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Challenging chemoresistant metastatic colorectal cancer: therapeutic strategies from the clinic and from the laboratory

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CHALLENGING CHEMORESISTANT METASTATIC COLORECTAL CANCER: THERAPEUTIC STRATEGIES FROM THE CLINIC AND FROM THE LABORATORY

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SELECTED HIGHLIGHTS

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KEY MESSAGES

- The rise of rational drug design and pharmacogenomics has led to renewed interest in established molecular targets, including HER2, RAS and BRAF
- Newer targets under investigation include MET, cytoplasmic targets, Wnt signalling and immune checkpoint inhibitors
- Overcoming resistance to anti-EGFR therapy is a key issue
- Serial analysis of tumour genetics is highly desirable to guide treatment decisions and monitor resistance. Liquid biopsy fulfils this need and is already providing insights into the molecular biology of mCRC

EXPANDING OPTIONS FOR REFRACTORY mCRC

- Two recent introductions, regorafenib and TAS-102, have expanded the therapeutic options for patients with refractory mCRC after both showed a survival benefit in placebo-controlled phase 3 trials[1,2]

- European and US guidelines include the multikinase inhibitor regorafenib as a standard option for second-line therapy and beyond[3,4]

- TAS-102 is an oral combination of trifluridine and tipiracil hydrochloride. Recently receiving a positive opinion by the CHMP from the EMA, it is approved in the US and Japan for mCRC refractory to standard therapies

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EMA, European Medicines Agency; CHMP, Committee for Medicinal Products for Human Use.

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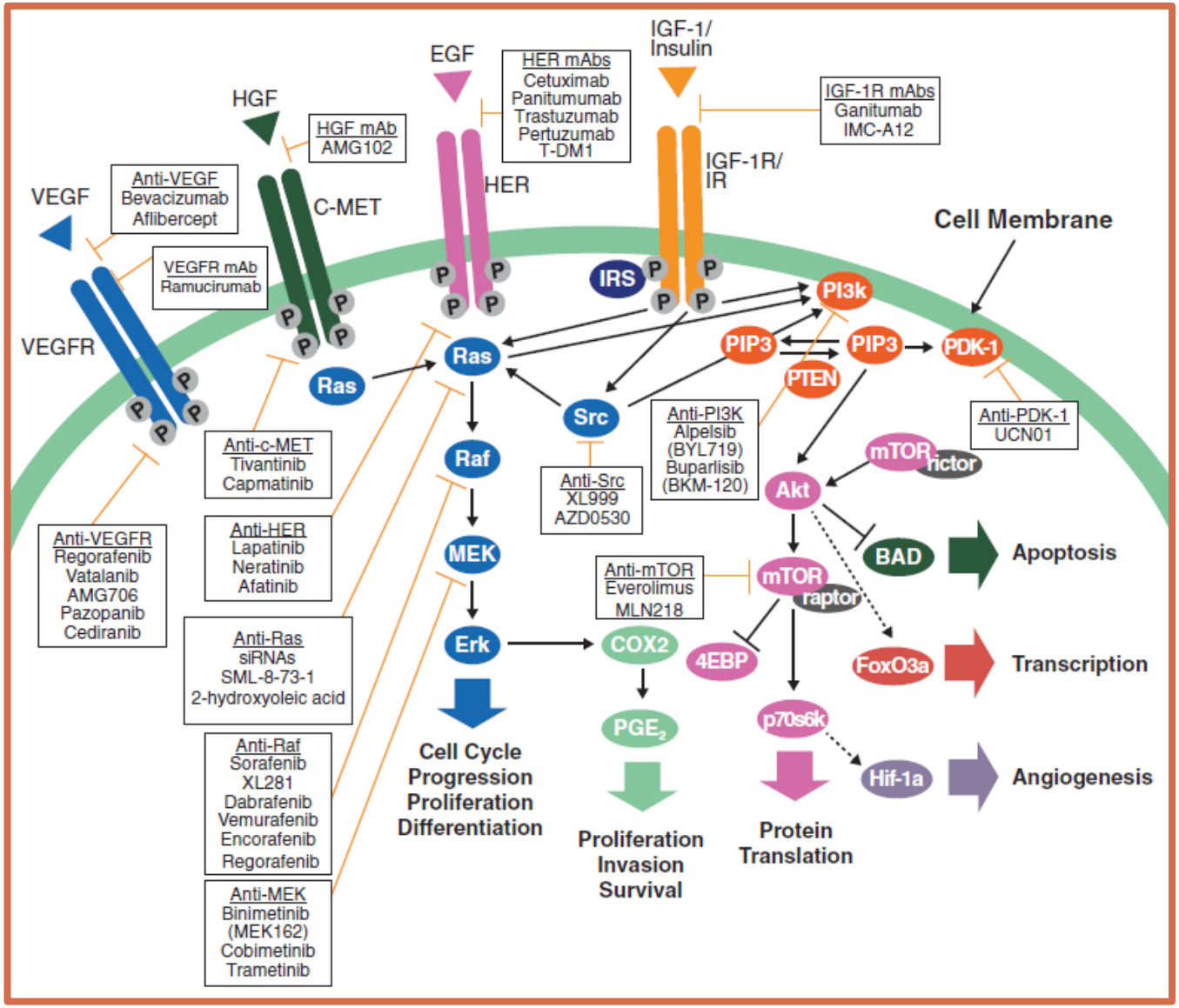
3. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colon Cancer. Version 2.2016; 4. Van Cutsem E, et al. Ann Oncol 2014; 25 Suppl 3: iii1-9.

OLD AND NEW TARGETS IN mCRC



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OLD TARGETS, NEW STRATEGIES: HER2

- The rise of rational drug design and pharmacogenomics has led to renewed interest in established molecular targets, including HER2, RAS and BRAF
- HER2 has had an uncertain role in CRC, but research using modern diagnostic technologies supports its relevance as a therapeutic target[1-6]
  - The HER2 positivity rate was 1.6% to 6.3% in two recent CRC series[2,3]
- In the recently-published phase 2, proof-of concept, HERACLES trial in KRAS exon 2 wild-type mCRC, which included 27 HER2 positive patients, treatment with trastuzumab and lapatinib was active and well tolerated:[7]
  - Of these 27 patients, 1 had a complete response, 7 had partial response and 12 had stable disease
  - The study was based on a diagnostic algorithm for CRC-specific detection of HER2 amplification*[8]

* HER2 positivity was defined as an immunohistochemistry (IHC) score of 3+ or 2+, and *HER2* gene amplification by in-situ hybridisation.

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RAS: RATIONALE AND CURRENT APPROACHES

- Activating *KRAS* mutations occur in around 40% of CRCs, and *NRAS* mutations in 8–10%;[1,2] both are associated with resistance to EGFR-directed therapy[2-5] and a poor prognosis[6,7]
- RAS is a long-standing but challenging target.[8] Due to the complex regulation of RAS signalling, various indirect targeting strategies have been evaluated.
- Other novel agents being evaluated include the lipid-based molecule, NaCHOleate, small interference RNAs and the tyrosine kinase inhibitor, SML-8-73-1[9-12]
- Further strategies, including combination strategies with MEK inhibitors are discussed in the review

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BRAF: AN UNCERTAIN ROLE IN CRC

- Activating *BRAF* mutations are common in hypermutated CRC tumours (47%; vs. 3% non-hypermutated),[1] and are linked to tumour aggression and worse survival,[2-5] as well as poor response to EGFR-directed therapy[6-9]

- BRAF kinase inhibition yielded disappointing results in BRAF-mutant CRC when given alone[10] or with a MEK inhibitor,[11] likely due to MEK-derived EGFR feedback activation of MAPK and/or Pi3K signalling[12,13]

- Outcomes for dual BRAF / EGFR blockade and triple regimens do not match those seen in other BRAF-mutant tumours,[14] thus the place of BRAF inhibition in CRC remains unclear

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MEMBRANE RECEPTORS: c-MET

- Aberrant MET activation is associated with cancer cell survival and resistance to therapy.[1] In CRC, *MET* amplification drives resistance to anti-EGFR therapy[2]
- MET inhibition has produced inconsistent results in clinical trials[3,4]
- mCRC trials are investigating whether MET inhibitors can overcome resistance to EGFR blockade in patients with proven *MET* amplification or c-MET overexpression[5-6]

1. Gherardi E, et al. Nat Rev Cancer 2012; 12: 89-103; 2. Bardelli A, et al. Cancer Discov 2013; 3: 658-673; 3. Van Cutsem E, et al. Clin Cancer Res 2014; 20: 4240-4250; 4. Eng C, et al. Int J Cancer 2016 Feb 17. doi: 10.1002/ijc.30049.[Epub ahead of print] PMID: 26891420; 5. https://clinicaltrials.gov/ct2/show/NCT01892527; 6. https://clinicaltrials.gov/ct2/show/NCT02205398

IMMUNE CHECKPOINT INHIBITORS

- The promise of immune checkpoint inhibitors in oncology is yet to have an impact in CRC, with little evidence of activity in the first trials of these agents[1,2]

- More recently, mismatch-repair status was shown to predict clinical benefit from the anti-PD-1 monoclonal antibody, pembrolizumab, in mCRC[3]
  - These findings highlight the need to identify tumours with microsatellite instability across all stages of CRC

- Two ongoing studies are investigating pembrolizumab in a naïve patient population (KEYNOTE 177 study) and in previously-treated advanced CRC (KEYNOTE 164 study)

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PD-1, programmed cell death protein 1

1. Brahmer JR, et al. N Engl J Med 2012; 366: 2455-2465; 2. Topalian SL, et al. N Engl J Med 2012; 366: 2443-2454; 3. Le DT, et al. N Engl J Med 2015; 372: 2509-2520.

CYTOPLASMIC TARGETS: PI3K, AKT AND PTEN

- Several molecular alterations can lead to activation of the phosphoinositide 3-kinase (Pi3K) pathway in CRC[1-4]
  - Mutations in *PIK3CA*, *PIK3R1* and *Akt*; mutation/deletion of *PTEN*

- Initial studies of Pi3K pathway inhibitors showed minimal activity in CRC and development was not pursued for this indication[5-7]

- However, Pi3K pathway activation in CRC increases over time due to clonal evolution,[8,9] suggesting potential for combining Pi3K inhibitors with standard therapies in order to overcome resistance

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TARGETING Wnt SIGNALLING

- Wnt pathway mutations occur in >90% of CRC tumours[1]
  - 81% have inactivation of the *APC* tumour suppressor gene[1-3]
  - 5% have activating mutations of the β-catenin gene (*CTNNB1*)[1]
  - A subset of CRC tumours that require sustained high Wnt levels is characterised by additional Wnt pathway mutations[4-6]
- Porcupine, an enzyme required for Wnt ligand processing, is another potential target

APC, adenomatous polyposis coli

1. Cancer Genome Atlas Network. Nature 2012; 487: 330-337; 2. Kinzler KW, Vogelstein B. Cell 1996; 87: 159-170; 3. Clevers H, Nusse R. Cell 2012; 149: 1192-1205; 4. Seshagiri S, et al. Nature 2012; 488: 660-664; 5. Giannakis M, et al. Nat Genet 2014; 46: 1264-1266; 6. Koo B-K, et al. Nature 2012; 488: 665-669.

NEW TOOLS: LIQUID BIOPSY

- Tumour-tissue biopsies are routinely obtained before the start of first-line treatment, leaving a potential gap of ⩾30 months before the initiation of salvage therapy
- Serial biopsies are desirable to guide treatment decisions and monitor response to targeted agents
- 'Liquid biopsy' techniques analyse tumour genetics in circulating tumour cells (CTCs) or cell-free tumour DNA (ctDNA) from the peripheral blood

LIQUID BIOPSY: CTCs OR ctDNA?

- CTC numbers strongly predict survival in mCRC[1]
  - CellSearch® (Janssen Diagnostics, LLC; Raritan, NJ) is approved in the US for monitoring CTC numbers in patients with mCRC
  - Isolation and characterisation of CTCs, including single-cell amplification and sequencing, enables detailed genomic analysis[2,3]
  - Drawbacks include the rarity of CTCs, failure to detect cells that undergo mesenchymal transition, and high cell-to-cell variability[4,5]
- ctDNA is EpCAM-independent, can be easily and cheaply isolated using standard DNA preparation, and may represent the average genotype of all tumour cells
  - BEAMing technology is used to quantitatively analyse a known tumour-specific mutation in plasma[6]

BEAMing, Beads, Emulsion, Amplification, and Magnetics; EpCAM, epithelial cell adhesion molecule.

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LIQUID BIOPSY: APPLICATIONS IN CRC

- Serial ctDNA levels tracked tumour dynamics over time, and patients with detectable mutant ctDNA after surgery had a higher recurrence rate (P=0.006)[1]
- ctDNA showed good concordance with tissue biopsy[2]
- ctDNA has provided insight into resistance mechanisms during EGFR blockade in *RAS* wild-type CRC[3,4]

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