Cetuximab biweekly plus mFOLFOX6 as 1st line therapy in patients (pts) with KRAS wild-type (wt) (exon 2) metastatic colorectal cancer (mCRC) – primary endpoint and subgroup analyses of the CEBIFOX trial

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Background:
The multicenter, single-arm, phase II trial (Simon’s two stage design) evaluated the efficacy of mFOLFOX6 + cetuximab (500 mg/m²) q2w as 1st line therapy in KRAS wt mCRC. Final extended molecular and subgroup analyses are presented. Clinical trial information: NCT01551167

Methods:
Primary endpoint was response rate (ORR) per RECIST 1.0. In stage 1 and 2, 13 and 25 responders were needed in 37 and 53 pts, respectively, to further evaluate this therapy. In order to calculate the sample size the following hypothesis was considered: H0: p≤0.35, H1: p≥0.55, (α=0.05, power=90%), meaning that a response rate (p) of at most 35% of the new therapy would have no clinical relevance whereas a response rate of at least 55% would lead to further investigation of that therapy. Secondary endpoints were PFS, OS, safety, metastasectomy and quality of life (QoL). Extended molecular profiling was performed using NGS-based panel sequencing including NRAS, KRAS, BRAF, PIK3CA and TP53. Clinical parameters included: tumor localization, left-sided LCRC (rectum to splenic flexure); right-sided RCRC (hepatic flexure to cecum); transverse T (splenic to hepatic flexure), early tumor-shrinkage (ETS), depth of response (DoR), metastasectomy and inflammation markers (neutrophil/lymphocyte ratio-NLR). Differences in ORR, PFS and OS were calculated using chi-square and log rank tests. Hazard ratios were calculated by Cox regression analysis. Results from the latest up-date (25.09.2016) with a median follow-up of 54.1 months (34.1-85.4) are presented.

Adverse Event (AE)grade (%) grade ≥3 (%)
RASH 45 (78.9%) 10 (17.5%)
Paronychia 6 (10.5%) 0 (0%)
Infusion reactions 3 (5.2%) 1 (1.8%)
Hypomagnesemia/ Hypocalcemia 6 (10.5%) 1 (1.8%)
Diarrhea 19 (33.3%) 5 (2.3%)
Sens. PNP 34 (69.6%) 0 (0%)
Leukopenia 21 (36.8%) 5 (8.8%)
Neutropenia 18 (31.6%) 9 (15.8%)
Anemia 12 (21.1%) 0 (0%)
Thrombopenia 12 (21.1%) 2 (3.5%)

Overall Response Rate-IT population
Complete Response (CR) 1 1.8%
Partial Response (PR) 38 66.7%
Stable Disease (SD) 19 33.3%
Progressive Disease (PD) 5 8.8%
Response pending or n.a. 4 7.0%
ORR (CR+PR) 39 68.4%
DCR (CR+PR+SD) 48 84.2%

Secondary Metastasectomy
ITT population (N=57) 19 33.3%
LLD (N=28) 11 42.3%

Patient Characteristics-ITT population (N=57)
Female 21 68.6%
Median age (range) 51 (23-79)
ECOG PS 0/1/2 47/8/2 82.5%/14.0%/3.5%
Tumor localization colorectum 33/24 57.9%/42.1%
Tumor localization LCRC/RCRC/T 42/13/2 73.7%/22.8%/3.5%
Liver limited disease (LLD) 28 49.1%
adj./neo.adi. therapy 8 14.0%
Resection of primary tumor 45 78.9%

NGS profiled population (N=44)
Overall survival:
Events Median (Months) 95% CI
PFS 29/44 (65.9%) 9.9 6.4-13.3
OS 27/44 (61.4%) 30.0 18.7-41.3

Conclusion:
The primary endpoint of this study was met (rejection of H0) with an ORR of 68.4%. The CEBIFOX study supports the efficacy and safety of q2w cetuximab given in combination with mFOLFOX6. Extended mutational analyses of key oncogenes and routinely assessed clinical parameters may help to identify patients with maximum likelihood of benefit from cetuximab-based chemotherapy.

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