Ligand expression of the EGFR ligands amphiregulin, epiregulin, and amplification of the EGFR gene to predict for treatment efficacy in KRAS wild-type mCRC patients treated with cetuximab plus CAPIRI and CAPOX: Analysis of the randomized AIO CRC-0104 trial


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Background

In the past several years, the expression of the EGFR ligands amphiregulin (AREG) and epiregulin (EREG) as well as the amplification of the EGFR gene (EGFR-FISH) have been identified as predictive biomarkers for response to cetuximab therapy in KRAS wild-type mCRC patients. In the present study, we investigated the expression of the EGFR ligands amphiregulin (AREG) and epiregulin (EREG) and an EGFR-FISH analysis to predict for treatment efficacy in KRAS wild-type mCRC patients treated with cetuximab plus CAPIRI or CAPOX. Expression levels were correlated with overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) to determine their relationship with effectiveness in this setting.

Methods

Within the subgroup of KRAS wildtype tumors, analysis of AREG- and EREG-expression was carried out using microdissection of FFPE tumor-cells. EGFR-FISH was calculated using ROC analysis for ORR.

Results

Within the subgroup of KRAS wildtype tumors, analysis of AREG and EREG-expression was carried out in 99 KRAS wildtype patients. EGFR-FISH and AREG expression have the strongest relationship with treatment efficacy. In the treatment setting of cetuximab combined with CAPIRI or CAPOX, AREG and EREG expression and EGFR-FISH amplification predicted treatment efficacy.

Conclusions

1. The treatment setting of cetuximab combined with CAPIRI or CAPOX, AREG and EREG amplification were strong predictors for treatment efficacy.
2. Within the subgroup of pts with KRAS wildtype tumors, EREG-FISH and AREG expression have the strongest relationship with treatment efficacy.

Design of Investigation

- AIO CRC-0104 trial recruited patients during the years 2000-2006, independent of the KRAS mutational status.
- Tumor specimen of 99 KRAS wildtype patients were available for investigation.
- Retrospective analyses of tumor material was done, looking for molecular factors predictive for response to Cetuximab- based treatment.

AIO CRC-0104 Study Design

Metastatic colorectal cancer

CAPIRI + Cetuximab

CAPOX + Cetuximab

CAPOX + Cetuximab

Capsule: 800 mg/m² on D1, Vincristine: 2 mg/m² on D1, Cetuximab: initial dose 400 mg/m² iv, 120 min, then 250 mg/m² q 3weeks; Cetuximab: q 3weeks.

CAPOX: Capecitabine 1000 mg/m² q 3weeks; irinotecan 200 mg/m² q 3weeks, q 3weeks.

EGFR-FISH

amphiregulin (AREG)

Epiregulin (EREG)

amplification predicted treatment efficacy.

Conclusions

1. In the treatment setting of cetuximab combined with CAPIRI or CAPOX, AREG and EREG amplification were strong predictors for treatment efficacy.
2. Within the subgroup of pts with KRAS wildtype tumors, EREG-FISH and AREG expression have the strongest relationship with treatment efficacy.