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Current Perspective

# The 'death pace' in the CO.17 trial

Vincenzo Formica [a,*], Domenico Formica [b], Giovanni Formica [c]

[a] *Medical Oncology Unit, Tor Vergata University Hospital, Viale Oxford, 81, 00133 Rome, Italy*
[b] *Unit of Biomedical Robotics and Biomicrosystems, Department of Engineering, Università Campus Bio-Medico di Roma, via Álvaro del Portillo, 21, 00128 Rome, Italy*
[c] *Dipartimento di Architettura, University of Roma Tre, via della Madonna dei Monti 40, IT-00184 Rome, Italy*

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**Abstract** In an era where the cost of care in oncology is rising, suggestions of new frameworks that may help in orienting biomarker discovery are highly desirable. We propose a different perspective for looking at survival data, which we call 'death pace' analysis, which focuses on the variation of the gap between survival curves over time and that may make it easier to identify subpopulations with distinct predictive molecular features. The recently published data on *EJC* on the impact of the primary colonic site in the CO.17 trial seem to be particularly suitable for the death pace analysis.


## 1. Current perspective

We read with great interest the recently published paper by Brulè et al [1], reporting a post hoc analysis of the role of the colonic primary site as a predictive/prognostic factor for patients treated within the phase III randomised trial of cetuximab versus BSC − NCIC CO.17 trial. We recently proposed a new perspective for looking at survival curves that focuses on the pace at which deaths occur in the different treatment arms of a randomised trial [2], and data published by Brulé et al are particularly suitable for our 'death pace' analysis that we think may help in predictive biomarker discovery.

When a new experimental treatment gives a significant gain in overall survival, Kaplan–Meier curves of experimental and control arms clearly separate over time, as seen in figure 3b of Brulè's paper [1].

Looking at the figure shape (a schematic representation of Brulè's figure 3b is provided in Fig. 1A), it is evident that the gain achieved with cetuximab in left-

* *Corresponding author*: Tel.: +39 06 2090 8190; fax: +39 06 2090 3544.
*E-mail addresses:* vincenzo.formica@uniroma2.it (V. Formica), d.formica@unicampus.it (D. Formica), formica@uniroma3.it (G. Formica).

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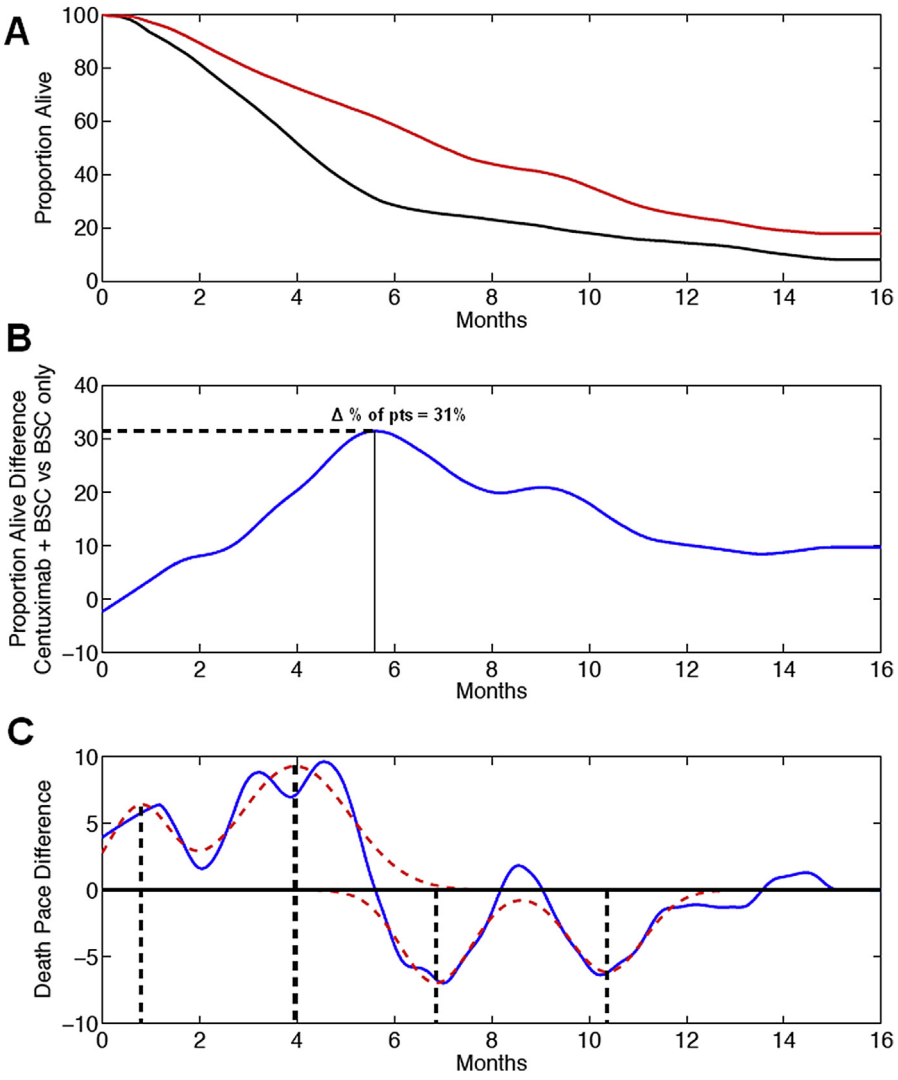


Fig. 1. Graphic representation of the 'death pace' analysis of CO.17 trial. A: Schematic representation of Brulè's figure. B: Change of survival gap over the time. C: First derivative of survival gap over the time (death pace).

sided colon cancers is produced between the 1st and 5th month when the curves start separating and the largest divergence is achieved. The curve divergence is quantifiable in a proportion of around 30% of patients not dying with cetuximab and dying with BSC.

This 'survival gap' seems to reduce between the 6th and 11th month, meaning that the 'pace' at which deaths occur in this phase is higher in the cetuximab arm as compared to BSC (Fig. 1B). In this period, most of the survival gain produced between the 1st and 5th month is lost. The survival gap then remains stable between the 12th and 14th month, meaning no survival difference between the two treatment groups. The curves eventually converge around the 15th month.

If one hypothesises the maximal possible effect of cetuximab concentrated in the smallest possible proportion of patients really benefitting from the drug (and the 'perfect' predictive biomarker would completely identify this 'small' subgroup of patients), it can be said that the net effect of cetuximab consists in saving a 20–30% of patients destined to die around the 1st–5th month who have died, instead, around the 6th–11th month, thanks to the experimental treatment. This 20–30% would be the subset of patients really benefitting from the drug and the perfect predictive biomarker would identify this 20–30% of subjects.

Since cetuximab in colorectal cancer treatment has a solidly established predictive molecular marker, the RAS/RAF mutation, it would be interesting to validate the utility of the death pace theory for biomarker discovering in the CO.17 cohort and check whether, based on the figure presented by Brulè et al (figure 3b), patients with left-sided colon cancer who die around the 1st–5th month in the BSC arm and around the 6th–11th month in the cetuximab arm are particularly 'enriched' with RAS/RAF wild type state.

The outcome of our proposed 'death pace' analysis is depicted in Fig. 1B and C.

Fig. 1B shows how the divergence between the cetuximab and the BSC curves varies over time, starting