Collaborative Trials in Lung Cancer:
The initiatives of the European Thoracic Oncology Platform

Lyon, April 2, 2013
Over forty individual research groups and trial institutions aiming for their local goals:

Groups working together:
- Establishing research priorities
- Combining resources and expertise in a modular system
- Accelerate accrual
- Foster translational research
- Integrate younger investigators
- Help to preserve academic independence
History

- April 2008: 1st European Lung Cancer Congress Geneva: formal structure needed to promote collaboration
- May 2008: Proposal of structure based on modified IBCSG documents
- September 08: ESMO Stockholm: 1st ETOP meeting with presentation and acceptance of concept, suggestions for members of foundation council, initiation of collection of funds by interested groups and institutions
- January 09: BTOG Dublin: First meeting of foundation council, approval of charter and bylaws
- March and May 09: Approval of foundation by authorities and acceptance by trade registry of Bern
The European Thoracic Oncology Platform (ETOP) is a foundation with the purpose to promote exchange and research in the field of thoracic malignancies in Europe.

Aims:
• To serve as a meeting platform for European study groups and institutions dealing with thoracic malignancies
• To foster intergroup studies among, but not exclusively, European study groups and institutions
• To sponsor and/or perform own studies
• To foster scientific exchange on laboratory and clinical issues among interested parties and beyond
• To provide knowledge to partners in the field
Recent Achievements: Extension of Web platform and web onco news

- Scientific news with updated articles
- Free access to “Lung Cancer”
- Events
- Slide sets and Web OncoNews (ASCO, WCLC, ECCO-ESMO, ESMO)
- e-rooms for trial participants

<table>
<thead>
<tr>
<th>Metric</th>
<th>Growth</th>
<th>2012</th>
<th>2011</th>
</tr>
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<tbody>
<tr>
<td>Registered Users</td>
<td>157%</td>
<td>702</td>
<td>273</td>
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<tr>
<td>Unique Visitors/Month</td>
<td>50%</td>
<td>1,800</td>
<td>1,200</td>
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</table>
Future ETOP meetings

• May 9-11, 2013 Lugano: ETOP is partner of EMCTO

• August 29-31, 2013 Lugano Second residential course

• November 22-23, 2013 Barcelona: 6th ETOP meeting, side to side with the yearly meeting of the SLCG
The emerging situation in non-small cell lung cancer

Pao, Nature Med 2012

Paik, ASCO 2012
Clinical trials and translational research in lung cancer: facing the new challenges

Non-small cell lung cancer is a heterogeneous disease

Paradigm shift in clinical trial design:

• *Empiric*: current standard, takes into consideration patient characteristics and physician experience. Expensive, few studies have met primary endpoint, if met: questions regarding clinical value and search for appropriate subgroups

• *Molecular-based*: based on molecular characteristics of tumor. New role of translational research as driver for clinical studies
Molecular pathology both at diagnosis and at relapse for definition or stratification of study population mandatory

• Centralized analysis or standardization of methodologies between sites
• Availability of integrated services at sites

Rarity of molecular subgroups

• Large networks of sites necessary to detect eligible patients
• Optimal number or sites for a given trial

Emphasis on early decision in molecularly-driven trials

• New models of collaboration with diagnostic and pharmaceutical companies
Lungscape project: Aims

• Lungscape addresses the challenges of studying the molecular epidemiology of lung cancer
  – by coordinating and harmonizing the procedures of lung cancer specialists working in translational research across Europe
  – By performing analysis of larger series of cases.

• This will:
  – Expedite knowledge of the prevalence and context of current and emerging molecular biomarkers
  – Facilitate more rapid application of biomarker usage in the clinic
  – Provide a platform for marker-driven trials of novel therapeutics.
Lungscape history

- May 2010 Lugano: ESMO – transETOP meeting supported by the San Salvatore Foundation
- July 2010: Emerging of idea “Lungscape” (BRAF, ALK)
- November 2010 Zürich ETOP meeting: Presentation of project, initiation of work on data base
- November and December 2011 Pfizer ALK contract and Roche unrestricted support agreement signed
- February 2011 Lugano: 1st investigators focusing on Lungscape project
- May 2011 Lungscape master protocol and Lungscape 001 (ALK) sent out to participating sites
- September 2012 Vienna: Presentations at ESMO
Lungscape project: Stepwise evolution

✓ **Step 1:**
Retrospective analysis of about 2400 completely resected NSCLC with at least 3 years of follow-up from 15 sites: Mutation testing, immunohistochemistry, selected FISH on formalin-fixed, paraffin-embedded tumor tissue with standardized protocols

- **Step 2:**
Expansion to prospective study with biopsies from advanced disease and increasing to the number of participating sites (SOAR-Lung)

- **Further steps and issues under considerations:**
  Enlargement of biobank, next generation sequencing, circulating biomarkers, technology platforms, resource utilization and health economics research
Organizational structure (1)

Chairs: R Stahel, R Rosell

Track chairs (updated, vertical organization):

Subproject chairs (updated, horizontal organization, to be expanded with each new marker):
- ALK: F Blackhall/S Peters;
- MET: L Bubendorf/A Adjei/S Peters
- PTEN/PI3KCA: E Felip/L Bubendorf/S Peters
- Multiplex testing: K Kerr/ A Molina/S Finn/S Peters
Belgium
- Leuven:
  J. Vansteenkiste, E. Verbeken, C. Dooms

Denmark
- Aarhus:
  P. Meldgaard, H. Hager

Greece
- Frontier Science Hellas:
  U. Dafni

Ireland
- Dublin:
  K. O’Byrne, S. Finn, S. Gray

Italy
- Chieti:
  A. Marchetti, S. Malatesta

Poland
- Gdansk:
  R. Dziadziuszko, W. Biernat, A. Sejda, A. Wrona

Germany
- Heidelberg:
  T Muley, A. Warth

Outside of Europe
- China – Shanghai Chest Hospital (S. Lu, Z. Jie)
- USA – Roswell Park Cancer Institute (R. Cheney, A. Adjei)

Spain
- Barcelona:
  E. Felip, J. Hernandez-Losa, M. T. Salcedo, M. Canela
- Badalona:
  R. Rosell, M. Taron
- Valencia:
  C. Camps, M. Martorell, E. Jantus-Lewintre

Switzerland
- ETOP Coordinating Center:
  A. Hiltbrunner, S. Peters, R. Kammler, R. King, R. Stahel
- Basel:
  L. Bubendorf, S. Savic
- Zurich:
  W. Weder, A. Soltermann

The Netherlands
- Amsterdam VU (E. Thunnissen, E. Smit
- Amsterdam NKI:
  P. Baas, J. de Jong
- Maastricht:
  A.-M. Dingemans, E-J.M. Speel

United Kingdom
- Aberdeen:
  K.M. Kerr, N. Price, M. Nicolson
- Manchester:
  F. Blackhall, D. Nonaka, R. Peck
The European Thoracic Oncology Platform Lungscape project: A way to bridge NSCLC molecular characteristics and clinical data

Methodology: Case inclusion criteria

• Histological diagnosis of NSCLC
• Diagnosis after January 2003 (10% before 2003)
• Adequate quantity and quality of formalin-fixed paraffin embedded tissue
• Documented ethical approval for tissue sample and associated clinical data
• Radically resected non-pretreated stage IA-IIIB NSCLC
• 3 years of follow-up
• Mandatory clinical data available
Data Acquisition Workflow: Focus on Upstream Quality Control

1. Provider:
   - Create Draft
   - Submit Case

2. ETOP QC:
   - Review Case
   - OK?
     - Yes, case is largely usable with further input
     - No, not yet Acceptable
     - Feedback:
       - No, for whatever reason, case is unusable for Biobank
       - Yes, case acceptable and complete as a research sample

3. Researchers:
   - Accepted Case

ETOP | Lungscape | ESMO Vienna, September 30, 2012
Cases by provider (n=2130)

Median follow-up: 58 months
Stage grouping

- IIIb: 1.69%
- IIIa: 20.62%
- IIb: 11.81%
- IIa: 16.68%
- Ia: 22.49%
- Ib: 26.71%
Note: Number of patients and 5-year OS by stage, depicted in the figure
Note: Number of patients and 5-year OS by Histology, depicted in the figure.
### Multivariate Cox model for OS (N=2128, deaths=991)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td><strong>Age – cat</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“60-70” vs “&lt;60”</td>
<td>1.39</td>
<td>(1.19, 1.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>“&gt;70” vs “&lt;60”</td>
<td>1.50</td>
<td>(1.27, 1.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs Female</td>
<td>1.13</td>
<td>(0.98, 1.30)</td>
<td>0.032</td>
</tr>
<tr>
<td><strong>Performance status at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vs 0</td>
<td>1.31</td>
<td>(1.08, 1.59)</td>
<td>0.0071</td>
</tr>
<tr>
<td>2&amp;3 vs 0</td>
<td>1.83</td>
<td>(1.16, 2.90)</td>
<td>0.018</td>
</tr>
<tr>
<td>Unknown vs 0</td>
<td>1.25</td>
<td>(1.04, 1.50)</td>
<td>0.012</td>
</tr>
<tr>
<td>Missing vs 0</td>
<td>1.66</td>
<td>(1.41, 1.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current vs Never</td>
<td>1.26</td>
<td>(1.02, 1.56)</td>
<td>0.032</td>
</tr>
<tr>
<td>Former vs Never</td>
<td>1.20</td>
<td>(0.98, 1.47)</td>
<td>0.079</td>
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<tr>
<td>Unknown vs Never</td>
<td>1.42</td>
<td>(0.98, 2.06)</td>
<td>0.063</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iib vs Ia</td>
<td>1.38</td>
<td>(1.11, 1.71)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Ila vs Ia</td>
<td>1.90</td>
<td>(1.51, 2.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Iib vs Ia</td>
<td>2.56</td>
<td>(2.01, 3.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Illa vs Ia</td>
<td>4.11</td>
<td>(3.36, 5.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IIIb vs Ia</td>
<td>6.44</td>
<td>(4.28, 9.71)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Note: Excluding 118 patients with missing date of death or relapse diagnosis and 2 patients without reported “Status at last follow-up”
Conclusions: Lungscape collection

- Through Lungscape, we have collected a large clinical dataset of resected NSCLC including not only raw survival data but also OS, RFS and TTR outcomes according to main clinical and pathological characteristics.
- All patients have tissue available for biomarker analysis.
- Application of the 7th TNM classification has been successful in distinguishing prognostic categories in our dataset and OS similar to published data.
- We report on the first multivariate survival analysis of OS identifying age, gender, PS and smoking status as independent prognostic characteristics in addition to TNM.
- TTR outcome, by omitting deaths from other causes, will represent an optimal parameter to define the impact of biomarkers in NSCLC outcome.
Prevalence and clinical outcomes for patients with ALK positive adenocarcinoma in Europe: preliminary results from the European Thoracic Oncology Platform Lungscape Project


*equal contribution
Immunohistochemistry (IHC) and Fluorescent In Situ Hybridisation (FISH) for detection of ALK gene fusion

ALK IHC 3+

ALK FISH+
(single red signals)
Adenocarcinoma patients with available ALK IHC data

N=1099

ALK IHC +
N=69 (6.3%)

ALK IHC -
N=1030

ALK IHC 1:2 Matched Cohort
N=207
Matching factors in order of importance:
Stage, Gender/Smoking Status,
Center/Year of surgery/ Age

ALK IHC +
N=69

ALK IHC –
N=138

22 FISH +
1 FISH +

23 (2.1%)
FISH +

46 FISH -

ALK FISH 1:2 Matched sub-cohort
N=69

137 FISH -
Association of ALK IHC and FISH, N=198

36.7% of IHC+ are FISH+
RFS and OS by ALK IHC status, matched cohort, N=207

Matching Factors: Stage, Gender/Smoking Status, Center/Year of surgery/ Age

Stratified log-rank test: p=0.091

Stratified log-rank test: p=0.012

Note: Number of patients and 5-year RFS / OS, depicted in the pictures

Conditional Logistic Regression – RFS event at 3 years
N=207; RFS events at 3 years=96
OR Yes vs No=0.52, 95% CI (0.26, 1.01), p=0.06

Conditional Logistic Regression – OS event at 3 years
N=207; Deaths at 3 years=82
OR Yes vs No=0.53, 95% CI (0.26, 1.07), p=0.077
Do ALK-positive adenocarcinomas have a better natural history?

Review: Scagliotti, EJC 2012; Shaw Lancet Oncol 2011
32 | RFS and OS by ALK FISH status, matched cohort, N=69

Matching Factors: Stage, Gender/Smoking Status, Center/Year of surgery/ Age

Stratified log-rank test: p=0.15

Stratified log-rank test: p=0.058

Note: Number of patients and 5-year RFS / OS, depicted in the pictures

Conditional Logistic Regression – RFS event at 3 years
N=69; RFS events at 3 years=33
OR Yes vs No=0.19, 95% CI (0.04, 0.91), p=0.037

Conditional Logistic Regression – OS event at 3 years
N=69; Deaths at 3 years=25
OR Yes vs No=0.22, 95% CI (0.05, 1.10), p=0.057
Conclusions

• We report on the first large European dataset evaluating prevalence and outcome of ALK positive stage I-III resected lung adenocarcinoma patients, using IHC and FISH confirmation.

• Case matching according to main prognostic clinical parameters was performed for ALK IHC and FISH positive cases in a 1:2 ratio with IHC negative and FISH negative cases respectively.

• A high concordance between ALK IHC (0 and 3+) with FISH (-ve and +ve, respectively) has been demonstrated

• In early stage completely resected adenocarcinoma:
  • Prevalence of ALK IHC is 6.3% and of ALK FISH is at least 2.1%
  • ALK FISH + is associated with a trend to better survival
<table>
<thead>
<tr>
<th>Provider</th>
<th>Cases</th>
<th>Cases pledged</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNK003 University Hospital Aarhus</td>
<td>336</td>
<td>200</td>
</tr>
<tr>
<td>CHE005 University Hospital Zürich</td>
<td>309</td>
<td>200</td>
</tr>
<tr>
<td>IRL004 St James’s Hospital</td>
<td>280</td>
<td>200</td>
</tr>
<tr>
<td>POL011 Medical University Gdansk</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>BEL015 University Hospital Leuven</td>
<td>199</td>
<td>100</td>
</tr>
<tr>
<td>ESP006 Vall d'Hebron University Hospital</td>
<td>170</td>
<td>200</td>
</tr>
<tr>
<td>ITA007 Ospedale Clinicizzato Chieti</td>
<td>167</td>
<td>200</td>
</tr>
<tr>
<td>GBR012 Royal Infirmary Aberdeen</td>
<td>157</td>
<td>100</td>
</tr>
<tr>
<td>CHN017 Shanghai Lung Cancer Center</td>
<td>137</td>
<td>n/a</td>
</tr>
<tr>
<td>NLD009 Free University Medical Center Amsterdam</td>
<td>102</td>
<td>100</td>
</tr>
<tr>
<td>NLD010 University Medical Centre Maastricht</td>
<td>93</td>
<td>200</td>
</tr>
<tr>
<td>CHE002 University Hospital Basel</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>GBR014 Lung Cancer Group Manchester</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td>NLD008 The Netherlands Cancer Institute Amsterdam</td>
<td>65</td>
<td>100</td>
</tr>
<tr>
<td>ESP001 University Hospital Valencia</td>
<td>41</td>
<td>100</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>2420</strong></td>
<td><em>(2400)</em></td>
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</table>
• MET project (2400 cases)
  • MET IHC on full sections
  • MET CISH on TMA
• PIK3CA project (2400 cases)
  • PTEN IHC on TMA
  • PIK3KI CISH on TMA
• Multiplex genetic testing (2400 cases)
Why targeting MET and HGF in NSCLC: Met amplification

- NSCLC cell lines with met amplification depend on MET for growth and survival
  Lutterbach, CR 2007

- MET amplification occurs in up to 5-21% of NSCLC with acquired EGFR TKI resistance, but is otherwise a rare event (3%)
  Bean, PNAS 2007

- Increased MET copy number associated with worse prognosis in resected NSCLC.
  Amplification in 4%
  Cappuzzo, JCO 2009; Park Histol and Histopathol 2012
Global, double-blind, placebo-controlled, phase II study of MetMAb in NSCLC

**Primary objectives**
- PFS in ‘Met diagnostic positive’ patients
- PFS in overall ITT population

‘Met diagnostic positive’
≥50% of tumour cells having a Met IHC staining intensity of 2+ or 3+

---

Spigel, ASCO 2011
The addition of MetMAb to erlotinib in this population resulted in a 2-fold reduction in the risk of progression and a near 3-fold reduction in the risk of death.

<table>
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<tr>
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<th>Erlotinib + placebo</th>
<th>Erlotinib + MetMAb</th>
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<tr>
<td>Events, n</td>
<td>31</td>
<td>35</td>
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<tr>
<td>Events, n</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>Median, months</td>
<td>1.5</td>
<td>2.9</td>
</tr>
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</table>

**HR=0.53 (0.28–0.99)**  
Log-rank p=0.04

**HR=0.37 (0.19–0.72)**  
Log-rank p=0.002

Spigel, ASCO 2011
Randomised, double-blind phase II study of tivantinib (ARQ197) in NSCLC

- Advanced NSCLC
- ≥1 prior chemo (no prior EGFR TKI) (n=167)

Endpoints
- Primary: PFS
- Secondary: ORR, OS
- Molecular subset analyses
- Crossover: ORR

MARQUEE phase III study negative (no patient selection)
Multiplex testing: Genentech 11-gene allele specific mutation panel including 120 mutations

<table>
<thead>
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<th>Genes</th>
<th>Exons</th>
<th>Mutation</th>
<th>Control</th>
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<td>1</td>
<td>EGFR</td>
<td>4</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>PIK3CA</td>
<td>5</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>KRAS</td>
<td>2</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>BRAF</td>
<td>1</td>
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<td>1</td>
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<tr>
<td>5</td>
<td>NRAS</td>
<td>2</td>
<td>4</td>
<td>4</td>
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<td>AKT1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>FGFR3</td>
<td>4</td>
<td>9</td>
<td>4</td>
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<td>8</td>
<td>FLT3</td>
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<td>4</td>
<td>1</td>
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<tr>
<td>9</td>
<td>HRAS</td>
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<td>11</td>
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<td>KIT</td>
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<td>3</td>
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<td>11</td>
<td>MET</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>RNaseP</td>
<td>1</td>
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<td>1</td>
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<tr>
<td></td>
<td>Total</td>
<td>12</td>
<td>29</td>
<td>120</td>
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</tbody>
</table>
HER2 mutations in NSCLC

• HER2 mutated NSCLC represent a small distinct subgroup of oncogene addicted cancers with specific demographics and potentially outcomes (1.7% of cases examined)

• Prognostic features related to HER2 mutations remains to be studied in large cohorts of patient

• NSCLC patients with mutated HER2 are mainly female, non-smokers, exclusively suffering from adenocarcinoma subtype

• We identified some men and heavy smokers (up to 60 packs-year) suggesting that HER2 testing should not be restricted to clinically defined subgroups

• The relative efficacy of trastuzumab as well as afatinib clearly deserves prospective evaluation in larger prospective international clinical trials

Mazière and Peters, JCO, 2013 in press
Lungscape step 2: SOAR-lung - Survival impact of molecular based treatment decisions in advanced non-small cell lung cancer

Concept:
• Through determination of molecular subtypes of NSCLC and by providing the access to the best targeted treatment available, the survival of patients with NSCLC will significantly improve.
• The impact of specific targeted therapies for molecularly defined subgroups will make it ethically difficult for future trials not to include a cross-over design. Thus new ways need to be established to document survival improvement by targeted therapy in the context of the small subgroups lung cancer defined by oncogenic driver mutations.
Lungscape step 2: SOAR-lung - Survival impact of molecular based treatment decisions in advanced non-small cell lung cancer

Primary objective:
• Overall survival improvement of an advanced NSCLC prospective cohort with treatment decision based on tumor molecular characterization as compared to matched historical cohort

Design:
• Prospective cohort: 900 newly diagnosed patients, tested for same biomarkers, optimal targeted therapy available if appropriate, follow-up
• Retrospective cohort: 2:1 clinically matched from clinical trial databases
Project overview: Clinical studies

BELIEF
- First Discussion
- Protocol Completed
- Activation
- Enrollment
- Closure
- Follow-up

EMPHASIS
- First Discussion
- Protocol Completed
- Activation
- Enrollment
- Closure
- Follow-up

STIMULI
- First Discussion
- Protocol Completed
- Activation
- Enrollment
- Closure

SPLENDOUR
- First Discussion
- Protocol Completed
- Activation
- Enrollment
- Closure

T790M: Multitargeted inhibition including angiogenesis holds promise based on preclinical studies

- Adding VEGF inhibition might be beneficial in the presence of T790M mutations
  - Vandetanib in xenograft models
    Ichihara CR 2009
  - Bevacizumab and vandetanib in xenograft model
    Naumov, CCR 2009
An open-label phase II trial of erlotinib and bevacizumab in patients with advanced non-small cell lung cancer and activating EGFR mutations
Sample seize 102 patients, coordinating group SLCG
# BELIEF: Participation countries and coordinators

<table>
<thead>
<tr>
<th>COUNTRY (total 9)</th>
<th>COUNTRY COORDINATOR</th>
<th>Nº SITES</th>
<th>STATUS (19 out of 54 activated)</th>
<th>Accrual</th>
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<tbody>
<tr>
<td>Switzerland</td>
<td>Oliver Gautschi</td>
<td>9</td>
<td>8 centers activated 1 pending</td>
<td>4</td>
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<tr>
<td>Spain</td>
<td>Enric Carcereny</td>
<td>11</td>
<td>11 centers activated</td>
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<tr>
<td>Ireland</td>
<td>Kenneth Byrne</td>
<td>6</td>
<td>Approved by health authority and EC centers will start before Christmas</td>
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<tr>
<td>Italy</td>
<td>Paolo Bidoli</td>
<td>7</td>
<td>Documentation delivered to EC, pending approval</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>Sanjay Popat</td>
<td>7</td>
<td>Pending approval by health authorities Starting planned for January 13</td>
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<tr>
<td>Greece</td>
<td>Vassilis Georgoulas</td>
<td>3</td>
<td>Pending delivery of documentation to ECs</td>
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</tr>
<tr>
<td>Germany</td>
<td>Christian Schumann</td>
<td>3</td>
<td>Pending delivery of documentation to ECs and health authorities</td>
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<tr>
<td>Denmark</td>
<td>Jens Benn Sorensen</td>
<td>1</td>
<td>Process not yet started</td>
<td></td>
</tr>
</tbody>
</table>
BELIEF: Translational research

• BIM mRNA levels a major determinant of response

• EML4-ALK variants 1 and 3 fusion transcripts could be present in 15% of cases

• HGF mRNA stromal expression a potential harmful effect on bevacizumab

• T790M expression level to be recorded (less or more than 20%)
EGFR TKI or chemotherapy in second line therapy for NSCLC?

INTEREST: Kim, 2008

TITAN: Ciuleanu, 2012
How To Choose Between Different Options?
Proteomics signature (Veristrat test) and survival following Treatment With Gefitinib

P-diff = 0.15

HR 0.49 [0.22-0.79]
MS: 73 vs. 192 days (bad v. good)

P-diff = 0.10

HR 0.52 [0.25-0.83]
MS: 92 vs. 207 days (bad v. good)

Effect of MALDI-ToF MS test in subset of patients with confirmed squamous histology (n=37)

Solomon et al. Proc. ASCO 2006
A randomized phase III trial of erlotinib versus docetaxel in patients with advanced squamous cell non-small cell lung cancer who failed first line platinum based doublet chemotherapy stratified by VeriStrat Good vs VeriStrat Poor
Sample size: 500 patients, partner group NVALT
Ipilimumab combined with paclitaxel and carboplatin in extensive disease SCLC, double-blind randomized phase II trial (concurrent versus phased ipilimumab)
A randomized phase II trial of consolidation ipilimumab vs placebo in limited-stage SCLC after chemoradiotherapy

260 randomized patients, partner group IFCT

PET-CT (mandatory)
- Contrast-enhanced CT Thorax and upper Abdomen (CT T/A)
- Brain MRI
- FFPE tissue and blood collection

CT TA q3 mos for 12 months*
then q6 mos for 24 months from randomization

Iplimumab

Observation

R

CHEMOTHERAPY

THORACIC RADIOTHERAPY

THORACIC RADIOTHERAPY

PCI

Chemotherapy: 4 cycles of Cisplatin 25 mg/m2 iv D1-3 or 75 mg/m2 D1 Etoposide 100 mg/m2 iv D1-3 q21d.
Thoracic Radiotherapy: Accelerated twice-daily, administration of 1.5 Gy x 30 over three weeks (preferred) or once-daily radiotherapy, administration 1.8-2Gy per fraction up to 55-60Gy. Two options are allowed: start from D1 of cycle 1 or cycle 2.

Prophylactic Cranial Irradiation (PCI): 25 Gy in 10 fractions started between D8 and D15 of cycle 4 (to D22-29)

Randomization: should take place 5-6 weeks after Day 1 (between D35-42) of cycle 4

Iplimumab schedule: Induction course of ipilimumab, at a dose of 10 mg/kg, once every 3 weeks x4, started 6-8 weeks after cycle 4 of chemotherapy (Day 42-56 of cycle 4)
Maintenance: 10mg/kg, once every 12 weeks, for a maximum of 3 years after randomization

* CT at 8, 16 and 24 weeks and then every 3 months during 1st yr then every 6 months for 2 yrs until interim/safety analysis
Etop 5-13 Splendour

A randomized phase III trial evaluating the addition of denosumab to standard first-line anticancer treatment in advanced NSCLC

1000 randomized patients, coordinating group EORTC, partner groups CECOG, SLCG and GFPC

Key Inclusion
Advanced NSCLC (Stage IV)
PS 0-2
PET/CT or Bone scan at inclusion
1st line chemotherapy (adjuvant allowed)

Stratification
Bone mets vs no bone mets
PS
Histology
Region

Chemotherapy* + denosumab 120mg sc q 1 mos

Supplement calcium and Vitamin D

Chemotherapy* + BSC

* Platinum-based chemotherapy
Cis/carbo and gem or pem

Secondary Endpoints:
Progression Free Survival
QOL
Toxicity
Tumor Tissue and blood biomarkers

Primary endpoint:
Overall Survival
Lung cancer post-hoc subgroup of randomised, double-blind, active-controlled, Phase 3 trial

- **Key inclusion**
  - Adults with lung cancer and bone metastases

- **Key exclusion**
  - Current or prior intravenous bisphosphonate administration

- **Zoledronic acid 4 mg IV**
  - Placebo SC Q4W (n = 400)

- **Denosumab 120 mg SC + Placebo IV* Q4W (n = 411)**
  - Calcium (500 mg) and Vitamin D (400 IU) strongly recommended

<table>
<thead>
<tr>
<th>Lung cancer type, n (%)</th>
<th>Zoledronic acid</th>
<th>Denosumab</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>352 (88)</td>
<td>350 (85)</td>
<td>702 (100)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>211 (60)</td>
<td>189 (54)</td>
<td>400 (57)</td>
</tr>
<tr>
<td>Squamous Cell</td>
<td>75 (21)</td>
<td>88 (25)</td>
<td>163 (23)</td>
</tr>
<tr>
<td>Other</td>
<td>66 (19)</td>
<td>73 (21)</td>
<td>139 (20)</td>
</tr>
<tr>
<td>SCLC</td>
<td>48 (12)</td>
<td>61 (15)</td>
<td>109 (100)</td>
</tr>
</tbody>
</table>
Survival improvement in NSCLC with bone metastases treated with denosumab versus zoledronic acid

KM estimate of median, months
Denosumab 9.5
Zoledronic acid 8.1

Proportion of patients survived

HR, 0.78 (95% CI, 0.65–0.94)
P = 0.0104

Patients at risk:
Zoledronic acid 352 275 185 123 91 40 23 12
Denosumab 350 278 203 148 110 66 39 24

Scagliotti, JTO 2012
Survival improvement in NSCLC with bone metastases treated with denosumab versus zoledronic acid

### Adenocarcinoma

- **KM estimate of median, months**
  - Denosumab: 9.6
  - Zoledronic acid: 8.2

- **Proportion of patients survived**
  - HR, 0.80 (95% CI, 0.62–1.02)
  - \( P = 0.0751 \)

**Patients at risk:**
- Zoledronic acid: 211, 169, 113, 71, 55, 21, 14, 8
- Denosumab: 189, 154, 114, 83, 59, 40, 22, 16

### Squamous cell carcinoma

- **KM estimate of median, months**
  - Denosumab: 8.6
  - Zoledronic acid: 6.4

- **Proportion of patients survived**
  - HR, 0.68 (95% CI, 0.47–0.97)
  - \( P = 0.0350 \)

**Patients at risk:**
- Zoledronic acid: 75, 56, 38, 28, 17, 7, 4, 2
- Denosumab: 88, 66, 47, 34, 25, 13, 10, 3

Scagliotti, JTO 2012
Thank you for listening!

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