European Journal of Cancer (2015) 51, 833–840

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with *BRAF* V600 metastatic melanoma

Dirk Schadendorf [a,*], Mayur M. Amonkar [b], Daniil Stroyakovskiy [c], Evgeny Levchenko [d], Helen Gogas [e], Filippo de Braud [f], Jean-Jacques Grob [g], Igor Bondarenko [h], Claus Garbe [i], Celeste Lebbe [j], James Larkin [k], Vanna Chiarion-Sileni [l], Michael Millward [m], Ana Arance [n], Mario Mandalà [o], Keith T. Flaherty [p], Paul Nathan [q], Antoni Ribas [r], Caroline Robert [s], Michelle Casey [b,1], Douglas J. DeMarini [b], Jhangir G. Irani [b], Gursel Aktan [b,1], Georgina V. Long [t]

[a] *Universitätsklinikum Essen, Hufelandstr. 55, Essen 45147, Germany*
[b] *GlaxoSmithKline, 1250 S Collegeville Rd, Collegeville, PA 19426, United States*
[c] *Moscow City Oncology Hospital #62, Moscow 143423, Russia*
[d] *Petrov Research Institute of Oncology, 68 Leningradskaya Street, Saint Petersburg 197758, Russia*
[e] *University of Athens, Aghiou Thoma 17, Athens 11527, Greece*
[f] *Fondazione IRCCS Istituto Nazionale Tumori, via Giacomo Venezian, 1, Milan, Italy*
[g] *Service de Dermatologie, Centre Hospitalo-Universitaire Sainte-Marguerite, 270 Boulevard de Sainte-Marguerite, Marseille 13009, France*
[h] *Dnepropetrovsk State Medical Academy, Dzerzhyns'koho Street 9, Dnepropetrovsk 49044, Ukraine*
[i] *Department of Dermatology, University Hospital Tuebingen, Liebermeisterstraße 25, Tuebingen 72076, Germany*
[j] *APHP Dermatology CIC Hôpital Saint Louis, University Paris Diderot, INSERM U976, Avenue Claude Vellefaux, Paris 75010, France*
[k] *Royal Marsden Hospital, Fulham Road, London SW3 6JJ, United Kingdom*
[l] *Melanoma and Esophageal Oncology Unit, Veneto Oncology Institute-IRCCS, via Gattamelata, 64, Padua 35128, Italy*
[m] *Sir Charles Gairdner Hospital, Hospital Avenue, Perth, WA 6009, Australia*
[n] *Hospital Clinic, Carrer Villarroel 170, Barcelona 08036, Spain*

* *Corresponding author at:* Department of Dermatology, Universitätsklinikum Essen, Hufelandstr. 55, Essen 45147 Germany. Tel.: +49 201 723 4342; fax: +49 (0) 201 723 59 35.

E-mail addresses: Dirk.Schadendorf@uk-essen.de (D. Schadendorf), mayur.m.amonkar@gsk.com (M.M. Amonkar), sdaniel@mail.ru (D. Stroyakovskiy), levchenko@newmail.ru (E. Levchenko), hgogas@hol.gr (H. Gogas), filippo.debraud@istitutotumori.mi.it (F. de Braud), jean-jacques.grob@ap-hm.fr (J.-J. Grob), oncology@dsma.dp.ua (I. Bondarenko), claus.garbe@med.uni-tuebingen.de (C. Garbe), celeste.lebbe@sls.aphp.fr (C. Lebbe), james.larkin@rmh.nhs.uk (J. Larkin), mgaliz@tiscali.it (V. Chiarion-Sileni), michael.millward@uwa.edu.au (M. Millward), amarance@clinic.ub.es (A. Arance), mmandala@hpg23.it (M. Mandalà), kflaherty@partners.org (K.T. Flaherty), p.nathan@nhs.net (P. Nathan), aribas@mednet.ucla.edu (A. Ribas), Caroline.Robert@igr.fr (C. Robert), meshellcasey@yahoo.com (M. Casey), douglas.j.demarini@gsk.com (D.J. DeMarini), jhangir.g.irani@gsk.com (J.G. Irani), gursel.aktan@gmail.com (G. Aktan), georgina.long@sydney.edu.au (G.V. Long).

[1] Affiliation of M. Casey and G. Aktan at the time of the study.

http://dx.doi.org/10.1016/j.ejca.2015.03.004

[o] Papa Giovanni XIII Hospital, Piazza OMS 1, Bergamo 24127, Italy
[p] Massachusetts General Hospital Cancer Center, 55 Fruit St, Boston 02114, MA, United States
[q] Mount Vernon Cancer Centre, Rickmansworth Road, Northwood HA6 2RN, United Kingdom
[r] David Geffen School of Medicine, UCLA, 10833 Le Conte Avenue, Los Angeles 90095, CA, United States
[s] Gustave Roussy and Paris 11 University, 114 Rue Edouard Vaillant, Villejuif-Paris-Sud 94805, France
[t] Melanoma Institute Australia & The University of Sydney, 40 Rocklands Road, Sydney 2060, Australia

Received 26 February 2015; accepted 4 March 2015
Available online 17 March 2015

KEYWORDS
Melanoma
Protein kinase inhibitors
Molecular targeted therapy
Proto-oncogene proteins
B-raf
Dabrafenib
Trametinib

Abstract ***Aim:*** To present the impact of treatments on health-related quality of life (HRQoL) from the double-blind, randomised phase III COMBI-d study that investigated the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with *BRAF* V600E/K-mutant metastatic melanoma. COMBI-d showed significantly prolonged progression-free survival for the combination.
Methods: HRQoL was evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30, a generic cancer questionnaire (completed at baseline, during study treatment, at progression and post progression) assessing various dimensions (global health/QoL, functional status, and symptom impact). A mixed-model, repeated-measures analyses of covariance evaluated differences between arms.
Results: Questionnaire completion rates were >95% at baseline, >85% to week 40 and >70% at disease progression. Baseline scores across both arms were comparable for all dimensions. Global health dimension scores were significantly better at weeks 8, 16 and 24 for patients receiving the combination during treatment and at progression. The majority of functional dimension scores (physical, social, role, emotional and cognitive functioning) trended in favour of the combination. Pain scores were significantly improved and clinically meaningful (6–13 point difference) for patients receiving the combination for all follow-up assessments versus those receiving dabrafenib monotherapy. For other symptom dimensions (nausea and vomiting, diarrhoea, dyspnoea, and constipation), scores trended in favour of dabrafenib monotherapy.
Conclusion: This analysis demonstrates that the combination of dabrafenib and trametinib provides better preservation of HRQoL and pain improvements versus dabrafenib monotherapy while also delaying progression. (Clinicaltrials.gov registration number: NCT01584648).

1. Introduction

The treatment landscape for metastatic melanoma has changed significantly since 2011 following the approval by the US Food and Drug Administration of three immunologic agents and three small molecules for the treatment of metastatic melanoma. The former include inhibitors of CTLA4 (ipilimumab) and PD-1 on T cells (pembrolizumab and nivolumab) and the latter include the BRAF inhibitors vemurafenib and dabrafenib and the MEK inhibitor trametinib for patients with *BRAF* V600-mutant melanoma.

Despite the improved response rates, progression-free survival (PFS) and overall survival (OS) in patients treated with these recently approved agents compared with dacarbazine chemotherapy [1–6], severe immune-mediated toxicities and the lack of a validated biomarker for patient selection may restrict the use of ipilimumab. The onset of resistance limits the efficacy of single-agent BRAF inhibitors [7], with approximately 50% of patients developing resistance within 6–7 months of treatment initiation [8,9].

The combination of BRAF and MEK inhibition delayed resistance and decreased the incidence of cutaneous hyperproliferative lesions compared with single-agent BRAF inhibition in preclinical models, and hence the combination was tested in phase I, II and III studies in patients with *BRAF* V600 mutation-positive metastatic melanoma [6,10–12]. As a result, the combination of dabrafenib and trametinib received accelerated approval in the United States in 2014 based on the results of a randomised phase of an open-label phase I/II study comparing the combination with dabrafenib monotherapy in patients with *BRAF* V600-positive metastatic melanoma [6]. A double-blind, randomised, phase III study comparing the combination with dabrafenib monotherapy as first-line therapy in patients who had unresectable stage IIIC or stage IV melanoma with *BRAF* V600E or V600K mutations (COMBI-d) [10] demonstrated a statistically significant improvement in