GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

www.esmo.org

Improving clinical research on rare cancers

JY Blay
Lyon, France
FSG, EORTC

Issues

- Recogition
- Fragmentation
- Solutions

Pathology review !

Brussels 25 5 2012

Rate of concordance by patient sub-group

188
Second opinion requested

- **53 (28%) Total discordance**
- **53 (28%) Partial concordance**
- **82 (44%) Total concordance**

For 56 % the diagnosis is not totally correct

178
Second opinion not requested

- **17 (10%) Total discordance**
- **44 (25%) Partial concordance**
- **117 (65%) Total concordance**

For 35 % the diagnosis is not totally correct

Clinical practice guidelines

Soft tissue sarcomas: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

P. G. Casali[1], L. Jost[2], S. Sleijfer[3], J. Verweij[4] & J.-Y. Blay[5]
On behalf of the ESMO Guidelines Working Group*

Bone sarcomas: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

P. C. W. Hogendoorn†
On behalf of the ESMO/EUROBONET Working Group*
University Medical Center, Leiden, Netherlands

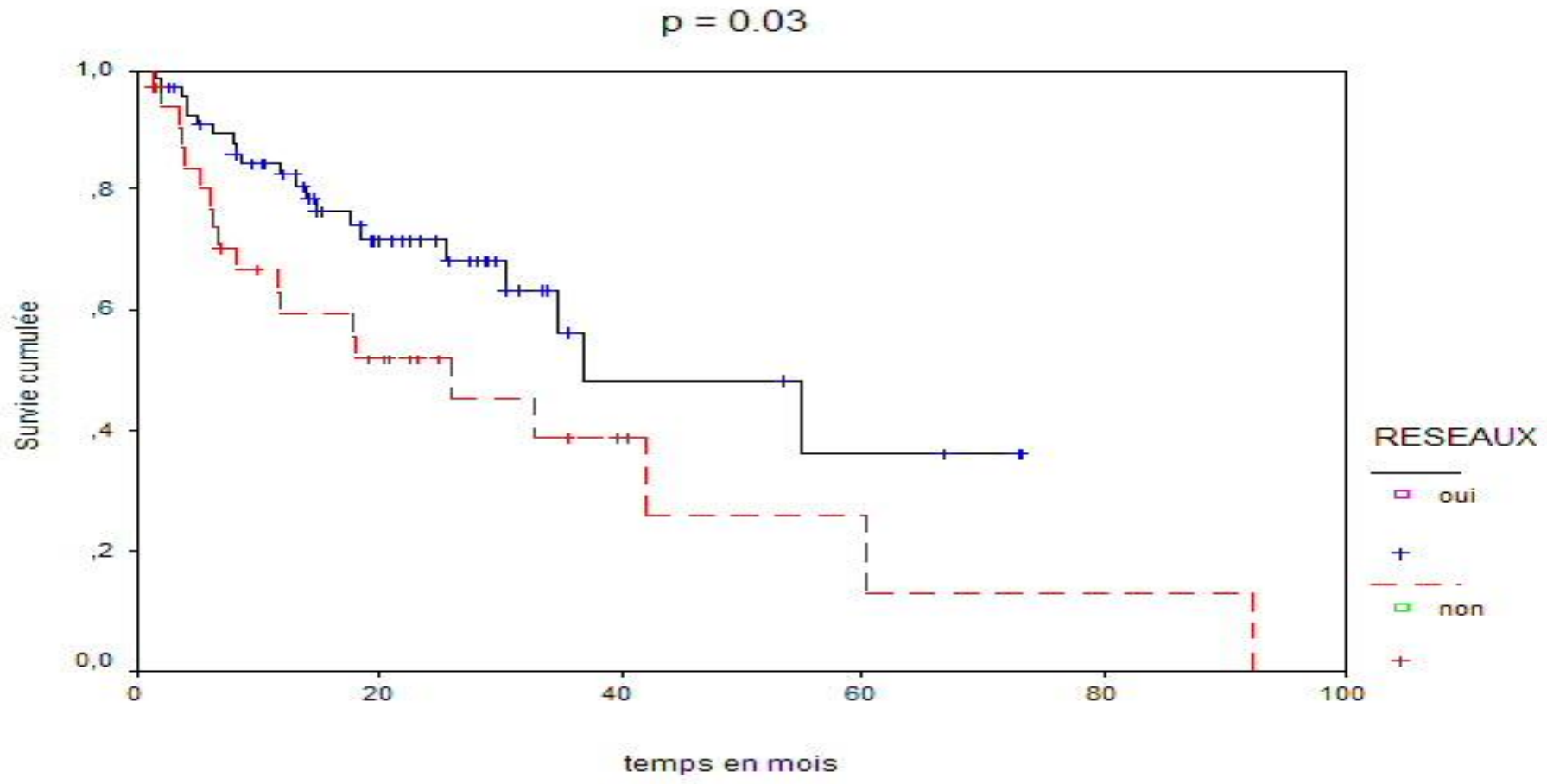
clinical recommendations

Annals of Oncology 21 (Supplement 5):
doi:10.1093/a

Gastrointestinal stromal tumours: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

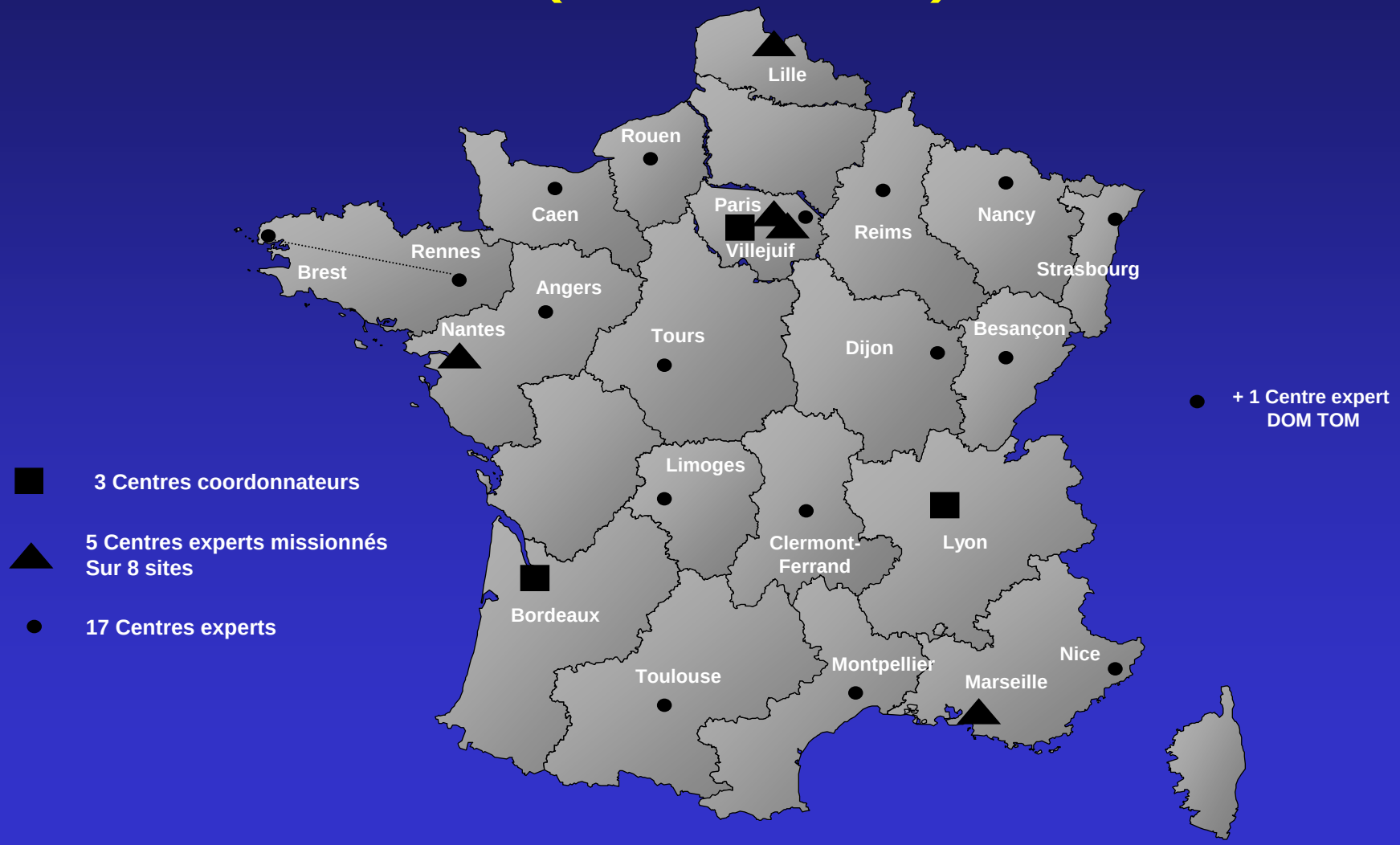
P. G. Casali[1] & J.-Y. Blay[2]
On behalf of the ESMO/CONTICANET/EUROBONET Consensus Panel of Experts*

Distant metastasis and multidisciplinary assessment



French Clinical network (NetSarc)

Brussels 25 5 2012



Netsarc 2010-2012

- N=8954 patients with sarcomas
- Primary surgery in
  - Reference center
    - R0 : 60%, R1: 36%, R2: 4%
  - Primary care or non reference center
    - R0 : 30%, R1: 49%, R2: 21%

(p<0.000)

Issues

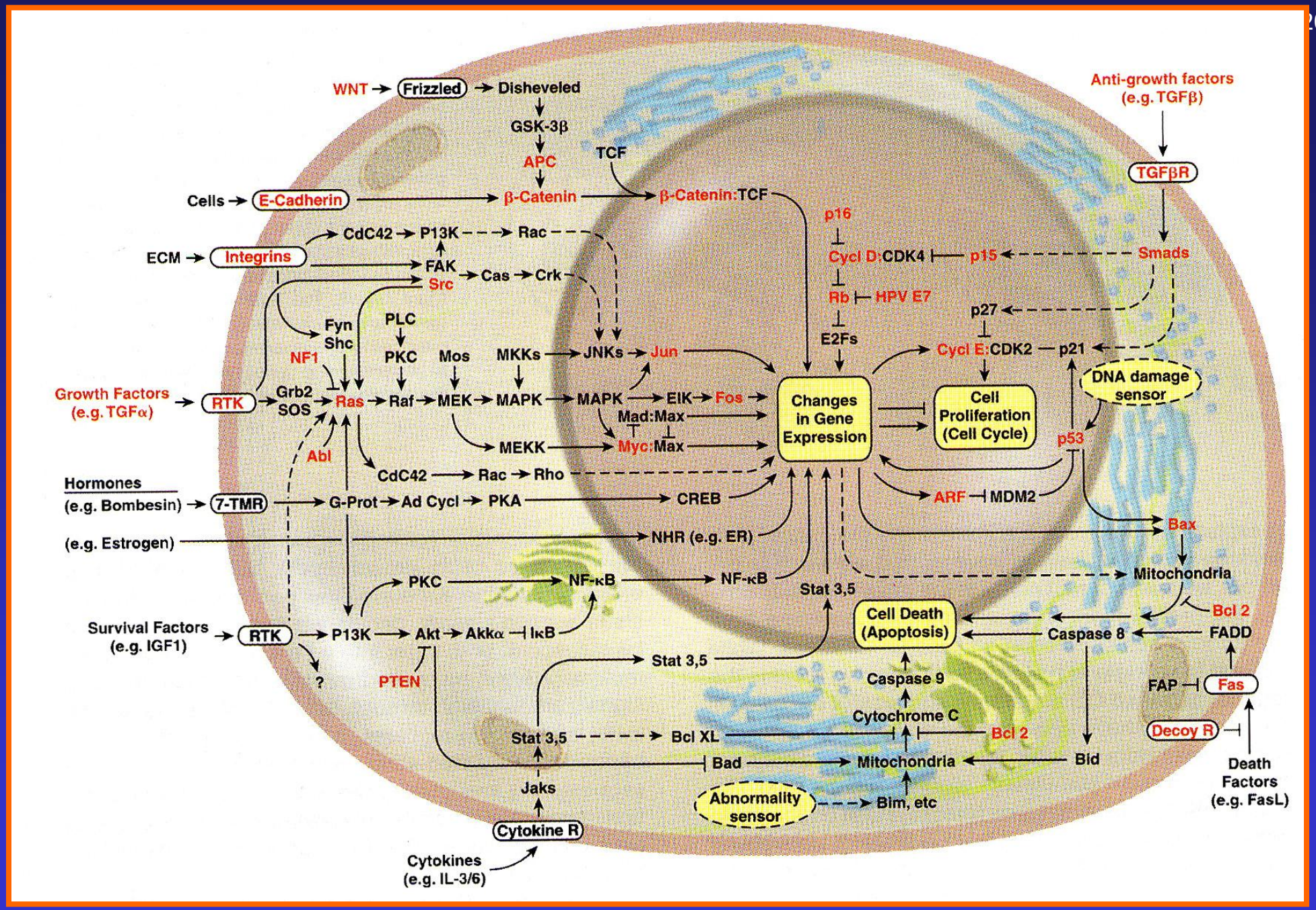
- Recogition
- Fragmentation
- Solutions

Sciencexpress Research Article

The Consensus Coding Sequences of Human Breast and Colorectal Cancers

Tobias Sjöblom,[1]* Siân Jones,[1]* Laura D. Wood,[1]* D. Williams Parsons,[1]* Jimmy Lin,[1] Thomas Barber,[1] Diana Mandelker,[1] Rebecca J. Leary,[1] Janine Ptak,[1] Natalie Silliman,[1] Steve Szabo,[1] Phillip Buckhaults,[2] Christopher Farrell,[2] Paul Meeh,[2] Sanford D. Markowitz,[3] Joseph Willis,[4] Dawn Dawson,[4] James K. V. Willson,[5] Adi F. Gazdar,[6] James Hartigan,[7] Leo Wu,[8] Changsheng Liu,[8] Giovanni Parmigiani,[9] Ben Ho Park,[10] Kurtis E. Bachman,[11] Nickolas Papadopoulos,[1] Bert Vogelstein,[1]† Kenneth W. Kinzler,[1]† Victor E. Velculescu[1]†

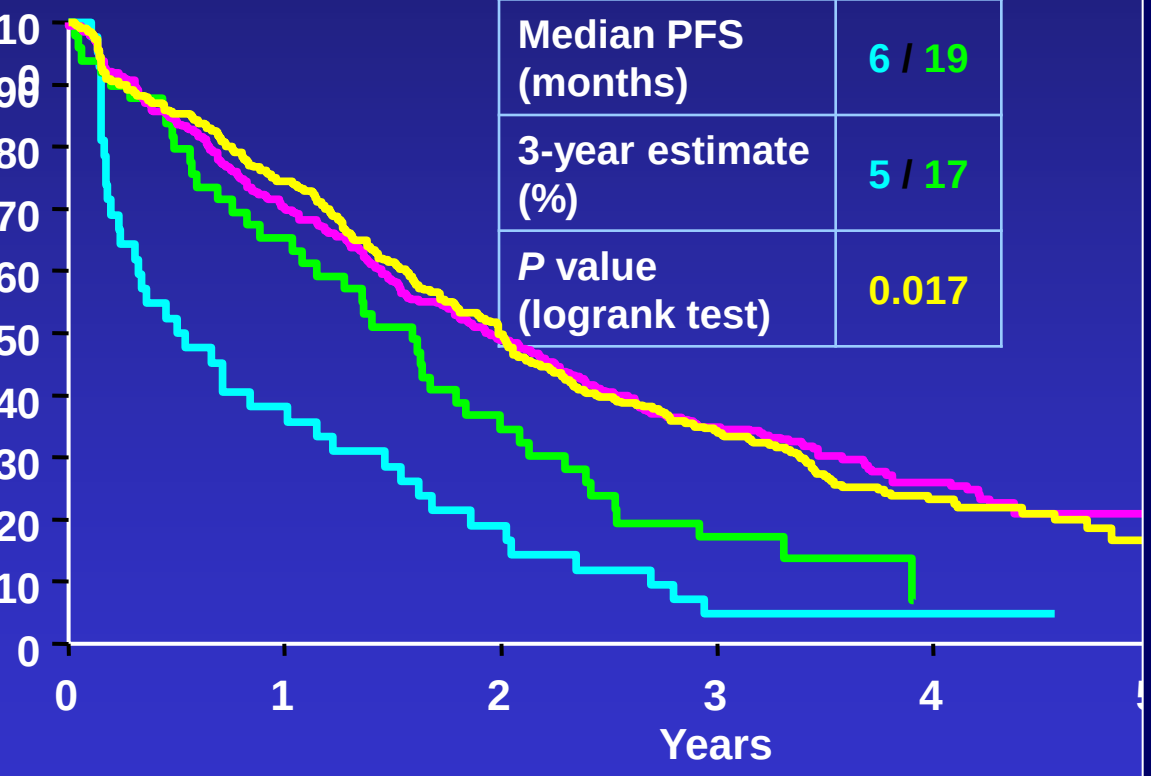
- Breast or colon carcinoma: cell lines oru xenografts (n=22)
- 13023 genes sequenced, 3 millions PCR, 452 MB
- otal : n=90 mutated genes per cell lines
- Identification of n=189 significant genes
- Mean: n=11 (total genome n=14 à 20)
- Transcription, adhesion, invasion
- CANdidates CANcer (CAN) genes
  - « Expected »: p53, KRAS, APC, MRE11…
  - Oncogenes for other tissues : MLL3, EPHB6..
  - Unexpected: PKHD1, tubuline tyr ligase TTLL3
- CAN genes C. du sein ≠ C. colorectal


WNT
Frizzled
Disheveled
GSK-3β
APC
TCF
β-Catenin
β-Catenin:TCF
Cells
E-Cadherin
ECM
Integrins
CdC42
P13K
Rac
FAK
Src
Cas
Crk
Fyn
Shc
PLC
PKC
NF1
Mos
MKKs
JNKs
Jun
Growth Factors
(e.g. TGFα)
RTK
Grb2
SOS
Ras
Raf
MEK
MAPK
MAPK
EIK
Fos
Mad:Max
Myc:Max
MEKK
Abl
CdC42
Rac
Rho
Hormones
(e.g. Bombesin)
7-TMR
G-Prot
Ad Cycl
PKA
CREB
(e.g. Estrogen)
NHR (e.g. ER)
Survival Factors
(e.g. IGF1)
RTK
?
PKC
NF-κB
NF-κB
P13K
Akt
Akkα
IκB
PTEN
Stat 3,5
Stat 3,5
Jaks
Cytokine R
Cytokines
(e.g. IL-3/6)
Anti-growth factors
(e.g. TGFβ)
TGFβR
Smads
p16
Cycl D:CDK4
p15
Rb
HPV E7
E2Fs
p27
Cycl E:CDK2
p21
DNA damage
sensor
Changes
in Gene
Expression
Cell
Proliferation
(Cell Cycle)
p53
ARF
MDM2
Bax
Mitochondria
Stat 3,5
Cell Death
(Apoptosis)
Bcl 2
Caspase 8
FADD
Caspase 9
FAP
Fas
Cytochrome C
Decoy R
Stat 3,5
Bcl XL
Bcl 2
Bad
Mitochondria
Bid
Death
Factors
(e.g. FasL)
Abnormality
sensor
Bim, etc

Treatment of cancer needs genomics

GIST are at least 10 diseases

***KIT* exon 9 mutants (10% of patients)**



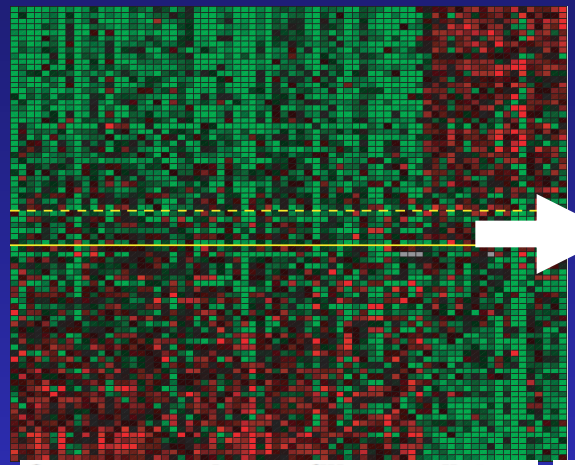
Median PFS (months)	6 / 19
3-year estimate (%)	5 / 17
P value (logrank test)	0.017

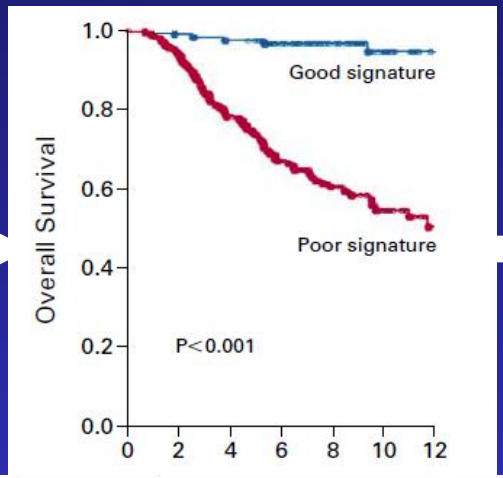
***KIT* exon 9 mutants: 400 mg / 800 mg**
Other patients: 400 mg / 800 mg

	Dose	Adjuvant
KIT Exon 11	Im 400	+
KIT exon 9	Im 800	+
PDGFRA		
Non D842V	Im 400	+
D842V:	0	0
KIT/PDGFR WT	Im 400	+/?
NF1	?/Im 400	+/?
SDHB	?/Im 400	+/?
Raf	?	?
Pediatric	?	?

Rapid complexification of the molecular informations

- Gene expression profile





Gene expression profiling predicts clinical outcome of breast cancer

Laura J. van 't Veer*†, Hongyue Dai†‡, Marc J. van de Vijver*†, Yudong D. He‡, Augustinus A. M. Hart*, Mao Mao‡, Hans L. Peterse*, Karin van der Kooy*, Matthew J. Marton‡, Anke T. Witteveen*, George J. Schreiber‡, Ron M. Kerkhoven*, Chris Roberts‡, Peter S. Linsley‡, René Bernards* & Stephen H. Friend‡

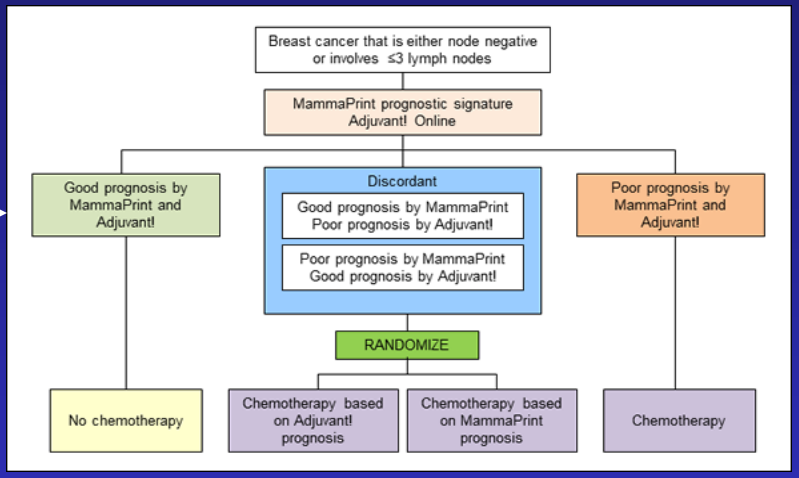
NATURE | VOL 415 | 31 JANUARY 2002

VOLUME 347 DECEMBER 19, 2002 NUMBER 25

A GENE-EXPRESSION SIGNATURE AS A PREDICTOR OF SURVIVAL IN BREAST CANCER

Marc J. van de Vijver, M.D., Ph.D., Yudong D. He, Ph.D., Laura J. van 't Veer, Ph.D., Hongyue Dai, Ph.D., Augustinus A.M. Hart, M.Sc., Dorien W. Voskuil, Ph.D., George J. Schreiber, M.Sc., Johannes L. Peterse, M.D., Chris Roberts, Ph.D., Matthew J. Marton, Ph.D., Mark Parrish, Douwe Atsma, Anke Witteveen, Annuska Glas, Ph.D., Leonie Delahaye, Tony van der Velde, Harry Bartelink, M.D., Ph.D., Sjoerd Rodenhuis, M.D., Ph.D., Emiel T. Rutgers, M.D., Ph.D., Stephen H. Friend, M.D., Ph.D., and René Bernards, Ph.D.

Mindact EORTC 10041



Prediction of cancer outcome with microarrays: a multiple random validation strategy

Stefan Michiels, Serge Koscielny, Catherine Hill

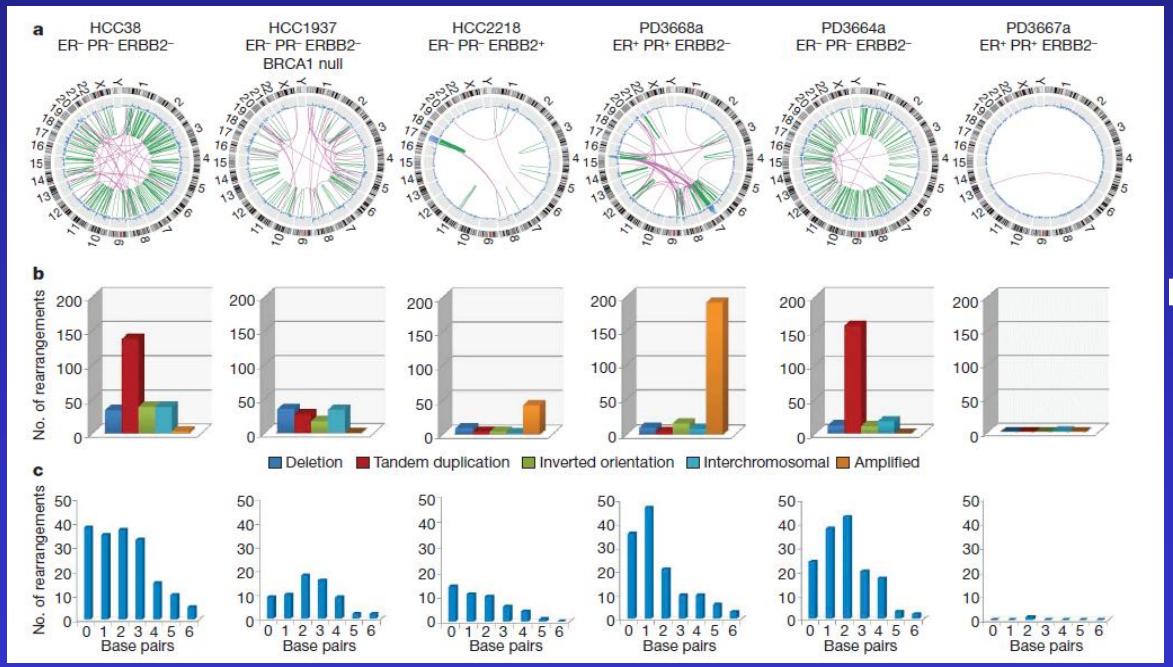
Lancet 2005; 365: 488–92

Rapid complexification of the molecular informations

Complex landscapes of somatic rearrangement in human breast cancer genomes

Philip J. Stephens[1], David J. McBride[1], Meng-Lay Lin[1], Ignacio Varela[1], Erin D. Pleasance[1], Jared T. Simpson[1], Lucy A. Stebbings[1], Catherine Leroy[1], Sarah Edkins[1], Laura J. Mudie[1], Chris D. Greenman[1], Mingming Jia[1], Calli Latimer[1], Jon W. Teague[1], King Wai Lau[1], John Burton[1], Michael A. Quail[1], Harold Swerdlow[1], Carol Churcher[1], Rachael Natrajan[2], Anieta M. Sieuwerts[3], John W. M. Martens[3], Daniel P. Silver[4], Anita Langerød[5], Hege E. G. Russnes[5], John A. Foekens[3], Jorge S. Reis-Filho[2], Laura van 't Veer[6], Andrea L. Richardson[4,7], Anne-Lise Børresen-Dale[5,8], Peter J. Campbell[1], P. Andrew Futreal[1] & Michael R. Stratton[1,9]

Vol 462|24/31 December 2009|doi:10.1038/nature08645



Which subset? Which target? Which agents?

Scientific challenges

The environment of the cancer cell

- uPA/PAI1

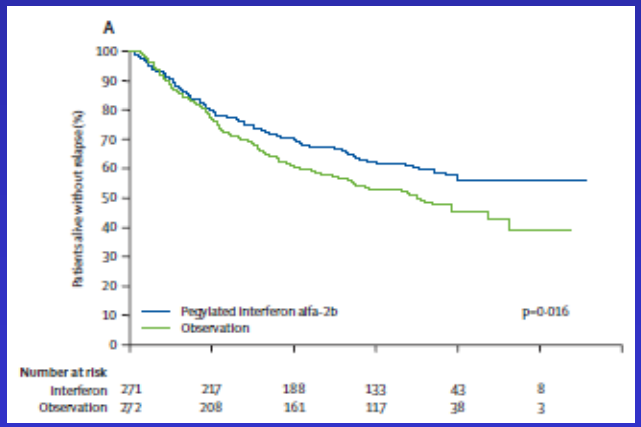
TUMOR-ASSOCIATED PROTEOLYTIC FACTORS uPA AND PAI-1: Critical Appraisal of Their Clinical Relevance in Breast Cancer and Their Integration into Decision-Support Algorithms

Nadia Harbeck, Manfred Schmitt, and Stefan Paepke

Critical Reviews in Clinical Laboratory Sciences, 44(2):179–201 (2007)

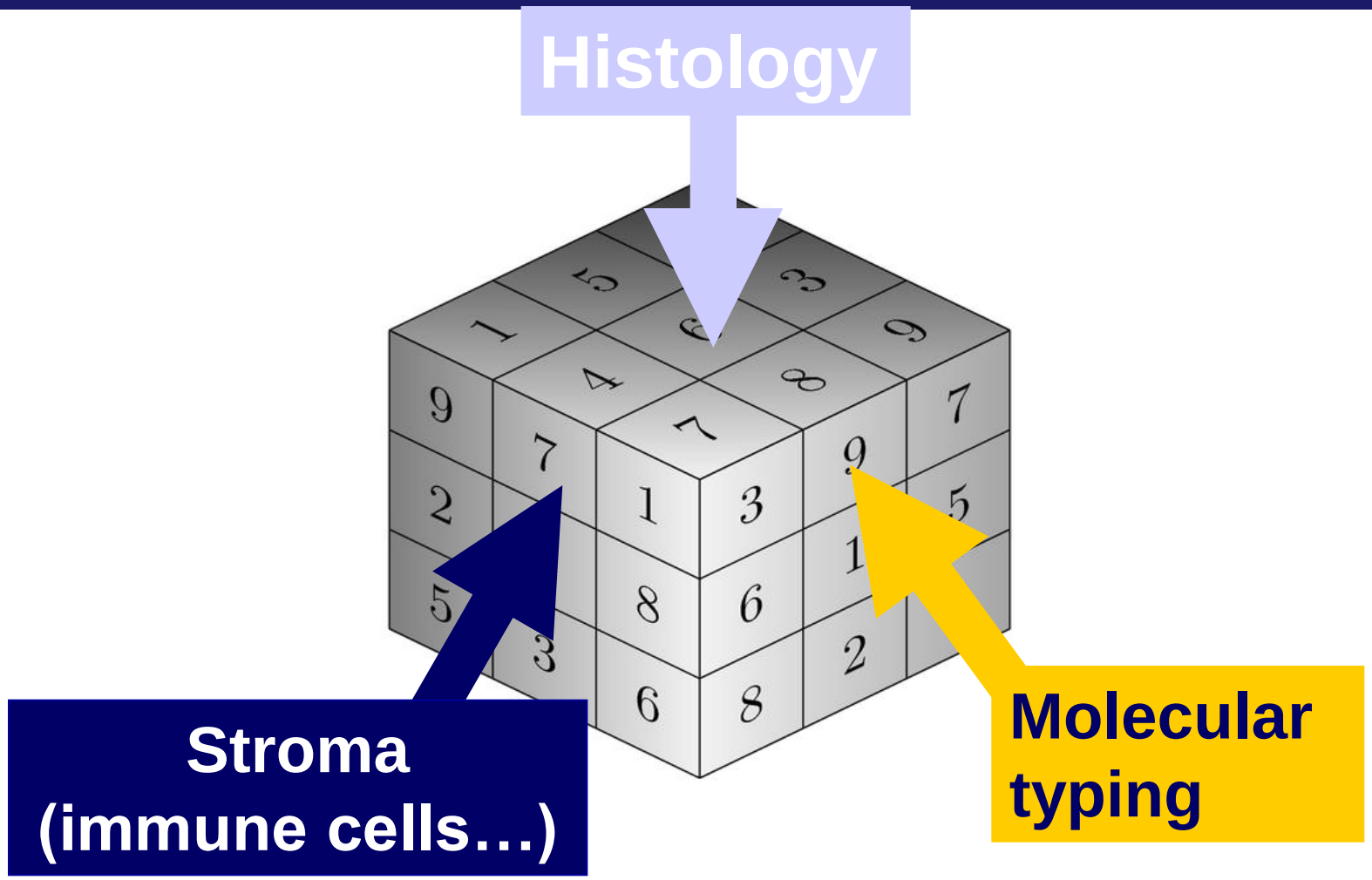
- Immune effectors

18991: Interferon

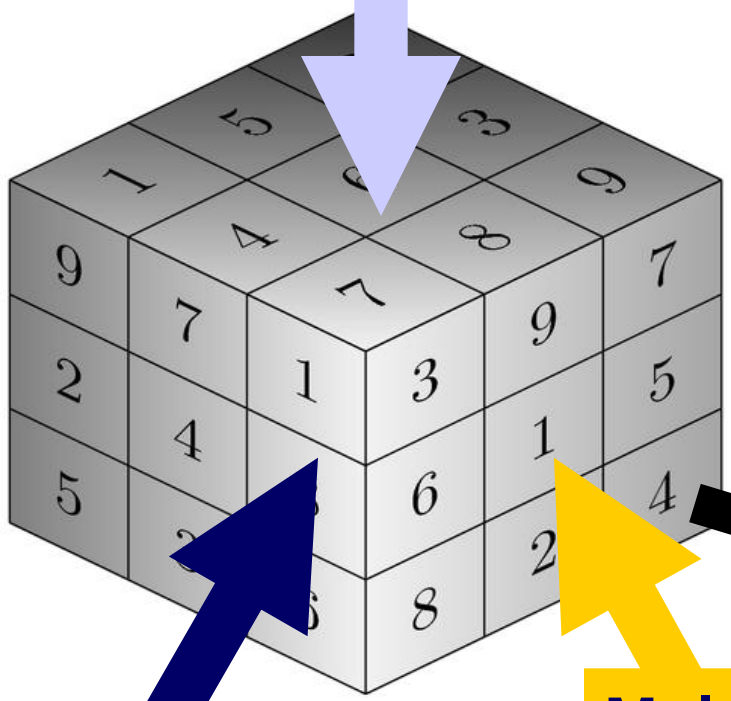


18071 Adjuvant ipilimumab

A new vision of the disease

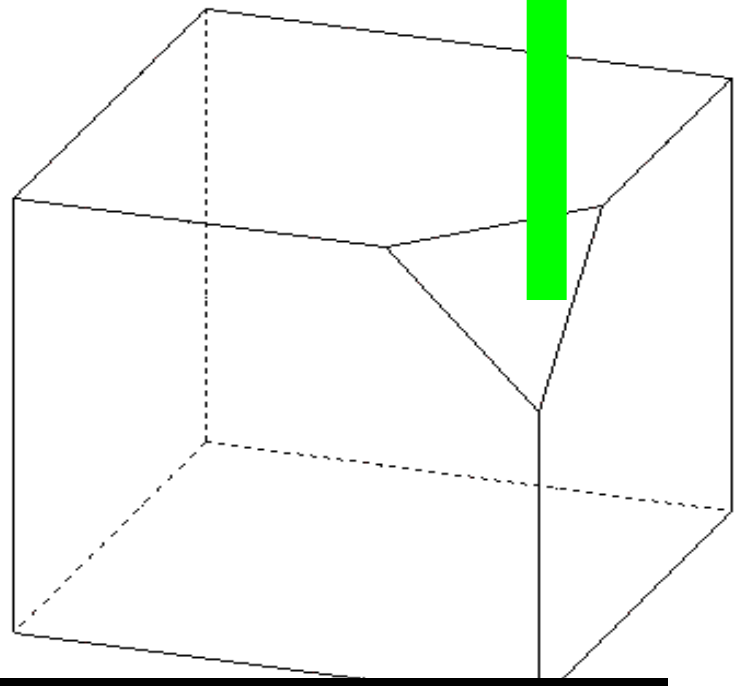


A new vision of the disease



Histology

Trials on subsets of histotypes



Stroma (immune cells …)

Molecular typing

Trials on genotype? e.g. CREATE

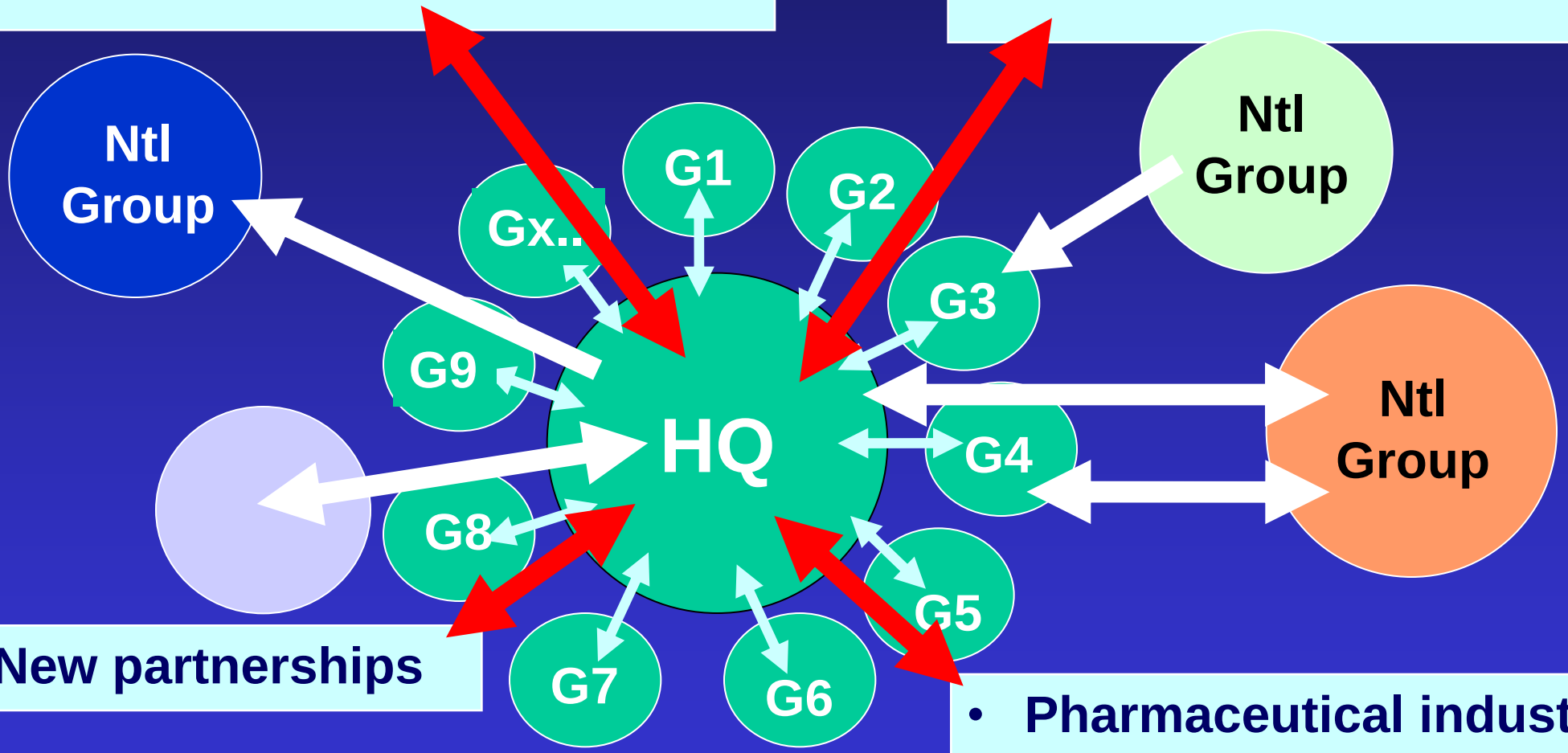
Issues

- Recogition
- Fragmentation
- Solutions

Reinforcing interactions

- New academic partners
- Novel models of collaboration

- Cancer Leagues
- Patient advocacy groups



- New partnerships

- Pharmaceutical industry

Tumor banking and registries

- Tumor banks
- Facilitating the donation of tumor tissues across countries
  - Less specific informed consent
  - useful for advancing science
  - Economic value (competition with Far east)
- Prospective clinical data bases and registries
- Collaborative networks focusing on health care
  - properly funded for quality of care reasons,
- Observational clinical studies on selected patient subgroups
  - tailored to answer specific open questions
  - value of retrospective and observational research
  - research resource allocation decisions.

EORTC CRC Screening platform

Tumor blocks screened for mutations / expression

ras/raf wt, high ligands	1 st line Phase II trial: EGFR monotherapy	treatment outside EORTC trials	treatment outside EORTC trials
MSI	treatment outside EORTC trials	Trial X and chemotherapy	Phase I with X and Y
b-raf mut	b-raf inhibitor and chemotherapy	treatment outside EORTC trials	treatment outside EORTC trials
k-ras mut	treatment outside EORTC trials	MEK-inhibitor (?) + chemotherapy	treatment outside EORTC trials
k-ras mut	treatment outside EORTC trials		treatment outside EORTC trials
PI3KCAmut	Chemotherapy and antibody W	treatment outside EORTC trials	Phase I with A and B
xxx	treatment outside EORTC trials	Phase II with new chemotherapy	
xxx	No Chemotherapy Inhibitor X and imaging	treatment outside EORTC trials	treatment outside EORTC trials
xxx	treatment outside EORTC trials	treatment outside EORTC trials	Phase I with Drug F
xxx	treatment outside EORTC trials	treatment outside EORTC trials	treatment outside EORTC trials

EORTC Clinical Trials

“Rational treatments to right patients”

Menu

- Home
- Charter
- Survey
- Export
- Patient
- Audit
- Online Help

Welcome to conticabase

The CONTICANET database and tumour bank

This database contains anonymised information describing the tumour, treatment and follow-up as well as tumour sample availability and molecular biology analyses for mesenchymal tumours except GIST and bone tumours.

The tool can be used as a local center database thanks to its **rules for access to patient data and material**. It will be maintained and updated centrally. Please follow this **this link** to fill the account application form

The query tool allows users to ask questions about the overall content of the database in order to evaluate the feasibility of specific collaborative studies.

We hope this database will become an important tool for increasing our knowledge on these rare tumours and for developing joint research programmes.

Website requirements

This website has been designed for both **Firefox 3** (advised) and **Internet Explorer 7** (or older versions). Please note that some features may not work correctly with other web browsers.

Content overview

conticabase currently contains the following data from **26** out of the **43** registered centres :

- **4804** Patients
- **4826** Tumours
- **5699** Samples (**5493** Paraffins and **2600** Frozens)

Networks and PAGs

- Health care Networks
- Reference centers, within quality control programs. They improve health care and they improve accrual in trials as well as clinical quality within clinical trials.
- Patient information about trials (what they are, where they are available). There is even a greater added value for the today patient in entering a trial.

How can YOU help?

Sign our petition NOW...

...and ask FRIENDS, COLLEAGUES and CONTACTS...

...to support this initiative by SIGNING UP too!

The European Action Against Rare Cancers is a joint initiative based on a partnership between the European Society for Medical Oncology (ESMO), the European Organisation for Rare Diseases (Eurordis), the European Cancer Patient Coalition (ECPC), Conticanet, the Association of European Cancer Leagues (ECL), the Chronic Myeloid Leukaemia Support Group, the International Brain Tumour Alliance (IBTA), Orphanet, the Chronic Myeloid Leukaemia Advocates Network, the European Institute of Oncology (EIO) and the Fondazione IRCCS Istituto Nazionale dei Tumori, as well as Novartis Oncology as the founding sponsor.

The organisations collaborate as equal partners and all decisions are made on the basis of consensus. The initiative is moreover supported by eight corporate organisations.

For more information about this European initiative, please visit our Web site:
www.rarecancers.eu

or contact us:
European Action Against Rare Cancers
c/o Robert Schaefer

Brunnenstrasse 179/179
10119 Berlin, Germany
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Collaborating Partners:

ESMO · EURORDIS · IBTA · European Cancer Patient Coalition · Conticanet · ECL · orphanet · NOVARTIS ONCOLOGY · IEO · Fondazione IRCCS Istituto Nazionale dei Tumori

Initiating Sponsors:

AMGEN · ALEXION · MSD ONCOLOGY · Bristol-Myers Squibb · Celgene · NOVARTIS ONCOLOGY · Pfizer Oncology · EUROPABIO · Pharma Mar

RARE CANCERS: MORE COMMON THAN YOU THINK!

☑ Sign the call to
ACTION AGAINST RARE CANCERS

www.rarecancers.eu

European Action Against Rare Cancers

18 SPAEN Full Members

Das Lebenshaus
GIST-GRUPPE SCHWEIZ
GROUPE GIST SUISSE

sos desmoid

SOS DESMOÏDE

Das Lebenshaus

A.I.G.
Associazione Italiana GIST

ASSOCIAZIONE
Paola
PER I TUMORI MUSCOLO-SCHELETRICI Onlus

Sarcoma UK

GIST

gist support uk

Ensemble contre le GIST

Info Sarcomes
Ensemble contre les Sarcomes

Contactgroep GIST
Nederland - Belgie

Luogo di incontro per scambiarsi informazioni
sul tumore Desmoide o Fibromatosi aggressiva

Sarcoma

SUOMEN
SYÖPÄPOTILAAT

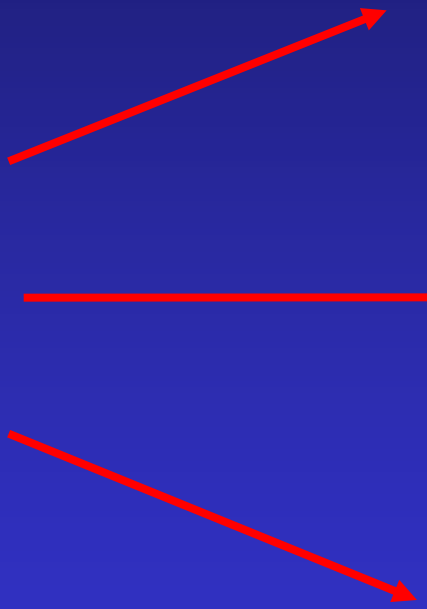
Pharma and academic trials

- Share the results across trials including with industry sponsored trials.
- Collaboration across companies
  - Comparing drugs in tumors with unmet needs
  - Combining drugs
- Large multisources Databases, Registries
  - Funding issues

How to improve collaboration ?

Centres

National
European
Worldwide



Phase II, not so rare subtypes

Phase III - not so rare subtypes

Phase II super rare subtypes

Incentives for clinical trials

- Incentives for orphan drugs devpt for pharma companies
- Drug supply by pharma to academics before any approval?
- Screen rare tumors in Phase 1 setting
  - based on molecular screening ?
- A need framework study protocols on specific rare cancers liable to be sequentially exploited for different drugs ?

Enrich clinical trials

- Enrich the informations collected from Rare cancer trials need to be richer in information in order to maximize their efficiency, e.g. a long follow up for each patient

Collaborations

- In rare cancers, national, international, even global collaborations should be pursued to make investigator-driven studies possible.
- Clinical Trial Directive is currently under revision. It is recommended that it is improved in some crucial aspects.
- Sponsorship of international trials for investigator-driven studies are sponsored by academic institutions, collaborative groups,
  - difficult to comply with regulations which differ from country to country,

A World Sarcoma Network is needed

Conticanet

AUSTRALASIAN SARCOMA STUDY GROUP

GSF GETO Groupe Sarcome Français Groupe d'Etude des Tumeurs Osseuses

EORTC European Organisation for Research and Treatment of Cancer

SARC Sarcoma Alliance for Research through Collaboration *Collaborating for a Cure.*

GISG German Interdisciplinary Sarcoma Group

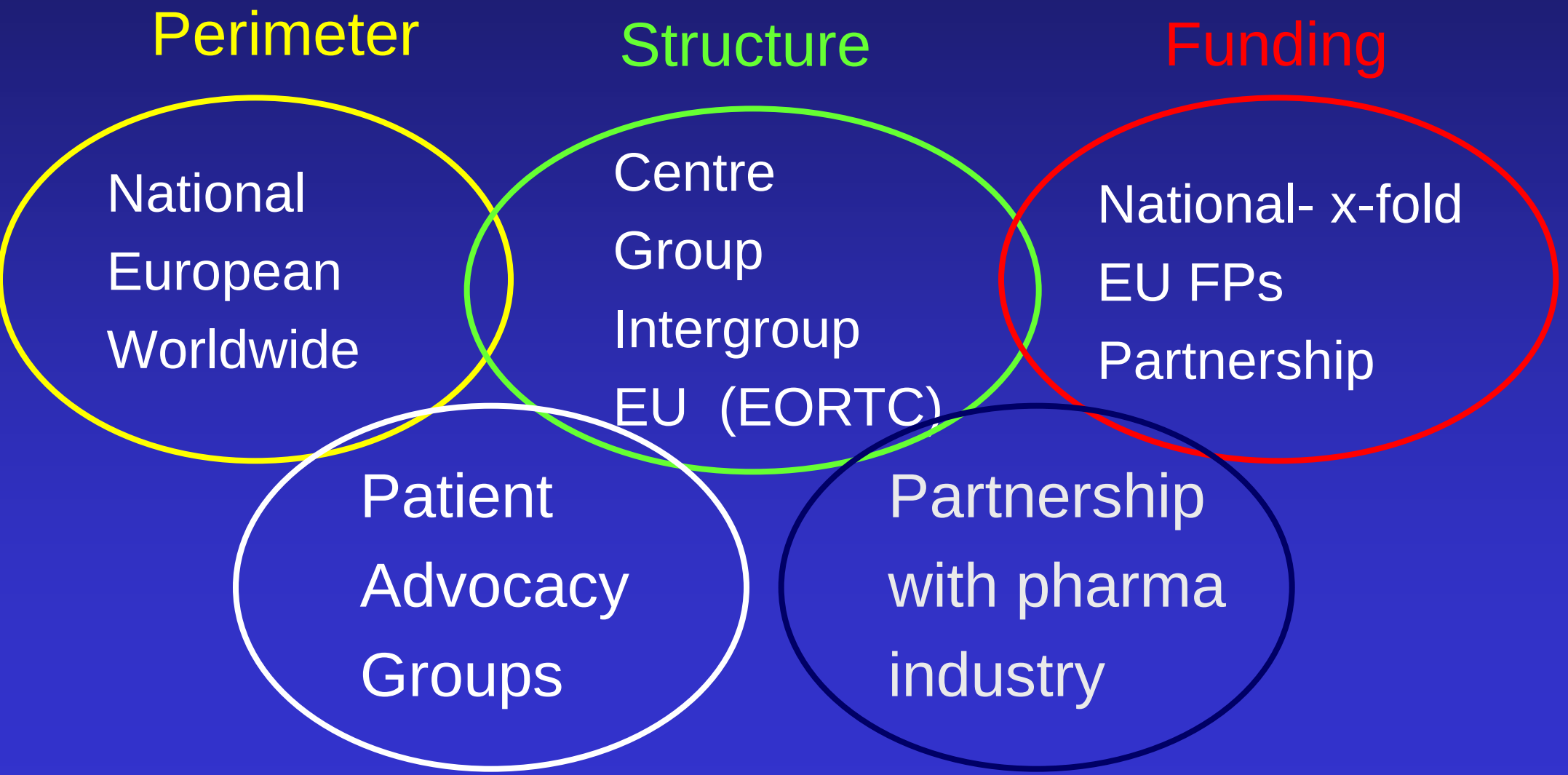
EuroBoNeT

The World Sarcoma Network (2009)

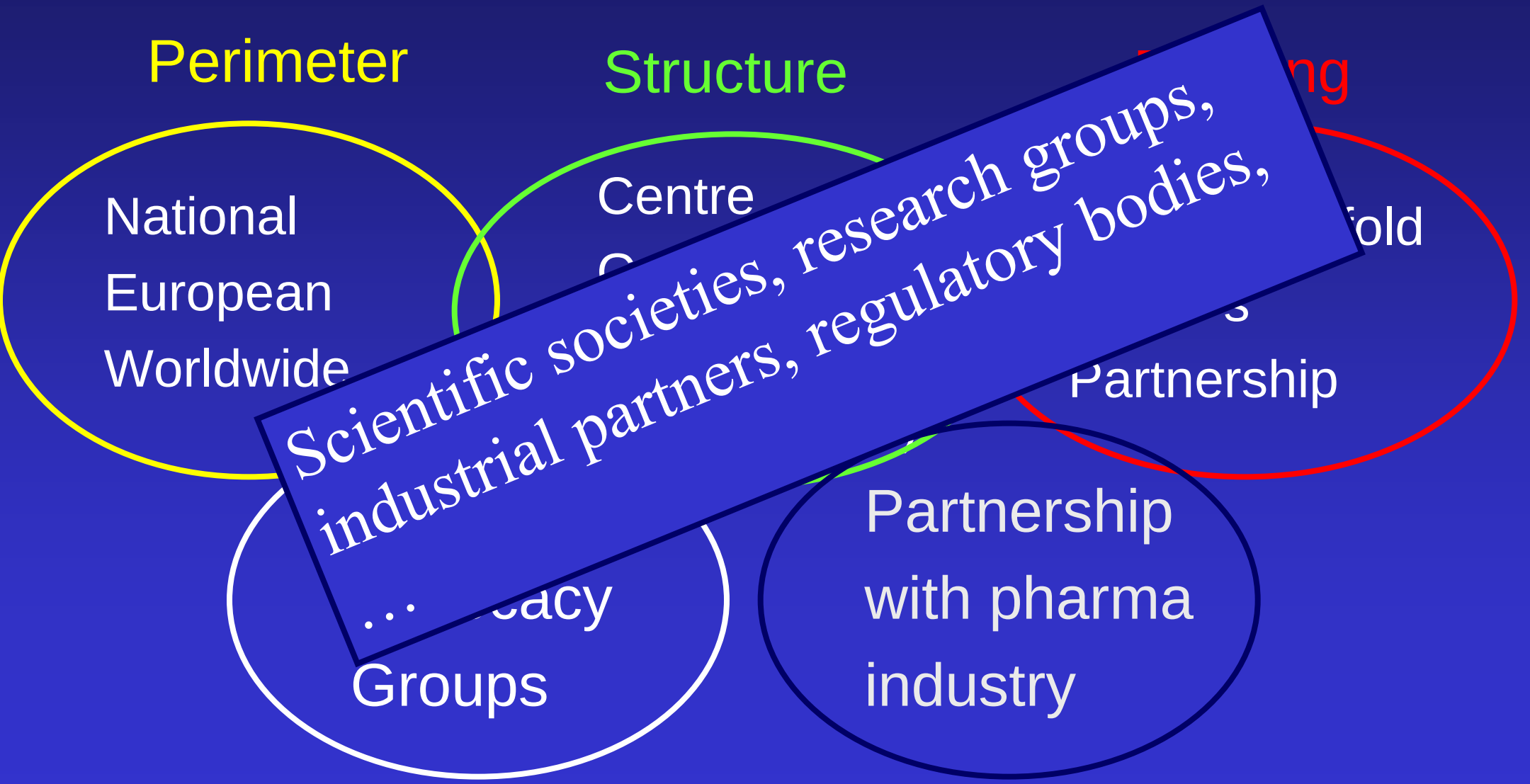
Studies pipeline

- nilotinib in PVNS with t(1,2) M-CSF-col6A3 fusion gene
- mTOR inhibitors in PEComas, and in tumours of the TSC complex
- Aplidin in Dedifferenciated Liposarcomas with JUNK overexpression
- Alk inhibitors in inflammatory myofibroblastic tumours with Alk amplification and over expression
- IGF1R inhibitors in GIST with IGF1R over-expression and amplification
- MDM2 inhibitors (nutlin3a) in WDLPS with MDM2 amplification
- MET inhibitors in sarcomas with translocation involving fusion genes encoding for abnormal transcription factors (ASPS, CCS)
- VEGFR2 inhibitors in ASPS

How to improve collaboration ?



How to improve collaboration ?



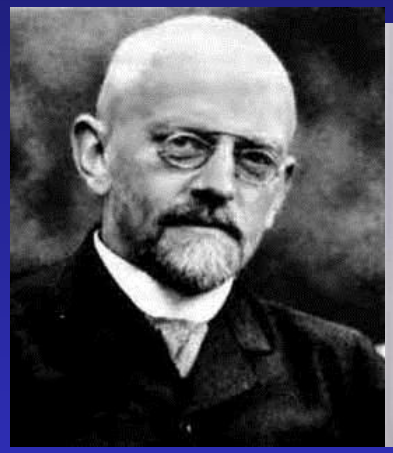
Regulatory aspects

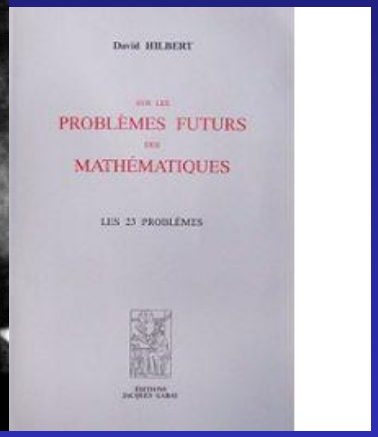
- Regular consultations between regulatory bodies, pharma, academia, scientifc societies-ESMO, and PAGs
- Simplify and streamline the access to compassionate use programs

To address major scientific questions

Oncology research … a « hard science » with multidimensional complexity

1900





17/23 solved

2000

1/7 solved

Questions for the next 20 years

Some are organisational

1. Is it possible to organize the health care systems to ensure optimal local treatments, surgery and radiotherapy, for all patients?

2. How to build simple academic clinical trials?

3. Is it possible to organize annotated multinational tumor collection and storage to enable clinical research on molecular subtypes?

4. How can we integrate the volume of molecular information generated to the routine care of the patient?

5. Can health care systems absorb the cost of targeted treatments?

Questions for the next 20 years

Some are scientific

6. How to recognize the driving mutations in individual patients to guide the treatment?
7. How to generate algorithms with tumors+ constitutional genomics+patients info to guide treatment decisions?
8. Does adjuvant treatment with targeted therapies prevent or postpone relapse?
9. Can we define better surrogate markers for overall survival?

Questions for the next 20 years

10. Is resistance to targeted treatment unavoidable in advanced phase?
11. What are the paradigms of combination or sequential treatment to prevent resistance?
12. Can surgical removal of the metastatic burden reduce the risk of emergence of clonal and clinical resistance?
13. Can immunotherapy cure minimal residual disease in man?
14. Is it possible to generate models on when to stop specific treatment?

Conclusions

Improving clinical research on rare cancers

- Recognition : improved through education and networking
- Management : poor to be improved with reference center
- Fragmentation : ineluctable- an opportunity
- Solutions : collaboration, interactions