Optimizing targeted therapy in colorectal cancer: How do the latest data impact clinical practice?

Disclaimer

- *Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions*
- *The presenting faculty have been advised by touchIME® to ensure that they disclose any such references made to unlabelled or unapproved use*
- *No endorsement by touchIME® of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in touchIME® activities*
- *touchIME® accepts no responsibility for errors or omissions*

How can we refine first-line therapy choice in mCRC? Molecular biomarkers and clinical features

Prof. Rachel Riechelmann

A.C. Camargo Cancer Center
São Paulo, Brazil

touch ONCOLOGY®

What biomarkers and clinical features are available to refine first-line treatment selection in mCRC?

Predictive and prognostic value of mCRC biomarkers and clinical features

ESMO
ESMO^{ASIA}
NCCN

RAS (*KRAS* and *NRAS*) mutation[1–3]

- Negative **predictive** biomarker for anti-EGFR treatment response

BRAF-V600E mutation[1–3]

- Negative **prognostic** biomarker
- Tested at same time as *RAS* mutational status for prognostic assessment

MSI status[1–3]

- Negative **prognostic** biomarker
- Positive **predictive** biomarker for immune checkpoint inhibitor treatment response

Tumour sidedness[2,3]

- Location of primary tumour can be **prognostic and predictive** of response to anti-EGFR treatment

NCCN only

HER2 and *NTRK* fusions in *RAS* wt and *BRAF*[2]

CMS classification (subtypes CMS 1, 2, 3 and 4) is not yet recommended by ESMO, ESMO^{ASIA} or NCCN guidelines for use in clinical practice[2]

BRAF, v-Raf murine sarcoma viral oncogene homolog B; CMS, consensus molecular sub-type; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; *HER2*, human epidermal growth factor receptor 2; *KRAS*, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; *NTRK*, neurotrophic tyrosine receptor kinase; *NRAS*, neuroblastoma *RAS* oncogene homolog; *RAS*, rat sarcoma oncogene; wt, wild-type.

1. Van Cutsem E, et al. *Ann Oncol.* 2016;27:1386–422; 2. Yoshino T, et al. *Ann Oncol.* 2018; 29:44–70; 3. NCCN Clinical Practice Guidelines – Colon Cancer v.2.2021. Updated January 21, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 29 March 2021).

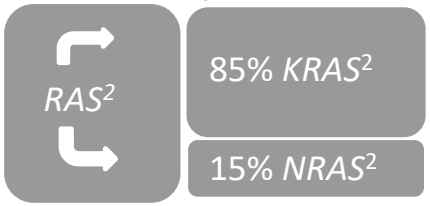
touch ONCOLOGY®

What is the role of *RAS* mutational status when determining first-line treatment for mCRC?

The role of *RAS* mutations in newly diagnosed mCRC

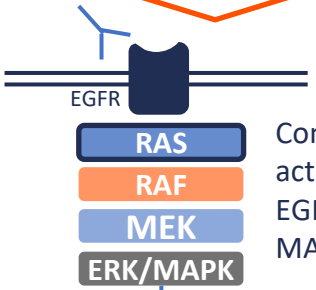
RAS-mutant mCRC is a negative predictive biomarker for anti-EGFR treatment response[1]

RAS mutations occur in ~44% of patients with mCRC[1]



Prevalence of *RAS* mutations by tumour location[3]

RAS-mutant mCRC confers poor response to anti-EGFR treatment[1]



Constitutive activation of the EGFR-mediated MAPK pathway

Cancer cell proliferation, differentiation and survival

RAS mutation status determines first-line treatment[4–6]

***RAS* status testing** should be carried out in newly diagnosed mCRC and **is mandatory before anti-EGFR treatment** (cetuximab and panitumumab)[4–6]

Preferred treatment for *RAS*-mutant mCRC:[4–6]
Cytotoxic doublet/triplet + bevacizumab, in suitable patients

EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; *KRAS*, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; mCRC, metastatic colorectal cancer; NCCN, National Comprehensive Cancer Network; *NRAS*, neuroblastoma *RAS* oncogene homolog; RAF, rapidly accelerated fibrosarcoma; *RAS*, rat sarcoma oncogene; wt, wild-type.

1. Kafatos G, et al. *Biomark Med.* 2017;11:751–60; 2. Li Z-N, et al. *Gastroenterol Rep.* 2020; 8:192–205; 3. Bylsma L, et al. *Cancer Medicine.* 2020;9:1044–57; 4. Van Cutsem E, et al. *Ann Oncol.* 2016;27:1386–422; 5. Yoshino T, et al. *Ann Oncol.* 2018;29:44–70; 6. NCCN Clinical practice guidelines – Colon Cancer v.2.2021. Updated January 21, 2021. Available at www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 29 March 2021).

touch ONCOLOGY®

Presence of the *BRAF*-V600E mutation is a known adverse prognostic factor in mCRC: What are the molecular and clinical characteristics of this subgroup of patients?

BRAF-V600E-mutated mCRC: Clinical implications

Clinical features

***BRAF* prevalence**:[1]

Right side **16.3%** | Left side **4.3%**

Right-sided primary tumour location[2]

Older women >60 years[2]

Unique metastatic pattern[2]

90% of *BRAF* mutations are *BRAF*-V600E[2]

Molecular features

MSI high[2]

45% CMS1 (hypermutated, MSI, immune subtype)[2]

Some studies report that *BRAF* mutations occur exclusively in *KRAS* wt mCRC[3]

***BRAF*-V600E mutation** is indicative of a poor response to anti-EGFR therapies[2]

Standard first-line treatment:[2,4] Double/triple CT + bevacizumab; ~60% receive second-line CT

Beyond first-line:[4] Evaluation of combination targeted approaches with EGFR and *BRAF*/MEK/ERK inhibitors ± standard CT

BRAF, v-Raf murine sarcoma viral oncogene homolog B; CMS, consensus molecular sub-type; CT, chemotherapy; EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; mCRC, metastatic colorectal cancer; MEK, mitogen-activated protein kinase; MSI, microsatellite instability; wt, wild-type.

1. Bylsma L, et al. *Cancer Medicine.* 2020;9:1044–57; 2. Fanelli G, et al. *Cancer Cell Int.* 2020;20:30; 3. Li Z-N, et al. *Gastroenterol Rep.* 2020;8:192–205; 4. Ducreux M, et al. *Ther Adv Med Oncol.* 2019;11:1–15.

touch ONCOLOGY®

How does knowledge of MSI status help guide treatment choice for patients with mCRC in the first-line setting?

touch ONCOLOGY®

Rationale for identifying MSI-H tumours in mCRC

MSI refers to the hypermutable state of cells caused by impaired DNA MMR[1]

Characteristics of MSI-H tumours in mCRC

- Low prevalence (4–8%)[2]
- dMMR system[2]
- High TMB[3]
- High PD-L1 expression[3]
- Anti-EGFR therapy resistance[3]
- Overlap with right-sided primary tumours[3]
- 30% harbour *BRAF*-V600E mutation[2]

MSI-H predicts benefit from immune checkpoint inhibitor use in mCRC[3]

Testing for MMR proteins or MSI recommended by ESMO and ESMO[ASIA] guidelines in the metastatic disease setting[2,4] and by NCCN guidelines in all newly diagnosed CRC[5]

FDA and EMA approval of first-line pembrolizumab for unresectable or MSI-H or dMMR CRC offers a new guideline-recommended treatment approach for these patients [5–7]

BRAF, v-Raf murine sarcoma viral oncogene homolog B; CRC, colorectal cancer; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; mCRC, metastatic CRC; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NCCN, National Comprehensive Cancer Network; PD-L1, programmed death ligand 1; TMB, tumour mutational burden.

1. Gatalica Z, et al. *Fam Cancer.* 2016;15:405–12; 2. Van Cutsem E, et al. *Ann Oncol.* 2016;27:1386–422; 3. Kim S, Kim T. *ESMO Open.* 2020;5:e000634; 4. Yoshino T, et al. *Ann Oncol.* 2018;29:44–70; 5. NCCN Clinical practice guidelines – Colon Cancer v.2.2021. Updated January 21, 2021. Available at www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 29 March 2021); 6. FDA News Release. June 2020. Available at: www.fda.gov/news-events/press-announcements/fda-approves-first-line-immunotherapy-patients-msi-hdmmr-metastatic-colorectal-cancer#:~:text=Today%2C (accessed 29 March 2021); 7. EMA 28 January 2021. Available at: www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-keytruda-ii-90_en.pdf (accessed 29 March 2021).

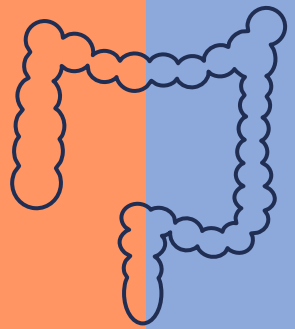
touch ONCOLOGY®

How important is location of the primary tumour for first-line mCRC management?

Primary tumour location in newly diagnosed mCRC

Left-sided tumours are associated with significantly reduced risk of mortality vs right-sided tumours (HR, 0.82; 95% CI, 0.79–0.84; p<0.001)[1]

Right-sided[2]	Left-sided[2]
• **Worse prognosis** • **Lack of benefit with first-line anti-EGFR therapy** • Mucinous histology • CMS1 • Serrated pathway • JAK-STAT gene signature • MSI-H/dMMR • *RAS* or *BRAF* mutations • CIMP high	• **Better prognosis** • **Benefit with first-line anti-EGFR therapy in *RAS* wt mCRC** • CMS2 • Activation of Wnt and MYC pathways • Beta-catenin activation • *EGFR* and *HER2* upregulation



- ESMO 2016 guideline recommendations do not consider primary tumour location[3]
- **ESMO[ASIA] and NCCN guidelines recommend first-line anti-EGFR therapy in left-sided *RAS* wt mCRC[4,5]**
- Potential use of tumour sidedness as a predictive marker in second and subsequent lines of mCRC requires further investigation[2]

BRAF, v-Raf murine sarcoma viral oncogene homolog B; CIMP, CpG island methylator phenotype; CI, confidence interval; CMS, consensus molecular sub-type; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; *HER2*, human epidermal growth factor receptor 2; HR, hazard ratio; JAK-STAT; janus kinase-signal transducer and activator of transcription; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; NCCN, National Comprehensive Cancer Network; *RAS*, rat sarcoma oncogene; wt, wild-type.

1. Petrelli F, et al. *JAMA Oncol.* 2017;3:211–9; 2. Bahl A, et al. *Front Oncol.* 2020;10:964; 3. Van Cutsem E, et al. *Ann Oncol.* 2016;27:1386–422; 4. Yoshino T, et al. *Ann Oncol.* 2018;29:44–70. 5. NCCN Clinical Practice Guidelines – Colon Cancer v.2.2021. Updated January 21, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 29 March 2021).

touch ONCOLOGY®

How to address resistance to anti-EGFR therapy: A focus on rechallenge therapies

Dr Diana Hanna
Hoag Cancer Center and
Keck School of Medicine of
University of Southern California
California, USA

touch ONCOLOGY®

Why is rechallenge with anti-EGFR treatments an important strategy in mCRC?

Rechallenge as a treatment strategy in *RAS* wt mCRC

First-line treatment for *RAS* wt mCRC[1–3]

Initial response

- Anti-EGFR agents (e.g. cetuximab) + chemotherapy

Toxicity/acquired resistance

- Discontinuation
- Progressive disease
- Lack of alternative treatment lines

Rechallenge strategy[1–4]

Anti-EGFR therapy-free interval

- May mitigate toxicity and reduce resistant clones
- No consensus on specific duration of interval

Re-administration of anti-EGFR therapy

- In patients with *RAS* wt mCRC who have **previously responded** to anti-EGFR therapy

Difference between rechallenge and reintroduction strategies

- **Rechallenge** is the re-administration of an agent in patients who had initially responded and then **discontinued** treatment owing to **development of resistance** and **progressive disease**[1,4,5]
- **Reintroduction** is the re-administration of an agent in patients whose **tumour was not resistant** and **discontinuation was due to reasons other than progressive disease**[1]

EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; *RAS*, rat sarcoma oncogene; wt, wild-type.

1. Karani A, et al. *Ecancermedicalscience.* 2020;14:1069; 2. Goldberg RM, et al. *ESMO Open*. 2018;3:e000353; 3. Parseghian CM, et al. *Clin Cancer Res*. 2019;25:6899–908; 4. Martinelli E, et al. *Ann Oncol*. 2020;31:30–40; 5. Chong L, et al. *Target Oncol.* 2020;15:751–7.

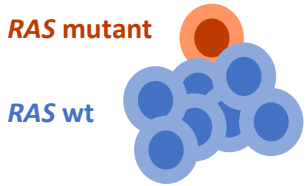
What mechanisms are involved in resistance to anti-EGFR therapies?

touch ONCOLOGY®

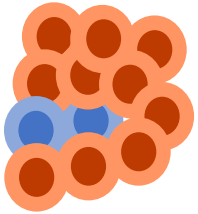
Mechanisms of anti-EGFR resistance in *RAS* wt mCRC

First-line EGFR blockade

***RAS* wt mCRC responders[1]** → **Tumour heterogeneity and drug-induced clonal expansion[1]** → **Acquired resistance to anti-EGFR therapy[1]**



Reduction of *RAS* wt tumour cell population[2,3]



Proliferation of pre-existing or newly evolving mutant subclones with **resistance mechanisms –** activation of signalling pathways that 'bypass' the drug target[2,3]

Mechanisms of resistance may also be driven by:

EGFR ECD mutations[2,4]
- *EGFR* mutations are rare in untreated tumours

HER2 amplification[4,5]
- 2% of patients have acquired mutations or amplification of *HER2* gene after anti-EGFR therapy

MET amplification[4,6]
- Prevalence in mCRC=2%

***RAS-MEK-ERK* pathway alterations[2,4]**
- ~50% of patients with acquired resistance have a detectable secondary *RAS* mutation

Angiogenesis[4]
- Increase in VEGF

ECD, ectodomain; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; *HER2*; human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; MEK, mitogen-activated protein kinase; MET, MET proto-oncogene receptor tyrosine kinase; *RAS*, rat sarcoma oncogene; VEGF, vascular endothelial growth factor; wt, wild-type.

1. Karani A, et al. *Ecancermedicalscience* 2020;14:1069; 2. Parseghian CM, et al. *Ann Oncol.* 2019;30:243–9. 3. Goldberg RM, et al. *ESMO Open*. 2018;3:e000353.
4. Martinelli E, et al. *Ann Oncol.* 2020;31:30–40; 5. Li Q-H, et al. *Gastroenterol Rep.* 2020;8:179–91; 6. Martini G, et al. *Cancer Treat Rev.* 2020;86:102023.

touch ONCOLOGY®

What is the evidence for rechallenge with anti-EGFR therapies in *RAS* wt mCRC?

Evidence for anti-EGFR rechallenge in *RAS* wt mCRC

Santini et al, 2012[1] Multicentre phase II prospective study	N=39, refractory mCRC, rechallenge with cetuximab + irinotecan	**ORR: 53.8%** **PFS: 6.6 months**	First demonstration of a potential clinical benefit of anti-EGFR rechallenge in *RAS* wt mCRC
Cremolini et al, 2019[2] Single-arm, proof-of-concept prospective study	N=28, *RAS* and *BRAF* wt mCRC and acquired resistance, rechallenge with cetuximab + irinotecan	**ORR: 21%** **DCR: 54%**	Rechallenge with cetuximab + irinotecan may be active in in *RAS* and *BRAF* wt mCRC
Karani et al, 2020[3] Retrospective analysis	N=68, mCRC, prior anti-EGFR therapy interrupted due to PD (**ReCh group**) or for other reasons (**ReIn group**) Retreatment with anti-EGFR + CT	ReCh and ReIn groups: **ORR: 18% and 52%** **PFS: 3.3 and 8.4 months**	Rechallenge resulted in short PFS and low ORR, but reintroduction of anti-EGFR + CT before complete resistance arose prolonged PFS
Chong et al, 2020[4] South Australian registry study	N=22 mCRC with PD had a first anti-EGFR rechallenge (**ReCh 1**), n=7 had a second rechallenge (**ReCh 2**)	For ReCh 1 and ReCh 2: **DCR: 45.4% and 28.6%** **PFS: 4.1 and 3.5 months** **OS: 7.7 months** (from ReCh)	Rechallenge provided clinical benefit in *RAS* wt mCRC

BRAF, v-raf murine sarcoma viral oncogene homolog B; CT, chemotherapy; DCR, disease control rate; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; mCRC, metastatic colorectal cancer; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; *RAS*, rat sarcoma oncogene; ReCh, rechallenge; ReIN, reintroduction; wt, wild-type.

1. Santini D, et al. *Ann Oncol.* 2012;23:2313e2318; 2. Cremolini C, et al. *JAMA Oncol.* 2019;5:343e350; 3. Karani A, et al. *Ecancermedicalscience.* 2020;14:1069; 4. Chong L, et al. *Target Oncol.* 2020;15:751–7.

What ongoing trials are investigating different rechallenge strategies for *RAS* wt mCRC?

Selected ongoing trials are exploring different rechallenge strategies in *RAS* wt mCRC

CAVE[1,2]

- **Phase II, single-arm trial (EudraCT 2017-004392-32)**
- **Aim:** Determine OS with cetuximab + avelumab
- **Population:** Third-line; PR/CR achieved in first-line with anti-EGFR therapy; second-line treatment >4 months ago; pre-treated with >2 lines

FIRE-4[1,3]

- **Phase III, randomized trial (NCT02934529)**
- **Aim:** Compare OS of cetuximab + irinotecan vs third-line SOC
- **Population:** Third-line; previous therapy with FOLFIRI + cetuximab in first-line; prior PR/CR (PFS >6 months); second-line treatment with FOLXFOX + bevacizumab

PULSE[4,5]

- **Phase II, open-label trial (NCT03992456)**
- **Aim:** Compare OS of panitumumab rechallenge vs SOC (TAS102 or regorafenib)
- **Population:** Third-line; progression/intolerance/ contraindication to CT, anti-VEGF and anti-PD-1; progression after >4 months after anti-EGFR therapy

Other rechallenge treatment strategies[1,6]

- Cetuximab or panitumumab alone
- Panitumumab + TAS102
- Panitumumab followed by regorafenib vs the reverse sequence

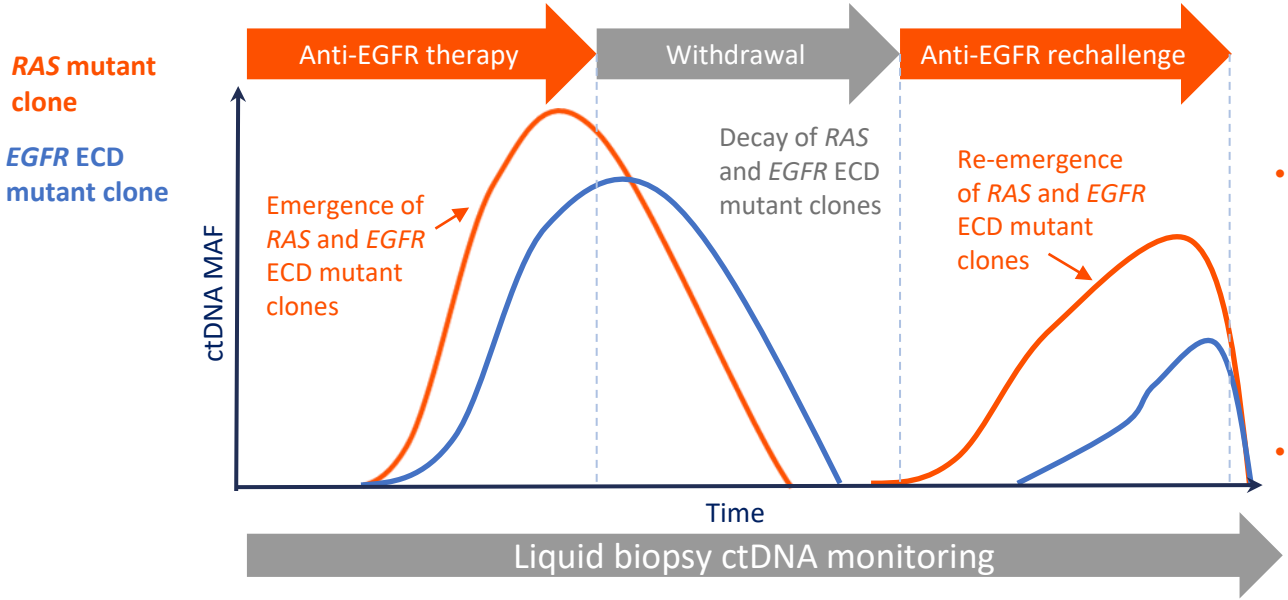
CR, complete response; CT, chemotherapy; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; mCRC, metastatic colorectal cancer; PD-1, programmed cell death protein 1; PFS, progression-free survival; PR, partial response; OS, overall survival; *RAS*, rat sarcoma oncogene; SOC, standard of care; TAS102, trifluridine-tipiracil; VEGF, vascular endothelial growth factor; wt, wild-type.

1. Martinelli E, et al. *Ann Oncol.* 2020;31:30–40; 2. EudraCT 2017-004392-32. Available at: clinicaltrialsregister.eu (accessed 29 March 2021); 3. NCT02934529. Available at: clinicaltrials.gov (accessed 29 March 2021); 4. Strickler J, et al. *J Clin Oncol.* 2021:39: Abstr TPS143; 5. NCT03992456. Available at: clinicaltrials.gov (accessed 29 March 2021). 6. NCT04787341. Available at: clinicaltrials.gov (accessed 29 March 2021).

What is the role of liquid biopsy ctDNA testing in guiding rechallenge therapy in mCRC?

Use of liquid biopsy ctDNA to monitor tumour dynamics in mCRC

Illustration of ctDNA-guided rechallenge therapy in mCRC[1]



- Monitoring the emergence and decay of mutant clones using liquid biopsy ctDNA could help guide rechallenge therapy[1,2]
- Using ctDNA, one study found that percentage of mutated *KRAS* alleles declines when anti-EGFR therapy is suspended and remains below the LoD across subsequent lines of therapy[3]
- High cost remains a limitation to the potential clinical utility of ctDNA analysis[2]

BRAF, v-raf murine sarcoma viral oncogene homolog B; ctDNA, circulating tumour DNA; ECD, ectodomain; EGFR, epidermal growth factor receptor; LoD, limit of detection; MAF, mutant allele frequency; mCRC, metastatic colorectal cancer; *RAS*, rat sarcoma oncogene.

1. Siravegna G, Bardelli A. *Ann Oncol.* 2019;30:1671; 2. Vera R, et al. *Clin Transl Oncol.* 2020;22:647–62; 3. Siravegna, et al. *Nat Med*. 2015;21:827.

touch ONCOLOGY®

Treatment of *BRAF*-V600E-mutated mCRC: Current landscape and latest data

Prof. Takayuki Yoshino

National Cancer Center
Hospital East
Kashiwa, Japan

touch ONCOLOGY®

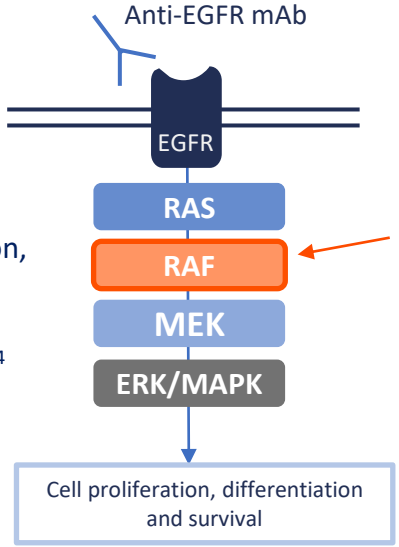
What are the challenges in the treatment of patients with *BRAF*-mutated mCRC?

BRAF-V600E-mutated mCRC is an aggressive subtype with a poor prognosis and treatment response

- **8–15%** of CRCs have a *BRAF* gene mutation and **90%** of *BRAF* mutations are **V600E**[1]
- *BRAF*-V600E-mutated mCRC is associated with **poor response to all the standard treatments, including first-line therapy,**[1] and a median OS of approximately 11 months[2]
- Poor response may in part be due to ***RAS*-independent stimulation** of the MAPK pathway[3]

BRAF is associated with anti-EGFR therapy resistance[4]

BRAF plays an important role in cell differentiation, proliferation and survival through MAPK pathway[1,4]



Anti-EGFR therapies are unable to block the downstream signal of EGFR in *BRAF*-mutated mCRC leading to **constitutive activation of MAPK pathways**[4]

BRAF, v-raf murine sarcoma viral oncogene homolog B; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; mCRC, metastatic CRC; MEK, mitogen-activated protein kinase; OS, overall survival; *RAS*, rat sarcoma oncogene.

1. Fanelli G, et al. *Cancer Cell Int.* 2020;20:30; 2. Seligmann JF, et al. *Ann Oncol.* 2017;28:562–8; 3. Taieb J, et al. *Br J* Cancer. 2019;121:434–42; 4. Li Z-N, et al. *Gastroenterol Rep.* 2020; 8:192–205.

touch ONCOLOGY®

What is the current treatment approach for patients with *BRAF*-V600E-mutated mCRC?

touch ONCOLOGY®

Treatment approaches for *BRAF*-V600E-mutated mCRC

First-line

Current approach

- Double/triple chemotherapy combination of 5-fluorouracil with irinotecan and/or oxaliplatin plus bevacizumab[1]
- 40% patients unable to receive second-line chemotherapy treatment due to the aggressiveness of *BRAF*-V600E-mutated mCRC[2]

Beyond first-line

Limited therapeutic effect with single-agent BRAF inhibitors[1]

- *BRAF* inhibition causes rapid feedback activation of EGFR and continued proliferation *BRAF*-V600E-mutated tumour cells[1]

A new standard for previously treated *BRAF*-V600E-mutated mCRC?

FDA approved approach: doublet therapy of encorafenib + cetuximab[3]

- Combining BRAF, MEK and EGFR inhibitors has shown promising activity[2]
- Double or triple combination targeted therapy may overcome the feedback activation of EGFR[4]

2020 JSMO guidelines: *BRAF*-V600E-mutation testing is strongly recommended to determine optimal treatment[5]
2021 NCCN Guidelines: Encorafenib + cetuximab or panitumumab for previously treated *BRAF*-V600E-mutated mCRC[6]

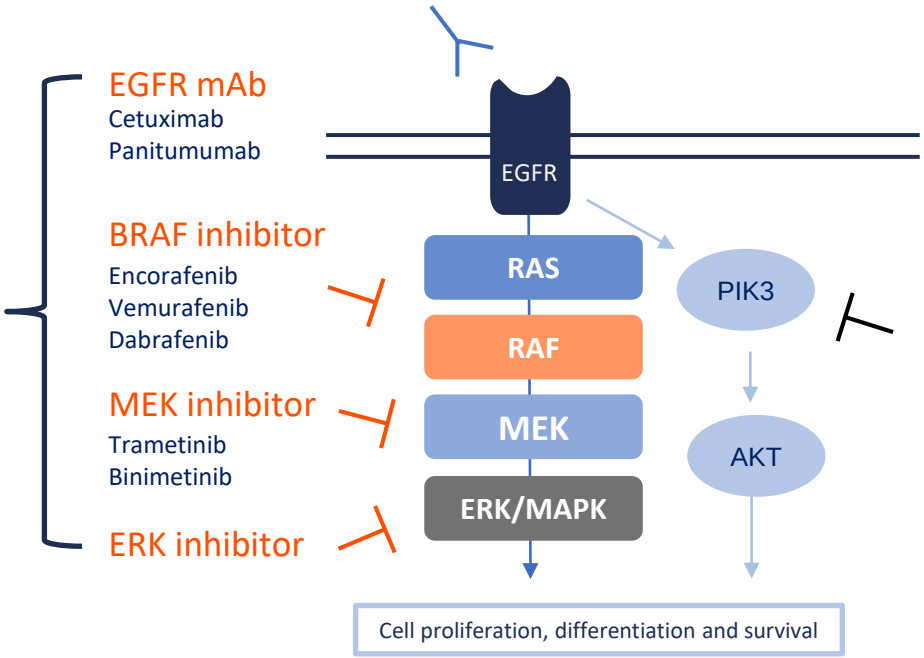
BRAF, v-raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; JSMO, Japanese Society of Medical Oncology; MEK, mitogen-activated protein kinase; mCRC, metastatic colorectal cancer; NCCN, National Comprehensive Cancer Network.

1. Ducreux M, et al. *Ther Adv Med Oncol.* 2019;11:1–15; 2. Fanelli G, et al. *Cancer Cell Int.* 2020;20:30; 3. FDA. April 2020. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-combination-cetuximab-metastatic-colorectal-cancer-braf-v600e-mutation (accessed 7 March 2021);
4. Li Z-N, et al. *Gastroenterol Rep.* 2020;8:192–205; 5. Ebi H, et al. *Cancer Sci.* 2020;111:3962–9; 6. NCCN Clinical Practice Guidelines – Colon Cancer v.2.2021. Updated January 21, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 7 March 2021).

Combination targeted approaches under evaluation

Broader combination approaches for *BRAF*-V600E-mutated mCRC are being explored[1,2]

- EGFR and BRAF/MEK/ERK inhibitors ± standard CT[1,2]
- MAPK-targeted agents combined with checkpoint inhibitors (e.g. nivolumab)[1,2]



Early studies have evaluated possible combination approach with a PIK3C alpha inhibitor[1]

AKT, protein kinase B; *BRAF*, v-raf murine sarcoma viral oncogene homolog B; CT, chemotherapy; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; mCRC, metastatic colorectal cancer; MEK, mitogen-activated protein kinase; MET, MET proto-oncogene receptor tyrosine kinase; PIK3, phosphoinositide 3-kinases; *RAS*, rat sarcoma oncogene.

1. Ducreux M, et al. *Ther Adv Med Oncol.* 2019;11:1–15; 2. Mauri G, et al. *Cancers (Basel).* 2021;13:137.

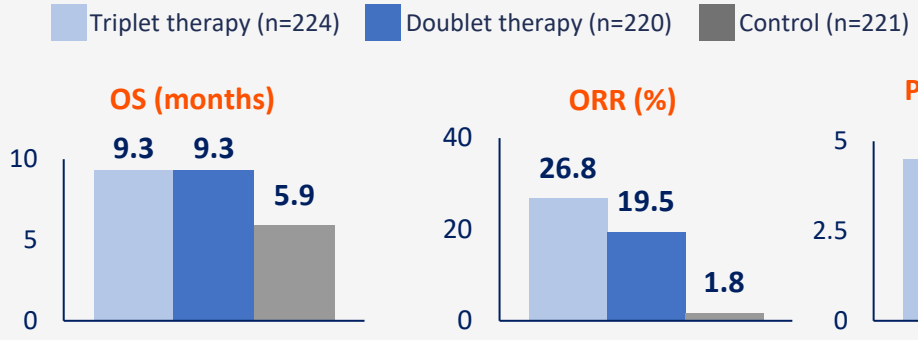
touch ONCOLOGY®

What are the latest data from the BEACON trial, which aims to investigate the use of BRAF, MEK, and EGFR inhibitors in *BRAF*-V600E-mutated mCRC in the second-line setting?

Evidence for doublet therapy in *BRAF*-V600E-mutated mCRC

- Phase III BEACON trial data led to **approval of doublet therapy with encorafenib + cetuximab in *BRAF*-V600E-mutated mCRC, following prior therapy**[1–4]
- **Outcomes:** Encorafenib + cetuximab ± binimetinib improved OS and ORR in previously treated patients with *BRAF*-V600E-mutated mCRC vs standard CT + cetuximab (control)[1–3]

Updated analysis, February 2021[3]



- **Significantly improved survival and tumour response** with doublet and triplet therapy vs control[3]
- **Substantial improvement in patient-reported QOL** with doublet and triplet therapy vs control[5]
- Safety consistent with the primary analysis, with **no new safety signals observed**[3]

BRAF, v-raf murine sarcoma viral oncogene homolog B; CT, chemotherapy; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; ORR overall response rate; OS, overall survival; PFS, progression-free survival; QOL, quality of life.

1. NCT02928224. Available at: ClinicalTrials.gov (accessed 7 March 2021); 2. Kopetz S, et al. *J Clin Oncol.* 2020;38:Abstr 4001; 3. Tabernero J, et al. *J Clin Oncol.* 2021;39:273–84; 4. FDA. April 2020. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-combination-cetuximab-metastatic-colorectal-cancer-braf-v600e-mutation (accessed 7 March 2021); 5. Kopetz S, et al. *J Clin Oncol. 2020;*38:Abstr 8.

touch ONCOLOGY®

What data are available for a combination approach using BRAF, MEK and EGFR inhibitors in *BRAF*-V600E-mutated mCRC in the first-line setting?

Evidence for a combination approach in *BRAF*-V600E-mutated mCRC

Phase II ANCHOR trial: BRAF, MEK and EGFR inhibitor combination[1,2]

Study design and patients

- Open-label, single-arm, two-stage study in patients without prior mCRC therapy
- Study drugs: **encorafenib, binimetinib and cetuximab**
- N=40 (stage 1 analysis)
- High proportion of patients ≥65 years old and advanced stage at diagnosis

Efficacy outcomes

- **ORR: 50%**
- **PFS: 4.9** months
- **85%** of patients had a **reduced tumour size**

Safety

- **68%** had grade ≥3 AEs
- Most common AEs: diarrhoea, acute kidney injury and anaemia

Ongoing phase III BREAKWATER trial: BRAF and EGFR inhibitor combination[3]

Encorafenib + cetuximab ± chemotherapy as first-line treatment in *BRAF*-V600E-mutated mCRC[3]

Stage 2 of this trial has been initiated with enrolment of 54 additional patients to complete the study recruitment

AE, adverse event; *BRAF*, v-raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; MEK, mitogen-activated protein kinase; PFS, progression-free survival; ORR overall response rate.

1. Grothey A, et al. *Ann Oncol.* 2020:31:S242–3; 2. NCT03693170. Available at: ClinicalTrials.gov (accessed 7 March 2021);
3. NCT04607421. Available at: ClinicalTrials.gov (accessed 7 March 2021).

What other potential targets are being explored for the treatment of *BRAF*-V600E-mutated mCRC?

touch ONCOLOGY®

Potential therapeutic targets in previously treated *BRAF*-V600E-mutated mCRC

Research into new potential treatment targets and combination therapies aim to overcome MAPK pathway resistance[1]

Immune checkpoint inhibitors

- Association between *BRAF*-V600E mutations and MSI suggests role of immune checkpoint inhibitors in *BRAF*-positive and MSI-H CRC[2]

Novel targeted agents

- Many novel targeted agents remain in preclinical status or phase I trials, e.g. Wee-1, CDK4/6 and Wnt-pathway inhibitors[2]
- Chemokine receptors (CXCR4) may be a potential new target in *BRAF*-mutated CRC[1]
- ERK inhibitors are also being investigated[3]

Crosstalk and bypass mechanisms between signalling pathways in mCRC makes blockade difficult[1]

BRAF, v-raf murine sarcoma viral oncogene homolog B; CDK4/6 cyclin-dependant kinase 4/6; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; MSI-H, MSI-high.

1. Molina-Cerrillo J, et al. *Cancers* 2020;12:157; 2. Caputo F, et al. *Int J Mol Sci.* 2019;20:5369; 3. Bhagwat SV, et al. *Mol Cancer Ther.* 2020;19:325–36.