Plenary Session 3:
Correlative Studies in Phase III Trials:
Biomarkers

Statistical Analyses

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NCIC Groupe des essais cliniques

Statisticians *vs* Epidemiologists

- 5 statisticians and 5 epidemiologists are travelling together on a train. They all start chatting and it transpires that all the epidemiologists have bought a ticket, but the statisticians have only bought a ticket between the 5 of them. *"How did you do that?"* asks one of the epidemiologists. *"Simple, we just threw all the train?"* *"Just wait and see!"*, says
- As the ticket inspector is ap… tickets, the statisticians all go off to the nearest toilet – th… logists and inspects all their tickets then moves on and … *"Tickets please!"*, shouts the inspector. One of the statis… the toilet door, which the inspector checks and the … ector has gone, all the statisticians return to their … t of the epidemiologists: *"That's incredibly clever!"*
- A few weeks later they all … n again. They sit together and start chatting once more … ", says one of the epidemiologists. *"And … ve of us!"* *"Oh really"*, says one of the statisticians. *"w… s time!"* The epidemiologists look at each other in amaze… *you is fine but not buying any at all is ridiculous!"* *"We … he statisticians.*
- As the ticket inspector appr… y off to the toilet. Once they're inside, the statistici… f" shouts one of the statisticians.

Topics to be covered

- **Analysis of Correlative Biomarker Studies**
  - Prognostic Markers
  - Predictive Markers
  - Statistical differentiation of the two
  - Examples**

** - extra examples provided

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Statistical thinking will one day be as necessary a qualification for efficient citizenship as the ability to read and write.

H.G. Wells

Anyone who cannot cope with mathematics is not fully human. At best he is a tolerable subhuman, who has learned to wear shoes, bathe, and not make messes in the house.

Robert Heinlein

Cancer Treatment and Biomarkers

- Many drugs are found to improve disease free or overall survival for patients with various types of cancer
- However, no regimen is found universally effective for all patients
- The selection of a particular treatment which is best for a given patient is challenging and currently more of an art than a science
- There is a need to find good biomarkers which would be used to “personalize” treatment for cancer patients

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Types of Tumor Biomarkers

- Prognostic markers
- Predictive markers

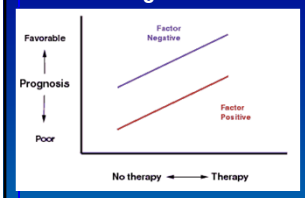
Prognostic markers

- The biomarker is called prognostic if it provides information concerning the anticipated natural history of the disease process in a given individual
- ...but where the outcome is independent from therapy
- Answers the question *"When?"*
- Example: Prostate specific antigen (PSA) in prostate cancer which is used to classify the risk of the patients

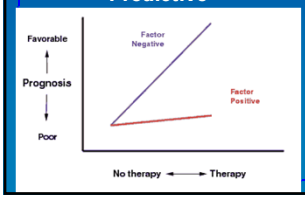
Predictive biomarkers

- A predictive marker is a marker that allows the prospective identification of individuals who will or will not benefit from the use of a particular therapy
- Predicts the outcome of a specific therapy
- Answers question *"With what?"* or *"How much?"*
- Example: Estrogen receptor in breast cancer which is used to select hormonal treatments for the breast cancer

Prognostic



Predictive



- **Differential** Efficacy
- Parallel *versus* non-parallel lines
- In statistical terms this is termed **interaction** and can be specifically tested for, i.e. a p-value for interaction can be generated.
- Assuming there is sufficient power, this can be used to assess the null hypothesis that there is no differential efficacy between the therapies (no interaction) or that the marker is not predictive of efficacy

Example: KRAS as a Biomarker in Colorectal Cancer


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 23, 2008 VOL. 359 NO. 17

K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer

Christos S. Karapetis, M.D., Shirin Khambata-Ford, Ph.D., Derek J. Jonker, M.D., Chris J. O'Callaghan, Ph.D., Dongsheng Tu, Ph.D., Niall C. Tebbutt, Ph.D., R. John Simes, M.D., Haji Chalchal, M.D., Jeremy D. Shapiro, M.D., Sonia Robitaille, M.Sc., Timothy J. Price, M.D., Lois Shepherd, M.D.C.M., Heather-Jane Au, M.D., Christiane Langer, M.D., Malcolm J. Moore, M.D., and John R. Zalcberg, M.D., Ph.D.*

The Influence of *K-ras* Exon 2 Mutations on Outcomes

In

A Randomized Phase III Trial of Cetuximab + Best Supportive Care (BSC) versus BSC Alone in Patients with Pre-treated Metastatic EGFR-Positive Colorectal Cancer (NCIC CTG CO.17)

A trial of the

National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)

and the

Australasian Gastro-Intestinal Trials Group (AGITG)

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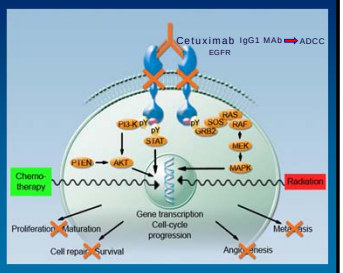
Cetuximab: Multiple Mechanisms of Action

- IgG1 monoclonal antibody
- Binds to EGFR and competitively inhibits ligand binding (e.g. EGF)
- Blocks receptor dimerization, tyrosine kinase phosphorylation, and signal transduction
- IgG1-induced Antibody-Dependent Cell Cytotoxicity (ADCC)



Harari P. *Clin Cancer Res.* 2004;10:428.

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Cetuximab: Phase II Clinical Data

Study	Treatment	N	Efficacy ORR	Efficacy TTP
Irinotecan Failure				
Saltz L. *J Clin Oncol* 2004 (IMC 0141)	Cetuximab	57	8.8%	1.4 mo
Cunningham D. *N Eng J Med* 2004 (EMR 007 / BOND)	Cetuximab	111	10.8%	1.5 mo
	Cetuximab + Irinotecan	218	22.9%	4.1 mo
Irinotecan, Oxaliplatin, Fluoropyrimidine Failure				
Lenz H-J. *J Clin Oncol* 2006 (IMC 0144)	Cetuximab	346	12.4%	1.4 mo

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NCIC CTG CO.17: Randomized Phase III Trial in mCRC

Failed or intolerant to all recommended therapies, ECOG 0-2, No Prior EGFR directed therapy

REGISTER → EGFR testing by IHC → RANDOMIZE 1:1

- Cetuximab* + BSC
- BSC alone

→ Disease Progression or Unacceptable Toxicity

* Cetuximab 400 mg/m² IV week 1 then 250 mg/m² IV weekly

Primary Endpoint: Overall Survival

Secondary Endpoints: Progression Free Survival; Objective Response Rate (RECIST criteria); Safety and Quality of Life

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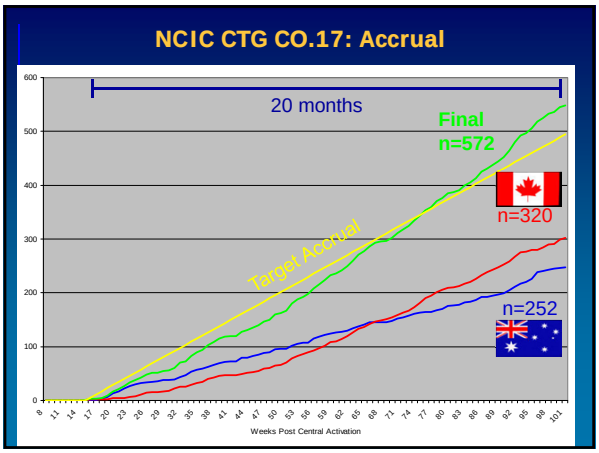
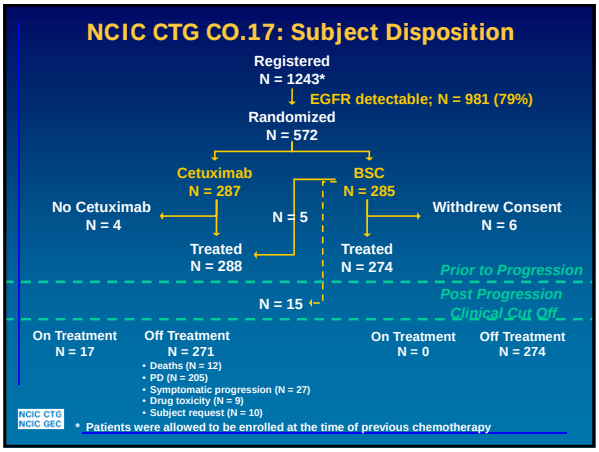

NCIC CTG CO.17: Accrual
20 months
Final
n=572
n=320
n=252
Target Accrual
Weeks Post Central Activation


NCIC CTG CO.17: Subject Disposition
Registered
N = 1243*
EGFR detectable; N = 981 (79%)
Randomized
N = 572
Cetuximab
N = 287
BSC
N = 285
No Cetuximab
N = 4
N = 5
Withdrew Consent
N = 6
Treated
N = 288
Treated
N = 274
Prior to Progression
Post Progression
Clinical Cut Off
N = 15
On Treatment
N = 17
Off Treatment
N = 271
On Treatment
N = 0
Off Treatment
N = 274
• Deaths (N = 12)
• PD (N = 205)
• Symptomatic progression (N = 27)
• Drug toxicity (N = 9)
• Subject request (N = 10)
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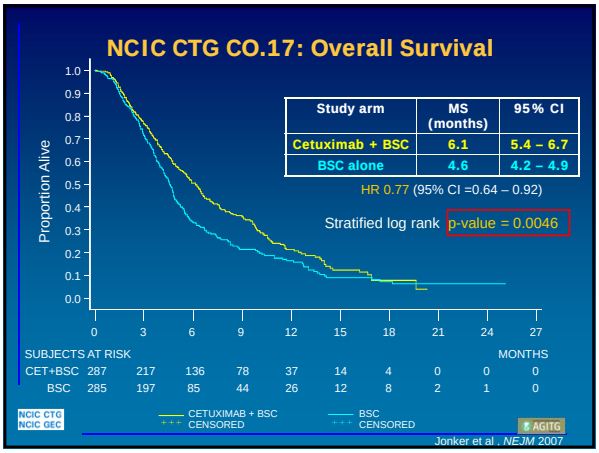
* Patients were allowed to be enrolled at the time of previous chemotherapy


NCIC CTG CO.17: Overall Survival
Proportion Alive
Study arm
MS (months)
95% CI
Cetuximab + BSC
6.1
5.4 – 6.7
BSC alone
4.6
4.2 – 4.9
HR 0.77 (95% CI =0.64 – 0.92)
Stratified log rank p-value = 0.0046
SUBJECTS AT RISK
MONTHS
CET+BSC 287 217 136 78 37 14 4 0 0 0
BSC 285 197 85 44 26 12 8 2 1 0
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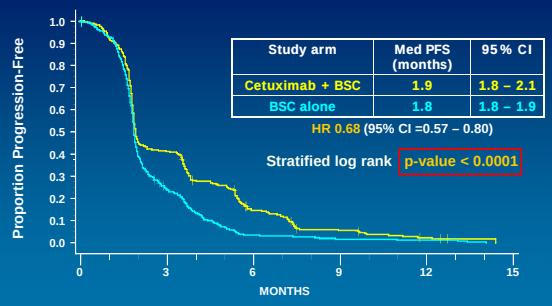
CETUXIMAB + BSC
CENSORED
BSC
CENSORED
AGITG
Jonker et al . NEJM 2007

NCIC CTG CO.17: Progression Free Survival



Study arm	Med PFS (months)	95 % CI
Cetuximab + BSC	1.9	1.8 – 2.1
BSC alone	1.8	1.8 – 1.9

HR 0.68 (95% CI =0.57 – 0.80)

Stratified log rank p-value < 0.0001

CETUXIMAB + BSC
CENSORED
BSC
CENSORED

Jonker et al , *NEJM* 2007

Which patients benefit?

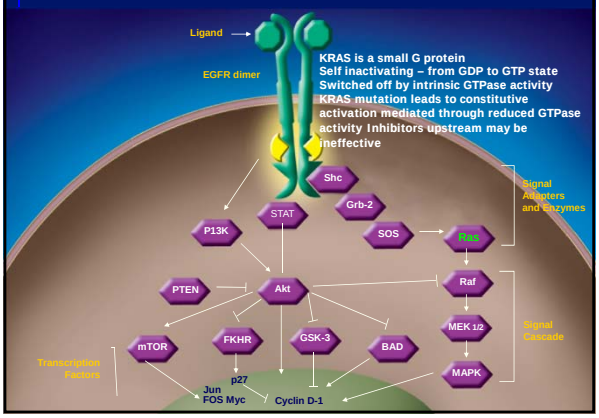
A reliable biomarker is needed:

- **to provide an accurate prediction of who will respond and benefit from cetuximab**
- **to improve the therapeutic index**
- **to improve cost effectiveness of EGFR monoclonal antibody based therapy of pre-treated colorectal cancer**

The predictive value of the biomarker would need to be differentiated from its prognostic implications

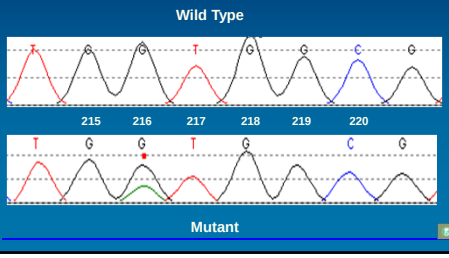
The *KRAS* mutation status of the bowel cancer may be such a marker of response and a predictor of benefit

EGFR Signaling Cascade and *KRAS*



KRAS Mutation Detection

- DNA extracted from slides containing FFPE tissue sections
- *KRAS* exon 2 is amplified by PCR and subjected to bidirectional sequencing
- Sequence traces are analyzed by mutation detection software & visual inspection
- Mutations are most common on codons 12 & 13



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KRAS as a potential predictive marker from single-arm retrospective studies

Reference	Treatment	Number WT:M	ORR % WT	ORR % M
Lievre, A et al *J Clin Oncol* 2007	Cetuximab + / - CT	89 65:24	40	0
Di Fiore, F et al *BJC 2007*	Cetuximab + CT	59 43:16	28	0
Khambata-Ford et al *JCO 2007*	Cetuximab	80 50:30	10	0
De Roock, W et al *Ann Oncol 2007*	Cetuximab + / - CT	108 66:42	41	0

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NCIC CTG CO.17 *KRAS* Analysis

N=572 randomized: ITT subset

N=394: *KRAS* assessed subset (69%)

N=164 (42%) mutant

N=230 (58%) wild-type

- **No difference between *KRAS* mutated and WT patients re: demographics, previous treatment or other variables**

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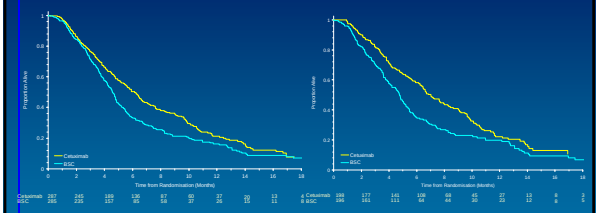
Comparison of ITT and *KRAS* assessed subsets

Baseline Characteristic		ITT (N = 572)	Mutated *K-ras* (N = 164)	Wild-type *K-ras* (N = 230)	p-value*
Age – median		63.2	62.0	63.5	0.569
Gender	F	204 (35.7)	63 (38.4)	74 (32.2)	0.200
	M	368 (64.3)	101 (61.6)	156 (67.8)	
ECOG PS	0	136 (23.8)	34 (20.7)	56 (24.3)	0.695
	1	302 (52.8)	94 (57.3)	127 (55.2)	
	2	134 (23.4)	36 (22.0)	47 (20.4)	
Prior XRT		202 (35.3)	50 (30.5)	77 (33.5)	0.531
Prior chemoRx					
adjuvant		211 (36.9)	57 (34.8)	83 (36.1)	0.786
antiTS		572 (100.0)	164 (100.0)	230 (100.0)	
irinotecan		550 (96.2)	161 (98.2)	219 (95.2)	0.119
oxaliplatin		559 (97.7)	163 (99.4)	222 (96.5)	0.080
Arm	CET	287 (50.2)	81 (49.4)	117 (50.9)	0.772
	BSC	285 (49.8)	83 (50.6)	113 (49.1)	

*between mutated and wild-type K-RAS groups from chi-square test for categorical variables and t-test for continuous variables.

NCIC CTG C0.17: Primary endpoint overall survival



Total study population (ITT analysis)

KRAS assessed subset

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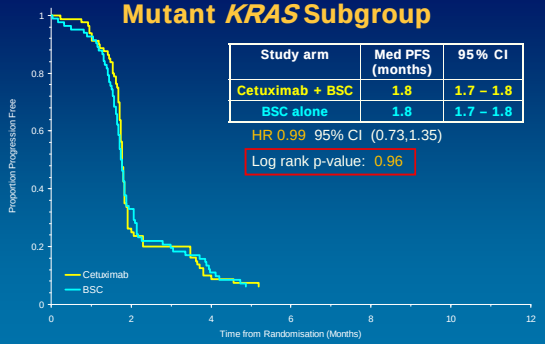
NCIC CTG C0.17: PFS in the Mutant *KRAS* Subgroup



Study arm	Med PFS (months)	95% CI
Cetuximab + BSC	1.8	1.7 – 1.8
BSC alone	1.8	1.7 – 1.8

HR 0.99 95% CI (0.73,1.35)

Log rank p-value: 0.96

Cetuximab	81	21	8	3
BSC	83	27	9	4

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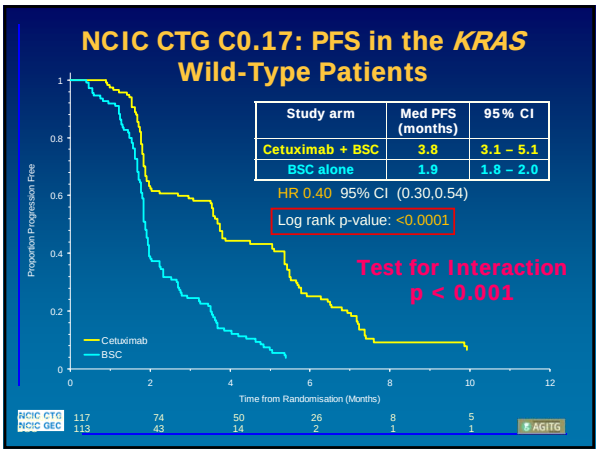
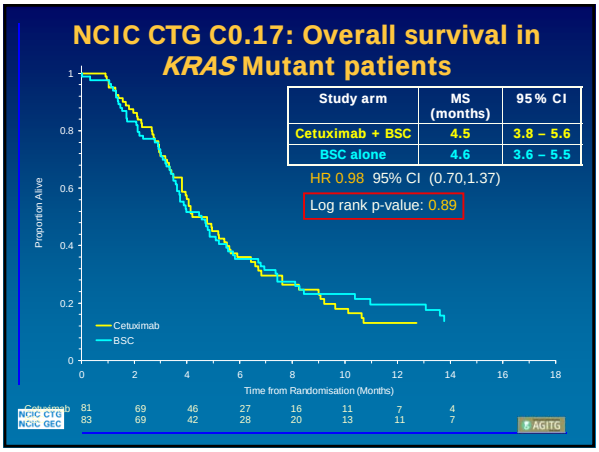
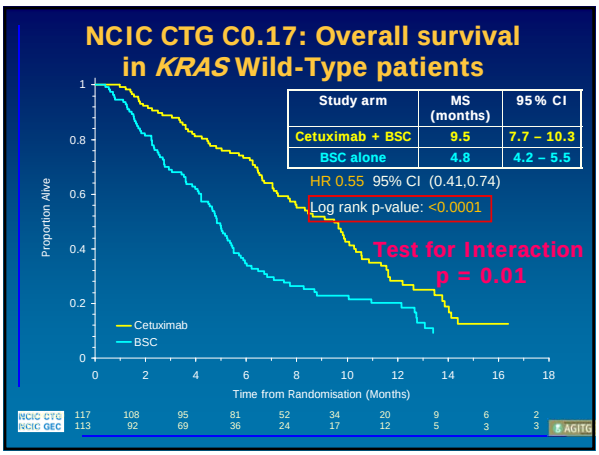
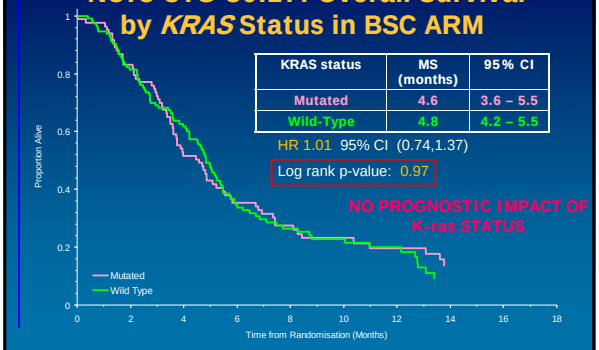

NCIC CTG C0.17: PFS in the KRAS Wild-Type Patients
Study arm | Med PFS (months) | 95% CI
Cetuximab + BSC | 3.8 | 3.1 – 5.1
BSC alone | 1.9 | 1.8 – 2.0
HR 0.40 95% CI (0.30,0.54)
Log rank p-value: <0.0001
Test for Interaction p < 0.001
Proportion Progression Free
Cetuximab
BSC
Time from Randomisation (Months)
NCIC CTG 117 74 50 26 8 5
NCIC GEC 113 43 14 2 1 1
AGITG


NCIC CTG C0.17: Overall survival in KRAS Mutant patients
Study arm | MS (months) | 95% CI
Cetuximab + BSC | 4.5 | 3.8 – 5.6
BSC alone | 4.6 | 3.6 – 5.5
HR 0.98 95% CI (0.70,1.37)
Log rank p-value: 0.89
Proportion Alive
Cetuximab
BSC
Time from Randomisation (Months)
Cetuximab 81 69 46 27 16 11 7 4
NCIC CTG
NCIC GEC 83 69 42 28 20 13 11 7
AGITG


NCIC CTG C0.17: Overall survival in KRAS Wild-Type patients
Study arm | MS (months) | 95% CI
Cetuximab + BSC | 9.5 | 7.7 – 10.3
BSC alone | 4.8 | 4.2 – 5.5
HR 0.55 95% CI (0.41,0.74)
Log rank p-value: <0.0001
Test for Interaction p = 0.01
Proportion Alive
Cetuximab
BSC
Time from Randomisation (Months)
NCIC CTG 117 108 95 81 52 34 20 9 6 2
NCIC GEC 113 92 69 36 24 17 12 5 3 3
AGITG

NCIC CTG C0.17: Overall Survival by *KRAS* Status in BSC ARM



KRAS status	MS (months)	95% CI
Mutated	4.6	3.6 – 5.5
Wild-Type	4.8	4.2 – 5.5

HR 1.01 95% CI (0.74,1.37)

Log rank p-value: 0.97

NO PROGNOSTIC IMPACT OF K-ras STATUS

83	69	42	28	20	13	11	7
113	92	69	36	24	17	12	5

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NCIC CTG CO.17: *KRAS* and Cetuximab Conclusions

In the context of pre-treated advanced colorectal cancer:

- **There is no benefit in using cetuximab monotherapy in patients that have mutated *K-ras* tumours**
- **There is 4.7 month improvement in median survival with cetuximab in patients with *K-ras* wild-type tumours**
- **The p-value for the interaction between *K-ras* status and treatment is 0.01**
- **There is an improvement in PFS with cetuximab in *K-ras* wild-type tumours**
- ***K-ras* mutation status does not have a treatment-independent prognostic effect**

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NCIC CTG CO.17: Additional Correlative Studies

- Approved
  - Epiregulin & Amphiregulin expression – ASCO 2009
  - BRAF mutations, PIK3CA mutations, Loss of PTEN (IHC, FISH) – in progress
  - K-Ras validation – pending FDA/BMS
- Proposed
  - FCγR polymorphisms
  - IGF-1R expression

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"Play some Frisbee, chew on an old sock, bark at a squirrel. If that doesn't make you feel better, eat some cheese with a pill in it."

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Correlative Study Analyses

Examples

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Example: HER2 as a Biomarker for Early Breast Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 18, 2006 VOL. 354 NO. 20

HER2 and Responsiveness of Breast Cancer to Adjuvant Chemotherapy

Kathleen I. Pritchard, M.D., Lois E. Shepherd, M.D., Frances P. O'Malley, M.D., Irene L. Andrulis, Ph.D., Dongsheng Tu, Ph.D., Vivien H. Bramwell, M.B., B.S., and Mark N. Levine, M.D., for the National Cancer Institute of Canada Clinical Trials Group

NCIC CTG-MA5
Pre-menopausal
node positive
(n=710)

RANDOMIZATION

CMF 6 cycles every 4 weeks

- Cyclophosphamide 100 mg/m^2 po x 14 d
- Methotrexate 40 mg/m^2 iv d 1& 8
- 5FU 600 mg/m^2 iv d 1& 8

CEF 6 cycles every 4 weeks

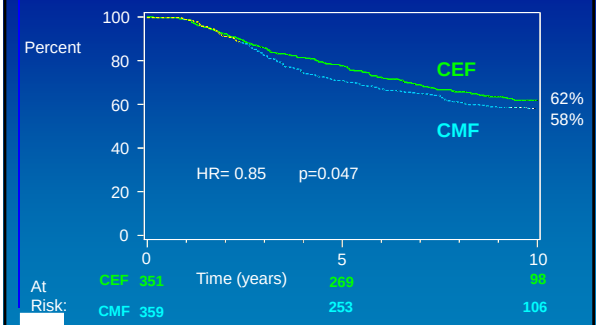
- Cyclophosphamide 75 mg/m^2 po x 14d
- Epirubicin 60 mg/m^2 iv d 1 & 8
- 5FU 500 mg/m^2 iv d 1 & 8

Cotrimoxazole or norfloxacin/ciprofloxacin

NCIC CTG MA. 5

- Patients accrued from 1989 to 1993
- First results published in 1998 which showed that CEF is superior to CMF in both relapse free and overall survivals
- FDA approved CEF for the treatment of early breast cancer in 1999
- CEF became a standard treatment in Canada for premenopausal women with node positive breast cancer
- CEF is however more toxic than CMF (associated with increased risk in heart failure and leukemia) and also more expensive
- There was a need for a biomarker which would be used to identify patients who will benefit from CEF

MA.5 Overall Survival



Levine et al, JCO 2005

Correlative (translational) Studies in MA.5

- HER2 overexpression by
  - Immunohistochemistry with
    - CB 11 Antibody
    - TAB 250 Antibody
- HER2 amplification by
  - Polymerase chain reaction (PCR)
  - Fluorescence-in-situ hybridization (FISH)
- All work carried out on paraffin embedded specimens

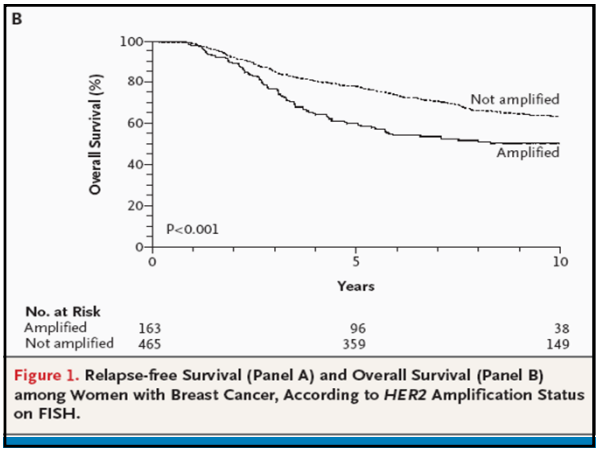
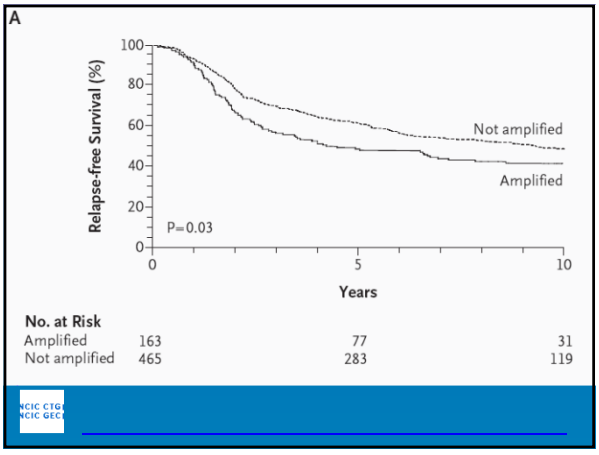


Figure 1. Relapse-free Survival (Panel A) and Overall Survival (Panel B) among Women with Breast Cancer, According to *HER2* Amplification Status on FISH.



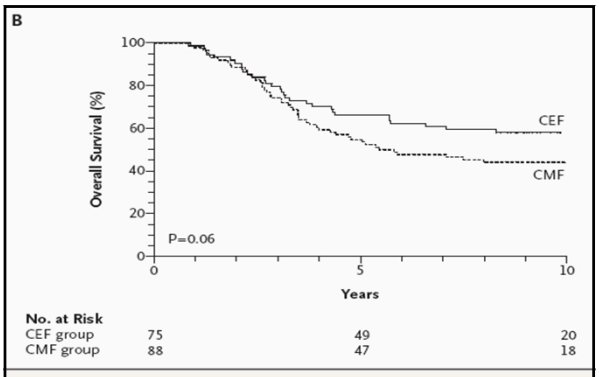
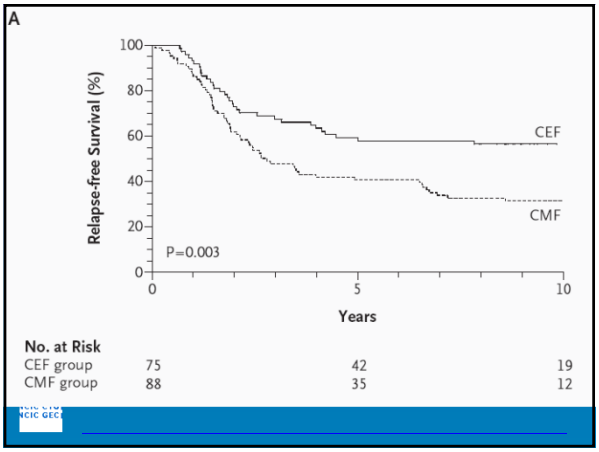


Figure 2. Relapse-free Survival (Panel A) and Overall Survival (Panel B) According to the Type of Adjuvant Chemotherapy in Women with *HER2* Amplification on FISH.



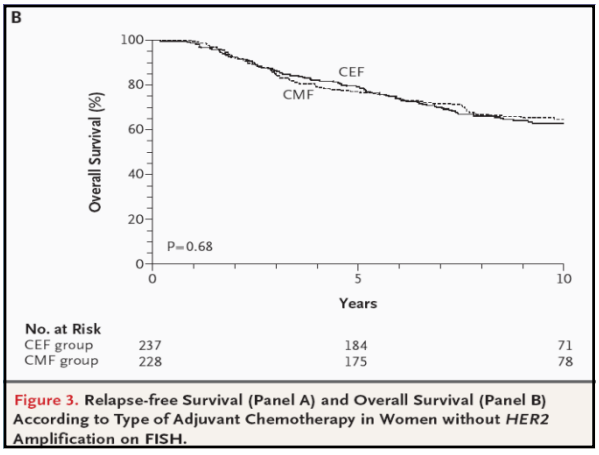
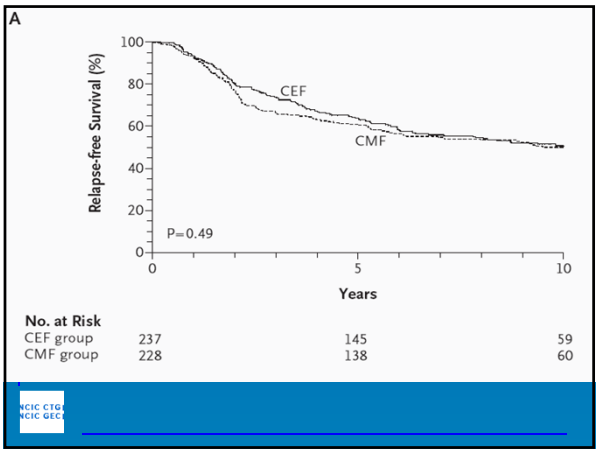


Figure 3. Relapse-free Survival (Panel A) and Overall Survival (Panel B) According to Type of Adjuvant Chemotherapy in Women without *HER2* Amplification on FISH.



Adjusted* Hazard Ratios by HER2 Status (CEF vs. CMF)

	Relapse Free Survival			Overall Survival		
HER2	HR	95% CI	p-value	HR	95% CI	p-value
Amplified	0.52	0.34 - 0.80	0.003	0.65	0.42 – 1.02	0.06
Not Amplified	0.91	0.71 - 1.18	0.49	1.06	0.83 - 1.44	0.68

* adjusted for age, nodal status, grade, ER status, surgical procedure, tumour size

Test for interaction: p=0.02 for DFS; p=0.01 for OS

Pritchard NEJM 2006

Conclusions from MA.5 Correlative Analyses

- HER2 amplification or overexpression in breast cancer is associated with a larger benefit from CEF than CMF
- Patients whose tumours do not amplify or overexpress HER2 receive virtually no benefit from CEF, as compared to CMF
- Patients whose tumours do not exhibit HER2 amplification or overexpression could be treated with less toxic regimen of CMF
- Those with tumours which show amplified or overexpressed HER2 should receive dose-intense anthracycline-containing regiments such as CEF.

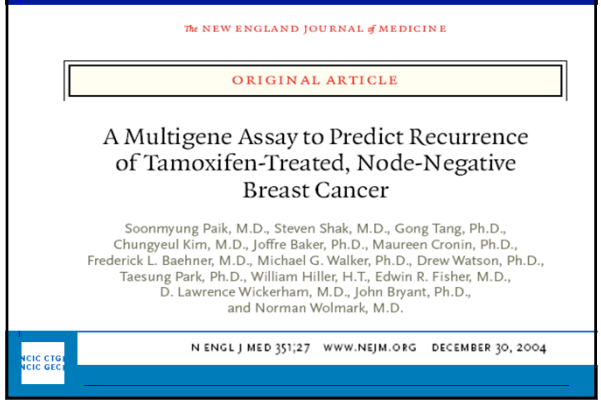
Limitations of MA. 5 Results to Clinical Practice (From Editorial by Martine Piccart-Gebhart)

- A benefit of CEF to patients whose tumours do not amplify or overexpress HER2 cannot be firmly ruled out
- It is now known from high-throughput gene-expression profiling of breast cancer that HER2 negative tumour includes at least three different subforms: basal-like; luminal B; luminal A
- Chemotherapy may still be beneficial for HER2 negative patients with luminal B and basal-like breast cancer

The Need for Better Biomarkers

- "It is thought provoking that after 30 years of modern tumour marker research, clinically useful cancer markers are still rare"
- "Gene expression profiling and other high-throughput genomic techniques are likely to find their own niche in the near future"
- Molecular signatures identified from genomics and proteomics studies could prove to be more "accurate" than a single gene biomarker since any particular gene that functions as part of a complex network may contain only limited information about the activity of the entire pathway.

Example: A multigene Biomarker for Breast Cancer



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

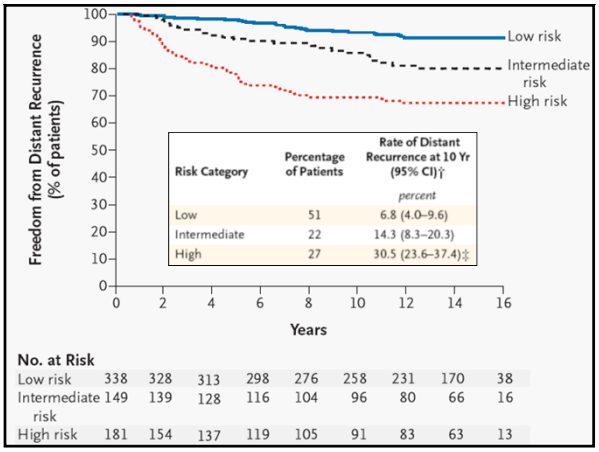
A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

Soonmyung Paik, M.D., Steven Shak, M.D., Gong Tang, Ph.D., Chungyeul Kim, M.D., Joffre Baker, Ph.D., Maureen Cronin, Ph.D., Frederick L. Baehner, M.D., Michael G. Walker, Ph.D., Drew Watson, Ph.D., Taesung Park, Ph.D., William Hiller, H.T., Edwin R. Fisher, M.D., D. Lawrence Wickerham, M.D., John Bryant, Ph.D., and Norman Wolmark, M.D.

N ENGL J MED 351;27 WWW.NEJM.ORG DECEMBER 30, 2004

Development of Oncotype DX™ 21-Gene Assay

- Development of a high-throughput, real-time, RT-PCR method to quantify gene expression with the use of sections of fixed, paraffin-embedded tumor tissue
- Selection of 250 candidate genes from published literature, genomic databases, and experiments based on DNA arrays performed on fresh-frozen tissue
- Analysis of data from three independent clinical trials of breast cancer to test the relationship between expression of the 250 candidate genes and the recurrence of breast cancer
- Selection of a panel of 16 cancer-related genes and 5 reference genes to generate an algorithm to calculate a recurrence score based on levels of expression of these genes

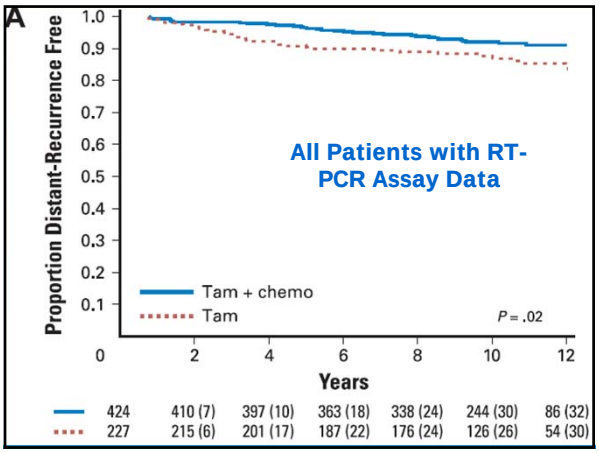


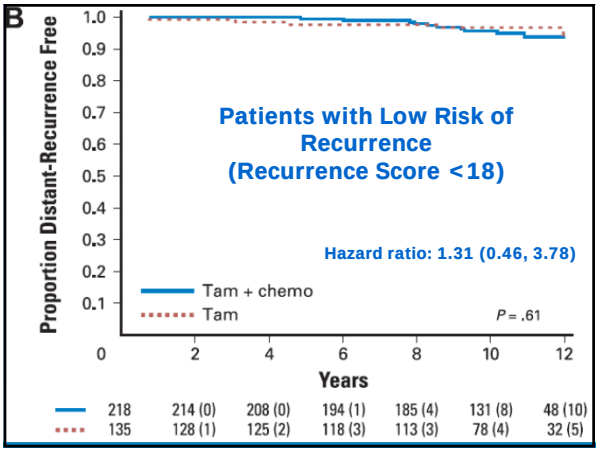
Recurrence Scores and Benefit of Chemotherapy

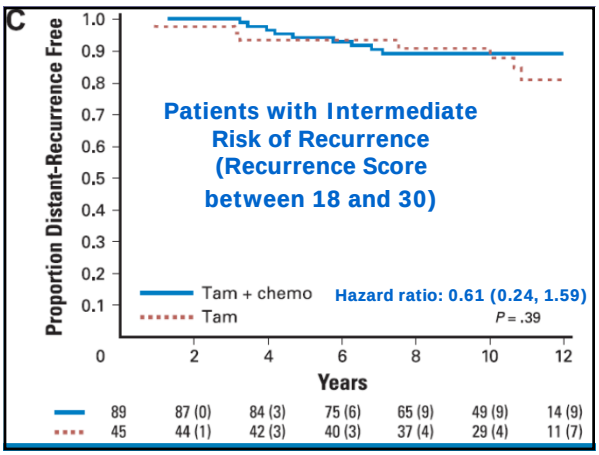
VOLUME 24 · NUMBER 23 · AUGUST 10 2006
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

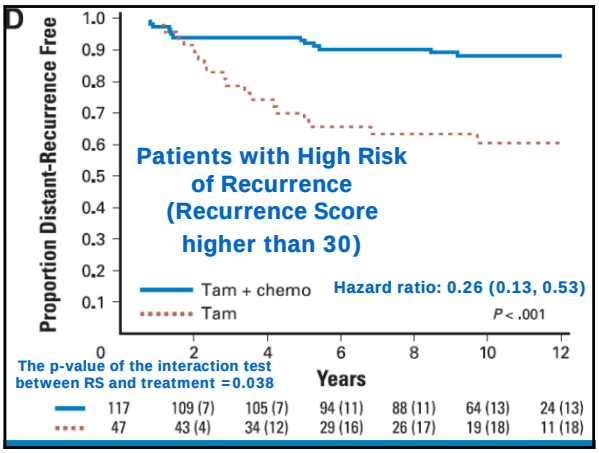
Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor–Positive Breast Cancer

Soonmyung Paik, Gong Tang, Steven Shak, Chungyeul Kim, Joffre Baker, Wanseop Kim, Maureen Cronin, Frederick L. Baehner, Drew Watson, John Bryant, Joseph P. Costantino, Charles E. Geyer Jr, D. Lawrence Wickerham, and Norman Wolmark


A
Proportion Distant-Recurrence Free
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
All Patients with RT-PCR Assay Data
Tam + chemo
Tam
P = .02
2
4
6
8
10
12
Years
424 410 (7) 397 (10) 363 (18) 338 (24) 244 (30) 86 (32)
227 215 (6) 201 (17) 187 (22) 176 (24) 126 (26) 54 (30)


B
Proportion Distant-Recurrence Free
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Patients with Low Risk of Recurrence (Recurrence Score <18)
Hazard ratio: 1.31 (0.46, 3.78)
Tam + chemo
Tam
P = .61
2
4
6
8
10
12
Years
218 214 (0) 208 (0) 194 (1) 185 (4) 131 (8) 48 (10)
135 128 (1) 125 (2) 118 (3) 113 (3) 78 (4) 32 (5)


C
Proportion Distant-Recurrence Free
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Patients with Intermediate Risk of Recurrence (Recurrence Score between 18 and 30)
Tam + chemo
Tam
Hazard ratio: 0.61 (0.24, 1.59)
P = .39
2
4
6
8
10
12
Years
89 87 (0) 84 (3) 75 (6) 65 (9) 49 (9) 14 (9)
45 44 (1) 42 (3) 40 (3) 37 (4) 29 (4) 11 (7)



Conclusions from RS and Chemotherapy Analysis

- Patients with tumours that had low recurrence score derived minimal, if any, benefit from chemotherapy treatment, while patients with tumours that had high recurrence score experienced a large chemotherapy benefit.
- Patients with tumours that had intermediate recurrence score did not appear to receive a substantial benefit, but the uncertainty in the estimate (relative risk=0.61 with 95% CI from 0.24 to 1.59) cannot exclude a clinically important benefit from chemotherapy treatment
- The Oncotype DX 21 Gene Assay not only quantifies the likelihood of breast cancer recurrence in women with node-negative, estrogen receptor-positive breast cancer (i.e., as a prognostic marker), but also predicts the magnitude of chemotherapy benefit (i.e., as a predictive marker)

The Trial Assigning IndividuaLized Options for Treatment (Rx), or TAILORx (N=10,046)