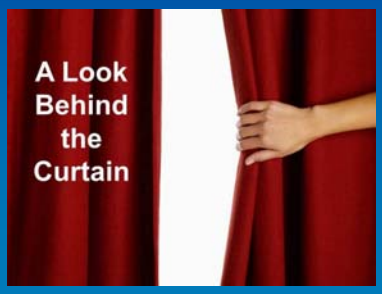
Plenary Session 2:

Key Elements of a Successful Phase III Trial:

Examples from the NCIC CTG



C.J. O'Callaghan *DVM MSc PhD*

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NCIC GEC

What is a "Successful" Trial?

Academic Clinical Trialist's Perspective!

- A well designed trial, properly conducted in a timely manner, resulting in high quality data, which is stringently analyzed and fully and transparently reported, providing valid information permitted future decision-making.
- NOT necessarily a positive trial...
  - a negative trial can be as important and may also change practice

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What is a "Failed" Trial?

- A poorly designed or executed trial that, even if 'completed', fails to answer the question
  - biased, uninterpretable, inconclusive, underpowered, flawed, fraudulent
- A "well designed" trial that simply fails to accrue!
- Both = waste of time, effort, resources, huge opportunity cost

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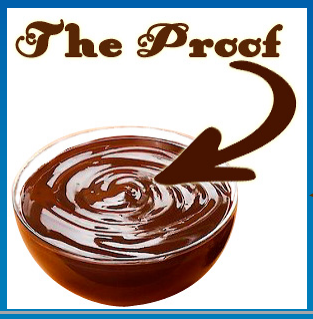
Surely its simple?

- DESIGN a clinical trial
- ACCRUE patients
- Collect DATA (+/- samples)
- ANSWER the question(s)

Smart people
Careful planning
Peer review
Monitoring
Science



Patient preference
Investigator preference
"Red Tape"
Intangibles

Eligiblity Criterion*

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Design, Data & Analysis
(The NCIC CTG Mantra)

- Hypothesis robust and well supported
- Valid design
  - Statistical components of design critical
- Consensus (collaborators, pharma) needed
  - Comparators / standard of care, placebo control
  - "Access" to IMP
    - regulatory status, funding status, availability of placebo, distribution, storage, shelf-life & extensions, packaging, labeling, inventory tracking, import/export requirements, shipping costs, temperature excursions
- Efficient conduct
  - Collect only relevant data/samples
  - Collect 'necessary' biospecimens (think to the future!)
- Ensure high quality
  - Clean data, conduct compliance & quality assurance activities (e.g. monitor, audit, pharmacovigilance, etc.)
  - Analysis and publication/dissemination

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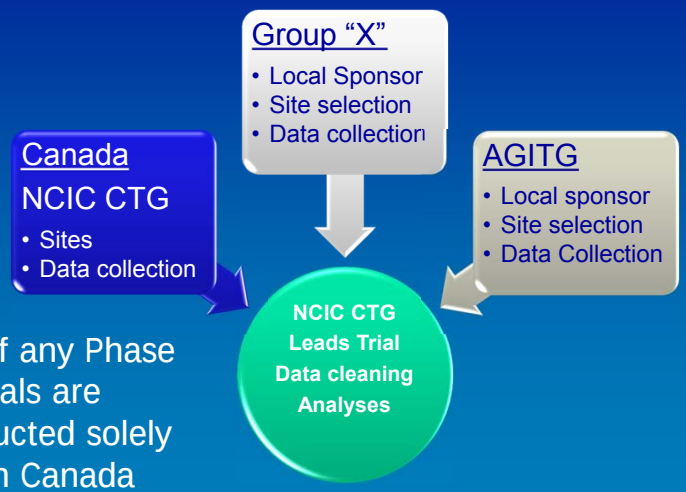
Creating Collaborators: The 'Intergroup' Trial Model



Few if any Phase III trials are conducted solely within Canada

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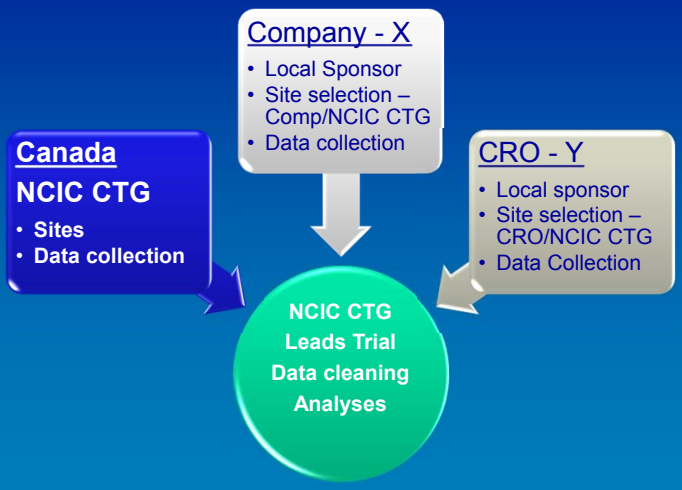
Creating Accrual: The 'International' Trial Model



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Good Accrual

- Investigators are interested in putting patients on the study
- Sites/Institutions are interested and capable of in supporting Investigators
- Patients are interested in participating in the study... and are eligible to do so

= rapid activation and timely accrual

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What makes a trial interesting?

- Relevant question that will change practice, NOT superseded by changing practice (equipoise)
- Promising data from earlier stage trials, other disease sites
- New, particularly 'novel', drugs or treatments always of interest
- Simple is more attractive – i.e. complexity as scientifically necessary
- Limited therapeutic options – e.g. end stage settings
- Good risk/benefit ratio (real or perceived)
- Unique - Not already planned, in progress… or complete!
- Well funded/resourced

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Eligible?

Again, it sounds simple = Be sure patients…

- Meet the eligibility criteria
- Do not meet the ineligiblity criteria

Sometimes "science" trumps pragmatism…

- Validity – e.g. population with disease of interest
- Ethics – e.g. consent
- Safety – e.g. comorbidity, pregnancy, baseline AEs
- Efficacy – e.g. prior (future) therapy, assessable for outcome, optimize potential
- Quality – e.g. surgical QA, S.O.C.

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Funding and Resource

- Critical to resource and fund appropriately or run the risk of the trial failing
- Everything costs more than you think
  - Centrally & for participating sites
  - *"… per-patient clinical trials costs have gone up by a stunning 70% in just the past three years, with the largest increases coming in the pivotal Phase III trials required by the FDA. There, costs were up by over 85%**."*
- Slower than expected accrual substantially increases costs → longer duration thus increased staffing costs

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***Clinical Operations: Benchmarking Per-Patient Costs, Staffing and Adaptive Design*, Cutting Edge Information

ASIDE: Funding and Resource

1. Fund yourself
   - not feasible for phase III
2. Apply for a peer-reviewed grant
   - e.g. CIHR = ↓15% success rate
3. Submit proposal to a group
   - may still need #2 ± #4
4. Submit proposal to a company
   - Supported proportionate to interest
   - Investigator/Sponsor independence?
   - Faster timelines, more oversight, more demands…

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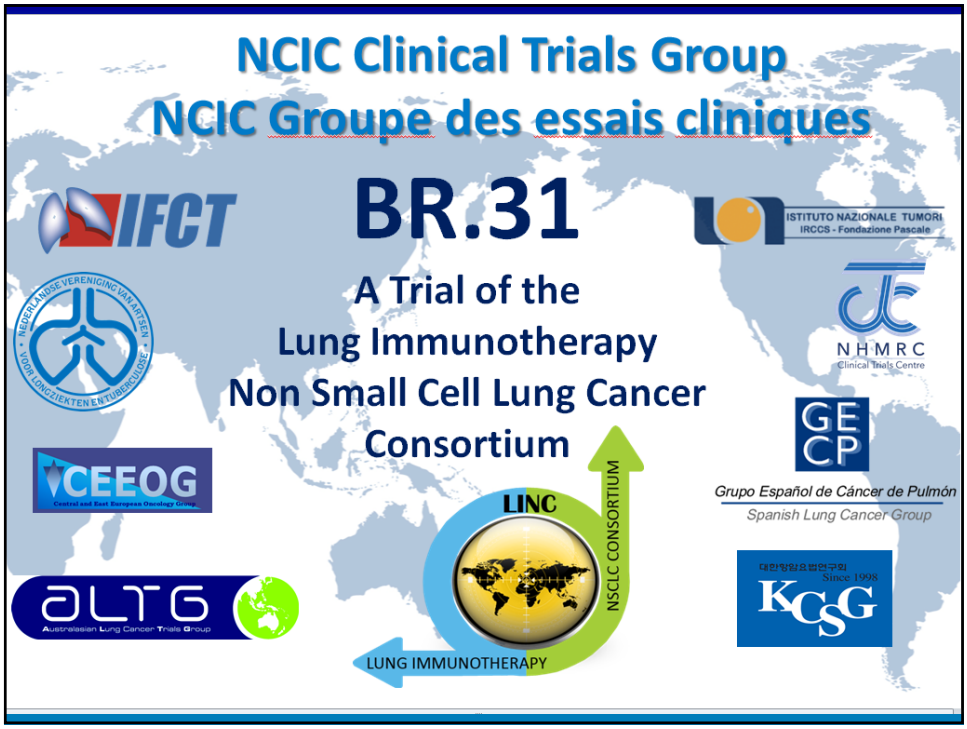
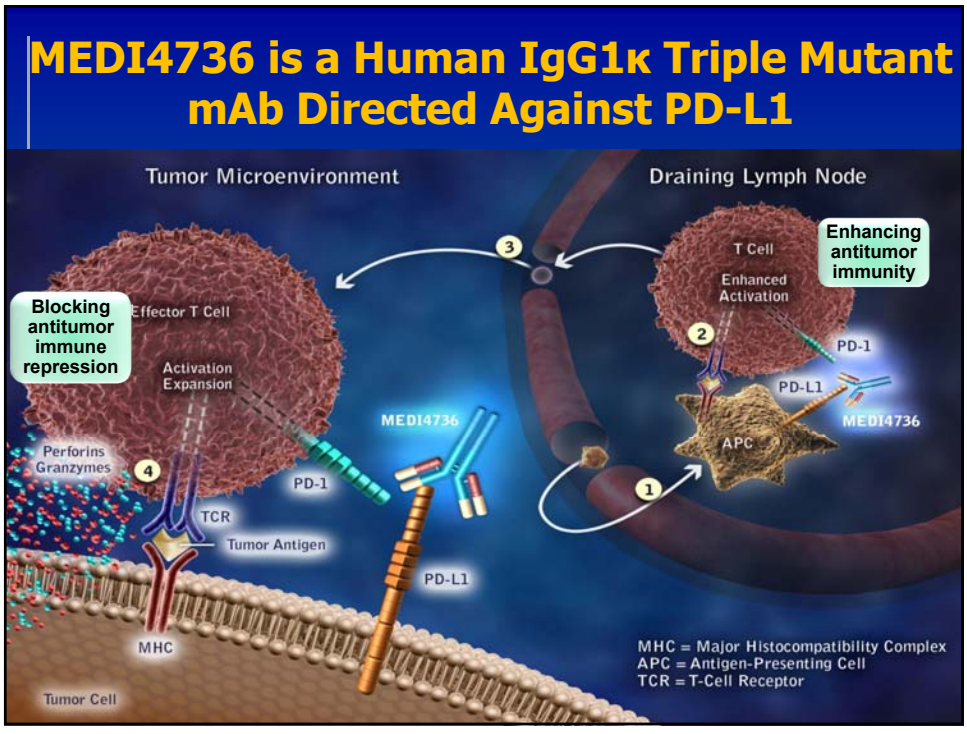

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques
BR.31
A Trial of the
Lung Immunotherapy
Non Small Cell Lung Cancer
Consortium
IFCT
ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale
NHMRC
Clinical Trials Centre
GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group
CEEOG
ALTG
Australasian Lung Cancer Trials Group
KCSG
Since 1998
LINC
NSCLC CONSORTIUM
LUNG IMMUNOTHERAPY


MEDI4736 is a Human IgG1κ Triple Mutant mAb Directed Against PD-L1
Tumor Microenvironment
Draining Lymph Node
Blocking antitumor immune repression
Enhancing antitumor immunity
Effector T Cell
Activation
Expansion
Perforins
Granzymes
PD-1
TCR
Tumor Antigen
MHC
Tumor Cell
MEDI4736
PD-L1
T Cell
Enhanced Activation
PD-1
PD-L1
MEDI4736
APC
MHC = Major Histocompatibility Complex
APC = Antigen-Presenting Cell
TCR = T-Cell Receptor

MEDI4736 is Well Tolerated in NSCLC

	MEDI4736 10 mg/kg q2w n=143	MEDI4736 all doses[a] n=155
All Events, n (%)		
Any AE	98 (69)	109 (70)
Grade 3/4 AE	37 (26)	39 (25)
Serious AE	33 (23)	36 (23)
Related Events[b] Only, n (%)		
Any AE	40 (28)	45 (29)
Grade 3/4 AE	**5 (4)**	**5 (3)**
Serious AE	**2 (1)**	**2 (1)**
AEs leading to discontinuation	**0**	**0**
AEs leading to death	0	0

No colitis of any Grade and no Grade 3/4 pulmonary toxicities

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Brahmer et al. ASCO Abs 8021. Clinical Activity and Biomarkers of MEDI4736,

BR31: A Phase III Prospective Double Blind Placebo Controlled Randomized Study of Adjuvant MEDI4736 in Completely Resected Non-Small Cell Lung Cancer

- Stage IB (≥ 4cm), II, IIIA NSCLC
- Completely resected
- ECOG PS 0-1
- Stratified by:
  - Stage
  - Pre-treatment PD-L1 status*
  - Prior adj. platinum-based chemo
  - Centre

*First 600 patients not selected for PD-L1 status, thereafter 500 PD-L1+ only = TOTAL Sample size = 1100

2:1 Randomization

MEDI4736
10mg/kg intravenously Q2W (6 mo)
20mg/kg intravenously Q4W (6 mo)

PLACEBO
10mg/kg intravenously Q2W (6 mo)
20mg/kg intravenously Q4W (6 mo)

19 infusions over 1 year

Primary Endpoint = DFS (PDL1+)

Secondary endpoints = DFS (all), OS, QoL

NCIC CTG
NCIC GEC

Interesting?

- ✓ Relevant question that will change practice, NOT superseded by changing practice (equipoise)
- ✓ Promising data from earlier stage trials, other disease sites
- ✓ New, particularly 'novel', drugs or treatments always of interest
- X Simple is more attractive – i.e. complexity as scientifically necessary
- X Limited therapeutic options – e.g. end stage settings
- ± Good risk/benefit ratio (real or perceived)
- ✓ Unique - Not already planned, in progress... or complete!
- ± Well funded/resourced (CDN$15,250 PCF)

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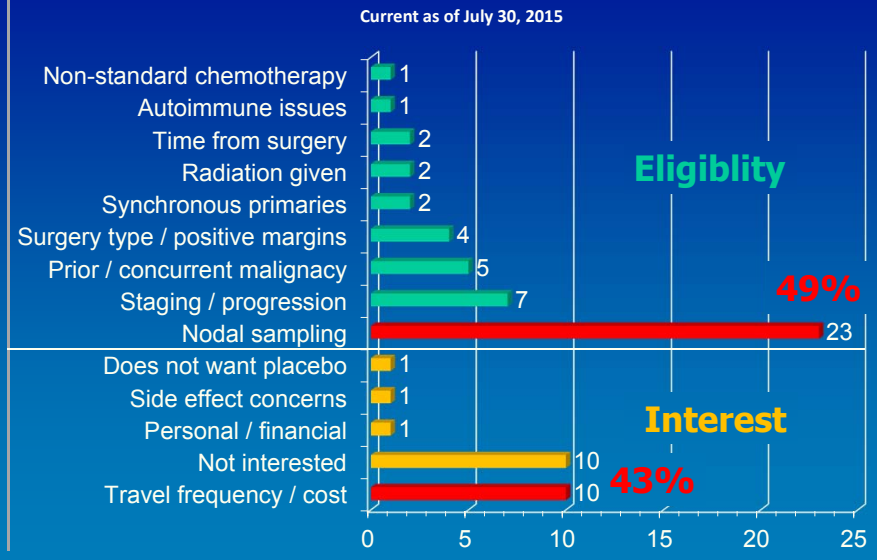
How's it going so far?

- Centrally activated = October 9, 2014
- First site locally activated = November 25, 2014 (47 days)
- First patient registered = January 29, 2015 (65 days)
- First patient randomized = February 24, 2015 (26 days)
- To-date (295 days from Central Activation)....
  - 49 of ~250 (20%) planned sites are locally activated
  - 8 patients registered (... 2 will not be randomized)
    - **~ 1 patient per site per every 24 months of activity**
  - 4 patients randomized
  - 70 patients reported as "screen failures"
    - **70/78 = 90% screen failure rate**

Sample Size = 600 (all comers) + 500 PD-L1+ (~25% prevalence)

NCIC CTG
NCIC GEC

BR.31 Submitted Screen Failures



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Eligibility – Lymph Node Sampling

As per protocol eligibility criteria:

- Lymph node mapping is defined by The International Association for the Study of Lung Cancer (IASLC) lymph node map.
- The nodal tissue must be labelled according to the recommendations of the American Thoracic Society.
- Surgeons are encouraged to dissect or sample all accessible nodal levels in accordance with the European Society of Thoracic Surgeons guidelines.
  - Accordingly, a minimum of **3** (three) lobe specific mediastinal nodal stations (**N2**), one of which must include **station 7**, and at least **one N1** station - inclusive of the ones removed with the pulmonary specimen - ***must have been sampled*** at the end of the procedure.

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NCIC GEC

Will BR.31 be a "Success" ?

YES! ⟶ WHY?

- Target sample size of 1100 patients
  - 250 sites active by 1Q2016
  - requires 4.4 pts/site
- Target accrual period of 3 years
  - ~2 years left = 2.2 pts/site/year

- Discussions ongoing:
  - ? Amend eligibility criteria w.r.t. lymph node sampling
  - ? Amend infusion frequency to monthly throughout
  - ? Add additional collaborators

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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

NCIC Clinical Trials Group (NCIC CTG)

and the

Australasian Gastro-Intestinal Trials Group (AGITG)

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

AUSTRALASIAN GASTRO-INTESTINAL AGITG TRIALS GROUP

Advanced Colorectal Cancer Therapeutics

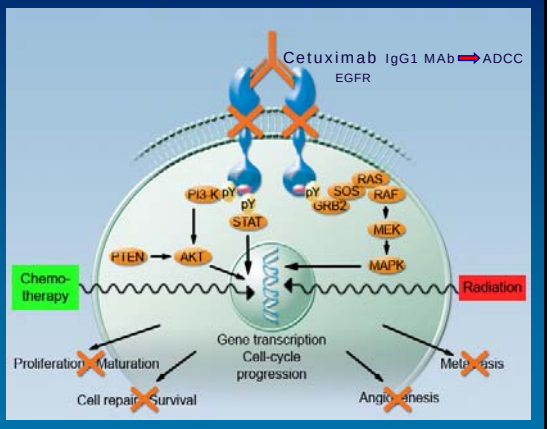
Chemotherapeutic	Survival Benefit Demonstrated
TS inhibitors (5-fluorouracil, capecitabine)	Yes[1,2]
Irinotecan	Yes[3,4,5,6]
Oxaliplatin	Yes[7]
Biologically Targeted therapy	
Bevacizumab (anti-VEGF) added to fluropyrimidines	Yes[8,9]
Panitumumab (anti-EGFR)	No
Cetuximab (anti-EGFR)	No

NCIC CTG
NCIC GEC

[1]Simonds, BMJ 2000; [2]Jonker, BJC 2000; [3]Cunningham, Lancet 1998; [4]Rougier, Lancet 1998; [5]Saltz, NEJM 2000; [6]Douillard, Lancet 2000; [7]Goldberg, JCO 2004; [8]Hurwitz, NEJM 2004

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)



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

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

Failed or intolerant to all recommended therapies

(TS, Oxaliplatin, Irinotecan)

1243 screened
79% EGFR +ve

REGISTER

EGFR testing by IHC

RANDOMIZE

1:1

572 randomized

Cetuximab* + BSC — 287

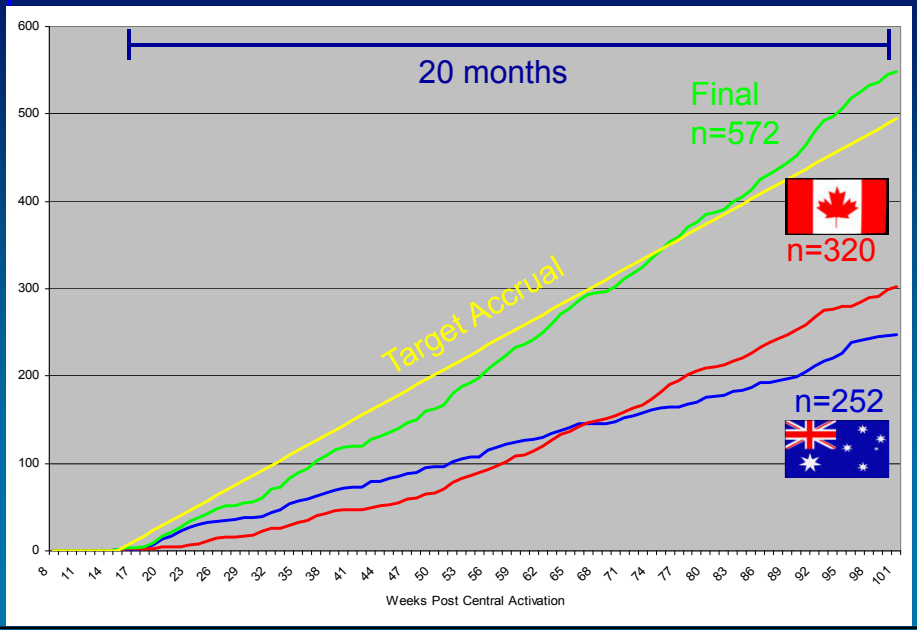
BSC alone — 285

Disease Progression or Unacceptable Toxicity

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

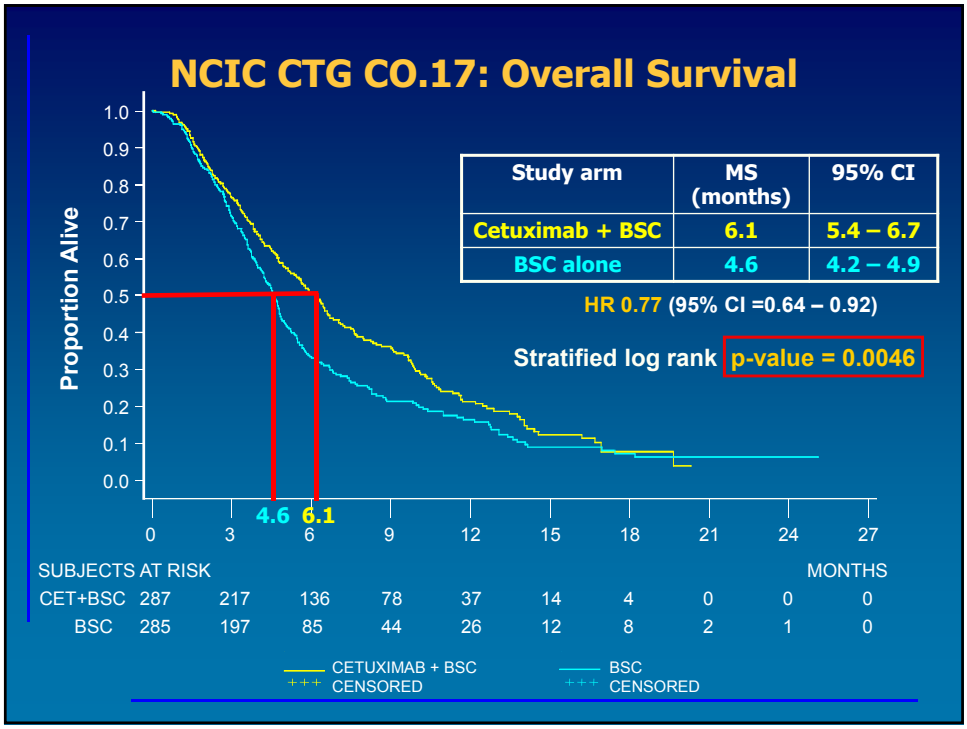
- **Primary Objective: Overall Survival** (5% alpha, 90% power, HR=0.74, 445 deaths)
- **Secondary: Progression Free Survival, Objective Response Rate Safety, Quality of Life, Health Economics, Correlative Biomarkers** (optional)

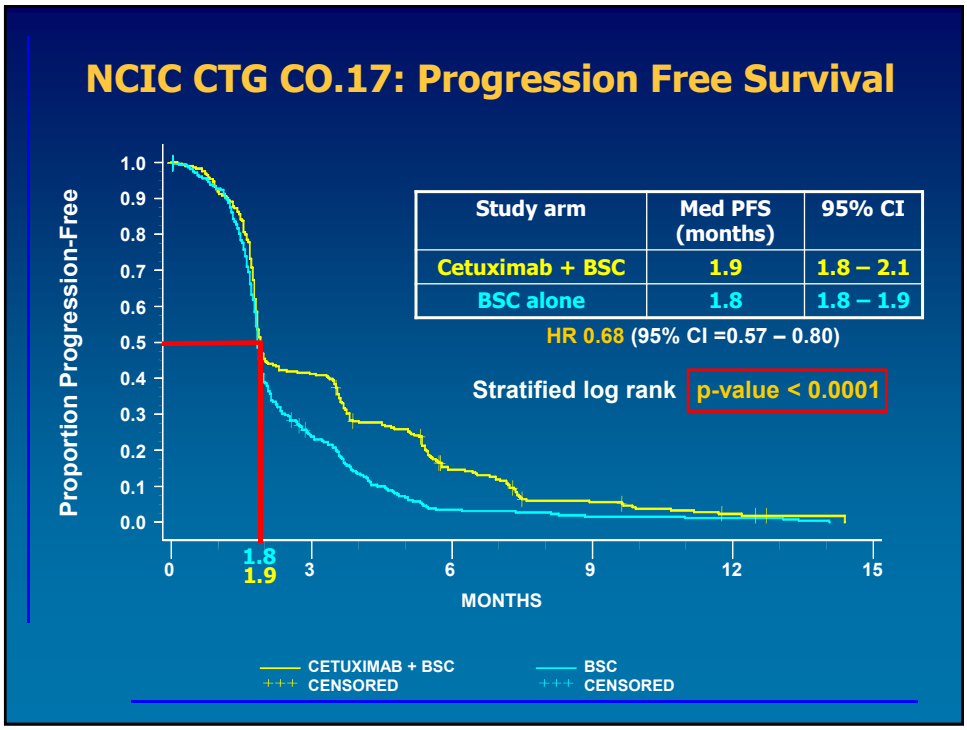
NCIC CTG CO.17: Accrual



CO.17 Top Accruing NCIC CTG Centres (/32)

Rank	Centre	# Patients
1	UHN – Princess Margaret Hospital (CAMP)	41 (7%)
2	Ottawa Health Research Institute (CAKO)	34
3	Cross Cancer Institute (CATW)	28
4	Odette Cancer Centre (CAMN)	22
5	CancerCare Manitoba (CARM)	21
6	BCCA – Vancouver Cancer Centre (CAVA)	19
7	Lakeridge Health Oshawa (CALO)	18
8	Hopital Charles LeMoyne (CAHO)	17
9	Allan Blair Cancer Centre (CASA)	13
10	CHUM - Hôpital Notre-Dame (CAHN)	11
11	Grand River Regional Cancer Centre (CANG)	10


NCIC CTG CO.17: Overall Survival
Proportion Alive
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
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
4.6 6.1
0 3 6 9 12 15 18 21 24 27
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
CETUXIMAB + BSC
CENSORED
BSC
CENSORED


NCIC CTG CO.17: Progression Free Survival
Proportion Progression-Free
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
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
1.8
1.9
0 3 6 9 12 15
MONTHS
CETUXIMAB + BSC
CENSORED
BSC
CENSORED

Proportion of Patients Who Had QoL Deterioration* at 8 and 16 Weeks

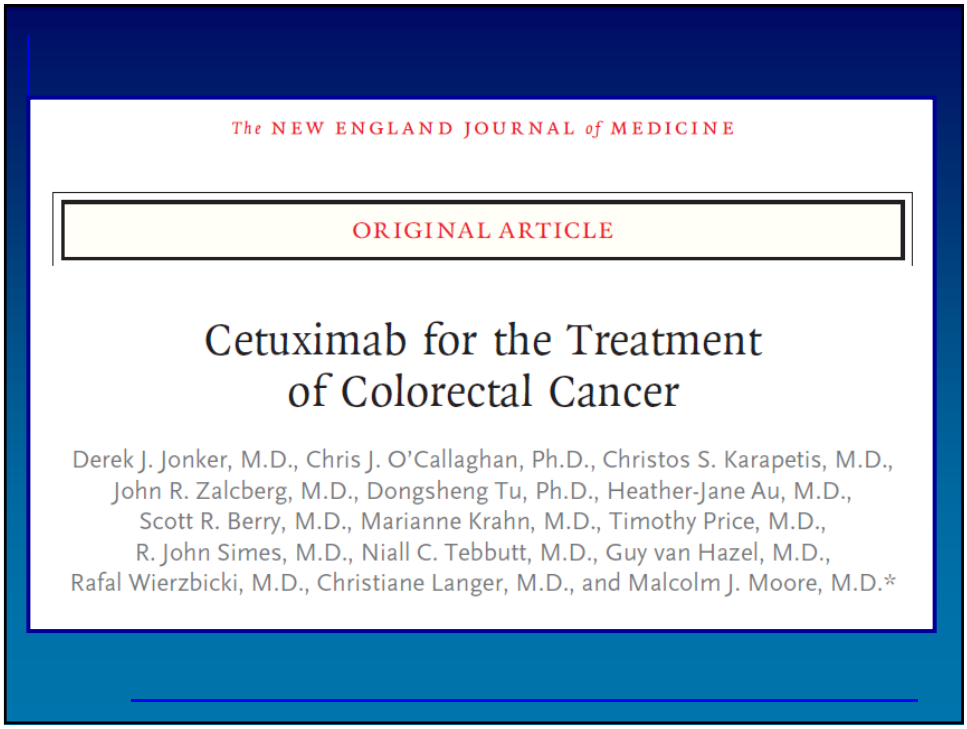
Variable	Cetuximab + BSC	BSC	p-value**
Week 8			
Physical Function	24.9%	34.7%	0.051
Global Health Status	23.2%	38.3%	0.004
Week 16			
Physical Function	30.4%	43.4%	0.069
Global Health Status	31.3%	49.3%	0.011

*Change score from baseline $\leq$ -10 ** From Fisher's exact test

NCIC CTG CO.17: Primary Study Conclusions

- The safety profile of cetuximab monotherapy was acceptable and consistent with the reported incidence from previous mono-therapy studies
- Cetuximab significantly (but modestly) prolonged Overall Survival compared to Best Supportive Care in patients in which all other therapy had failed.
- Progression Free Survival and Response Rate were also significantly improved and Quality of Life significantly sustained with cetuximab over Best Supportive Care, but cost efficacy and utility values were high.

This was the first time single-agent biologic targeted therapy had shown a survival benefit in colorectal cancer.



CO.17 Timeline

- "First Contact" = April 2002
- Protocol finalized = April 2003 (12)
- Contract signed = July 2003 (3)
- Central activation = Aug 2003 (1)
- First site activated = Nov 2003 (AGITG) , Dec 2003 (NCIC CTG) (3)
- First patient randomized = Dec 2003 (AGITG & NCIC CTG) (1)
- Last patient randomized = Aug 2005 (20)
- Clinical cut-off (data mature) = March 2006 (7)
- Database locked & final analysis = November 2006 (8)
- AACR plenary presentation = April 2007 (5)
- NEJM publication = November 2007 (7)

Total = 5 years, 7 months

Was CO.17 a "Success" ?

"A well designed trial, properly conducted in a timely manner, resulting in high quality data, which is stringently analyzed and fully and transparently reported?"

YES! ⟶ WHY?

- ✓ Relevant question that will change practice, NOT superseded by changing practice (equipoise)
- ✓ Promising data from earlier stage trials, other disease sites
- ✓ New, particularly 'novel', drugs or treatments always of interest
- ± Simple is more attractive – i.e. complexity as scientifically necessary
- ✓ Limited therapeutic options – e.g. end stage settings
- X Good risk/benefit ratio (real or perceived) (BSC arm)
- ✓ Unique - Not already planned, in progress... or complete!
- ✓ Well funded/resourced ($6,000 + $150 EGFR negatives)

CO.17 "the gravy"

… which patients benefited?

Median PFS the same in both arms

A reliable biomarker was needed:

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

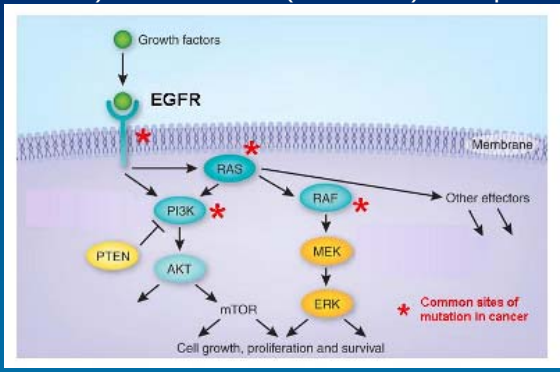
Ideally, the predictive value of the biomarker would need to be differentiated from its prognostic implications

The *KRAS* mutation status of the tumour was proposed as a potential marker of response and a predictor of benefit

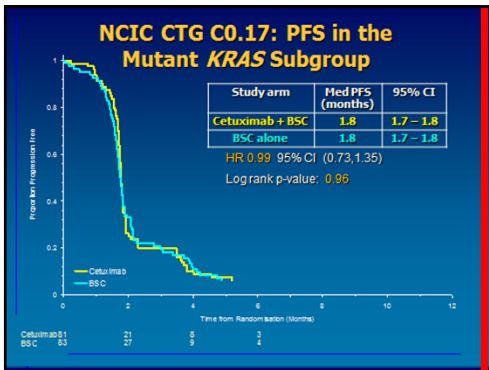
- **Preliminary evidence from several single-arm studies**
- **Biological plausibility**

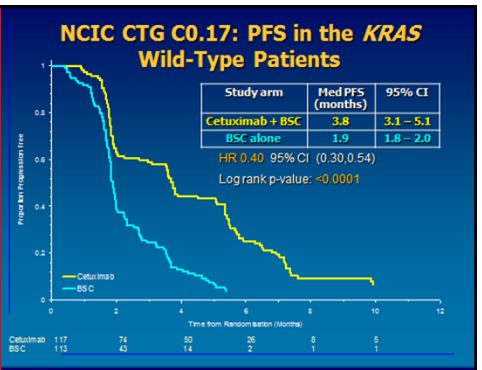
The *KRAS* Oncogene

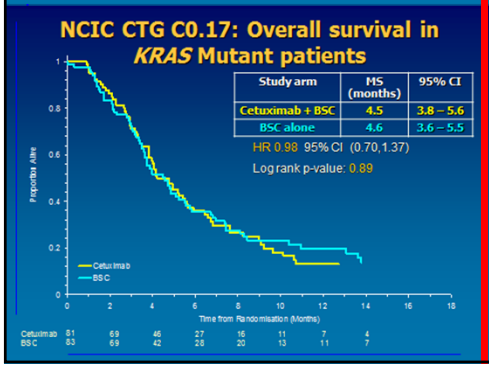
- KRAS is a small G-protein downstream of EGFR and is an essential self-inactivating component of the EGFR signalling cascade, normally cycling from from GDP bound ("off" state) to GTP bound ("on" state) in response to receptor activation
- Mutations in the *KRAS* gene can lead to constitutive activation of KRAS independent of EGFR = "turning on" the signalling pathway.
- Inhibitors that are upstream of KRAS, eg EGFR receptor inhibitors, may be ineffective

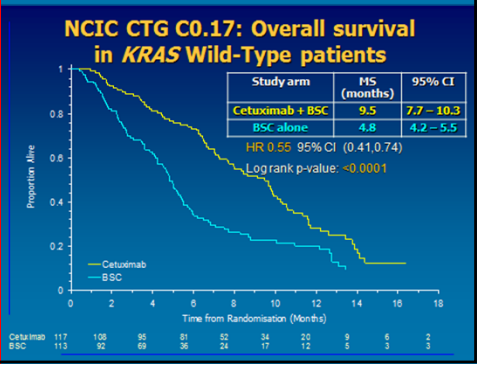


- These activating *KRAS* mutations are among the most common oncogenic alterations in cancer (particularly at codons 12 and 13), occur in the early stages of carcinogenesis and can be detected by DNA extraction, amplification and sequencing techniques, even using FFPE tissue









The NEW ENGLAND JOURNAL of MEDICINE

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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.*

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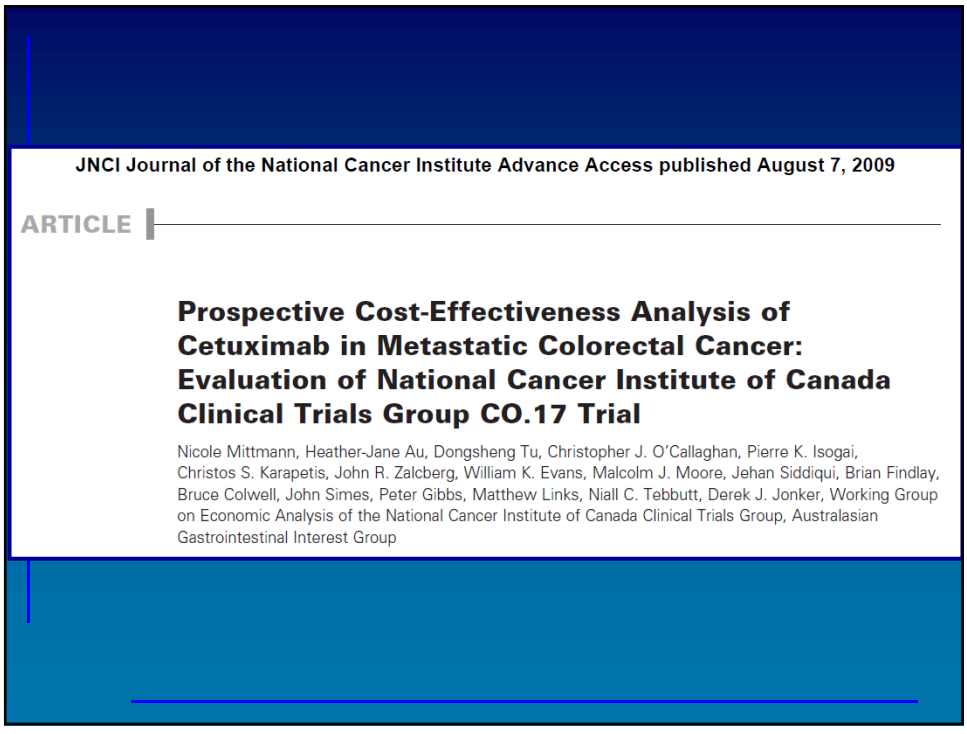
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Health-Related Quality of Life in Patients With Advanced Colorectal Cancer Treated With Cetuximab: Overall and *KRAS*-Specific Results of the NCIC CTG and AGITG CO.17 Trial

Heather-Jane Au, Christos S. Karapetis, Chris J. O'Callaghan, Dongsheng Tu, Malcolm J. Moore, John R. Zalcberg, Hagen Kennecke, Jeremy D. Shapiro, Sheryl Koski, Nick Pavlakis, Danielle Charpentier, David Wyld, Michael Jefford, Gregory J. Knight, Nadine M. Magoski, Michael D. Brundage, and Derek J. Jonker

From the Cross Cancer Institute, Edmonton, Alberta; National Cancer Institute of Canada Clinical Trials Group; and Departments of Oncology and Community Health and Epidemiology, Queen's University, Kingston; Princess Margaret Hospital, Toronto; Grand River Regional Cancer Centre, Kitchener; and



JNCI Journal of the National Cancer Institute Advance Access published August 7, 2009

ARTICLE

Prospective Cost-Effectiveness Analysis of Cetuximab in Metastatic Colorectal Cancer: Evaluation of National Cancer Institute of Canada Clinical Trials Group CO.17 Trial

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CO.17 Other Metrics of "Success"

- Multiple (10+) peer-reviewed scientific presentations and publications in in high-impact journals
  - → Primary, secondary and unplanned post-hoc analyses of trial data and biological samples
- Multiple authorship positions for NCIC CTG investigators & fellows (... virtually every PI)
- Establish collaborative academic cooperative group partnership with AGITG (NHMRC CTC)
  - 6 GI trials + lung, brain, prostate, etc.
- Demonstrate NCIC CTG capability to run international multi-centre registrational phase III trials
- Correlative biomarker studies STILL ongoing

Phase III randomized trial of cetuximab + either brivanib alaninate or placebo in patients with metastatic, chemotherapy refractory, *K-RAS* wild-type colorectal carcinoma:

The NCIC Clinical Trials Group and AGITG CO.20 trial

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

AUSTRALASIAN GASTRO-INTESTINAL AGITG TRIALS GROUP

Brivanib Alaninate

- Potent, orally available multikinase inhibitor targeting pathways driving tumour angiogenesis:
  - Vascular Endothelial Growth Factor Receptor (VEGFR)
  - Fibroblast Growth Factor Receptor (FGFR)

VEGFR-2 (IC_{50} = 23 nM)
VEGFR-3 (IC_{50} = 10 nM)

FGFR-1 (IC_{50} = 150 nM)
FGFR-2 (IC_{50} = 125 nM)
FGFR-3 (IC_{50} = 68 nM)

- Study Rationale
  - Combination of two targeted agents
    - Cetuximab targets EGFR signalling driving tumour growth
    - Brivanib targets receptors driving tumour angiogenesis
  - Synergistic inhibition of EGFR and VEGFR/FGFR
  - Potent *in vivo* activity in xenograft models
  - Full doses of both drugs can be safely combined

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Jonker et al. Ann Oncol 2011; 22:1413-19; Garrett et al. Br J Cancer 2011; 105:44-52

NCIC CTG CO.20: Background

Retrospective analysis of *K-RAS* status demonstrated benefit from cetuximab only in wild-type tumors – NCIC CTG CO.17 correlative analysis	Retrospective phase III	*K-RAS* wt CET + BSC (n = 110)	*K-RAS* wt BSC (n = 105)
		OS = 9.5 m PFS = 3.7 m	OS = 4.8 m PFS = 1.9m
Retrospective analysis of *K-RAS* wild-type colorectal cancer patients treated with cetuximab + brivanib in a phase I/II trial	Retrospective phase I/II	*K-RAS* wt CET + BRIV	
		•PFS = 5.4 m (n = 24) •PFS = 10.9 m (n =15 with no prior anti-EGFR therapy)	

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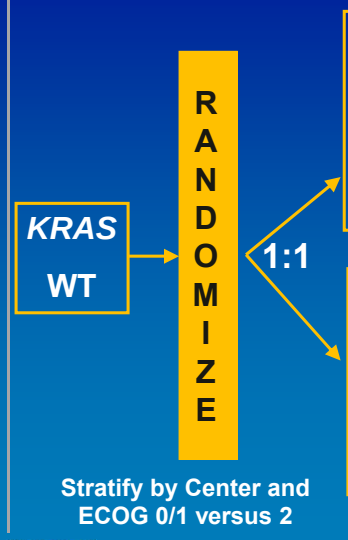
Jonker et al. N Engl J Med 2007; 357:2040-8; Karapetis et al. N Engl J Med 2008; 359: 757-65; Garrett et al. Br J Cancer 2011; 105:44-52; Ayers et al. 2009 ASCO GI Cancers Symposium, abstract 375

NCIC CTG CO.20: Schema



1 endpoint:
- OS

2 endpoints:
- PFS, ORR, QoL, HUI, Economics, Safety, Molecular markers, Tissue banking

Design:
- 1-sided $\alpha = 0.025$, Power = 0.9 yields 750 pts needed to detect a 3.2 months difference (HR=0.75) in median OS between 2 arms

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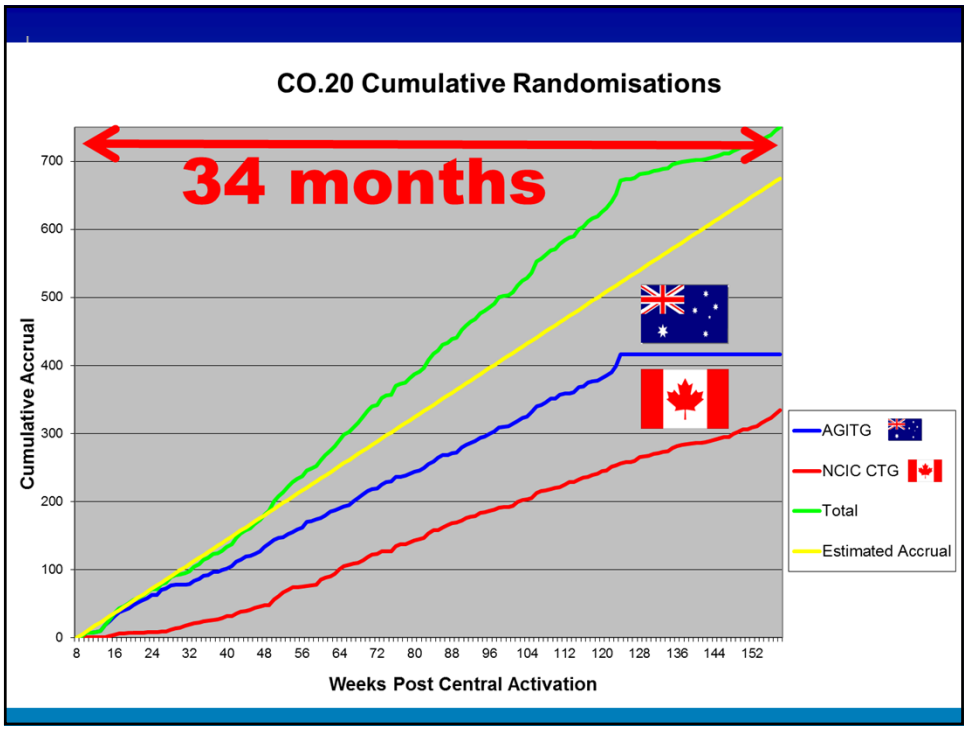
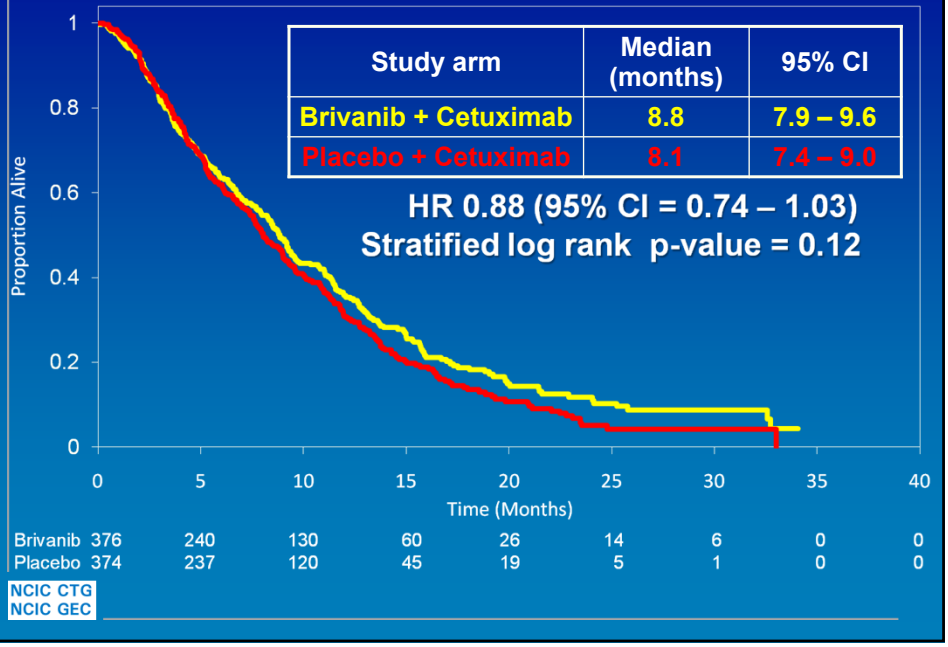


CO.20 Top Accruing NCIC CTG Centres (/39)

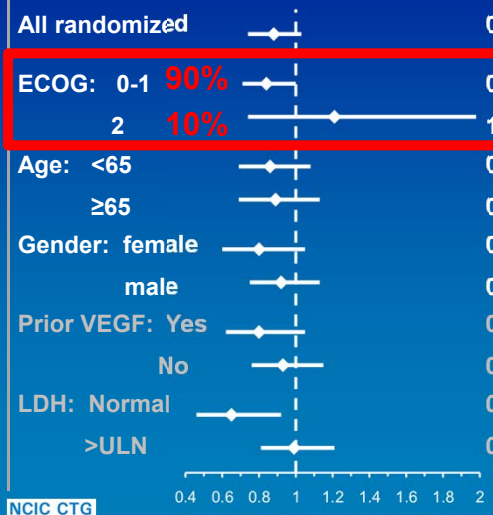
Rank	Centre	# Patients
1	Ottawa Health Research Institute (CAKO)	48 (7%)
2	CHUQ – Pavillon Hôtel-Dieu de Québec (CAGQ)	42
3	UHN – Princess Margaret Hospital (CAMP)	31
4	Dr. H. Bliss Murphy Cancer Centre (CAAJ)	29
5	CHUM - Hôpital Notre-Dame (CAHN)	26
6	Cross Cancer Institute (CATW)	17
7	Centre hospitalier universitaire de Sherbrooke (CAGH)	10
	Lakeridge Health Oshawa (CALO)	10
9	Allan Blair Cancer Centre (CASS)	9
	Hôtel Dieu de Lévis (CAGV)	9
	McGill University – Department of Oncology (CAHC)	9

Overall Survival



Survival Result by Subgroups

Subset	Hazard Ratio and 95% CI	Median Survival: Brivanib + Cetuximab	Median Survival: Placebo + Cetuximab
All randomized	0.88 (0.74 – 1.03)	8.8 mo	8.1 mo
ECOG: 0-1 90%	0.84 (0.71 – 1.00)	9.2 mo	8.7 mo
2 10%	1.21 (0.74 – 1.98)	3.5 mo	4.8 mo
Age: <65	0.86 (0.69 – 1.08)	9.1 mo	8.8 mo
≥65	0.89 (0.69 – 1.13)	8.7 mo	7.6 mo
Gender: female	0.80 (0.60 – 1.05)	8.6 mo	7.7 mo
male	0.92 (0.75 – 1.13)	8.8 mo	8.5 mo
Prior VEGF: Yes	0.80 (0.62 – 1.05)	8.4 mo	7.5 mo
No	0.93 (0.76 – 1.15)	9.2 mo	8.5 mo
LDH: Normal	0.65 (0.46 – 0.92)	13.3 mo	10.8 mo
>ULN	0.99 (0.81 – 1.21)	7.9 mo	7.7 mo



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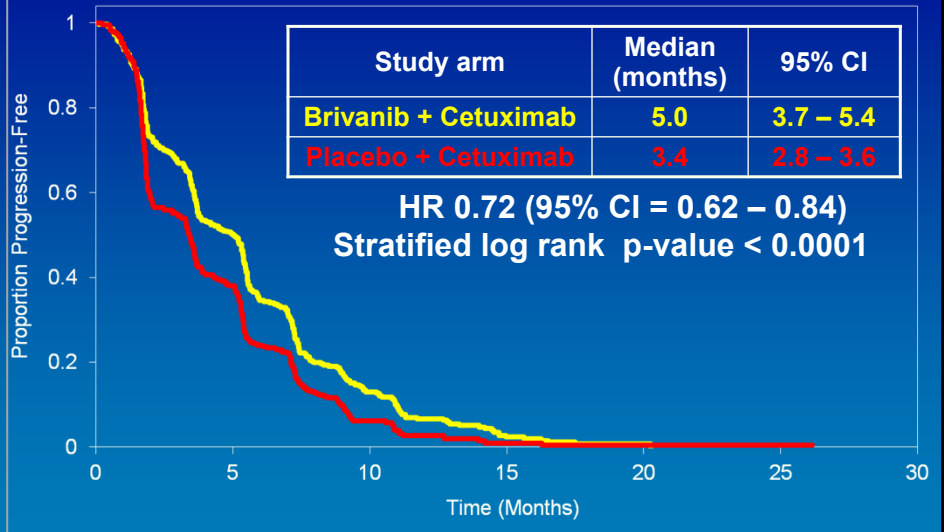
Favours Brivanib Favours Placebo

Progression Free Survival

Study arm	Median (months)	95% CI
Brivanib + Cetuximab	5.0	3.7 – 5.4
Placebo + Cetuximab	3.4	2.8 – 3.6

HR 0.72 (95% CI = 0.62 – 0.84)
Stratified log rank p-value < 0.0001



Brivanib	376	176	39	6	1	0	0
Placebo	374	133	18	2	1	1	0

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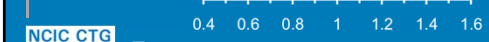
PFS Result by Subgroups

Subset	Hazard Ratio and 95% CI	Median PFS Brivanib + Cetuximab	Median PFS Placebo + Cetuximab
All randomized	0.72 (0.62 – 0.84)	5.0 mo	3.4 mo
ECOG: 0-1	0.71 (0.60 – 0.83)	5.2 mo	3.4 mo
2	0.88 (0.55 – 1.41)	2.9 mo	1.8 mo
Age: <65	0.74 (0.60 – 0.91)	5.2 mo	3.4 mo
≥65	0.70 (0.56 – 0.88)	4.3 mo	3.4 mo
Gender: female	0.64 (0.50 – 0.82)	4.7 mo	1.9 mo
male	0.75 (0.50 – 0.82)	5.2 mo	3.6 mo
Prior VEGF: Yes	0.67 (0.53 – 0.86)	5.0 mo	2.5 mo
No	0.77 (0.63 – 0.93)	4.9 mo	3.5 mo
LDH: Normal	0.66 (0.49 – 0.88)	5.4 mo	3.3 mo
>ULN	0.74 (0.62 – 0.90)	4.6 mo	3.6 mo



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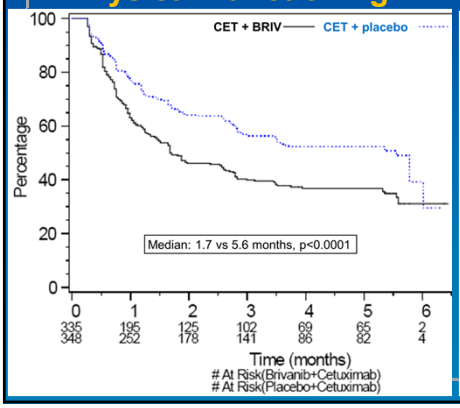
Favours Brivanib Favours Placebo

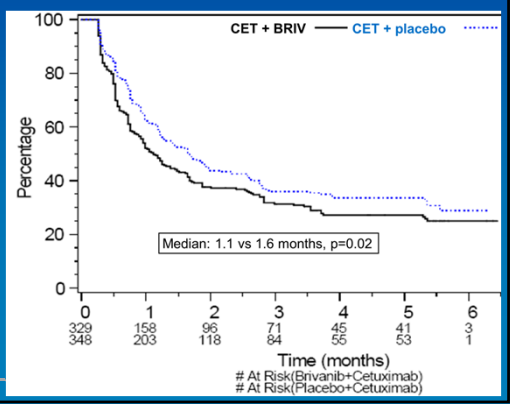
NCIC CTG CO.20: Quality of Life

- 96% of patients assessable for QoL
- No imbalance in baseline QoL or compliance
- Co-primary QoL endpoints: Time to deterioration (≥ 10 points) on Physical Functioning and Global subscales of EORTC QLQ-C30

Physical Functioning



Global Health Status



NCIC CTG CO.20: Grade 3+ On-Treatment Adverse Events

Adverse Event (all p<0.05)	Brivanib + Cetuximab n = 372	Placebo + Cetuximab n = 373
	No. of pts (%)	No. of pts (%)
Fatigue	94 (25)	39 (11)
Hypertension	39 (11)	4 (1)
Rash	38 (10)	20 (5)
Abdominal pain	36 (10)	19 (5)
Diarrhea	27 (7)	11 (3)
Dehydration	25 (7)	6 (2)
Anorexia	20 (5)	4 (1)
Overall non-hem AE incidence	290 (78)	198 (53)
AST elevation	62 (17)	21 (6)
ALT elevation	79 (21)	16 (4)
Hyponatremia	48 (13)	26 (7)
TSH elevation	90 (24)	14 (4)

NCIC CTG CO.20: Treatment Dose Intensities

Drug	Dose Intensity Parameter	Brivanib + Cetuximab n = 372	Placebo + Cetuximab n = 373
		No. of pts (%)	No. of pts (%)
Cetuximab	≥ 90% Planned Intensity	213 (57)	311 (83)
	At least 1 dose reduction	132 (35)	40 (11)
	At least 1 dose omission	275 (74)	199 (53)
Brivanib/ Placebo	≥ 90% Planned Intensity	180 (48)	324 (87)
	At least 1 dose reduction	162 (44)	27 (7)
	At least 1 dose omission	301 (81)	188 (50)

NCIC CTG CO.20: Treatment Discontinuations

	Brivanib + Cetuximab n = 372	Placebo + Cetuximab n = 373
	No. of pts (%)	No. of pts (%)
DC cetuximab due to AE	29 (8)	14 (4)
DC brivanib due to AE	81 (22)	12 (3)

- Most common reasons for discontinuation of cetuximab/brivanib were fatigue (5%), ALT (2%), AST (2%), dyspnea (2%)
- Only one death on brivanib arm was considered possibly related by investigator

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NCIC CTG CO.20: Conclusions

In this phase III trial of Brivanib + Cetuximab *versus* Placebo + Cetuximab in metastatic, chemorefractory *K-RAS* wild-type colorectal cancer:

- the primary endpoint of improvement in overall survival was not met
- both objective response and progression free survival were improved
- time to deterioration on physical function and global health quality of life subscales worsened
- on-treatment adverse events were consistent with those reported for each drug given as monotherapy
- dose intensity of cetuximab was reduced when administered in combination with brivanib

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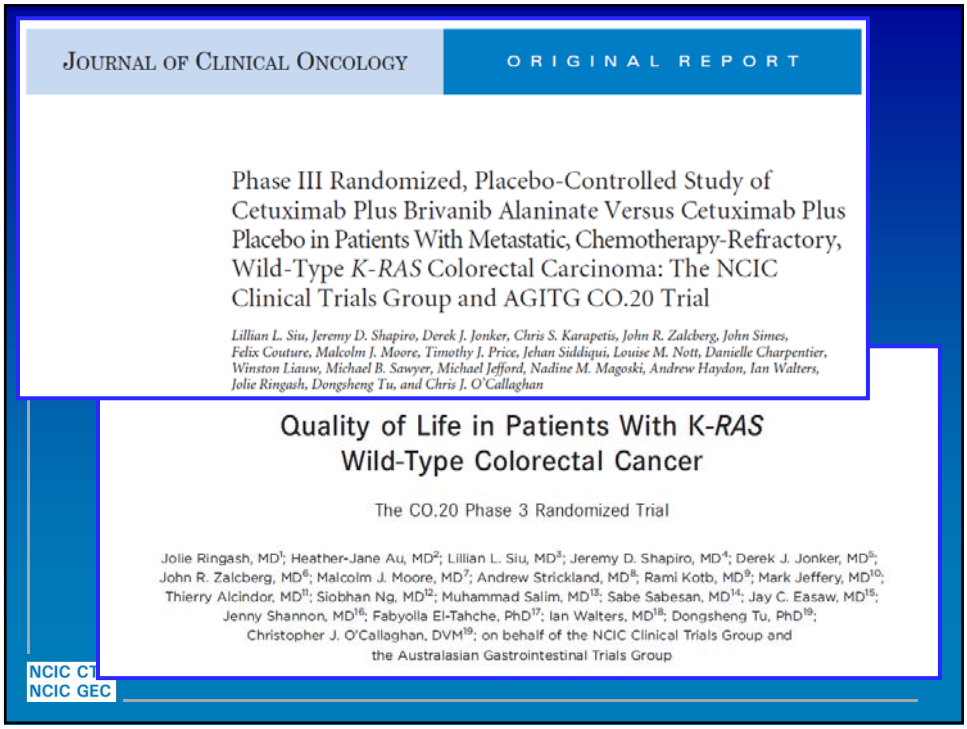

CO.20 Timeline

- "First Contact" = June 2005 (CO.17 Final Analysis = March 2006)
- Protocol finalized = August 2007 (26)
- Contract signed = December 2007 (4)
- Central activation = February 2008 (2)
- First pt rand = March 2008 (AGITG) , May 2008 (NCIC CTG) (2)
- Last patient randomized = February 2011 (34)
- Clinical cut-off (data mature) = March 2011 (1)
- Database locked & final analysis = September 2011 (6)
- GI ASCO oral presentation = January 2012 (4)
- ASCO oral (update of maturing data) = June 2012 (5)
- JCO publication (epub) = May 2013 (11)

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Total = 7 years, 11 months

Was CO.20 a "Success" ?

"A well designed trial, properly conducted in a timely manner, resulting in high quality data, which is stringently analyzed and fully and transparently reported?"

YES!

- ✓ Relevant question that would change practice, NOT superseded by changing practice (equipoise)
- ± Promising data from earlier stage trials, other disease sites
- ✓ New, particularly 'novel', drugs or treatments always of interest
- ± Simple is more attractive – i.e. complexity as scientifically necessary
- ✓ Limited therapeutic options – e.g. end stage settings
- ✓ Good risk/benefit ratio (real or perceived) (all received Cetuximab)
- ✓ Unique - Not already planned, in progress... or complete!
- ✓ Well funded/resourced ($9,000 + $250 correlative samples)

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

+ AUSTRALASIAN GASTRO-INTESTINAL AGITG TRIALS GROUP

Was CO.20 a "conventional" success?

NO

- **primary endpoint was NOT met**
- **insufficient results for regulatory approval**
- **detrimental QoL**
- **will not change standard of practice**

BUT…

- **there IS evidence of activity and efficacy….**

Biomarker analyses are ongoing!!

The New England Journal of Medicine

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Thank You

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