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Original Research

Evaluation of survival across several treatment lines in metastatic colorectal cancer: Analysis of the FIRE-3 trial (AIO KRK0306)☆

D.P. Modest [a,b,*], I. Ricard [c], S. Stintzing [a,b], L. Fischer von Weikersthal [d], T. Decker [e], A. Kiani [f], U. Vehling-Kaiser [g], S.-E. Al-Batran [h], T. Heintges [i], C. Kahl [j], G. Seipelt [k], F. Kullmann [l], W. Scheithauer [m], M. Moehler [b,n,o], C.B. Westphalen [a], J.W. Holch [a], J.C. von Einem [a], S. Held [p], V. Heinemann [a,b], for FIRE-3/AIOKRK0306-investigators[1]

[a] *Department of Medicine III and Comprehensive Cancer Center, University Hospital, LMU Munich, Germany*
[b] *German Cancer Consortium (DKTK), German Cancer Research Centre (DKFZ), Heidelberg, Germany*
[c] *Institute of Medical Informatics, Biometry, and Epidemiology, University of Munich, Munich, Germany*
[d] *Gesundheitszentrum St. Marien, Amberg, Germany*
[e] *Oncological Practice, Ravensburg, Germany*
[f] *Medizinische Klinik IV, Klinikum Bayreuth, Bayreuth, Germany*
[g] *Oncological Practice, Landshut, Germany*
[h] *Department of Hematology and Oncology, Krankenhaus Nordwest Frankfurt/Main, Germany*
[i] *Department of Medicine II, Städtisches Klinikum Neuss, Germany*
[j] *Haematology and Oncology, Staedtisches Klinikum Magdeburg, Germany*
[k] *Oncological Practice, Bad Soden, Germany*
[l] *Department of Medicine I, Klinikum Weiden, Germany*
[m] *Department of Internal Medicine I and Comprehensive Cancer Center, Medical University Vienna, Austria*
[n] *Medical Department 1, Johannes-Gutenberg Universität Mainz, Mainz, Germany*
[o] *University Cancer Center Frankfurt/Mainz, Germany*
[p] *ClinAssess GmbH, Leverkusen, Germany*

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* *Corresponding author*: Klinikum Grosshadern, University of Munich, Department of Medical Oncology and Comprehensive Cancer Center, Marchioninistrasse, 15, D-81377 Munich, Germany. Fax: +49 89 4400 75254.
E-mail address: dominik.modest@med.uni-muenchen.de (D.P. Modest).

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KEYWORDS
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Survival dynamics

Abstract ***Background:*** We explored the impacts of sequential application of various treatment lines on survival kinetics. Therefore, differences in overall survival (OS) observed in FIRE-3 were investigated in the context of time and exposure to applied treatment.
Patients and methods: OS analyses (stratified by treatment with FOLFIRI plus either cetuximab or bevacizumab) were performed according to time intervals as well as using a Cox model to define changes of hazard ratio (HR) over time.
Results: The fraction of patients with systemic treatment and time on treatment markedly decreases over treatment lines and time. OS evaluation by a Cox model indicated a trend towards a non-proportional hazard between treatment arms (P = 0.12/P = 0.09 for *KRAS*–intention-to-treat (ITT)/all-*RAS* wild-type populations, respectively). To improve the fit of the model, a change-point (point of curve separation) was estimated at 22.6 months (day 687) after randomisation. The HR between the two arms before 22.6 months was not significantly different from one. However, markedly different survival kinetics in favour of the cetuximab arm were apparent after the change-point (*KRAS*-ITT: P = 0.0018; HR, 0.60 [95% confidence interval [CI], 0.44–0.83] and *RAS*: P = 0.0006; HR, 0.51 [95% CI, 0.35–0.75]).
Conclusion: The differences in OS favouring the cetuximab arm become apparent about 22.6 months after randomisation, indicating that only those patients who survive 22.6 months after randomisation benefit from the superiority of the cetuximab arm. When OS curves separate, only few patients receive active systemic treatment in short courses, suggesting that earlier treatment effects are responsible for later kinetics of survival curves.

1. Introduction

FIRE-3 investigating the first-line therapy of *KRAS* exon 2 wild-type metastatic colorectal cancer (mCRC) with FOLFIRI in combination with cetuximab (arm A) or bevacizumab (arm B). Overall response rate (ORR) according to the Response Evaluation Criteria in Solid Tumours, version 1.0 (primary end-point), as well as progression-free survival (PFS) were comparable between study arms. Overall survival (OS) was longer in the cetuximab arm of the study. Clear separation of survival curves in Kaplan–Meier-plots was observed approximately 2 years after randomisation [1]. Better survival in the cetuximab arm may in part be explained by greater depth-of-response [2] but also by a more favourable sequence of treatment [3].

So far, defined concepts that allow to explain the (late) time point when survival curves separate in FIRE-3 and other randomised studies [4–6] are not available.

The present analysis of FIRE-3 aims to analyse survival kinetics by using fitted Cox models, including change-point (separation of survival curves) estimation. Furthermore, we explored whether additional variables influence outcome and if this effect is the same before and after the change-point. An additional aim was to evaluate survival within a framework of distinct time intervals. Therefore, we analysed the number of patients in subsequent lines of therapy as well as locoregional interventions in the course of therapy. Furthermore, time-to-start of subsequent agents was estimated and compared between the study arms. This analysis is retrospective and exploratory.

2. Patients and methods

2.1. Patient population

The present analysis includes the *KRAS* exon 2 wild-type population (intention-to-treat (ITT); n = 592 patients), as well as the *RAS* wild-type population (n = 400 patients). The data cut-off date for this analysis was 22nd August 2014. Data concerning subsequent treatments have been published [3].

2.2. Study

FIRE-3 evaluated first-line treatment of *KRAS* exon 2 wild-type mCRC with FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab in a randomised fashion. Responsibilities within the trial, including protocol and primary analyses were reported previously [1,3]. FIRE-3 is registered with ClinicalTrials.gov (NCT00433927).

2.3. Therapy in defined time intervals

Therapy in a defined time interval was evaluated if at least one application of the respective therapy was observed. Accordingly, interventions (surgery, radiation or ablation) were evaluated if at least one procedure was performed in the respective time interval. Duration of treatment was calculated from the first to the last application of the regimen (within the respective time interval).