The management of mCRC: later lines of treatment and molecular analysis

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Disclosures

Contracted Research	Amgen Inc, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Ipsen, Lilly, Merck, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, Sanofi

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Treatment of metastatic disease: later lines of treatment

Table 7. Systemic therapy choices according to the Zurich treatment algorithm for patients with unresectable metastatic disease (excluding those with oligometastatic disease)[a]

Category	Fit patients[b]					
Treatment goal	Cytoreduction (tumour shrinkage)			Disease control (control of progression)		
Molecular profile	*RAS* wt	*RAS* mt	*BRAF* mt	*RAS* wt	*RAS* mt	*BRAF* mt
Third line						
Preferred choice (s)	CT doublet + EGFR antibody[c,f] or irinotecan + cetuximab[f]	Regorafenib or trifluridine/ tipiracil	Regorafenib or trifluridine/ tipiracil	CT doublet + EGFR antibody[c] or irinotecan + cetuximab	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil
Second choice	EGFR antibody monotherapy[f]			EGFR antibody monotherapy[f]		
Third choice	Regorafenib or trifluridine/ tipiracil			Regorafenib or trifluridine/ tipiracil		

Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus 2016 Online Ann Oncol, July 2016

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Treatment of metastatic disease

Recommendation 21: Third-line therapy

- **In *RAS* wild-type and *BRAF* wild-type patients not previously treated with EGFR antibodies cetuximab or panitumumab therapy should be considered**
  - Cetuximab and panitumumab are equally active as single agents [I, A]
  - The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients [II, B]
  - There is no unequivocal evidence to administer the alternative EGFR antibody, if a patient is refractory to one of the EGFR antibodies [I, C].
- **Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies [I, B]**
  - Regorafenib is superior to placebo in terms of OS although there are toxicity concerns in frail patients.
- **Trifluridine/tipiracil is recommended for patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies [I, B].**

Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus 2016 Online Ann Oncol, July 2016

Later lines of treatment:
Which benefit?

	CORRECT		CONCUR		CONSIGN	RECOURSE		JAPANESE TAS	
	Regora-fenib (n=500)	Placebo (n=253)	Regora-fenib (n=136)	Placebo (n=68)	Regora-fenib (2864)	TAS-102 (n=534)	Placebo (n=266)	TAS-102 (n=113)	Placebo (n=57)
PFS	1.9	1.7	2.2	1.7	2.7	2.0	1.7	2.0	1.0
HR	0.49		0.31			0.48		0.41	
OS	6.4	5.0	8.8	6.3	NA	7.1	5.3	9.0	5.6
HR	0.77		0.55			0.68		0.56	

Later lines of treatment:

Adverse events (%)

	CORRECT		CONCUR		CONSIGN	RECOURSE	
	Rego (n=505)	Placebo (n=255)	Rego (n=136)	Placebo (n=68)	Rego (2872)	TAS-102 (534)	Placebo (266)
HFS	**17**	<1	**16**	0	**14**	0	**0**
Fatigue	10	5	3	1	**13**	4	6
HT	7	1	11	3	**15**	NS	NS
Diarrhea	7	1	1	1	5	3	<1
Hypophosp/ anaemia	4	<1	7	0	5	18	3
Rash/ alopecia	6	0	4	0	<5	7	1
Bilirubin	13	8	11	4	**13**	9	12
Neutropenia	<1	0	4	0	1	**38 (4*)**	0

RECOURSE: Onset of Neutropenia and Treatment Outcomes

Earliest onset of Grade ≥3 neutropenia	Overall survival		
	TAS-102	Placebo	HR
Cycle 1 (n = 75, 265)	9.7 mo	5.3 mo	0.45
Cycle 2 (n = 86, 215)	8.7 mo	6.3 mo	0.56
Cycle ≥3 (n = 39, 48)	16.4 mo	10.2 mo	0.36
None (n = 333, 265)	5.5 mo	5.3 mo	0.97

- Patients who developed Grade ≥3 neutropenia had longer median survival, regardless of the timing of onset

Ohtsu A et al. *Proc ASCO* 2016;Abstract 3556.

RECOURSE: Survival and Incidence of Neutropenia in Patients Who Experience Treatment Delays with TAS-102

Extent of Treatment Delay with TAS-102	Pts with Grade ≥3 Neutropenia	Median OS	OS HR
≥8 days (n = 108)	69%	17.3 mo	0.24
≥4 and <8 days (n = 137)	57%	10.1 mo	0.46
None (n = 288)	17%	4.9 mo	1.19
Placebo (n = 265)	0	5.3 mo	-

- Delays in TAS-102 treatment were associated with better survival outcomes and attributed mainly to the onset of Grade ≥3 neutropenia

Ohtsu A et al. *Proc ASCO* 2016;Abstract 3556.

Optimal sequence in chemorefractory patients

Regorafenib → TAS-102

or

TAS-102 → Regorafenib

Role for - nintedanib? NO
- MABp1? NO
- combinations?

Trifluridine/tipiracil: Studies in progress

Indication	Treatment	Phase	Study status
mCRC, 1L	Trifluridine/tipiracil + bevacizumab vs capecitabine + bevacizumab	Phase II	In progress
mCRC, 2L	Trifluridine/tipiracil + oxaliplatin + bevacizumab	Phase I	In progress
mCRC, 2L	Trifluridine/tipiracil + irinotecan + bevacizumab	Phase I	In progress
mCRC, pretreated	Trifluridine/tipiracil plus panitumumab	Phase I/II	In progress
mCRC, Maintenance Therapy Post Induction CT (ALEXANDRIA)	Trifluridine/tipiracil + bevacizumab	Phase II	In progress
mCRC, MSS	Trifluridine/tipiracil + nivolumab	Phase I/II	In progress

Ongoing advances in personalized treatment of mCRC

Targeting multiple signaling pathways involved in tumorigenesis	Induction of immune responses to target tumor cells	Further molecular definition of individual patient subgroups
RAS pathway **Anti-EGFR antibodies**	**MSI tumors:** **Anti-PD(L) antibodies** *** Pembrolizumab, Nivolumab**	**CMS 1-4 tumors**
BRAF pathway **combination therapy e.g.: anti-EGFR, BRAF and MEK inhibitors or PI3K inhibitors or chemotherapy**	**MSS tumors:** **Innovative combination treatment**	
HER2 **Trastuzumab + lapatinib**		

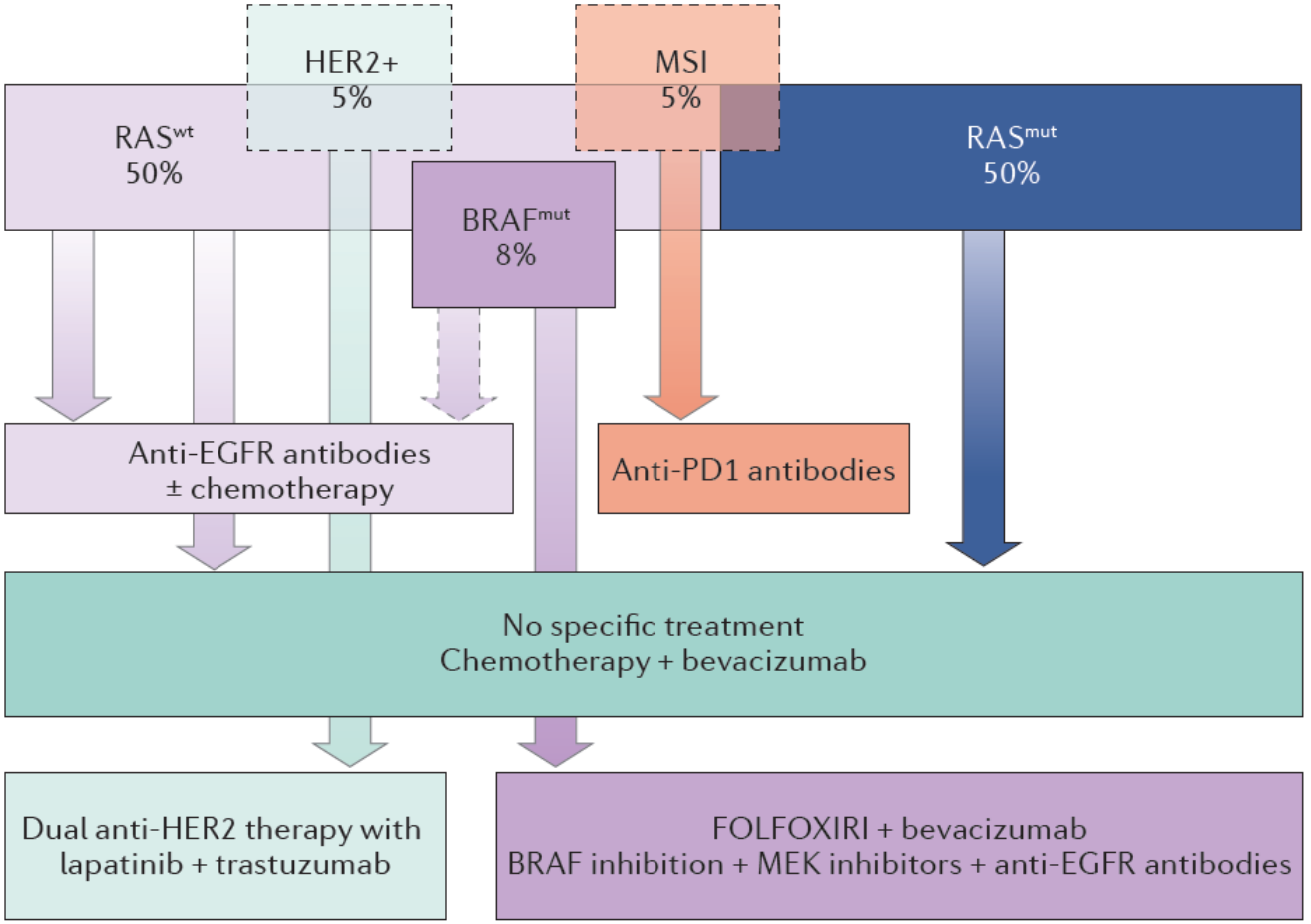


Figure 1| **Proposed landscape of molecularly targeted treatments for metastatic colorectal cancer.** The schematic summarizes the biomarker-based treatment options available and the typical proportions of patients in each biomarker subgroup. FOLFOXIRI, 5-fluorouracil, folinic acid, oxaliplatin, and irinotecan; MSI, microsatellite instability; mut, mutant, PD-1, programmed cell-death protein 1; wt, wild type.

Punt C et al, Nature Reviews Clinical Oncology. Online dec 6, 2016

Table 1 | **Emerging positive predictive biomarkers for treatment selection in advanced CRC**

Alteration	Prevalence in advanced CRC (%)	Agents	Clinical phase	Partial response (*n*/*n* (%))
BRAF^{V600E} mutations	5–8	BRAF TKI + MEK TKI	Phase II	5/43 (12)[142]
		BRAF TKI + MEK TKI + EGFR mAbs	Phase II	9/35 (26)[80]
		BRAF TKI + PI3K TKI + EGFR mAbs	Phase II	9/28 (32)[147]
ERBB2 amplification	5*	Anti-HER2 mAb + pan-ERBB TKI	Phase II	8/27 (30)[75]
NTRK1 fusion	<1	NTRK TKI	Phase I	Case report[150]
ALK fusion	<1	ALK TKI	Phase I	Case report[18]
RNF43 mutations	<5	Porcupine inhibitor	Phase I	Case report[153]
MSI	<5	PD1 mAbs	Phase II	4/10 (40)[155] 9/33 (27)[156]

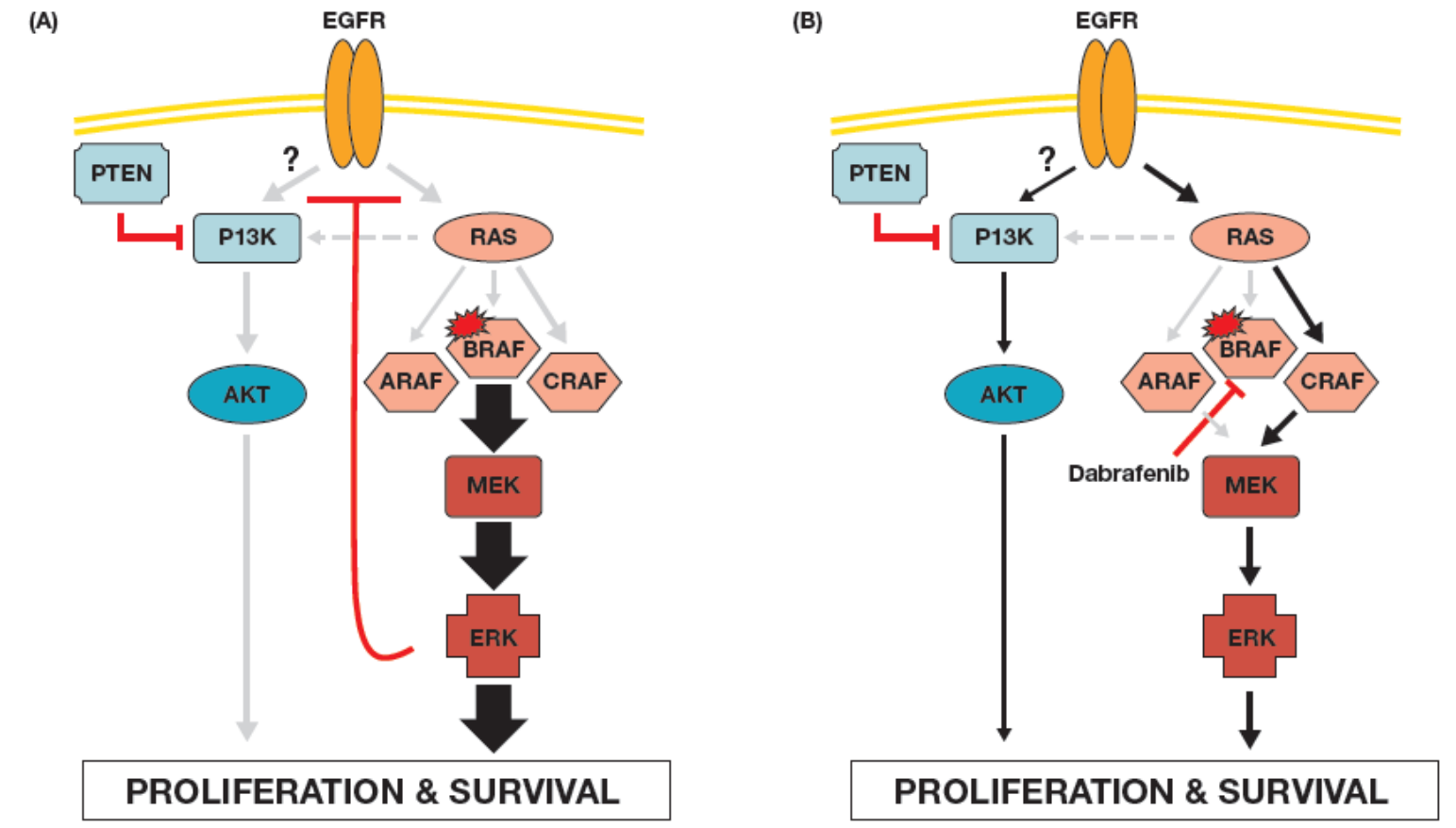
ALK, anaplastic lymphoma kinase; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; MSI, microsatellite instability; NTRK, neurotrophic receptor tyrosine kinase; PD1, programmed cell death protein 1; *RNF43*, ring finger protein 43; TKI, tyrosine kinase inhibitor. *Of patients with *KRAS* wild-type tumours.

Dienstmann R et al, Nat Rev Cancer, 2017, online jan 4

Targeting the RAF pathway in mCRC

Signaling in BRAF mt CRC

Reactivation of EGFR signaling upon BRAF inhibition



Bendell JC, et al. ASCO 2014 (Abstract No. 3515)

BRAF inhibitors for BRAF mt mCRC: Triple combinations

BRAF inhibitor + **EGFR inhibitor** + **MEK inhibitor** or **PI3K/AKT inhibitor** or **Chemo-therapy**

BRAF inhibitor-containing combination (n)	ORR, %	SD, %	Median PFS, months
Cetuximab + vemurafenib + irinotecan (n=17)[1]	35	59	7.7
Cetuximab + encorafenib + alpelisib (n=28)[2]	32	61	4.3
Panitumumab + dabrafenib + trametinib (n=35)[3]	26	57	4.1

1. Hong DS, et al. ASCO 2015 (Abstract No. 3511);
2. Elez E, et al. WCGC 2015 (Abstract No. LBA08);
3. Van Cutsem E, et al. WCGC 2015 (Abstract No. LBA07)

Lapatinib and trastuzumab in HER2 pos. mCRC

Figure 1: **Radiographic response**
Best tumour response of patients treated with lapatinib and trastuzumab (A) and dynamics of response in 25 patients with HER2-positive tumours who received lapatinib and trastuzumab and were assessed with CT scans until disease progression (B). In panel A, bars show the best percentage change in the target tumour burden from baseline. Two patients progressed before the first restaging, so the tumour response was unknown. The dashed line shows a 30% reduction from baseline. Crosses below individual bars denote patients who were responding at the time of data cutoff. In panel B, for each patient, individual lines represent the percentage change in target tumour burden from treatment start (day 0) to the day of objective disease progression, based on serial assessment every 8 weeks. Dashed lines show a 30% reduction (blue) or a 20% increase (red) from baseline. Crosses denote patients who were responding at the time of data cutoff.

Sartore-Bianchi A et al, Lancet Oncol 2016

CONSENSUS MOLECULAR SUBTYPES
summary of associations

CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
MSI, CIMP high Hypermutation	SCN high	Mixed MSI status SCNA low, CIMP low	SCN high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration TGF beta activation Angiogenesis

CIMP, CpG island methylator phenotype; MSI, microsatellite instability; TGF, transforming growth factor

Guinney J et al, Nature Medicine 2015

Table 2 | **Transcriptional identified consensus molecular subtypes (CMS)**

Tumour subtype	CMS1 MSI/immune	CMS2 canonical	CMS3 metabolic	CMS4 mesenchymal
Proportion*	~15%	~40%	~10%	~25%
Genomic features	Hypermutated	SCNA high	Mixed MSI	SCNA high
Genetic drivers	*BRAF*	*APC*	*KRAS*	Unknown
Associated precursors	Serrated	Tubular	Unknown	Serrated
Gene-expression signature	Immune	Wnt/MYC activity	Metabolic deregulation	• TGFβ / EMT • High stromal content
Prognosis	Intermediate	Good	Intermediate	Poor

EMT, epithelial–mesenchymal transition; MSI, microsatellite instability; SCNA, somatic copy-number alterations.*Approximately 10% of cases are not reliably classified into one tumour subtype. Adapted with permission from Guinney J. *et al.* The consensus molecular subtypes of colorectal cancer. *Nat. Med.* **21**, 1350–1356 (2015).

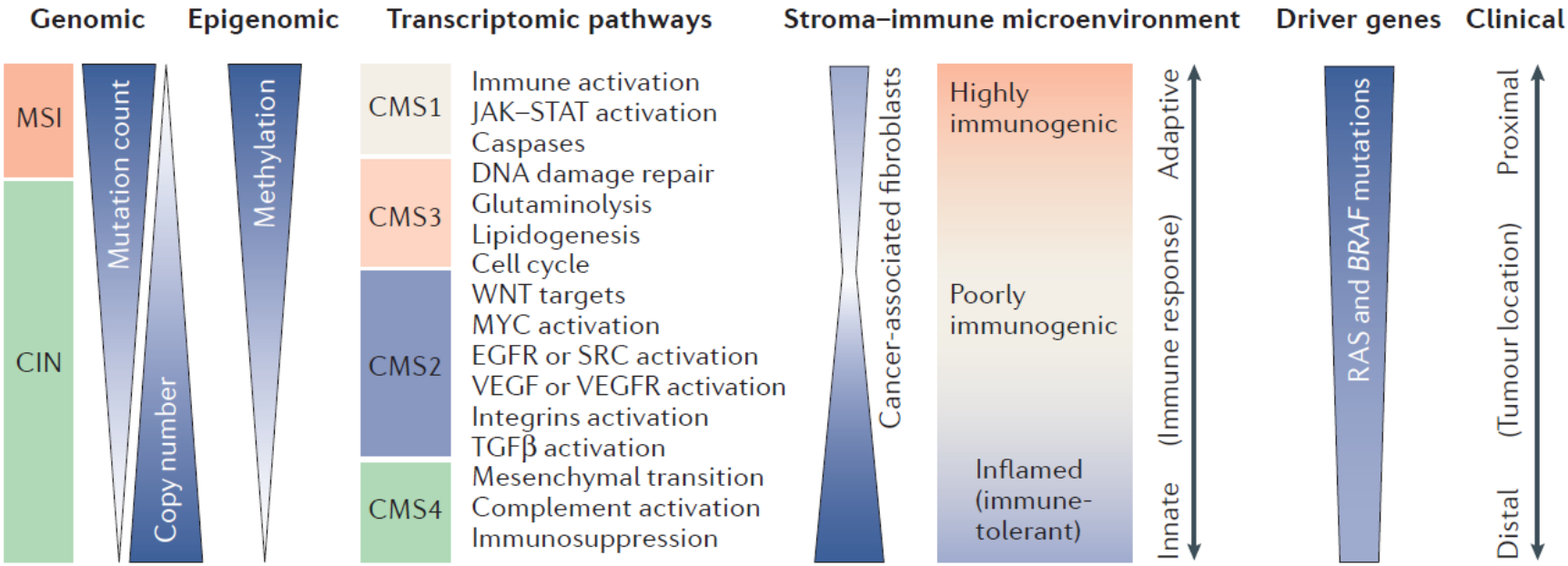


Figure 1 | **Schematic representation of CRC subtypes.** Microsatellite instability (MSI) is linked to hypermutation, hypermethylation, immune infiltration, activation of RAS, *BRAF* mutations, and locations in the proximal colon. Tumours with chromosomal instability (CIN) are more heterogeneous at the gene-expression level, showing a spectrum of pathway activation ranging from epithelial canonical (consensus molecular subtype 2 (CMS2)) to mesenchymal (CMS4). Tumours with CIN are mainly diagnosed in left colon or rectum, and their microenvironment is either poorly immunogenic or inflamed, with marked stromal infiltration. A subset of CRC tumours enriched for RAS mutations has strong metabolic adaptation (CMS3) and intermediate levels of mutation, methylation and copy number events. EGFR, epidermal growth factor receptor; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor-β; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Dienstmann R et al, Nat Rev Cancer, 2017, online jan 4