

Supplementary Table 1. RTK fusion tumor stage by microsatellite status at diagnosis and during disease course.

Microsatellite status	Total number of patients	Stage IV at presentation	Statistics (stage IV at presentation)*	Progression to stage IV	Patients with stage IV at any time point	Statistics (stage IV at any time point)*
MSS	4	3	Chi-square statistic 2.47, p = 0.09	1	4	Chi-square statistic 6, p = 0.01
MMR-D	8	2		0	2	

* Statistics compares stage distribution at diagnosis or at any time point during the clinical course between MMR-D and MSS tumors with RTK fusion.

Supplementary Table 2. Genomic classification of patients with MMR-D CRC who underwent OncoPanel testing. “Unclear category” includes patients who did not receive full testing (germline and *MLH1* hypermethylation) or who have no clear category despite receiving all available testing.

Identifier	Number of cases
<i>BRAF</i> V600E mutated	42
Lynch syndrome	29
Fusion associated	8
MLH1 promoter hypermethylation+ NOS (no <i>BRAF</i> mutation or fusion)	11
Somatic MMR gene mutation	9
Presumed Lynch syndrome	3
Unclear category	22
Total MMR-D cases with OncoPanel	124

Supplementary Table 3. List of all non-synonymous mutations identified in the alectinib-resistant sample (xenograft line) by targeted genomic testing (alphabetized by gene symbol).

Gene	Analysis tool name	Variant classification	Protein change	cDNA change	Category	Allele fraction	Coverage
ALK	MuTect	Missense	p.L1196Q	c.3587T>A	COSMIC	0.3291	939
ARID1A	MuTect	Missense	p.A226P	c.676G>C	NOVEL	0.0427	726
ARID1A	MuTect	Missense	p.P227Q	c.680C>A	NOVEL	0.0461	737
ARID1A	Phased variant	Missense	p.S317G	c.949_951delAGTinsGGC	NOVEL	0.0513	195
ARID1B	MuTect	Missense	p.M266L	c.796A>T	NOVEL	0.2658	79
ARID1B	Phased variant	Missense	p.M479L	c.1435_1437delATGinsCTA	NOVEL	0.0629	365.5
NSD1	MuTect	Missense	p.S51P	c.151T>C	NOVEL	0.0971	917
PHOX2B	MuTect	Missense	p.S172L	c.515C>T	NOVEL	0.4455	220
RNF43	GATK	Frameshift	p.A23Rfs*29	c.65_66dupAG	NOVEL	0.8834	1029
TLX3	Phased variant	Missense	p.T55A	c.163_165delACAIinsGCG	NOVEL	0.0738	562
TP53	MuTect	Missense	p.R273C	c.817C>T	COSMIC	1	827

Supplementary Table 4. Deidentified genie patient IDs and group assignment for cases used in our study.

genie_patient_id	genie_sample_id	group	fusion
GENIE-DFCI-002138	GENIE-DFCI-002138-4207	MSI-H-BRAFV600E	NA
GENIE-DFCI-007518	GENIE-DFCI-007518-3870	MSI-H-Lynch	NA
GENIE-DFCI-002491	GENIE-DFCI-002491-4412	MSI-H-Lynch	NA
GENIE-DFCI-006447	GENIE-DFCI-006447-4426	MSI-H-Lynch	NA
GENIE-DFCI-007275	GENIE-DFCI-007275-5110	MSI-H-BRAFV600E	NA
GENIE-DFCI-003366	GENIE-DFCI-003366-4666	MSI-H-BRAFV600E	NA
GENIE-DFCI-007716	GENIE-DFCI-007716-3954	MSI-H-Lynch	NA
GENIE-DFCI-008105	GENIE-DFCI-008105-7479	MSI-H-BRAFV600E	NA
GENIE-DFCI-008343	GENIE-DFCI-008343-5430	MSI-H-Lynch	NA
GENIE-DFCI-002898	GENIE-DFCI-002898-7501	MSI-H-BRAFV600E	NA
GENIE-DFCI-008662	GENIE-DFCI-008662-7261	MSI-H-BRAFV600E	NA
GENIE-DFCI-008391	GENIE-DFCI-008391-5705	MSI-H-Lynch	NA
GENIE-DFCI-001715	GENIE-DFCI-001715-7791	MSI-H-BRAFV600E	NA
GENIE-DFCI-010088	GENIE-DFCI-010088-9592	MSI-H-BRAFV600E	NA

GENIE-DFCI-009315	GENIE-DFCI-009315-6400	MSI-H-Lynch	NA
GENIE-DFCI-000581	GENIE-DFCI-000581-8947	MSI-H-BRAFV600E	NA
GENIE-DFCI-008284	GENIE-DFCI-008284-6855	MSI-H-Lynch	NA
GENIE-DFCI-010081	GENIE-DFCI-010081-8432	MSI-H-Lynch	NA
GENIE-DFCI-007921	GENIE-DFCI-007921-6428	MSI-H-BRAFV600E	NA
GENIE-DFCI-001271	GENIE-DFCI-001271-7945	MSI-H-BRAFV600E	NA
GENIE-DFCI-001632	GENIE-DFCI-001632-7453	MSS-MAPK	ROS1
GENIE-DFCI-006237	GENIE-DFCI-006237-10634	MSI-H-Lynch	NA
GENIE-DFCI-025866	GENIE-DFCI-025866-36004	MSI-H-Lynch	NA
GENIE-DFCI-010288	GENIE-DFCI-010288-10337	MSI-H-BRAFV600E	NA
GENIE-DFCI-036570	GENIE-DFCI-036570-74466	MSI-H-MAPK	NTRK
GENIE-DFCI-010561	GENIE-DFCI-010561-8376	MSI-H-BRAFV600E	NA
GENIE-DFCI-011695	GENIE-DFCI-011695-10716	MSI-H-BRAFV600E	NA
GENIE-DFCI-010400	GENIE-DFCI-010400-9865	MSI-H-BRAFV600E	NA
GENIE-DFCI-002769	GENIE-DFCI-002769-9861	MSI-H-BRAFV600E	NA

GENIE-DFCI-011222	GENIE-DFCI-011222-11823	MSI-H-BRAFV600E	NA
GENIE-DFCI-026326	GENIE-DFCI-026326-48545	MSI-H-BRAFV600E	NA
GENIE-DFCI-000408	GENIE-DFCI-000408-11450	MSI-H-Lynch	NA
GENIE-DFCI-036772	GENIE-DFCI-036772-75012	MSI-H-BRAFV600E	NA
GENIE-DFCI-034167	GENIE-DFCI-034167-74854	MSI-H-BRAFV600E	NA
GENIE-DFCI-001131	GENIE-DFCI-001131-11269	MSI-H-BRAFV600E	NA
GENIE-DFCI-010603	GENIE-DFCI-010603-9978	MSS-MAPK	ALK
GENIE-DFCI-037398	GENIE-DFCI-037398-74706	MSI-H-MAPK	NTRK
GENIE-DFCI-013270	GENIE-DFCI-013270-23816	MSI-H-Lynch	NA
GENIE-DFCI-010632	GENIE-DFCI-010632-10572	MSI-H-BRAFV600E	NA
GENIE-DFCI-048397	GENIE-DFCI-048397-173776	MSI-H-BRAFV600E	NA
GENIE-DFCI-090146	GENIE-DFCI-090146-266229	MSI-H-BRAFV600E	NA
GENIE-DFCI-094284	GENIE-DFCI-094284-710704	MSI-H-BRAFV600E	NA
GENIE-DFCI-040235	GENIE-DFCI-040235-188644	MSI-H-MAPK	NTRK
GENIE-DFCI-109336	GENIE-DFCI-109336-436649	MSS-Wnt	RSPO3

GENIE-DFCI-093572	GENIE-DFCI-093572-436863	MSI-H-MAPK	RET
GENIE-DFCI-090476	GENIE-DFCI-090476-332679	MSI-H-BRAFV600E	NA
GENIE-DFCI-051635	GENIE-DFCI-051635-173768	MSI-H-BRAFV600E	NA
GENIE-DFCI-050749	GENIE-DFCI-050749-173868	MSI-H-Lynch	NA
GENIE-DFCI-053471	GENIE-DFCI-053471-203560	MSI-H-BRAFV600E	NA
GENIE-DFCI-051206	GENIE-DFCI-051206-218966	MSI-H-BRAFV600E	NA
GENIE-DFCI-080992	GENIE-DFCI-080992-282566	MSI-H-BRAFV600E	NA
GENIE-DFCI-078731	GENIE-DFCI-078731-282097	MSI-H-Lynch	NA
GENIE-DFCI-075877	GENIE-DFCI-075877-298981	MSI-H-Lynch	NA
GENIE-DFCI-089869	GENIE-DFCI-089869-350896	MSI-H-MAPK	NTRK
GENIE-DFCI-108474	GENIE-DFCI-108474-437249	MSS-Wnt	RSPO3
GENIE-DFCI-108385	GENIE-DFCI-108385-436918	MSI-H-BRAFV600E	NA
GENIE-DFCI-109546	GENIE-DFCI-109546-437267	MSS-Wnt	RSPO3
GENIE-DFCI-095111	GENIE-DFCI-095111-526448	MSI-H-BRAFV600E	NA
GENIE-DFCI-090505	GENIE-DFCI-090505-299076	MSI-H-MAPK	BRAF

GENIE-DFCI-049001	GENIE-DFCI-049001-188660	MSS-MAPK	FGFR2
GENIE-DFCI-047001	GENIE-DFCI-047001-249650	MSI-H-BRAFV600E	NA
GENIE-DFCI-095498	GENIE-DFCI-095498-617835	MSI-H-Lynch	NA
GENIE-DFCI-107816	GENIE-DFCI-107816-437112	MSS-Wnt	RSPO3
GENIE-DFCI-101032	GENIE-DFCI-101032-437131	MSI-H-BRAFV600E	NA
GENIE-DFCI-038987	GENIE-DFCI-038987-234186	MSI-H-MAPK	RET
GENIE-DFCI-093804	GENIE-DFCI-093804-436973	MSI-H-BRAFV600E	NA
GENIE-DFCI-111370	GENIE-DFCI-111370-617780	MSI-H-Lynch	NA
GENIE-DFCI-108472	GENIE-DFCI-108472-526288	MSI-H-Lynch	NA
GENIE-DFCI-050991	GENIE-DFCI-050991-203536	MSS-Wnt	RSPO3
GENIE-DFCI-092813	GENIE-DFCI-092813-282053	MSS-Wnt	RSPO3
GENIE-DFCI-087455	GENIE-DFCI-087455-266370	MSI-H-BRAFV600E	NA
GENIE-DFCI-148146	GENIE-DFCI-148146-1525798	MSI-H-Lynch	NA
GENIE-DFCI-118359	GENIE-DFCI-118359-757698	MSS-MAPK	NRG1
GENIE-DFCI-136048	GENIE-DFCI-136048-1099701	MSI-H-BRAFV600E	NA

GENIE-DFCI-132242	GENIE-DFCI-132242-1469723	MSI-H-BRAFV600E	NA
GENIE-DFCI-168441	GENIE-DFCI-168441-1786805	MSI-H-Lynch	NA
GENIE-DFCI-094914	GENIE-DFCI-094914-901995	MSI-H-BRAFV600E	NA
GENIE-DFCI-113227	GENIE-DFCI-113227-950834	MSI-H-Lynch	NA
GENIE-DFCI-136454	GENIE-DFCI-136454-1049720	MSI-H-BRAFV600E	NA
GENIE-DFCI-174511	GENIE-DFCI-174511-1729387	MSI-H-Lynch	NA
GENIE-DFCI-118438	GENIE-DFCI-118438-805357	MSS-Wnt	RSPO3
GENIE-DFCI-136476	GENIE-DFCI-136476-1304448	MSI-H-Lynch	NA
GENIE-DFCI-124208	GENIE-DFCI-124208-1358755	MSI-H-MAPK	ALK
GENIE-DFCI-111511	GENIE-DFCI-111511-757556	MSI-H-BRAFV600E	NA
GENIE-DFCI-183743	GENIE-DFCI-183743-2839119	MSI-H-Lynch	NA
GENIE-DFCI-203700	GENIE-DFCI-203700-2518580	MSI-H-Lynch	NA