

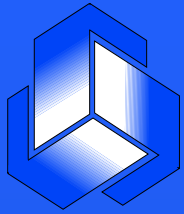
Developments in Biomarker Identification and Validation for Lung Cancer

Alexandre Passioukov, MD, PhD

EORTC

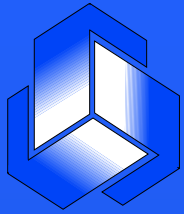
Alexandre.Passioukov@eortc.be

EORTC

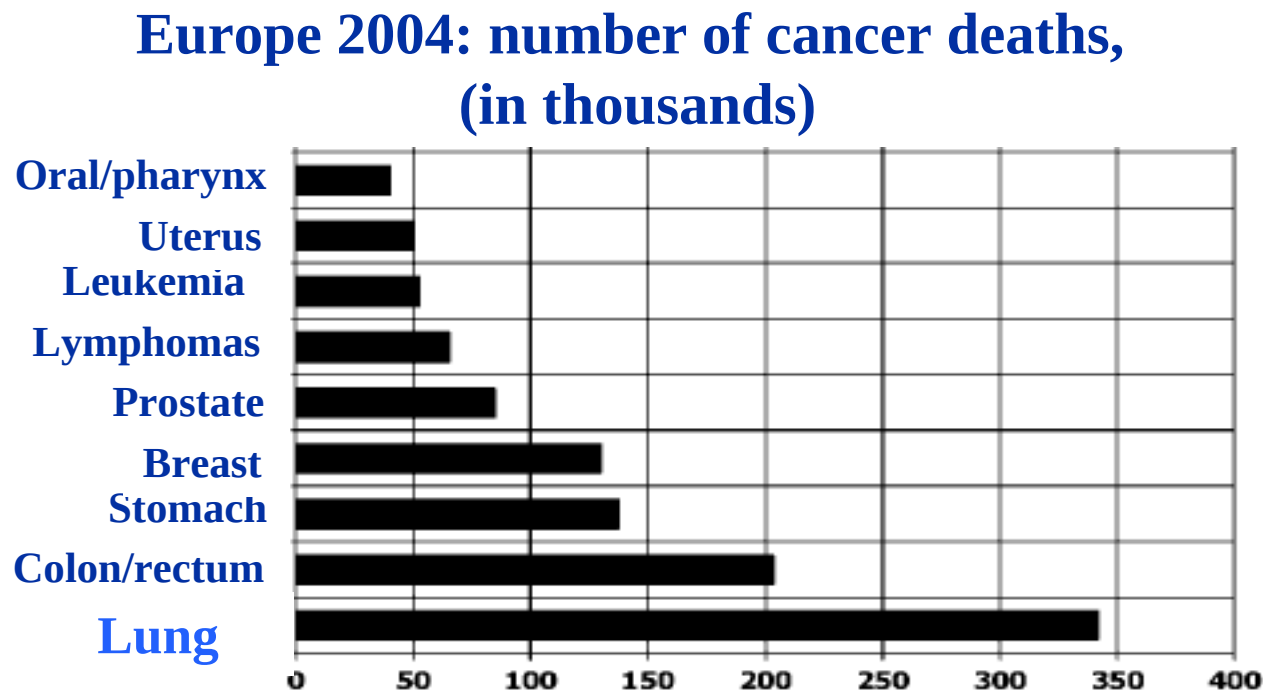


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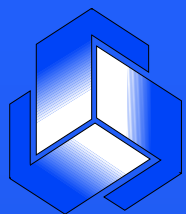
- **Introduction**
- **Lung cancer pathogenesis**
- **NSCLC treatment options**
- **Biomarkers for early detection/diagnosis**
- **Biomarkers for prognosis in lung cancer**
- **Biomarkers for prediction of treatment outcome**
- **Clinical validation of biomarkers in lung cancer**
- **Conclusions**



Lung Cancer Mortality

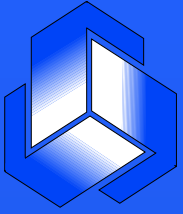


Lung cancer remains the most deadly cancer type worldwide



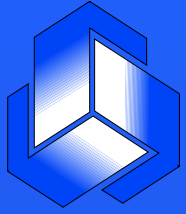
Lung Cancer Patients long term survival (%)

	<u>1970</u>	<u>2005</u>
• Advanced testis cancer	0	95
• Leukemia in children	0	80
• Hodgkin's disease	10	85
• Colon cancer	30	60
• Breast cancer	40	85
• Non-small cell lung cancer	0	15



Lung cancer major traits

- strong environmental risk factor:
smoking
- older age of onset
- high case fatality ratio



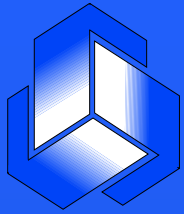
Lung cancer pathogenesis (I)

Major susceptibility loci

A large genome-wide linkage study assuming simple autosomal dominant model:

MSL for lung cancer risk localized to 6q23-25

(Bailey-Wilson JE, et al. 2004)



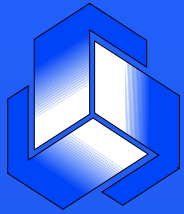
Lung cancer pathogenesis (II)

Major histological types

- ◆ Non-small cells lung cancer (around 85%)
 - squamous cell
 - large cell
 - adenocarcinoma

- ◆ Small cell lung cancer (around 15%)

- ◆ May each have unique molecular aspects for precursor lesions and steps in progression



Lung cancer pathogenesis (III)

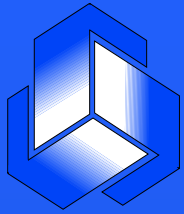
Molecular pathology traits

Tumour suppressor gene loss of function

P53	50% NSCLC and 75-100% SCLC
Rb	15-30% NSCLC and 90% SCLC
p16	70% NSCLC

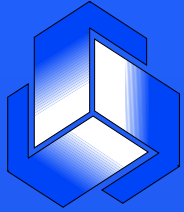
Oncogene activation

RAS	KRAS mutation in NSCLC
EGFR	EGFR overexpression in NSCLC
MYC	MYC family overexpression.



NSCLC main treatment options

- Localized (stage I – II)
 - Surgery
 - Adjuvant platinum-based chemotherapy
- Locally advanced (stage III)
 - Combinations: chemotherapy, radiotherapy, surgery
- Advanced (IIIB-IV)
 - Platinum-based chemotherapy
 - Targeted agents

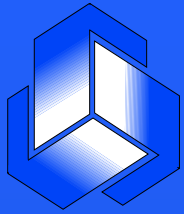


Lung cancer biomarkers

Applicability



- Early detection/diagnosis
- Prognosis in case of resectable lung tumors
- Prediction of:
 - toxicity
 - response
 - relapse

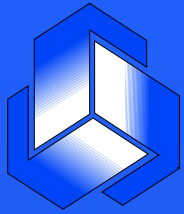


Lung cancer biomarkers (I)

Current status

There are no biomarkers universally recommended to help in the clinical management of lung cancer today

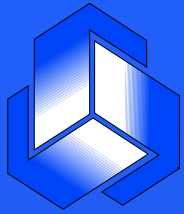
- **Probable valid biomarkers**
- **Candidate biomarkers**
- **General trends**



Lung cancer biomarkers (II)

EGTM recommendations

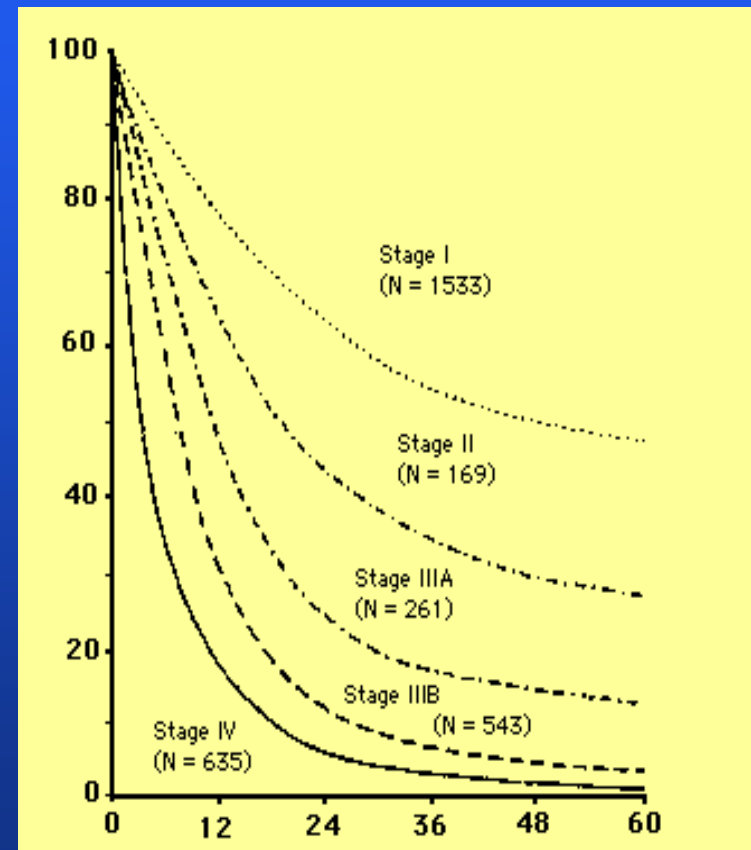
- **NSCLC (therapy monitoring)**
 - cytokeratin fragment 19 (CYFRA 21-1)
 - carcinoembryonic antigen (CEA)
- **SCLC (differential diagnosis)**
 - neuron-specific enolase (NSE)

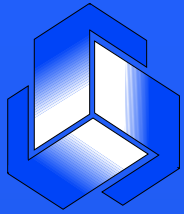


Early detection/diagnosis (I)

Applicability of biomarkers

- Curative surgery for more patients (only 20% now)
- Surgery (resection of the entire lobe concerned) avoided for tumors of a low-risk biomolecular profile

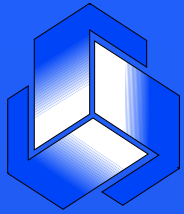




Early detection/diagnosis (II)

Ideal biomarker

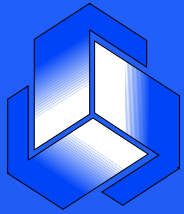
- Minimally invasive sampling
- Reliable assessment in:
 - Blood
 - Sputum
 - Bronchiolo-alveolar lavage (BAL)
- Low costs
- High sensitivity



Early detection/diagnosis (II)

Diagnostic biomarkers

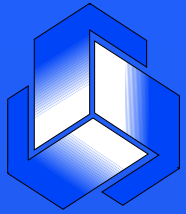
- *c-myc* x E2F-1/p21 gene expression index measured in fine-needle aspirate by StaRT-PCR
- **Validation ongoing in CA 103594 study (NCI)**



Early lung cancer detection (III)

Current status / perspectives

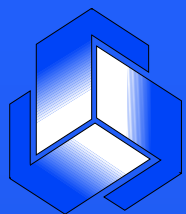
- Large number of candidate biomarkers
- Validation is a major challenge
- Multiple biomarkers approaches seem to be inevitable
- Miniaturised/automatic techniques are needed (microarrays, microproteomics, methylation profiles etc)



Prognostic biomarkers in lung (I)

Implications

- Adjuvant chemotherapy (CT) is becoming a standard:
 - IALT, JBR.10, CALGB 9633 phase III trials' results showing survival benefit after platinum-based CT
- **Robust biomarkers could help to avoid CT to patients at negligible risk of relapse**



Prognostic biomarkers in lung (II)

Best single candidates

Gene

Molecular function

Favorable prognosis

p16

cell cycle

p21

cell cycle

p27

cell cycle

Unfavorable prognosis

Cyclin B1

cell cycle

Cyclin E

cell cycle

Survivin

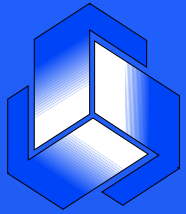
apoptosis

VEGF

angiogenesis

Collagen XVIII

angiogenesis



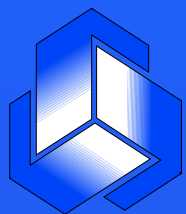
Prognostic biomarker in lung (III)

Array candidates

- “Risk index” top 50 genes with difference in survival for stage I lung adenocarcinomas *(D. Beer et al 2002)*

HOWEVER:

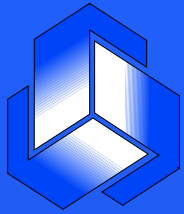
- Small studies and validation in larger studies is needed
- **NCI consortium pooling the data from multi-center oligonucleotide arrays (around 600 adenocarcinomas)**



Prognostic biomarker validation (IV)

Validation guidelines

- NCI – EORTC guidelines (2000)
 - **Poor study design/analysis**
 - **Assay variability**
 - **Inadequate reporting**
- CONSORT: randomized clinical trials (2001)
- STARD: diagnostic test accuracy (2003)
- REMARK: Reporting recommendations for tumor marker prognostic studies (NCI, 2005)



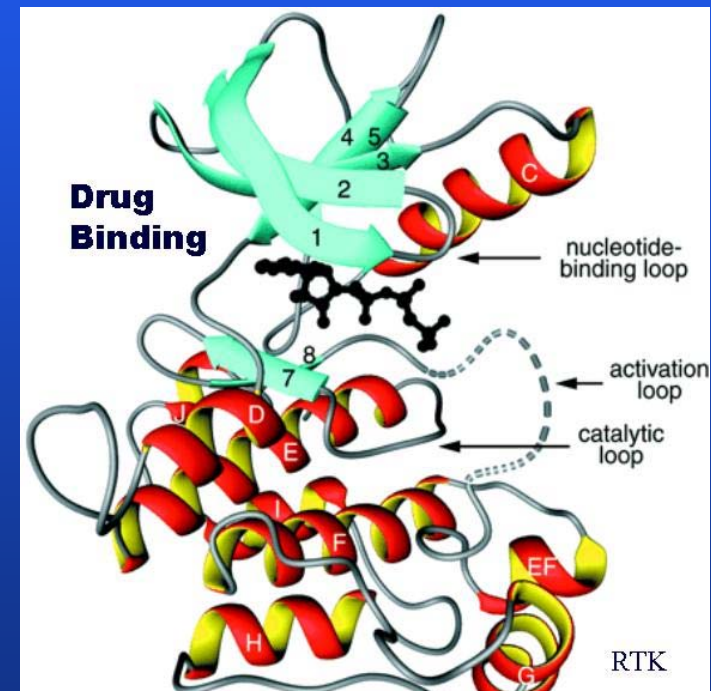
Predictive biomarkers in NSCLC

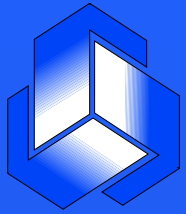
Response to TKIs example (1)

Gefitinib, erlotinib:

**Response in 10% of patients
with advanced NSCLC**

Molecular predictors of
response?





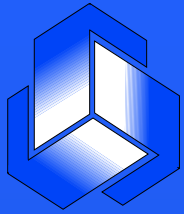
Predictive biomarkers in NSCLC

Response to TKIs example (2)

- EGFR mutations seem to be associated with response to TKIs
- Increased EGFR copy number (FISH analysis) correlates with response, SD, TTP and OS
- **Combination of EGFR mutational status/FISH seems to be the best predictive factor**
- **Development of genomic-based predictive models**

(Hirsh FR, 2005)

(Petersen RP et al. 2005)



Predictive biomarkers in NSCLC

antiangiogenic agents example

Tumor tissue:

VEGFR (expression and mutation status)

Hif-1alpha, Hif-2alpha, Glut-1, CA-IX, VEGF (hypoxia)

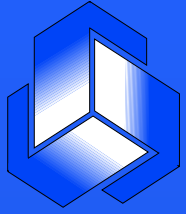
CD31 (vessel density)

Plasma:

VEGF, LDH, endothelial progenitor cells

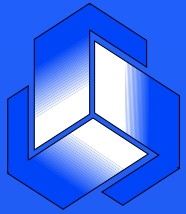
Imaging:

DCE-MRI



Predictive biomarkers in NSCLC

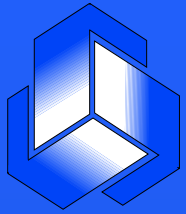
How to predict for response AND survival ?



Predictive biomarkers in NSCLC

Response to CT

- Platinum compounds are essential element
- Doublet combinations (with **paclitaxel, gemcitabine, vinorelbine**) are superior to single-agent
- “Plateau” reached with CT in NSCLC



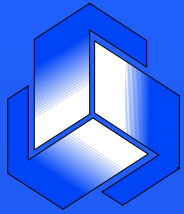
Predictive biomarkers in NSCLC

Response to CT

Polymorphism for DNA repair enzymes:

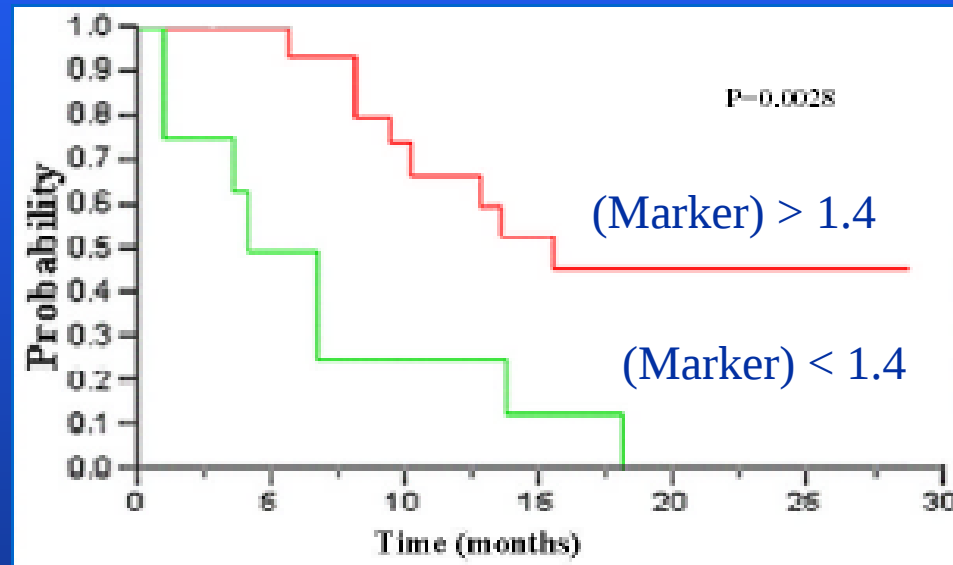
- **ERCCI (excision repair cross-complementing I)**
- **RRM1 (Ribonucleotide reductase subunit M)**
- **XPD (Xeroderma Pigmentosum group D)**

Correlation of status with response/survival?

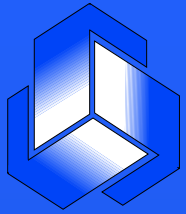


Predictive biomarkers in NSCLC

An “invalid validation” example

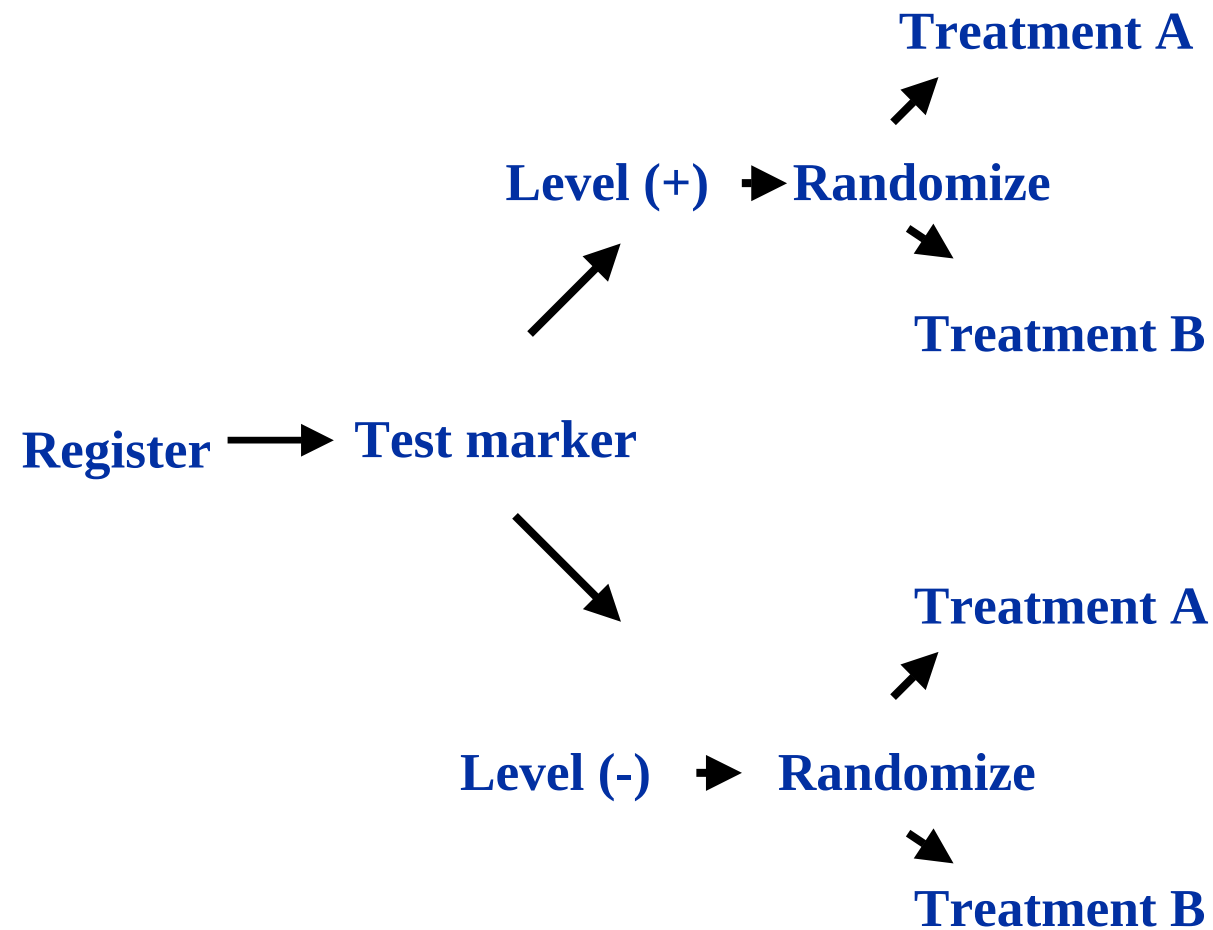


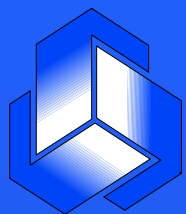
Survival by (Marker) Expression in patients treated with a cisplatin-based combination:
PROGNOSTIC EVIDENCE!



Predictive biomarkers validation (I)

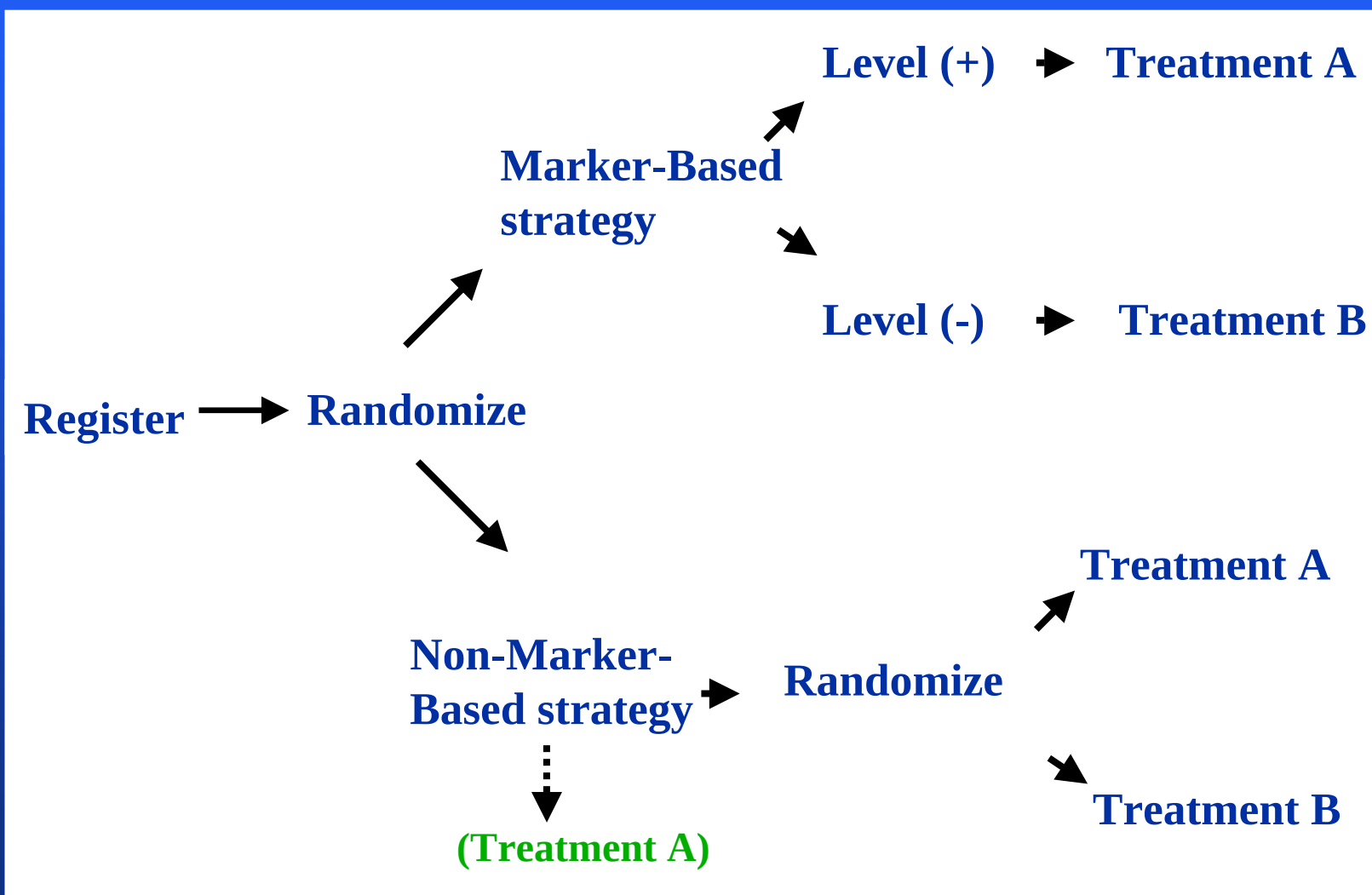
Marker by treatment interaction design

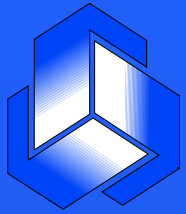




Predictive biomarkers validation (II)

Marker-based strategy design



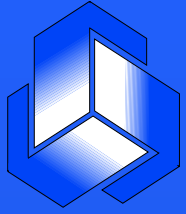


Predictive biomarkers in NSCLC

Response to CT

Perspectives:

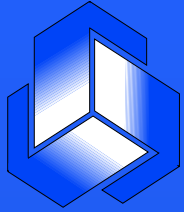
- building larger databases from existing smaller studies
- developing strategies to simultaneously evaluate multiple polymorphisms and genes within the same pathway
- **Prospectively evaluate clinical value in randomized clinical trials**



Predictive biomarkers in NSCLC

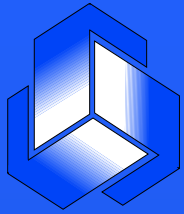
What alternative can we propose to non-responding patients?

- **New efficient agents are needed in lung cancer!**



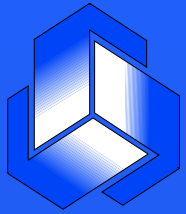
Conclusions (I)

- **Single biomarker approaches have not proven to have a strong potential in lung cancer**
- **Use of molecular technologies bring a key-promise for identification of clinically meaningful biomarkers**
- **Clinical validation of candidate biomarkers remains a major challenge**

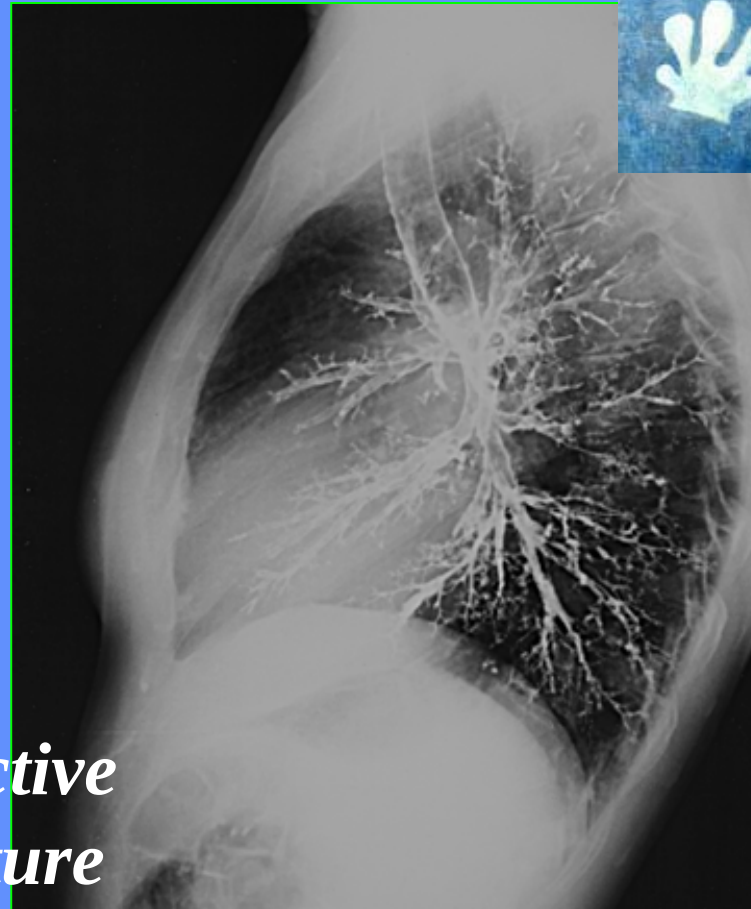


Conclusions (II)

- Use of biomarkers for early detection of lung cancer is promising but still methodologically challenging
- Clinical management of NSCLC will most probably first benefit from use of biomarkers
- **Development of new therapeutic options for lung cancer will stimulate identification and clinical validation of new biomarkers**



Biomarkers in lung cancer:



Biomarkers are active partners in the future research and lung cancer care