Supplementary Materials

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Supplementary Methods

RNA isolation and RT-qPCR test for CMS4 selection

RNA isolation and the 4-gene RT-qPCR test was performed as previously described.[1] Three of the five collected endoscopic biopsies were initially used for RNA isolation. In brief, biopsies were homogenized using the tissue homogenizing CKMix ceramic beads (Precellys, P000918-LYSK0-A) and subsequently processed for RNA isolation using the column-based RNA isolation (RNeasy Kit, Qiagen). RNA yield and quality were evaluated using spectrometry (Nanodrop 2000/200c, Thermo Fisher) and the BioAnalyzer (2100 Bioanalyzer, Agilent), respectively. If the yield and/or quality of two out of three samples was too low (i.e. concentration >20 ng/ul or RIN value < 6), one of the remaining biopsies was used for RNA isolation and CMS classification as well. A minimum of two biopsies with sufficient yield and quality were used for final RT-qPCR CMS4 classification.

cDNA was prepared using the High-Capacity RNA-to-cDNA kit (Applied Biosciences). The reverse transcription (RT) product was used for quantitative real time polymerase chain reaction (qPCR) analysing the following targets: *PDGFRA, PDGFRB, PDGFC, KIT, GAPDH*. ΔCt values of each sample individually served as input for the test algorithm. We mathematically pooled all samples per patient to derive a weighed mean change of CMS4, so that the relative contribution of each of the biopsies to the final test score is determined by the RNA concentration of that sample. The mean ΔCt values are then entered into the 4-gene RT-qPCR prediction test to yield the final weighed mean probability of CMS4. The patient was considered CMS4 positive with a CMS4 probability of ≥0.5.

Library preparation and next generation sequencing

Library preparation and Next Generation Sequencing (NGS) was performed by USEQ (Utrecht Sequencing Facility, Utrecht, The Netherlands). For the generation of sequencing libraries, Truseq RNA strated polyA (Illumina) was used. Libraries were sequenced on the Illumina NextSeq500 platform on the High Output 1 x 75bp configuration. This resulted in a minimal sequencing depth of 23 million reads per sample. RNA sequencing was performed on the same RNA of the pre-imatinib biopsies that was used for CMS4 classification by RT-qPCR. Sequencing data have been made available in the NCBI's Gene Expression Omnibus repository (GEO:)

Immunohistochemistry

For immunohistochemistry the diagnostic colonoscopy biopsies and the diagnostic surgical resection specimens were used, as the research biopsies obtained in the ImPACCT trial are used for molecular analyses. Specimens were formalin fixed and paraffin embedded and cut into 4 µm sections. Slides were deparaffinized by immersing the slides in xylene and subsequently rehydrated in a graded alcohol series (100% ethanol to 70% ethanol). Briefly, after epitope retrieval was carried out in 10 mM Sodium Citrate (pH 6.0), endogenous peroxidase was blocked in a PBS H_2O_2 buffer. Tissue sections were incubated overnight at 4°C using antibodies against phosphorylated S6 (1:200; CST2211, Cell Signaling Technology). Goat-anti-Rb-poly-HRP was used as secondary antibody and signal amplification. All slides were developed with diaminobenzidine (DAB) followed by hematoxylin counterstaining. Slides were air dried and subsequently cover slipped. Stained slides were scanned using a NanoZoomer Digital Slide Scanner (Hamamatsu).

Histopathological quantification

Immunohistochemically stained sections of pre- and post-imatinib treatment biopsies were loaded into QuPath v0.3.0. For each patient (in the pre-treatment and post-treatment condition), representative annotations were created in the epithelial compartment of the tumor with a minimum of n=11 and a maximum of n=86 representative annotations per condition. The image was color deconvoluted across both the DAB and the Hematoxylin staining vectors and subsequently thresholded to calculate a positive staining area percentage for the epithelial compartment. The mean

DAB positive area percentages were calculated for each patient per condition and compared using a two-sided paired Student's *t*-test.

Prognostic relevance of imatinib-induced gene expression changes

To determine the potential prognostic relevance of imatinib-induced gene expression changes, the list of significantly upregulated genes after imatinib treatment in the five treated ImPACCT patients (n=228 genes) to generate HIGH and LOW expression tumor clusters in an independent cohort of 3232 primary colorectal tumors (CMS-3232; [2]) using the k-means algorithm (n=2)) with annotated CMS status and survival. The HIGH and LOW expression subgroups were then analyzed for the distribution of CMS1-4 and time-to-relapse and overall survival (OS). Survival curves were compared using the log-rank test and hazard ratios (HRs) were estimated by Cox regression. The assumption of proportional hazards was assessed according to inspection of Schoenfeld residual plots.

References

1. Ubink I, Elias SG, Moelans CB*, et al.* A Novel Diagnostic Tool for Selecting Patients With Mesenchymal-Type Colon Cancer Reveals Intratumor Subtype Heterogeneity. J Natl Cancer Inst 2017;109(8).

2. Guinney J, Dienstmann R, Wang X*, et al.* The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21(11):1350-6.

3. Subramanian A, Tamayo P, Mootha VK*, et al.* Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proc Natl Acad Sci U S A 2005;102(43):15545-50.

4. Bindea G, Mlecnik B, Tosolini M*, et al.* Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. Immunity 2013;39(4):782-95.

Supplementary Table S1. In- and exclusion criteria for treatment with Imatinib in patients with CMS4 colon cancer in the ImPACCT trial.

Inclusion criteria	Exclusion criteria
- Male or female aged ≥18 years;	- The presence of synchronous distant metastases;
- Histologically proven adenocarcinoma of the colon;	- Current hospital standard of care dictates that subject should undergo any neoadjuvant therapy;
- Completed cancer staging with CT-abdomen and CT-thorax/X-thorax according to hospital's standard of care;	- Concurrent participation in another clinical trial using any medicinal product, or participation in such a trial in the period of three months prior to the current trial;
- Confirmed eligibility for surgery with curative intent as deemed by the hospital's multidisciplinary board review;	- Women who are pregnant, plan to become pregnant or are lactating during the study or for up to 30 days after the last dose of imatinib;
- Test positive for CMS4 subtype;	- Known HIV or Hepatitis B/C infection;
- ≥4 properly stored pre-treatment biopsies for gene expression analysis/ELISA;	- Known symptomatic congestive heart failure;
- WHO performance status 0 or 1;	- Co-morbidity requiring concomitant treatment with drugs that act as strong inducers of CYP3A4 or with drugs with a narrow therapeutic range influenced by imatinib.
- Adequate haematology status and organ function (defined as: normal creatinine clearance (≥60 ml/min (MDRD)), ALAT within 2.5× upper limit of normal (ULN), PT-INR < 1.5, leukocytes >1,5*10^9/L, Hb > 6.0 mmol/L, platelets >100*10^9/L);	
- Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests;	
- Provision of written informed consent.	

ELISA, enzyme-linked immunosorbent assay; WHO, World Health Organization, MDRD, Modification of Diet in Renal Disease; ALAT, Alanine Transaminase; PT-INR, Prothrombin time International Normalized Ratio; Hb, Hemoglobin.

Supplementary Table S2. Gene set signatures used in the analyses of the ImPACCT study.

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
XBP1	ABCE1	ABCF2	ACTA2	AURKB	ABL1	EEF1A1A	ACP1	DSC1	PDGFRA
ERBB3	ACP1	ACACA	ADAM12	BYSL	ANAPC1	EEF1B2A	ACTB	DSC2	PDGFRB
KRT19	AIMP2	ACLY	ADAMTS12	C12ORF14	ANAPC10	EEF1GA	ACTG1	DSC3	PDGFC
JUP	AP3S1	ACSL3	AEBP1	C16ORF35	ANAPC11	EEF2A	ACTN1	DSG1	KIT
TACSTD2	APEX1	ACTR2	AKAP12	C1ORF33	ANAPC2	EF1DA	ACTN2	DSG2	
SERPINB6	BUB3	ACTR3	ANK2	C20ORF64	ANAPC4	EIF1AY	ACTN3	DSG3	
CHP1	C1QBP	ADD3	ANTXR1	CAD	ANAPC5	EIF2AA	ACTN4	DSG4	
PSME3	CAD	ADIPOR2	AOC3	CD320	ANAPC7	EIF2B3	ACVR1B	DSP	
MLPH	CANX	AK4	AQP1	CD44	ATM	EIF2S2	ACVR1C	JUP	
SSR4	CBX3	ALDOA	ARMCX1	CDC25A	ATR	EIF2S3	BAIAP2	PKP1	
RPS4X	CCNA2	ARPC5L	ASPN	CDCA7	BUB1	EIF3AA	CDC42	PKP2	
RPL32	CCT2	ASNS	BGN	CDK4	BUB1B	EIF3C	CDH1	PKP3	
RGL2	CCT3	ATP2A2	BICC1	CDKN3	BUB3	EIF3D	CREBBP	PKP4	
PSMD4	CCT4	ATP5MC1	BNC2	CDT1	CCNA1	EIF3EA	CSNK2A1		
NUCB2	CCT5	ATP6V1D	BOC	CGI-96	CCNA2	EIF3FA	CSNK2A2		
LRPAP1	CCT7	AURKA	C1R	CIRH1A	CCNB1	EIF3HA	CSNK2B		
UBE2L3	CDC20	BCAT1	C1S	CLDN2	CCNB2	EIF3K	CTNNA1		
HSP90AA1	CDC45	BHLHE40	C3	COG8	CCNB3	EIF3L	CTNNA2		
SDHA	CDK2	BTG2	CACNA2D1	CRTAP	CCND1	EIF4A2	CTNNA3		
TUG1	CDK4	BUB1	CALD1	CTPS	CCND2	EIF4BA	CTNNB1		
MYL6	CLNS1A	CACYBP	CCDC80	DCUN1D5	CCND3	GNB2L1A	CTNND1		
AGR2	CNBP	CALR	CLDN11	DDX10	CCNE1	HNRNPA1A	EGFR		
ELF3	COPS5	CANX	CNN1	DDX20	CCNE2	PABPC1A	EP300		
KRT18	COX5A	CCNF	COL14A1	DDX21	CCNH	PABPC4A	ERBB2		
ATP5A1	CSTF2	CCNG1	COL15A1	DDX56	CDC14A	QARSA	FARP2		

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
RPL24	CTPS1	CCT6A	COL1A1	DKC1	CDC14B	RPL10A	FER		
EIF3F	CUL1	CD9	COL1A2	EIF5A2	CDC16	RPL12A	FGFR1		
C20orf24	CYC1	CDC25A	COL3A1	ENC1	CDC20	RPL13A	FYN		
PAPOLA	DDX18	CDKN1A	COL5A1	ETS2	CDC23	RPL14A	IGF1R		
CHCHD2	DDX21	CFP	COL5A2	ETV4	CDC25A	RPL15A	INSR		
SNAP23	DEK	COPS5	COL6A3	FARSLA	CDC25B	RPL17A	IQGAP1		
BTG2	DHX15	CORO1A	COL8A1	FLJ10774	CDC25C	RPL18	LEF1		
RPS6	DUT	CTH	COL8A2	FLJ20249	CDC26	RPL18A	LMO7		
LRRFIP1	EEF1B2	CTSC	COLEC12	FLJ20315	CDC27	RPL19	MAP3K7		
NHP2L1	EIF1AX	CXCR4	CRISPLD1	FLJ20425	CDC6	RPL21	MAPK1		
C19orf43	EIF2S1	CYB5B	CRYAB	FLJ23476	CDC7	RPL22A	MAPK3		
HSP90AB1	EIF2S2	CYP51A1	CTSK	FOXQ1	CDK2	RPL23A	MET		
ARPC2	EIF3B	DAPP1	CXCL12	GEMIN5	CDK4	RPL24	MLLT4		
RAC1	EIF3D	DDIT3	CYP1B1	HEATR1	CDK6	RPL26	NLK		
NDUFB9	EIF3J	DDIT4	DCLK1	HES6	CDK7	RPL27	PARD3		
RAN	EIF4A1	DDX39A	DCN	HIG2	CDKN1A	RPL27A	PTPN1		
NPLOC4	EIF4E	DHCR24	DDR2	HNRPDL	CDKN1B	RPL29A	PTPN6		
CAPNS1	EIF4G2	DHCR7	DPT	HSPC111	CDKN1C	RPL3	PTPRB		
UBC	EIF4H	DHFR	DPYSL3	IMP4	CDKN2A	RPL30	PTPRF		
RHOA	EPRS1	EBP	ECM2	KIAA0179	CDKN2B	RPL31A	PTPRJ		
DSP	ERH	EDEM1	EDNRA	KIAA0690	CDKN2C	RPL32A	PTPRM		
CDIPT	ETF1	EEF1E1	EFEMP1	KIAA1068	CDKN2D	RPL34A	PVRL1		
BANF1	EXOSC7	EGLN3	FBLN1	KIAA1199	CHEK1	RPL35	PVRL2		
HSPA5	FAM120A	EIF2S2	FBN1	LOC150223	CHEK2	RPL36A	PVRL3		
S100A11	FBL	ELOVL5	FBXO32	LOC285958	CREBBP	RPL37A	PVRL4		
MLEC	G3BP1	ELOVL6	FERMT2	LOC389362	CUL1	RPL39A	RAC1		

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
DYNLL1	GLO1	ENO1	FIBIN	LOC56902	DBF4	RPL40	RAC2		
ELOVL5	GNL3	EPRS1	FLNA	MAC30	E2F1	RPL41A	RAC3		
MRPL43	GOT2	ERO1A	FN1	MET	E2F2	RPL4A	RHOA		
TUBA1A	GSPT1	ETF1	FNDC1	METTL1	E2F3	RPL5A	SMAD2		
HNRNPC	H2AZ1	FADS1	FSTL1	MGC13096	EP300	RPL6A	SMAD3		
SIRT3	HDAC2	FADS2	FXYD6	MGC13170	ESPL1	RPL7	SMAD4		
UFC1	HDDC2	FDXR	GEM	MGC2408	FZR1	RPL7AA	SNAI1		
SNF8	HDGF	FGL2	GLT8D2	MGC2574	GADD45A	RPL8A	SNAI2		
HSPA4	HNRNPA1	FKBP2	GPC6	MGC40397	GADD45B	RPL9	SORBS1		
CNOT8	HNRNPA2B1	G6PD	GREM1	MGC4677	GADD45G	RPLP0A	SRC		
NUP93	HNRNPA3	GAPDH	GUCY1A3	MKI67IP	GSK3B	RPLP1A	SSX2IP		
CYTH2	HNRNPC	GBE1	GUCY1B3	MRPL36	HDAC1	RPLP2A	TCF7		
NDRG1	HNRNPD	GCLC	HDGFRP3	MRPS12	HDAC2	RPS10A	TCF7L1		
TOMM6	HNRNPR	GGA2	HMCN1	MRPS26	MAD1L1	RPS11A	TCF7L2		
PRICKLE4	HNRNPU	GLA	HOPX	MRPS30	MAD2L1	RPS12	TGFBR1		
HBXIP	HPRT1	GLRX	HSD17B6	MTVR1	MAD2L2	RPS13	TGFBR2		
CMPK1	HSP90AB1	GMPS	HSPB8	MYBBP1A	MCM2	RPS14A	TJP1		
OS9	HSPD1	GOT1	HTR2B	MYC	MCM3	RPS15	VCL		
PSMA1	HSPE1	GPI	IGFBP5	NLE1	MCM4	RPS15AA	WAS		
TRIB1	IARS1	GSK3B	INHBA	NOB1P	MCM5	RPS16A	WASF1		
NACA	IFRD1	GSR	ISLR	NOC3L	MCM6	RPS17A	WASF2		
SKP1	ILF2	GTF2H1	KCTD12	NOL1	MCM7	RPS18	WASF3		
ABHD11	IMPDH2	HK2	LBH	NOL5A	MDM2	RPS19A	WASL		
RPLP0	KARS1	HMBS	LHFP	NOLA1	PCNA	RPS20A	YES1		
RPL11	KPNA2	HMGCR	LMOD1	NS	PKMYT1	RPS21			
PPIA	KPNB1	HMGCS1	LOX	NXT1	PLK1	RPS23			

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
RPL13A	LDHA	HPRT1	LUM	ODC1	PRKDC	RPS24			
RPLP1	LSM2	HSP90B1	MAP1B	PDCD11	PTTG1	RPS25			
TMSB10	LSM7	HSPA4	MEIS1	PEO1	PTTG2	RPS26			
P4HB	MAD2L1	HSPA5	MFAP2	PHLDA1	RB1	RPS27			
IRF1	MCM2	HSPA9	MGP	PMSCL1	RBL1	RPS27AA			
DNM1L	MCM4	HSPD1	MIR100HG	POLR1B	RBL2	RPS28			
SCAMP4	MCM5	HSPE1	MMP2	POLR1C	RBX1	RPS29			
BRK1	MCM6	IDH1	MN1	POLR1D	SFN	RPS2A			
RPL7A	MCM7	IDI1	MOXD1	PPAN	SKP1	RPS3			
MACF1	MRPL23	IFI30	MRGPRF	PPIL1	SKP2	RPS30			
PGRMC1	MRPL9	IFRD1	MSRB3	PSF1	SMAD2	RPS3AA			
RPS19	MRPS18B	IGFBP5	MXRA5	RAB9P40	SMAD3	RPS4XA			
EEF1A1	MYC	IMMT	MYL9	RFP	SMAD4	RPS4Y			
HNRNPM	NAP1L1	INSIG1	MYLK	RHEB	SMC1A	RPS5A			
ZFAND5	NCBP1	ITGB2	NAP1L3	RNU3IP2	SMC1B	RPS6A			
EFNA1	NCBP2	LDHA	NDN	RRP41	TFDP1	RPS7			
RPS3A	NDUFAB1	LDLR	NEXN	SCD	TGFB1	RPS8			
RPL19	NHP2	LGMN	PCDH7	SDCCAG16	TGFB2	RPS9A			
ARG2	NME1	LTA4H	PCOLCE	SF3A2	TGFB3	RPSA			
ARRB1	NOLC1	M6PR	PDE1A	SLC19A1	TP53				
SRRM2	NOP16	MAP2K3	PDGFC	SLC29A2	WEE1				
MAPRE1	NOP56	MCM2	PDLIM3	SLC39A10	YWHAB				
IDS	NPM1	MCM4	PEG3	SLC3A2	YWHAE				
STRAP	ODC1	ME1	PHLDB2	SLC7A5	YWHAG				
ACTG1	ORC2	MLLT11	PLN	SORD	YWHAH				
RPSA	PA2G4	MTHFD2	PPP1R3C	SOX4	YWHAQ				

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
TLN1	PABPC1	MTHFD2L	PRELP	SOX9	YWHAZ				
RBM8A	PABPC4	NAMPT	PRICKLE1	SRM					
YIF1B	PCBP1	NFIL3	PTGIS	TEAD4					
RPL3	PCNA	NFKBIB	RAB31	TERE1					
RPS25	PGK1	NFYC	RARRES2	TGIF					
RPL23	PHB	NIBAN1	RBMS1	TM4SF9					
ETF1	PHB2	NMT1	RBMS3	TREX2					
RPL35	POLD2	NUFIP1	RUNX1T1	TRMT1					
IMPDH2	POLE3	NUP205	S1PR3	WDR12					
CD63	PPIA	NUPR1	SDC2	WDR3					
TMED10	PPM1G	P4HA1	SERPINF1	WDR74					
UQCRC2	PRDX3	PDAP1	SERPING1	WDR77					
SSBP1	PRDX4	PDK1	SFRP2	XPOT					
HMGN1	PRPF31	PFKL	SFRP4	YAP1					
SLC1A4	PRPS2	PGK1	SGCE	ZNF259					
NDUFA13	PSMA1	PGM1	SLIT2	ZNF511					
EEF1B2	PSMA2	PHGDH	SNAI2	ZNF593					
ALDOA	PSMA4	PIK3R3	SPARCL1	ZNF703					
PUF60	PSMA6	PITPNB	SPOCK1						
NEDD8	PSMA7	PLK1	SSPN						
NDUFS2	PSMB2	PLOD2	STON1						
CNPY2	PSMB3	PNO1	SULF1						
ATP6V1F	PSMC4	PNP	TAGLN						
ARPP19	PSMC6	POLR3G	TCEAL7						
EZR	PSMD1	PPA1	TGFB1I1						
AZIN1	PSMD14	PPIA	THBS1						

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
WHSC1L1	PSMD3	PPP1R15A	THBS2						
MXD3	PSMD7	PRDX1	THY1						
EIF3J	PSMD8	PSAT1	TIMP2						
GSK3A	PTGES3	PSMA3	TIMP3						
MYL12B	PWP1	PSMA4	TMEM47						
CAND1	RACK1	PSMB5	TNC						
RAB13	RAD23B	PSMC2	TNS1						
SLC35B1	RAN	PSMC4	TPM2						
CS	RANBP1	PSMC6	VCAN						
TPD52	RFC4	PSMD12	WISP1						
ITFG3	RNPS1	PSMD13	WWTR1						
CLDN4	RPL14	PSMD14	ZCCHC24						
AATF	RPL18	PSME3	ZFPM2						
SPTAN1	RPL22	PSMG1	ZNF521						
GAS5	RPL34	PSPH							
TMCO1	RPL6	QDPR							
FLOT1	RPLP0	RAB1A							
PPP2CB	RPS10	RDH11							
GTF3A	RPS2	RIT1							
CIAO1	RPS3	RPA1							
TSPAN1	RPS5	RPN1							
SEPHS2	RPS6	RRM2							
TBCA	RRM1	RRP9							
41897	RRP9	SC5D							
FAF2	RSL1D1	SCD							
COX7A2L	RUVBL2	SDF2L1							

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
GNAI2	SERBP1	SEC11A							
PPM1G	SET	SERP1							
CAST	SF3A1	SERPINH1							
SPATA20	SF3B3	SHMT2							
REEP5	SLC25A3	SKAP2							
NCOA6	SMARCC1	SLA							
ERGIC3	SNRPA	SLC1A4							
TMEM115	SNRPA1	SLC1A5							
ZNF385A	SNRPB2	SLC2A1							
PRRC2C	SNRPD1	SLC2A3							
NAA60	SNRPD2	SLC37A4							
TNFRSF1A	SNRPD3	SLC6A6							
FNBP1	SNRPG	SLC7A11							
OCIAD1	SRM	SLC7A5							
ITGB5	SRPK1	SLC9A3R1							
UBE2D3	SRSF1	SORD							
AP1B1	SRSF2	SQLE							
TRPS1	SRSF3	SQSTM1							
TAF9	SRSF7	SRD5A1							
GPR56	SSB	SSR1							
SERINC1	SSBP1	STARD4							
NRD1	STARD7	STC1							
DCAF5	SYNCRIP	STIP1							
GDI1	TARDBP	SYTL2							
CLU	TCP1	TBK1							
RPL27A	TFDP1	TCEA1							

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
TXN	TOMM70	TES							
RPL7	TRA2B	TFRC							
JUND	TRIM28	TM7SF2							
RPL18	TUFM	TMEM97							
RPL28	TXNL4A	TOMM40							
PSMB2	TYMS	TPI1							
NBPF10	U2AF1	TRIB3							
RPS10	UBA2	TUBA4A							
ERP29	UBE2E1	TUBG1							
RAD21	UBE2L3	TXNRD1							
HNRNPR	USP1	UBE2D3							
RAD9A	VBP1	UCHL5							
CDC37	VDAC1	UFM1							
SF3B2	VDAC3	UNG							
BAG1	XPO1	USO1							
CCDC84	XPOT	VLDLR							
METTL9	XRCC6	WARS1							
PRLR	YWHAE	XBP1							
SON	YWHAQ	YKT6							
CYB5R1									
SNW1									
TCP1									
CDC16									
RPL14									
RPS26									
TTC3									

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
KIAA1324									
C17orf49									
RPS5									
PEBP1									
RPL22									
ATP1B1									
CSNK1A1									
NQO1									
CANX									
SRP14									
DYNLRB1									
UBA1									
41884									
PPP2CA									
TOMM20									
UQCRFS1									
HN1									
FKBP4									
GDI2									
PSMA6									
PSME2									
CHD4									
RER1									
NDUFB2									
HINT1									
SRSF7									

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
SUPT5H									
COX4I1									
APLP2									
SEPW1									
PRELID1									
UNKL									
TMEM50A									
FIS1									
CHMP2A									
CTNNA1									
PYCR1									
SUGT1									
PRDX2									
TRIM28									
PLP2									
WDR34									
PSMD8									
CRIP1									
KCP									
POLR2L									
BHLHE40									
TXNL4A									
ACBD6									
NDUFA1									
CREB3									
NAPA									

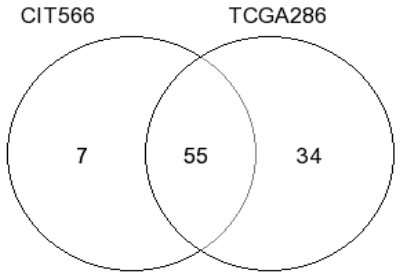
Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
ATP5J2									
AFTPH									
PGD									
TFG									
SAP30L									
JTB									
ANAPC5									
IDH3B									
MAGT1									
GORASP2									
ANXA2									
LASP1									
DCAF7									
MTIF3									
BICD2									
STX16									
ATP6V1C1									
ARF3									
RNF139									
NAGK									
PNRC2									
DNAJC12									
RAB7A									
TUSC3									
CDK2AP1									
NDEL1									

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
URI1									
LINC00094									
WARS									
FAM102A									
TOR1A									
RHEB									
FAM127A									
ARPC4									
NSD1									
AKIRIN1									
ID2									
ACTN1									
SCRIB									
SAP30BP									
KIAA1244									
PQBP1									
ACTN4									
RAB10									
LRRC37BP1									
RHBDD2									
CDCP1									
ZKSCAN1									
CHPF									
IRX5									
C17orf28									
PRSS53									

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
VPS37C									
VKORC1									
ABHD12									
BAIAP2L1									
LIMS1									
CIR1									
ATP6V1E1									
NUDT9									
SDF2									
RABL5									
GNB2L1									
PIGX									
PTPN2									
BTF3									
SLC25A39									
PSME1									
ZNF274									
SCNM1									
NDUFA4									
CCT3									
C20orf11									
GOT2									
FBXW4									
YIPF6									
HAX1									
SEL1L									

Circulating cell cluster	HALLMARK_MYC_TARGETS_V1	HALLMARK_MTORC1 SIGNALING	CMS4 upregulated genes	WNT	KEGG cell cycle	mTOR TOP targets	KEGG adherens junctions	Desmosome	4-gene signature
MCM3AP									
ARCN1									
EID1									
ORC4									
ZYX									
PSMD13									
BRP44L									
TTC39A									
TRPM4									

Supplementary Table S3. Kinases correlated with CMS4

Kinases significantly (p<e-6) correlated with CMS4 signature genes						
CIT566	**R**	**TCGA286**	**R**		**overlap (55 kinases)**	**overlap (22 tyrosine kinases)**
DDR2	0.929	PDGFRB	0.941		AAK1	AXL
AXL	0.86	DDR2	0.932		AKT3	BTK
AKT3	0.835	AKT3	0.919		AXL	DDR2
PDGFRB	0.823	AXL	0.897		BMPR1B	EPHA3
FGFR1	0.816	PKD2	0.877		BMPR2	EPHA7
PKD2	0.808	TIE1	0.873		BTK	FER
NUAK1	0.804	FGFR1	0.867		DAPK1	FES
LATS2	0.745	NUAK1	0.831		DDR2	FGFR1
TIE1	0.737	FLT4	0.827		DYRK3	FGR
EPHA3	0.659	EPHA3	0.791		EPHA3	FLT1
MAP3K3	0.656	MAP3K3	0.79		EPHA7	FYN
ILK	0.63	PDGFRA	0.757		FER	HCK
FYN	0.595	FGR	0.744		FES	ITK
HCK	0.594	ROR2	0.741		FGFR1	JAK1
PDGFRA	0.584	KDR	0.728		FGR	JAK3
ROR2	0.567	LRRK2	0.724		FLT1	KDR
LRRK2	0.558	HCK	0.721		FYN	KIT
KDR	0.534	BTK	0.716		HCK	PDGFRA
TGFBR1	0.526	FES	0.716		HIPK3	PDGFRB
FGR	0.517	LATS2	0.715		ILK	ROR1
FLT1	0.496	CAMK1G	0.71		IRAK3	ROR2
BMPR2	0.485	FLT1	0.705		ITK	TIE1
JAK3	0.477	SPEG	0.653		JAK1	
BTK	0.453	TGFBR1	0.636		JAK3	
SNRK	0.436	BMPR1B	0.63		KDR	

Kinases significantly (p<e-6) correlated with CMS4 signature genes					
CIT566	**R**	**TCGA286**	**R**	**overlap (55 kinases)**	**overlap (22 tyrosine kinases)**
ROR1	0.434	BMPR2	0.626	KIT	
PIM1	0.403	WNK3	0.624	LATS2	
FES	0.401	CDKL5	0.608	LRRK2	
OSR1	0.384	ROR1	0.605	MAP3K3	
DAPK1	0.382	ILK	0.604	MAP3K8	
PLK2	0.361	IRAK3	0.602	MARK4	
SPEG	0.351	SNRK	0.602	MAST4	
ULK2	0.347	TTBK2	0.602	NEK1	
TRIO	0.347	PAK3	0.581	NEK7	
IRAK3	0.34	JAK3	0.578	NEK9	
HIPK3	0.336	BRSK1	0.569	NUAK1	
ITK	0.333	FYN	0.569	OSR1	
TTBK2	0.322	CAMK2A	0.567	PDGFRA	
AAK1	0.316	HIPK3	0.551	PDGFRB	
NEK7	0.312	DYRK3	0.532	PIM1	
FER	0.312	ALK	0.527	PKD1	
DYRK3	0.306	MAST4	0.519	PKD2	
MAP3K8	0.302	FLT3	0.512	PLK2	
MAPKAPK2	0.294	EPHA5	0.511	ROCK1	
KIT	0.288	CAMK4	0.508	ROR1	
TGFBR2	0.284	ITK	0.5	ROR2	
EPHA7	0.282	EPHB6	0.491	SNRK	
ZAK	0.279	NEK1	0.484	SPEG	
NEK9	0.274	TRIO	0.475	TGFBR1	
PLK3	0.272	BMX	0.473	TGFBR2	
MARK4	0.264	EPHA7	0.452	TIE1	
PKN1	0.256	ROCK1	0.451	TRIO	

Kinases significantly (p<e-6) correlated with CMS4 signature genes					
CIT566	**R**	**TCGA286**	**R**	**overlap (55 kinases)**	**overlap (22 tyrosine kinases)**
BMPR1B	0.255	EPHA6	0.447	TTBK2	
PINK1	0.25	GCK	0.447	ULK1	
MAST4	0.244	KIT	0.44	ULK2	
ULK1	0.242	PHKG1	0.432		
ROCK1	0.236	PKD1	0.427		
NEK1	0.231	LATS1	0.42		
RNASEL	0.224	TGFBR2	0.414		
JAK1	0.22	HIPK4	0.412		
MAP3K6	0.218	OSR1	0.404		
PKD1	0.216	MUSK	0.402		
		FER	0.399		
		MAP3K2	0.399		
		NEK7	0.398		
		RET	0.387		
		DAPK1	0.386		
		JAK1	0.381		
		PIM1	0.375		
		IGF1R	0.371		
		DAPK3	0.369		
		NEK9	0.367		
		BLK	0.363		
		ATM	0.361		
		AAK1	0.356		
		WNK1	0.355		
		NRBP1	0.35		
		ULK1	0.349		
		PLK2	0.348		

Kinases significantly (p<e-6) correlated with CMS4 signature genes					
CIT566	**R**	**TCGA286**	**R**	**overlap (55 kinases)**	**overlap (22 tyrosine kinases)**
		ZAP70	0.348		
		EPHA4	0.334		
		PIM2	0.325		
		MAP3K1	0.313		
		MYO3A	0.311		
		TAF1L	0.308		
		ULK2	0.305		
		MARK4	0.304		
		PIK3R4	0.301		
		MAP3K8	0.3		

Supplementary Table S4. Kd values of 72 tyrosine kinase inhibitors for CMS4 related kinases.

	# targets		selectivity score	KIT	PDGFRA	PDGFRB	FLT1	DDR2	KDR	AXL	TIE1	FGR	FYN	HCK	BTK	EPHA3	EPHA7	FER	FES	FGFR1	ITK	JAK1	JAK3
	all	<300	σ (3 uM)																				
VX-745	4	0	0.0233		8800	8400						1300	2100										
PTK-787	5	5	0.0311	5.1	96	25	9.6		62														
MLN-518	6	4	0.057	2.7	2.4	4.5	3100	120		6300													
Imatinib*	6	4	0.057	13	31	14		15				2400	3100										
AB-1010	8	5	0.0622	8.1	25	8.4		26				640	140	690		2500							
CP-690550	3	2	0.0622										1100									1.6	0.16
AC220	9	5	0.0751	4.8	11	7.7	41	1100	87		3200					6500	3700						
AMG-706	10	5	0.0777	3.7	10	9.1	12		26			6900	2800	8600						6200		5200	
BMS-540215	9	6	0.0855	36	11	50	10		5		1100			2700			1700			99			
MLN-8054	11	1	0.0984				1000			440	1600	220	1300	1500	4200	2100	1000	4400		2400			
Gefitinib	4	0	0.1114							1800		2600		4400		5500							
AZD-1152HQPA	10	4	0.114	17	38	41	110	6600	500	390	350			3900	1200								
CHIR-265/RAF-265	11	3	0.1166	200	1100	240	800	960	1300		150		2100	1200				8600		4700			
Nilotinib*	9	5	0.1244	29	180	73		33			1000	320	1600	390		110							
LY-317615	4	0	0.1321			3300				3300										4000			1700
Ki-20227	11	7	0.1347	0.69	0.49	0.29	130	88	18	140		1800	7100	440	7400								
BIRB-796	10	3	0.1373	170	1200	1100	410	33	3900		8.3					880	860			4300			
GSK-1838705A	4	2	0.1373							300								9.3	52				4700
PLX-4720	11	4	0.1399	180	190	200	1900	4100	2100			62	2300	2700					3600	5300			
CI-1033	13	0	0.1606	7800	5200	7500	7500			5700	2200	2800	5300	4200	1600	2100					5600		630
Cediranib	15	8	0.1632	0.38	0.41	0.32	0.74	48	1.1	490	290	1100	1200	590	4300	3700	620			53			
Sorafenib*	15	7	0.1684	28	62	37	31	6.6	59	4500	68	7800	8400	8500		1900	5300			2800			7300
HKI-272	8	2	0.1813							190	390	1900	6400	490	160			510	590				2000
Erlotinib	12	0	0.1813	1700	1800	1400	4400		5700	4000	850	1100		1800		2400	1400						700
ABT-869	10	7	0.1839	2	4.2	1.9	7.5	3800	8.1	340	110					3500	110						

AG-013736	12	6	0.1969	3.2	0.51	0.57	5.8	5300	5.9	420	97	1800								380	1200		3100		
Pazopanib*	14	6	0.215	2.8	4.9	2	14	98	14		700	1600	2700	5700				2700	1400	990			6900		
Vandetanib*	15	6	0.2358	260	230	88	260	320	820	250	1500	270	360	360	1700	2000	2400			560					
INCB18424	3	2	0.2565													6100						3.4	2		
Flavopiridol	4	0	0.2617		5900					3500						3300							1600		
Dasatinib*	13	9	0.2668	0.81	0.47	0.63	5000	3.2	2900			0.5	0.79	0.35	1.4	0.093				3700			640		
PHA-665752	8	1	0.3031	3200	2000	1900		7600		110	1200	1900											470		
Crizotinib	13	4	0.3212				2300			7.8	110	670	1300		7800	700	470	270	450		2000	330	200		
PD-173955	17	11	0.3446	1.8	5.6	1.4	23	12	690		1200	2.4	4.9	3.3	220	7.6		3500	680	62		330	510		
VX-680/MK-0457	19	5	0.3472	240	1600	310	100	230	2000	210	270	790	530	6200	4400	1500		4200	7400	550	350	5900	630		
CHIR-258/TKI-258	14	7	0.3601	7.5	54	3.8	69	8600	68	3800	4000	190	440	3300						150	530		410		
JNJ-28312141	19	11	0.3886	3.6	27	28	53	100	460	5.3		220	340	3700	77	1600	6700	120	1100	3500	490	200	18		
SKI-606	15	8	0.4249	420	5100	200		140		52	2900	6.3	11	3.4	4.8	5.8		360	330		1700		1200		
PKC-412	14	3	0.4301	220	380	110	450		3200	620	1400	730	2100	720				1200		1600		670	12		
PP-242	15	5	0.4352	360	220	78	1200	6100	1200	1200		160	300	190	3200	390				570		300	86		
Foretinib*	18	17	0.4404	2.5	4.5	0.96	3.8	3.6	12	0.093	0.79	40	88	15	76	1	2.5	37	110	690	69				
AST-487	19	12	0.4922	5.4	27	8.1	86	11	200	570	0.29	190	50	880		80	1100	590	360	620	990	74	260		
BIBF-1120 (derivative)	19		0.5181	5.7	16	15	63	42	2.9	12	2200	300	630	5300	310	8600		73	1200	92	210	2500	8.2		
TG-101348	20		0.5389	130	2700	45	4300	950	5200	160	700	82	38	2100	850	7100	6500	1100	530	280	490	18	74		
SU-14813	19		0.5415	0.68	1.1	0.29	4.7	9900	2.3	84	5700	390	2600	2200	4000	2300	1500	34		1900	190	5900	580		
Sunitinib	20		0.5959	0.37	0.79	0.075	1.8	2900	1.5	9	3900	270	520	880	2100	2100	2400	1100	960	520	13	6000	1200		
R406	20		0.6088	6.8	60	3.3	16	43	40	82	76	33	28	150	190	360	39	130	200	44	400	21	36		
KW-2449	20		0.658	53	130	30	73	2100	120	180	300	440	660	4300	1000	810	390	1100	750	370	240	1200	39		
TAE-684	20		0.671	110	840	150	550	4100	940	12	15	120	1400	410	23	4000	200	1.4	4.8	47	34	410	17		
CEP-701	20		0.8031	150	350	29	120	400	220	35	680	52	84	270	66	160	260	28	370	310	290	8.8	2.3		
Staurosporine	20		0.8782	19	10	1.8	150	42	220	6.8	65	17	33	20	210	27	630	24	23	90	19	6.1	12		
GSK-461364A	2		0.101			2900					1400														
BIBW-2992	2		0.0751							5300				2200											
CI-1040	1		0.0078			3100																			
GSK-690693	1		0.1451			3900																			

Unspecific (σ>0.5)

SB-203580	1	0.0933			5000						
BI-2536	1	0.1425							1900		
BMS-387032/SNS-032	1	0.1606	9900								
LY-333531	1	0.1969								1200	
A-674563	1	0.2772								1500	
AZD-6244/ARRY-886	0	0.0052									
GW-2580	0	0.0104									
SGX-523	0	0.0104									
Lapatinib	0	0.0155									
MLN-120B	0	0.0207									
GDC-0879	0	0.0415									
BMS-345541	0	0.044									
PI-103	0	0.057									
GDC-0941	0	0.0803									
AT-7519	0	0.0933									
R547	0	0.1192									
TG-100-115	0	0.1321									

Ineffective (<3 targets and all IC50 >1000)

Supplementary Table S5. FDA approved tyrosine kinase inhibitors against CMS4 related kinases.

	# targets		selectivity score	Kd for CMS4 tyrosine kinases																		
	all	<300	σ (3 uM)	KIT	PDGFRA	PDGFRB	FLT1	DDR2	KDR	AXL	TIE1	FGR	FYN	HCK	BTK	EPHA3	EPHA7	FER	FES	FGFR1	ITK	JAK1	JAK3
Dasatinib	13	9	0.2668	0.81	0.47	0.63	5000	3.2	2900			0.5	0.79	0.35	1.4	0.093				3700			640
Vandetanib	15	6	0.2358	260	230	88	260	320	820	250	1500	270	360	360	1700	2000	2400			560			
Pazopanib	14	6	0.215	2.8	4.9	2	14	98	14		700	1600	2700	5700				2700	1400	990			6900
Sorafenib	15	7	0.1684	28	62	37	31	6.6	59	4500	68	7800	8400	8500		1900	5300			2800			7300
Nilotinib	9	5	0.1244	29	180	73		33			1000	320	1600	390		110							
Imatinib	6	4	0.057	13	31	14		15				2400	3100										

Supplementary Table S6. Patient characteristics of all patients who underwent additional research biopsies for a suspect lesion during colonoscopy in the ImPACCT study.

Characteristic	N	N = 70[1]
Age at diagnosis, median (min-max)	69	70 (48-86)
Sex, n (%)	69	
Male		39 (57)
Female		30 (43)
Diagnosis, n (%)	70	
Colorectal Cancer		64 (91)
Adenoma		3 (4.3)
Neuroendocrine tumor		3 (4.3)
Sidedness, n (%)	70	
Right colon		36 (51)
Left colon		29 (41)
Rectum		5 (7.1)
(Serious) Adverse Event after colonoscopy, median (min-max)	69	2 (2.9)

[1]Median (Minimum-Maximum); [2] n (%)

Table S7. Differentially expressed genes in PRE- vs POST-imatinib biopsies[a]

Ensembl ID	hugo	corrected-pvalue	foldchange	sublist	Ensembl ID	hugo	corrected-pvalue	foldchange	sublist
ENSG00000236976	RP11-165H4,2	0.000254561	-9.604872494	POST>PRE	ENSG00000199161	MIR126	1.74E-05	43.55143247	PRE>POST
ENSG00000199568	RNU5A-1	0.000554939	-4.983270179	POST>PRE	ENSG00000270706	CTD-2301A4,5	7.06E-06	14.92752009	PRE>POST
ENSG00000224993	RPL29P12	0.000278115	-4.306487765	POST>PRE	ENSG00000271687	MTND5P10	6.01E-06	14.86090339	PRE>POST
ENSG00000223001	RNU2-61P	0.000169927	-1.846289845	POST>PRE	ENSG00000207757	MIR93	0.000443905	13.85513958	PRE>POST
ENSG00000230364	RPL4P3	0.000692985	-1.626980673	POST>PRE	ENSG00000260035	CTD-2651B20,6	0.000371415	13.45459821	PRE>POST
ENSG00000222414	RNU2-59P	7.31E-05	-1.533473725	POST>PRE	ENSG00000258565	BLZF2P	0.000412976	9.810880073	PRE>POST
ENSG00000202538	RNU4-2	0.000137045	-1.487956627	POST>PRE	ENSG00000207870	MIR221	9.60E-05	8.503229711	PRE>POST
ENSG00000228502	EEF1A1P11	0.000356147	-1.187913785	POST>PRE	ENSG00000213600	U73169,1	0.0001527	7.992931264	PRE>POST
ENSG00000250182	EEF1A1P13	0.000132623	-1.16049888	POST>PRE	ENSG00000199133	MIRLET7D	7.59E-09	7.854577158	PRE>POST
ENSG00000172062	SMN1	5.20E-05	-1.151810902	POST>PRE	ENSG00000213538	KRT8P41	0.000924539	7.51902616	PRE>POST
ENSG00000086300	SNX10	0.000354664	-1.150187298	POST>PRE	ENSG00000223916	RP11-353H3,1	0.000508765	7.256642747	PRE>POST
ENSG00000200434	RNA5-8SP2	0.000439784	-1.146066804	POST>PRE	ENSG00000270188	MTRNR2L11	3.21E-05	6.612767625	PRE>POST
ENSG00000099194	SCD	0.000269303	-1.138903323	POST>PRE	ENSG00000259045	RP11-320M16,1	2.76E-05	5.599620472	PRE>POST
ENSG00000132763	MMACHC	0.000242187	-1.11763497	POST>PRE	ENSG00000249271	HNRNPA1P44	0.000929322	5.304927967	PRE>POST
ENSG00000127337	YEATS4	0.000888737	-1.112575205	POST>PRE	ENSG00000213414	CTB-47B8,5	0.000233413	5.131195902	PRE>POST
ENSG00000077152	UBE2T	0.00045149	-1.102631672	POST>PRE	ENSG00000207949	MIR214	1.32E-06	4.825396357	PRE>POST
ENSG00000172893	DHCR7	0.000482777	-1.097835013	POST>PRE	ENSG00000210107	MT-TQ	5.41E-09	4.64489647	PRE>POST
ENSG00000167536	DHRS13	0.000216121	-1.091332053	POST>PRE	ENSG00000202566	MIR421	4.86E-05	4.567437877	PRE>POST
ENSG00000124767	GLO1	0.000174367	-1.091067054	POST>PRE	ENSG00000149506	ZP1	9.55E-05	4.409360991	PRE>POST
ENSG00000113272	THG1L	1.79E-06	-1.090617503	POST>PRE	ENSG00000232680	AC002511,3	0.00038122	4.344827134	PRE>POST
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ENSG00000169246	NPIPB3	0.000459379	1.125991381	PRE>POST
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ENSG00000260565	ERVK13-1	0.000833837	1.12258058	PRE>POST
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ENSG00000166436	TRIM66	1.01E-05	1.120321771	PRE>POST
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ENSG00000173209	AHSA2	9.11E-05	1.11805223	PRE>POST
ENSG00000196123	KIAA0895L	0.000938323	1.115623502	PRE>POST
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ENSG00000186866	POFUT2	0.000533472	1.103784721	PRE>POST
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ENSG00000215908	CROCCP2	8.91E-05	1.102678783	PRE>POST
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ENSG00000198804	MT-CO1	0.000759696	1.100135634	PRE>POST
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ENSG00000108654	DDX5	6.02E-05	1.04489053	PRE>POST
ENSG00000169045	HNRNPH1	0.000509716	1.043936005	PRE>POST

	ENSG00000100201	DDX17	0.000221642	1.043930579	PRE>POST
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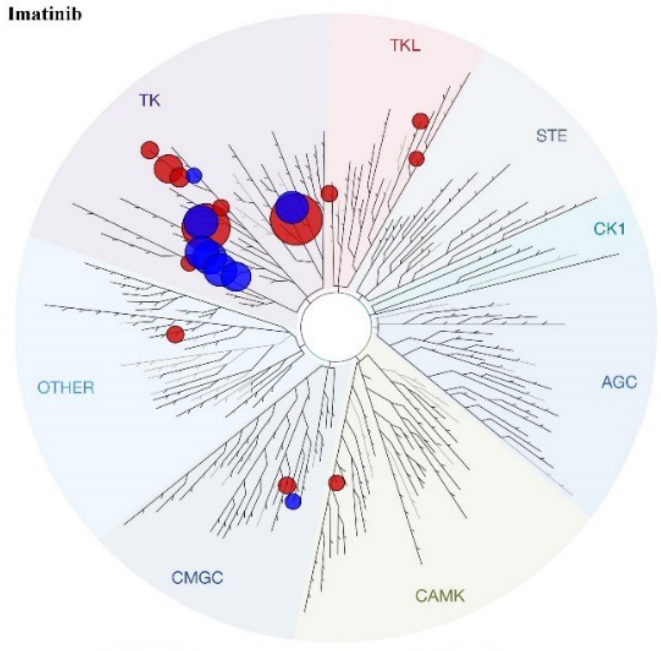
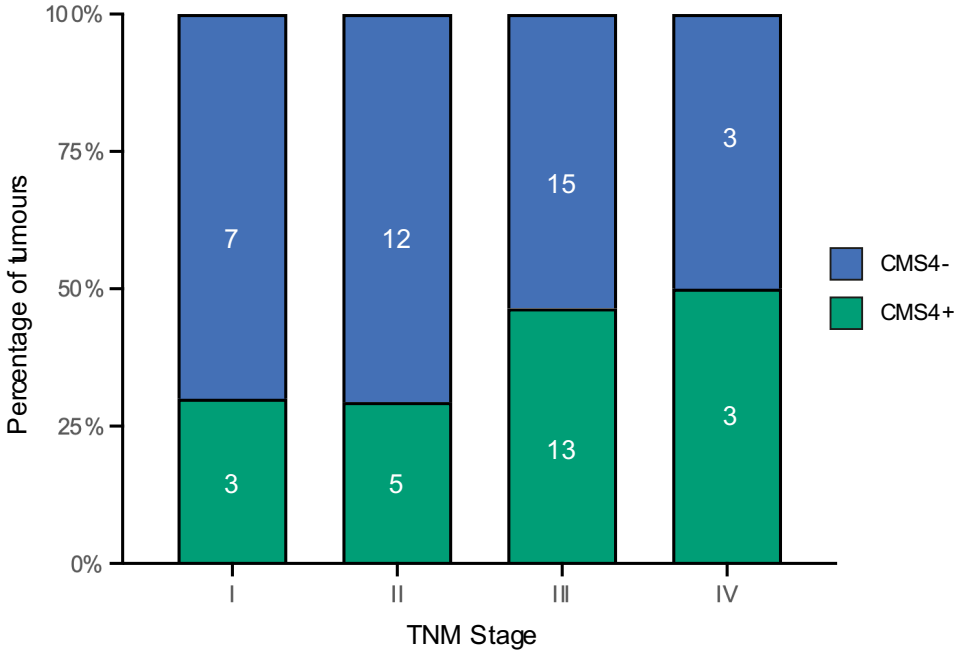
	ENSG00000198408	MGEA5	0.000835622	1.03511337	PRE>POST

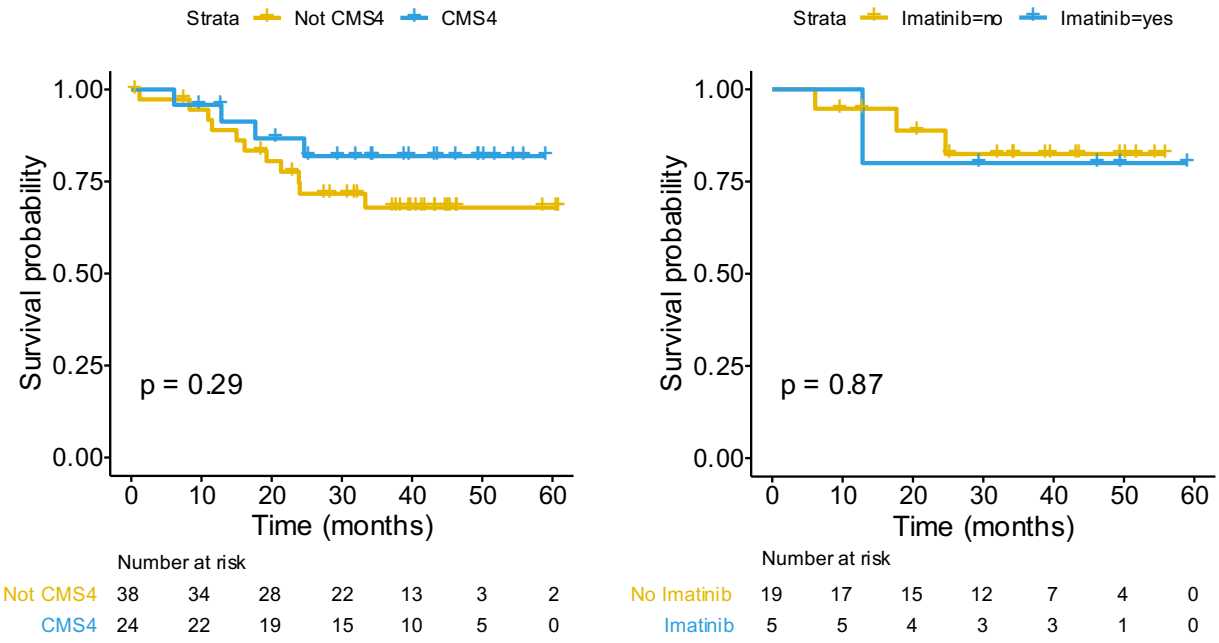
aThis analysis was performed using the R2 omics data analysis platform using a differentially gene expression analysis (ANOVA; FDR <0.001). Gene lists are sorted by the magnitude of fold-change.



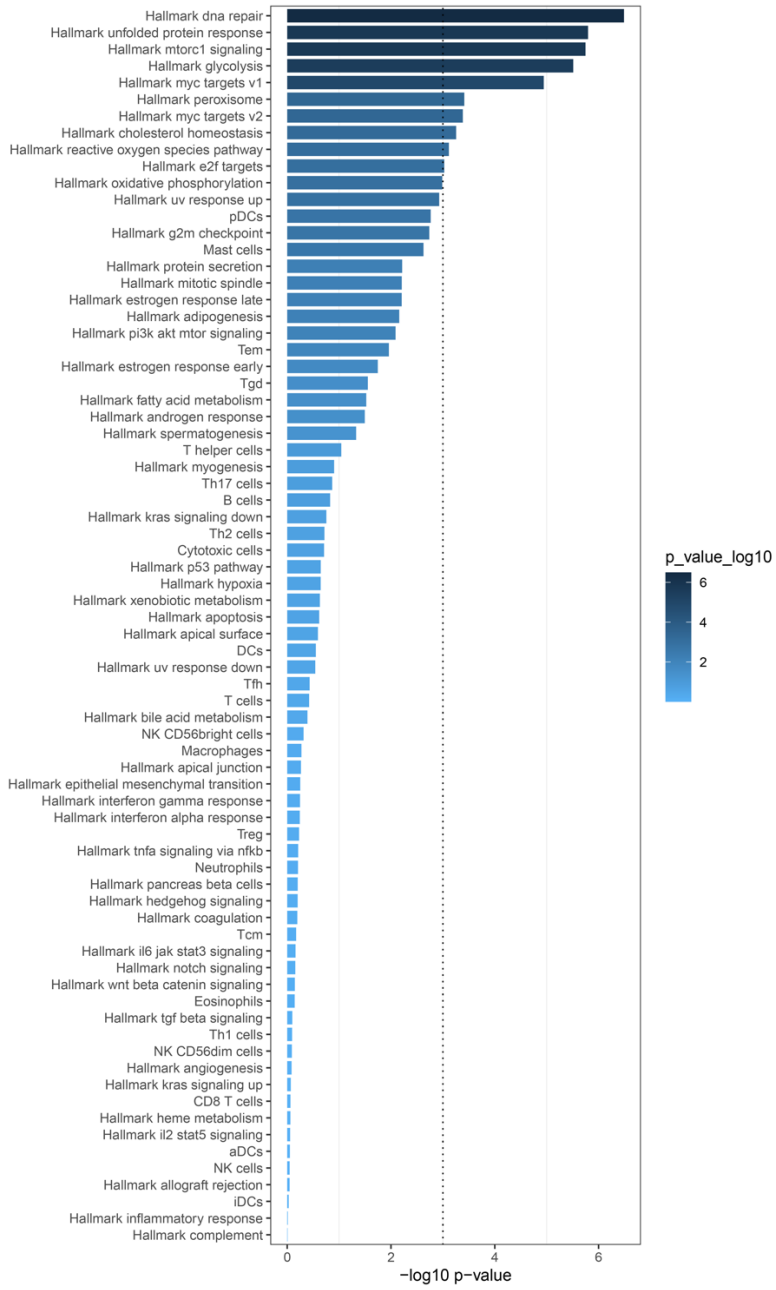
Supplemental Figure S1. Imatinib is a selective inhibitor of tyrosine kinases overexpressed in CMS4 CRC. The activity spectrum of imatinib was mapped on the human kinome. The size of each dot reflects the IC50 of each drug for specific kinases. Larger spots indicate lower IC50s and more efficient inhibition. Imatinib targets that are significantly overexpressed in CMS4 CRC (See Table S4) are highlighted in blue. All other imatinib targets are in red. The image was generated using the TREEspot™ software tool and reprinted with permission from KINOMEscan®, a division of DiscoveRx Corporation, © DISCOVERX CORPORATION 2010.



Supplemental Figure S2. Bar graph showing the incidence of CMS4 across CRC AJCC TNM stages in the ImPACCT cohort.



Supplemental Figure S3. Kaplan Meier survival estimate plots demonstrating overall survival of CRC patients in the ImPACCT cohort. The left panel shows overall survival of patients with CMS4 and non-CMS4 tumors. The right panel shows overall survival of patients with CMS4 tumors who received imatinib treatment *versus* those who did not. Survival distributions were compared using the log-rank test.



Supplemental Figure S4. Bar plot showing the significant and non-significant up- or down-regulated pathways between pre- and post-imatinib biopsies ranked according to significance (min-log10 p-values). The geneset pathways that were used are derived from the MSigDB hallmark geneset collection [3] and the immune compendium signature collection [4].