

## Condition: Colorectal cancer

### Treatment 1: Crizotinib

Chosen clinical trials:

1. 'MEK and MET Inhibition in Colorectal Cancer' completed phase1 [\(link\)](#)

Population: 30

Time: Dose Expansion phase: change from baseline and up to 12 months.

Stable Disease: 7

Progressive Disease: 22

Early death from malignant disease: 1

Chosen papers:

1. 'Partial response to crizotinib + regorafenib + PD-1 inhibitor in a metastatic' [\(link\)](#)

Crizotinib Results: 'Administration of crizotinib combined with regorafenib and tislelizumab obtained an obvious response.' Based on:

*'reported a co-existence of a BRAF V600E mutation, c-MET amplification and TPM4-ALK fusion in a CRC patient. Administration of crizotinib combined with regorafenib and tislelizumab obtained an obvious response. Furthermore, continuous ctDNA detection appears to be a promising technique to monitor tumor burden, which may provide better clinical decision support during the disease course.'*

2. 'A phase Ia study of the MEK1/2 inhibitor PD-0325901 with the c-MET inhibitor crizotinib in patients with advanced solid cancers.' [\(link\)](#)

Crizotinib Results: 'The best clinical response was stable disease in seven patients (29%) when treated with crizotinib.' Based on:

*'B.D, days 1-21 every 28 days. One in six patients exhibited a dose-limiting toxicity at this dose level. Drug-related adverse events were in keeping with single-agent toxicity profiles. The best clinical response was stable disease in seven patients (29%). CONCLUSIONS: PD-0325901/crizotinib can be given together at pharmacologically-active doses. The MTD for PD-0325901/crizotinib was 8â€‰%mg B.D (days 1-21) and 200â€‰%mg B.D continuously in a 28-days cycle. The combination was further explored'*

3. 'Radiotherapy-Related Autophagy Genes Predict Prognosis and Reveal Immunoscape Features and Immunotherapeutic Agents in Colorectal Cancer Patients.' [\(link\)](#)

Crizotinib Results: 'Drugs such as Crizotinib were more sensitive to low-risk group.' Based on:

*'populations showed significantly greater levels of immune infiltration (P P ARHGEF17 mutation rate was 6%. Medications such as CGP-082996, Dasatinib, Erlotinib, and Salubrinal were more sensitive to high-risk group, whereas drugs such as FTI-277, DMOG, and Crizotinib were more sensitive to low-risk group. UGT1A6 and IRGM were significantly upregulated in tumor group as revealed by qRT-PCR. This study constructed a new prognostic model for CRC patients based on RRAGs, and a series of analysis'*

4. 'Identification of a novel immune signature for optimizing prognosis and treatment prediction in colorectal cancer.' [\(link\)](#)

Crizotinib Results: 'AZD4547, Cytochalasin B and S-crizotinib might have potential therapeutic implications in the immune risk score-high CRCs.' Based on:

*'Further analyses demonstrated that CRCs with low immune risk scores achieved better therapeutic benefits from immunotherapy, while AZD4547, Cytochalasin B and S-crizotinib might have potential therapeutic implications in the immune risk score-high CRCs. CONCLUSIONS: Overall, this IRGs-based signature not only afforded a useful tool for determining the prognosis and evaluating the TIME features of CRCs, but also shed new light on tailoring CRCs with precise treatment.'*

*'identify agents with subclass-specific efficacy. RESULTS: The established signature was shown to be a promising biomarker for evaluating clinical outcomes in CRC. The immune risk score as calculated by this classifier was significantly correlated with over-riding malignant phenotypes and immunophenotypes. Further analyses demonstrated that CRCs with low immune risk scores achieved better therapeutic benefits from immunotherapy, while AZD4547, Cytochalasin B and S-crizotinib might have potential'*

5. 'Albumin-Based Cyanine Crizotinib Conjugate Nanoparticles for NIR-II Imaging-Guided Synergistic Chemophototherapy.' [\(link\)](#)

Crizotinib Results: 'Under 808 nm laser irradiation, Crizotinib-IR808@BSA NPs exhibited synergistic chemophototherapy effects on tumors.' Based on:

*'by using bovine serum albumin (BSA) nanoparticles (NPs) with excellent biocompatibility and biosafety. The prepared Crizotinib-IR808@BSA NPs showed tumor targeting capability as well as use for noninvasive biomedical vascular NIR-II imaging with intraoperative real-time NIR-II imaging to guide tumor resection. Under 808 nm laser irradiation, Crizotinib-IR808@BSA NPs exhibited synergistic chemophototherapy effects on tumors. In conclusion, this innovative imaging-mediated multifunctional'*

*'tumor resection. Under 808 nm laser irradiation, Crizotinib-IR808@BSA NPs exhibited synergistic chemophototherapy effects on tumors. In conclusion, this innovative imaging-mediated multifunctional combination therapy strategy with good c-Met targeting ability may provide a new approach for colorectal cancer treatment.'*

6. 'Personalized targeted therapy prescription in colorectal cancer using algorithmic analysis of RNA sequencing data.' [\(link\)](#)

7. 'ARID1A loss enhances sensitivity to c-MET inhibition by dual targeting of GPX4 and iron homeostasis, inducing ferroptosis.' [\(link\)](#)

Crizotinib Results: 'Crizotinib selectively inhibits the growth of ARID1A-deficient CRC cells in vitro and in xenograft tumor models.' Based on:

*'colorectal cancer (CRC) cells induce synthetic lethality when treated with inhibitors of c-MET receptor tyrosine kinase. c-MET specific inhibitor PHA-665752 as well as two other FDA-approved drugs, crizotinib and cabozantinib, selectively inhibited the growth of ARID1A-deficient CRC cells in vitro and in xenograft tumor models. Mechanistically, we identified a tripartite functional association among ARID1A, c-MET, and NRF2, where ARID1A and c-MET pathways converge on the NRF2 transcription'*

8. 'ROS1 genomic rearrangements are rare actionable drivers in microsatellite stable colorectal cancer.' [\(link\)](#)

Crizotinib Results: 'Molecularly targeted treatment with crizotinib induced a rapid and sustained partial response. After 15 months on crizotinib disseminated tumor progression occurred and KRAS Q61H emerged in tissue and liquid biopsies.' Based on:

*'induced a rapid and sustained partial response. After 15 months on crizotinib disseminated tumor progression occurred and KRAS Q61H emerged in tissue and liquid biopsies. ROS1 rearrangements define a small, yet therapeutically actionable molecular subgroup of MSS CRC. In summary, the high prevalence of GOPC-ROS1 and noncanonical ROS1 fusions pose diagnostic challenges. We advocate NGS-based comprehensive molecular profiling of MSS CRCs that are wild type for RAS and BRAF and patient'*

*'exclusively in microsatellite stable (MSS) CRCs. KRAS mutations were significantly less abundant in ROS1-rearranged vs ROS1 wild type cases. The index patient presented with chemotherapy-refractory metastatic right-sided colon cancer harboring GPC-ROS1. Molecularly targeted treatment with crizotinib induced a rapid and sustained partial response. After 15 months on crizotinib disseminated tumor progression occurred and KRAS Q61H emerged in tissue and liquid biopsies. ROS1 rearrangements'*

9. 'A Phase Ia/b study of MEK1/2 inhibitor binimetinib with MET inhibitor crizotinib in patients with RAS mutant advanced colorectal cancer (MErCuRIC).' ([link](#))

Crizotinib Results: 'Combination binimetinib/crizotinib showed a poor tolerability with no objective responses observed in RASMT advanced CRC patients.' Based on:

*'allele frequency. CONCLUSIONS: Combination binimetinib/crizotinib showed a poor tolerability with no objective responses observed in RASMT advanced CRC patients. EudraCT-Number: 2014-000463 -â€%40 (20/06/2014: A Sequential Phase I study of MEK1/2 inhibitors PD- 0325901 or Binimetinib combined with cMET inhibitor Crizotinib in RAS Mutant and RAS Wild Type with aberrant c-MET).'*

*'MET-amplification only present in 1 of these patients. This patient discontinued treatment early during cycle 1 due to toxicity. Patients with high baseline RASMT allele frequency had a significant shorter median overall survival compared with that seen for patients with low baseline KRASMT allele frequency. CONCLUSIONS: Combination binimetinib/crizotinib showed a poor tolerability with no objective responses observed in RASMT advanced CRC patients. EudraCT-Number: 2014-000463 -â€%40'*

10. 'Inhibition of autocrine HGF maturation overcomes cetuximab resistance in colorectal cancer.' ([link](#))

Crizotinib Results: 'Crizotinib effectively overcomes HGF-induced cetuximab resistance.' Based on:

*'Conversely, HGF overexpression was necessary and sufficient to induce cetuximab resistance and loss of polarity. Moreover, HGF-induced cetuximab resistance could be overcome by the downstream MET inhibitor, crizotinib, and upstream protease inhibitors. Additionally, HAI-1, an endogenous inhibitor of HGF proteases, (i) was downregulated in CRC, (ii) exhibited increased genomic methylation that correlated with poor prognosis, (iii) HAI-1 expression correlated with cetuximab response in a panel of'*

11. 'ALK fusions in the pan-cancer setting: another tumor-agnostic target?' ([link](#))

12. 'TBX15 and SDHB expression changes in colorectal cancer serve as potential prognostic biomarkers.' ([link](#))

Crizotinib Results: 'The expression level of SDHB was correlated with drug sensitivity to Crizotinib.' Based on:

*'healthy tissue. Also, PharmacoGx data indicated that the expression level of SDHB was correlated with drug sensitivity to Crizotinib and Dovitinib. Our findings highlight the potential association between alterations in the expression of genes such as HOXC6, HOXC13, HOXC8, TBX15, SDHB, COX5A, and UQCRC1 and increased mortality rates in CRC patients. As revealed by the PPI network, these genes exhibited the most connections with other genes linked to survival.'*

*'Applying the risk model developed with the mentioned genes revealed a markedly higher incidence of deceased patients in the high-risk group compared to the low-risk group. RT-qPCR results indicated a decrease in SDHB expression and an elevation in TBX15 levels in cancer samples relative to adjacent healthy tissue. Also, PharmacoGx data indicated that the expression level of SDHB was correlated with drug sensitivity to Crizotinib and Dovitinib. Our findings highlight the potential association'*

13. 'Epithelial cell adhesion molecule (EpCAM) regulates HGFR signaling to promote colon cancer progression and metastasis.' ([link](#))

Crizotinib Results: 'The combined treatment of an anti-EpCAM neutralizing antibody (EpAb2-6) and an HGFR inhibitor (crizotinib) significantly inhibits tumor progression and prolongs survival in metastatic and orthotopic animal models of colon cancer.' Based on:

*'antibody (EpAb2-6) and an HGFR inhibitor (crizotinib) significantly inhibits tumor progression and prolongs survival in metastatic and orthotopic animal models of colon cancer. CONCLUSION: Our findings illuminate the molecular mechanisms underlying EpCAM signaling promotion of colon cancer metastasis, further suggesting that the combination of EpAb2-6 and crizotinib may be an effective strategy for treating cancer patients with high EpCAM expression.'*

*'epithelial-to-mesenchymal transition and metastatic potential of colon cancer cells by activating ERK and FAK-AKT signaling pathways, and it further stabilizes active  $\beta$ -catenin and Snail proteins by decreasing GSK3 $\beta$  activity. Finally, we show that the combined treatment of an anti-EpCAM neutralizing antibody (EpAb2-6) and an HGFR inhibitor (crizotinib) significantly inhibits tumor progression and prolongs survival in metastatic and orthotopic animal models of colon cancer. CONCLUSION: Our'*

This is a paragraph with a **bold part**, a [link](#), a footnote<sup>1</sup>

---

<sup>1</sup> description of the footnote