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Original Article

RET fusions in a small subset of advanced colorectal cancers at risk of being neglected

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ABSTRACT

Background: Recognition of rare molecular subgroups is a challenge for precision oncology and may lead to tissue-agnostic approval of targeted agents. Here we aimed to comprehensively characterize the clinical, pathological and molecular landscape of *RET* rearranged metastatic colorectal cancer (mCRC).

Patients and methods: In this case series, we compared clinical, pathological and molecular characteristics of 24 *RET* rearranged mCRC patients with those of a control group of 291 patients with *RET* negative tumors. *RET* rearranged and *RET* negative mCRCs were retrieved by systematic literature review and by taking advantage of three screening sources: 1) Ignyta's phase 1/1b study on RXDX-105 (*NCT01877811*); 2) cohorts screened at two Italian and one South Korean Institutions; 3) Foundation Medicine Inc. database. Next generation sequencing data were analyzed for *RET* rearranged cases.

Results: *RET* fusions were more frequent in older patients (median age of 66 vs. 60 years, p=0.052), with ECOG PS 1-2 (90% vs. 50%, p=0.02), right-sided (55% vs. 32%, *P*=0.013), previously unresected primary tumors (58% vs. 21%, *P*<0.001), *RAS* and *BRAF* wild-type (100% vs. 40%, p<0.001) and MSI-high (48% vs. 7%, *P*<0.001). Notably, 11 (26%) out of 43 patients with right-sided, *RAS* and *BRAF* wild-type tumors harbored a *RET* rearrangement.

At a median follow-up of 45.8 months, patients with *RET* fusion-positive tumors showed a significantly worse OS when compared with *RET*-negative ones (median OS 14.0 vs. 38.0 months, HR: 4.59; 95% CI, 3.64-32.66; *P*<0.001). In the multivariable model, *RET* rearrangements were still associated with shorter OS [HR: 2.97; 95% CI, 1.25-7.07; *P*=0.014], while primary tumor location, *RAS* and *BRAF* mutations and MSI status were not.

Conclusions: Though very rare, *RET* rearrangements define a new subtype of mCRC that shows poor prognosis with conventional treatments and is therefore worth of a specific management.

Key words: RET, colorectal cancer, gene fusions, targeted therapy, MSI-high, prognosis

Key message: RET fusions are significantly associated with right sided, MSI-high, RAS/BRAF wild-type metastatic colorectal cancer, and with an independent poor prognostic impact on survival. This molecular subtype is at risk of being neglected due to its rarity, but it is worth of being screened in clinically and molecularly defined populations to potentially achieve benefit from RET targeting strategies.

INTRODUCTION

Gene fusions are found in about 1% of metastatic colorectal cancers (mCRC) and represent potentially actionable therapeutic targets [1,2]. Phylogenetically-related *ALK*, *ROS1* and *NTRK1-3* fusions are associated with specific clinical/molecular features and poor prognosis of mCRCs [3]. Tyrosine kinase inhibitors (TKI) such as entrectinib [4] or ceritinib [5] have shown clinical activity in this molecular subgroup and entrectinib received a tissue-agnostic FDA breakthrough therapy designation for advanced cancers bearing *NTRK1-3* fusions.

RET fusions have been described in a variety of solid tumors including thyroid, non-small cell lung cancer and a small fraction (<1%) of CRCs [6,7,8]. RET over-expression is associated with primary resistance to anti-EGFR agents in *RAS* and *BRAF* wild-type CRC preclinical models [2], whereas *RET* fusions may be drugged by multi-targeted TKIs such as regorafenib and cabozantinib, or novel selective inhibitors such as RXDX-105.

Here we carried out a multinational effort aimed at unveiling the clinical and molecular landscape of mCRCs harboring *RET* fusions, in order to potentially help physicians to identify those tumors more likely to be *RET* rearranged and potentially screen an enriched subgroup rather than all comers.

MATERIALS AND METHODS

Patient population

RET rearranged mCRC cases were retrieved by systematic literature review and by taking advantage of three screening sources (**Figure 1**): 1) Ignyta's phase 1/1b study on RXDX-105 (*NCT01877811*); 2) cohorts screened at two Italian and one South Korean Institutions; 3) Foundation Medicine database. We were able to retrieve data for 24 *RET* fusion-positive mCRCs and we compared them with a cohort of 291 *RET* negative ones. Clinical, pathological and molecular characteristics at the time of diagnosis of mCRC were collected, including age, gender, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), primary tumor location, primary tumor resection, time-to-metastases, microsatellite instability (MSI) and next-generation sequencing data.

All patients signed a written informed consent and this study was centrally approved by the Institutional Review Board of Fondazione IRCCS Istituto Nazionale dei Tumori of Milan

Patients screening and molecular analyses

Independently from fluorescent in-situ hybridization (FISH) or immunohistochemistry (IHC) pre-screening, all *RET* fusions were confirmed by means of comprehensive genomic profiling [9] or RNA sequencing, as previously described [3].

Supplementary Table S1 available at *Annals of Oncology* online, reports the list of patients bearing *RET* fusions with screening source, retrieving source, identified gene fusion and NGS panel used.

FISH and IHC analysis

FISH analysis was carried out in 3 available cases (*NCOA4-RET*, *CCDC6-RET* and the novel *SNRNP70-RET*) by means of a commercially available break-apart (ZytoLight ® SPEC *RET* Dual Color Break Apart Probe) gene-specific probe at the 10q11.21, according to the manufacturer's protocol. The probe was specifically designed so to identify any rearrangement involving *RET*, regardless of the partner gene. At least 100 tumor cells were evaluated for each sample following the criteria: a)

two or more fusion orange and green signals (yellowish) indicated *RET* wild type (*RET*-WT); b) one or more fusion yellowish signals (*RET*–WT), along with separate green and orange signals, identified *RET* rearrangements. IHC analysis was performed as previously described [10].

Statistical analyses

We investigated the association of *RET* rearrangements with the following variables collected at the diagnosis of mCRC: age, gender, ECOG performance status (0, ≥1), primary tumour location (right colon, left colon, rectum), primary tumour resection, time to metastases (synchronous, metachronous), *RAS* and *BRAF* status (mutated, wild-type), MSI status (MSS, MSI-high). Fisher's exact test, $\chi 2$ test or Mann-Whitney tests were used when appropriate to assess the associations of *RET* rearrangements with investigated characteristics. We investigated the impact of *RET* rearrangements on overall survival (OS), defined as the time from diagnosis of metastatic disease to death or last follow up for alive patients. OS analysis was determined according to the Kaplan-Meier method and survival curves were compared using the log-rank test. Statistical significance was set at P=0.05 for a bilateral test. The correlation of *RET* status and clinicopathological characteristics with OS was assessed in univariate analysis. In order to minimize the bias of multiple comparisons, according to the false discovery rate correction [11], statistical significance was set at P=0.006 for a bilateral test. Cox proportional hazard model was adopted in the multivariate analysis, including as covariates variables correlated with survival with P<0.1 in the univariate analyses. All analyses were carried out by means of Prism 7 for Mac OS X v7.0.

RESULTS

Clinical, pathological and molecular features of RET rearranged mCRC patients

The list and prevalence of specific fusions (mainly *NCOA4-RET* and *CCDC6-RET*) is detailed in **Figure 1** and the two novel fusions (*TNIP1-RET* and *SNRNP70-RET*) are depicted in **supplementary Figure S1** available at *Annals of Oncology* online.

As shown in **Table 1**, *RET* fusions were more frequent in older patients (median age: 66 vs. 60 years, *P*=0.052), with ECOG PS 1-2 (90% vs. 50%, *P*=0.02), right-sided (55% vs. 32%, *P*=0.013) and unresected primary tumors (58% vs. 21%, *P*<0.001). Regarding molecular features, all *RET* rearranged samples were *RAS* and *BRAF* wild-type (100% vs. 40%, *P*<0.001) and a higher proportion was MSI-high (48% vs. 7%, *P*<0.001). Notably, 11 (26%) out of 43 patients with right-sided, *RAS* and *BRAF* wild-type tumors harbored a *RET* rearrangement. These patients had approximately 10-fold higher chances of harboring *RET* rearrangements (OR: 9.59; 95%CI, 3.69-24.91; *P*<0.001). When considering also MSI status, 6 (67%) out of 9 patients with right-sided, *RAS* and *BRAF* wild-type, and MSI-high tumors harbored a *RET* rearrangement. These patients had approximately 23-fold higher chances of harboring *RET* rearrangements (OR: 23.18; 95%CI, 5.32-100.98; *P*<0.001).

Despite being intra-chromosomal inversions (**Figure 2**, panel A), both *CCDC6-RET* and *NCOA4-RET* fusions were detectable with immunohistochemistry (**Figure 2**, panel B) or fluorescent in-situ hybridization (**Figure 2**, panels C-D). Next-generation sequencing analyses (**Figure 2**, panel E) revealed a high prevalence of potentially targetable *RNF43*/*ZNRF3* mutations or DNA repair genes mutations in the MSI-high subset.

Prognostic role of RET rearrangements

At a median follow-up of 45.8 months, patients with *RET*-positive mCRC showed a significantly worse median OS when compared with *RET*-negative ones (14.0 vs. 38.0 months, HR: 4.59; 95% CI, 3.64-32.66; *P*<0.001) (**Figure 3**). When applying the false discovery rate correction, the association of *RET* rearrangements with OS was still significant (*P*<0.006). In the multivariable model (**Table 2**) including other covariates associated with OS with *P*<0.1 (age, ECOG PS, primary tumor location, primary resection, *RAS* and *BRAF* mutations and MSI), *RET* rearrangements were still associated with shorter OS [HR: 2.97; 95% CI, 1.25-7.07; *P*=0.014], while primary tumor location, *RAS* and

BRAF mutations and MSI status were not (**Table 2**). Patients bearing *RET* rearrangements had shorter OS than those with negative tumors in both right- (HR: 3.06; 95% CI, 1.77-27.81; *P*=0.006) and left-sided tumors (HR: 3.59; 95% CI, 2.39-63.9; *P*=0.003), and in both MSI-high (HR: 2.78; 95% CI, 1.10-11.79; *P*=0.040) and MSS ones (HR: 45.76; 95% CI, 4.45-123.60; *P*<0.001) (**Figure 4**).

Predictive role of RET rearrangements

Only one patient with right sided, MSS *RET*-positive mCRC received an anti-EGFR-based therapy and rapidly progressed. Conversely, an immunotherapy-naïve patient affected by a right sided, MSI-high and *CCDC6-RET* positive mCRC achieved a complete response to RXDX-105 and is currently progression-free after more than 19 months of therapy (**supplementary Figure S2** available at *Annals of Oncology* online).

When excluding from OS analysis patients treated with RXDX-105 during the course of their disease, the negative prognosis of *RET*-positive patients was similarly evident (10.0 vs. 38.0 months, HR: 4.57; 95% CI, 3.48-32.64; *P*<0.001; figure not shown).

DISCUSSION

The cost-effectiveness of assessing rare actionable targets may be questionable in the daily clinical practice. Even if the incidence of *RET* fusions in mCRC patients is extremely low [6,7,8], individuals harboring such actionable target may be suitable candidates for a personalized management strategy. Here we provide evidence that more than two out of three right-sided, *RAS* and *BRAF* wild-type and MSI-high mCRCs bear a *RET* fusion, thus leading to highly recommend RET immunohistochemical/FISH screening or even comprehensive genomic profiling in these cases. The association of specific gene fusions with MSI-high status has been shown by our previous work [3] and is confirmed here also for *RET* fusions. Resembling to BRAF V600E mutations [12], *RET* fusions independently predict a poorer prognosis of mCRC patients, thus underlining the importance of early recognition of these alterations so as not to miss the opportunity to adopt a

targeted strategy in these patients, instead of choosing conventional and mostly ineffective treatment options.

The potential negative predictive impact of *RET* fusions with respect to anti-EGFR agents has been proposed by preclinical and case-control studies [2,13]. Even if the strength of this evidence is low, acknowledging the limited possibility of a further validation of *RET* fusion as a negative predictive biomarker due to its rarity, physicians should be to encouraged to enroll patients in trials with RET inhibitors, instead of using all available treatment lines including anti-EGFR agents. Basket design trials in multiple tumor types could be appropriate and potentially lead to tissue-agnostic drug approvals. Considering RET as a therapeutic target might be a practice-changing strategy in this poor prognosis subtype, leading to a new precision oncology field that should not be limited to mCRC, but is indeed under development in non-small cell lung cancer, thyroid cancer and neuroendocrine tumors, among others [14-16]. It should be pointed out that regorafenib showed signs of activity in a case of *RET* rearranged mCRC [6]. The selective, VEGFR-sparing RET inhibitors RXDX-105, BLU-667 and LOXO-292 may be the most promising agents. Even if the hypermutant status found in MSI-high tumors was proposed as a potential mechanism of *de novo*/rapid resistance to anti-EGFRs [13], here we report a long-lasting complete response to selective RET inhibition in a MSI-high mCRC. On the contrary, the impact of gene fusions on response to immunotherapy of MSI-high cancers has not been explored, even if negative prognostic markers such as *BRAF* mutations did not seem to affect immunotherapy efficacy [17]. The combination of targeted therapy and immunotherapy might represent a successful strategy in the subset of patients with *RET* fusion-positive and MSI-high mCRC.

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DISCLOSURE

A.S., K.G., G.M.F., V.M. and S.A. are employees and have equity interest in Foundation Medicine, Inc.

J.C. and R.P. are employees and have equity interest in Ignyta, Inc.

All other authors declare no potential competing interests.

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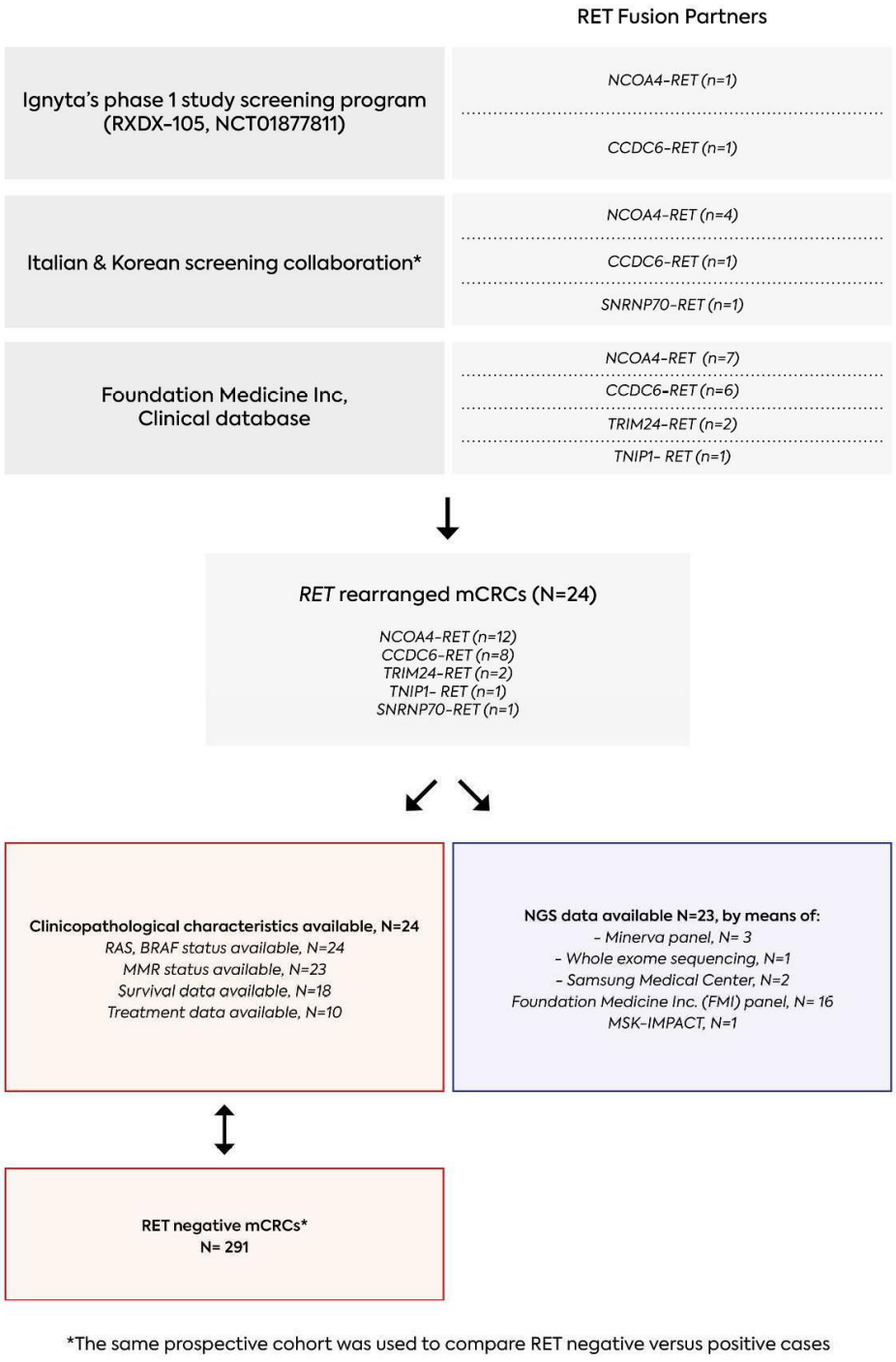
FIGURE LEGENDS

Figure 1. Study flow-chart. A total of 24 metastatic colorectal cancer (mCRC) cases with *RET* translocations were collected. Patients were retrieved by: Ignyta's phase 1 screening program; Italian and Korean screening collaboration; Foundation Medicine Inc. (FMI) dataset in USA. Clinicopathological characteristics, *RAS* and *BRAF* status, Mismatch-repair (MMR) status, survival and treatment outcome data in the *RET* rearranged population (*N*=24) were compared with those from a cohort of *RET* negative mCRC patients (*N*=291) included in the Italian and Korean screening collaboration program. Annotated genetic variants were retrieved from targeted next-generation sequencing analyses of tumor samples (*N*=23) from *RET* rearranged mCRC patients. The number of samples analyzed by different gene panels is shown.

Figure 2. Screening methods and next generation sequencing analyses of *RET* rearranged cases. **Panel A** illustrates an ideogram of chromosome 10, showing a physical map of region 10q11.21-21.2 with the precise localization of *RET*, *NCOA4*, and *CCDC*; **Panel B** depicts results of immunoistochemical approach in a sample harboring a confirmed *RET* rearrangement; **Panel C-D** confirm the presence of *RET* rearrangements by FISH analysis on samples, identified as carrying *CCDC6-RET* and *NCOA4-RET* fusions, respectively. **Panel E** shows the OncoPrint map depicting alterations in top mutated colorectal cancer genes in *RET* rearranged cancers. Individual sample cases are designated by rows (left) and grouped by MSI status, while individual genes are presented by columns. Alterations in *POLE*, *BRAF* and *HRAS* are either frameshift variants in MSI-high tumors, or likely passenger mutations. Missense mutations are classified as likely driver or likely passenger according to the scores resulting by Poly-phen2 and Mutation Assessor tools.

Figure 3. Survival in metastatic colorectal cancer patients carrying *RET* rearranged tumors. Kaplan-Meier curves for overall survival (OS) in patients with *RET* rearrangements (red line) as compared with those with *RET* negative tumors (blue line).

Figure 4. Survival in metastatic colorectal cancer patients in subgroups defined by *RET* rearrangements plus primary tumor location or MSI status. Panel A shows Kaplan-Meier curves for overall survival (OS) in patients with left-sided primary and *RET* rearranged tumors as compared to those with left-sided primary and *RET* negative tumors and in patients with right-sided primary and *RET* rearranged tumors as compared to those with right-sided primary and *RET* negative tumors. **Panel B** shows Kaplan-Meier curves for overall survival (OS) in patients with MSS and *RET* rearranged tumors as compared to those with MSS and *RET* negative tumors and in patients with MSI-high and *RET* rearranged tumors as compared to those with MSI-high and *RET* negative tumors.



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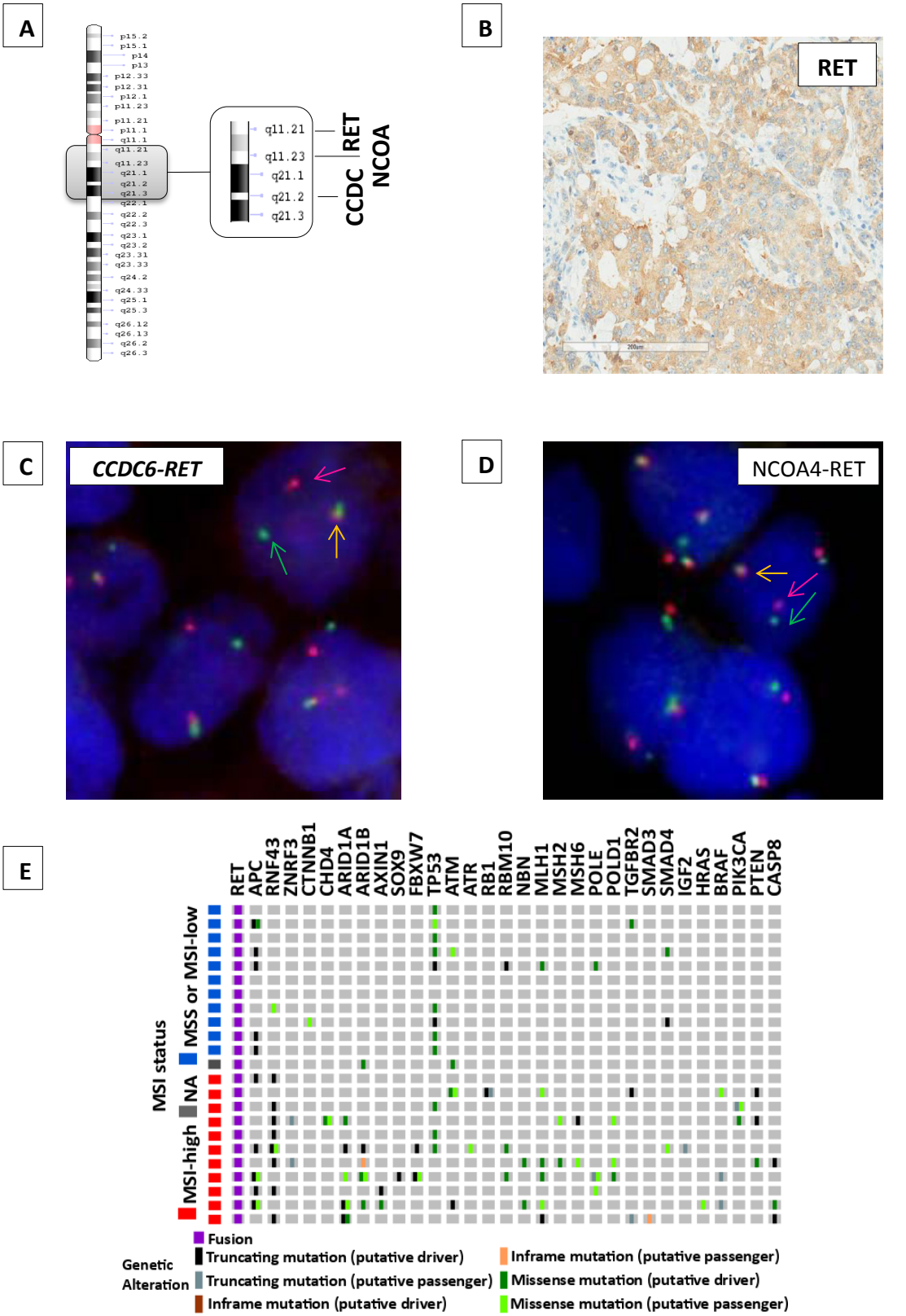

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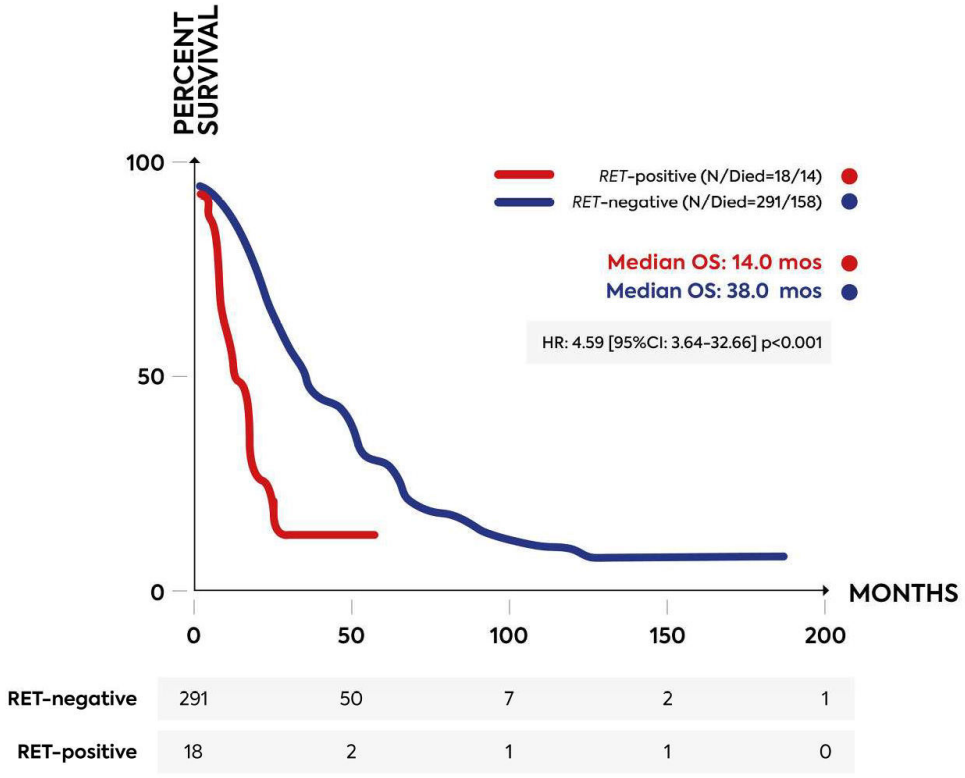

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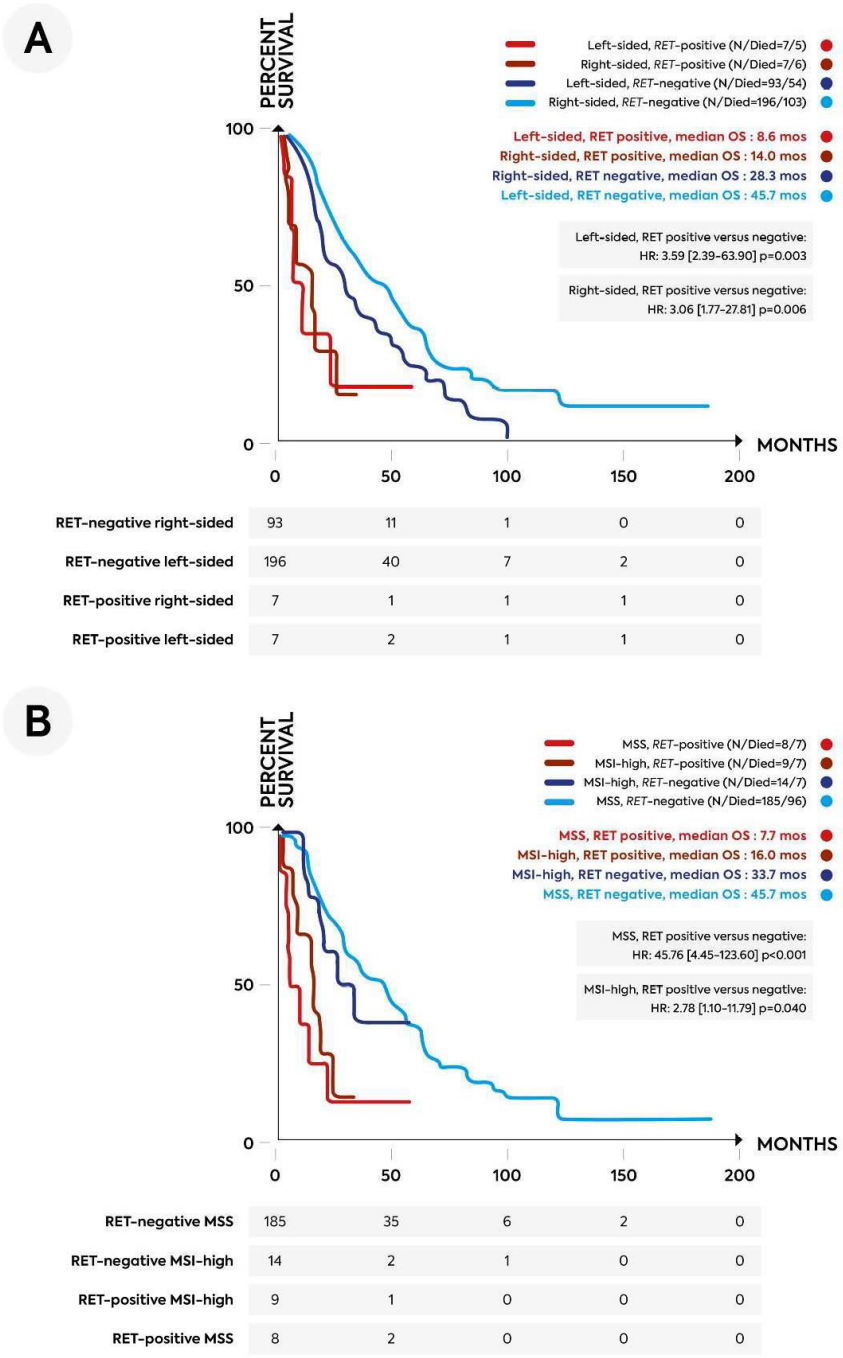

Figure 4. Survival in metastatic colorectal cancer patients in subgroups defined by RET rearrangements plus primary tumor location or MSI status. Panel A shows Kaplan-Meier curves for overall survival (OS) in patients with left-sided primary and RET rearranged tumors as compared to those with left-sided primary and RET negative tumors and in patients with right-sided primary and RET rearranged tumors as compared to those with right-sided primary and RET negative tumors. Panel B shows Kaplan-Meier curves for overall survival (OS) in patients with MSS and RET rearranged tumors as compared to those with MSS and RET negative tumors and in patients with MSI-high and RET rearranged tumors as compared to those with MSI- high and RET negative tumors.

Table 1. Patients' and disease characteristics according to the presence or absence of RET rearrangements.

Characteristics		**RET Negative** (*N*=291) *N* (%)	**RET Rearranged** (*N*=24) *N* (%)	**OR [95% CI]**	***P*[a]**
Sex	Male	172 (59)	10 (42)	1	0,131
	Female	119 (41)	14 (58)	2,02 [0,87-4,71]	
Age	Median (range)	60 (17-88)	66 (25-80)	-	**0,052**
	< 65 years	187 (64)	10 (42)	1	**0,031**
	> 65 years	104 (36)	14 (58)	2,52 [1,08-5,87]	
ECOG PS	0	143 (50)	1 (10)	1	**0,020**
	1-2	142 (50)	9 (90)	9,06 [1,13-72,48]	
	NA	6	14		
Primary tumor location	Left colon / Rectum	114/82 (39/28)	9/0 (45/0)	1	
	Right colon	93 (32)	11 (55)	2,58 [1,03-6,43]	**0,049**
	NA	2	4		
Primary tumor resected	Yes	230 (79)	10 (42)	1	**<0,001**
	No	61 (21)	14 (58)	5,28 [2,24-12,46]	
Time to metastases	Synchronous	195 (67)	19 (79)	1	
	Metachronous	96 (33)	5 (21)	0,53 [0,19-1,48]	0,262
RAS and BRAF status	*BRAF* mutated	26 (10)	0 (0)	-	
	RAS mutated	127 (46)	0 (0)		**<0,001**
	All wild-type	122 (44)	23 (100)		
MSI status	NA	16	0		
	MSS	185 (93)	12 (52)	1	
	MSI-high	14 (7)	11 (48)	12,1 [4,54-32,34]	**<0,001**
	NA	92	1		

List of abbreviations: ECOG, Eastern Cooperative Oncology Group; MSI-high, microsatellite instability-high; MSS, microsatellite-stable; NA, not available.

[a] *P* values were based on Fisher's exact test, χ^2, or Mann-Whitney tests, whenever appropriate.

All statistical tests were two-sided.

Table 2. Association of RET rearrangements and known prognostic baseline characteristics with overall survival.

				Univariable analysis			Multivariable analysis		
Characteristics		**Median**	***N***	HR	95% CI	*P*	HR	95% CI	*P*
RET status	Negative	38.0	236	1	-	-	1	-	-
	Rearranged	14.0	18	4.59	3.64 - 32.66	**<0.001**	2.97	1.25 - 7.07	**0.014**
Primary tumor cation	Left colon/Rectum	42.1	203	1	-	-	-	-	-
	Right colon	27.4	99	1.56	1.17 - 2.3	**0.005**	1.41	0.92 - 2.15	0.112
Age	< 65 years	36.7	195	1	-	-	1	-	-
	> 65	33.4	113	1.40	1.04 - 2.00	**0.030**	1.00	0.65 - 1.53	0.995
ECOG PS	0	47.5	144	1	-	-	1	-	-
	1-2	33.3	151	1.57	1.17 - 2.18	**0.034**	1.87	1.24 - 2.84	**0.003**
Primary resection	Yes	38.9	237	1	-	-	1	-	-
	No	23.0	72	1.70	1.27 - 2.89	**0.002**	2.18	1.32 - 3.59	**0.002**
Time to resection	Metachronous	47.1	99	1	-	-	-	-	-
	Synhronous	29.7	210	1.19	0.86 - 1.63	0.293	-	-	-
RAS and BRAF status	BRAF mutated	18.0	26	1	-		1	-	
	RAS mutated	36.2	127	0.51	0.22 - 0.82	**0.054**	0.74	0.53 - 1.04	**0.083**
	All wild-type	38.0	140	0.64	0.33 - 1.07		0.80	0.50 - 1.08	
MSI status	*MSS*	42.1	193	1	-	-	1	-	-
	MSI-high	20.0	23	1.79	1.06 - 4.36	**0.036**	1.31	0.44 - 1.69	0.379

List of abbreviations: ECOG, Eastern Cooperative Oncology Group; MSI-high, microsatellite instability-high; MSS, microsatellite-stable; NA, not available.
All statistical tests were two-sided.

SUPPLEMENTARY DATA

RET fusions in a small subset of advanced colorectal cancers at risk of being neglected

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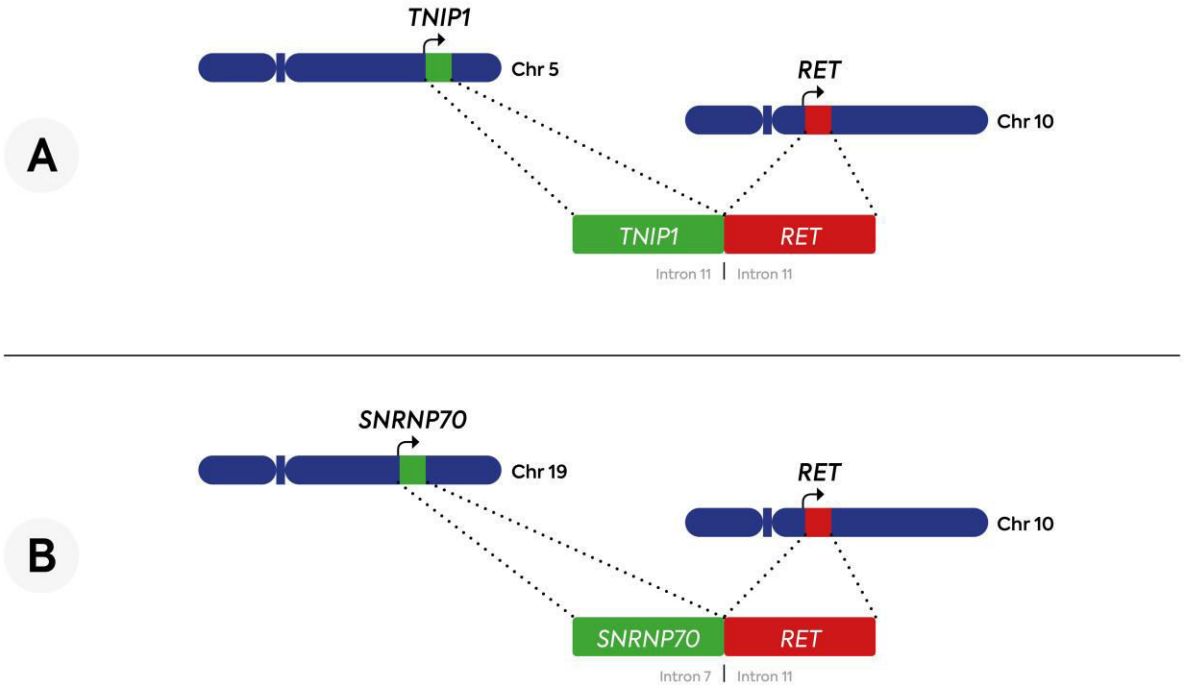
Supplementary Table S1. List of patients bearing *RET* fusions with screening source, retrieving source, identified gene fusion and NGS panel used.

ID	Screening Source	Retrieving Source	Gene Fusion	NGS panel
#1	Ignyta phase 1/1b study*	MSKCC, USA	*NCOA4-RET*	MSK-IMPACT[1]
#2	Ignyta phase 1/1b study*	UCBC, USA	*CCDC6-RET*	Minerva panel[2]
#3	Italy/Korea collaboration	SMC, South Korea	*NCOA4-RET*	NA
#4	Italy/Korea collaboration	SMC, South Korea	*NCOA4-RET*	Samsung panel[3]
#5	Italy/Korea collaboration	SMC, South Korea	*NCOA4-RET*	Samsung panel[3]
#6	Italy/Korea collaboration	INT, Italy	*CCDC6-RET*	Minerva panel[2]
#7	Italy/Korea collaboration	INT, Italy	*SNRNP70-RET*	Minerva panel[2]
#8	Italy/Korea collaboration	Candiolo, Italy	*NCOA4-RET*	Whole exome seq[4]
#9	FMI clinical databse	University of California, USA	*NCOA4-RET*	FMI panel[3]
#10	FMI clinical databse	University of California, USA	*CCDC6-RET*	FMI panel[3]
#11	FMI clinical databse	Unknown	*NCOA4-RET*	FMI panel[3]
#12	FMI clinical databse	Unknown	*NCOA4-RET*	FMI panel[3]
#13	FMI clinical databse	Unknown	*NCOA4-RET*	FMI panel[3]
#14	FMI clinical databse	Unknown	*NCOA4-RET*	FMI panel[3]
#15	FMI clinical databse	Unknown	*NCOA4-RET*	FMI panel[3]
#16	FMI clinical databse	Unknown	*NCOA4-RET*	FMI panel[3]
#17	FMI clinical databse	Unknown	*CCDC6-RET*	FMI panel[3]
#18	FMI clinical databse	Unknown	*CCDC6-RET*	FMI panel[3]
#19	FMI clinical databse	Unknown	*CCDC6-RET*	FMI panel[3]
#20	FMI clinical databse	Unknown	*CCDC6-RET*	FMI panel[3]
#21	FMI clinical databse	Unknown	*CCDC6-RET*	FMI panel[3]
#22	FMI clinical databse	Unknown	*TRIM24-RET*	FMI panel[3]
#23	FMI clinical databse	Unknown	*TRIM24-RET*	FMI panel[3]
#24	FMI clinical databse	Unknown	*TNIP1-RET*	FMI panel[3]

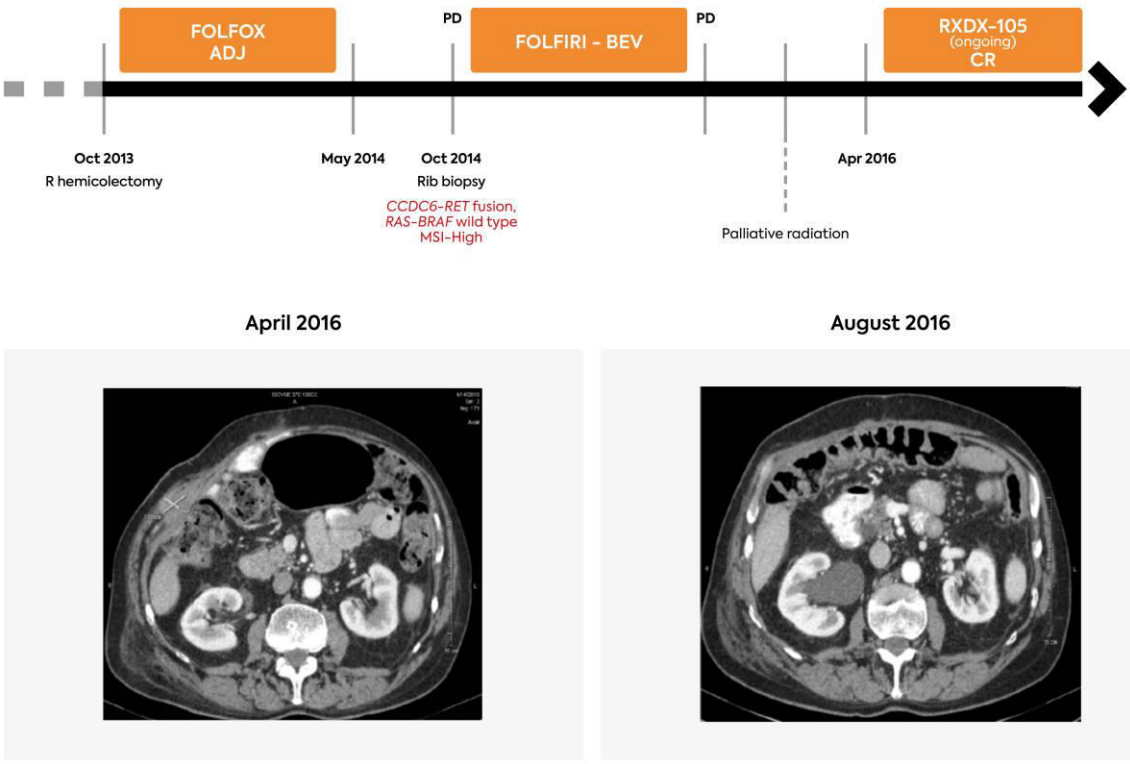
List of abbreviations: NGS=next generation sequencing; MSKCC=Memorial Sloan-Kettering Cancer Center; UCBC=University Cancer & Blood Center; SMC=Samsung Medical Center; NA=not available; INT=Istituto Nazionale dei Tumori; FMI=Foundation Medicine Inc.

*ClinicalTrials.gov Identifier: *NCT01877811.*

Supplementary Figure S1.



Supplementary Figure S2.



Legends to Supplementary Figures

Supplementary Figure S1. Identification and characterization of two novel *TNIP1-RET* and *SNRNP70-RET* fusions in colorectal cancer primary tumor samples. Panel A illustrates the *TNIP1-RET* rearrangement created by the fusion of intron 11 of the *TNIP1* gene on chromosome 5 and intron 11 of the *RET* gene region on chromosome 10 containing the kinase domain. **Panel B** shows the generation of the *SNRNP70-RET* rearrangement by fusion of a breakpoint in intron 7 of the *SNRNP70* gene on chromosome 19 with a breakpoint in intron 11 of the *RET* gene region on chromosome 10 containing the kinase domain.

Supplementary Figure S2. Summary of the clinical history of the patient with *CCDC6-RET* fusion and MSI-high status receiving targeted treatment with RXDX-105. As shown, the 76 years old male patient underwent right hemicolectomy in October 2013 for *RAS* and *BRAF* wild-type right colon adenocarcinoma. After experiencing a disease progression to first line FOLFIRI plus bevacizumab, the patient was screened at University Cancer & Blood Center (Athens, GA, USA) for the RXDX-105-01 phase 1/1b study of RXDX-105 in advanced solid tumors. Molecular characterization of a rib tumor biopsy performed in October 2014 at the time of bone relapse, showed an MSI-high status and revealed the presence of a *CCDC6-RET* fusion. Based on this specific molecular alteration, patient was enrolled in the clinical study and started RXDX-105 in April 2016. Tumor assessment after 2 months of treatment showed a radiological complete response. To date, RXDX-105 is still ongoing without any sign of disease relapse.

References to Supplementary Data

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