PERGAMON

European Journal of Cancer 37 (2001) S1–S2

European Journal of Cancer

www.ejconline.com

Introduction

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Received 7 March 2001; accepted 25 June 2001

Since its identification more than 15 years ago, the epidermal growth factor receptor (EGFR) has emerged as a significant factor in the development and growth of many types of solid tumours. The advent of a range of molecular techniques has revealed that the EGFR signal transduction network is involved in multiple tumorigenic processes, contributing to cancer-cell proliferation, angiogenesis and metastasis, as well as protection from apoptosis (reviewed in Ref. [1]). These techniques have also shown that this receptor tyrosine kinase is the growth-factor receptor most frequently overexpressed in a variety of common solid tumours, including squamous-cell carcinoma of the head and neck (SCCHN) and colorectal, renal-cell, ovarian and non-small cell lung cancers [2].

This supplement focuses on the biological role and clinical implications of the EGFR in tumour growth and brings together the contributions of several distinguished scientists. The papers presented here include an analysis of the biology of the EGFR illustrating the complexity of this signal transduction network, a discussion of the clinical implications of EGFR expression and results from clinical trials with the anti-EGFR monoclonal antibody (MAb), cetuximab.

Yosef Yarden of the Weizmann Institute of Science has contributed a paper entitled, 'The EGFR family and its ligands in human cancer: signalling mechanisms and therapeutic opportunities'. This review begins by tracing the evolution of the EGFR family over 1 billion years, highlighting its fundamental importance in cellular biology. A central theme is the complexity of EGFR family signalling in mammals, given the interaction between the four EGFR family members and the multiplicity of growth factors which stimulate them—an important perspective when considering that most therapeutic strategies are directed only at individual family members. Dr Yarden also discusses the central role of EGFR in cancer. As an example, he describes how many tumour viruses target the EGFR, employing a number of different strategies to activate this signalling pathway.

The next contribution contains a stimulating analysis of EGFR and cancer prognosis, based on an exhaustive PubMed search of the relevant literature from 1985 to the present. In this report, Nicholson and colleagues, of Cardiff University, find considerable heterogeneity in the studies conducted and in the assays used to detect EGFR. Nevertheless, they identify five cancer types—ovarian, cervical, bladder, head and neck and oesophageal—in which a strong correlation between EGFR expression or autocrine production of ligands and poor prognosis is demonstrated across a majority of studies. Four other cancer types—namely gastric, breast, endometrial and colorectal—also show a correlation, albeit not quite as strong. However, in the opinion of Nicholson and colleagues, the published results are highly likely to underestimate the true overall picture, and they call for systematic assays detecting active EGFR signalling rather than just EGFR protein. This should allow both accurate selection of patients who will benefit from anti-EGFR therapies and accurate monitoring of their effectiveness.

A number of anti-EGFR therapeutic strategies are currently being developed and José Baselga of Universitari Vall d'Hebron has had a great deal of experience with more than one of them. In this report, he discusses the development of the anti-EGFR MAb cetuximab and reviews the compelling preclinical data that supported its further development. He examines the antibody's numerous mechanisms of action and also describes the very promising clinical data that has been accumulating from phase I and II trials, particularly

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PII: S0959-8049(01)00232-5

those presented at the American Society of Clinical Oncologists (ASCO) conference last year. In addition to low immunogenicity and generally low toxicity, cetuximab yields adverse events (AEs) that have come to be expected of such an antibody, namely manageable allergic reactions and skin reactions. Dr Baselga highlights the results presented by Mark Rubin at ASCO, who reported clinical responses to cetuximab in patients with a variety of solid tumours that had been refractory to various chemotherapeutic regimens. Of special note also are the results of Jim Bonner, who reported 87% complete responses following radiotherapy plus cetuximab treatment among 15 patients with unresectable SCCHN and an especially poor prognosis. The encouraging results with cetuximab in phase I studies has led to a number of planned and ongoing phase II and III trials.

In conclusion, as the contributions to this supplement show, much has been learned about the biology and prognostic significance of the EGFR in tumour growth. These findings indicate the exciting potential for anti-EGFR therapy and have led to the development of cetuximab which has recently shown promising signs of providing patients with clinical benefits.

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