PREDICTIVE BIOMARKERS

THE HOLY GRAIL OF PERSONALISED MEDICINE FOR CANCER PATIENTS

Themes to discuss

1. Predictive vs prognostic biomarkers. Trial design - Placebo controls

2. Standardardized biomarker assays implemented to Good Clinical Practice

3. Mimimally invasive vs tissue biomarkers.
cf Nucleic acids, Disseminated Tumour cells in bone marrow
Circulating tumour cells. Longitudinal monoitory of drug resistance and disease relapse.

Mazzoni et al – do SNPs in ERCC1 and RRM1 predict response of NSCLC to chemotherapy

Impact:

To spare patients toxic therapy that they are resistant to.
To give chemotherapy to patients most likely to respond

Followed a body of work pioneered by Jean Charles Soria where
protein or RNA levels were measured in tumours
and a general finding that low levels of ERCC1 and RRM1 is associated with
better outcome. Response measured by RECIST.

Is there a less invasive way to predict chemotherapy response?
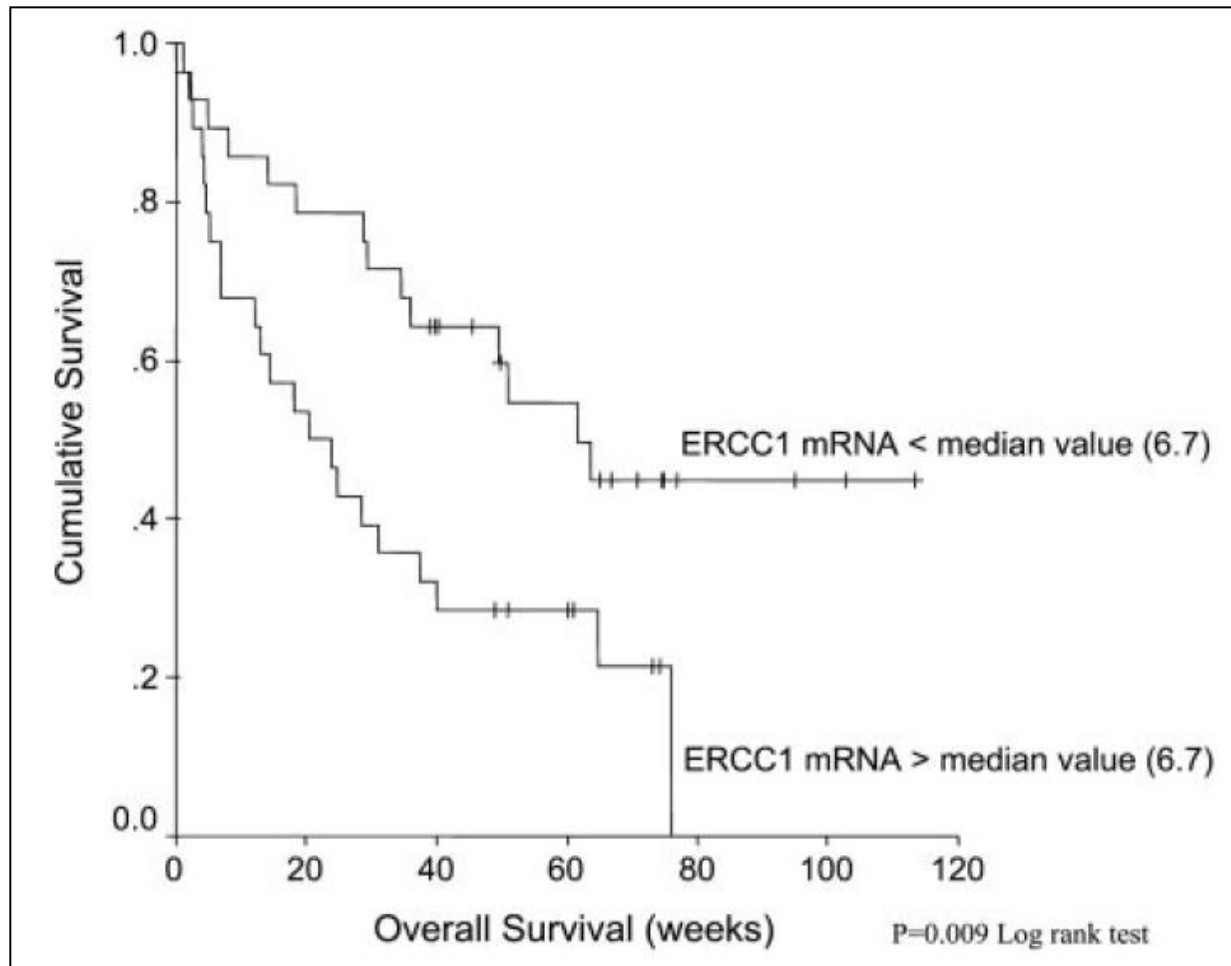
PCR on DNA purfication from a blood sample.
Rapid turnaround and cheap.
Assumed SNPs would correlate with protein expression in tumour

Low ERCC1 expression correlates with prolonged survival after Cisplatin + Gemcitabine Chemotherapy in NSCLC

Lord et al 2002

ERCC1 levels in mRNA isolated from FFPE tumour blocks from n=56 patients

Lower ERCC1 is associated with better outcome

New England Journal of Medicine

Olaussen et al 2006

IHC ERCC1 on the International Adjuvant Lung Cancer Trial

N =761 patients

Conclusions: *Patients with completely resected NSCLC and ERCC1 –negative Tumours appear to benefit from adjuvant cisplatin based chemotherapy whereas patients with ERCC1 positive tumours do not.*

In 2011 They also showed that ERCC1 protein expression and mRNA expression were correlated , but there are inconsistencies in come cases.
Fiboulet et al Clin Cancer Research

Later this group showed that the predictive utility of DNA repair enzymes co-segregates with Squamous Cell Carcinomas
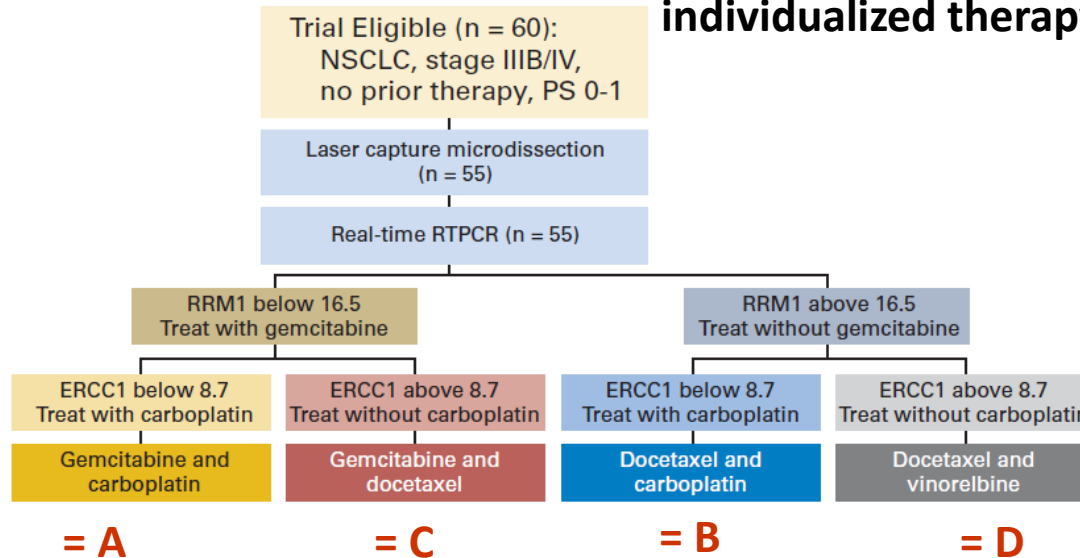Pierceall et al Ann Oncol 2012

Latest work focussed on role of p38MAPK and relationship to ERCC1 expression in Light or never smokers with NSCLC. Planchard et al Cancer 2012

Gene Expression

Feasibility and efficacy of molecular analysis-directed individualized therapy in advanced NSCLC

Simon et al 2007 JCO

Trial Eligible (n = 60):
NSCLC, stage IIIB/IV,
no prior therapy, PS 0-1

Laser capture microdissection
(n = 55)

Real-time RTPCR (n = 55)

RRM1 below 16.5
Treat with gemcitabine

RRM1 above 16.5
Treat without gemcitabine

ERCC1 below 8.7
Treat with carboplatin

ERCC1 above 8.7
Treat without carboplatin

ERCC1 below 8.7
Treat with carboplatin

ERCC1 above 8.7
Treat without carboplatin

Gemcitabine and carboplatin

Gemcitabine and docetaxel

Docetaxel and carboplatin

Docetaxel and vinorelbine

= A   = C   = B   = D

These are the equivalent cohorts in the Mazzoni et al abstract
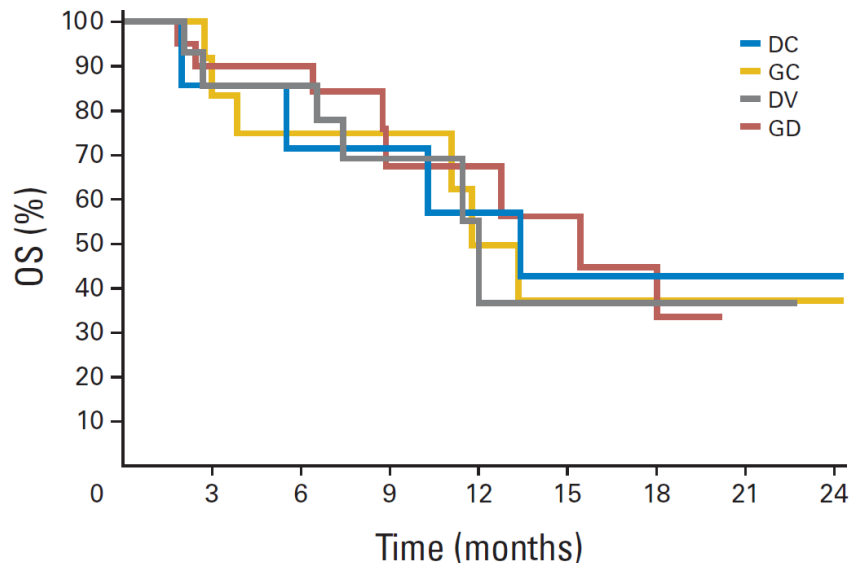
Prospective collection of dedicated tumour biopsy for determination of *RRM1* and *ERCC1* gene expression by real-time quantitative RTPCR
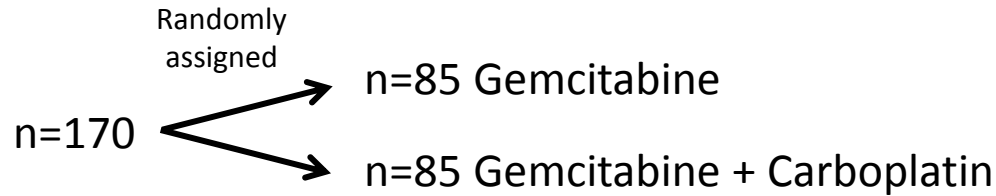
85 recruited, 55 usable data

Double-agent chemotherapy consisting of carboplatin, gemcitabine, docetaxel, and vinorelbine was selected based on gene expression

"Therapeutic decision making based on RRM1 and ERCC1 gene expression in advanced NSCLC I feasible and promising for improvement of patient outcome"
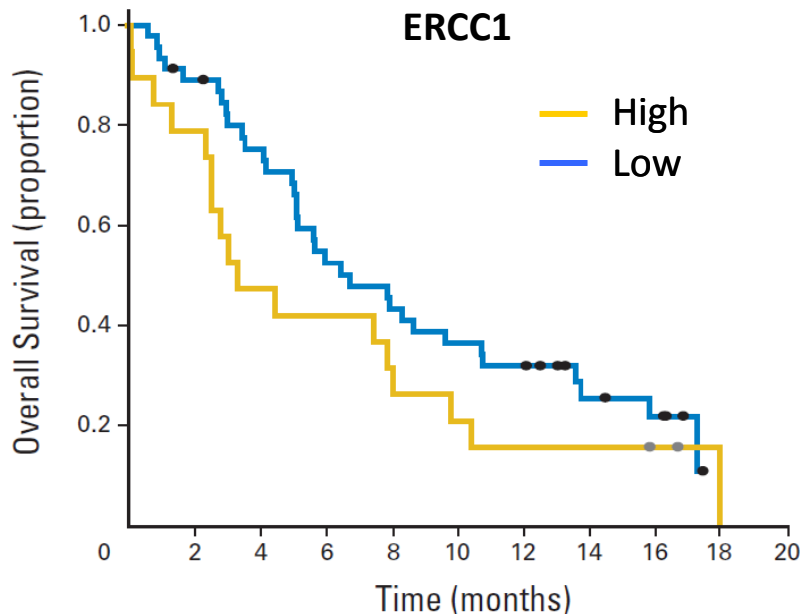
Randomized Phase III trial of gemcitabine-based chemotherapy with *In Situ* RRM1 and ERCC1 protein levels for response prediction in NSCLC
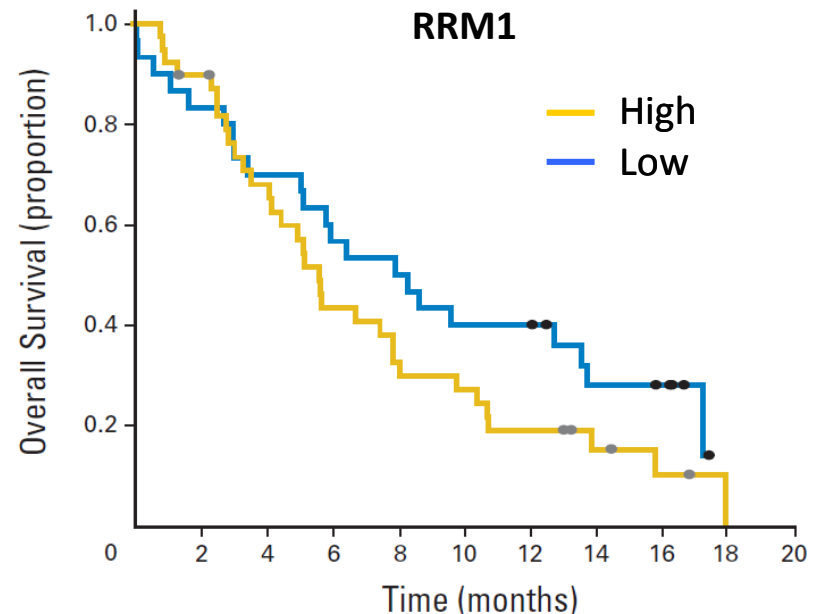
Reynolds et al 2009 JCO

Randomly assigned

n=170 → n=85 Gemcitabine

→ n=85 Gemcitabine + Carboplatin
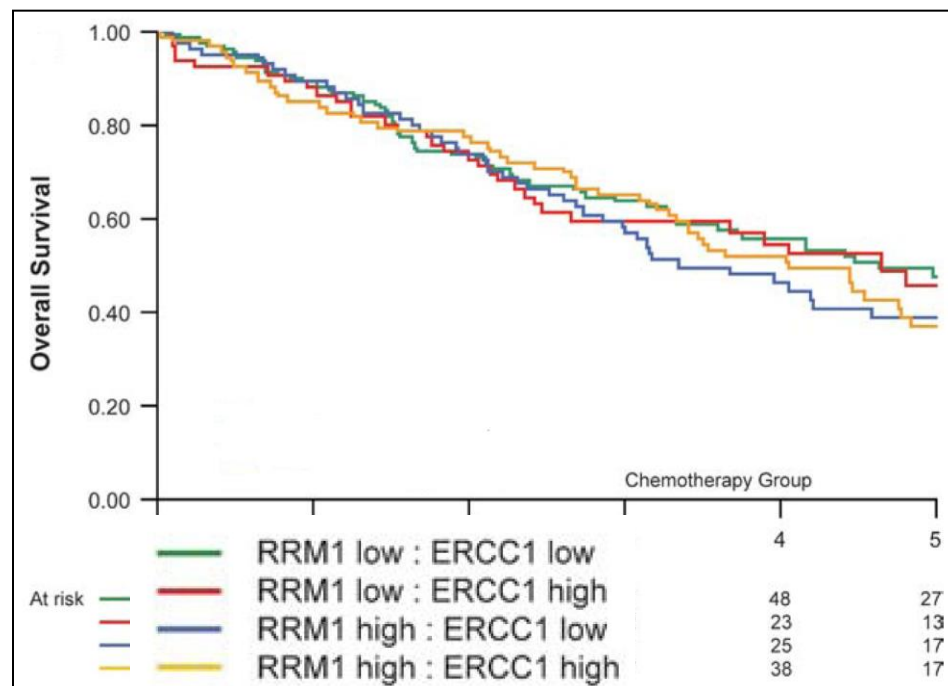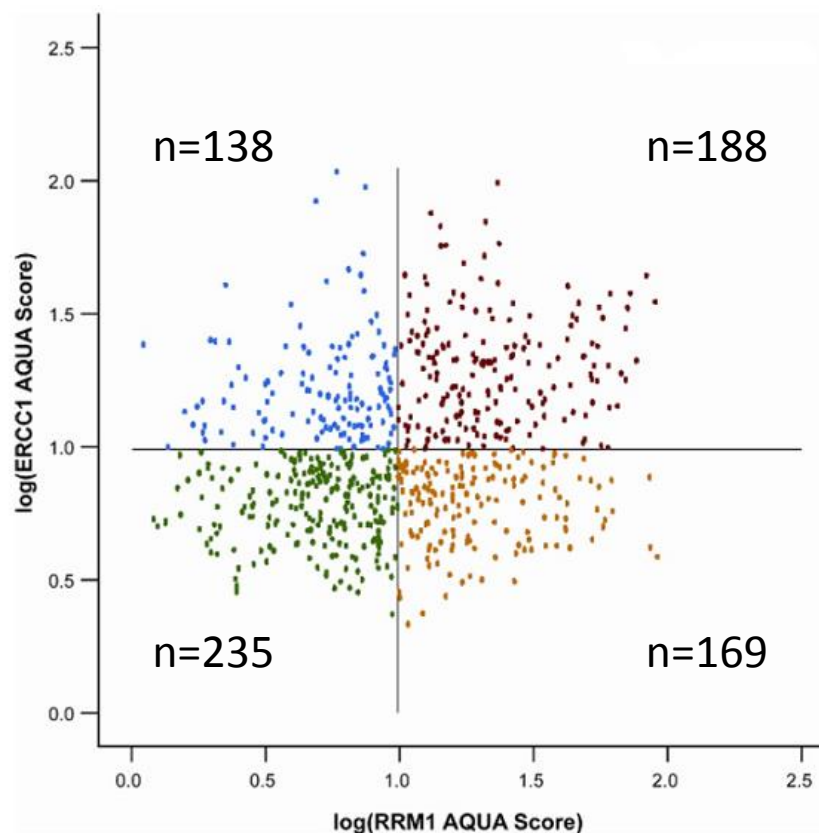
Lower levels of ERCC1 = longer PFS

By 4 months+ out lower levels of RRM1 = longer PFS

"Quantitative analysis of RRM1 and ERCC1 in routinely collected tumour specimens in community oncology practice is predictive of response to chemotheapy"

ERCC1 and RRM1 in the international adjuvant lung trial by automated quantitative *in Situ* analysis

Belper et al 2011 Am J Path

Distribution of ERCC1 & RRM1 *in situ* protein expression scores in n=730 patients

OS in the chemotherapy group

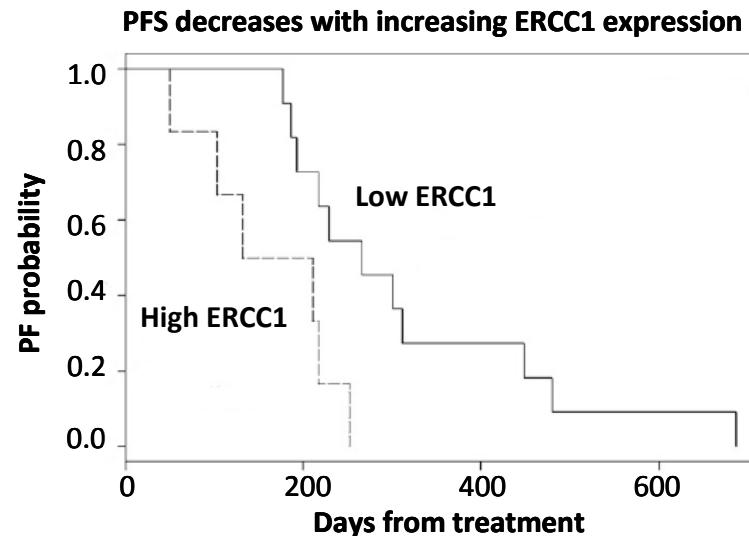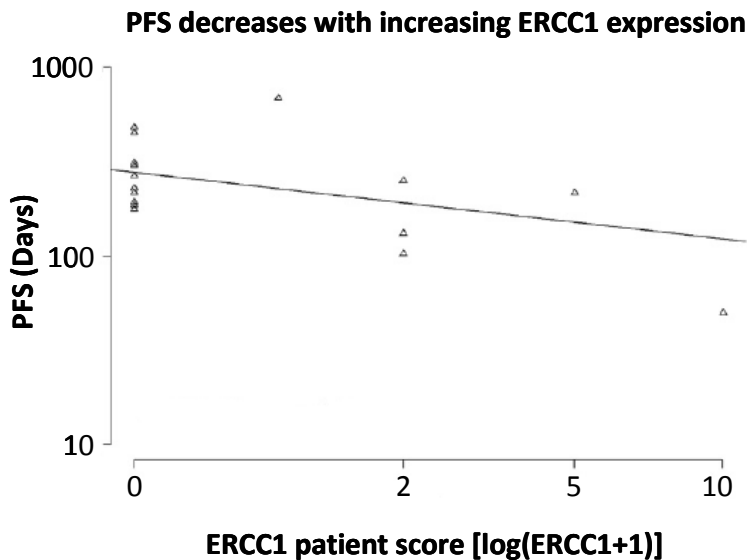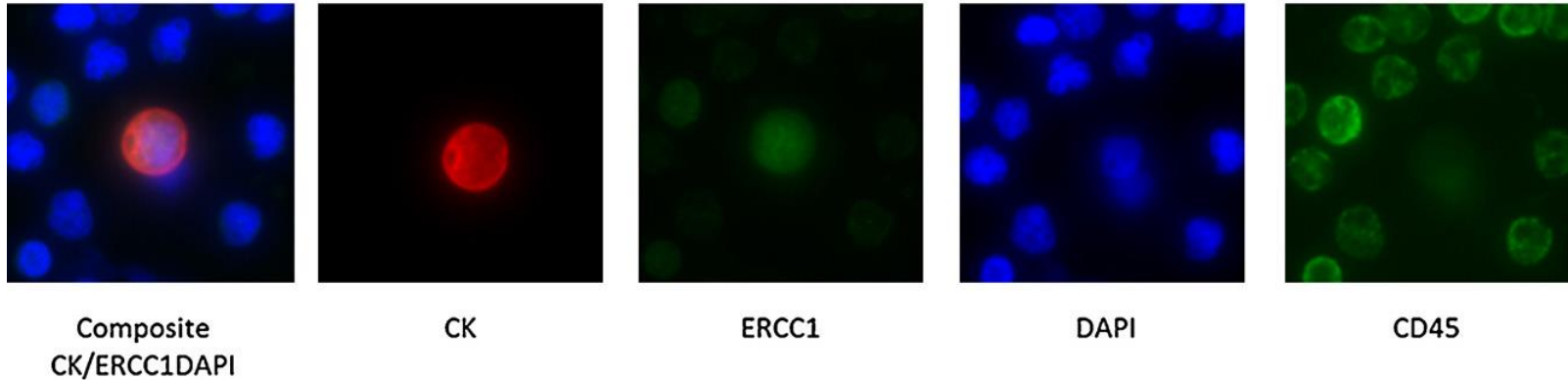Problems with skewed data based on contributing centre
Future trials need prospective collection, standardised protocols,
to better reveal impact....

CTCs?

ERCC1 expression in CTCs using a novel detection platform correlates with PFS in patients with metastatic NSCLC receiving platinum chemotherapy

Das et al 2012

ERCC1 expression was measured in 17 metastatic NSCLC patients who received platinum-based therapy and had ≥2 intact CTCs with acceptable ERCC1 expression assay results

Composite CK/ERCC1DAPI — CK — ERCC1 — DAPI — CD45

PFS decreases with increasing ERCC1 expression

PFS (Days) vs ERCC1 patient score [log(ERCC1+1)]

PFS decreases with increasing ERCC1 expression

Low ERCC1

High ERCC1

PF probability vs Days from treatment
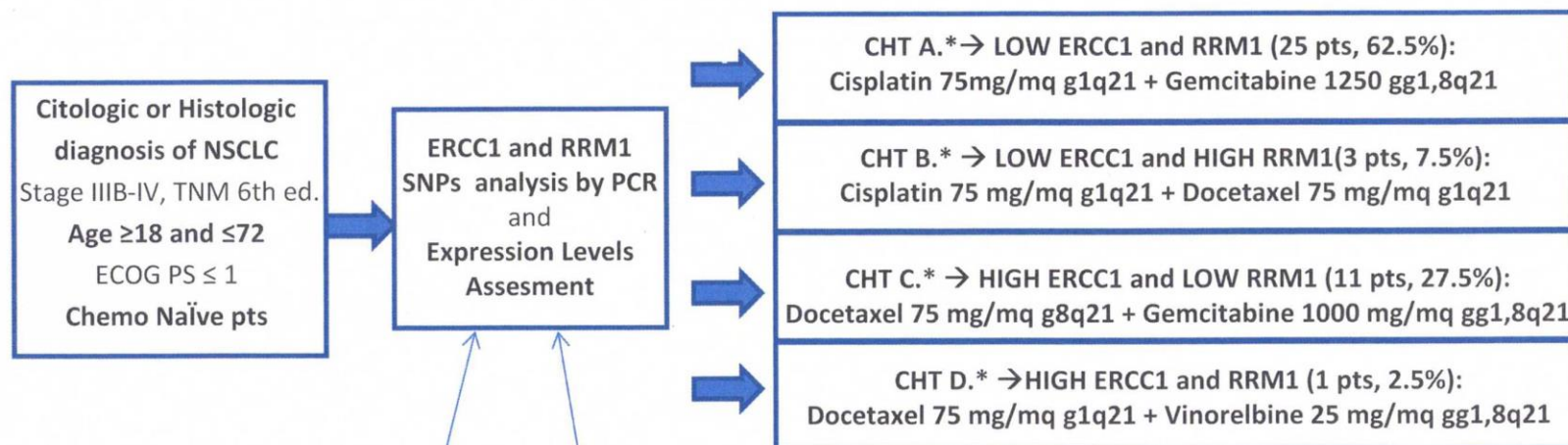
Is this feasible in many centres?

CellSearch only finds CTCs in small percentage of Stage IV patients

ISET filtration?

CUSTOMIZED FIRST LINE CHEMOTHERAPY ACCORDING TO ERCC1 AND RRM1 SNPs IN ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS: A PHASE II STUDY.

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Citologic or Histologic diagnosis of NSCLC
Stage IIIB-IV, TNM 6th ed.
Age ≥18 and ≤72
ECOG PS ≤ 1
Chemo Naïve pts

→

ERCC1 and RRM1 SNPs analysis by PCR and Expression Levels Assesment

→

CHT A.* → LOW ERCC1 and RRM1 (25 pts, 62.5%): Cisplatin 75mg/mq g1q21 + Gemcitabine 1250 gg1,8q21

CHT B.* → LOW ERCC1 and HIGH RRM1(3 pts, 7.5%): Cisplatin 75 mg/mq g1q21 + Docetaxel 75 mg/mq g1q21

CHT C.* → HIGH ERCC1 and LOW RRM1 (11 pts, 27.5%): Docetaxel 75 mg/mq g8q21 + Gemcitabine 1000 mg/mq gg1,8q21

CHT D.* →HIGH ERCC1 and RRM1 (1 pts, 2.5%): Docetaxel 75 mg/mq g1q21 + Vinorelbine 25 mg/mq gg1,8q21

ERCC1 codon	ERCC1 SNPs	ERCC1 Expression Level	Cisplatin sensitivity
	C/C	LOW	RESPONDER
118 T>C	T/C		NO RESPONDER
	T/T	HIGH	
	C/C	LOW	RESPONDER
8029 C>A	C/A		NO RESPONDER
	A/A	HIGH	

RMM1 codon	RRM1 SNPs	RRM1 Expression Level	Gemcitabine sensitivity
	C/C		
-37 C>A	A/C	LOW/NORM	RESPONDER
	A/A	HIGH	NO RESPONDER
	T/T		
-524 T>C	T/C	LOW/NORM	RESPONDER
	C/C	HIGH	NO RESPONDER

*
- Pts receive up to 6 cycles of CHT;
- Response evaluation is performed with CT scan every 2 cycles (RECIST 1.0);
- The CT scan performed after the 4° cycle (or after the last cycle if early discontinuation of therapy occurs) is considered to define treatment response.

Conclusions (1):

- The trial met the **primary end-point** with **55% RR** in the ITT population, which compares favourably with the 20-40% RR that we observe with chemotherapy as delivered in clinical practice.

- The treatment related **G3-G4 toxicity** occurred in the **42% of the ITT** population and this configures an accetable toxicity profile, also assuming that there were no treatment related deaths.

- **Median PFS (5.3 months) and OS (8.0 months)** are consistent with what we could aspect for stage IIIB-IV NSCLC pts, unselected for biomolecular or histological features.

Conclusions (2):

- The trial supports the correlation between **ERCC1 /RRM1 SNPs** and **ERCC1/RRM1 expression levels** which are supposed to influence **Cisplatin and Gemcitabine chemosensitivity** respectively.

- The trial generates the hypotesis that **pts with squamous histotype could benefit mostly** from this customized approach (71,4% RR and 85.72% DCR in squamous pts vs 46.2% RR and 69.23% DCR in non squamous pts).

- ERCC1/RRM1 SNPs are assessed by PCR after DNA purification from a blood sample. This is a **rapid and relatively cheap assay** which could be reasonably adopted in our clinical practice. Neverthless further studies are required to confirm the results of our experience.

Next Steps?

Assay validation to GCP?

Cross site validation of data?

The potential of exploiting DNA-repair defects for optimizing lung cancer Treatment. Postel-Vinay et al 2012 Nature Reviews Clinical Oncology *Jean Charles Soria.*

Cuzick et al – Prediction of late recurrence by the ROR (PAM50) score in postmenapausal women in the transATAC cohort.

Impact:
ER +ve tumours (70-80%)
To identify those at risk or late relapse (~50%) provide extended adjuvant therapy and spare those not at risk the drug toxicities associated with prolonged treatment.
Clear economic impact also.

Usually extended adjuvant therapy given for > 5 years only if there there axillary lymph node involvement.

For non breast cancer experts: Complex set of data leading up to this study

PAM50 – affymetrix 50 gene signature Perou >10years ago.
Defines luminal A, B, Basal and Her2 subtypes - prognostic

OncoDx 21 gene signature – prognostic and predictive for endocrine trreatment in ER +ve cancer

IHC4 – ER, PR, Ki67, HER2 equivalent to OncoDx for prognosis

ROR = OncoDx plus tumour size

Question Which of all these scores performs best to predict time to distant relapse.
Issue   Dissecting predictive vs prgnostic biomarkers?

- <u>Background</u>: 4 immunohistochemical markers (ER, PgR, Ki67, HER-2), both alone and combined into the IHC4 score are significantly correlated with time to distant recurrence (TTDR)

- ROR provides significantly more prognostic information in endocrine treatment than the Oncotype Dx Recurrence Score (RS)

- <u>Objective</u>: To investigate the relationship between IHC4, RS and ROR (based on PAM50 and tumour size) score in predicting distant recurrence in years 0-5 and years 5-10 separately

- <u>Methods</u>: 940 postmenopausal women were included in this analysis

- Univariate and multivariate analyses were performed to determine prognostic value of all scores in the **0-5 year period** and **5-10 year period** separately

- To compare the IHC4 score with all other scores, the previously described sample splitting procedure was used for all four scores

Conclusions

Overall, all scores provided significant additional information in the period between 5 and 10 years with CTS being the strongest prognostic factor in all time periods

IHC4 was the strong prognostic factor in the multivariate model for all patients and node negative patients in years 0-5.

None of the scores provided any significant prognostic information in years 0-5 for node positive patients in the multivariate model, but some added prognostic information is seen in the late period.

CTS and ROR are the only scores that added clinically significant prognostic information in years 5 to 10. The results presented here may be used to select patients who may benefit from hormonal treatment beyond 5 years. Is this going to be taken up by clinicians?
Or is more evidence required?

What next? Placebo controlled trials?

What about DTCs? Pantel and colleagues in Germany
1 DTC in the bone marrow carries adverse prognosis? Would women take this test?
Monitor DTCs or CTCs with time? HER2 measured in CTCs?

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Circulating tumour cells. Longitudinal monoitory of drug resistance and disease relapse.