The efficacy and safety of irinotecan plus raltitrexed as second-line treatment in advanced colorectal cancer (ACC) patients: A summary analysis of a multicenter, phase II trial


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Background: Colorectal cancer (CRC) is the third most common cancer. There are limited therapeutic options for the treatment of advanced CRC which fail first-line chemotherapy. Pre-clinical and phase I/II studies have shown that the combined application of the irinotecan and raltitrexed has significant synergistic effect and acceptable toxicity. The aim of this multicenter study was to assess the efficacy and toxicity of second-line raltitrexed plus irinotecan in Chinese patients with advanced colorectal cancer.

Methods: This is an open-label, single-arm, multicenter, phase II trial (Registered in clinicaltrial.gov with NCT03053167). Brief inclusion criteria: patients aged 18 to 75 years with locally advanced or metastatic CRC after failure of oxaliplatin and fluorouracil, Enrolled patients received irinotecan (180 mg/m2, d1) and raltitrexed (3 mg/m2, d1) each 21-day cycle until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were disease control rate (DCR), objective response rate (ORR), overall survival (OS), quality of life (QOL) and safety. In all, 100 patients were required for primary point testing.

Results: Between October 2016 and May 2020, a total of 108 patients were screened for enrollment, The median age was 61 years (range: 38-75 years), ECOG 1 scored 67.6%. A total of 502 cycles were completed, with an average of 4.6 cycles and a median of 4 cycles. 97 patients reached the PFS, and 83 patients reached the OS. 108 patients were evaluable and ORR was 17.6%, DCR was 76.9%. The median follow-up time was 15.2 months at data cut-off on Oct 9, 2020. Median PFS was 4.5 months and median OS was 12.7 months. The most common adverse events were elevated alanine aminotransferase increased (47.1%), aspartate aminotransferase increased (44.3%), fatigue (23.9%), diarrhea (31.3%), thrombocytopenia (30.6%), and hypo-hemoglobin (30.6%). Most of the adverse events were grade I/II, and there were no treatment-related death.

Conclusions: We have demonstrated that irinotecan plus raltitrexed is active and feasible in patients with second-line treatment in advanced colorectal cancer.

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Update results from ALTER-C-001 study: Efficacy and safety of anlotinib plus XELOX regimen as first-line treatment followed by maintenance monotherapy of anlotinib for patients with mCRC: A single arm, multi-center, phase II clinical trial

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Background: The standard therapy followed by maintenance treatment is an optional approach to balance the efficacy and toxicity for metastatic colorectal cancer (mCRC). But clinical trials have largely remained inconclusive regarding the maintenance strategy. Anlotinib, a novel multi-target TKI, significantly prolonged the PFS of refractory mCRC in a phase III clinical trial. The preliminary results of anlotinib plus XELOX regimen followed by anlotinib as first-line treatment (ALTER-C-001) exhibited antitumor efficacy and manageable toxicity for mCRC. Here we updated the results with more patients enrolled.

Methods: 53 patients with unresectable mCRC, aged 18-75, without prior systemic treatment and ECOG performance status 0-1 will be prospectively recruited. Anlotinib 10mg and capecitabine 1000mg/m2 was given for 14 days, q3w; oxalaplatin 130mg/m2

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Cetuximab could be administered once every two weeks instead of once weekly.


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Background: Cetuximab (ERBITUX®), an anti-EGFR monoclonal antibody, has been approved for the treatment of metastatic colorectal cancer (mCRC). The pharmacokinetics (PK) of cetuximab has a nonlinear elimination due to the turnover of EGFR. (1) Target-mediated drug disposition (TMDD) models (2,3) have been commonly used to describe target-mediated pharmacokinetics (TMPPK) of monoclonal antibodies. This study aimed at investigating TMPPK of cetuximab, the relationship between the target occupancy (TO) of EGFR and progression free survival (PFS), and the impact of dosage adjustments.

Methods: Ninety-one patients with mCRC were enrolled in a retrospective multi-center phase II study investigating FOLFIri-cetuximab regimens (4). Patients received cetuximab as an infusion with a loading dose of 400 mg/m² followed by weekly infusions of 250 mg/m². Concentration-time data were analysed using a population-target-mediated drug disposition (TMDD) model. The association between TO and PFS was investigated by using Kaplan-Meier methods and Cox proportional-hazards models (5). Several dosing strategies based on increased injection schedule were simulated.

Results: Cetuximab PK data were satisfactorily described using TMDD model. Median PFS of included patients (n=91) was 6.4 months (95% CI : 4.1-7.4 months), a relationship between EGFR concentration (R) and PFS was significant after the first administration (p=0.019) and at steady state (p=0.0012). The target occupancy reached at 250mg/m² QW and 500mg/m² Q2W was similar (99.96% vs 99.98%).

Conclusions: This is the first study describing TMPPK of cetuximab using a QSS TMDD model. Our model allowed quantifying EGFR kinetics over time, which was associated to PFS. Our simulations suggested that a 500mg/m² Q2W regimen could be used instead of 250mg/m² QW in some patients. This dosing regimen would lead to the same efficacy with fewer constraints in terms of administration for patients.

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