Phase I/II study of cetuximab dose-escalation in patients with metastatic colorectal cancer (mCRC) with no or slight skin reactions on cetuximab standard dose treatment (EVEREST): pharmacokinetic (PK), pharmacodynamic (PD) and efficacy data

Background

- The optimal growth factor receptor (HER) inhibition is 74–100% of colorectal cancer (CRC) and in the majority of most patients, a brisk and sustained clinical response to treatment is achieved.
- Although most patients show only a modest skin rash, 15–30% of patients experience a life-threatening skin reaction (i.e., grade 3–4 skin toxicity). Patients with EGFR-expressing tumors are particularly prone to skin toxicity and require dose reductions.
- At current cetuximab doses, most patients have a partial response, and complete response is rarely seen.

Study objectives

- To compare the safety and efficacy of a cetuximab dose escalation regimen in patients with metastatic colorectal cancer (mCRC) with a skin rash at standard cetuximab doses.
- To investigate the relationship between efficacy, skin reactions and gene expression.

Study design

- Controlled, multicenter, phase I/II randomized study in patients with EGFR-expressing mCRC.
- Patients were stratified by number of prior lines of therapy and by the number of organs involved, and were then randomized to one of three dose levels of cetuximab: 250 mg/m², 400 mg/m², or 600 mg/m² (Arm A). Patients with a skin rash at standard cetuximab doses (Arm A) were then randomized to dose escalation (Arm B) or randomization (Arm C).

Patients

- Patients with colorectal cancer metastatic to liver or with synchronous unresectable colorectal cancer.
- A total of 275 patients were enrolled in the study.

Results

Patient baseline characteristics

- Of the 275 patients screened, EGFR was detected in the tumor samples of 219, and 166 patients developed rash by this time, and the rash is generally at its most severe at 12 months in the dose-escalation group.
- Survival data are awaited from a further 20 patients.

Safety

- Acne-like rash is a class effect of EGFR inhibitors such as cetuximab.
- In skin, an intra-patient down-regulation of pEGFR levels was observed, which was consistent with the known safety profile of cetuximab and indicated absence of potential mechanisms such as PD-L1 up-regulation.

Pharmacokinetic analysis

- Pharmacokinetic data (PK) analysis showed population PK parameters, including terminal elimination half-life (t 1/2), for cetuximab and its active fragment, in the safety population (n=77), were therefore excluded from the ITT population (n=68).
- Of the 275 patients screened, EGFR was detected in the tumor samples of 219, and 166 patients developed rash by this time, and the rash is generally at its most severe at 12 months in the dose-escalation group.
- Survival data are awaited from a further 20 patients.

Conclusions

- Pharmacokinetics and pharmacodynamics highlight the importance of celecoxib as a candidate drug for further investigation.
- Further details of the study design have been published previously.1

References

6. Merck KGaA, Darmstadt, Germany.
7. University Hospital Gent, Gent, Belgium; University Hospital St-Luc, Brussels, Belgium; Leden University Medical Centre; Leden, The Netherlands; University Hospital Antwerp, Antwerp, Belgium; Institut Paul Calmettes, Marseille, France; Akademiiska University Hospital, Uppsala, Sweden; General University Hospital, Nuremberg, Germany.

Appendix

A. Efficacy

B. Pharmacodynamics

C. Safety

D. Pharmacokinetic analysis

Figure 1. Cetuximab dose escalation (escalation arm) showed improved efficacy compared with those in Arm A (standard cetuximab regimen) in relation to confirmed overall response rates, partial response rates, complete response rates, and progression-free survival (PFS) at 12 months, respectively. The median survival time in the dose-escalation group was 18 months in the dose-escalation group.

Figure 2. Changes in pEGFR levels in skin biopsies and best overall response in Arm A (standard cetuximab regimen) and Arm B (dose escalation).

Figure 3. Changes in pERK levels in skin biopsies and best overall response in Arm A (standard cetuximab regimen) and Arm B (dose escalation).

Figure 4. Changes in pSTAT3 levels in skin biopsies and best overall response in Arm A (standard cetuximab regimen) and Arm B (dose escalation).

Figure 5. Changes in microarray-highlighted genes comprising EREG, AREG (amphiregulin), PHLDA1, DUSP4 patterns putatively associated with the degree of tumor response and PFS time were observed.

Figure 6. Changes in PK parameters, including terminal elimination half-life (t 1/2), for cetuximab and its active fragment, in the safety population (n=77), were therefore excluded from the ITT population (n=68).

Figure 7. Changes in plasma proteins with significant on-treatment changes from baseline to pre-randomization (A) and from baseline to post-randomization (B). Baseline data are shown as the mean ± SEM, and the normalized changes from baseline are shown as the normalized mean ± SEM. The changes in plasma proteins are shown for patients with a skin rash at standard cetuximab doses.

Figure 8. Changes in microarray-highlighted genes comprising EREG, AREG (amphiregulin), PHLDA1, DUSP4 patterns putatively associated with the degree of tumor response and PFS time were observed.

Plasma proteomic analysis

- Analysis of the levels of total complement proteins in plasma samples from treated cancer patients and healthy volunteers did not reveal any significant on-treatment changes. The normalization methods used for the plasma proteomic analysis were the same as those used for the cancer proteomic analysis.

Acknowledgment

- The authors gratefully acknowledge the contributions of their teams at M. D. Anderson's Cancer Center, Houston, TX; the Dana-Farber Cancer Institute, Boston, MA; the University of California, San Francisco; and the National Cancer Institute, Bethesda, MD.