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Circulating tumor DNA (ctDNA)-guided re-treatment (re-tx) with encorafenib and cetuximab (EC) in patients (pts) with chemorefractory BRAFV600E mutated metastatic colorectal cancer (mCRC): The proof-of-concept single arm phase II BRICKET trial by GONO

M.M. Germani¹, V. Studiale², A. Chiaramonte³, F. Bergamo⁴, L. Salvatore⁵, A.A. Prete⁶, A. Passardi⁷, S. Di Donato⁸, V. Pasquinucci², C. Villa⁹, R. Intini⁴, M.A. Calegari⁵, G. Masi², V. Fanotto¹⁰, G. Martini¹¹, T.P. Latiano¹², E. Lai¹³, F. Pietrantonio³, S. Lonardi⁴, C. Cremolini²

¹ Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy, ² Medical Oncology 2, University of Pisa and Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, ³ Medical Oncology Department, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, ⁴ Department of Oncology, IOV - Istituto Oncologico Veneto IRCCS, Padua, Italy, ⁵ Medical Oncology, Università Cattolica del Sacro Cuore and Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy, ⁶ Department of Unit of Oncology and Palliative Care, Azienda Ospedaliera Cardinale Giovanni Panico, Tricase, Italy, ⁷ Medical Oncology Department, IRST - Istituto Romagnolo per lo Studio dei Tumori Dino Amadori IRCCS S.r.l., Meldola, Italy, ⁸ Department of Medical Oncology, Nuovo Ospedale di Prato Santo Stefano, Prato, Italy, ⁹ Department of Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, ¹⁰ Department of Oncology, ASU FC - Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy, ¹¹ Department of Medical Oncology, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, ¹² Department of Oncology, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy ¹³ Dipartimento di Oncologia Medica, AOU di Cagliari - Ospedale Civile, Cagliari, Italy

Background

Current therapies for *BRAFV600E*-mutant mCRC after progression (PD) to EC are modestly effective. Resistance is largely driven by genomic alterations that can potentially decay after EC withdrawal, providing a rationale for ctDNA-guided EC re-tx.

Methods

BRICKET (NCT06578559) is a proof-of-concept single arm phase II trial where *BRAFV600E* mut mCRC pts who achieved disease control for ≥ 6 months (mos) with previous EC and then experienced PD underwent centralized ctDNA analysis (GUARDANT360 CDx, Guardant Health) after failure of one intervening EC-free line of therapy. Only pts with *BRAFV600E* mutation (mut), and no *KRAS*, *NRAS*, *MAP2K1* mut and *MET* amplification (ampl) in their ctDNA were eligible. The primary endpoint was objective response rate (ORR). With an ORR of 0.05 for p0 (null hypothesis) and 0.25 for p1 (alternative hypothesis), and 2-sided- α and β errors of 0.05 and 0.20, 16 pts were required and p0 could be rejected if ≥ 3 had an objective response.

Results

Between August 2024 and December 2025, 30 pts underwent molecular screening and ctDNA was successfully detected in 29 cases (96.7%). One or more resistance alterations were found in 11 (37.9%) of them, being *KRAS* mut (N=17), *NRAS* mut (N=3) and *MET* ampl (N=2) the most frequent. In other 2 pts (6.9%), *BRAFV600E* mut was not detectable. 14 (87.5%) out of 16 enrolled pts had received previous EC without concomitant chemotherapy and 13 (81.3%) were re-treated after the 3rd line. No objective responses were reported. 6 pts (37.5%) had disease stabilization, lasting a median of 2.9 mos (95% CI: 1.0 – not assessable). All pts experienced PD and 11 (68.8%) died, resulting in median PFS and OS of 2.9 (95% CI: 2.0 – 3.4) and 9.1 mos (95% CI: 4.0 – 13.0), respectively. No new safety signals were observed.

Conclusions

EC re-tx did not show signals of activity in *BRAFV600E*-mutant mCRC pts without common genomic drivers of resistance to EC in their ctDNA. Whether pts treated upfront with chemotherapy plus EC as per current guidelines, potentially less likely to develop genomic resistance, may benefit from ctDNA-guided EC re-tx, could be object of future studies.

Clinical trial identification

NCT06578559.

Legal entity responsible for the study

Gruppo Oncologico del Nord Ovest (GONO).

Funding

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Disclosure

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