TREATMENT SEQUENCING IN METASTATIC COLORECTAL CANCER

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SELECTED HIGHLIGHTS

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KEY MESSAGES

- The optimal use and sequencing of cytotoxic and targeted agents in mCRC remains unclear
- Choice of therapy in the 1st-line setting is critical as it affects treatment decisions in all other lines of treatment
- Molecular profiling has established new targets, while recent insights into tumour evolution under drug pressure may impact on sequencing

mCRC, metastatic colorectal cancer

TREATMENT LINE: DIMINISHING OUTCOMES

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- Optimising treatment across multiple lines of therapy in mCRC is challenging, with 1st-line therapy a key to success:

Outcome*	First-line[1-8]	Second-line[9-16]	Third-line[17-21]
Response rate	38–65%	5–36%	1–31%
Progression-free survival	9–12 months	4–7 months	2–5 months

* Efficacy ranges taken from the targeted/experimental treatment arms of studies reporting the specified outcome (for EGFR trials, results are shown for *RAS* wild-type subsets where applicable)

- When no potential curative path is reached by 1st-line therapy, the question of sequencing gains in importance
- This review explores current treatment approaches and optimal sequencing across the 1st-, 2nd- and 3rd-line settings in mCRC, including biological aspects affecting sequencing and rechallenge

EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; *RAS, RAS* proto-oncogene GTPase

1. Saltz LB, et al. J Clin Oncol 2008;26:2013-9; 2. Heinemann V, et al. Lancet Oncol 2014;15:1065-75; 3. Douillard JY, et al. J Clin Oncol 2010;28:4697-705; 4. Loupakis F, et al. N Engl J Med 2014;371:1609-18; 5. Douillard JY, et al. Ann Oncol 2014;25:1346-55; 6. Falcone A, et al. J Clin Oncol 2007;25:1670-6; 7. Van Cutsem E, et al. J Clin Oncol 2011;29:2011-9; 8. Venook AP, et al. JAMA 2017;317:2392-2401; 9. Giantonio BJ, et al. J Clin Oncol 2007;25:1539-44; 10. Peeters M, et al. J Clin Oncol 2010; 28:4706-13; 11. Bennouna J, et al. Lancet Oncol 2013;14:29-37; 12. Van Cutsem E, et al. J Clin Oncol 2012;30:3499-506; 13. Tabernero J, et al. Lancet Oncol 2015; 16:499-508; 14. Sobrero AF, et al. J Clin Oncol 2008;26:2311-9; 15. Seymour MT, et al. Lancet Oncol 2013;14:749-59; 16. Peeters M, et al. Ann Oncol 2014;25:107-16; 17. Amado RG, et al. J Clin Oncol 2008;26:1626-34; 18. Grothey A, et al. Lancet 2013;381:303-12; 19. Karapetis CS, et al. N Engl J Med 2008;359:1757-65; 20. Mayer RJ, et al. N Engl J Med 2015;372:1909-19; 21. Kim TW, et al. Br J Cancer 2016;115:1206.

FIRST-LINE THERAPY: MOLECULAR MARKERS

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- **Choosing an effective 1st-line therapy is crucial and should take into account both clinical factors and molecular markers**
- European and US guidelines recommend testing for *RAS* and *BRAF* prior to 1st-line therapy[1,2]
  - Patients with *RAS*-mutant CRC are unlikely to benefit from EGFR-targeted therapy[1]
  - Evidence suggests this is also true for those with *BRAF*-mutant CRC, although data are less robust[1,3]
- 1st-line options for patients with wild-type *RAS* include a cytotoxic doublet plus anti-EGFR therapy, a doublet with bevacizumab, or a triplet regimen with or without bevacizumab[1,2]

BRAF, B-Raf proto-oncogene, serine/threonine kinase; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; *RAS, RAS* proto-oncogene GTPase

1. Van Cutsem E, et al. Ann Oncol 2016;27(8):1386-422;
2. Benson AN, 3rd, et al. J Natl Compr Canc Netw 2017; 15(3):370-98;
3. Pietrantonio F, et al. Eur J Cancer 2015;51(5):587-94.

FIRST-LINE THERAPY: CLINICAL CONSIDERATIONS

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- **Disease extent** (oligo- vs poly-metastases, specific organs involved)[1]
  - Aim for metastatic resection where possible[1,2]
  - Combination regimens may enable conversion to resectable disease[1-3]
- **Primary tumour location** influences prognosis and the efficacy of EGFR-based therapy in CRC:[4,5]
  - Left-sided tumours – clear benefit
  - Right-sided tumours – benefit less likely beyond the initial response rate
- **Patient fitness** and willingness to receive combination chemotherapy
  - Elderly patients – consider fluoropyrimidine plus oxaliplatin or bevacizumab[6,7]

CRC, colorectal cancer; EGFR, epidermal growth factor receptor

1. Van Cutsem E, et al. Ann Oncol 2016;27(8):1386-422; 2. Benson AN, 3rd, et al. J Natl Compr Canc Netw 2017;15(3):370-398; 3. De Greef K, et al. World J Gastroenterol 2016;22(32):7215-25; 4. Holch JW, et al. Eur J Cancer 2017;70:87-98; 5. Arnold D, et al. Ann Oncol 2017;28(8):1713-1729; 6. Seymour MT, et al. Lancet 2011;377(9779):1749-59; 7. Cunningham D, et al. Lancet Oncol 2013;14(11):1077-85.

SECOND-LINE THERAPY

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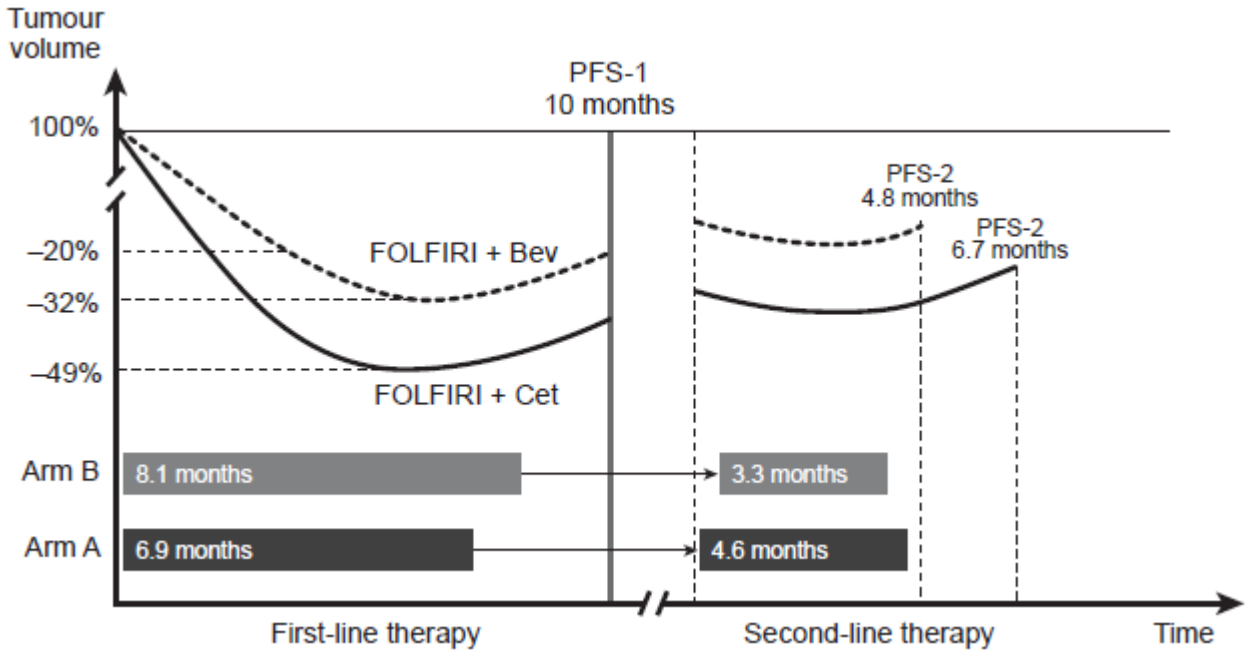
- **FOLFIRI and FOLFOX** are typical 2nd-line options,[1,2] depending on the 1st-line treatment given
  - Chemotherapy sequence (1st-line FOLFOX then FOLFIRI, or vice versa) does not seem to significantly affect outcomes[3]
  - Does this hold true for antibodies?
- **VEGF-targeted agents** improved survival in phase 3 trials,[4-7] and are indicated for most patients in 2nd-line[1,2]
  - Patients who progress rapidly on 1st-line bevacizumab- and oxaliplatin-containing regimens can be treated with aflibercept or ramucirumab, but only in combination with FOLFIRI[1,2]
- **EGFR antibodies** have to date failed to demonstrate a survival benefit in the 2nd-line setting[8-10]

EGFR, epidermal growth factor receptor; FOLFIRI, infusional fluorouracil, folinic acid and irinotecan; FOLFOX, infusional fluorouracil, folinic acid and oxaliplatin; VEGF, vascular endothelial growth factor

1. Van Cutsem E, et al. Ann Oncol 2016;27(8):1386-422; 2. Benson AN, 3rd, et al. J Natl Compr Canc Netw 2017;15(3):370-98; 3. Tournigand C, et al. J Clin Oncol 2004;22(2):229-37; 4. Bennouna J, Lancet Oncol 2013;14(1):29-37; 5. Van Cutsem E, et al. J Clin Oncol 2012;30(28):3499-506; 6. Tabernero J, et al. Lancet Oncol 2015;16(5):499-508; 7. Masi G, et al. Ann Oncol 2015; 26(4):724-30; 8. Sobrero AF, et al. J Clin Oncol 2008;26(14):2311-9; 9. Seymour MT, et al. Lancet Oncol 2013;14(8):749-59; 10. Peeters M, et al. Ann Oncol 2014; 25(1):107-16.

SEQUENTIAL TARGETS:
EGFR THEN VEGF?

- The success of 2nd-line therapy after initial cetuximab in FIRE-3 supports using an EGFR inhibitor followed by a VEGF-targeted agent[1-3]



Arm A: first-line FOLFIRI + Cet

Arm B: first-line FOLFIRI + Bev

Bev, bevacizumab; Cet, cetuximab; FOLFIRI, infusional fluorouracil, folinic acid and irinotecan; FOLFOX, infusional fluorouracil, folinic acid and oxaliplatin; PFS, progression-free survival from start of first-line [PFS-1] or second-line [PFS-2] therapy; VEGF, vascular endothelial growth factor

1. Stintzing S, et al. Lancet Oncol 2016;17(10):1426-34;
2. Modest DP, et al. J Clin Oncol 2015;33(32):3718-26;
3. Heinemann V, et al. Lancet Oncol 2014;15(10):1065-75.

THIRD-LINE AND BEYOND

- **Recommended treatments** in this setting include:[1,2]
  - regorafenib
  - trifluridine/tipiracil (TAS-102)
  - cetuximab or panitumumab in *RAS*- and *BRAF* wild-type patients not previously treated with EGFR antibodies
- Unfortunately, the survival benefit obtained with 3rd-line treatment in phase 3 trials is modest[3,4]
- **Immunotherapy** with pembrolizumab or nivolumab appears effective in tumours with deficient DNA mismatch repair (MMR)[5-7]
- ***HER2* amplification is an emerging therapeutic target** for the 1.6–6.3% of CRC displaying this molecular abnormality[8]
  - Early trial results for HER2-directed therapy appear promising[9-13]

BRAF, B-Raf proto-oncogene, serine/threonine kinase; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HER2, Human Epidermal Growth Factor Receptor 2; MMR, mismatch repair; *RAS, RAS* proto-oncogene GTPase;

1. Van Cutsem E, et al. Ann Oncol 2016;27(8):1386-422; 2. Benson AN, 3rd, et al. J Natl Compr Canc Netw 2017;15(3):370-98; 3. Grothey A, et al. Lancet 2013;381:303-12; 4. Mayer RJ, et al. N Engl J Med 2015;372:1909-19; 5. Le Tourneau C, et al. Lancet Oncol 2015;16:1324-34; 6. Overman MJ, et al. J Clin Oncol 2017;35(4_suppl):519; 7. Overman MJ, et al. J Clin Oncol 2018:JCO2017769901; 8. Sartore-Bianchi A, et al. JAMA Oncol 2018;4:19-20; 9. Sartore-Bianchi A, et al. Lancet Oncol 2016;17:738-46; 10. Siena S, et al. Cancer Res 2017;77(13 Suppl):Abstract nr CT005; 11. Hainsworth JD, et al. J Clin Oncol 2018;36:536-42; 12. Hurwitz H, et al. J Clin Oncol 2017;35(4_suppl):676; 13. Siena S, et al. J Clin Oncol 2016;34(suppl 4S):abstr TPS774.

SEQUENCING AND RECHALLENGE: CLINICAL ASPECTS

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- Sequencing in mCRC is complicated by the frequent need for treatment breaks or de-escalation[1,2]
- **Maintenance therapy** vs treatment breaks remains controversial
  - No clear survival benefit[3-6]
  - Toxicity and quality-of-life considerations are also important
- **The specific context of progression** may influence subsequent therapy, including the potential for rechallenge:
  - Failure of the regimen
  - Failure of maintenance therapy
  - Progression off-treatment (e.g. failure due to toxicity)
- Given our limited understanding of residual tumour sensitivity after progression, molecular characterization is needed to guide sequential treatment decisions

mCRC, metastatic colorectal cancer

1. Saltz LB, et al. J Clin Oncol 2008;26(12):2013-9; 2. Modest DP, et al. J Clin Oncol 2015;33(32):3718-26;
3. Hegewisch-Becker S, et al. Lancet Oncol 2015;16(13):1355-69; 4. Simkens LH, et al. Lancet 2015;385(9980):1843-52; 5. Aranda E, et al. Eur J Cancer 2018;101:263-72; 6. Wasan H, et al. Lancet Oncol 2014;15(6):631-9.

SEQUENCING AND RECHALLENGE: BIOLOGICAL ASPECTS

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- **EGFR-targeted agents may be less effective after bevacizumab**
  - Bevacizumab increases serum levels of VEGF-A, which can induce resistance to cetuximab in *RAS* wild-type CRC cells[1-4]
- However, exposure to **EGFR-targeted antibodies in 1st-line is associated with the emergence/expansion of *RAS* mutations**,[5] while KRAS activation induces VEGF expression[6]
- Acquired *KRAS* mutations associated with resistance to EGFR blockade did not reduce the efficacy of the multikinase inhibitor regorafenib, which includes a VEGFR-targeted component[7]
- **Tumour evolution under drug pressure is dynamic**
  - A decrease in mutated *KRAS* clones is associated with renewed response to EGFR inhibitors[5]

CRC, colorectal cancer; EGFR, epidermal growth factor receptor; *KRAS, KRAS* proto-oncogene, GTPase; *RAS, RAS* proto-oncogene GTPase; VEGF, vascular endothelial growth factor

1. Stefanini MO, et al. Cancer Res 2010;70(23):9886-94; 2. Derangere V, et al. Oncotarget 2016;7(8):9309-21; 3. Kopetz S, et al. J Clin Oncol 2010;28(3):453-9; 4. Van Cutsem E, et al. Ann Oncol 2017;28(suppl_3), mdx262.011, Abstract O-012; 5. Siravegna G, et al. Nat Med 2015; 21(7):827:doi: 10.1038/nm0715-827b; 6. Zeng M, et al. PLoS One 2010;5(6):e10966; 7. Tabernero J, et al. Lancet Oncol 2015;16(8):937-48.

CURRENT AND FUTURE DIRECTIONS

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- **Trials investigating treatment across lines of therapy**
  - STRATEGIC-1 (ClinicalTrials.gov Identifier: NCT01910610)
  - FIRE-4 (NCT02934529)
  - TRIBE-2 (NCT02339116)
- **Use of VEGF-targeted agents beyond and after progression** is an established strategy,[1] but the optimal timing to switch from bevacizumab to drugs with broader activity such as aflibercept or regorafenib is unknown
- **Tumour cell plasticity and the dynamic clonal competition that takes place during EGFR-targeted therapy may be exploited**
  - using rechallenge strategies[2-5]*
  - by switching to alternative EGFR-targeted drugs[6]

* Ongoing trials include a phase 3 trial using cetuximab (FIRE-4) and two phase 2 trials of panitumumab (NCT03087071 Cohort 3; CHRONOS [NCT03227926]).

EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor

1. Hofheinz RD, et al. Gastroenterol Res Pract 2016;2016:9189483; 2. Santini D, et al. Ann Oncol 2012;23(9):2313-8; 3. Rossini D, et al. Ann Oncol 2017;28(suppl_3), mdx263.025; 4. Wadlow RC, et al. Oncologist 2012;17(1):14; 5. Siena S, et al. Ann Oncol 2017;28(suppl_3), mdx261.317; 6. Sanchez-Martin FJ, et al. Clin Cancer Res 2016;22(13):3260-7.

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