Phase II study of panitumumab with irinotecan for patients with KRAS wild-type metastatic colorectal cancer (MCRC) refractory to standard chemotherapy. A GERCOR study
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Background
- Panitumumab alone in third-line chemotherapy in patients with chemorefractory AFKAS wild-type MCRC (1) increases Response Rate from 0 to 17%.
- Prolonged PFS versus best supportive care from 1.7 months to 2.8 months (HR 0.46).

This trial (NCT00305454) evaluated the combination of panitumumab and irinotecan in the same population.


Methods

- Main inclusion criteria:
  - KRAS/Wilp Type-Metastatic Colorectal Cancer
  - Refractory to standard FOLOFOX or FOLFIRI: bevacizumab and irinotecan alone or FOLFOX or CAPFIR: 5 bevaculubea.
  - Performance status 0-2.
  - Age >60 years.
  - Bilirubin level ≤1.5xULN.
  - No prior therapy with EGFR inhibitors.

- Prospective KRAS assessment:
  - Local assessment before inclusion.
  - Validation by central assessment using allelic discrimination by TaqMan Probe, Applied Biosystems (F-Laurier, Pug, Hopital-Européen Georges Pompidou, Paris).

- Tumor evaluations (baseline then every 2 months):
  - Clinical.
  - Biological (CEA maker).
  - Radiological (CT-scan).

- Statistics:
  - Design: open-label single-arm multicenter phase II study.
  - Primary endpoint: Overall Response Rate (RECIST).
  - Sample size: Anticipated ORR X 20% x [1-0.2] = 41.6; N = 68 (50 evaluable).
  - Analysis: Intent-To-Treat exp Efficacy ITT.

- Treatment: Panitumumab + Irinotecan (FIR3486).
  - HD: Panitumumab 6 mg/kg IV infusion over 60 min (day 1).
  - HD: Irinotecan: 180 mg/m² IV infusion over 90 min (day 1).
  - Cycles: every 14 days (4 cycles).
  - Treatment until disease progression or unacceptable toxicity.

- Quality assurance program development for proper selection of patients.

Treatment delivery & Toxicity
- Treatment delivery: 541 cycle (average: 8.9 cycle/patient).
- HD of panitumumab: 53.4 (4.5).
- Grade of study (N=5): progression or death (N=4), treatment break (N=1), toxicity (N=4), other (N=4).

- Grade 3/4 toxicity:
  - Diarrhea 9 14.8
  - Neutropenia 1 1.6
  - Anemia 0 0.0

- Median PFS: 6.0 months (95% CI: 4.6 - 7.9 months).
- OS: 14.5 months (95% CI: 12.6 - 24.1 months).

KRAS assessment

- Local KRAS assessment (tumor sample):
  - Tumor was centrally re-examined at 10% of patients to confirm the KRAS status (confirmed real-time PCR).

- KRAS status:
  - Local assessment: confirmed in 50 patients (81.3%).
  - A mutated version of the KRAS gene was found in 4 patients (6.5%), one was a T506C mutation and the others were unknown.
  - A total of 13 patients had evidence of KRAS mutation and analysis.

- Tumor blocks were not available in 4 patients (6.5%).
- Tumor sample sets not sufficient for analysis per patient (1.7%).

- KRAS status confirmed in 50 patients (81.3%).

- Tumor was centrally re-examined at 10% of patients to confirm the KRAS status (confirmed real-time PCR).

- No prior therapy with EGFR inhibitors.

- Final 313 tumor negative samples were tested in the same laboratory.

KRAS status & Tumor cellularity

Tumor cellularity in patients with central KRAS assessment (N=0400)

KRAS mutation 56 patients (81.1%),
- Rectum: Both
- Normal >1xULN
- Progression at first evaluation

In patients with KRAS mutation (N=4), 2 patients had SD and 2 patients had PD at first evaluation.

Discussion

- This trial reached its primary endpoint with an ORR of 32.8%.
- The identification of 6.5% discrepancies in this multi-site testing trial underlines the importance of methodology validation and the need for quality assurance program development for proper selection of patients.

- These results suggest that the fourth-line combination of panitumumab + irinotecan in third-line should be preferred to pautumumab monotherapy in patients with KRAS WT MCRC refractory to standard chemotherapy without prior EGFR inhibitor.

- Ongoing ancillary studies: KRAS codon 61 mutations, BRAF, NRAS, P1EN INC, CISH for EGFR.