



Annual Report 2014



etop

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EDITORIAL

February 2015

Dear Reader

2014 was another busy and successful ETOP year. ETOP was celebrating its fifth year, and it is with pride that we appreciate the efforts of these pioneer years that have started to pay off. ETOP has evolved greatly over the past years and continuously enlarged its network. Today ETOP comprises more than 50 members, collaborative groups and institutions from all over Europe and beyond. We take this opportunity to thank you for your continued partnership and collaboration and for your valuable contribution to the success of ETOP.

With this annual report ETOP would like to provide you with an update on its projects, trials and activities. Enjoy reading!

Kind regards



Prof. Rolf A. Stahel
President, ETOP Foundation Council



Dr. Solange Peters
Communication Chair and
Scientific Coordinator ETOP

KEY DATA

Full publications	3
Abstracts/presentations	3
Number of newly activated clinical trials	2
Number of patients included in	
• Clinical trials	196
• Observational studies	2709

ETOP MILESTONES IN 2014

Five years of successful growth

The interest in promoting and improving collaboration in clinical and translational research in lung cancer and mesothelioma in Europe prompted investigators representing collaborative study groups and institutions concerned with thoracic malignancies to explore new ways of working together. Out of this discussion the European Thoracic Oncology Platform was founded in 2009. This was the final step after two years of consultation between friends and leaders in the field of thoracic oncology throughout Europe.

The first major undertaking that was started is Lungscope, a translational research project to study the molecular epidemiology of lung cancer in Europe. From the start ETOP has also decided to advance clinical research by conducting therapeutic trials in collaboration with its members. Each trial is financially supported by a pharmaceutical company, and ETOP vouches for the academic independency in the conduct, evaluation and publication of the results. The safety of the patients participating in these trials is assessed by ETOP's Independent Data Monitoring Committee. In addition, ETOP also strived to present a platform for the exchange of knowledge and for dissipation of latest insight on thoracic malignancies. First of all, www.etop-eu.org is the place where ETOP members find a valuable collection of scientific evidence. Slide sets summarizing the most important presentations from major cancer conferences like ASCO, ESMO, WLCC and ELCC are compiled by a series of editors within a few days of these events.

The ETOP Residential Workshop brings together young investigators and experienced faculty and allows in an informal setting to develop and discuss with peers new ideas for clinical research. This format is a great opportunity for the next generation of researchers to improve their skills and to network. The members of ETOP are either single academic hospitals and clinics or collaborative groups like SAKK, Spanish Lung Cancer Group SLCG, or the Central European Collaborative Oncology Group CECOG.

Such groups take over some of the responsibilities in the projects and often act as intermediary between ETOP and their own sites. This provides the necessary flexibility to take into account local requirements and traditions and allows conducting research in a way which is familiar for the respective investigators and their staff.

ETOP still expands and consolidates its activities. During its first five years it has already become one of the leading organisations conducting research in the field of thoracic malignancies and certainly continues to grow in expertise, recognition and leadership.

Rolf A. Stahel, ESMO President 2014/2015

Rolf A. Stahel, president-in-office and founder of ETOP was elected as president of the Society for Medical Oncology (ESMO) for the years 2014/2015. ESMO is the leading European professional organization, committed to advancing the field of medical oncology in many respects. One of the missions is to enable oncologists to deliver the best possible diagnostic and therapeutic options to their patients. ESMO sets high priority to the education and training of professionals involved in clinical cancer care, to ensure a high standard of qualification within the multidisciplinary team. The ESMO community is a powerful alliance of over 10'000 committed oncology professionals from over 120 countries.

Rolf A. Stahel started serving ESMO as national representative of Switzerland (1998-2004), chaired the ESMO guidelines task force (1999-2005) and the educational committee (2006-2011). Since 2003 Rolf A. Stahel is a member of the ESMO board of directors and served as president-elect from 2012 to 2013 before he became ESMO president in January 2014.

Leading ESMO as president is one of the highest honours for a European medical oncologist. We sincerely congratulate Rolf A. Stahel and wish him a successful presidency.

ETOP iBiobank: 2nd Place in the ESBB Research Biobank of the Year Competition

Biobanks are an indispensable resource for today's strive towards more precise, 'personalized' medicine. But what makes a great biobank? One of Europe's largest biobanking organizations, ESBB, aims to stimulate this discussion with its 'Research Biobank of the Year Competition' (RBYC). On behalf of ETOP Lungscape and with help of Rolf A. Stahel, Lukas Bubendorf, Erik Thunnissen, Keith M. Kerr, and Solange Peters the ETOP Coordinating Office submitted a proposal, which was shortlisted and selected for oral presentation at the ESBB Annual Meeting 2014 in Leipzig (21 – 24 November). ETOP Translational Research Coordinator, Rosita Kammler, gave a 10 minute overview of the ETOP Lungscape program and its de-centralized, 'virtual' iBiobank, which eventually was awarded second place of the RBYC by vote of the meeting attendees of biobank specialists. The audience and RBYC chairs were deeply impressed by the collaborative nature of the ETOP Lungscape iBiobank and the innovative approaches taken to ensure high quality standards across sites. We would like to congratulate all Lungscape participants and thank all the colleagues whose hard work made this exciting undertaking possible.

ETOP PROJECTS AND TRIALS

Molecular epidemiology projects

Lungscape

The Lungscape program aims to address the challenges of studying the molecular epidemiology of lung cancer by coordinating and harmonizing the procedures of a group of lung cancer specialists working in translational research across Europe and allowing analysis of larger series of cases. This initiative has the potential to expedite knowledge of the prevalence and context of current and emerging molecular biomarkers with clinical significance and facilitate more rapid translation of biomarker knowledge to the clinic. The international collaborative effort provides a platform for molecular correlative studies and thus creates a basis for the development of clinical trials of novel therapeutics. Lungscape also aims to build comprehensive and practical diagnostic algorithms for personalized medicine in the clinic.

The basis of Lungscape is a decentralised biobank with fully annotated tissue samples from resected stage I - III NSCLC. An electronic database (termed iBiobank) is used to store the anonymised comprehensive molecular and clinical data and tracking biological material and

derivatives thereof. Participating centres use a secure web-based application to enter data into this central database.

The virtual nature of iBiobank and the introduction of stringent standardised biomolecular assessments, a so called external quality assurance (EQA) process to establish laboratory performance levels, remove the need of transferring samples to a central location for evaluation.

The system captures detailed parameters like tumour stage, grade, histological subtype, precise surgical procedure as well as patient characteristics.

The Lungscape Master protocol defines the setting in which specific hypotheses will be investigated. It describes the mode of cooperation of the participating investigators, the selection of documentation of the NSCLC cohort, laboratory requirements as well as the regulatory framework. Specific protocol modules then formulate a hypothesis to be investigated in the framework of Lungscape. The clinical and pathological characteristics of the cohort in relation to the outcome after curative resection have been presented at ESMO 2012 and ASCO 2013 and have been published in the Journal of Thoracic Oncology (Peters S, Weder W, *et al.*, Lungscape: resected non-small cell lung cancer outcome by clinical and pathological parameters. Journal of Thoracic Oncology 9 (11): 1675-1684)

Lungscape 001 – ALK

This is a retrospective cohort study of ALK gene rearrangement: prevalence and clinical outcomes in patients with lung adenocarcinoma in Europe. The goals are to describe the expression of ALK and its clinical significance for the patients, their long-term outcome, the correlation of ALK with other biomolecular markers, and to determine the optimal method of ALK evaluation in clinical practice. The results have been presented at ESMO 2012 in Vienna and have been published in the Journal of Clinical Oncology (Blackhall FH, Peters S, and Bubendorf L, *et al.*, Prevalence and clinical outcomes for patients with ALK-positive resected stage I-III adenocarcinoma: Results from the European Thoracic Oncology Platform Lungscape Project. Journal of Clinical Oncology 32 (25): 2780-7).

Lungscape 002 – MET/PI3K/PTEN

This is a retrospective cohort study of MET protein expression and MET gene amplification (PI: Lukas Bubendorf), of PI3K gene amplification (PI: Verena Tischler), and of PTEN protein expression (PI: Alexander Soltermann) is well under way. The preliminary results of MET protein expression have been presented at ESMO 2014.

Lungscape 003 – Multiplex Mutation Testing

This is a retrospective cohort study of multiplex mutation testing of resected non-small cell lung cancer. The project is lead in collaboration with Genentech with the ETOP lead pathologists Keith Kerr, Lukas Bubendorf and Erik Thunnissen and Miguel Angel Molina as chair for the central lab. The prevalence and clinical significance of 120 selected somatic mutations, considered harbouring a potential pro-oncogenic or driver characteristic, from 11 cancer related genes will be established on tumour material from about 2400 patients which form the current Lungscape cohort. Most of the tumours have been examined and the results will be analysed soon.

New projects

Mesoscape

Mesoscape is a project to study the molecular epidemiology of malignant mesothelioma in Europe and has a similar set-up as Lungscape. A number of major cancers centres will contribute at least 1100 cases diagnosed in the last years. The master protocol is under development the PIs are Isabelle Opitz and Paul Baas.

Mesoscape 001 pS6

The first module of the Mesoscape project will describe the prevalence of phosphorylated ribosomal protein S6 in patients with mesothelioma and the clinical outcomes according to pS6. pS6 is a marker of the PI3K pathway and its description within this module may guide the development and testing of targeted therapies. This module will be activated along with the master Mesoscape protocol in 2014. The PI is Bart Vrugt.

Radioscape

The Radioscape program aims to address challenges of studying the molecular characteristics of lung cancer in relation to radiation therapy by coordinating and harmonizing the procedures of a group of lung cancer specialists working in translational research across Europe, and facilitating analysis of larger series of cases. This will expedite knowledge of the influence of current and emerging molecular biomarkers on the outcome of radiotherapy, delivered with or without systemic therapies, thus facilitating more rapid translation of biomarker knowledge to the clinic, and provide a platform for future molecular correlative studies conducted in prospective trials of novel therapeutics. The project has been submit the Swiss Cancer League for funding of the Swiss participation. The PI is Matthias Guckenberger.

Clinical trial

ETOP 2-11 BELIEF

BELIEF, a phase II prospective trial sponsored by ETOP and coordinated together with the Spanish Lung Cancer Group (SLCG), is the first therapeutic ETOP trial. BELIEF will determine the long-term outcome of patients with advanced non-squamous NSCLC with activating EGFR mutations (L858R and exon 19 deletion) with or without T790M resistance mutation at diagnosis and treated with the combination of erlotinib and bevacizumab. The accrual goal of 102 patients was reached in October 2014. Treatment and follow-up continue as planned.

ETOP 3-12 EMPHASIS-lung

In the EMPHASIS-lung trial, the potential of Veristrat, a clinically validated serum proteomic test, to predict response to treatment by erlotinib or docetaxel is being assessed in pre-treated patients with advanced squamous cell lung carcinoma. Over 50 centres from several European countries were activated and by the end of January 2014, 81 patients were randomized. Recruitment was terminated prematurely due to an accrual rate that was deemed insufficient and publication of controversial new data from another study. No safety concerns led to the decision to close accrual. Treatment and follow-up of all included patients continued as specified in the protocol.

ETOP 4-12 STIMULI

The combination of chemotherapy and thoracic radiotherapy is currently the standard treatment approach in limited stage SCLC. Several studies now showed that stimulation of immune cells may stop tumour growth. Ipilimumab, a humanized monoclonal antibody, activates the immune system by targeting CTLA-4, a protein receptor that down-regulates anticancer immune response.

This randomized multicentre open-label trial tests the efficacy and tolerability of the standard treatment alone or with subsequent consolidation with ipilimumab in patients with limited disease SCLC, with overall survival as primary endpoint. ETOP will conduct the trial in collaboration with the Intergroupe Francophone de Cancérologie Thoracique (IFCT). The protocol has been sent out to the participating sites in France, Spain, Germany, Belgium, Poland, the Netherlands, the UK and Switzerland. By the End of 2014, 15 sites have been activated and 5 patients have been enrolled in the trial.

ETOP 5-12 SPLENDOUR

Denosumab is a monoclonal antibody targeting and inhibiting RANKL, a protein that acts as the primary signal for bone resorption. The purpose of this study is to investigate the potential of the combination of standard treatment (chemotherapy) with denosumab as compared to the standard treatment alone to increase survival of patients with advanced NSCLC with or without bone metastasis in advanced unselected treatment-naïve patients.

ETOP is the sponsor of this trial that is conducted in collaboration with the EORTC as coordinating group. The 1000 patients will be enrolled within approximately 3 years. The first sites have been activated in December 2014.

ETOP 6-14 NICOLAS

Over the past decade, sequential or concomitant chemotherapy and radiotherapy have become the treatment of choice for stage III NSCLC. One attempt to improve the long-term survival is an immunotherapeutic strategy, for example by targeting PD-1, a cell surface molecule on activated T-cells that is abrogating anti-cancer immune response. Nivolumab, a monoclonal antibody, is able to prevent the interaction between PD-1 and its ligands. This feasibility trial evaluates nivolumab consolidation treatment in patients with locally advanced stage III NSCLC treated with standard first-line chemotherapy and radiotherapy. The trial protocol will be distributed for activation in Q1 2015.

ETOP 7-14 NICHE

The erbB family of proteins comprises the receptor tyrosine kinase EGFR and the closely related HER2, HER3 and HER4. HER2 mutations are identified in about 2% of NSCLC and appear to be critical for lung carcinogenesis. Clinically relevant HER2 mutations are clustered in exon 20 of the HER2 gene and commonly include small exon 20 insertions, single amino acid or clustered substitutions. Afatinib is a selective and irreversible small molecule inhibitor of the erbB family of proteins. It has been shown to effectively inhibit EGFR, HER2 and HER4 phosphorylation resulting in subsequent suppression of tumour growth. The primary objective of this trial is to evaluate the ability of afatinib to control disease in pre-treated patients with advanced NSCLC harbouring HER2 exon 20 mutations. The trial protocol has been distributed for activation in December 2014 and first site activation is ongoing.

PUBLICATIONS

Publications

Patton SE, Normanno N, Blackhall FH, Murray S, Kerr KM, Dietel M, Filipits M, Benlloch S, Popat S, Stahel RA, and Thunnissen E. Assessing standardization of molecular testing for non-small cell lung cancer: Results of a worldwide External Quality Assessment (EQA) scheme for EGFR mutation testing. *British Journal of Cancer* 111(2): 413-20.

Peters S, Weder W, Dafni U, Kerr KM, Bubendorf L, Meldgaard P, O'Byrne KJ, Wrona A, Vansteenkiste J, Felip E, Marchetti A, Savic S, Lu S, Smit E, Dingemans AMC, Blackhall FH, Baas P, Camps C, Rosell R, and Stahel RA, on behalf of the ETOP Lungscape investigators. Lungscape: resected non-small cell lung cancer outcome by clinical and pathological parameters. *Journal of Thoracic Oncology* 9 (11): 1675-1684.

Blackhall FH, Peters S, Bubendorf L, Dafni U, Kerr KM, Hager H, Soltermann A, O'Byrne KJ, Doms C, Sejda A, Hernández-Losa J, Marchetti A, Savic S, Tan Q, Thunnissen E, Speel EJM, Cheney R, Nonaka D, de Jong J, Martorell M, Letovanec I, Rosell R, and Stahel RA. Prevalence and clinical outcomes for patients with ALK-positive resected stage I-III adenocarcinoma: Results from the European Thoracic Oncology Platform Lungscape Project. *Journal of Clinical Oncology* 32 (25): 2780-7.

Abstracts

Bubendorf L, Dafni U, Tischler V, Finn SP, Biernat W, Verbeken E, Hager H, Murtra N, Thunnissen E, Nonaka D, Warth A, Speel EJM, Savic S, Martorell M, Tsourti Z, Schulze K, Das Gupta A, Kerr KM, Peters S, and Stahel RA. Prevalence and clinical outcomes for patients with MET protein expression in patients with non-small cell lung cancer in Europe: Results from the European Thoracic Oncology Platform Lungscape Project. Presented at ESMO 2014 in Madrid, Spain, *Ann Oncol*, 25(suppl 4): iv418.

Presentation

Lungscape iBiobank – a 'Virtual' Biobank of the European Thoracic Oncology Platform (ETOP) Oral presentation at the ESBB Annual Meeting 2014 in Leipzig (21 – 24 November) presented by Rosita Kammler, on behalf of the Lungscape consortium as a whole.

Posters

Lukas Bubendorf, *et al.*, External Quality Assessment (EQA) of predictive markers in non-small cell lung cancer within the European Thoracic Oncology Platform (ETOP) Lungscape project. Presented at the ESP European Congress of Pathology in London, 3 September 2014. Poster number: 020. Presenting author: Lukas Bubendorf.

Lukas Bubendorf, *et al.*, Prevalence and clinical outcomes for patients with MET protein expression in patients with non-small cell lung cancer in Europe: Results from the European Thoracic Oncology Platform Lungscape Project. Presented at the ESMO Congress 2014 in Madrid. Poster number: 1199PD. Presenting author Stephen P. Finn.

Thomas R. Geiger, *et al.*, poster presentation on iBiobank, the 'Virtual' Biobank of ETOP Lungscape at the ESBB Annual Meeting, Leipzig, Germany, Oct 21-24, 2014. Presenting author Thomas R. Geiger.

MEETINGS / ACTIVITIES

Several meetings with a high-level scientific exchange took place also in 2014. Furthermore, various ETOP representatives participated to a number of meetings with pharmaceutical industry regarding further ETOP research avenues.

ETOP Residential Workshop

The 3rd ETOP Residential Workshop under the topic, "current trends in research and cancer care" was held 27- 29 August 2014 in Gdansk, Poland. Beside many valuable contributions from lung cancer experts, the participants were asked to bring their own research project. These projects were presented and discussed in different groups, each chaired by one or two senior scientists from the faculty, including multidisciplinary support from ETOP pathologists, radio-oncologists and statisticians. The many excellent presentations were followed by lively discussions that continued over coffee breaks and dinners. The workshop was financed by ESMO through an educational grant and the generous support from Roche and Amgen. In response to the very positive feedback received, we decided to continue with this tradition. The next ETOP Residential Workshop will take place 20 – 22 August 2015 in Amsterdam.

ETOP Annual Meeting

The 6th ETOP Annual Meeting was held 14 – 15 November, 2014 in Vienna, Austria, hosted by the Central European Cooperative Oncology Group (CECOG). Ongoing projects and trials as well as new ideas and concepts were presented and discussed either during the plenary meeting or in the break-out sessions. More than 100 participants from over 20 countries attended the meeting and used the opportunity to engage in stimulating high-level scientific exchange with other ETOP participants. The wonderful ETOP Dinner allowed to continue discussions in a convivial atmosphere. The next ETOP Annual Meeting will be held 13 – 14 November 2015 at the University Hospital in Zürich.

Foundation Council Meetings

- 26.03.2014 ELCC, Geneva
- 15.11.2014 ETOP Annual Meeting, Vienna

Independent Data Monitoring Committee Meetings

- 26.03.2014 ELCC, Geneva
- 16.10.2014 by teleconference

Meetings under auspices/in collaboration with ETOP

- 29 – 31 January 2014 BTOG Meeting 2014, Dublin
- 26 – 29 March 2014 ELCC 2014, Geneva
- 21 – 24 October 2014 ESMO 2014, Madrid

Educational and collaboration activities

The mission of ETOP is to serve as meeting platform for European study groups and institutions engaged in research on thoracic malignancies. In its website ETOP hosts a series of scientific resources for scientists in the field of lung cancer. The ETOP conferences slide decks are designed to highlight and summarise key findings in thoracic oncology from the major congresses like ASCO, ESMO, WLCC and ELCC. These open access slide sets are realised with the kind support of Eli Lilly. ETOP members who are registered to the webpage <http://www.etop-eu.org> can profit from additional resources such as video news presentations from the major congresses, panel discussions of the main 2014 highlights in thoracic oncology research as well as from free access to the Lung Cancer Journal.

ETOP collaboration with IBCSG

In order to complete the various tasks entailed by all these projects, ETOP has undergone a strategic collaboration with the International Breast Cancer Study Group IBCSG and its Coordinating Centre in Berne. The ETOP Coordinating Office is hosted by IBCSG and supports all activities in the above projects. In addition, Frontier Science Hellas, a non-profit organisation based in Athens, Greece, is providing statistical expertise for all ETOP projects.

GROUP STRUCTURE

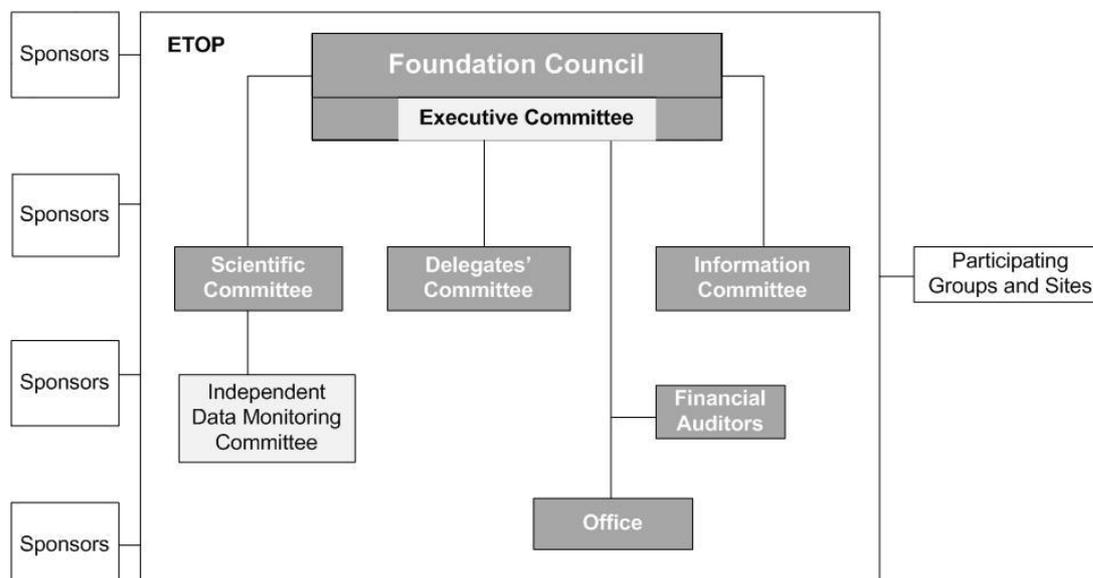
The European Thoracic Oncology Platform (ETOP) is a not-for-profit foundation under Swiss law with the purpose of promoting information and research in the field of thoracic malignancies.

Members

ETOP includes 54 leading European groups and institutions, as well as an institution in the USA and in China with a focus on clinical and translational research in thoracic oncology.



ETOP Organigram



ETOP ORGANIZATION

Foundation Council

President: Rolf. A. Stahel, Switzerland

Paul Baas, Netherlands, Keith Kerr, U.K., Kenneth O'Byrne, Australia, Rafael Rosell, Spain, Suresh Senan, Netherlands, Walter Weder, Switzerland, Christoph Zielinski, Austria

Scientific Committee

Chair: Rolf A. Stahel, Switzerland

Tetsuya Mitsudomi, Japan, Paris Kosmidis, Greece, Fortunato Ciardiello, Italy

Scientific Coordinator

Solange Peters, Switzerland

Independent Data Monitoring Committee

Chair: Jean-Pierre Armand, France

Nick Thatcher, U.K., Renato Galeazzi, Switzerland, Richard Gelber, USA, Paul Van Houtte, Belgium

FINANCIAL STATEMENT 2014 (IN THOUSAND CHF)

All ETOP trials with full academic independence from the pharmaceutical industry, even if sponsored wholly or in part by industry. The financial statements have been audited and approved by KPMG on March 17, 2015.

Income	2014	2013
Income from collaboration with industry	3629.7	2'253.2
Further research grants	60.9	32.4
Total	3'690.6	2'285.6
Expenses	2014	2013
Contributions to members, participating centres	994.3	531.9
Pathology, translational research	387.1	201.7
Production slide decks, training	21.5	20.9
Website, internet	7.8	39.5
Scientific exchange and coordination, travel expenses	163.9	221.2
Personnel costs and external services (database, statistics, etc.)	2'058.5	1'157.4
Insurance, consulting, financial audit	183.7	105.0
Administrative costs	113.4	52.9
Currency exchange	42.6	17.6
Total	3'972.8	2'348.1