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Information | Research

Academic Clinical Lung Cancer Research in Europe

ESMO-Asia 2015

Rolf A. Stahel

Methodology

- Direct contact with European collaborative groups for information on ongoing trials
- Presentation “Development of oncology platforms in lung cancer across Europe” at ELCC2015 in Geneva
- Supplementary trial information retrieved from ClinicalTrials.gov
- ETOP meeting 2015 in Zürich
- Selection criteria:

  - NSCLC, SCLC, mesothelioma

  - interventional trials (including radiation therapy)

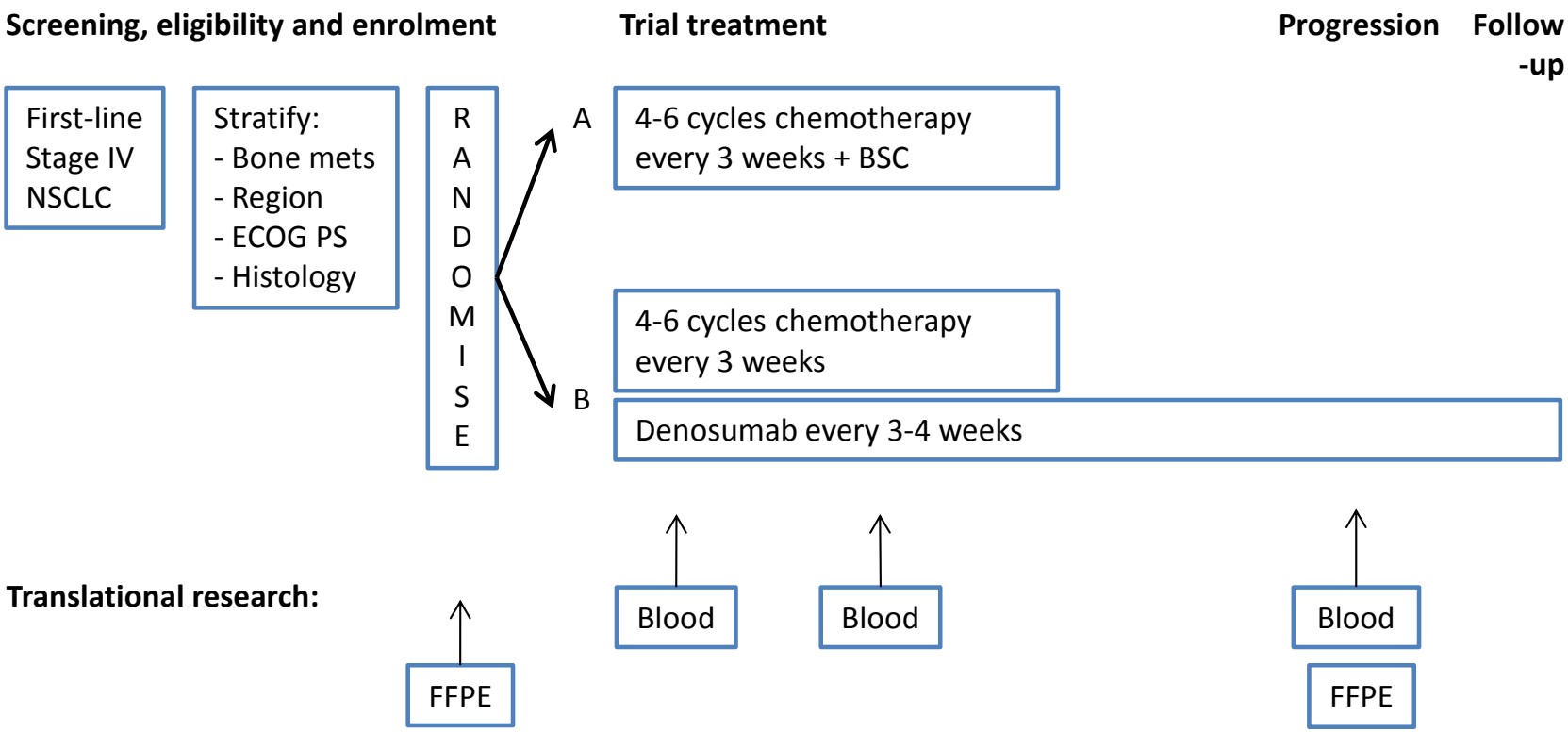
  - currently recruiting or not yet recruiting trials

  - European, non-industry sponsors

Advanced NSCLC
Phase III – 1st line, not biomarker selected

	Primary endpoint	Sample size
MILES-3: Gemcitabine vs gemcitabine plus cisplatin in elderly patients (≥70 years) with advanced NSCLC (**NCI Naples**) [NCT01405586].	Overall survival	480 pts
MILES-4: Gemcitabine or pemetrexed, with or without cisplatin, in in elderly patients with non-squamous NSCLC (**NCI Naples**) [NCT01656551].	Overall survival	550 pts
SPLENDOUR: Addition of denosumab to standard first-line anticancer treatment in advanced NSCLC (**ETOP / EORTC**) [NCT02129699].	Overall survival	1000 pts

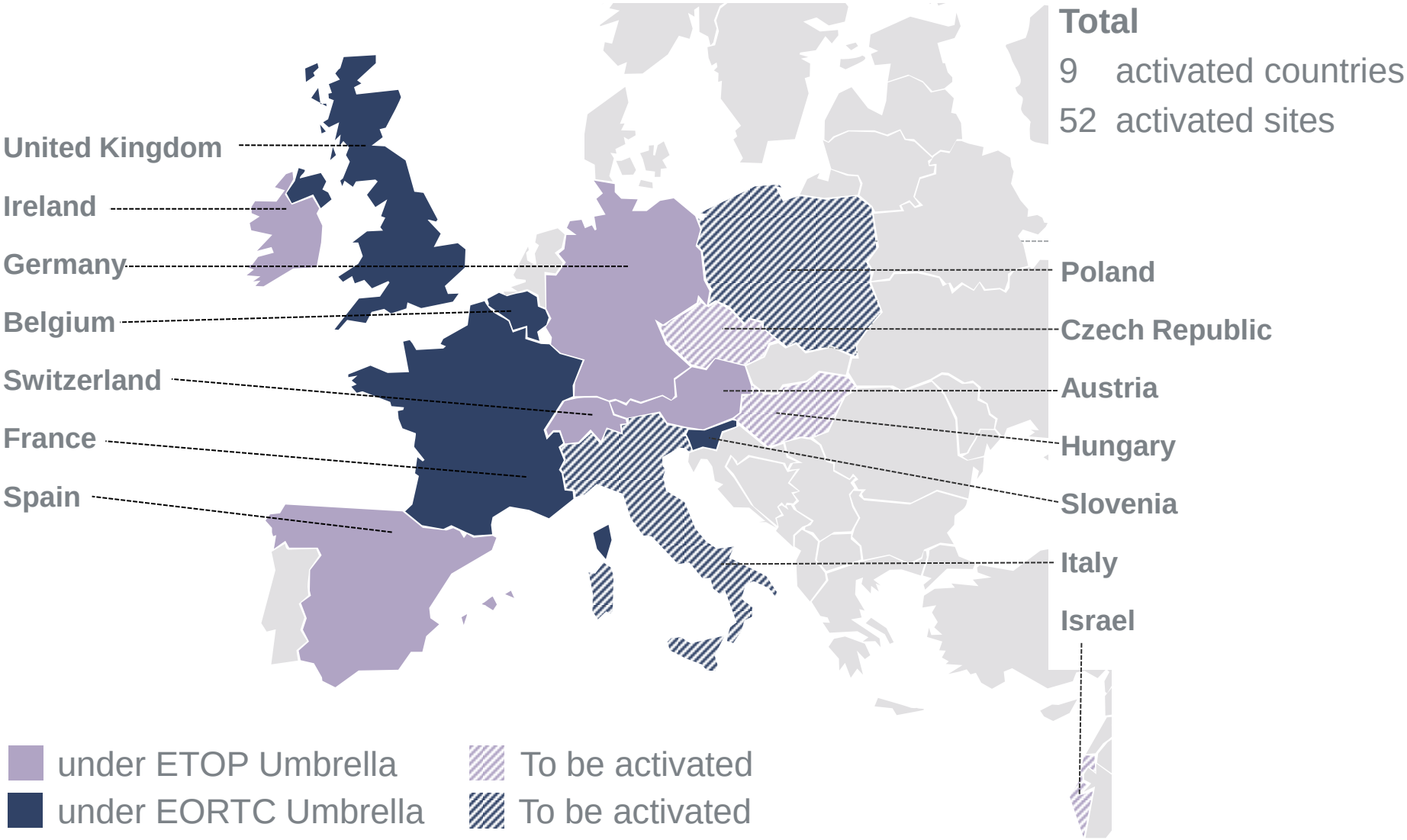
A randomised, open-label phase III trial evaluating the addition of denosumab to standard first-line anticancer treatment in advanced NSCLC



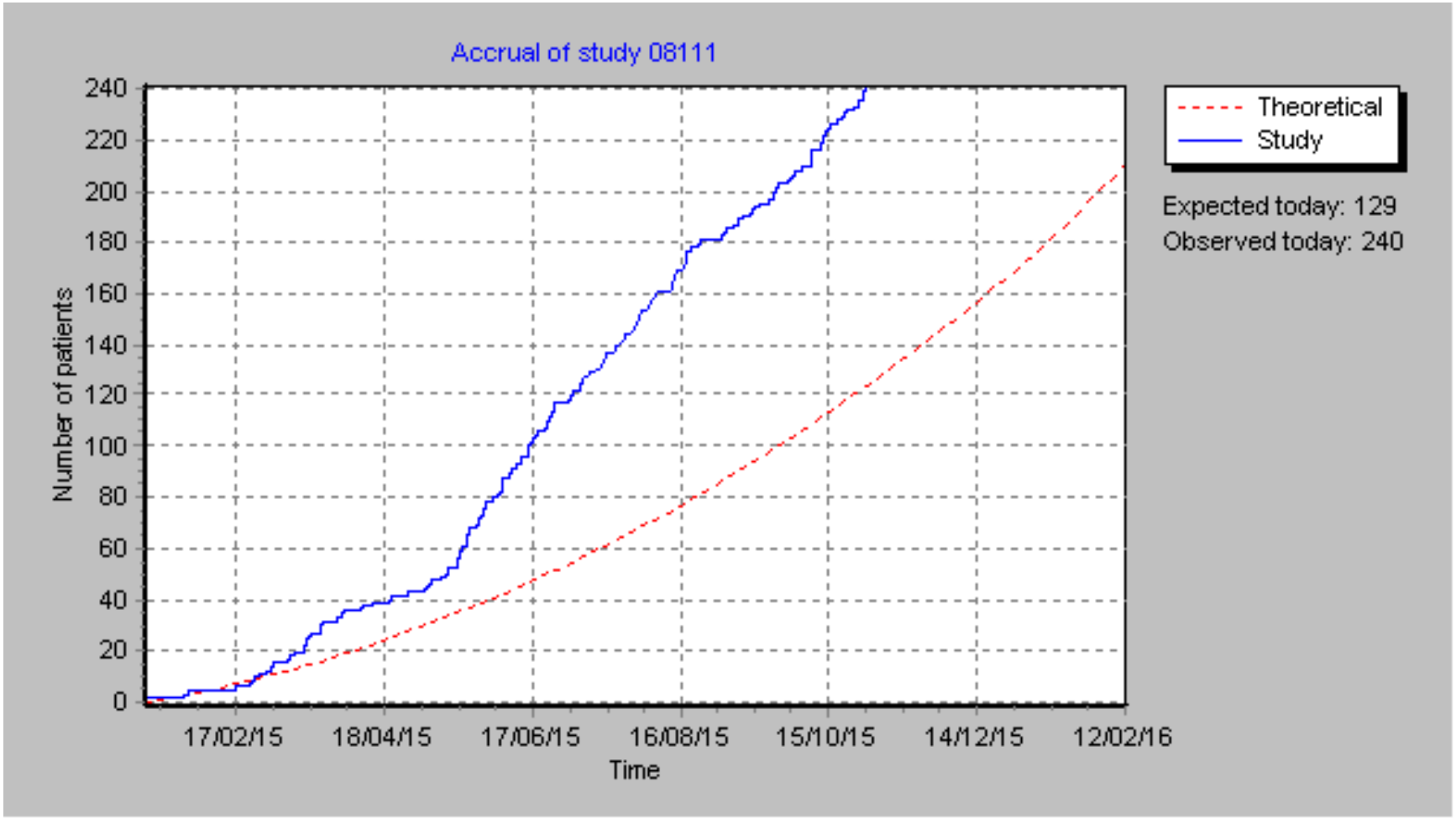
Sample size: 1000

Primary endpoint: Overall survival

Participating Countries



Accrual curve (as of 31 October 2015) – Registered Patients



Advanced NSCLC
Phase II – 1st line, not biomarker selected

Randomised	Primary endpoint	Sample size
CEDAR: Gemcitabine/carboplatin first-line chemotherapy +/- apatorsen in advanced squamous cell lung cancers (**Queen Mary University of London**) [NCT02423590].	Progression-free survival	140 pts
NVALT12: Paclitaxel-carboplatin-bevacizumab with or without nitroglycerin patches in patients with stage IV NSCLC (**NVALT**) [NCT01171170].	Progression-free survival	222 pts
GFPC 02-2013 CHIC: whole brain radiotherapy (WBRT) followed by chemotherapy vs exclusive chemotherapy in patients with advanced non-squamous NSCLC with asymptomatic inoperable brain metastases (**GFPC**) [NCT N/A].	Disease-free survival	50 pts

Single arm	Primary endpoint	Sample size
CHIVA: Carboplatin plus pemetrexed in HIV^+ patients with stage III or IV nonsquamous NSCLC (**IFCT**) [NCT01296113].	Disease control after 4 cycles	62 pts

Advanced NSCLC
Phase III – Maintenance, not biomarker selected

	Primary endpoint	Sample size
IDA: Maintenance pemetrexed therapy after induction chemotherapy vs pemetrexed at progression in advanced NSCLC (**Norwegian University of Science and Technology**) [NCT02004184].	Overall survival	436 pts
IFCT-GFPC-1101: Strategies for pemetrexed maintenance in advanced stage NSCLC (**IFCT**) [NCT01631136].	Overall survival	932 pts
IFCT-1201 – MODEL: Maintenance with pemetrexed or gemcitabine or surveillance in non-progressing elderly patients (≥70 years) with advanced NSCLC controlled by induction chemotherapy (**IFCT**) [NCT01850303].	Overall survival	549 pts

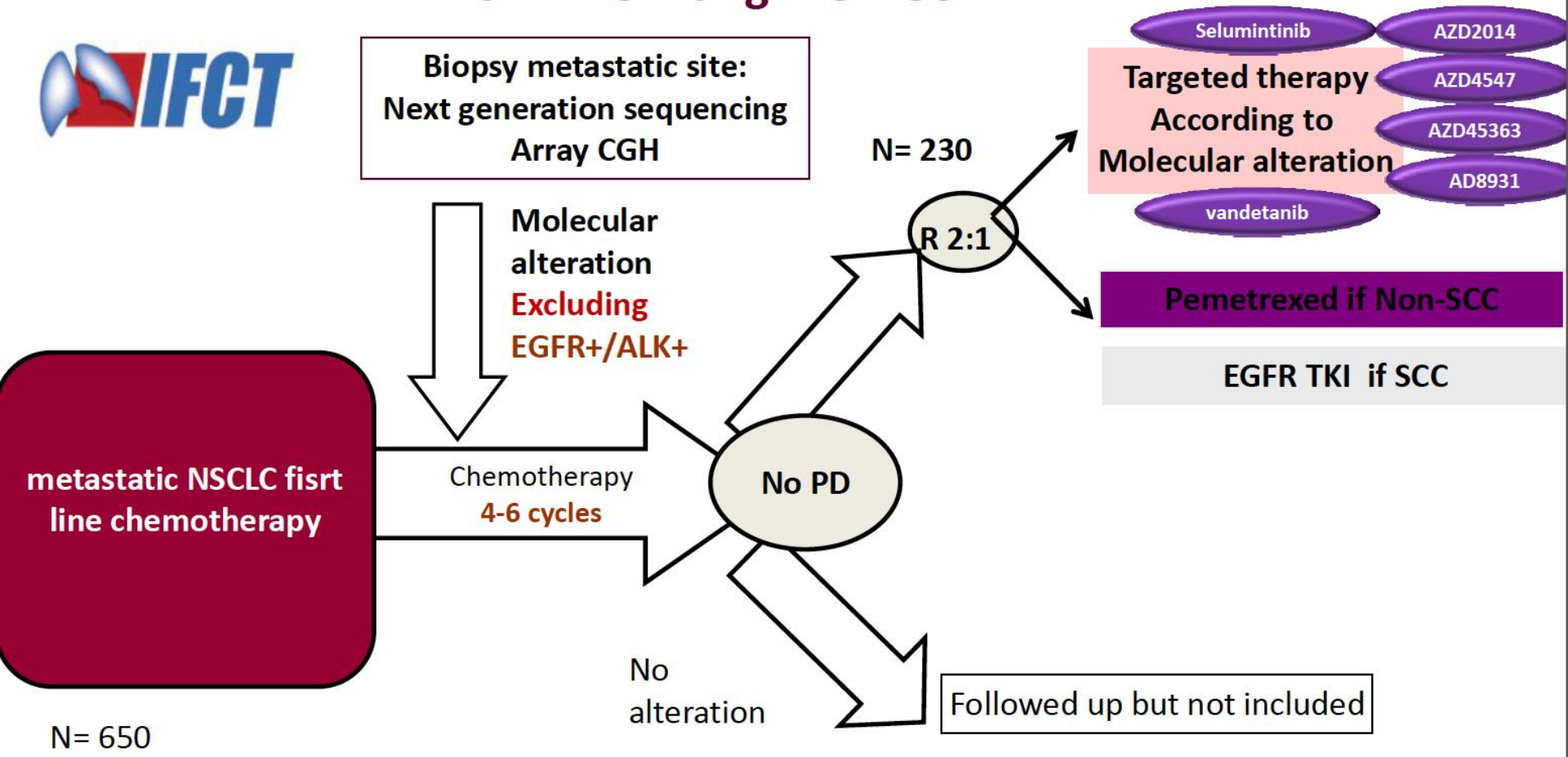
Advanced NSCLC
Randomized phase II – Maintenance, not biomarker selected

	Primary endpoint	Sample size
MA.NI.LA : Maintenance low dose oral vinorelbine in patients with NSCLC (I**RCCS Milano**) [NCT02176369].	Progression-free survival	120 pts
PIN: Efficacy and tolerability olaparib in maintenance vs placebo in chemosensitive advanced NSCLC. (**Cardiff, UK**) [NCT01788332].	Progression-free survival	114 pts

Advanced NSCLC: Randomized phase II – 2nd and later line, biomarker selected

	Primary endpoint	Sample size
GOAL: Gefitinib in combination with olaparib vs gefitinib alone, in patients with EGFR+ advanced NSCL (**GECP/SLCG**) [NCT01513174].	Maximum tolerated dose	186 pts
LADIE: Gefinitib or erlotinib (EGFR-TKI) vs gefinitib or erlotinib with fulvestrant in women with advanced stage EGFR+ NSCLC (**IFCT**) [NCT01556191].	Progression-free survival	358 pts
National lung matrix trial: multi-drug, genetic marker-directed, non-comparative, multi-arm trial in NSCLC (**Birmingham, UK**) [NCT N/A].		410 pts
SAFIR02_Lung: Efficacy of targeted drugs guided by genomic profiles in metastatic NSCLC (**IFCT**) **[NCT02117167].**	Progression-free survival	650 pts
In development: Activity of alectinib for pretreated RET-rearranged advanced NSCLC patients (**ETOP/EORTC/CGM – SPLECTAlung**)[NCT N/A].	Overall response	36 pts

SAFIR 02 lung-IFCT1301



All histologies

Ethics approval sept 2013; ANSM approval oct 2013

Pre-screening | NGS sequencing | MATRIX Lung Study

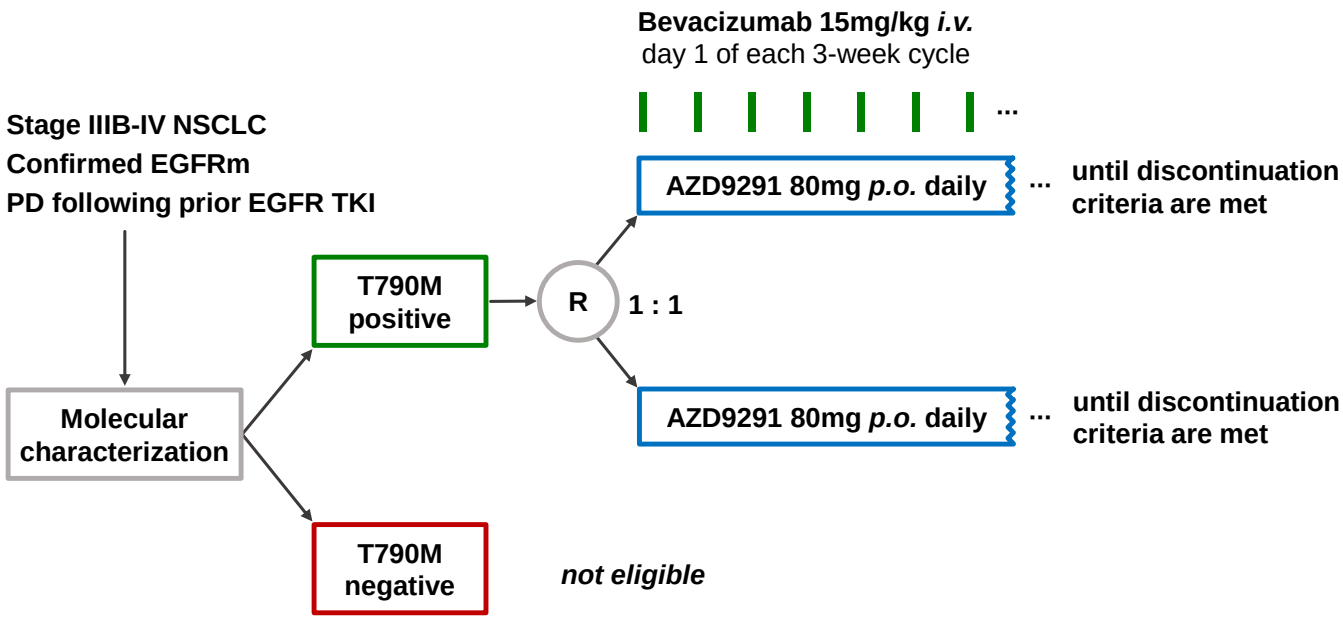
- Currently upto 2000 NSCLC patients screened per year
- Utilising DNA from routine FFPE biopsies
- 28 gene multiplexed NGS panel; detects mutations, deletions, CNV and DNA rearrangement
- National screening to national trial

- Phase 2a signal finding study
- 8 drugs, 21 stratified arms to begin with
- Sponsored by the University of Birmingham
- CI Professor Gary Middleton,
- Coordinated by Birmingham CRCTU
- Centralised pharmacy & recruitment across 18 ECMCs
- Rolling protocol, capable of incorporating new arms

ECMC | UNIVERSITY OF BIRMINGHAM | illumina | AstraZeneca | Pfizer | CANCER RESEARCH UK

BOOSTER: Osimertinib with or without bevacizumab t for mEGFR with T790M+ NSCLC

Study design:	Multicentre, randomized, open label, phase II trial, ETOP sponsored
Primary objectives:	To assess safety and efficacy of osimertinib in combination with bevacizumab versus AZD9291 monotherapy
Primary endpoint:	Progression-free survival
Sample size:	154 randomized patients



Advanced NSCLC: Single arm phase II – 2nd and later line, biomarker selected

	Primary endpoint	Sample size
EUCROSS: Crizotinib in advanced adenocarcinoma of the lung harbouring ROS1 translocations (**University of Cologne, Germany**) [NCT02183870].	Objective response	30 pts
NICHE: Afatinib in pre-treated patients with advanced NSCLC harbouring *HER2* exon 20 mutations (**ETOP**) [NCT02369484].	Disease control at 12 weeks	22 pts
NVALT-16 – IRENE: re-administration of gefitinib to EGFRm NSCLC patients, pretreated with at least one line of TKIs followed by another line of treatment (non-TKI) (**VU University Medical Center, Netherlands**) [NCT02025218].	Disease control	92 pts

Advanced NSCLC: Phase II – 2nd and later line, not biomarker selected

Randomised

	Primary endpoint	Sample size
NVALT 10: Erlotinib compared to single agent chemotherapy and erlotinib combination in pretreated patients with advanced NSCLC (**NVALT**) [NCT00835471].	Progression-free survival	230 pts

Single arm

	Primary endpoint	Sample size
REFRACT: Nintedanib plus docetaxel in second line of treatment in patients with non- squamous NSCLC refractory to first line chemotherapy (**GFPC**) [NCT N/A].	Disease-free survival	59 pts

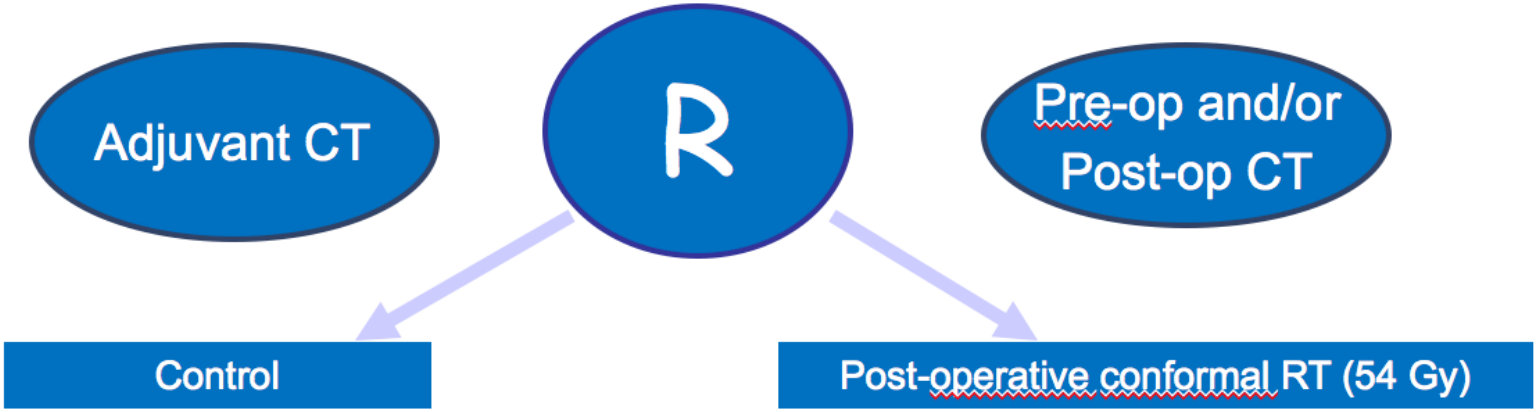
Locally advanced NSCLC: Randomized – Multimodality questions

Phase III	Primary endpoint	Sample size
LUNG ART: Post-operative conformal radiotherapy (PORT) to no post-operative radiotherapy in patients with completely resected NSCLC and mediastinal N2 involvement (**Gustave Roussy**) [NCT00410683].	Disease-free survival	700 pts

Phase II	Primary endpoint	Sample size
REMNANT: Neoadjuvant afatinib in early stage EGFR+ NSCLC (**EORTC**) [NCT02470065].	Decrease in ct stage at 8 weeks	38 pts

Lung ART

Completely resected NSCLC with mediastinal histologically or cytologically proven nodal involvement



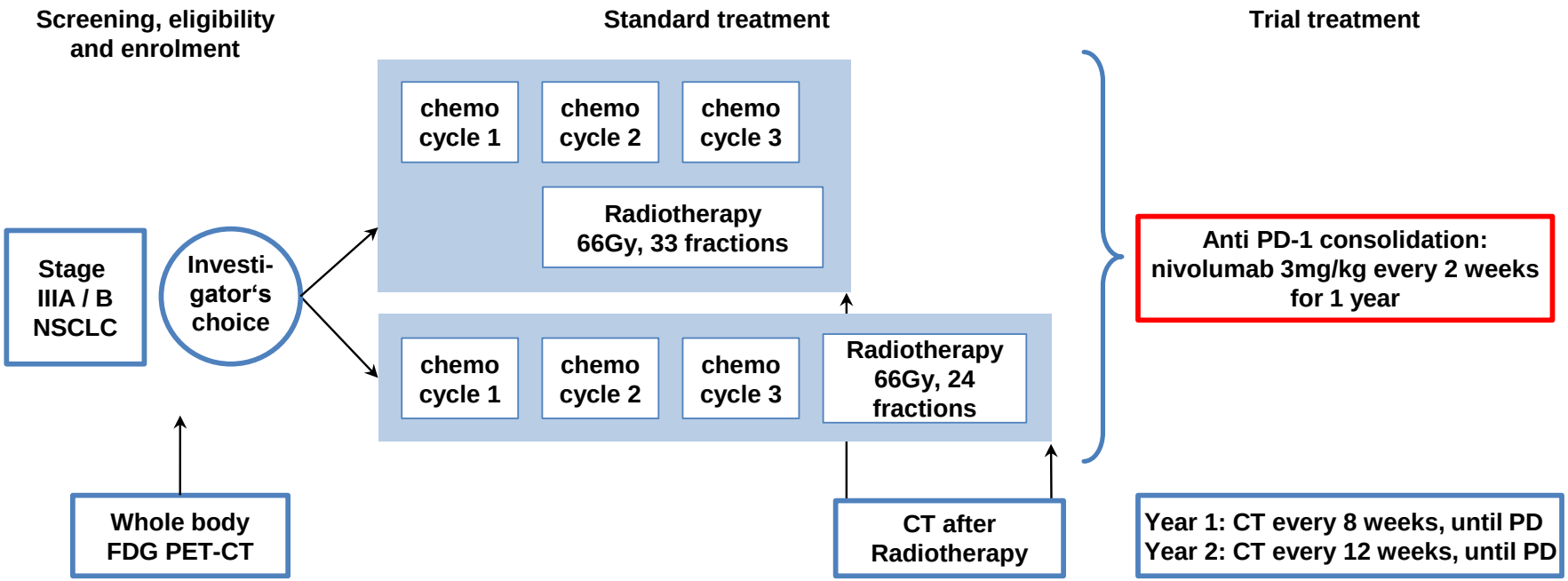
Primary end-point: Disease-free survival

CI Cecile Le Pechoux

Locally advanced NSCLC: Phase II – Multimodality questions

	Primary endpoint	Sample size
NICOLAS: Anti-PD1 nivolumab consolidation after standard first-line chemotherapy and radiation therapy in locally advanced stage NSCLC (**ETOP**) [NCT02434081].	Grade ≥3 pneumonitis at 6 month	43 pts
SAKK 16/08: Preoperative chemotherapy and radiotherapy concomitant to cetuximab in NSCLC patients with IIIB disease (**SAKK**) [NCT01059188].	Progression-free survival	69 pts
SAKK 16/14: Anti-PD-L1 antibody MEDI4736 in addition to neoadjuvant chemotherapy in patients with operable stage IIIA NSCLC (**SAKK**) [NCT N/A].	Event-free survival at 12 month	68 pts.

A feasibility trial evaluating anti-PD1 nivolumab consolidation after standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC



Chemotherapy: Cisplatin (or Carboplatin) doublet

Primary Endpoint: grade ≥3 pneumonitis

Sample Size: 43 patients

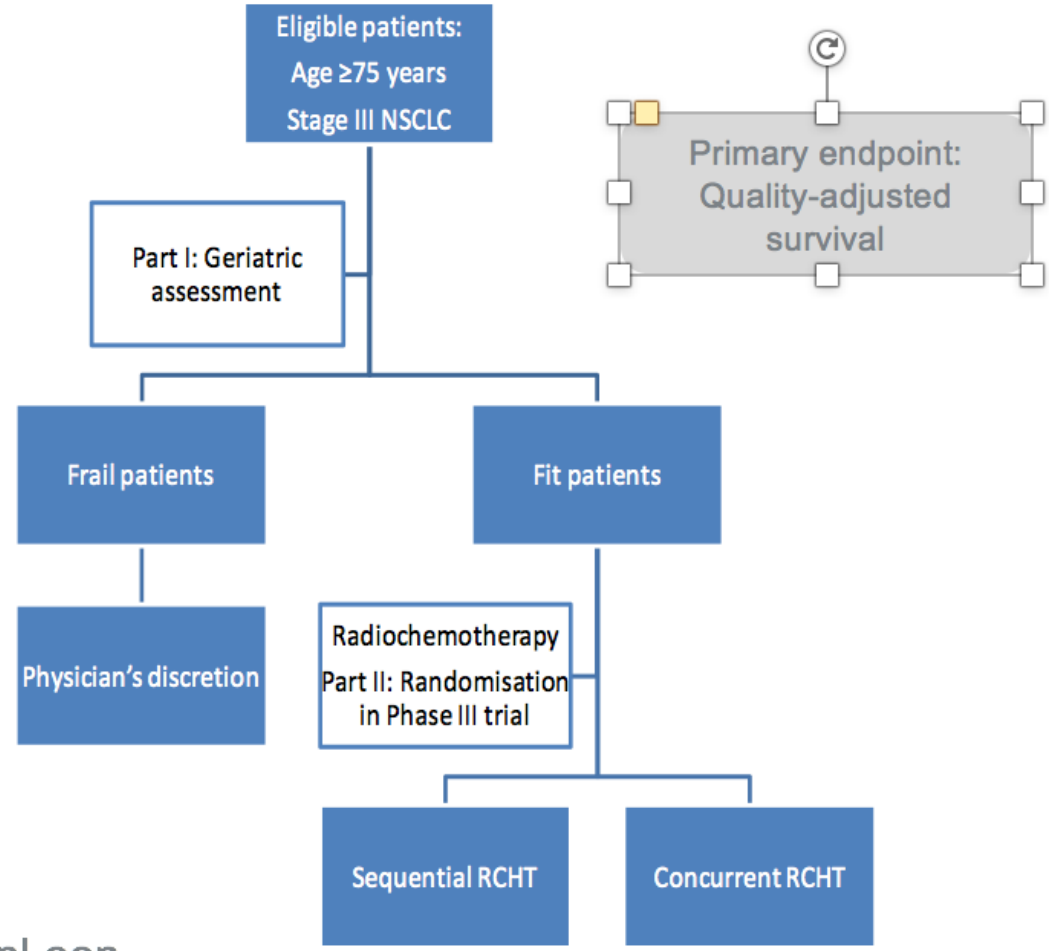
Locally advanced NSCLC: Phase II – Radiotherapy questions

	Primary endpoint	Sample size
GFPC_01-14: Study of the efficacy of SBRT after chemoradiotherapy on unresectable peripheral primary tumour (**GFPC**) [NCT02400424].	Local control rate	70 pts
Isotoxic IMRT: Isotoxic intensity modulated radiotherapy (IMRT) in stage III NSCLC - a feasibility study (Christie Hospital NHS) [NCT01836692].	Number of participants treated with IMRT	35 pts
ELDAPT: Primary therapy according to geriatric assessment (**Maastricht Radiation Oncology**) [NCT02284308].	Quality adjusted survival	300 pts

ELDAPT: Elderly With Locally Advanced Lung Cancer: Deciding Through Geriatric Assessment on the oPtimal Treatment Strategy

Intensified treatment with CRT results in better outcome with preserved quality of life in a *subgroup of medically fit elderly* stage III patients

How to select this "medically fit" subgroup of elderly patients?



CI Judith VanLoon

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Early NSCLC
Radiotherapy questions

Phase III	Primary endpoint	Sample size
SABRTooth: Comparing stereotactic ablative radiotherapy (SABR) with surgery in patients with peripheral stage I NSCLC considered to be at higher risk of complications from surgical resection (**University of Leeds, NHS**) [NCT N/A].		54 pts

Phase II - Single arm	Primary endpoint	Sample size
LungTech: Stereotactic body radiotherapy (SBRT) of inoperable centrally located NSCLC (**EORTC**) [NCT01795521].	Effectiveness of SBRT	150 pts

SABRTooth

National Institute for Health Research

A study to determine the feasibility and acceptability of conducting a phase III randomised controlled trial comparing stereotactic Ablative Radiotherapy (SABR) with surgery in paTients with peripheral stage I nOn-small cell lung cancer (NSCLC) cOnsidered To be at Higher risk of complications from surgical resection.

- **Average recruitment rate per month over formal monitoring period**
  - 21 month recruitment period (target 54 patients)
    - 6 month run-in period (May 15 – Oct 15)
    - 15 month formal monitoring period (Nov 15 – Jan 17)
- Average of 3 patients per month must be recruited over a consecutive 15 month period (a minimum of 45 patients)

✓ Provide evidence that recruitment targets for the main trial can be met within an adequate timeframe

✓ Provide evidence that clinician's are willing to recruit, and patients are willing to be randomised into a trial of SABR vs surgery

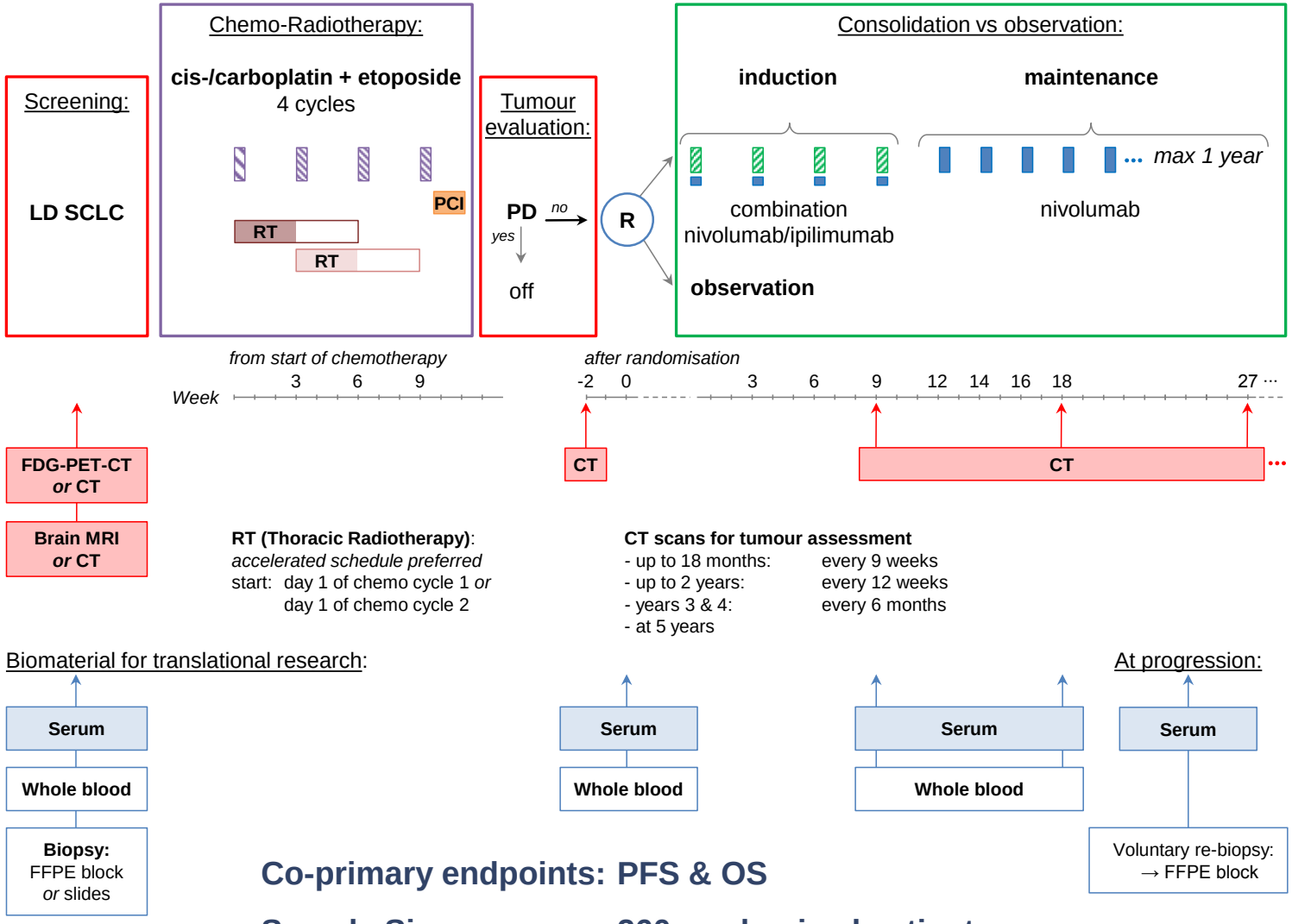
The Christie NHS
NHS Foundation Trust

CI Kevin Franks

SCLC: Phase III

	Primary endpoint	Sample size
GFPC 01-2013 study: Efficacy of topotecan vs carboplatin/etoposide in 2nd line SCLC (**GFPC**) [NCT N/A].	Disease-free survival	96 pts
HA-PCI: Prophylactic cranial irradiation with or without hippocampal avoidance in SCLC (**The Netherlands Cancer Institute**) [NCT01780675].	Neurocognitive decline	168 pts
RASTEN: Standard Treatment with or without enoxaparin in SCLC (**Lund University Hospital, Sweden**) [NCT00717938].	Significant increase of overall survival	390 pts

STIMULI protocol amendment 1 *(continued)*



Co-primary endpoints: PFS & OS

Sample Size: 260 randomized patients

SCLC: Phase II

Randomised

	Primary endpoint	Sample size
STIMULI: Consolidation of nivolumab plus ipilimumab in limited stage SCLC after chemo-radiotherapy (**ETOP/IFCT**) [NCT02046733].	Overall survival and progression-free survival	260 pts
THORA: Two schedules of hyperfractionated thoracic radiotherapy in limited disease SCLC (**Norwegian University of Science and Technology**) [NCT02041845].	2-Year survival	154 pts

Single arm

	Primary endpoint	Sample size
SAKK 15/12: Early hippocampal avoidance prophylactic cranial irradiation (PCI) in patients with limited disease SCLC (**SAKK**) [NCT02058056].	Neurocognitive functioning	42 pts

Mesothelioma

Phase III

	Primary endpoint	Sample size
PIT: Prophylactic irradiation of tracts in patients with malignant pleural mesothelioma (**Christie Hospital NHS, UK**) [NCT01604005].	Maximum tolerated dose	374 pts
PROMISE-ME (in development): Pembrolizumab vs standard chemotherapy for advanced pretreated malignant pleural mesothelioma (**ETOP**) [NCT N/A].	Progression-free survival	142 pts

Phase II - Single arm

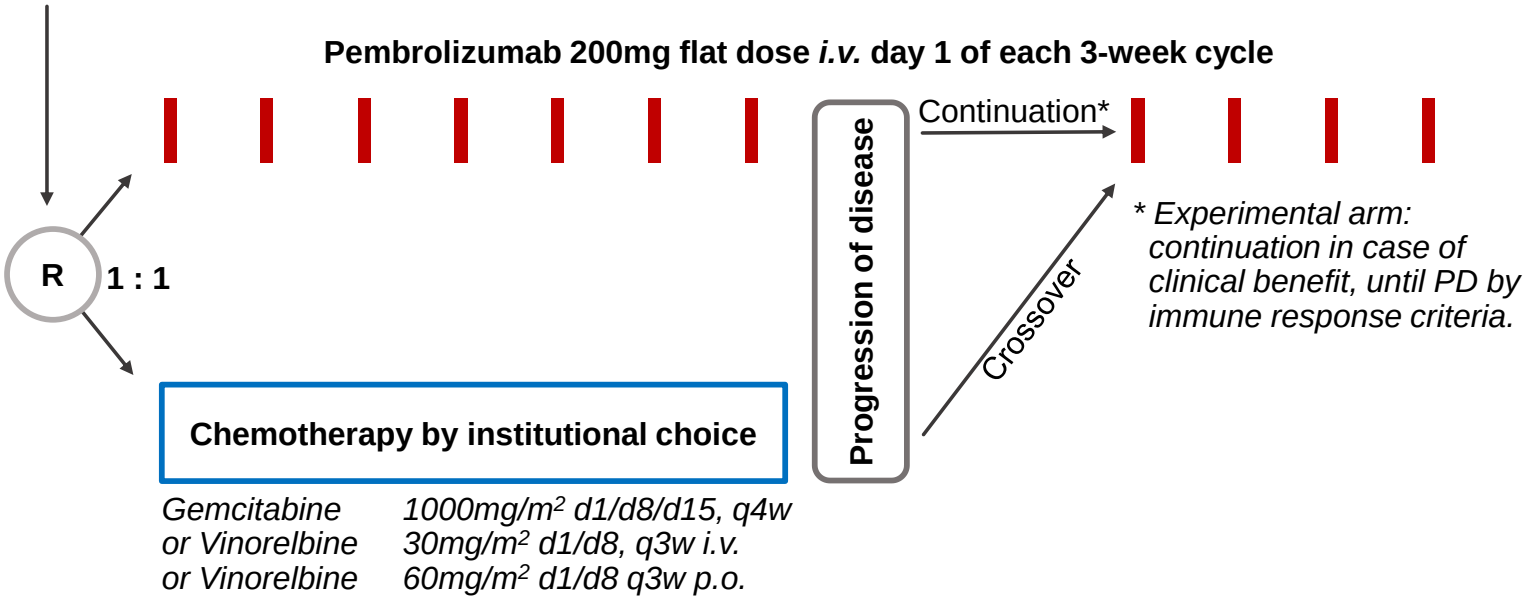
	Primary endpoint	Sample size
MESO-02: Ganetespib with platinum, in patients with malignant pleural mesothelioma (**University College, London**) [NCT01590160].	Maximum tolerated dose	24 pts

PROMISE-ME Pembrolizumab in advanced pre-treated malignant pleural mesothelioma

Study design:	Multicentre, randomised, phase III trial, ETOP sponsored
Primary objectives	To assess safety and efficacy of pembrolizumab versus standard chemotherapy in MPM
Primary endpoint:	Progression-free survival (based on independent radiological review)
Sample size:	142 randomized patients

Stage III–IV MPM

One previous line of chemotherapy



Platform Studies

	Primary endpoint	Current sample size
CPCT-02: Center for personalized cancer treatment. DNA-based cancer research. Next generation sequencing technology to map genetic changes (**The Netherlands**) [NCT01855477].	Observational	1240 pts
Network Genomic Medicine: Genomics-based classification of human lung tumours. Clinical trial program covering nearly all genotypes (**University Cologne, Germany**) [NCT N/A].	Observational	4000 pts
SPECTAlung: Screening patients with thoracic tumours for efficient clinical trial access (**EORTC / ETOP**) [NCT02214134].	Observational	3500 pts
TRACERx: Tracking NSCLC evolution through therapy (Rx). Sequencing study of NSCLC from diagnosis to relapse (**Cancer research UK**) [NCT01888601].	Observational	842 pts

18 SPECTAlung participating sites

Ireland
Stephen Finn - St James Institute

UK
Sanjay Popat – Royal Marsden

France
Benjamin Besse – Gustave Roussy
Julien Mazieres - Hôpital Larrey

Netherlands
Egbert Smit - VU University Medical Center

Germany
Martin Reck - Center of Pneumology and Thoracic Surgery of Grosshansdorf

Switzerland
Rolf Stahel – University Hospital of Zurich
Solange Peters – University of Lausanne

Belgium
Thierry Berghmans - Institute Jules Bordet
Johan Vansteenkiste - Institute KU Leuven
Jan Van Meerbeeck - Antwerpen University Hospital

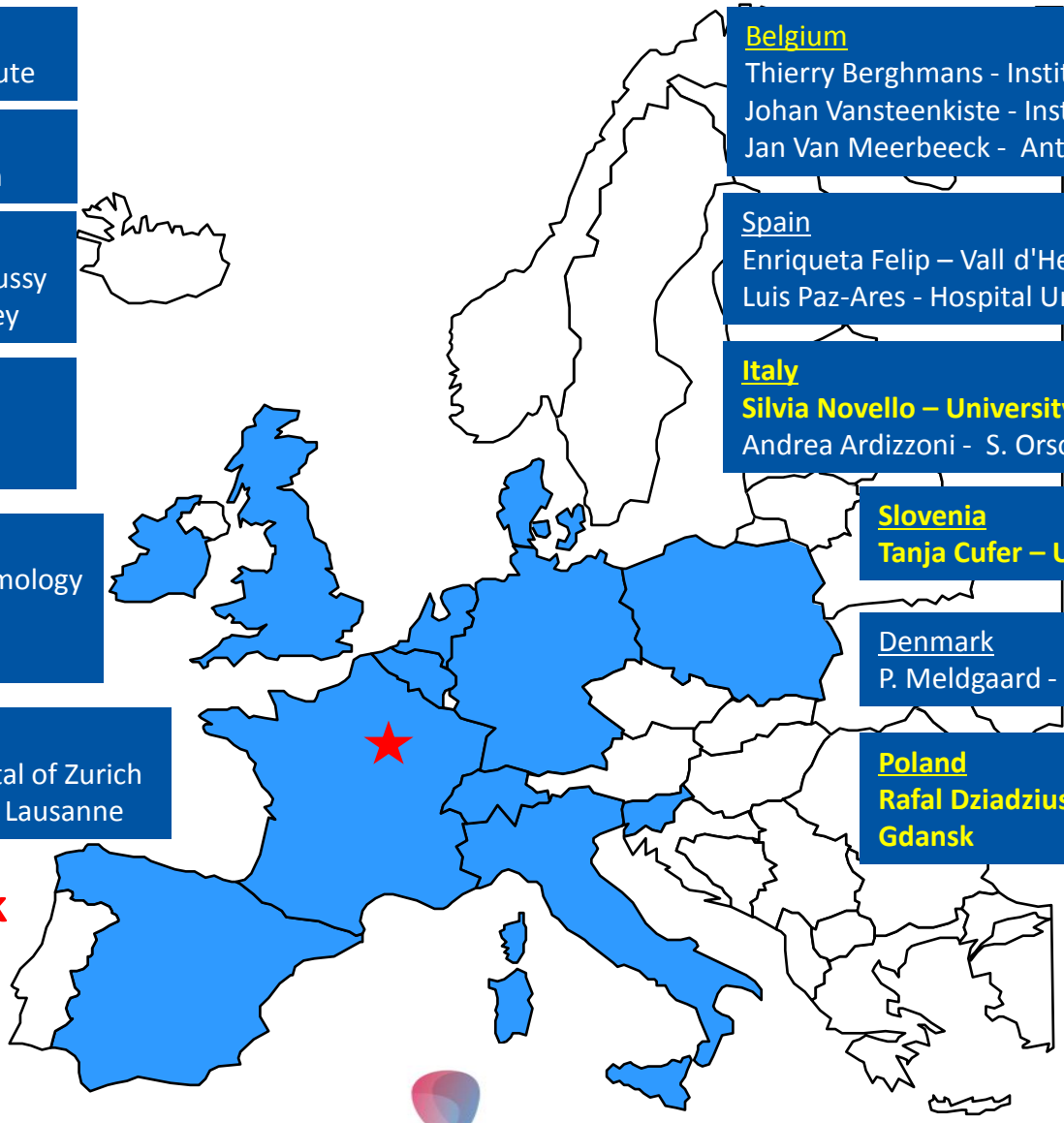
Spain
Enriqueta Felip – Vall d'Hebron University Hospital
Luis Paz-Ares - Hospital Universitario Doce de Octubre

Italy
Silvia Novello – University of Turin
Andrea Ardizzoni - S. Orsola-Malpighi Hospital

Slovenia
Tanja Cufer – University Clinic Golnik

Denmark
P. Meldgaard - Aarhus University Hospital

Poland
Rafal Dziadziuszko – Medical University of Gdansk



★ **Central Biobank Gustave Roussy Cancer Campus**

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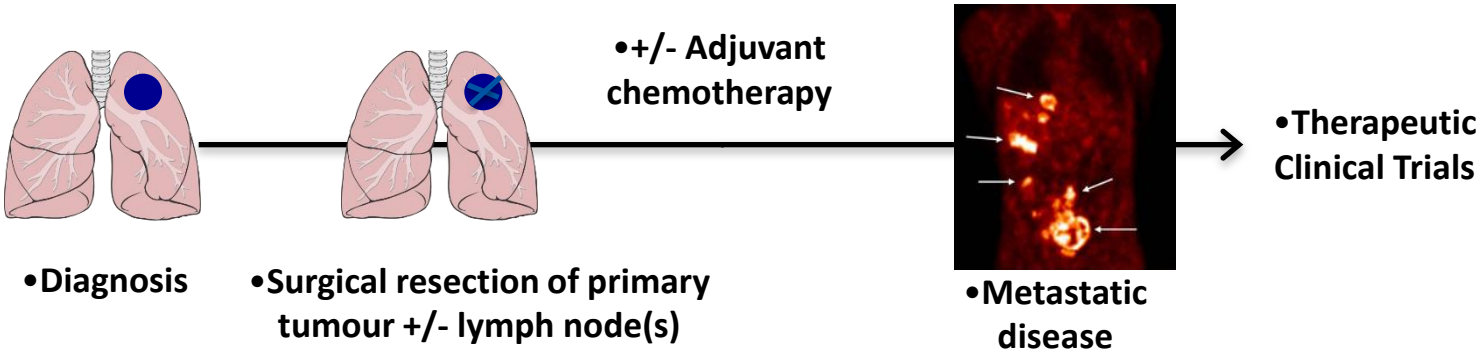
The future of cancer therapy

CERx



- UK-wide Sequencing study of NSCLC from diagnosis to relapse
  - Aim to sequence > 6000 exomes (500x) in 842 patients
  - Tracking the clonal evolution of tumours
- Multi-region sequencing of primary tumours
  - Stages I-IIIA eligible for surgical resection
- Relapse biopsy cohort
- Longitudinal sampling
  - Circulating biomarkers, e.g. cfDNA & CTCs
  - Immunological biomarkers, e.g. TILs & TCR phosphopeptides

Lungscape

A project by ETOP

- **Belgium**
- Leuven:
  J. Vansteenkiste,
  E. Verbeken, C. Dooms,
  L.Vliegen

- **Denmark**
- Aarhus:
  P. Meldgaard,
  L.B. Madsen

- **Greece**
- ETOP Statistical Center,
  Frontier Science Hellas:
  U. Dafni, Z. Tsourti,

- **Germany**
- Heidelberg:
  H.Dienemann, A. Warth,
  T. Muley

- **Ireland**
- Dublin:
  S. Finn, S. Gray, K. Gately

- **Italy**
- Chieti:
- A. Marchetti, F. Buttitta,
  A. Di Lorito

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

- **Spain**
- Barcelona:
  E. Felip, J. Hernandez-Losa,
  I.Sansano, M. T. Salcedo, M. Canela,
- Badalona:
  R. Rosell, M.A. Molina
- Valencia:
  C. Camps, M. Martorell,
  M.C. Calabuig, E. Jantus-Lewintre

- **Beyond Europe:**
- **China**
- Shanghai Chest Hospital:
  S. Lu, Z. Jie, Q. Tan
- **USA**
- Roswell Park Cancer Institute:
  A. Adjei, R. Cheney, M. Reid

- **Switzerland**
- ETOP Coordinating Office:
  A. Hiltbrunner, S. Peters,
  R. Kammler, T. Geiger, M.
  Marbot, R. King, R. Stahel
- Basel:
  L. Bubendorf, S. Savic
- Zurich:
  W. Weder, V. Tischler, A.
  Soltermann

- **The Netherlands**
- Amsterdam VUMC:
- E. Thunnissen, E. Smit
- Amsterdam NKI:
  P. Baas, K. Monkhorst
- 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, L. Priest

iBiobank usage

and more to come…

PD-L1 (IHC)

RANK/RANKL (IHC)

PIK3CA (FISH)

PTEN (IHC)

Multiplex Mutation (AKT, BRAF, EGFR, ERBB2, FLT3, HRAS, JAK2, KIT, KRAS, MET, MYD88, NRAS, PIK3CA)

MET (IHC, SISH)

ALK (IHC, FISH, RT-PCR)

ETOPdata

(demographics, histopathology, outcome)

Thank you for listening!

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