

European journal of cancer : official journal  
v. 47, no. 10 (July 2011)  
General Collection  
W1 EU72BA  
2011-08-02 06:47:49

# EJC

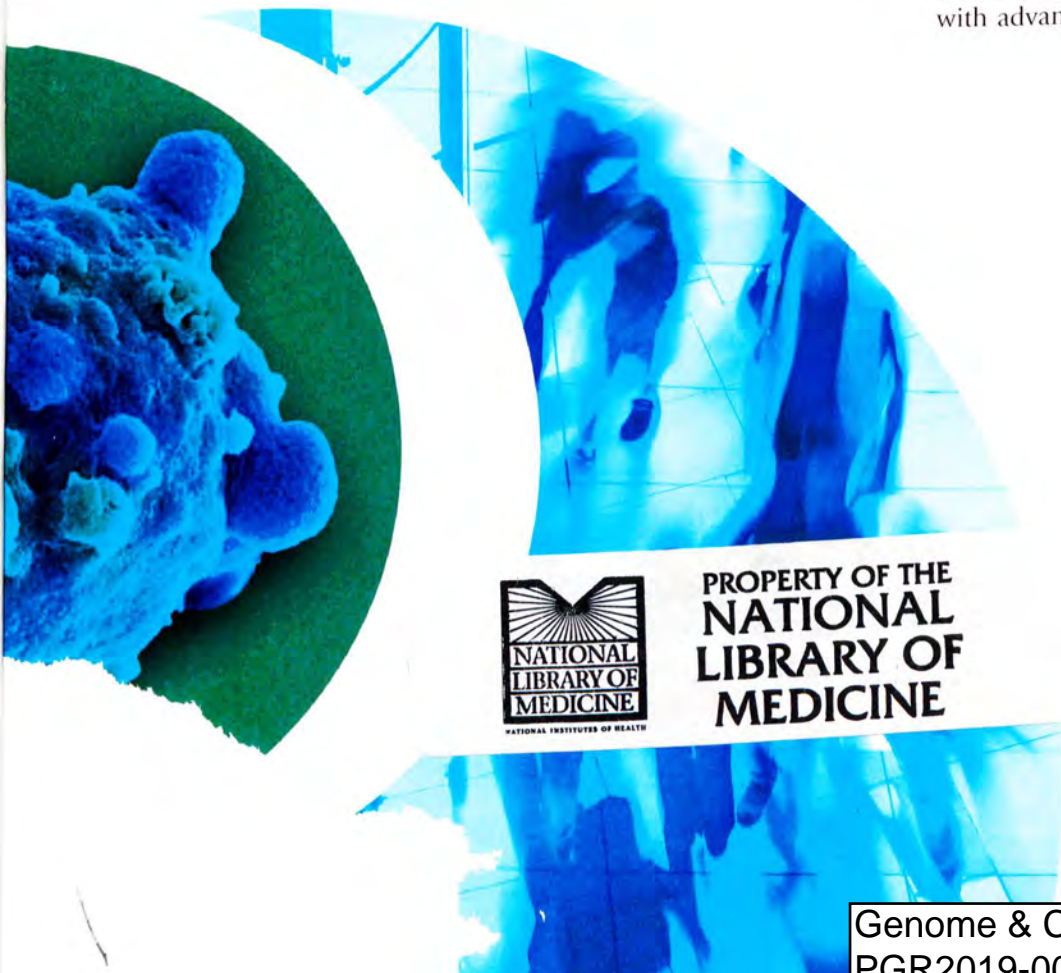
EUROPEAN JOURNAL OF CANCER

## IN THIS ISSUE

Phase 1 trials of molecular targeted therapies:  
Are we evaluating toxicities properly?

The preclinical and clinical activity of  
aviscumine: A potential anticancer drug

Effect of celecoxib on survival in patients  
with advanced non-small cell lung cancer



PROPERTY OF THE  
NATIONAL  
LIBRARY OF  
MEDICINE

THE OFFICIAL JOURNAL OF



Genome & Co. v. Univ. of Chicago  
PGR2019-00002  
UNIV. CHICAGO EX. 2060

# European Journal of Cancer

## Aims and Scope

The *European Journal of Cancer* (including *EJC Supplements*) is an international comprehensive oncology journal that publishes original research, editorial comments, review articles and news on experimental oncology, clinical oncology (medical, paediatric, radiation, surgical), translational oncology and on cancer epidemiology and prevention.

For a full and complete Guide for Authors, please go to <http://www.elsevier.com/locate/ejca>

**Advertising information.** Advertising orders and enquiries can be sent to: USA, Canada and South America: Pat Hampton Advertising Department, Elsevier Inc., 360 Park Avenue South, New York, NY 10010-1710, USA; phone: (+1) (212) 633 3181; fax: (+1) (212) 633 3820; e-mail: [p.hampton@elsevier.com](mailto:p.hampton@elsevier.com). Europe and ROW: Advertising Sales: Elsevier Pharma Solutions, 32 Jamestown Road, London NW1 7BY, UK; Tel.: +44 (0) 20 7424 4259; fax: +44 (0) 20 7424 4433; e-mail: [elsevierpharma.uk@elsevier.com](mailto:elsevierpharma.uk@elsevier.com).

**Publication information:** *European Journal of Cancer* (ISSN 0959-8049). For 2011, volume 47 (18 issues) is scheduled for publication. Subscription prices are available upon request from the Publisher or from the Elsevier Customer Service Department nearest you or from this journal's website (<http://www.elsevier.com/locate/ejca>). Further information is available on this journal and other Elsevier products through Elsevier's website (<http://www.elsevier.com>). Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis. Issues are sent by standard mail (surface within Europe, air delivery outside Europe). Priority rates are available upon request. Claims for missing issues should be made within six months of the date of despatch.

**Orders, claims, and journal enquiries:** please contact the Elsevier Customer Service Department nearest you:

**St. Louis:** Elsevier Customer Service Department, 3251 Riverport Lane, Maryland Heights, MO 63043, USA; phone: (800) 6542452 [toll free within the USA]; (+1) (314) 4478871 [outside the USA]; fax: (+1) (314) 4478029; e-mail: [JournalsCustomerService-usa@elsevier.com](mailto:JournalsCustomerService-usa@elsevier.com).

**Oxford:** Elsevier Customer Service Department, The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK; phone: (+44) (1865) 843434; fax: (+44) (1865) 843970; e-mail: [JournalsCustomerServiceEMEA@elsevier.com](mailto:JournalsCustomerServiceEMEA@elsevier.com).

**Tokyo:** Elsevier Customer Service Department, 4F Higashi-Azabu, 1-Chome Bldg, 1-9-15 Higashi-Azabu, Minato-ku, Tokyo 106-0044, Japan; phone: (+81) (3) 5561 5037; fax: (+81) (3) 5561 5037; e-mail: [JournalsCustomerServiceJapan@elsevier.com](mailto:JournalsCustomerServiceJapan@elsevier.com).

**Singapore:** Elsevier Customer Service Department, 3 Killiney Road, #08-01 Winsland House I, Singapore 239519; phone: (+65) 6349 0222; fax: (+65) 6733 1510; e-mail: [JournalsCustomerServiceAPAC@elsevier.com](mailto:JournalsCustomerServiceAPAC@elsevier.com).

### Author enquiries

For enquiries relating to the submission of articles (including electronic submission) please visit this journal's homepage at <http://www.elsevier.com/locate/ejca>. Contact details for questions arising after acceptance of an article, especially those relating to proofs, will be provided by the publisher. You can track accepted articles at <http://www.elsevier.com/trackarticle>. You can also check our Author FAQs at <http://www.elsevier.com/authorFAQ> and/or contact Customer Support via <http://support.elsevier.com>.

**Language services.** Authors who require information about language editing and copyediting services pre- and post-submission please visit <http://webshop.elsevier.com/languageediting/> or our customer support site at <http://support.elsevier.com>.

**Funding body agreements and policies.** Elsevier has established agreements and developed policies to allow authors whose articles appear in journals published by Elsevier, to comply with potential manuscript archiving requirements as specified as conditions of their grant awards. To learn more about existing agreements and policies please visit <http://www.elsevier.com/fundingbodies>.

**USA mailing notice:** *European Journal of Cancer* (ISSN 0959-8049) is published monthly with extra issues in January, March, May, July, September, November by Elsevier Ltd. (The Boulevard, Langford Lane, Kidlington, Oxon OX5 1GB, UK). Periodical postage paid at Rahway NJ and additional mailing offices.

USA POSTMASTER: Send change of address to *European Journal of Cancer*, Elsevier Customer Service Department, 3251 Riverport Lane, Maryland Heights, MO 63043, USA.

AIRFREIGHT AND MAILING in USA by Mercury International Limited, 365 Blair Road, Avenel, NJ 07001.

© 2011 Elsevier Ltd. All rights reserved

This journal and the individual contributions contained in it are protected under copyright by Elsevier Ltd and the following terms and conditions apply to their use:

**Photocopying.** Single photocopies of single articles may be made for personal use as allowed by national copyright laws. Permission of the Publisher and payment of a fee is required for all other photocopying, including multiple or systematic copying, copying for advertising or promotional purposes, resale, and all forms of document delivery. Special rates are available for educational institutions that wish to make photocopies for non-profit educational classroom use.

For information on how to seek permission visit [www.elsevier.com/permissions](http://www.elsevier.com/permissions) or call (+44) 1865 843830 (UK)/(+1) 215 239 3804 (USA).

**Derivative works.** Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution.

Permission of the Publisher is required for all other derivative works, including compilations and translations (please consult [www.elsevier.com/permissions](http://www.elsevier.com/permissions)).

**Electronic storage or usage.** Permission of the Publisher is required to store or use electronically any material contained in this journal, including any article or part of an article (please consult [www.elsevier.com/permissions](http://www.elsevier.com/permissions)).

Except as outlined above, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior permission of the Publisher

**Notice.** No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made.

Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made of it by its manufacturer.

© The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).



## Contents

### Editorial comment

- Phase 1 trials of molecular targeted therapies: Are we evaluating toxicities properly? 1443  
*J.-C. Soria*

### Short communication

- Motor vehicle exposure and risk of oesophageal adenocarcinoma 1446  
*J. Lagergren, C. Jansson and Y. Lu*

### Reviews

- The preclinical and clinical activity of aviscumine: A potential anticancer drug 1450  
*H. Zwierzina, L. Bergmann, H. Fiebig, S. Aamdal, P. Schöffski, K. Witthohn and H. Lentzen*
- Critical review of economic evaluations in multiple myeloma: An overview of the economic evidence and quality of the methodology 1458  
*J.G. Gaultney, W.K. Redekop, P. Sonneveld and C.A. Uyl-de Groot*

### Clinical oncology

- Heterogeneity in the definition of dose-limiting toxicity in phase I cancer clinical trials of molecularly targeted agents: A review of the literature 1468  
*C. Le Tourneau, A.R.A. Razak, H.K. Gan, S. Pop, V. Diéras, P. Tresca and X. Paoletti*
- Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV melanoma: Final results of a randomised phase III study (EORTC 18032) 1476  
*P.M. Patel, S. Suciú, L. Mortier, W.H. Kruit, C. Robert, D. Schadendorf, U. Trefzer, C.J.A. Punt, R. Dummer, N. Davidson, J. Becker, R. Conry, J.A. Thompson, W.-J. Hwu, K. Engelen, S.S. Agarwala, U. Keilholz, A.M.M. Eggermont and A. Spatz, on behalf of the EORTC Melanoma Group*
- A phase I study of sirolimus and bevacizumab in patients with advanced malignancies 1484  
*E.E.W. Cohen, M.R. Sharma, L. Janisch, M. Llobrera, L. House, K. Wu, J. Ramirez, G.F. Fleming, W.M. Stadler and M.J. Ratain*
- Reasons given by patients for participating, or not, in Phase 1 cancer trials 1490  
*S. Catt, C. Langridge, L. Fallowfield, D.C. Talbot and V. Jenkins*
- A randomised phase II trial of 1 month versus 1 year of adjuvant high-dose interferon  $\gamma$ -2b in high-risk acral melanoma patients 1498  
*L. Mao, L. Si, Z. Chi, C. Cui, X. Sheng, S. Li, B. Tang and J. Guo*
- Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995–2008 1504  
*D. Boll, R.H.A. Verhoeven, M.A. van der Aa, M.L.M. Lybeert, J.W.W. Coebergh and M.L.G. Janssen-Heijnen*
- An open-label, multicentre biomarker-oriented AIO phase II trial of sunitinib for patients with chemo-refractory advanced gastric cancer 1511  
*M. Moehler, A. Mueller, J.T. Hartmann, M.P. Ebert, S.E. Al-Batran, P. Reimer, M. Wehrauch, F. Lordick, T. Trarbach, S. Biesterfeld, M. Kabisch, D. Wachtlin and P.R. Galle, the German Arbeitsgemeinschaft Internistische Onkologie (AIO)*

One-month relative dose intensity of not less than 50% predicts favourable progression-free survival in sorafenib therapy for advanced renal cell carcinoma in Japanese patients 1521

A. Kawashima, H. Takayama, Y. Arai, G. Tanigawa, M. Nin, J. Kajikawa, T. Imazu, T. Kinoshita, Y. Yasunaga, H. Inoue, K. Nishimura, S. Takada, K. Nishimura, A. Tsujimura and N. Nonomura, *The Osaka Renal Cell Carcinoma Clinical Study Collaboration*

Primary breast cancer patients with high risk clinicopathologic features have high percentages of bone marrow epithelial cells with ALDH activity and CD44<sup>+</sup>CD24<sup>lo</sup> cancer stem cell phenotype 1527

J.M. Reuben, B.-N. Lee, H. Gao, E.N. Cohen, M. Mego, A. Giordano, X. Wang, A. Lodhi, S. Krishnamurthy, G.N. Hortobagyi, M. Cristofanilli, A. Lucci and W.A. Woodward

Peritumoural vascular invasion: A major determinant of triple-negative breast cancer outcome 1537

R. Sabatier, J. Jacquemier, F. Bertucci, B. Esterni, P. Finetti, F. Azario, D. Birnbaum, P. Viens, A. Gonçalves and J.-M. Extra

Effect of celecoxib on survival in patients with advanced non-small cell lung cancer: A double blind randomised clinical phase III trial (CYCLUS study) by the Swedish Lung Cancer Study Group 1546

A. Koch, B. Bergman, E. Holmberg, C. Sederholm, L. Ek, J. Kosieradzki, K. Lamberg, L. Thaning, S.-O. Ydreborg and S. Sörenson, *On behalf of the Swedish Lung Cancer Study Group*

### Paediatric oncology

Pharmacokinetics of cyclophosphamide and its metabolites in paediatric patients receiving high-dose myeloablative therapy 1556

G. Chinnaswamy, J. Errington, A. Foot, A.V. Boddy, G.J. Veal and M. Cole

### Epidemiology and cancer prevention

Couples' communication before the wife's death to cancer and the widower's feelings of guilt or regret after the loss – A population-based investigation 1564

J.M. Jonasson, A. Hauksdóttir, S. Nemes, P.J. Surkan, U. Valdimarsdóttir, E. Onelöv and G. Steineck

Adding familial risk assessment to faecal occult blood test can increase the effectiveness of population-based colorectal cancer screening 1571

N. Dekker, L.G.M. van Rossum, M. Van Vugt-van Pinxteren, S.H.C. van Stiphout, R.P.M.G. Hermens, W.A.G. van Zelst-Stams, M.G.H. van Oijen, R.J.F. Laheij, J.B.M.J. Jansen and N. Hoogerbrugge

### Experimental oncology/Translational research

Efficacy of a leptin receptor antagonist peptide in a mouse model of triple-negative breast cancer 1578

L. Otvos Jr., I. Kovalszky, M. Riolfi, R. Ferla, J. Olah, A. Sztodola, K. Nama, A. Molino, Q. Piubello, J.D. Wade and E. Surmacz

p62/SQSTM1 involved in cisplatin resistance in human ovarian cancer cells by clearing ubiquitinated proteins 1585

H. Yu, J. Su, Y. Xu, J. Kang, H. Li, L. Zhang, H. Yi, X. Xiang, F. Liu and L. Sun

VEGF-SPECT with <sup>111</sup>In-bevacizumab in stage III/IV melanoma patients 1595

W.B. Nagengast, M.N. Lub-de Hooge, E.M.E. van Straten, S. Kruijff, A.H. Brouwers, W.F.A. den Dunnen, J.R. de Jong, H. Hollema, R.A. Dierckx, N.H. Mulder, E.G.E. de Vries, H.J. Hoekstra and G.A.P. Hospers



ELSEVIER

Indexed/Abstracted in:  
Current Contents;  
EMBASE/Excerpta Medica;  
Index Medicus; MEDLINE;  
CABS, BIOSIS Database;  
PASCAL-CNRS Database; CINAHL.

ISSN 0959-8049





## Reasons given by patients for participating, or not, in Phase 1 cancer trials

S. Catt <sup>a,\*</sup>, C. Langridge <sup>a</sup>, L. Fallowfield <sup>a</sup>, D.C. Talbot <sup>b</sup>, V. Jenkins <sup>a</sup>

<sup>a</sup> CR-UK Psychosocial Oncology Group, Brighton and Sussex Medical School, UK

<sup>b</sup> Department of Medical Oncology, Churchill Hospital, University of Oxford, Oxford, UK

### ARTICLE INFO

#### Article history:

Received 7 January 2011

Received in revised form 23 February 2011

Accepted 25 February 2011

Available online 30 March 2011

#### Keywords:

Cancer  
Phase 1 trials  
Motivation  
Reasons  
Communication  
Trial participation

### ABSTRACT

**Background:** Communication with patients contemplating Phase 1 cancer trial participation can be challenging. Controversy exists as to whether they are provided with sufficient information to give genuinely informed consent. We present data examining the reasons patients gave for trial entry.

**Method:** Following discussions with oncologists about Phase 1 trials, participants completed a 19-item study specific 'accept or decline measure' exploring hope, expectations of benefit, altruism, concerns, and general perceptions of the trial information. They also completed 2 standardised questionnaires measuring psychological morbidity and predisposition towards optimism.

**Results:** Forty patients completed the study questionnaires. Patients were generally optimistic with few concerns about the experimental nature of Phase 1 trials. Most 36/40 (90%) consented to trial entry. Fifty-one percent thought the trial was the only treatment option available. The four main reasons for trial entry were: expectation of some medical benefit (21%); trial the best available option (21%); to maintain hope (15%) and to help with research (13%). Only one patient gave altruism as their main reason for trial participation. **Conclusion:** Patients considering Phase 1 trials may be a self-selected group with optimistic expectations of personal benefit driving trial entry rather than altruism. Achieving genuinely informed consent and avoidance of therapeutic misconceptions in such patients may be difficult.

© 2011 Elsevier Ltd. All rights reserved.

## 1. Introduction

Phase 1 (P1) clinical trials are crucial in the development of new anti-cancer treatments. New agents that have shown promise in the laboratory are usually tested in patients with advanced disease. The aims of P1 trials are to determine safe dosage range and identify side-effects. These trials convey small prospects of therapeutic benefit and carry varying possibilities of side-effects.<sup>1</sup> It is therefore not surprising that recruiting patients into these studies generates ethical debate<sup>2</sup> and creates challenging communication issues.<sup>3,4</sup>

A systematic review by Todd and colleagues<sup>5</sup> examined the positive and negative attitudes of patients with advanced cancer towards research. In this review 11 studies were identified for evaluation. Most involved hypothetical scenarios and only two were with patients in P1 trials – one qualitative<sup>6</sup> and one quantitative.<sup>7</sup> Common motives for participation were altruism, hope, and for personal benefit. Concerns about negative impact on symptoms and risk of increased hospital admissions emerged as reasons for declining participation. Most patients were positive in general about research despite having advanced disease. Conclusions were that more

\* Corresponding author. Address: Cancer Research UK Psychosocial Oncology Group, Brighton and Sussex Medical School, University of Sussex, Falmer, Brighton, East Sussex BN1 9QG, UK. Tel.: +44 1273 873024; fax: +44 1273 873022.

E-mail address: [S.L.Catt@sussex.ac.uk](mailto:S.L.Catt@sussex.ac.uk) (S. Catt).

0959-8049/\$ - see front matter © 2011 Elsevier Ltd. All rights reserved.

doi:10.1016/j.ejca.2011.02.020

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.