# ERCC-1 and response to chemotherapy

**Jean-Charles SORIA, MD, PhD**

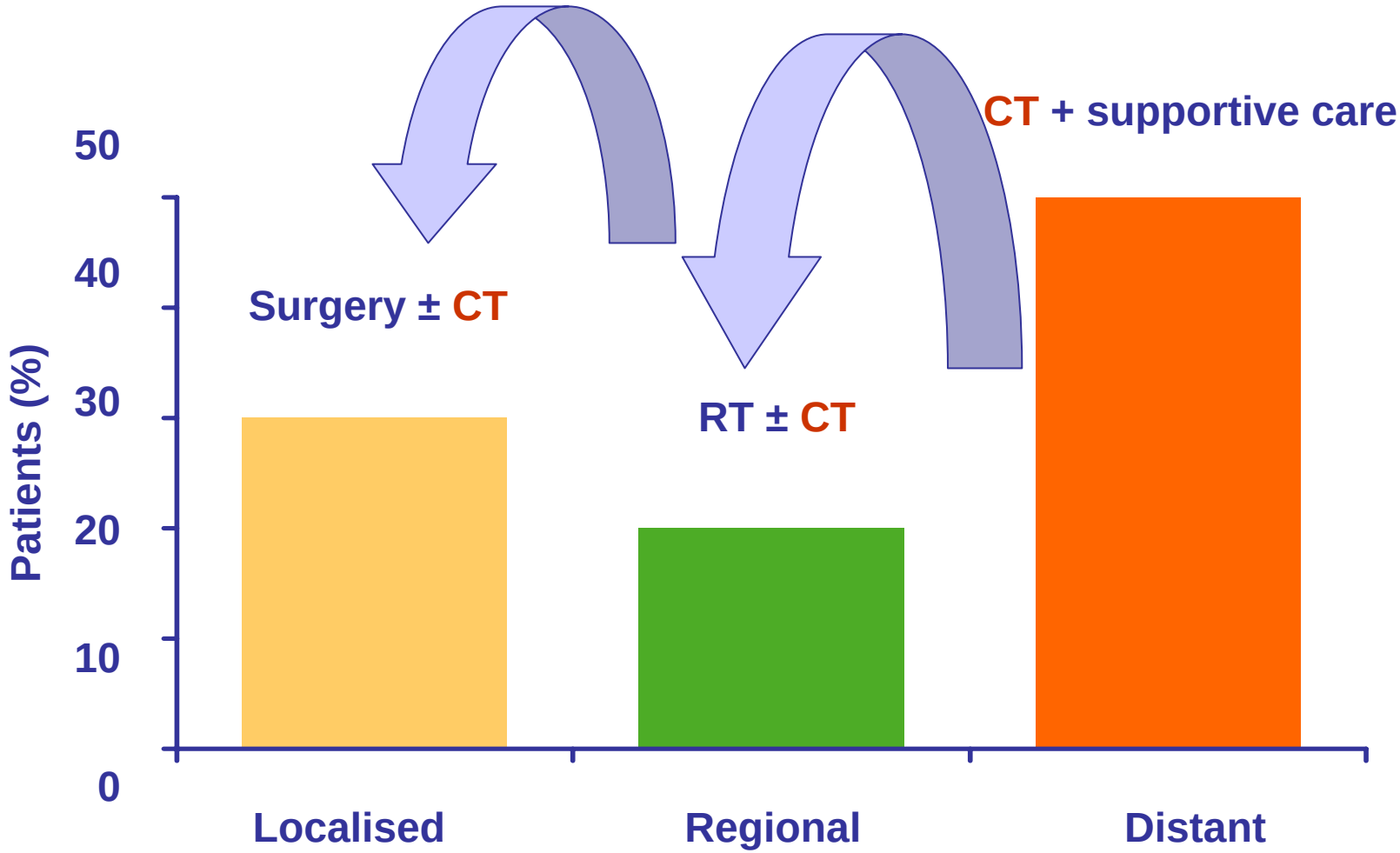
**Institut Gustave Roussy**

UNIVERSITÉ PARIS-SUD 11

Institut de cancérologie GUSTAVE ROUSSY VILLEJUIF - www.igr.fr

# Cancer and Chemotherapy: the exemple of Lung Cancer

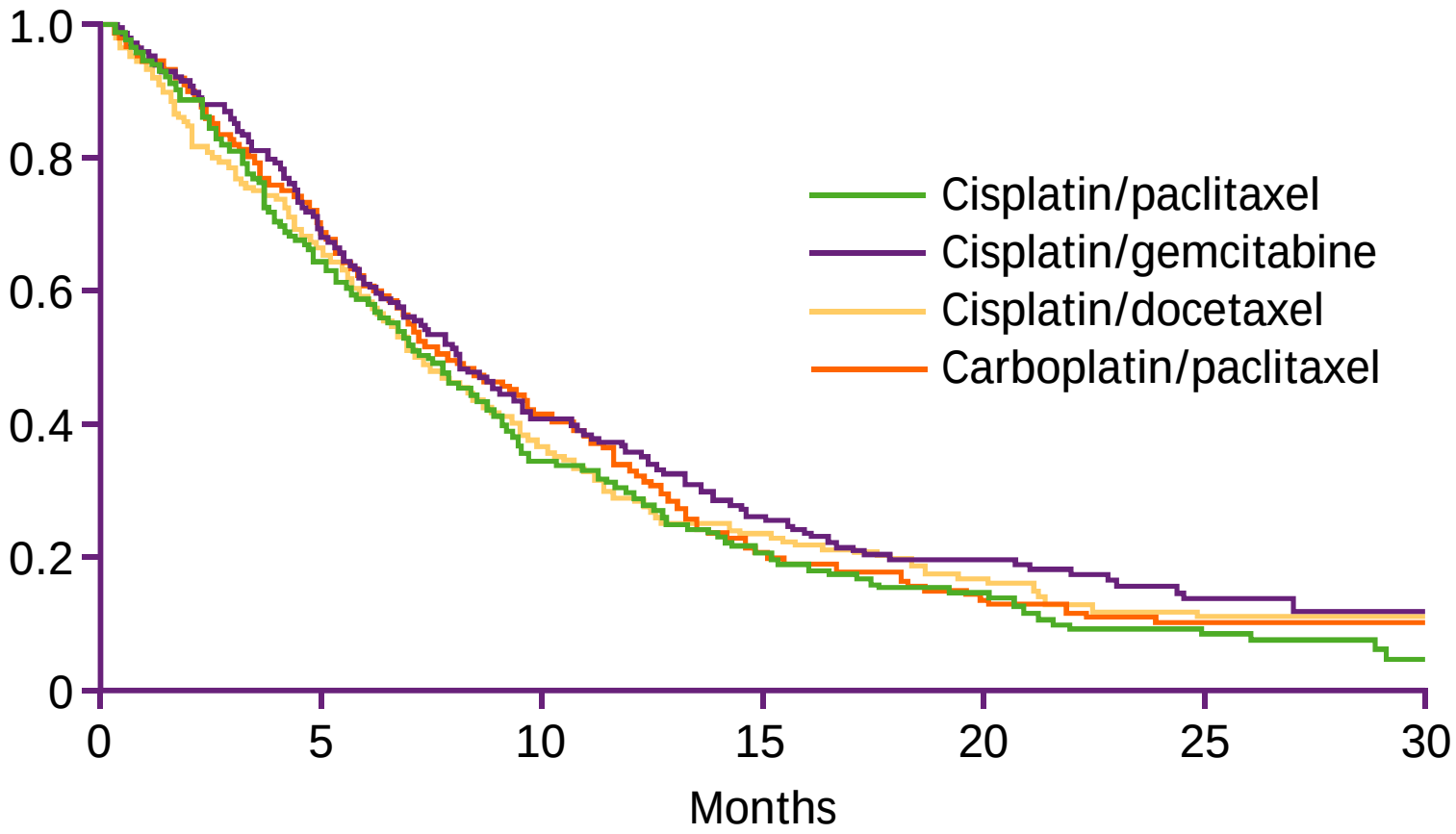





RT = radiotherapy
CT = chemotherapy

# Platin-based chemotherapy is the mainstay of first-line treatment for NSCLC

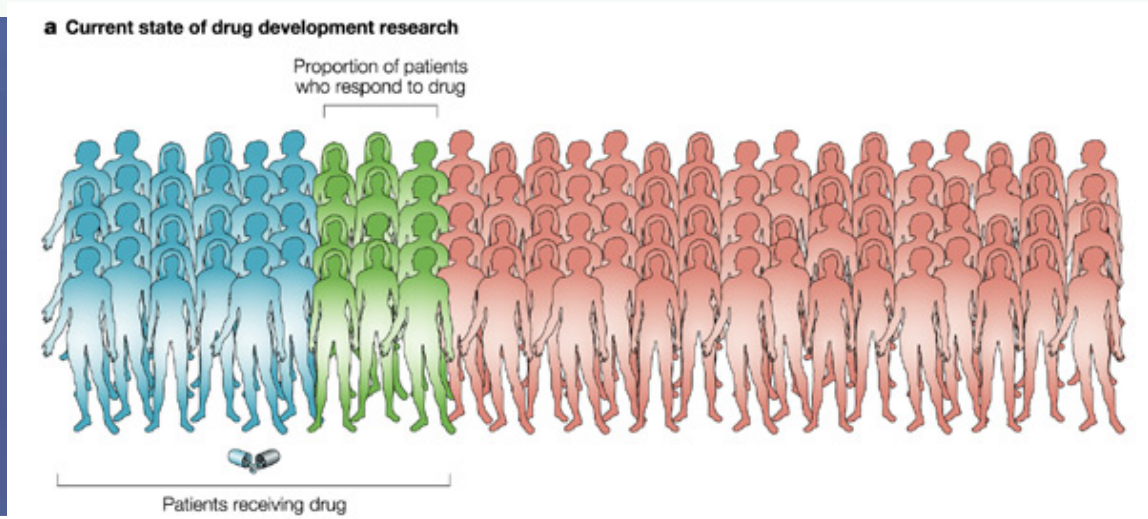





Schiller JH, et. al. N Engl J Med 2002;346:92–8

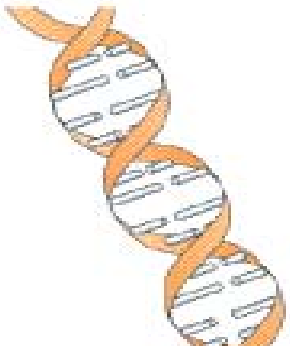
# Getting the right drug into the right patient

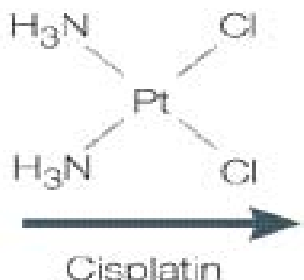
**Pharmacogenomics will help explain why drugs work better in some patients than in others. It also presents numerous commercial opportunities for both startups and established biotechnology companies.**

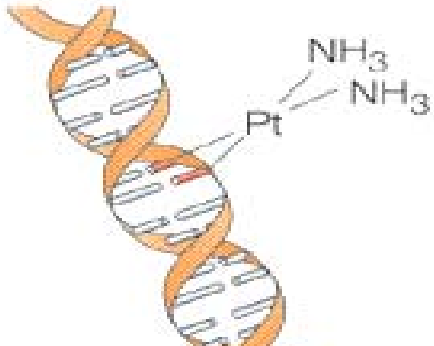


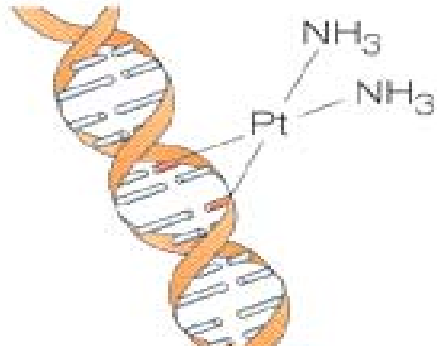

# Platinum derivatives and DNA repair pathway

- Platinum cytotoxic effects are related to DNA binding and DNA adducts
- Nucleotide excision repair (NER) plays a central role in DNA repair pathways
- ERCC1 enzyme plays a rate-limiting role in the NER pathway
- *In vitro* and clinical studies suggest a relation between ERCC1 mRNA and response to cisplatin

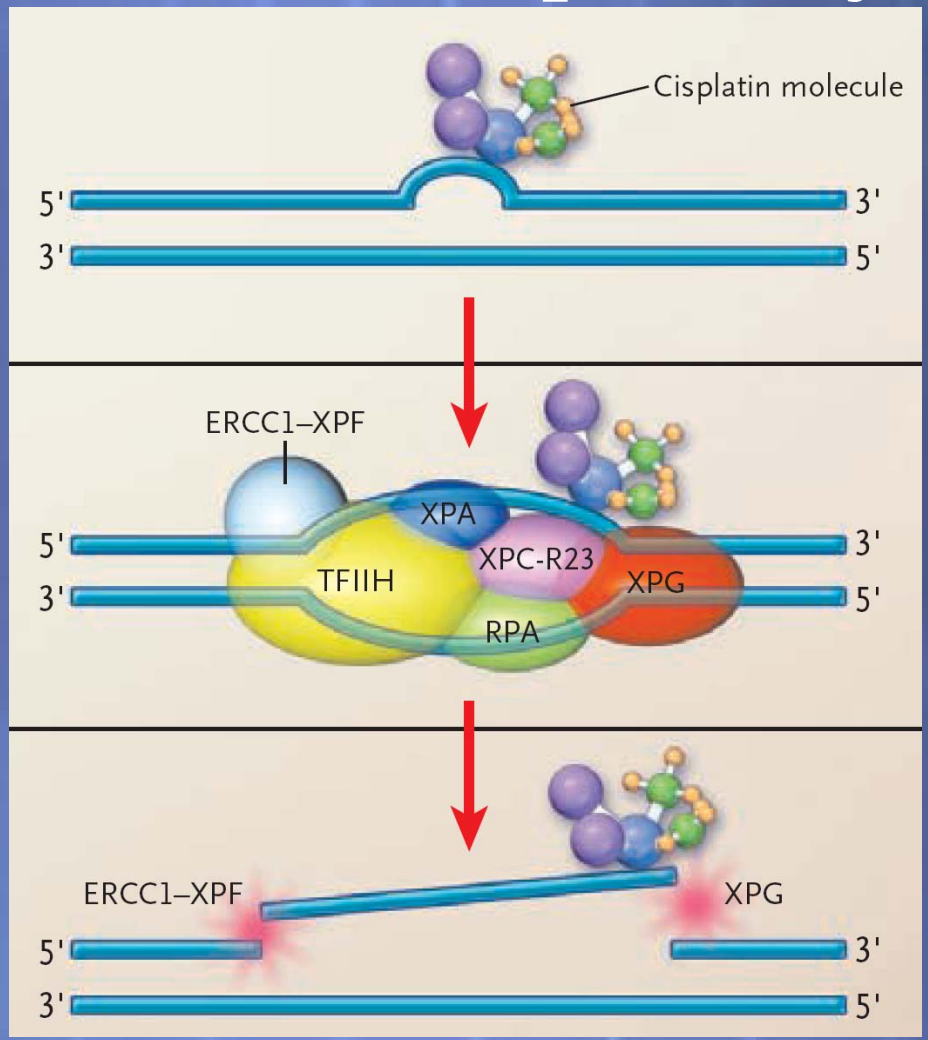




# ERCC1 is a rate-limiting partner in the NER pathway




Gazdar et al, New England J Med 2007

# Platinum resistance in vitro

- ERCC1 mRNA or protein expression levels correlate with cisplatin resistance in human cancer cell lines

| Cancer cell lines | ERCC1 expression | Phenotypic effets |
|---|---|---|
| ovarian | mRNA (3-fold ↑) | Cisplatine resistance |
| ovarian | mRNA and protein (2-fold ↓) | ↓ Repair of cisplatin-DNA adducts |
| ovarian | ERCC1 anti-sense mRNA | Restored sensitivity to cisplatine |
| ovarian | ERCC1 SiRNA | ↑ > 53-fold in cisplatin sensitivity |
| cervical | mRNA | Positively correlated with oxaloplatine resistance |
| testis | protein | Low levels of ERCC1 compared with other cell lines |
| lung | ERCC1 anti-sense mRNA | Decreased the repair capacity |

Gossage et al, Cancer Treat Rev. 2007

# ERCC1 as a predictive and/or prognostic marker in human cancers

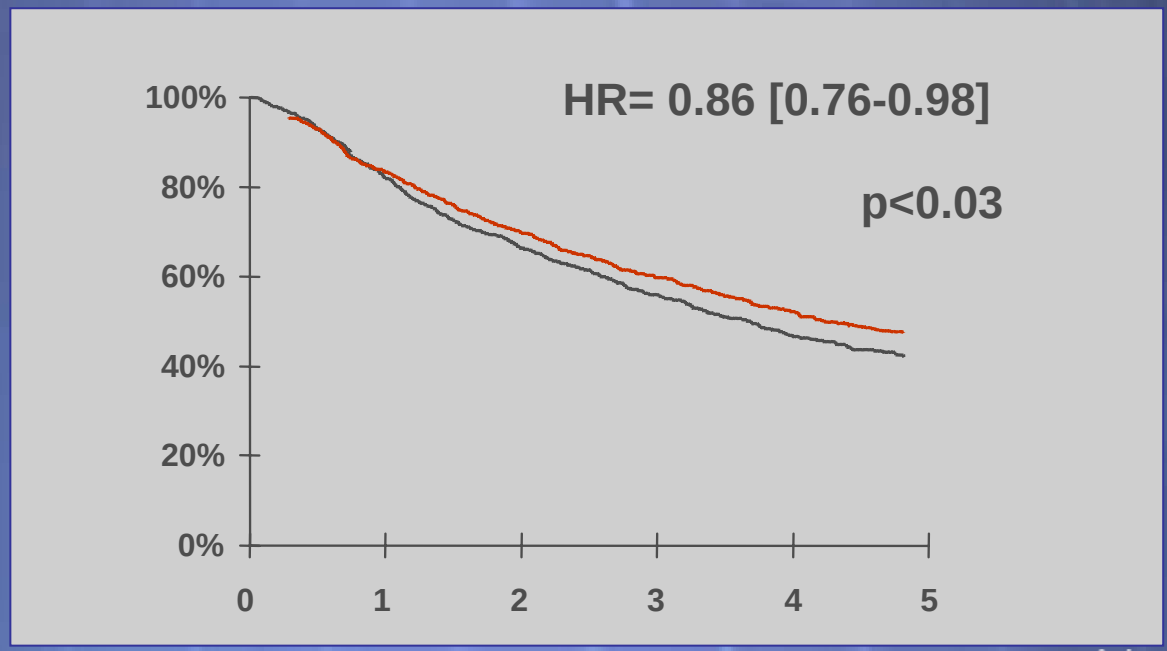


| Cancer type | Number of patients | Treatment | ERCC1 expression |
|---|---|---|---|
| Resected NSCLC | 761 | Adjuvant cisplatin-based therapy | Protein |
| Resected NSCLC | 51 | Majority received no chemotherapy | mRNA |
| Advanced NSCLC | 70 | G(gemcitabine)/C or C(cisplatin) | mRNA |
| Advanced NSCLC | >400 | Randomized to D/C, or D/C if ↓ ERCC1 or D/C if↑ ERCC1 | mRNA |
| Advanced NSCLC | 56 | G/C | mRNA |
| Advanced colorectal cancer | 50 | 5FU/oxaliplatin | mRNA |
| Advanced colorectal cancer | 33 | Irinotecan | mRNA |
| Advanced gastric cancer | 64 | Oxaliplatin/5FU | Protein |
| Operable gastric cancer | 38 | Neoadjuvant C(/F | mRNA |
| Oesophageal cancer | 99 | Neoadjuvant CRT(chemoradiotherapy) (C/F) | mRNA |
| Oesophageal cancer | 36 | Neoadjuvant CRT (C/F) | mRNA |
| Ovarian cancer | 26 | Platinum based therapy | mRNA |
| Ovarian cancer | 28 | Platinum based therapy | mRNA |
| Advanced bladder cancer | 57 | G/C or G/C/P | mRNA |

Gossage et al, Cancer Treat Rev. 2007

# ASCO 2003:
# International Adjuvant Lung Trial

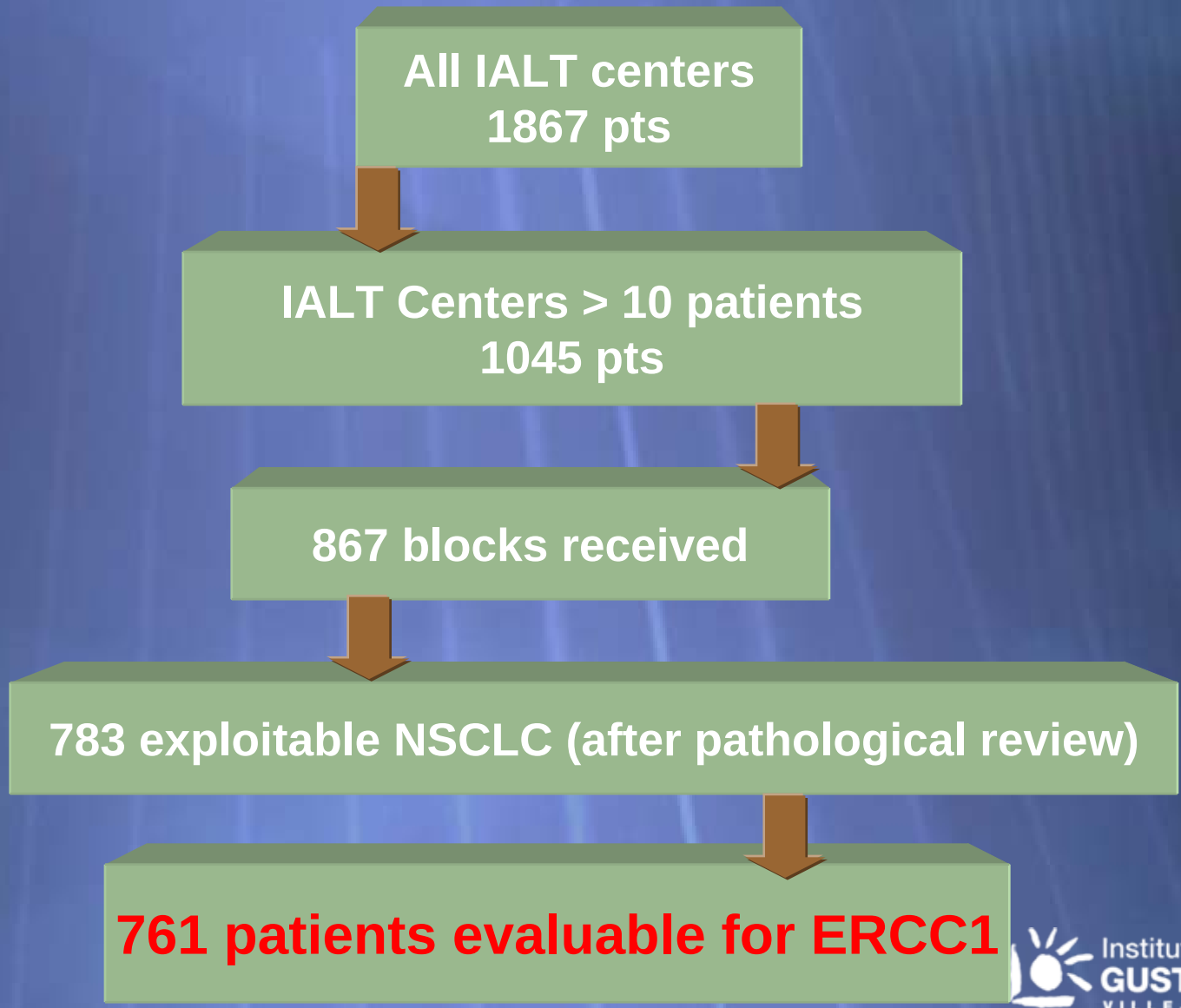
- 1867 patients with completely resected NSCLC I-II-IIIA
- Absolute benefit : 4.1% improvement of 5 year OS




*The IALT Collaborative Group, NEJM 2004*

# ASCO 2006: IALT-bio study

## ERCC1: a predictor of chemotherapy benefit ?




Institut de cancérologie
GUSTAVE ROUSSY

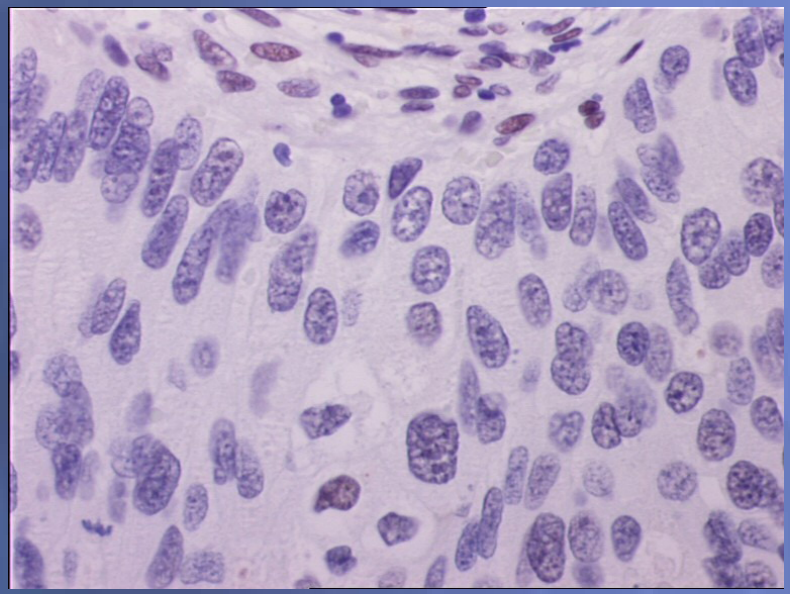
# Methods: ERCC1 immunohistochemistry

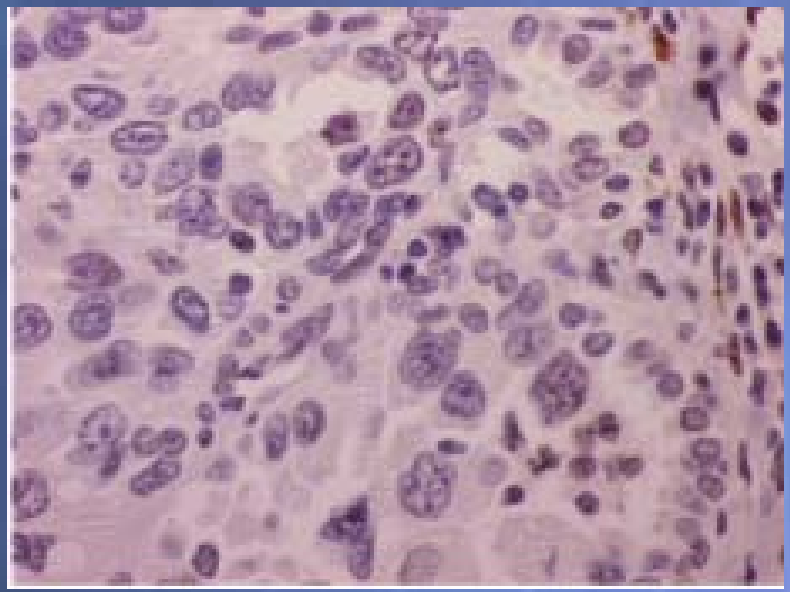
- Immunohistochemical analysis
- Standardized antigen retrieval
- ERCC1 monoclonal antibody (NeoMarkers)
- Evaluation of staining by two independent investigators, blinded to clinical data
  - → Internal controls (normal tissue)
  - → Staining intensity and percentage of positive cells

    (H-score)

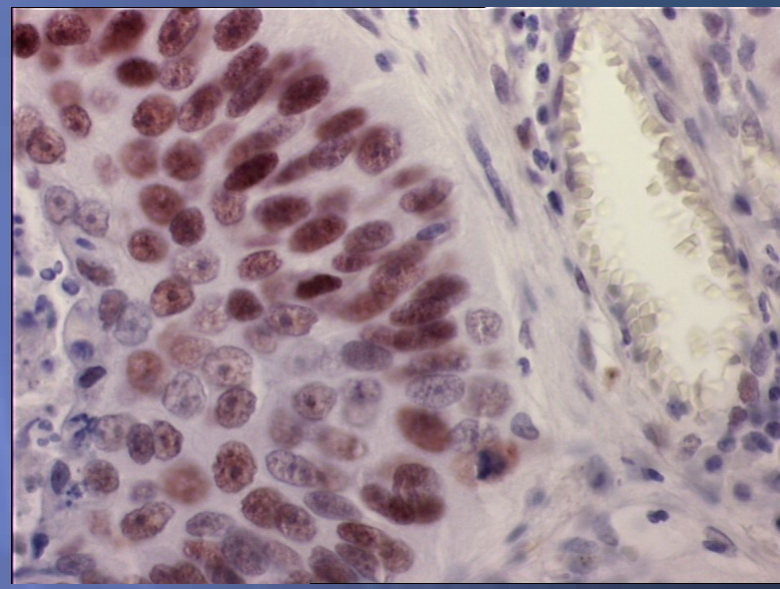

Institut de cancérologie GUSTAVE ROUSSY

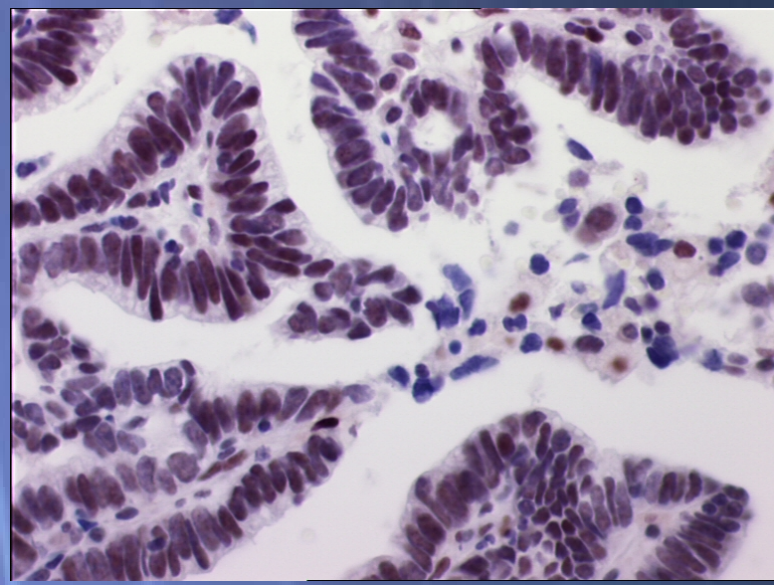
## ERCC1 negative





## ERCC1 positive





# Predictive Analysis

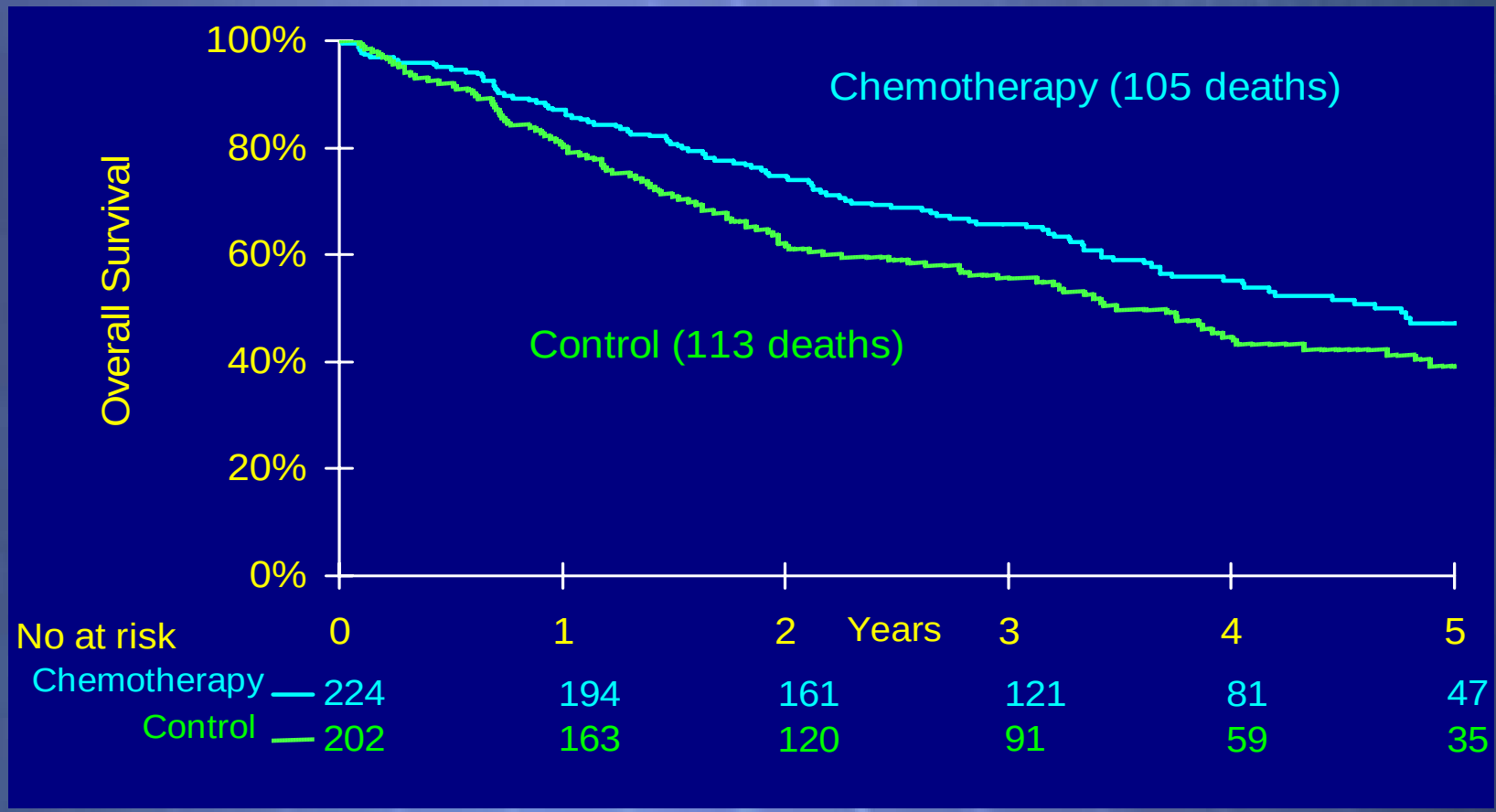
- Test of interaction ERCC1 treatment: p = 0.009

| | **Chemotherapy** n=389 5-year survival rate, Median survival | **Control group** n=372 5-year survival rate, Median survival | **Hazard ratio for death CT vs. no CT** |
|---|---|---|---|
| **ERCC1 negative tumors** n=426 | 47% [40%-55%] **56 months** | 39% [32%-47%] **42 months** | **0.65** [0.50-0.86] p = 0.002 |
| **ERCC1 positive tumors** n=335 | 40% [32%-49%] **50 months** | 46% [37%-55%] **55 months** | **1.14** [0.84-1.55] p = 0.40 |

Gain of **14 months** of overall survival from adjuvant chemotherapy in patients with ERCC1 negative tumor

Institut de cancérologie GUSTAVE ROUSSY

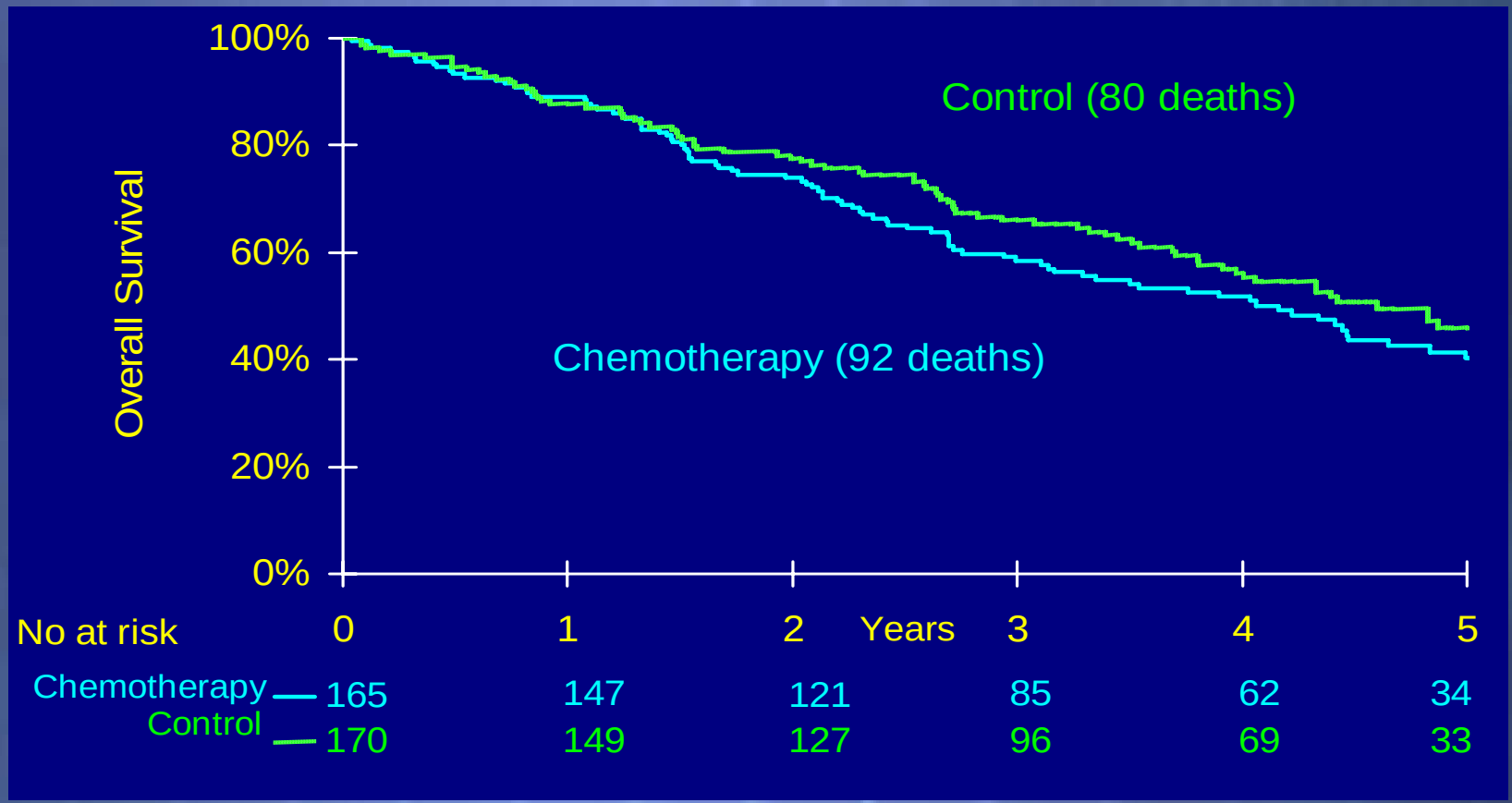
# Effect of adjuvant chemotherapy on overall survival in pts with ERCC1 negative tumor




**Adjusted HR=0.65, 95%CI [0.50-0.86], p = 0.002**

Institut de cancérologie GUSTAVE ROUSSY

# Effect of adjuvant chemotherapy on overall survival in pts with ERCC1 positive tumor




**Adjusted HR=1.14, 95%CI [0.84-1.55], P = 0.40**

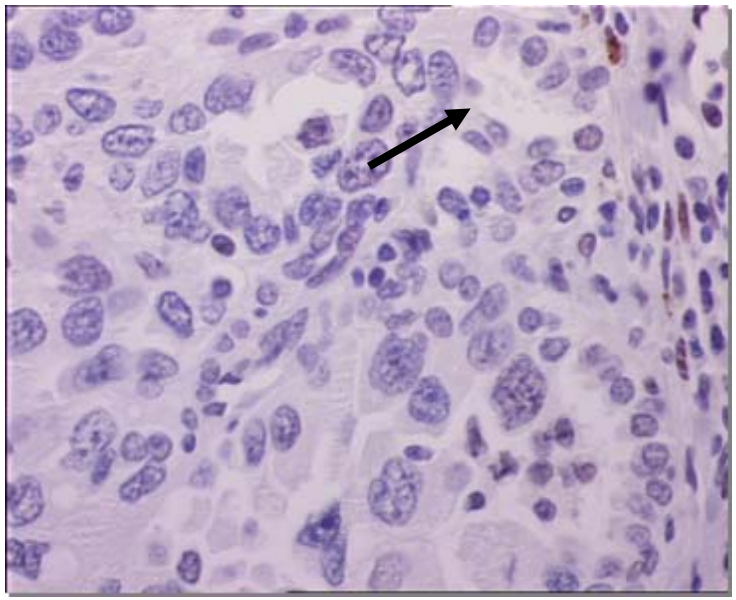
Institut de cancérologie GUSTAVE ROUSSY

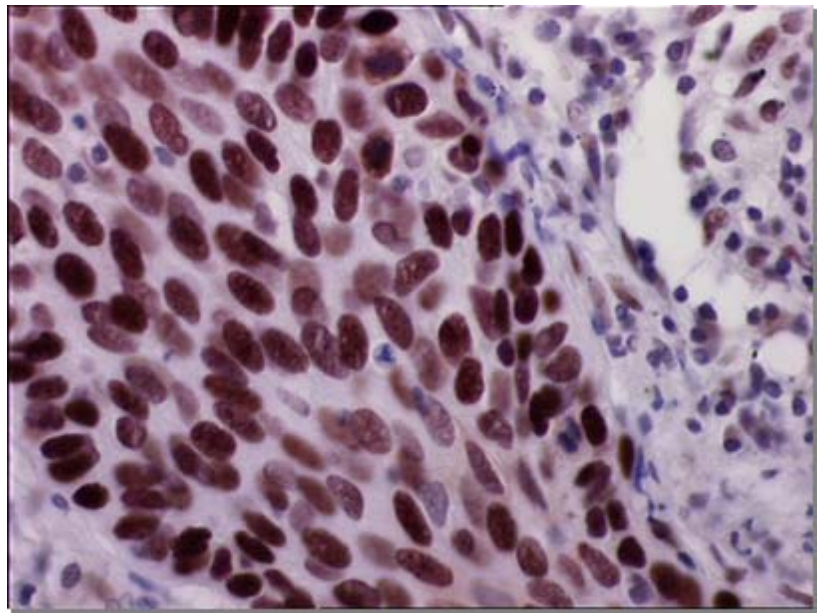
# Prognostic analysis

- In the control group, ERCC1 positive patients have a favorable prognosis

| | HR * | 95% CI | P value |
|---|---|---|---|
| **Control group** | | | |
| ERCC1 negative | 1 | | |
| ERCC1 positive | 0.66 | [0.49-0.90] | 0.009 |
| **Chemotherapy** | | | |
| ERCC1 negative | 1 | | |
| ERCC1 positive | 1.16 | [0.86-1.56] | 0.34 |
| **All patients** | | | |
| ERCC1 negative | 1 | | |
| ERCC1 positive | 0.88 | [0.71-1.10] | 0.26 |

# Results





**ERCC1 negative**

**ERCC1 positive**

**Benefit of Cisplatin-based CT in ERCC1 NEGATIVE patients**

Olaussen et al, New England J Med 2006

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# DNA Synthesis and Repair Genes *RRM1* and *ERCC1* in Lung Cancer

Zhong Zheng, M.D., Ph.D., Tingan Chen, M.D., Ph.D., Xueli Li, M.D., Eric Haura, M.D., Anupama Sharma, M.D., and Gerold Bepler, M.D., Ph.D.

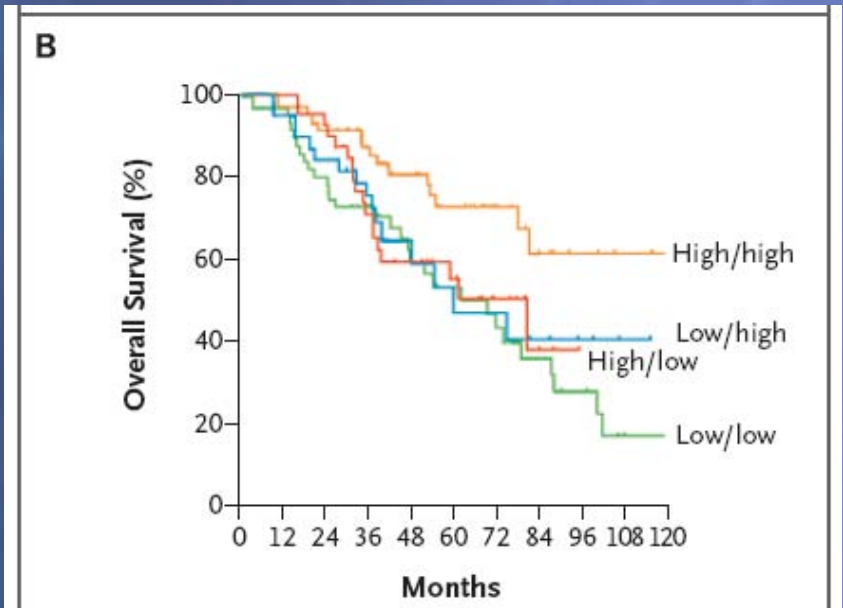


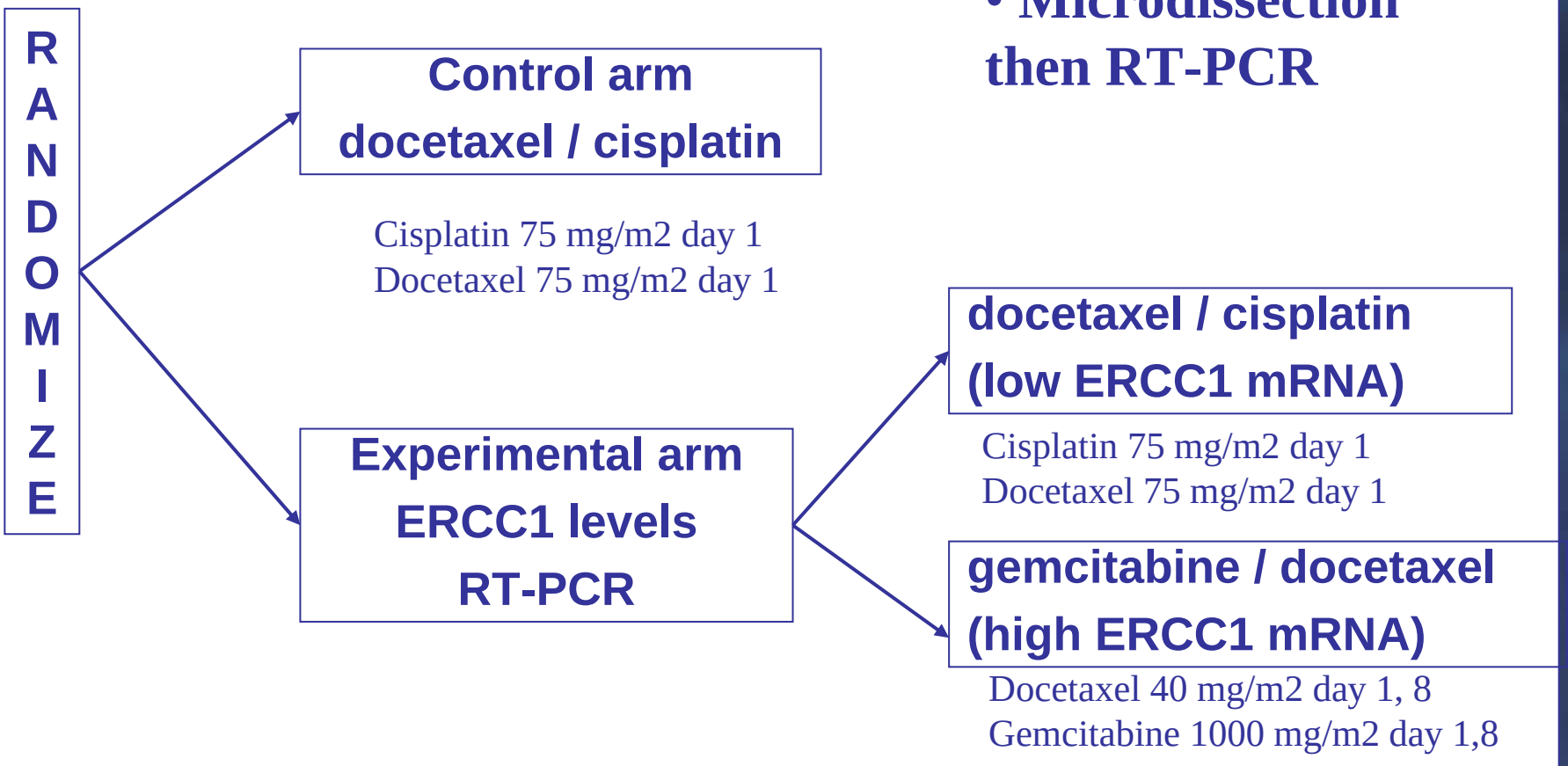

Figure 5. Disease-free Survival and Overall Survival among 184 Patients with AQUA Scores for RRM1 and ERCC1.

Prognostic value of ERCC1 and RRM1 in stage I NSCLC patients

Institut de cancérologie GUSTAVE ROUSSY

# GILT: the first ERCC1-based customized chemotherapy

- **Advanced NSCLC**
- **Microdissection then RT-PCR**




Rosell et al. ESMO 2006

# GILT: ERCC1-based customized chemotherapy

- Projected accrual 297
- 342 patients randomized : 283 patients 'enrolled'
  - → 17% dropped out !
  - → Of which 57% due to insufficient tissue
- An additional 102 patients were included
- Total randomized 444 and 366 'enrolled'
  - → Still 17% dropped out

# GILT: ERCC1-based customized chemotherapy

- Response rate
  - → Statistical difference (p=0.02)
  - → 39% in control vs. 51% in genotypic
    - OR in ERCC1 low: 53.7%
    - OR in ERCC1 high: 47.2%
- No difference in complete response rate
  - → 4.3% in control vs 3.1% in genotypic
- No differences in OS or PFS

# GILT: ERCC1-based customized chemotherapy



- Trial initiated in the early 2000s: visionary and extremely audacious!

- Why is this trial negative? Did ERCC1 failed in identifying patients who should receive cisplatin based chemotherapy ?
  - → Docexatel-gemcitabine the best non-platinum combination ?
  - → The control arm received the same chemotherapy as the low ERCC1 and no data on ERCC1 are known in the control arm
  - → It would have been better to prospectively confirm that low ERCC1 expressors respond better than high ERCC1 expressors to one platinum combination

- Methodological and technological issues complicate the interpretation of the study
  - → Reproductibility
  - → high drop out rate

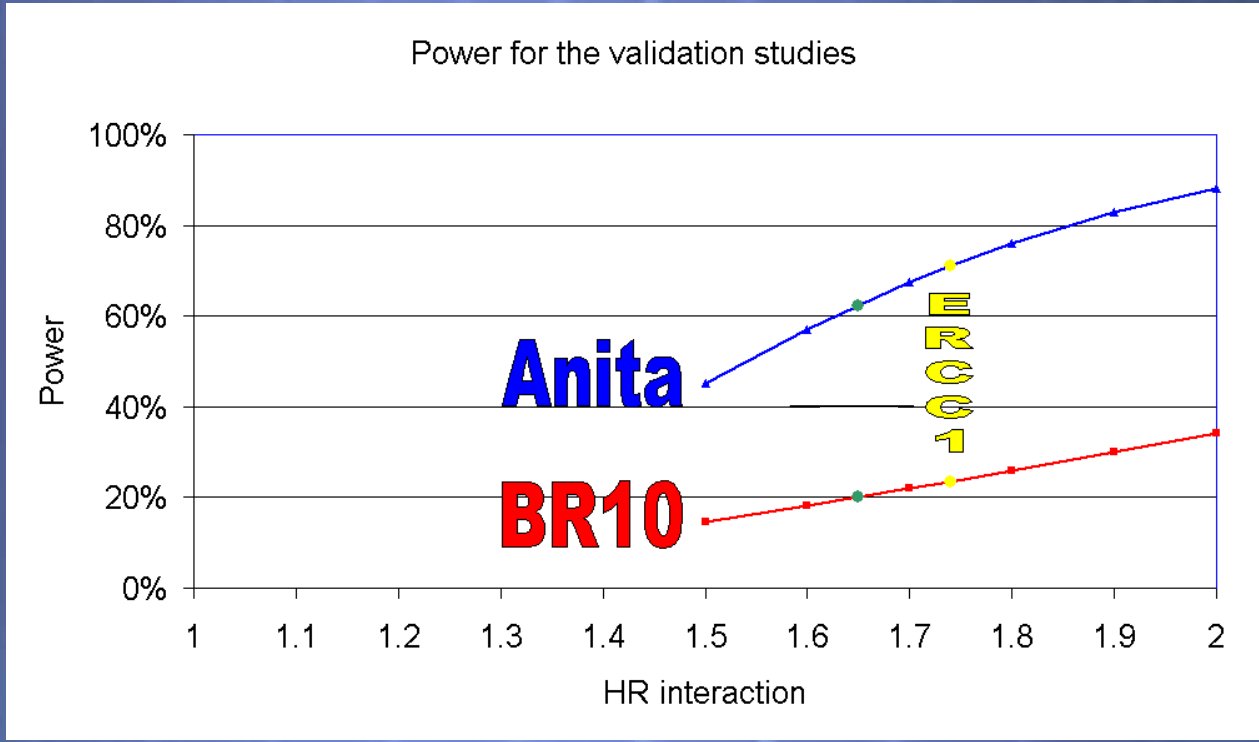
# Predictive biomarkers of Ct efficacy

- **Cisplatin**
  - ERCC1
    → RRM1 ?
- **Gemcitabine**
  - RRM1 ?
- **Pemetrexed**
  - FPGS ?
- **Paclitaxel**
  - MAPtau ?
- **Docetaxel**
  - Bcl2 ?

# ERCC1 open questions

- Clinical questions
  - Validation of ERCC1 predictive value
  - Molecular and clinical characterization ERCC1 pos/neg pts
  - Future clinical trials
  - Other tumor types
- Biological questions
  - ERCC1 partners (XPF, XPA, RPA…)
  - Biological function of ERCC1
  - Regulation of ERCC1 gene expression
- Methodological perspectives

# External validation of ERCC1 expression predictive/prognostic value

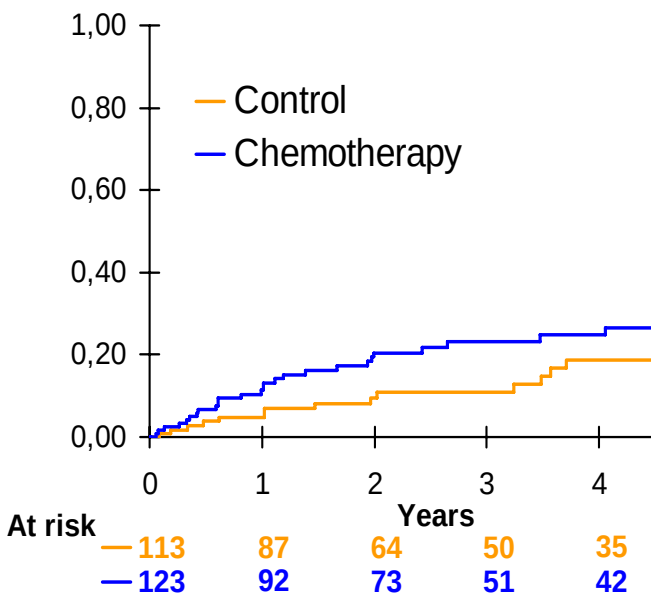



Assuming 200 patients for BR10 and 400 patients for Anita

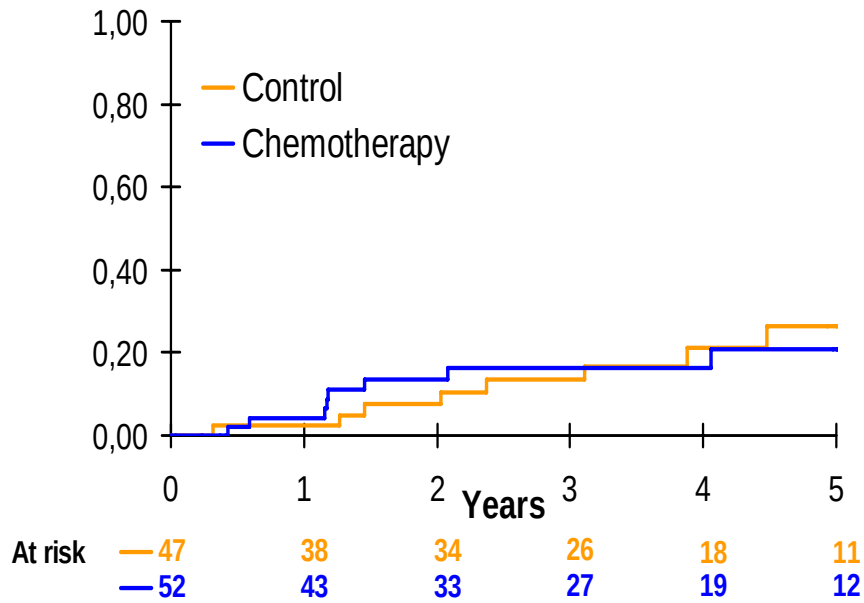
# Clinical characterization of ERCC1 neg/pos pts

Brain metastasis are increased in ERCC1 NEG patients treated by CT (non squamous histology, n=335)

**ERCC1 NEG**




**ERCC1 POS**




**Brain metastasis occurrence according to treatment**

Besse et al. ASCO 2007

Institut de cancérologie GUSTAVE ROUSSY

# Future clinical trials

- Design and implement a customized trial of adjuvant Ct integrating ERCC1 data
  - → should ERCC1 be associated with other markers (EGFR mut/FISH ?)
  - → to which compounds ERCC1 positive and negative patients are the most likely to respond (beyond cisplatin)
  - → should ERCC1 positive patients get a treatment?

# SWOG Pilot Study: Pharmacogenomic-directed Adjuvant Therapy of NSCLC

NSCLC
pT1(x≥2cm)
pT2N0M0

R0
resection

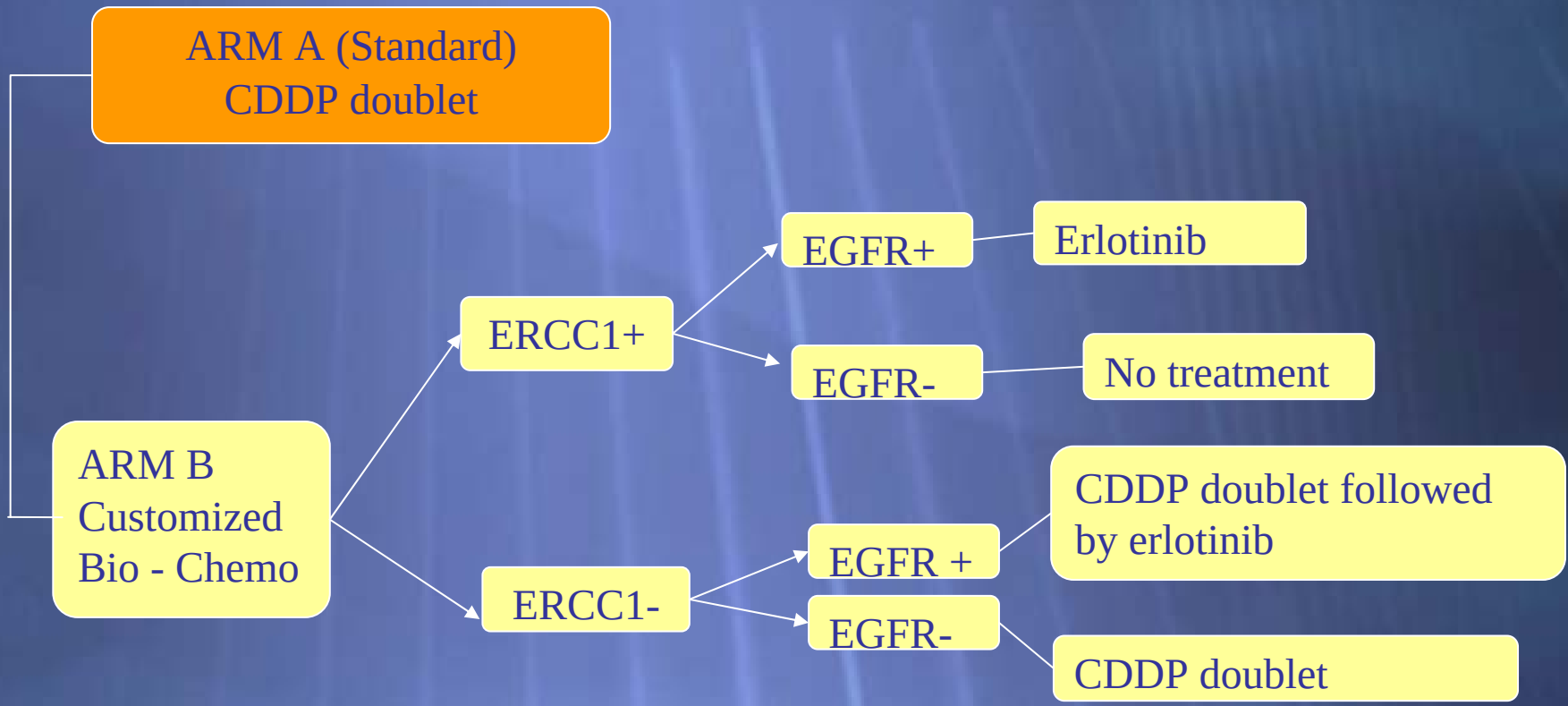
Age 18-75
PS 0-1

N~TBD

| RRMI ≥ 40.5 **AND** ERCC1> 66.0 | All Others (RRM1< 40.5 **OR** ERCC1 < 66.0 ) |
|---|---|
| Active Monitoring | Cisplatin-Gemcitabine |

*PI: Bepler*

# French adjuvant lung cancer study (IFCT)



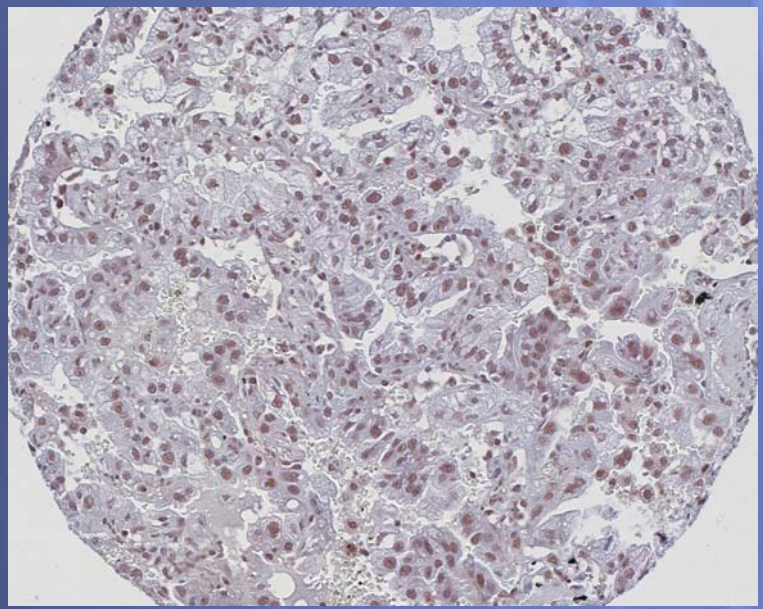
# ERCC1: open questions

- Clinical questions
  - Validation of ERCC1 predictive value
  - Molecular and clinical characterization ERCC1 pos/neg pts
  - Future clinical trials
  - Other tumor types
- Biological questions
  - ERCC1 partners (XPF, XPA, RPA…)
  - Biological function of ERCC1
  - Regulation of ERCC1 gene expression
- Methodological perspectives

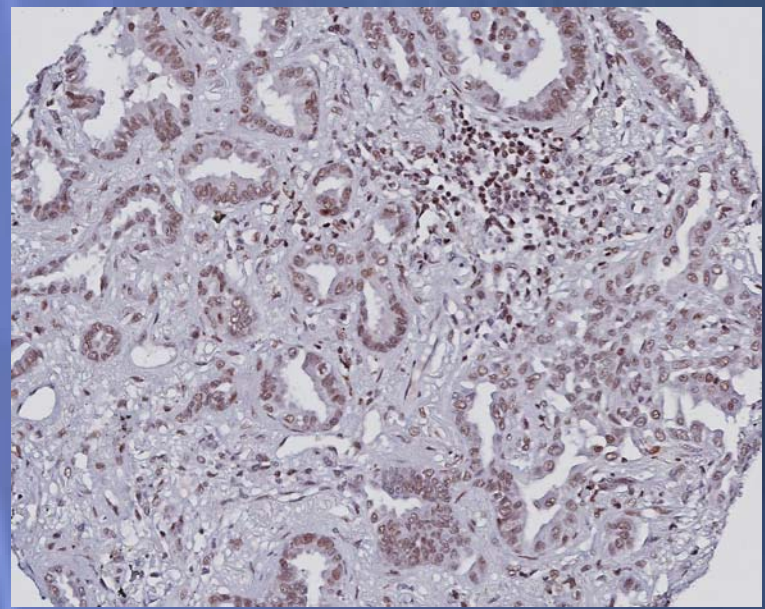
# ERCC1 partners in cancer

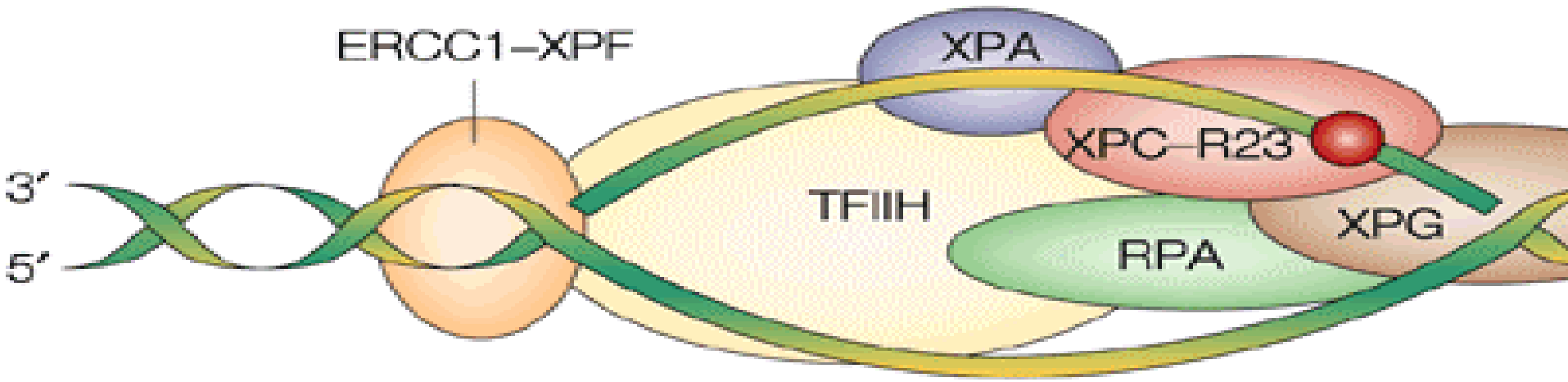


XPF



RPA

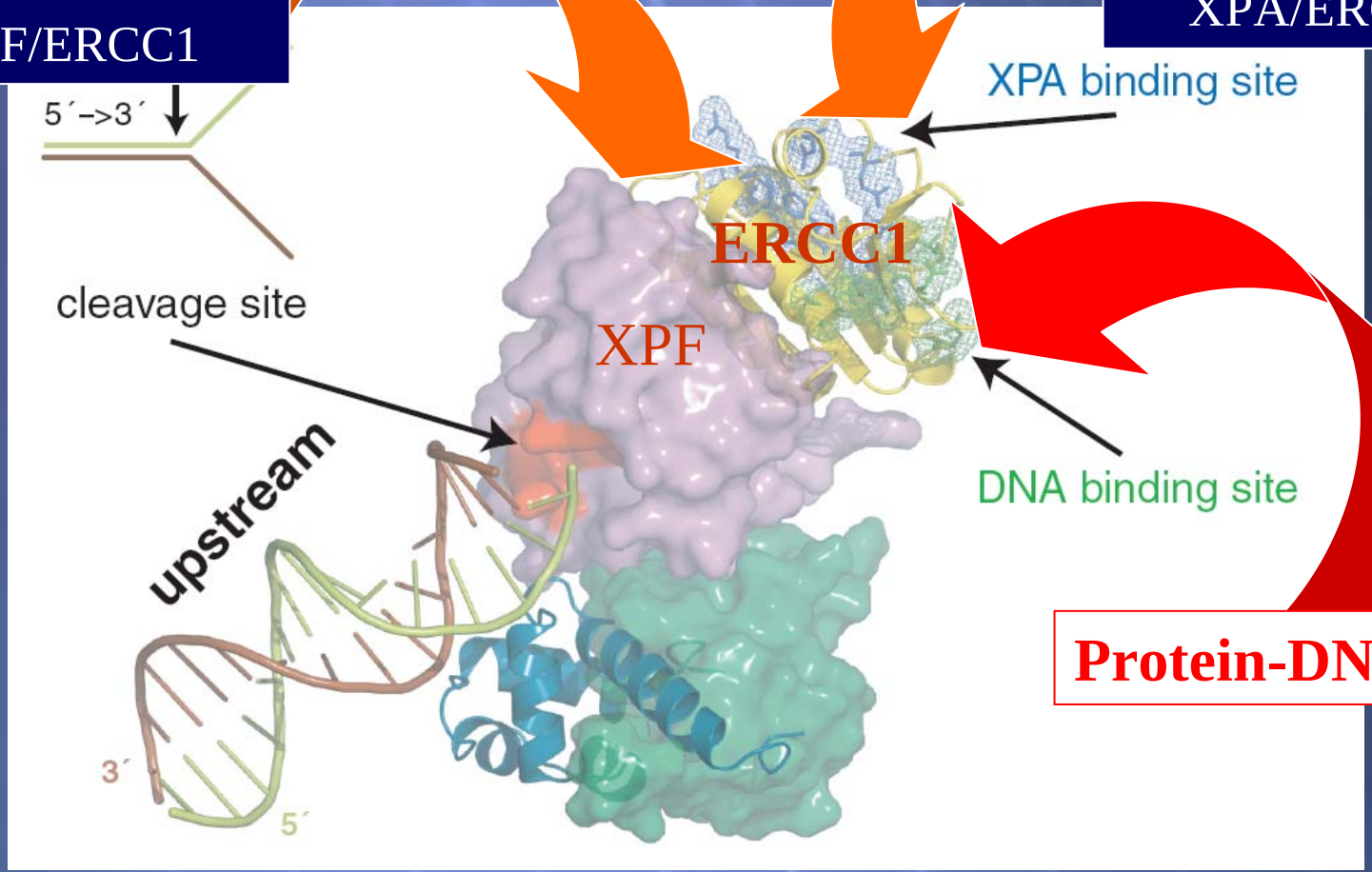




# Possible ERCC1 target sites

**Protein-Protein**
XPF/ERCC1

**Protein-Protein**
XPA/ERCC1

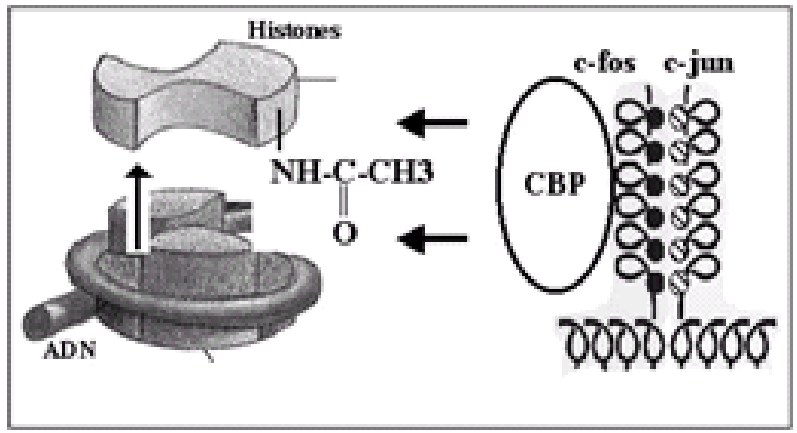



**Protein-DNA**

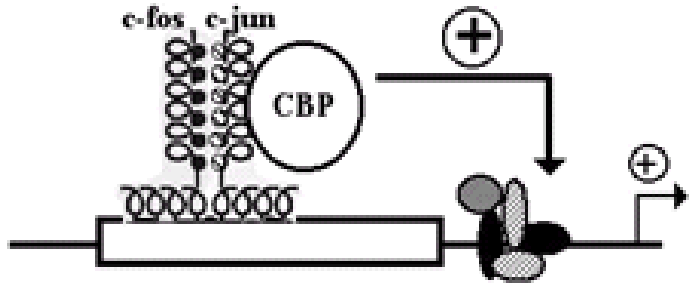
K.Tripsianes et al, Nucleic Acids Research, 2007

# ERCC1 gene expression regulation

- AP1: 2 sites
  - c-Fos
  - c-Jun
  - ATF2
  - CBP
- Ets-1: 2 sites
  - Ets-1 (AP1 =>TIMP-1)
  - CREB
- GATA-1: 1 site
- HMG2
- Antisens codant pour CD3-epsilon AP




La Phosphorylation de c-jun sur Ser63 et Ser73 Permet l'Interaction avec CBP et l'Ouverture de la Chromatine




(O. Coqueret)

# Conclusions

- ERCC1 expression is a predictive factor of chemotherapy benefit in patient treated by cisplatin-based adjuvant chemotherapy
- ERCC1 expression is a prognostic factor in patient not treated by chemotherapy
- ERCC1 plays a fundamental function in drug resistance and cancer susceptibility (Janus-faced of ERCC1)

# Conclusions

- Personalized medicine is one of the strongest expectations from patients and health-care takers

- The next step
  - integration of the best biomarkers in prospective trials
  - implementation of pharmacogenomic-based clinical trials

# Acknowledgements


## Laboratory Investigators

- Christophe Raynaud
- Laure Sabatier
- Ken Olaussen
- Pierre Fouret
- Elisabeth Brambilla
- David Planchard
- Estelle Taranchon

## Clinicians

- Julien Domont
- Christophe Massard
- Pierre Validire
- Benjamin Besse
- Fabrice André

## Statisticians

- Vincent Haddad
- Ariane Dunant
- Jean-Pierre Pignon
- Catherine Hill