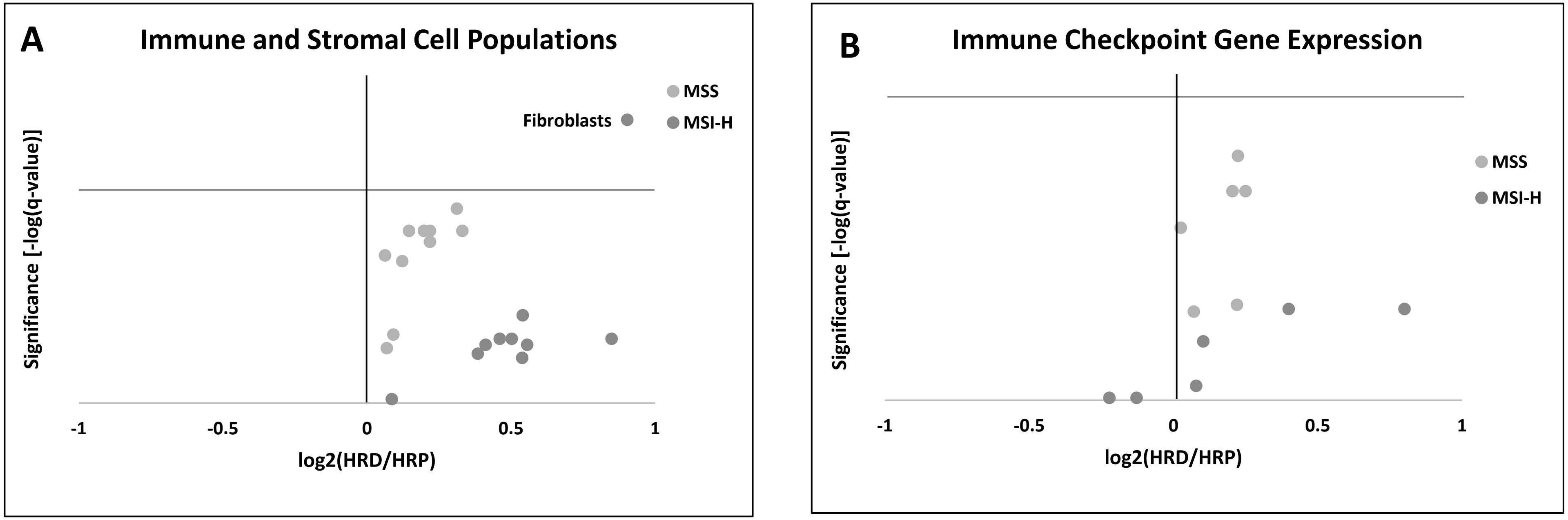
B

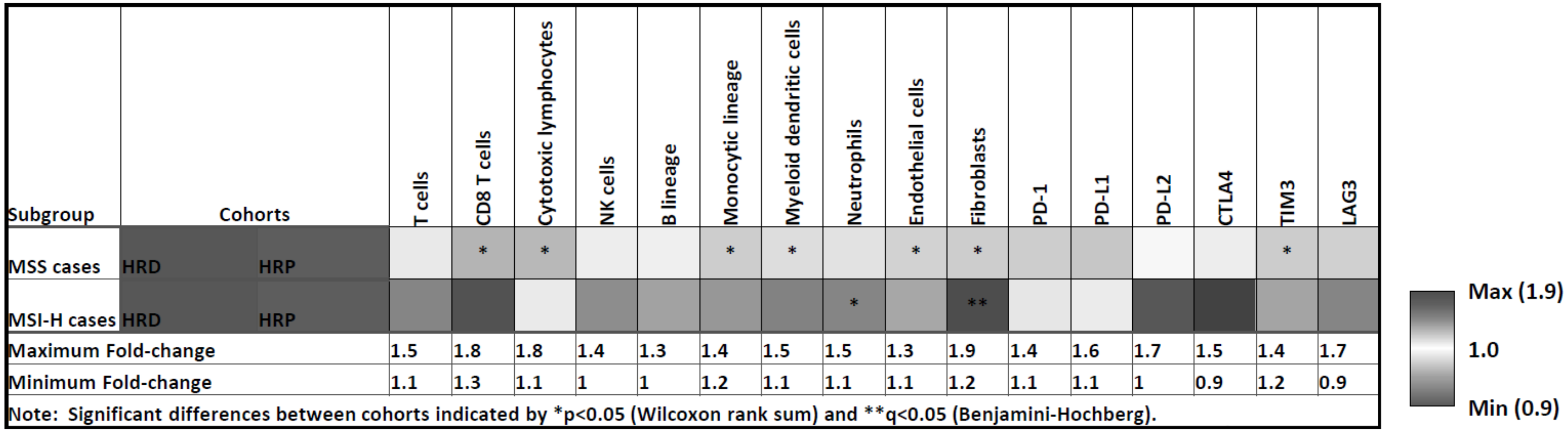

Alteration frequency (%)
60
50
40
30
20
10
0
1
2
3
4
5
6
7
>1
Number of HRD-related gene mutations

C


Alteration Frequency (%)
40
35
30
25
20
15
10
5
0
Core
Related
Core+Related
HRD-related gene mutations

Supplementary Figure 2: Immune and stromal cell populations according to HR status by the MCP-counter analysis (Panel A); Immune checkpoint gene expression according to HR status by the MCP-counter analysis (Panel B); Heatmap of fold-change (HRD/HRP) in median immune and stromal cell populations, and immune checkpoint gene expression by the MCP-counter analysis (Panel C); indicates fold-change (HRD/HRP) in median gene expression levels by the MCP-counter analysis. Darker color means higher expression levels in HRD compared to HRP, while brighter color means the opposite directions. The median gene expression levels were compared between each subgroup, and the fold change was calculated. To adjust *P* values for multiple hypothesis testing, the q values were calculated using the Benjamini–Hochberg method. Statistical tests are two-sided. HRD: homologous repair deficit; HRP: homologous repair proficient; MCP: microenvironment cell population; MSI-H: microsatellite instability-high; MSS: microsatellite stable.

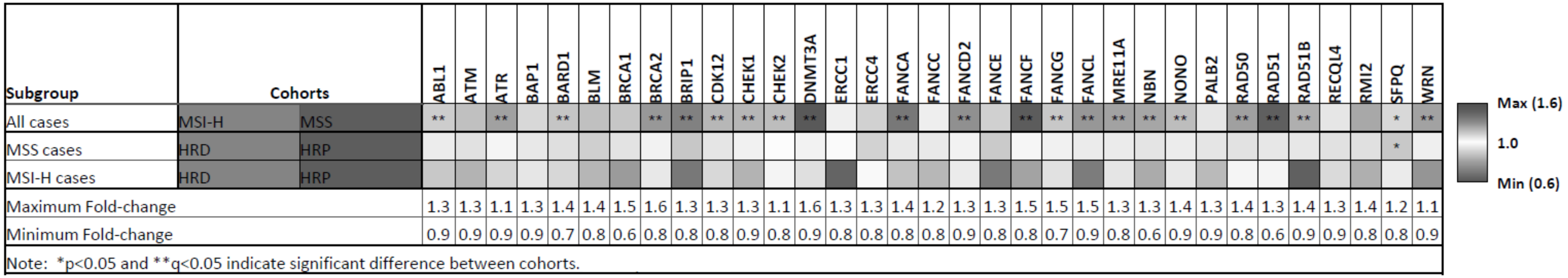




Subgroup	Cohorts		T cells	CD8 T cells	Cytotoxic lymphocytes	NK cells	B lineage	Monocytic lineage	Myeloid dendritic cells	Neutrophils	Endothelial cells	Fibroblasts	PD-1	PD-L1	PD-L2	CTLA4	TIM3	LAG3
MSS cases	HRD	HRP		*	*			*	*		*	*					*	
MSI-H cases	HRD	HRP								*		**						
Maximum Fold-change			1.5	1.8	1.8	1.4	1.3	1.4	1.5	1.5	1.3	1.9	1.4	1.6	1.7	1.5	1.4	1.7
Minimum Fold-change			1.1	1.3	1.1	1	1	1.2	1.1	1.1	1.1	1.2	1.1	1.1	1	0.9	1.2	0.9

Note: Significant differences between cohorts indicated by *p<0.05 (Wilcoxon rank sum) and **q<0.05 (Benjamini-Hochberg).

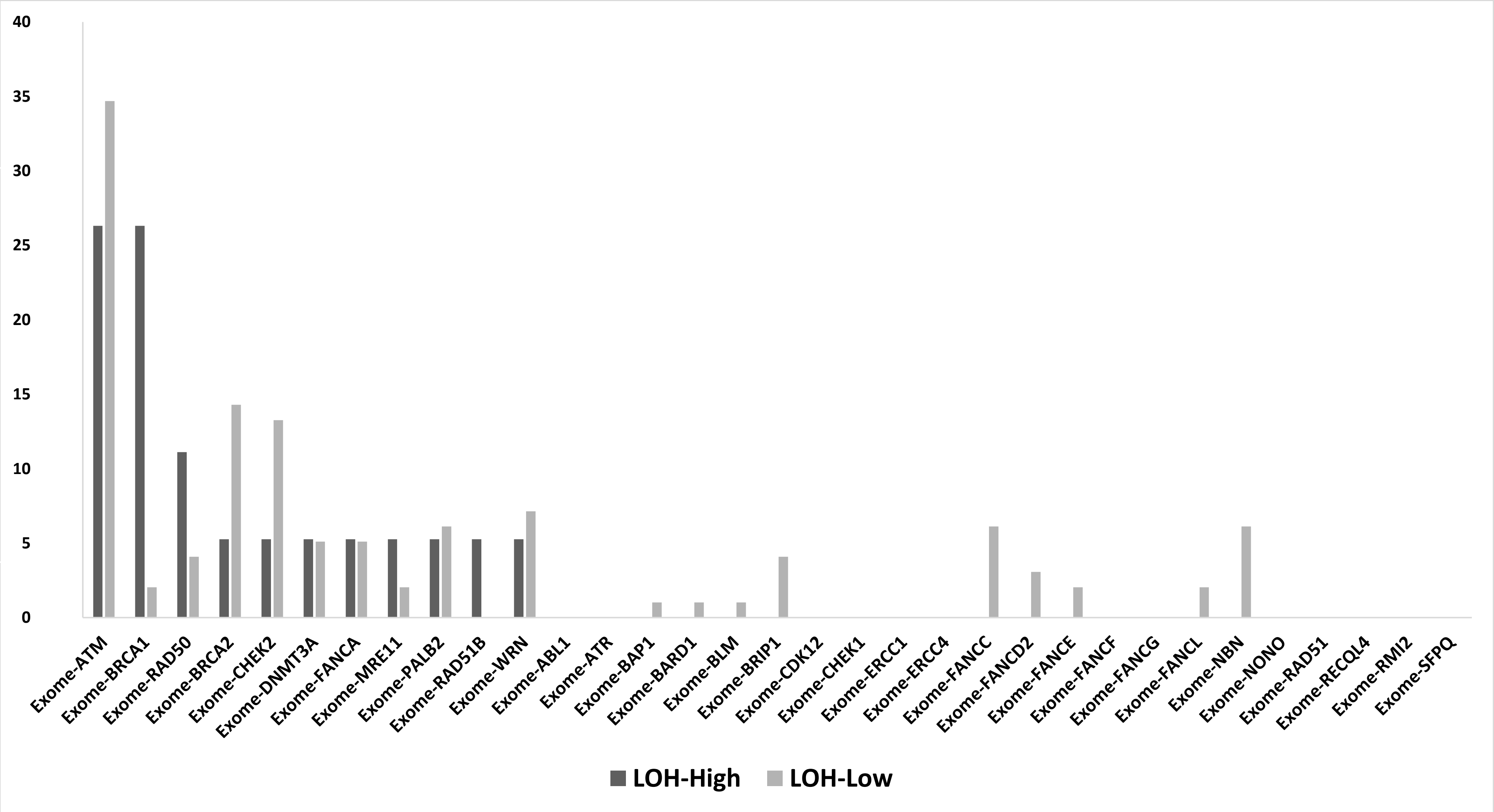
Supplementary Figure 3: Heatmap of fold-change (HRD/HRP) in median HR-related genes expression. Darker color means higher expression levels in HRD compared to HRP, while brighter color means the opposite directions. The median gene expression levels were compared between each subgroup, and the fold change was calculated. To adjust *P* values for multiple hypothesis testing, the q values were calculated using the Benjamini–Hochberg method. Statistical tests are two-sided. HR: homologous repair; HRD: homologous repair deficit; HRP: homologous repair proficient, MSI-H: microsatellite instability-high; MSS: microsatellite stable.



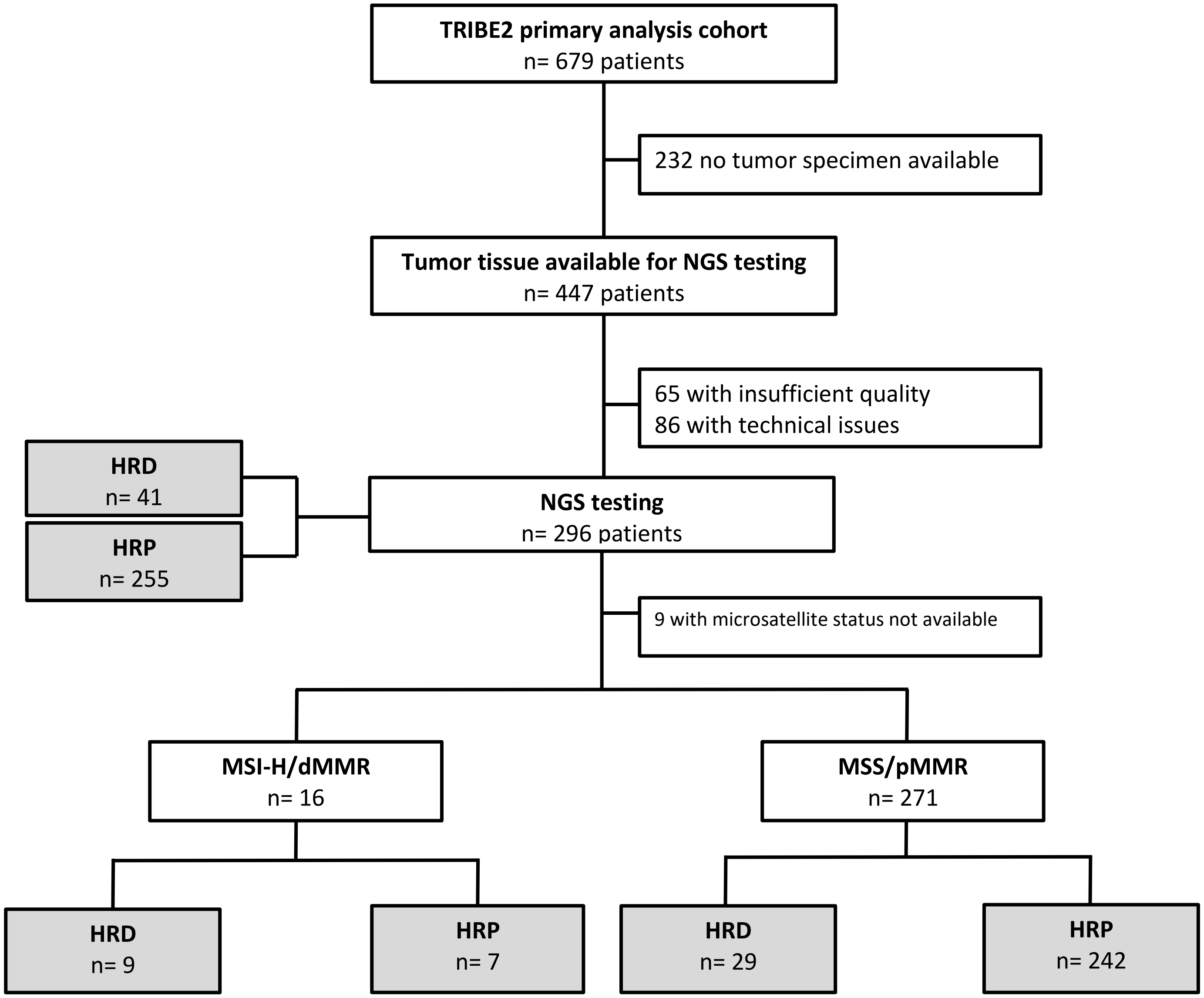
Subgroup	**Cohorts**		ABL1	ATM	ATR	BAP1	BARD1	BLM	BRCA1	BRCA2	BRIP1	CDK12	CHEK1	CHEK2	DNMT3A	ERCC1	ERCC4	FANCA	FANCC	FANCD2	FANCE	FANCF	FANCG	FANCL	MRE11A	NBN	NONO	PALB2	RAD50	RAD51	RAD51B	RECQL4	RMI2	SFPQ	WRN
All cases	MSI-H	MSS	**		**		**			**	**	**	**	**	**			**		**		**	**	**	**	**	**		**	**	**			*	**
MSS cases	HRD	HRP																																*	
MSI-H cases	HRD	HRP																																	
Maximum Fold-change			1.3	1.3	1.1	1.3	1.4	1.4	1.5	1.6	1.3	1.3	1.3	1.1	1.6	1.3	1.3	1.4	1.2	1.3	1.3	1.5	1.5	1.5	1.3	1.3	1.4	1.3	1.4	1.3	1.4	1.3	1.4	1.2	1.1
Minimum Fold-change			0.9	0.9	0.9	0.9	0.7	0.8	0.6	0.8	0.8	0.8	0.9	0.8	0.9	0.8	0.8	0.8	0.8	0.9	0.8	0.8	0.7	0.9	0.8	0.6	0.9	0.9	0.8	0.6	0.9	0.9	0.8	0.8	0.9

Note: *p<0.05 and **q<0.05 indicate significant difference between cohorts.

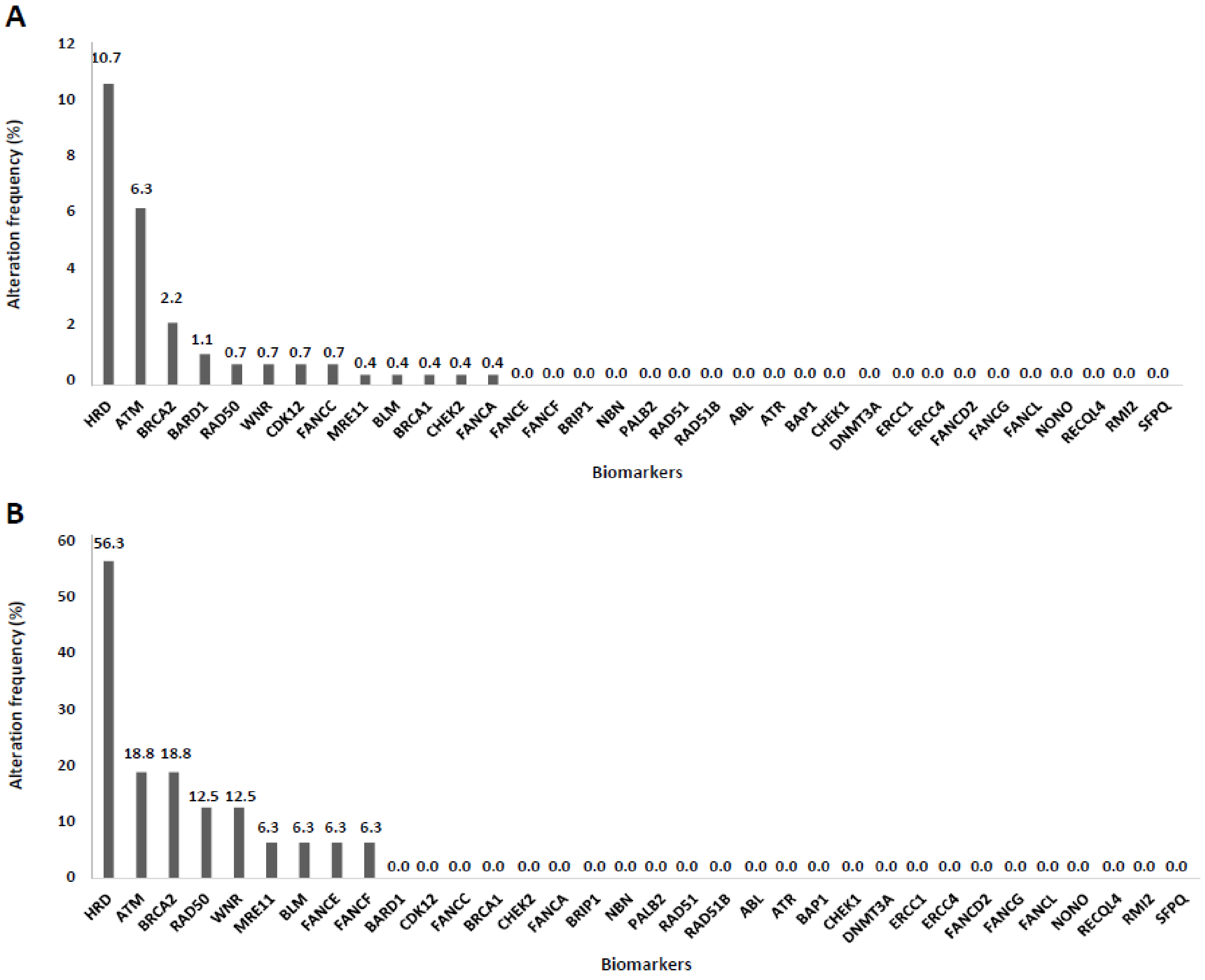
Supplementary Figure 4: Frequency of HR-related genes alterations according to loss of heterozygosity in the MSS/pMMR population. HR: homologous recombination; LOH: loss of heterozygosity; MSS: microsatellite stable; pMMR: proficient mismatch repair



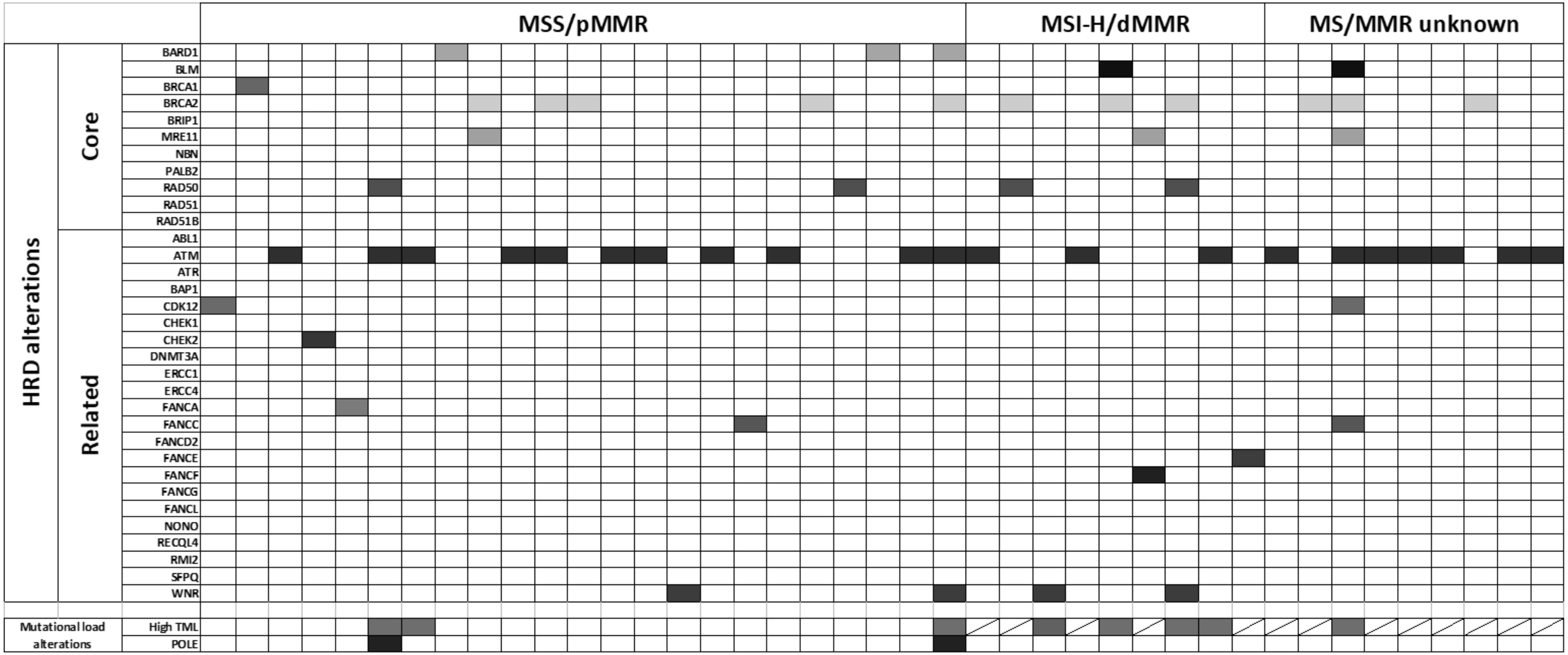
Supplementary Figure 5: Consort diagram of TRIBE2 population. dMMR: deficient mismatch repair; HRD: homologous repair deficient; HRP: homologous repair proficient; MSS: microsatellite stable; NGS: next generation sequencing; MSI-H: microsatellite instability-high; pMMR: proficient mismatch repair.



Supplementary Figure 6: Frequency of HR-related genes alterations in both MSS/pMMR (Panel A) and MSI-H/dMMR (Panel B) cohorts of the TRIBE2 population. dMMR: deficient mismatch repair; HR: homologous repair; MSS: microsatellite stable MSI-H: microsatellite instability-high; pMMR: proficient mismatch repair.

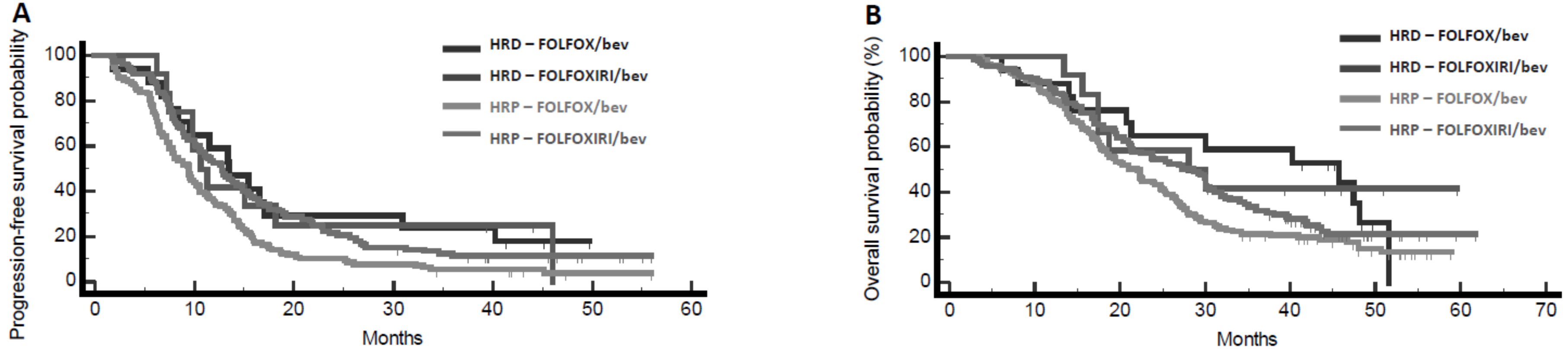


Supplementary Figure 7: Heatmap detailing HR-related genes incidence including mutational load alterations in TRIBE2 population (each column represents a patient). dMMR: deficient mismatch repair; MS: microsatellite; MSS: microsatellite stable; MSI-H: microsatellite instability-high; pMMR: proficient mismatch repair; TML: tumor mutational load



Supplementary Figure 8: Kaplan-Meier curves of progression-free survival (Panel A) and overall survival (Panel B) according to HR status and treatment arm in in MSS/pMMR patients of the TRIBE2 population. Survival curves were compared using a two-sided log-rank test. Two-sided interaction test between treatment arms and HR status is shown. Bev: bevacizumab; HR: homologous recombination; HRD: homologous recombination deficient; HRP: homologous recombination proficient; MSS: microsatellite stable; pMMR: proficient mismatch repair.

Supplementary figure 8



Number at risk (Panel A)

Group	0	10	20	30	40	50	60
Group: HRD - FOLFOX/bev	17	11	5	5	4	0	0
Group: HRD - FOLFOXIRI/bev	12	7	3	3	2	0	0
Group: HRP - FOLFOX/bev	130	56	15	10	6	1	0
Group: HRP - FOLFOXIRI/bev	112	69	32	17	8	4	0

Number at risk (Panel B)

Group	0	10	20	30	40	50	60	70
Group: HRD - FOLFOX/bev	17	15	13	11	10	1	0	0
Group: HRD - FOLFOXIRI/bev	12	12	7	5	4	2	0	0
Group: HRP - FOLFOX/bev	130	113	69	35	24	10	0	0
Group: HRP - FOLFOXIRI/bev	112	101	72	50	27	6	1	0

	HRD FOLFOX/bev n = 17	**HRD FOLFOXIRI/bev n = 12**	HRP FOLFOX/bev n = 130	HRP FOLFOXIRI/bev n = 112
Events, n (%)	14 (82.3%)	10 (83.3%)	123 (94.6%)	99 (88.4%)
Median PFS, months	**13.5**	**10.7**	9.4	12.7
HR [95% CI]	**1**	**1.07 [0.47 – 2.45]**	**1**	**0.63 [0.48 – 0.82]**
p	**0.87**		**<0.001**	
p	**0.002**			
p for interaction	**0.23**			

	HRD FOLFOX/bev n = 17	**HRD FOLFOXIRI/bev n = 12**	HRP FOLFOX/bev n = 130	HRP FOLFOXIRI/bev n = 112
Events, n (%)	12 (70.5%)	7 (58.3%)	108 (83.1%)	85 (75.9%)
Median OS, months	**45.7**	**28.0**	22.0	27.4
HR [95% CI]	**1**	**0.93 [0.37 – 2.35]**	**1**	**0.75 [0.56 – 0.99]**
p	**0.87**		**0.045**	
p	**0.04**			
p for interaction	**0.67**			