European Journal of Cancer 90 (2018) 63–72

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer

Eric Van Cutsem [a,b,*], Robert J. Mayer [c], Stéphanie Laurent [d], Robert Winkler [e], Cristina Grávalos [f], Manuel Benavides [g], Federico Longo-Munoz [h], Fabienne Portales [i], Fortunato Ciardiello [j], Salvatore Siena [k,l], Kensei Yamaguchi [m], Kei Muro [n], Tadamichi Denda [o], Yasushi Tsuji [p], Lukas Makris [q], Patrick Loehrer [r], Heinz-Josef Lenz [s], Atsushi Ohtsu [t] on behalf of the RECOURSE Study Group

[a] *University Hospital Gasthuisberg, Digestive Oncology, Herestraat 49, 3000 Leuven, Belgium*
[b] *KU Leuven, Oude Markt 13, 3000 Leuven, Belgium*
[c] *Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215, USA*
[d] *University Hospital Ghent, De Pintelaan 185, 9000 Gent, Belgium*
[e] *Taiho Oncology, Inc., 101 Carnegie Center, Princeton, NJ 08540, USA*
[f] *Hospital Universitario 12 de Octubre, Avenida de Córdoba s/n, 28041 Madrid, Spain*
[g] *Hospital Regional Universitario de Málaga, Avenida de Carlos Haya s/n, 29011 Málaga, Spain*
[h] *Hospital Universitario Ramón y Cajal, Carretera de Colmenar Viejo, Km.9,100, 28034 Madrid, Spain*
[i] *CRLC Val d'Aurelle, 208 Avenue des Apothicaires, 34298 Montpellier, France*
[j] *Seconda Università degli Studi di Napoli, Via Antonio Vivaldi, 43, 81100 Caserta, Italy*
[k] *Università degli Studi di Milano, Via Festa del Perdono, 7, 20122 Milan, Italy*
[l] *Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Piazza dell'Ospedale Maggiore, 3, 20162 Milan, Italy*
[m] *Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ward, Tokyo, 135-8550, Japan*
[n] *Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, 464-8681, Japan*
[o] *Chiba Cancer Center, 666-2 Nitona-Cho, Chuo-ku, Chiba, 260-8717, Japan*
[p] *Tonan Hospital, N1 W6 Chuo-ku, Sapporo, Hokkaido, 060-0001, Japan*
[q] *Stathmi, Inc., 125 Brownsburg Rd, New Hope, PA 18938-9239, USA*
[r] *Indiana University Melvin and Bren Simon Cancer Center, 535 Barnhill Dr, Indianapolis, IN 46202, USA*
[s] *USC Norris Comprehensive Cancer Center, 1441 Eastlake Ave, Los Angeles, CA 90089, USA*
[t] *National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan*

Received 11 July 2017; received in revised form 9 October 2017; accepted 13 October 2017

* *Corresponding author*: University Hospital Gasthuisberg, Digestive Oncology, Herestraat 49, 3000 Leuven, Belgium. Fax: +32 16 344419.
E-mail addresses: eric.vancutsem@uzleuven.be (E. Van Cutsem), Robert_Mayer@dfci.harvard.edu (R.J. Mayer), STEPHANIE.LAURENT@UGent.be (S. Laurent), rwinkler@taihooncology.com (R. Winkler), cgravalos@telefonica.net (C. Grávalos), manuel.benavides.sspa@juntadeandalucia.es (M. Benavides), fedelongomunoz@hotmail.com (F. Longo-Munoz), Fabienne.Portales@icm.unicancer.fr (F. Portales), fortunatociardiello@yahoo.com (F. Ciardiello), salvatore.siena@ospedaleniguarda.it (S. Siena), kensei.yamaguchi@jfcr.or.jp (K. Yamaguchi), kmuro@aichi-cc.jp (K. Muro), tdenda@chiba-cc.jp (T. Denda), ytsuji@tonan.gr.jp (Y. Tsuji), lmakris@taihooncology.com (L. Makris), ploehrer@iu.edu (P. Loehrer), LENZ@med.usc.edu (H.-J. Lenz), aohtsu@east.ncc.go.jp (A. Ohtsu).

https://doi.org/10.1016/j.ejca.2017.10.009

KEYWORDS
Fluoropyrimidine;
Metastatic colorectal cancer;
Randomised controlled trial;
TAS-102;
Tipiracil;
Trifluridine

Abstract ***Background:*** In the phase III RECOURSE trial, trifluridine/tipiracil (TAS-102) extended overall survival (OS) and progression-free survival (PFS) with an acceptable toxicity profile in patients with metastatic colorectal cancer refractory or intolerant to standard therapies. The present analysis investigated the efficacy and safety of trifluridine/tipiracil in RECOURSE subgroups.

Methods: Primary and key secondary end-points were evaluated using a Cox proportional hazards model in prespecified subgroups, including geographical subregion (United States of America [USA], European Union [EU], Japan), age (<65 years, ≥65 years) and v-Ki-ras2 Kirsten rat sarcoma 2 viral oncogene homologue (*KRAS*) status (wild type, mutant). Safety and tolerability were reported with descriptive statistics.

Results: Eight-hundred patients were enrolled: USA, n = 99; EU, n = 403; Japan, n = 266. Patients aged ≥65 years and those with mutant *KRAS* tumours comprised 44% and 51% of all patients in the subregions, respectively. Final OS analysis (including 89% of events, compared with 72% in the initial analysis) confirmed the survival benefit associated with trifluridine/tipiracil, with a hazard ratio (HR) of 0.69 (95% confidence interval [CI] 0.59–0.81; P = 0.0001). Median OS in the three regions was 6.5–7.8 months in the trifluridine/tipiracil arm and 4.3–6.7 months in the placebo arm (USA: HR 0.56; 95% CI 0.34–0.94; P = 0.0277; EU: HR 0.62; 95% CI 0.48–0.80; P = 0.0002; Japan: HR 0.75; 95% CI 0.57–1.00; P = 0.0470). Median PFS was 2.0–2.8 months for trifluridine/tipiracil and 1.7–1.8 months for placebo; HRs favoured trifluridine/tipiracil in all regions. Similar clinical benefits of trifluridine/tipiracil were observed in elderly patients and in those with mutant *KRAS* tumours. There were no marked differences among subregions in terms of safety and tolerability.

Conclusions: Trifluridine/tipiracil was effective in all subgroups, regardless of age, geographical origin or *KRAS* status.

This trial is registered with ClinicalTrials.gov: NCT01607957.

1. Introduction

Trifluridine/tipiracil (TAS-102, Lonsurf®; Taiho Oncology Inc., Princeton, NJ, USA) is an orally administered chemotherapy consisting of the antineoplastic thymidine-based nucleoside analogue trifluridine, and a thymidine phosphorylase inhibitor, tipiracil, at a molar ratio of 1:0.5 (weight ratio, 1:0.471). The primary cytotoxic mechanism of trifluridine is through incorporation into DNA, leading to DNA dysfunction and damage [1–3]. The addition of tipiracil improves the bioavailability of trifluridine by inhibiting its catabolism by thymidine phosphorylase [4].

Trifluridine/tipiracil has shown promise in a number of clinical trials, particularly in metastatic colorectal cancer [5–10]. In the phase III RECOURSE trial (NCT01607957), which was conducted in patients with metastatic colorectal cancer refractory to standard therapies, including fluoropyrimidines, irinotecan and oxaliplatin, treatment with trifluridine/tipiracil resulted in a significant improvement in median overall survival (OS) compared with placebo (7.1 versus 5.3 months; hazard ratio [HR] 0.68; P < 0.0001) and in median progression-free survival (PFS) (2.0 versus 1.7 months; HR 0.48; P < 0.0001) [5]. Trifluridine/tipiracil was well tolerated, with few serious adverse events (AEs) reported; neutropenia was the most frequently observed AE. Many patients in this trial [5], as well as all patients in the prior phase II trial [10], were Japanese. Therefore, it is of interest to compare the efficacy and safety of trifluridine/tipiracil in Western populations with those reported from Japan. The current analyses were performed to further evaluate trifluridine/tipiracil compared with placebo among different patient groups, including geographical subregions, older patients aged ≥65 and ≥70 years, and v-Ki-ras2 Kirsten rat sarcoma 2 viral oncogene homologue (*KRAS*) status.

2. Patients and methods

2.1. Study design

The RECOURSE trial design has been previously described in detail (Supplementary Fig. 1) [5]. Briefly, RECOURSE was a global, phase III, multicentre, randomised, double-blind, placebo-controlled trial comparing trifluridine/tipiracil plus best supportive care on the one hand with placebo plus best supportive care on the other. Patients were stratified according to (1) *KRAS* status (wild type, mutant), (2) time since diagnosis of first metastasis (<18 months, ≥18 months) and (3)