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Overview of past, present and future of the EORTC Lung Cancer Group

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Abstract

The EORTC Lung Cancer Group (LCG) is a multidisciplinary international group of experts performing clinical research in lung cancer since 1962. Originally, the group consisted mainly out of French and Belgian investigators and expanded gradually into a wide range of investigators from all European Union countries, as well as some investigators from Switzerland, Poland, Czech Republic, Egypt, Slovenia, South Africa, Peru, Brazil and Cyprus. Despite the wide collaboration, it remains a difficult task to perform high quality large clinical research trials to answer important scientific questions in the treatment of lung cancer. For this reason, the EORTC Lung Cancer Group has invested a lot of efforts in promoting worldwide, randomised phase III studies in collaboration with other Groups. Furthermore, the LCG promotes small phase II trials of new drugs or treatments for lung cancer and stimulates the investigation of new strategies and treatments for rare intrathoracic malignancies. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The EORTC Lung Cancer Group (LCG) (see Table 1 for active members), previously called the Bronchial Carcinoma Cooperative Group until 1981 and then the Lung Cancer Cooperative group (LCCG), is a multidisciplinary group involving oncologists, pulmonologists, thoracic surgeons, radiotherapists and pathologists, mainly from European countries. Since its creation in 1962 with the EORTC, all disciplines involved in lung cancer treatment have been represented in the Group.

Ever since it was founded, the Group has concerned itself with clinical research on thoracic neoplasms covering the entire spectrum from lung cancer chemoprevention to metastatic disease in non-small cell lung cancer (NSCLC), and treatment strategies of small-cell lung cancer (SCLC), malignant mesothelioma (MM) and thymoma. Phase II and phase III studies have been the group's primary research tools and the trials have focused on optimal local and systemic therapy, single-agent, combination therapy and/or multimodality treatment concepts, including also quality of life and recently also health economics. During the last 15 years, special attention went into setting up more intergroup collaborations, not only with other EORTC groups such as the Radiotherapy Group, Head and Neck Cancer Group and the Quality of Life Group, but also with other co-operative partners with equally high standards outside the EORTC (e.g. NCIC, ALPI, SLCG, SAKK, GFPC, ECOG and other North American groups). Within recent decades, the LCG has performed many phase II and phase III clinical studies including thousands of patients (Tables 2–6). Many of these studies have contributed to the clinical knowledge on the treatment of lung cancer. Actually, seven studies are open for accrual and five additional studies are to be activated in the near future.

2. Structure and organisation

The statutes of the Group describe the structure and organisation. The board of the Group (consisting of the chairman, secretary, treasurer, past-chairmen and subchairmen of each discipline) together with EORTC Data Centre representatives discuss on a regular basis (every 3–6 months) the strategy of the Group. The steering committee of the Group consists of the board

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Table 1
EORTC LCG: active members 2001

The Netherlands	Bosch Medicentrum—Groot Ziekengasthuis, s'Hertogenbosch
	St. Antonius Ziekenhuis, Nieuwegein
	Netherlands Cancer Institute, Amsterdam
	AZ—Daniel den Hoed Kliniek, Rotterdam
	Academisch Ziekenhuis der Vrije Universiteit, Amsterdam
	Sophia Ziekenhuis, Zwolle
	Erasmus Universiteit—Dijkzigt Hospital, Rotterdam
	Radiotherapeutisch Instituut, Arnhem
	Ziekenhuis St. Jansdal, Harderwijk
	Rijnstate Hospitaal, Arnhem
Spain	Hospital Universitario 12 de Octubre, Madrid, Spain
Germany	Thoraxklinik Rohrbach, Heidelberg
Poland	Maria Sklodowska—Curie Memorial Cancer Centre, Warsaw
	Medical University, Gdansk
Egypt	National Cancer Institute

members together with the study co-ordinators of ongoing trials and representatives of the active institutions and is responsible for setting up new trials in co-operation with the EORTC Data Centre Statistician and Medical advisor. Probationary membership is open to every institution interested in participating in the clinical studies. New members are elected for 2 years after having been approved by the quality assurance subcommittee of the Group. They then obtain the status of probationary member. After re-evaluation of quality, interest and recruitment aspects, the new member becomes an active member provided they include at least 10 evaluable cases each year into the Group's trials. If yearly recruitment is less, the new member maintains the status of probationary member. At present, the Group comprises 15 core active member-institutions, listed in Table 1 and 94 member institutions with a lower accrual or probational membership. Twice a year, the Group holds a meeting, during which important scientific and administrative matters are discussed, i.e. protocols, publications, special projects, membership, elections and finances.

3. Clinical research activities of the Group

3.1. Non-small cell lung cancer (NSCLC)

A major effort has been attempted by the Group along the years in the adjuvant therapy of NSCLC. As for many other co-operative groups, it has been rather difficult to have a sufficient accrual in adjuvant chemotherapy studies. A couple of studies were aborted due to poor accrual. One of these trials (08861) selected patients with radically resected NSCLC with mutations in the *k-ras* oncogene, for randomisation to chemotherapy or follow-up. Over 100 patients were screened for mutations, of which about one-third were randomised in the study. The logistics were too complex to allow timely accrual into this study, but this represented the first example of translational research within the group. More recently, after the meta-analysis of all randomised studies of chemotherapy in NSCLC [63]

Table 2
Non-small cell lung cancer (NSCLC) trials

EORTC trial number	Trial	Treatment	Stage of disease	Number of pts
08741 [1]	III	Postoperative randomisation between: RT versus no RT Second randomised between: CT *vs.* IT *vs.* IT + CT *vs.* no trt	Resectable NSCLC	634
08742 [2]	III	Post-irradiation randomised between: CT *vs.* IT *vs.* IT + CT *vs.* no trt	Unresectable NSCLC	235
08812 [8]	II	Ametantrone	Advanced SCLC + NSCLC	82
08822 [8,9]	II	Ellipticinium acetate	Advanced SCLC + NSCLC	45
08842 [6,11,37]	II (R)	Combination CT + split-dose RT	Inoperable NSCLC (M0)	75
08844 [23,28]	III	RT alone versus RT + weekly CDDP versus RT + daily low dose CDDP	Inoperable NSCLC (M0)	331
08861	III	Adjuvant therapy following complete resection	Resected NSCLC	132
08863	II	CT followed by S + RT	N2 NSCLC	27
08872 [13,20]	II	ACNU	Advanced NSCLC + SCLC	86
08875 [12,40]	III	VM26 with or without CDDP	M1 NSCLC	225
08902	II	Suramin	Advanced NSCLC	14
08911 [36]	II (R)	Oral ifosfamide/mesna versus i.v. ifosfamide/mesna	Advanced NSCLC	69
08912 [55]	I/II	High dose RT with daily CDDP	Inoperable NSCLC	40
08925 [39,43,48]	II–III	Teniposide/CDDP versus paclitaxel/CDDP	Advanced NSCLC	332
08955 [56]	II	Gemcitabine + CDDP	IIIaN2	53

EORTC, European Organisation for Research and Treatment of Cancer; RT, radiotherapy; CT, chemotherapy; IT, immunotherapy; S, surgery; SCLC, small-cell lung cancer; (R), randomised; pts, patients; trt, treatment; CDDP, cisplatin; i.v., intravenous.

Table 3
Small-cell lung cancer (SCLC) trials

EORTC trial number	Trial	Treatment	Stage of disease	Number of pts
08825 [7,25]	III	Induction CT versus induction + maintenance CT	LD + ED	687
08841 [10]	II	High-dose VP 16	SCLC with brain mets	33
08854 [22]	II	4-Epidoxorubicin	ED SCLC elderly/unfit	41
08862 [5,21]	II (R)	Two schemes of standard combination CT with carboplatin	Unresectable SCLC	289
08873 [33]	II	Teniposide	SCLC with brain mets	82
08877 [32,42]	III	Alternating versus sequential radio-CT	LD SCLC	389
08882 [27,38]	III	Standard CT versus alternating CT	ED SCLC	148
08883 [46]	III	Gamma IFN for intensification/maintenance	Complete responders SCLC	127
08891 [49,54]	II + III	Role RT in treatment of brain mets	SCLC with brain mets	163
08892 [26]	II	Navelbine	Progressive pretreated SCLC	26
08923 [58]	III	Standard versus intensified CDE with or without AB	LD + ED SCLC	245
08951 [50]	III	Sequential RT + or −CDDP	LD SCLC responders	13

EORTC, European Organisation for Research and Treatment of Cancer; LD, limited disease; ED, extensive disease; RT, radiotherapy; CT, chemotherapy; AB, antibiotic; (R), randomised; IFN, interferon; mets, metastases.

showing improved survival of cisplatin-based adjuvant chemotherapy, the EORTC Lung Cancer Group joined forces with the Italian ALPI study, which recently closed accrual with more than 1000 patients randomised to three cycles of MVP or follow-up. This study is pivotal in the understanding whether adjuvant systemic treatment has any role and for which stages of radically resected NSCLC. The data are presently being analysed and will be ready for next year's American Society of Clinical Oncologists (ASCO) meeting.

A huge effort was made to investigate whether chemoprevention with retinol palmitate and or N-acetylcysteine would prevent second primaries in early NSCLC and head and neck cancers. In this study, more than 2500 patients were randomised by the Lung Cancer Group and Head and Neck Group of the EORTC. Unfortunately, no efficacy was detected in this study by either agent alone or in combination [61]. This important study closes a decade of large chemoprevention trials with either negative or detrimental effects.

In locally advanced NSCLC disease, the EORTC Lung Cancer Group has made major contributions to the research on combined modality therapy. In the pivotal study by Shaake and colleagues [31], Cisplatin was added simultaneously to radiotherapy either given daily or weekly and was compared with radiotherapy alone. This study demonstrated that cisplatin and radiotherapy improved survival in locally advanced NSCLC and this was mainly obtained through an improvement of local control. This result, together with the results of several other studies, contributed to the present standard combined modality therapy of locally advanced disease, which is chemo-radiotherapy. Presently, the Lung Cancer Group is investigating whether two cycles of chemotherapy with cisplatin and gemcitabine followed by radiotherapy is better than high-dose concomitant boost radiotherapy with daily cisplatin at low doses (08972). The question asked by this study is in line with the general tendency of showing better results by concomitant chemoradiotherapy in SCLC and, more recently, also in NSCLC. The other trend is to place radiotherapy early in the therapy planning for locally advanced disease.

Another pivotal study, still ongoing within the Group is a large phase III randomised trial in stage IIIAN2 NSCLC patients comparing radiotherapy with surgery following clinical response after three cycles of an neoadjuvant platinum-based chemotherapy regimen. Several sequential phase II studies of new platinum-based chemotherapy regimens have been inserted within this phase III trial (08955, 08958, 08984).

Several studies have been performed by the Group in the therapy of advanced or metastatic NSCLC. Three large randomised studies have been performed in which the best arm of the past study has been consistently used to design the next study (08875, 08925 and 08975). The Group has shown that in a comparison of two cisplatin-containing chemotherapies, response rate is probably not a good surrogate marker, as survival did not improve by doubling response rate. Nowadays, other markers of efficacy and tolerance need to be considered in the choices of chemotherapy in advanced NSCLC, namely toxicity profiles, quality of life and cost-effectiveness. In the most recent study, a non-platinum regimen

Table 4
Malignant mesothelioma (MM) trials

EORTC trial number	Trial	Treatment	Number of pts
08852 [16]	II	Mitoxantrone	46
08864 [4,19]	II	4-Epidoxorubicin	63
08878 [45]	II	Etoposide	49
08901 [45]	II	Etoposide	45
08924 [41]	II	Paclitaxel (Taxol)	26
08943 [52]	II	Gemcitabine	32
08966 [53]	II	Liposomal doxorubicin (Caelyx)	33

EORTC, European Organisation for Research and Treatment of Cancer; pts, patients.

Table 5
Thymoma trials

EORTC trial number	Trial	Treatment	Stage of disease	Number of pts
08853 [35]	II	Thymoma: CDDP-etoposide	Advanced thymoma	16
08961 [59]	II	Thymoma: VIP	Invasive thymoma	3

EORTC, European Organisation for Research and Treatment of Cancer; pts, patients; CDDP, cisplatin.

seems to be inferior to platinum combinations, in terms of progression-free survival and survival, although this did not reach statistical significance. This last study stresses once more the difficulty even with the newer chemotherapy drugs to significantly improve survival and the need to consider other markers of efficacy in the setting of pure palliation.

3.2. Small-cell lung cancer (SCLC)

The EORTC Lung Group demonstrated that continuing the same chemotherapy beyond five cycles up to 12 cycles did not have any impact on survival, although progression-free survival was increased (08825). This is in line with several other maintenance studies in SCLC, and contributed to the present treatment of SCLC, which consists of 4–5 cycles of combination chemotherapy.

The most recent LCG study attempted to intensify the chemotherapy by using granulocyte-colony stimulating factor (G-CSF) support and/or antibiotics to prevent infectious complications (08923). This study was essentially negative in terms of overall survival and overall response rate.

The Group has had major contributions in the definition of sensitivity in the relapsing patients with SCLC. Several other groups have now adopted this definition, which is based on the time from end of prior first-line therapy and on the response to first-line chemotherapy. This is a common definition to be applied also in clinical practice as a way to identify patients who may still benefit from the presently available chemotherapy. The resistant patients are preferably included in the new drug therapy approaches. By using this definition, topotecan has been identified as an active agent in refractory patients with recurrent SCLC (08957).

The use of prophylactic cranial irradiation has been investigated intensively within the Group. The EORTC LCG together with the UK group have performed a PCI study, which once again allowed a significant protection from brain metastases development to be shown [60]. This study, included in a large meta-analysis of all randomised studies of PCI in SCLC, allowed an increase in survival to be demonstrated both a lower incidence in brain metastases and an increase in survival in patients with CR or nearly complete response to chemo-radiotherapy [61].

Presently, the Lung Cancer Group coordinates a large international study in limited disease patients who, after achievement of a major response to chemoradiation are randomised between vaccination to BEC2/BCG or follow-up. BEC2 is an anti-idiotypic antibody which targets the ganglioside GD3 constitutively expressed on the surface of 100% of SCLC cells. In a pilot study performed at Memorial Hospital in New York, patients with limited disease who were vaccinated had over 50% survival at 5-years follow-up [62].

3.3. Malignant mesothelioma (MM)

A large number of consecutive phase II studies have been performed by the Group (Table 4), in general with dismal results, and response rates always lower than 20%. Recently, the Group has engaged in an intergroup randomised phase III study in which cisplatin–Tomudex is compared with Tomudex alone (08983). The Group has also developed a risk assessment classification, which may be easily applied in future clinical studies in this disease [50].

3.4. Thymoma

This is a very rare disease. The Group has performed two studies in this disease (Table 5). The first investigated cisplatin–etoposide in a phase II study [38]. The

Table 6
Other trials

EORTC trial number	Trial	Treatment	Stage of disease	Number of pts
08871 [17,24,29,30,34,57]	III	EUROSCAN	Chemoprevention in Lung and HN cancer	2592
08881	III	ICS 205–930 + metoclopramide—containing antiemetic cocktail	Prevention of emesis	174

EORTC, European Organisation for Research and Treatment of Cancer; pts, patients; EUROSCAN, phase III randomised study of chemoprevention with vitamin A and N-acetylcysteine in patients curatively treated for carcinomas of the larynx, oral cavity and lung (jointly with the EORTC Head and Neck Group).

second has been an intergroup effort, together with the North American groups, investigating the VIP combination chemotherapy [59]. Presently, no studies are running within the Group.

3.5. Trials involving biological studies

Besides the study of adjuvant chemotherapy in radically resected NSCLC, in which only patients with K-*ras* mutations were selected for randomisation, the Group has attempted other translational research projects.

Within the EORTC-ALPI study of adjuvant chemotherapy, three markers of prognosis were retrospectively assessed: K-*ras* mutations, p53 accumulation and Ki-67 by immunohistochemistry. The data presented in over 200 patients analysed showed the prognostic value of K-*ras* mutations.

In a phase II trial of bronchioalveolar carcinoma (BAC), p53, K-*ras* mutations and Ki-67 staining are also being investigated. These may provide useful tools for the study of the biology and pathogenesis of BAC.

In malignant mesothelioma, there is an active interest by the pathology chair to perform correlative studies with a number of molecular markers of prognosis.

4. Future strategies

As for the treatment of several other solid tumour types, a future strategy of our Group is the investigation of biological therapies to be integrated into the present treatment modalities in SCLC, as well as in NSCLC.

Targeted therapies are going to be assessed carefully for all stages of the disease, starting with the most advanced stages.

Presently, the following important studies are ongoing or being planned:

1. Iressa (epidermal growth factor receptor (EGFR) inhibitor small molecule) + docetaxel versus docetaxel alone in second-line treatment of NSCLC (phase III double-blind intergroup trial).
2. Iressa with gemcitabine/CDDP as neo-adjuvant therapy in stage IIIaN2 NSCLC (phase II).
3. Definition of the role of BEC2/BCG vaccination in limited disease SCLC (phase III, intergroup).
4. Role of reinduction chemotherapy versus non-cross-resistant chemotherapy including docetaxel (Taxotere) and CPT-11 in sensitive recurrence of SCLC (phase III).
5. Raltitrexed (Tomudex) plus cisplatin versus cisplatin alone in inoperable malignant pleural mesothelioma (phase III, intergroup).

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