Plenary Session 2:

The NCIC CTG CO.17, CO.20 & CO.23 Colon Cancer Studies:

Examples of Successful Phase III Trials

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

NCIC CTG
NCIC GEC

What is a "Successful" Trial?

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

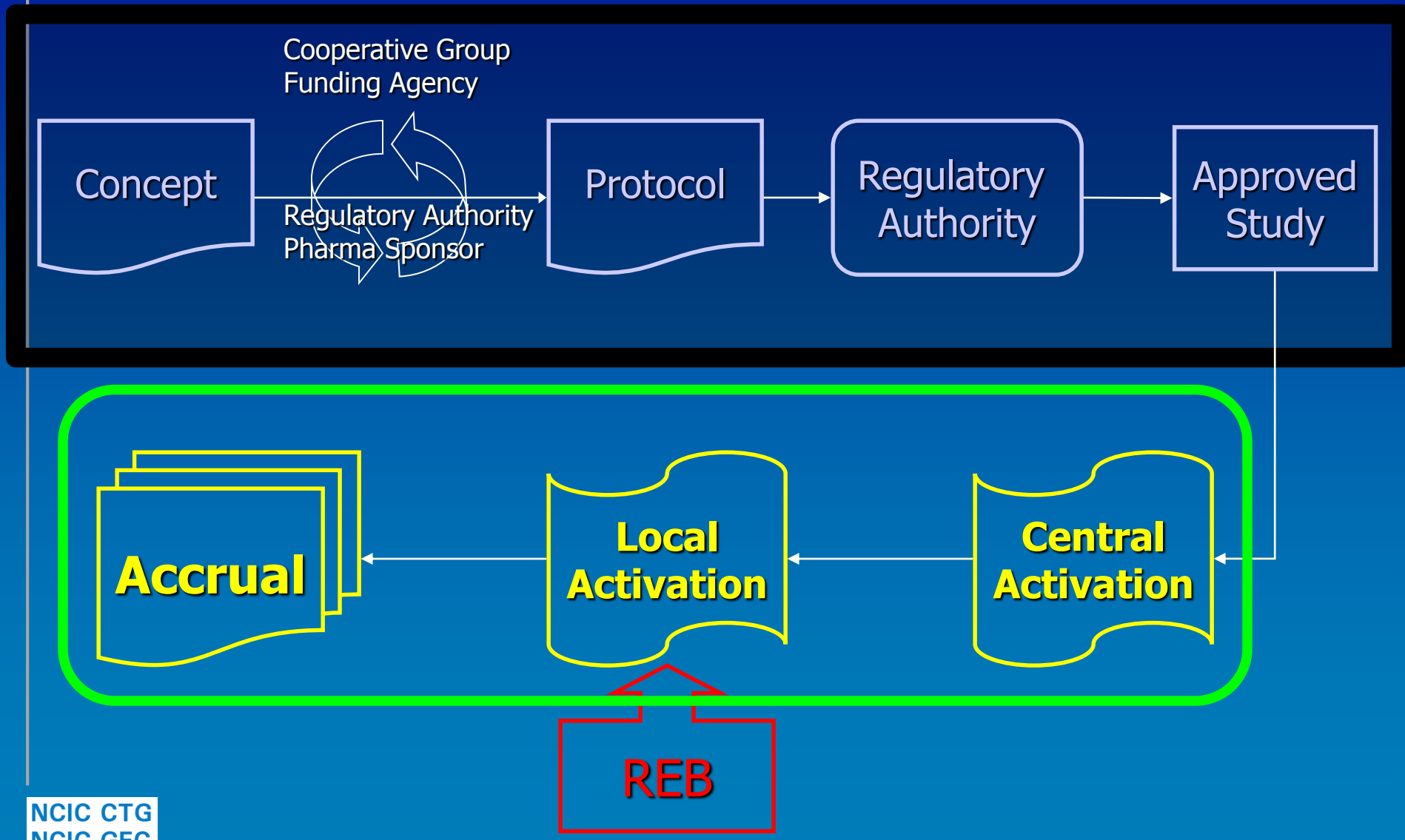
Surely its simple?

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

Design, Data & Analysis

- 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
- Ensure high quality
  - Clean data, conduct compliance & quality assurance activities (e.g. monitor, audit, pharmacovigilance, etc.)
  - Analysis and publication/dissemination

The Cooperative Group "Flow"



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Accrual?

- Investigators are interested in putting patients on the study
- Sites/Institutions are interested in supporting Investigators
- Patients are interested in participating in the study

= rapid activation and timely accrual

The Absolute Truths:
Death, Taxes and …

… seldom as good as predicted
…rarely, if ever, better

Interesting?

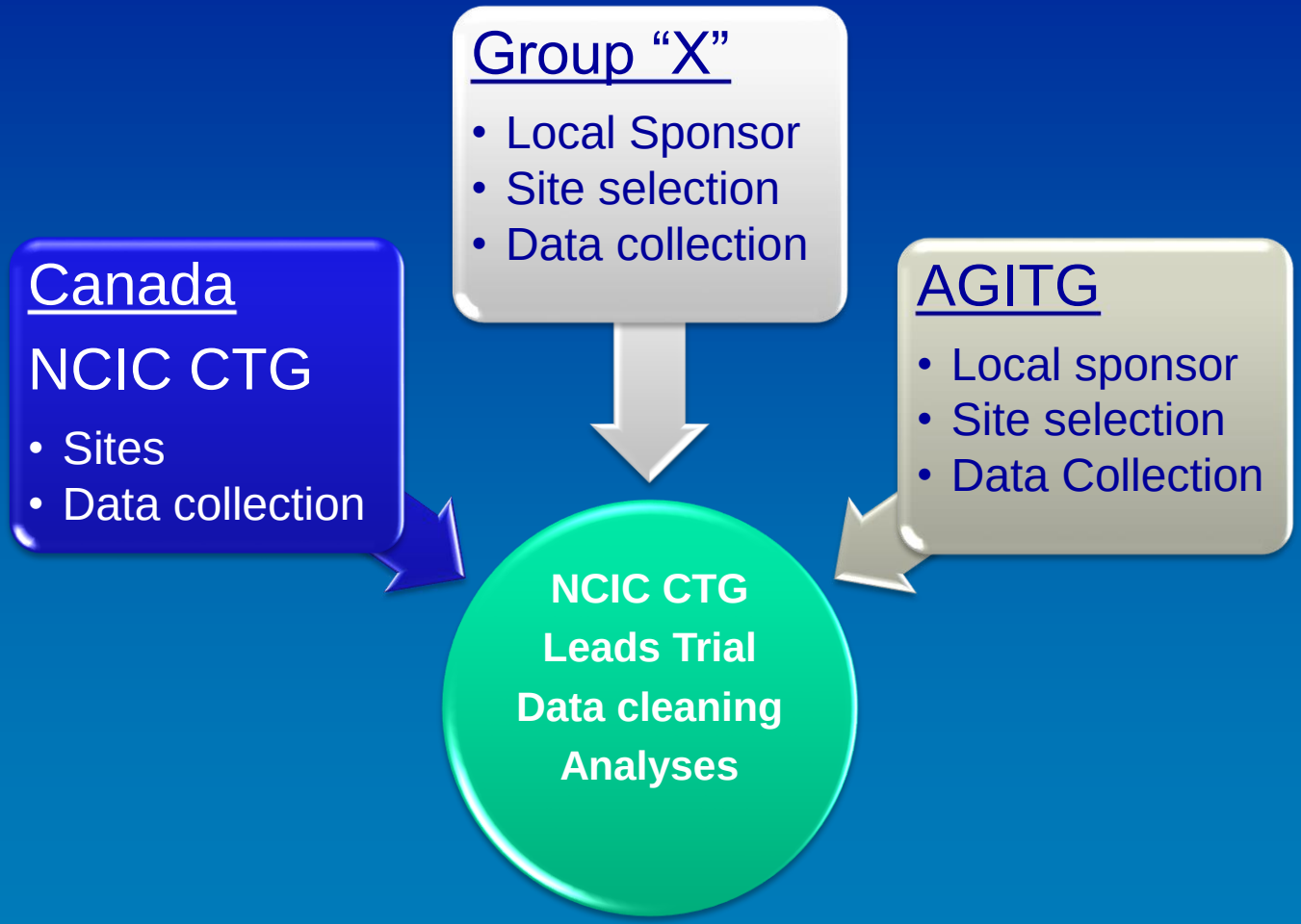
- Relevant question that will change practice, NOT superseded by changing practice (equipoise)
- Promising data from earlier stage trials, other disease sites
- New, particularly 'novel', drugs or treatments always of interest
- Simple is more attractive – i.e. complexity as scientifically necessary
- 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

Like rungs in a ladder…

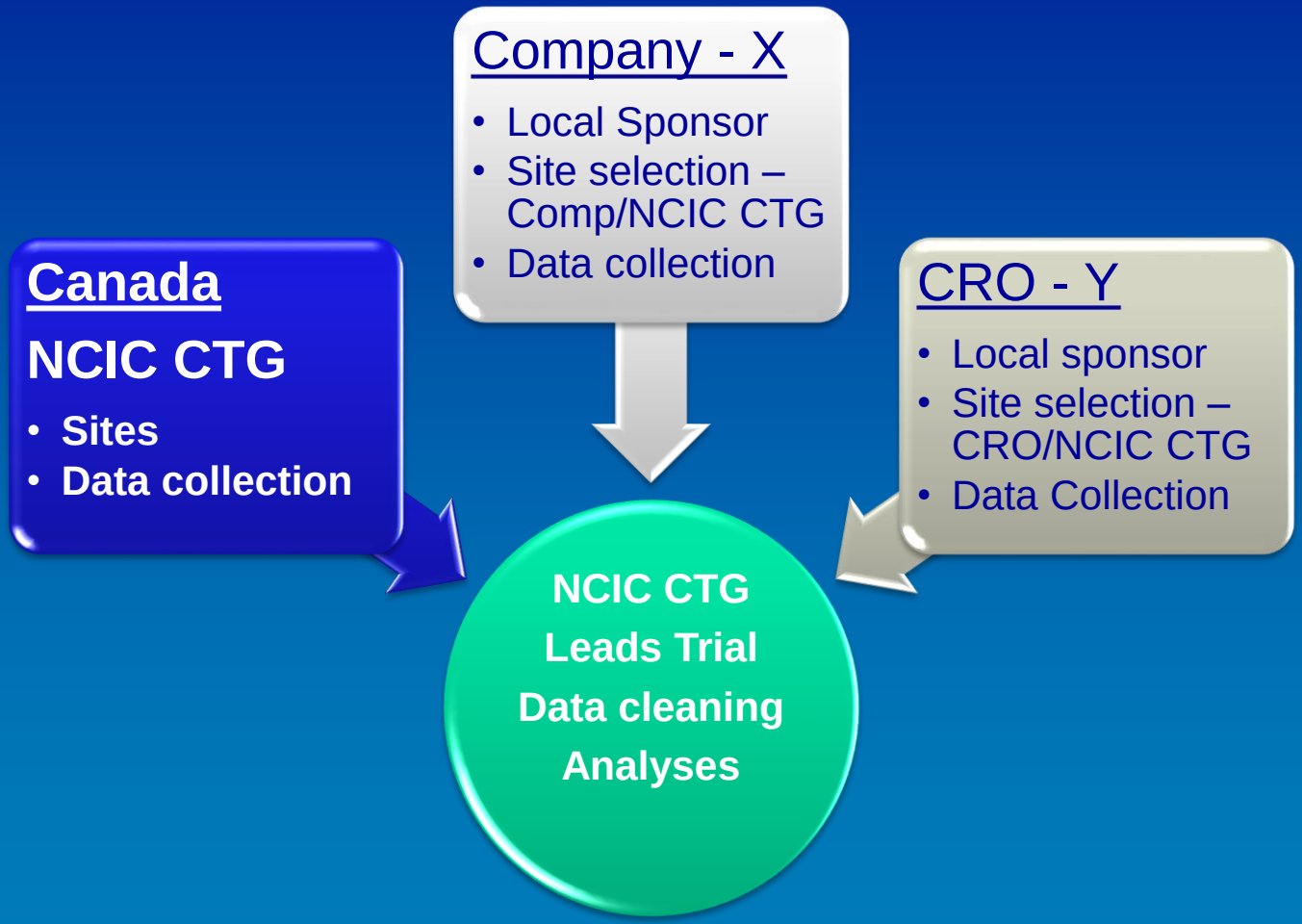
Not all are absolutely essential…

but the more that are missing….

Creating Collaborators: The 'Intergroup' Trial Model



Creating Accrual: The 'International' Trial Model



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
- Slower than expected accrual substantially increases costs → longer duration thus increased staffing costs

Resource and $ needed centrally…

- Randomization system (web, phone based)
- Drug supply, distribution, reconciliation
- Site selection and management
- Data collection (e.g. EDC) and cleaning
- Compliance activates (regulatory filings, reporting & inspections, audits, monitoring, safety/pharmacovigilance, Ethics Committees)
- Biobanking, including sample collection storage and assays
- Imaging QA (e.g. central radiology review)
- Contracts (lawyers!)
- Insurance (… hopefully NO lawyers!)
- Analyses and reports
- Collaborating groups and/or CRO costs

Resource and $ needed by sites…

- Site costs/per-capita payments

"… 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%."

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

Funding and Resource

1. Fund yourself
   - not feasible for phase III
2. Apply for a peer-reviewed grant
   - e.g. CIHR = 17% 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…

Working with pharma is like being pecked to death by chickens…

… no single blow is fatal, just very very irritating.

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

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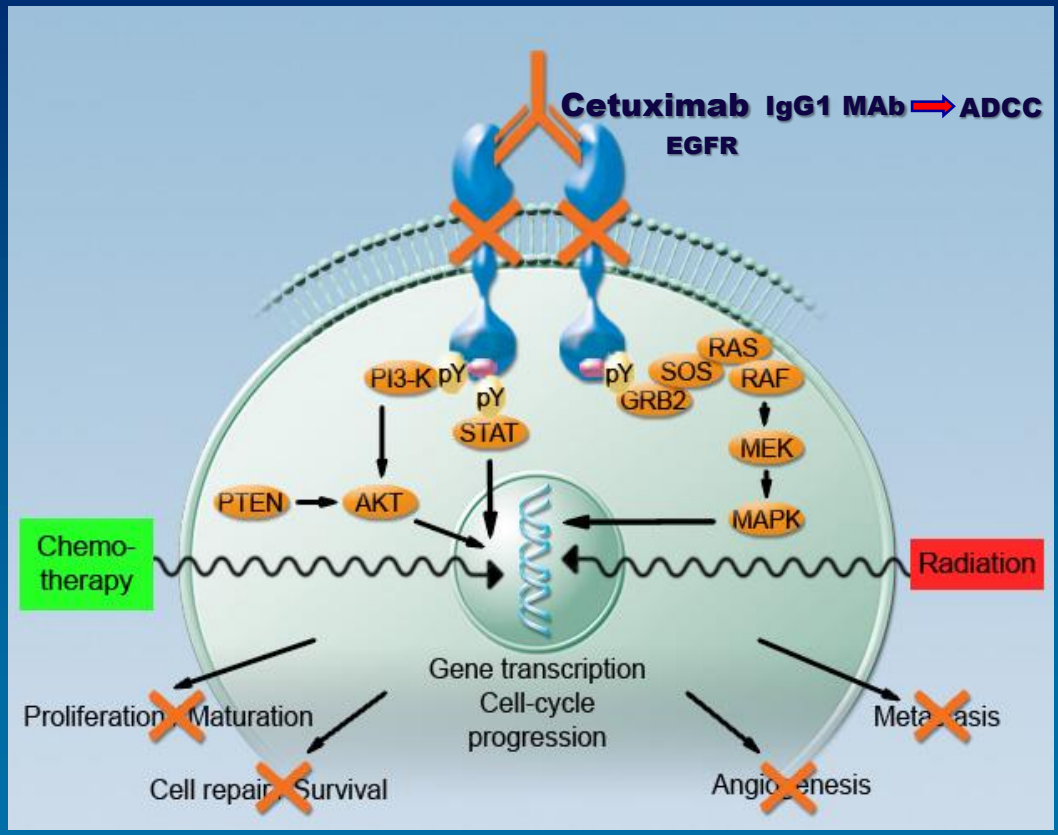
[1]Simonds, BMJ 2000; [2]Jonker, BJC 2000; [3]Cunningham, Lancet 1998; [4]Rougier, Lancet 1998; [5]Saltz, NEJM 2000; [6]Douillard, Lancet 2000; [7]Goldberg, JCO 2004; [8]Hurwitz, NEJM 2004

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)



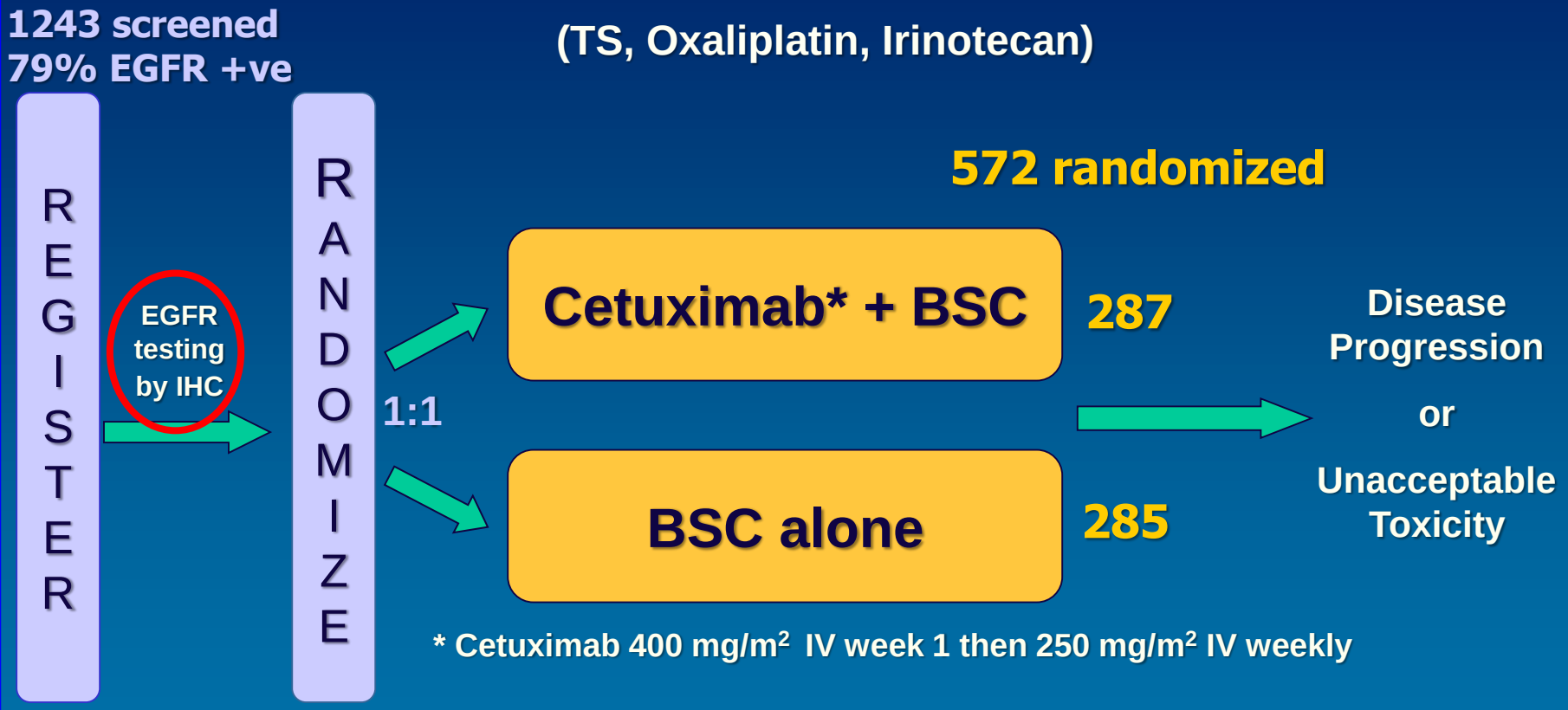
Cetuximab: Phase II Clinical Data

Study	Treatment	N	Efficacy	
			ORR	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

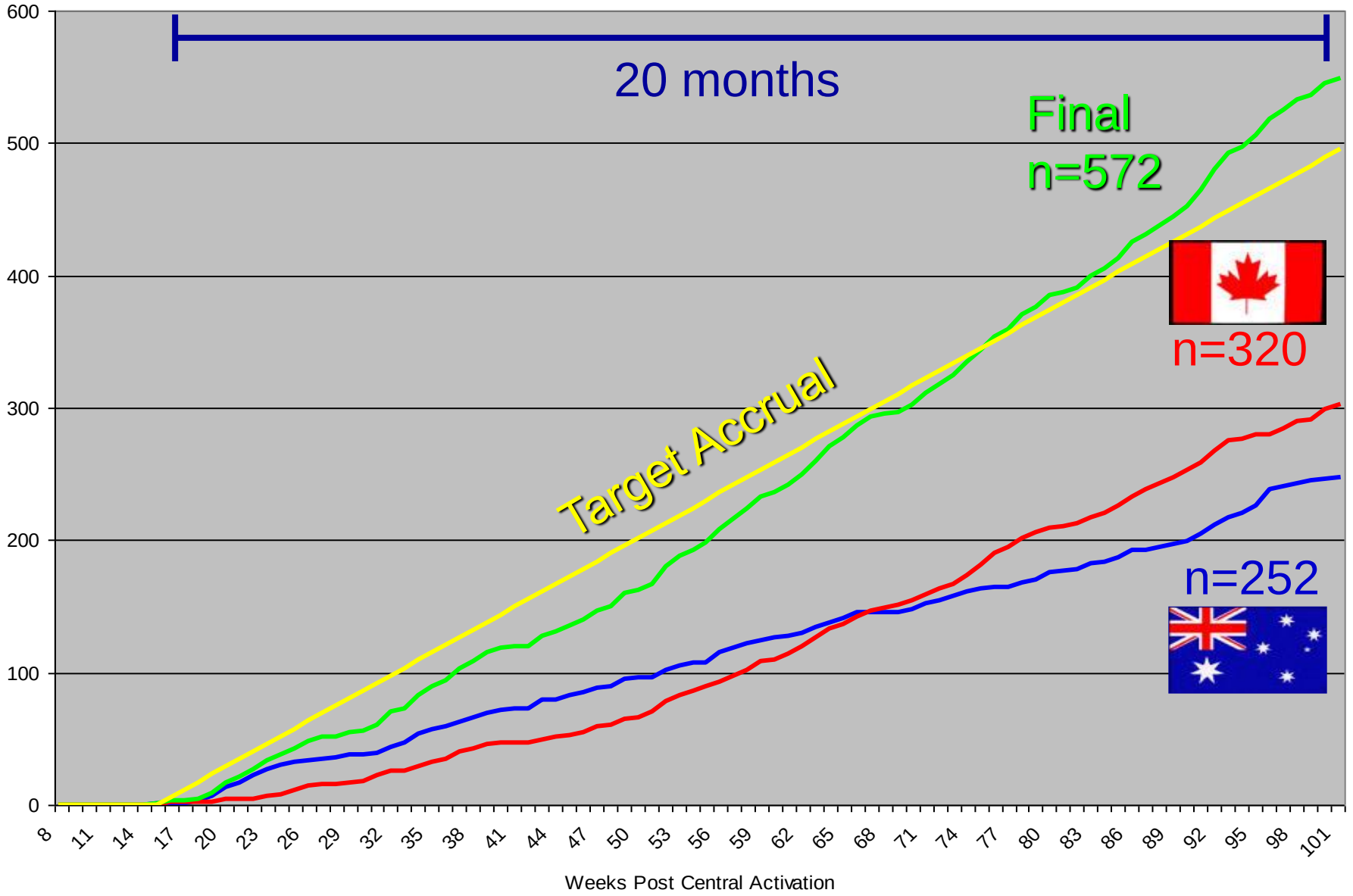
(TS, Oxaliplatin, Irinotecan)



* Cetuximab 400 mg/m^2 IV week 1 then 250 mg/m^2 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)

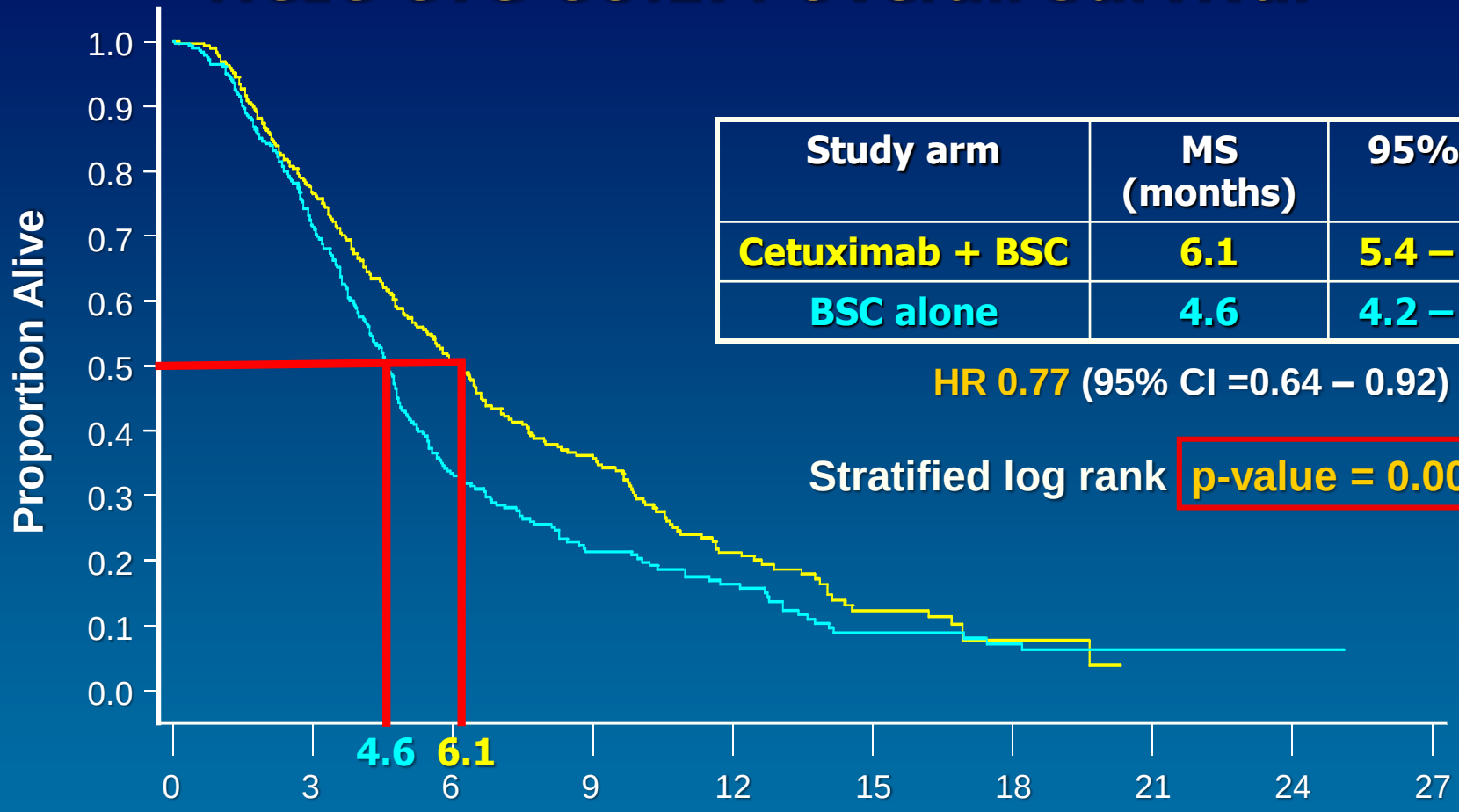
NCIC CTG CO.17: Accrual



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



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)

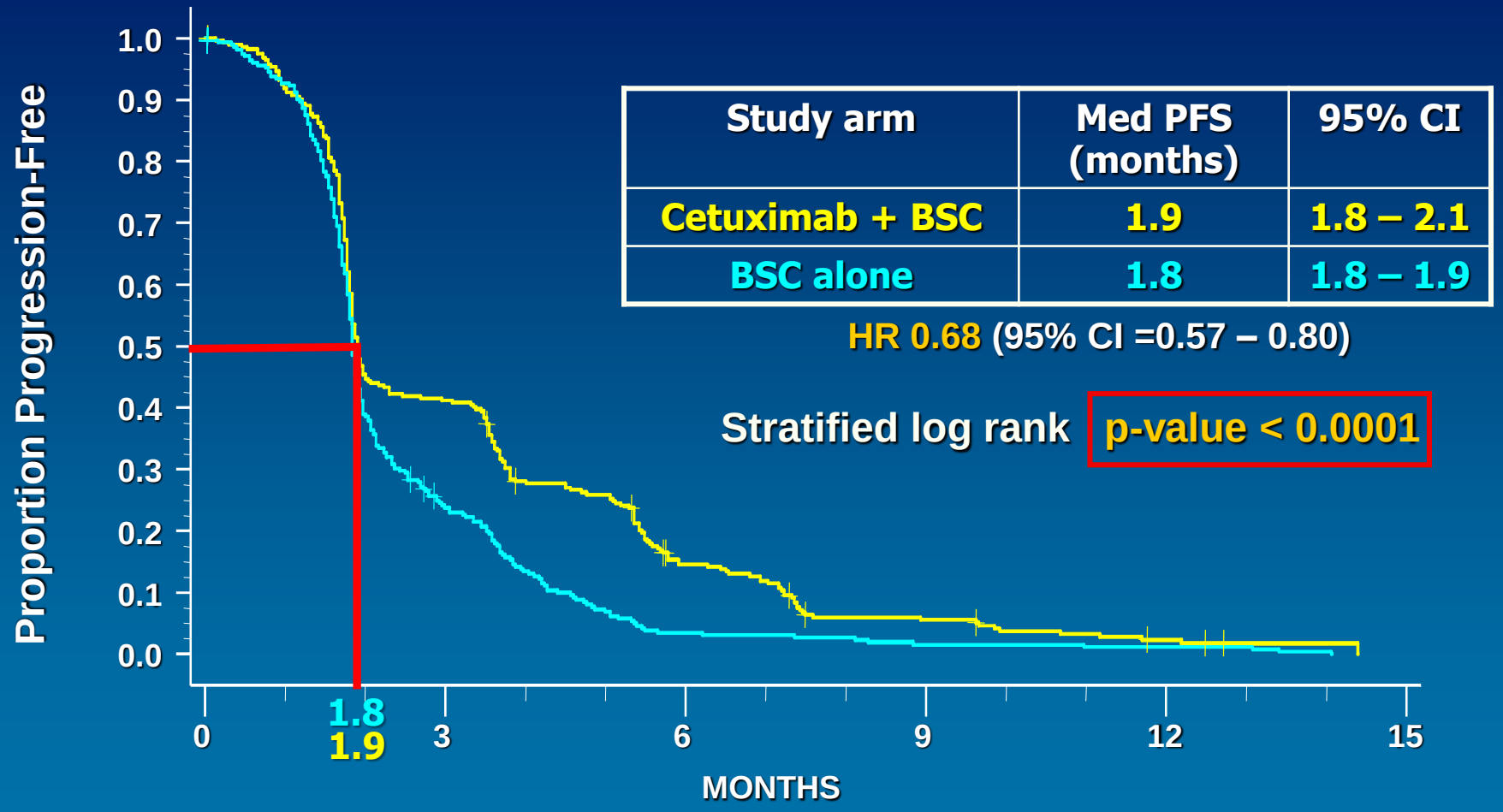
Stratified log rank p-value = 0.0046

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

CETUXIMAB + BSC
CENSORED

BSC
CENSORED

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

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 ≤ -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.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cetuximab for the Treatment of Colorectal Cancer

Derek J. Jonker, M.D., Chris J. O'Callaghan, Ph.D., Christos S. Karapetis, M.D., John R. Zalcberg, M.D., Dongsheng Tu, Ph.D., Heather-Jane Au, M.D., Scott R. Berry, M.D., Marianne Krahn, M.D., Timothy Price, M.D., R. John Simes, M.D., Niall C. Tebbutt, M.D., Guy van Hazel, M.D., Rafal Wierzbicki, M.D., Christiane Langer, M.D., and Malcolm J. Moore, M.D.*

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 prediction 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**

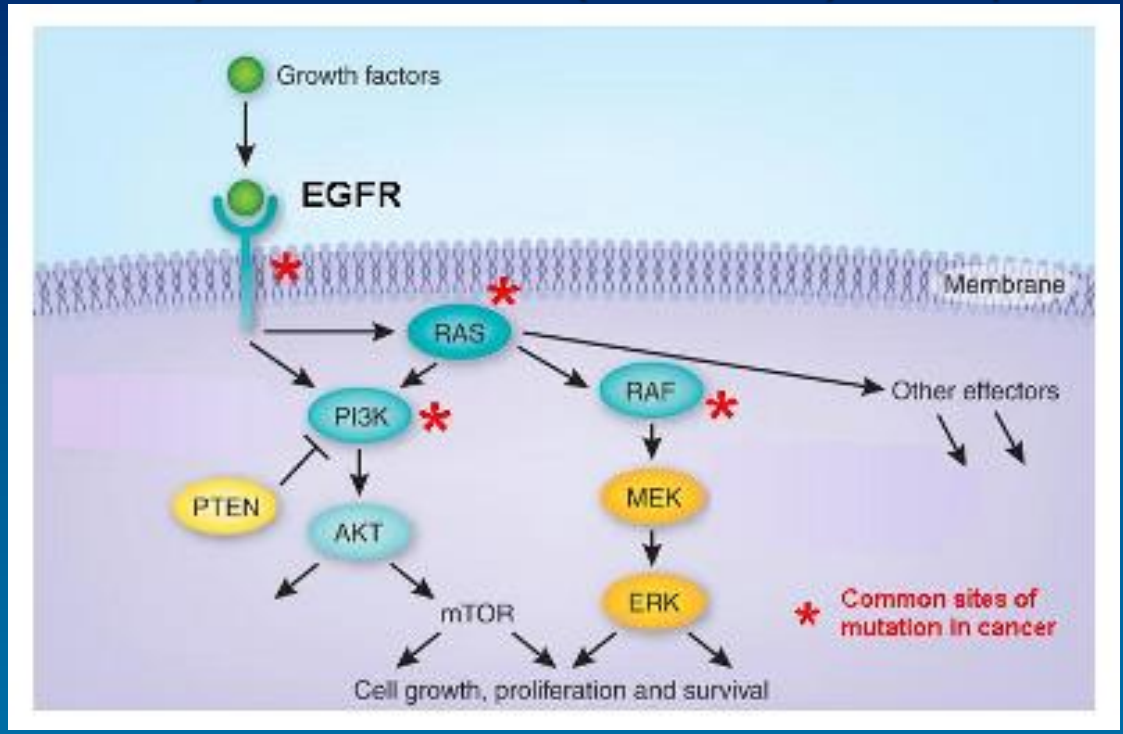
Ideally, the predictive value of the biomarker would need to be differentiated from its prognostic implications

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**

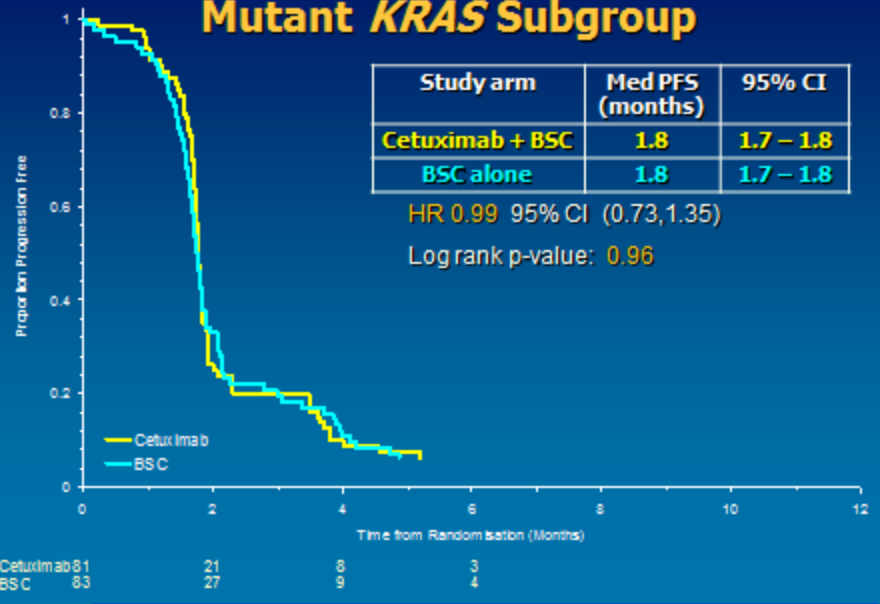
The *KRAS* Oncogene

- 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

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

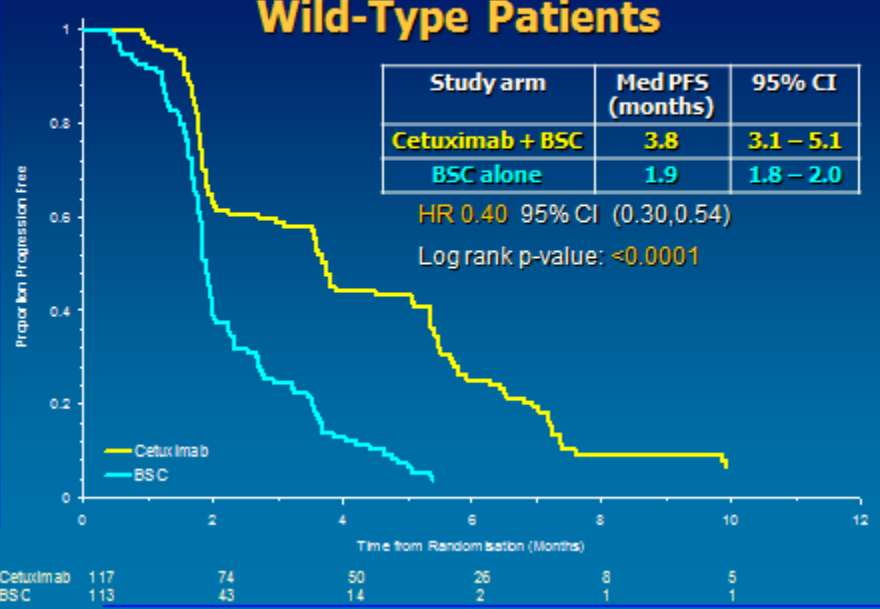


Study arm	Med PFS (months)	95% CI
Cetuximab + BSC	1.8	1.7 – 1.8
BSC alone	1.8	1.7 – 1.8

HR 0.99 95% CI (0.73,1.35)

Log rank p-value: 0.96

NCIC CTG C0.17: PFS in the *KRAS* Wild-Type Patients

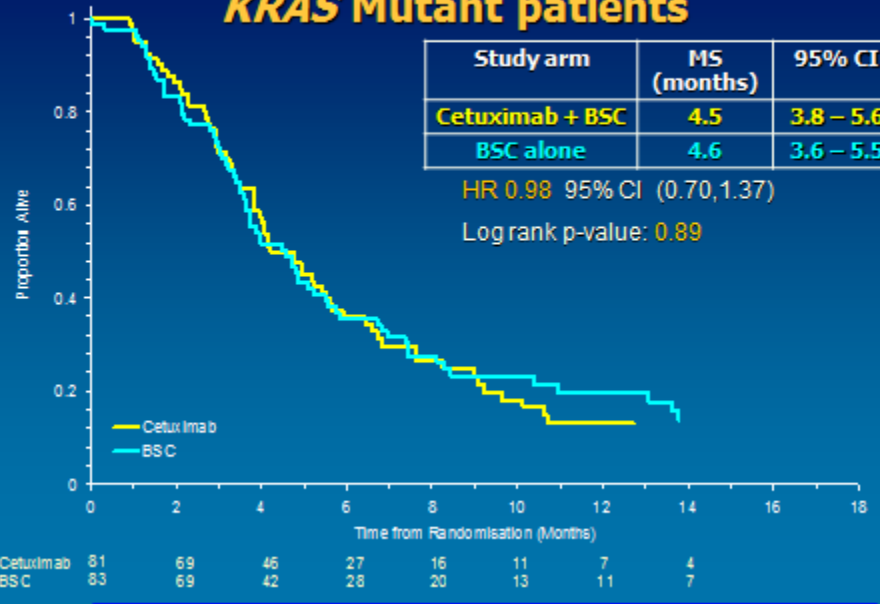


Study arm	Med PFS (months)	95% CI
Cetuximab + BSC	3.8	3.1 – 5.1
BSC alone	1.9	1.8 – 2.0

HR 0.40 95% CI (0.30,0.54)

Log rank p-value: <0.0001

NCIC CTG C0.17: Overall survival in *KRAS* Mutant patients

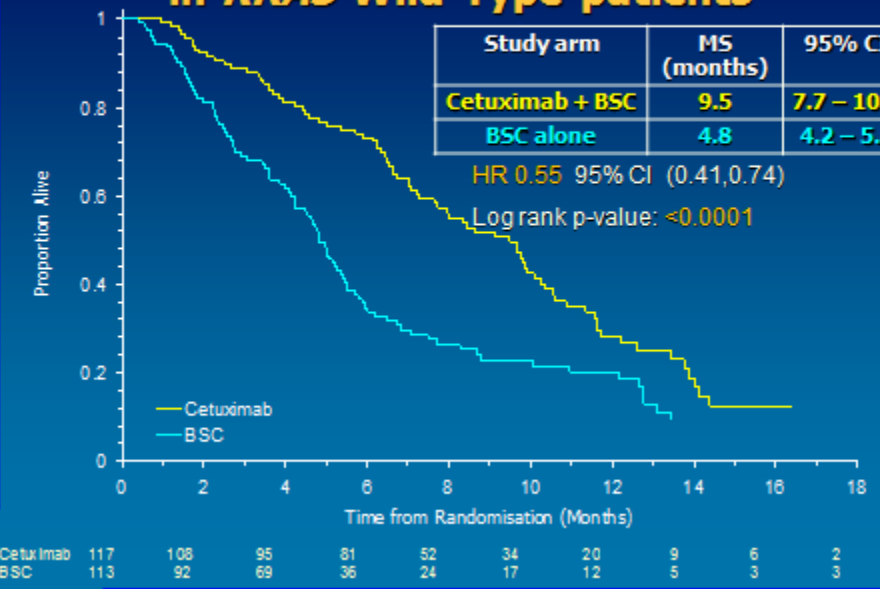


Study arm	MS (months)	95% CI
Cetuximab + BSC	4.5	3.8 – 5.6
BSC alone	4.6	3.6 – 5.5

HR 0.98 95% CI (0.70,1.37)

Log rank p-value: 0.89

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

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.*

VOLUME 27 · NUMBER 11 · APRIL 10 2009

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

Nicole Mittmann, Heather-Jane Au, Dongsheng Tu, Christopher J. O'Callaghan, Pierre K. Isogai, Christos S. Karapetis, John R. Zalcberg, William K. Evans, Malcolm J. Moore, Jehan Siddiqui, Brian Findlay, Bruce Colwell, John Simes, Peter Gibbs, Matthew Links, Niall C. Tebbutt, Derek J. Jonker, Working Group on Economic Analysis of the National Cancer Institute of Canada Clinical Trials Group, Australasian Gastrointestinal Interest Group

CO.17: Impact

ERBITUX, as a single agent, is also indicated for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma after failure of both irinotecan- and oxaliplatin-based regimens and who have received a fluoropyrimidine, whose tumours have a wild-type (non-mutated) Kirsten rat sarcoma (*KRAS*) gene. The benefit is based on overall survival in an analysis of patients whose tumours have a wild-type *KRAS* gene. In the same analysis, there was no treatment benefit with ERBITUX in patients whose tumours have *KRAS* mutations. Use of ERBITUX is not indicated for the treatment of colorectal cancer in patients with *KRAS* mutations.

Coverage/Reimbursement by Canadian Provincial/Territorial Programs

Province	Coverage	Program / Eligibility Criteria
AB	COVERED	Erbitux is **covered** according to eligibility criteria by the Alberta Cancer Board
BC	COVERED	Erbitux **is covered according to eligibility criteria** for some indications through the BC Cancer Agency
MB	UNDER REVIEW	Erbitux is **under review** by the provincial funding agency.
NB	UNDER REVIEW	Erbitux is **under review** by the provincial funding agency.
NL	UNDER REVIEW	Erbitux is **under review** by the provincial funding agency.
NT	UNDER REVIEW	Erbitux is **under review** by the territorial funding agency.
NS	COVERED	Erbitux **is covered according to eligibility criteria** for some indications through Cancer Care Nova Scotia
NU	UNDER REVIEW	Erbitux is **under review** by the territorial funding agency.
ON	COVERED	Erbitux **is covered according to eligibility criteria** for some indications through Cancer Care Ontario
PE	UNDER REVIEW	Erbitux is **under review** by the provincial funding agency.
QC	COVERED	Erbitux **is covered according to eligibility criteria** for some indications through Quebec hospitals.
SK	UNDER REVIEW	Erbitux is **under review** by the provincial funding agency.
YT	UNDER REVIEW	Erbitux is **under review** by the territorial funding agency.

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
- Demonstrate NCIC CTG capability to run international multi-centre registrational phase III trials

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**

NCIC CTG
NCIC GEC

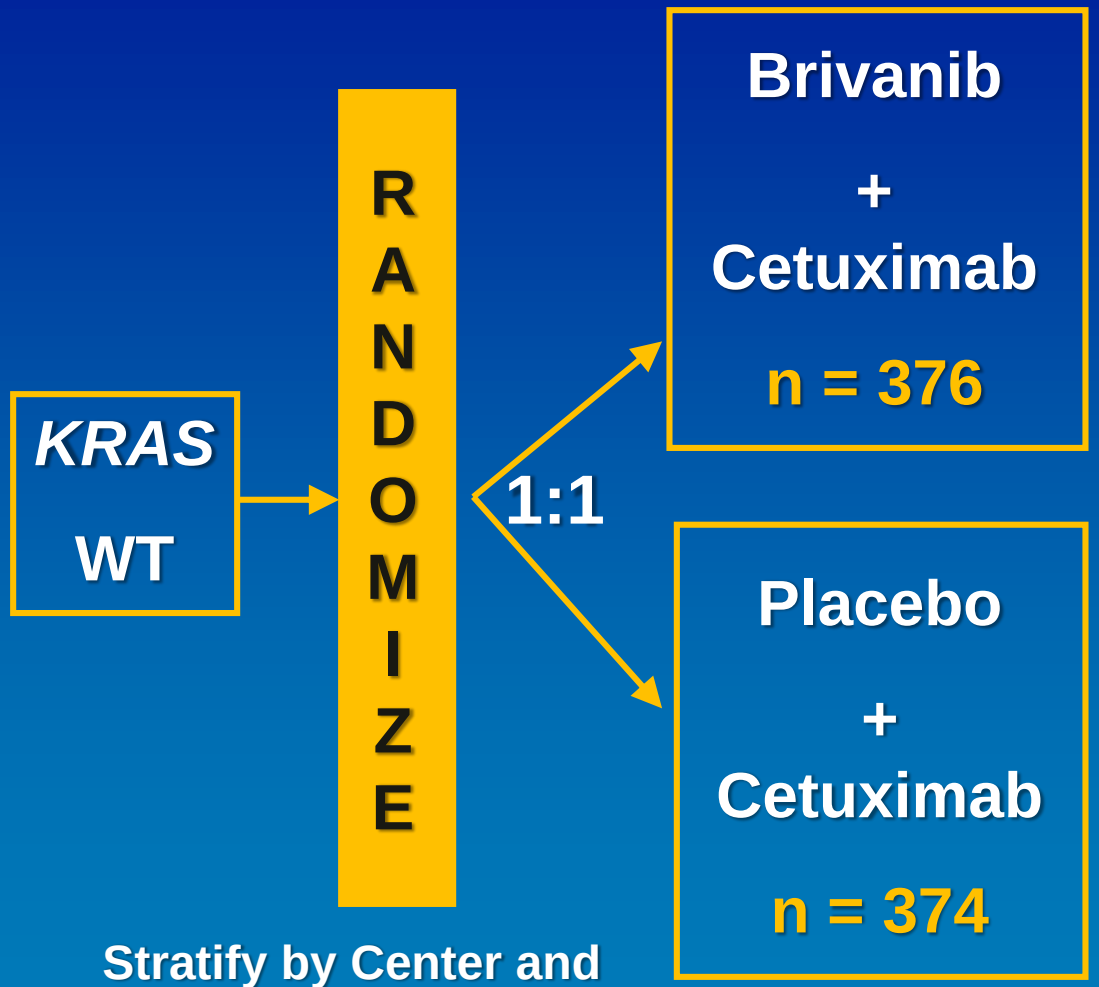
Jonker et al. Ann Oncol 2011; 22:1413-19; Garrett et al. Br J Cancer 2011; 105:44-52

NCIC CTG CO.20: Background

<table>
<tr><td rowspan="2">Retrospective analysis of K-RAS status demonstrated benefit from cetuximab only in wild-type tumors – NCIC CTG CO.17 correlative analysis</td><td rowspan="2">Retrospective phase III</td><td>K-RAS wt
CET + BSC
(n = 110)</td><td>K-RAS wt
BSC
(n = 105)</td></tr>
<tr><td>OS = 9.5 m
PFS = 3.7 m</td><td>OS = 4.8 m
PFS = 1.9m</td></tr>
<tr><td rowspan="2">Retrospective analysis of K-RAS wild-type colorectal cancer patients treated with cetuximab + brivanib in a phase I/II trial</td><td rowspan="2">Retrospective phase I/II</td><td colspan="2">K-RAS wt
CET + BRIV</td></tr>
<tr><td colspan="2">• PFS = 5.4 m (n = 24)
• PFS = 10.9 m (n =15 with no prior anti-EGFR therapy)</td></tr>
</table>

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

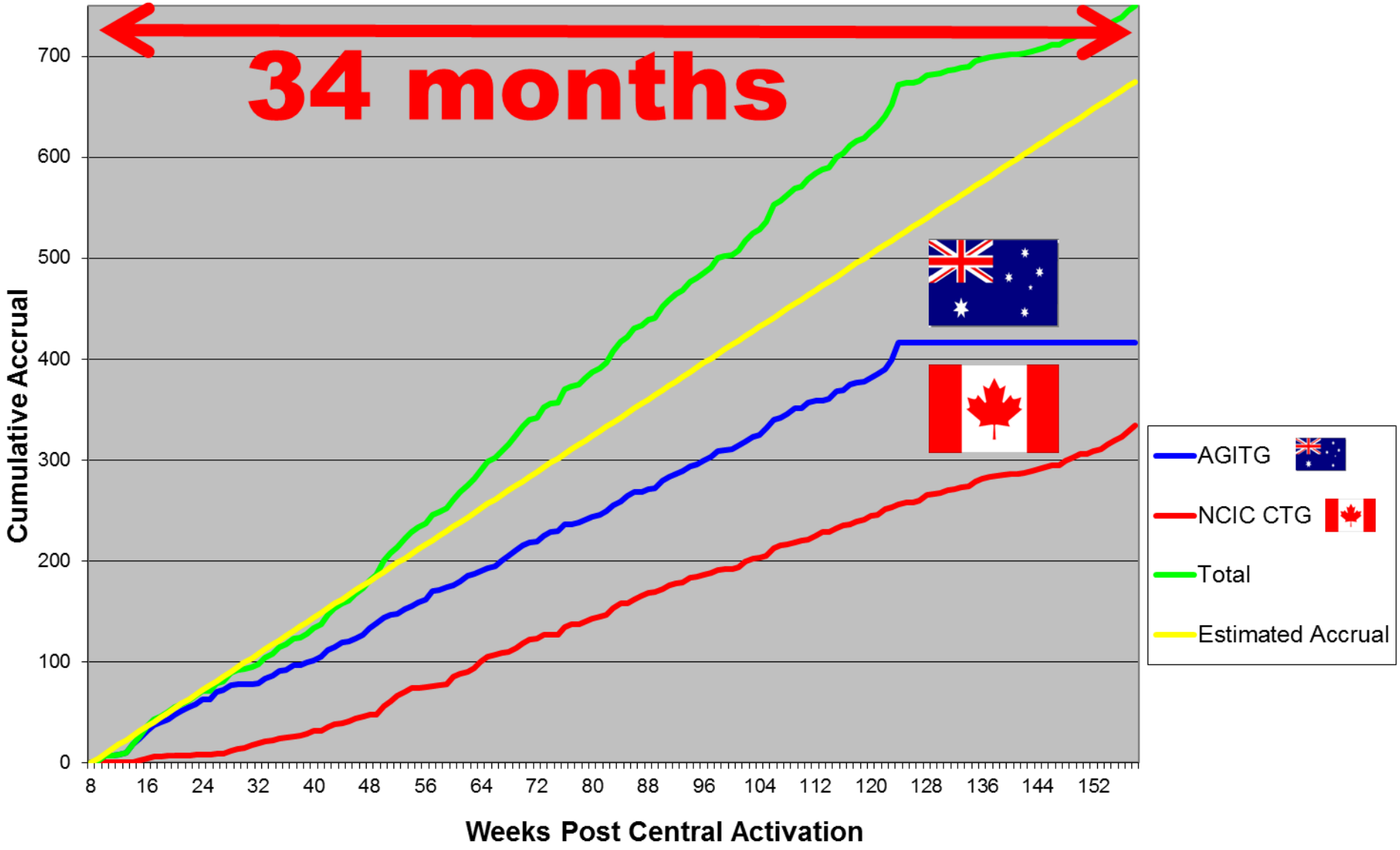
2 endpoints:

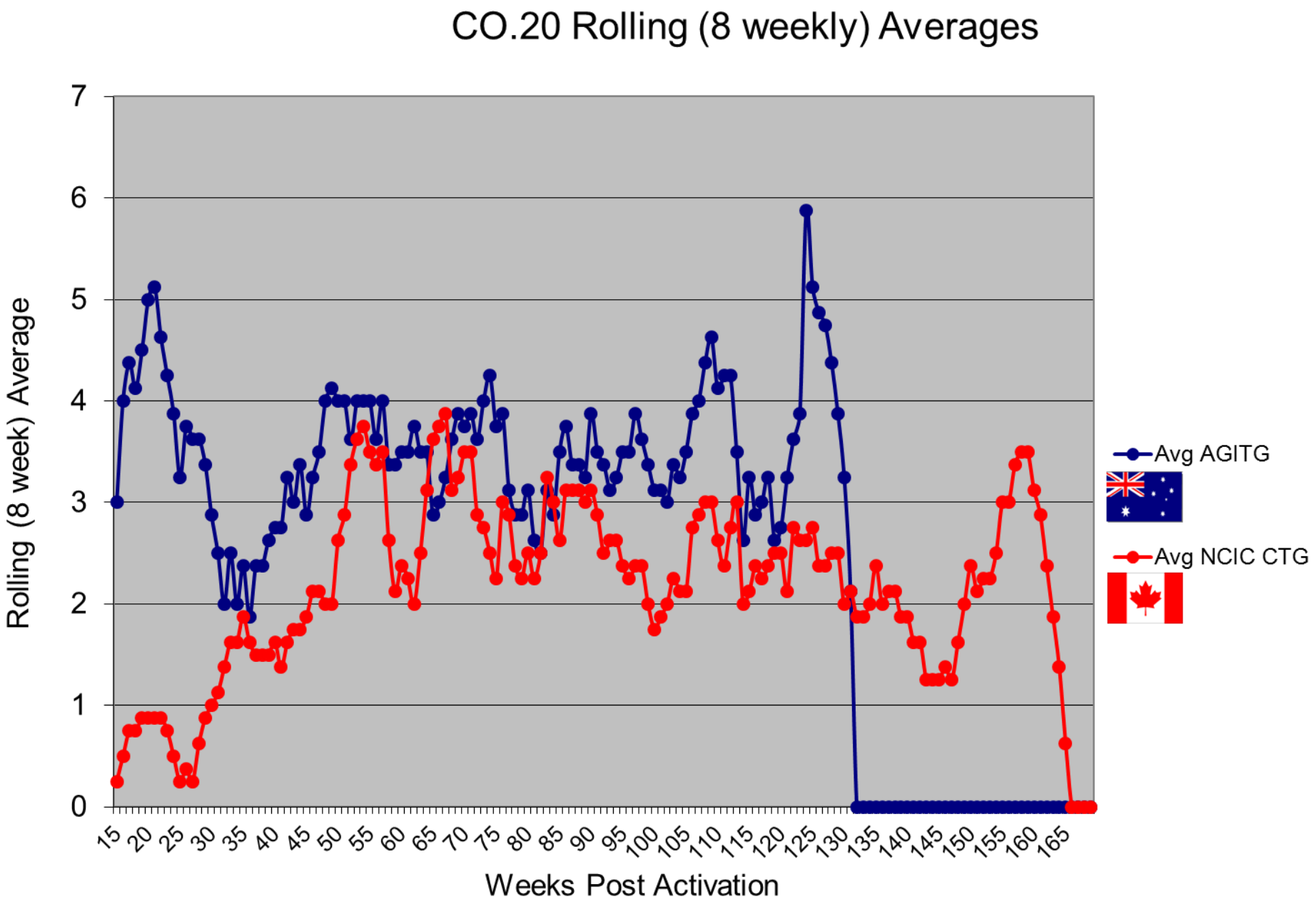
- PFS, ORR, QoL, HUI, Economics, Safety, Molecular markers, Tissue banking

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

CO.20 Cumulative Randomisations

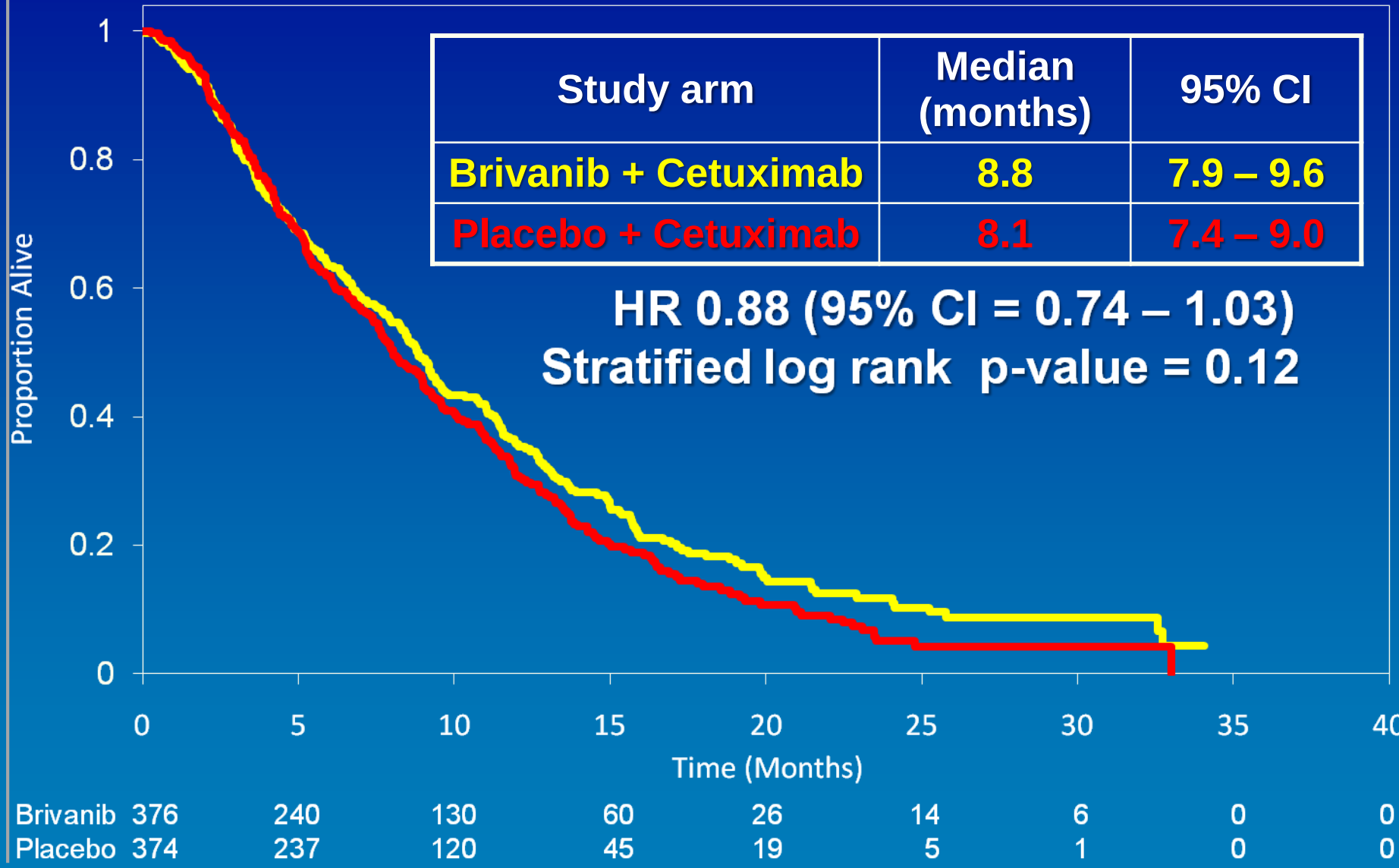



CO.20 Rolling (8 weekly) Averages
Rolling (8 week) Average
0
1
2
3
4
5
6
7
15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165
Weeks Post Activation
Avg AGITG
Avg NCIC CTG

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

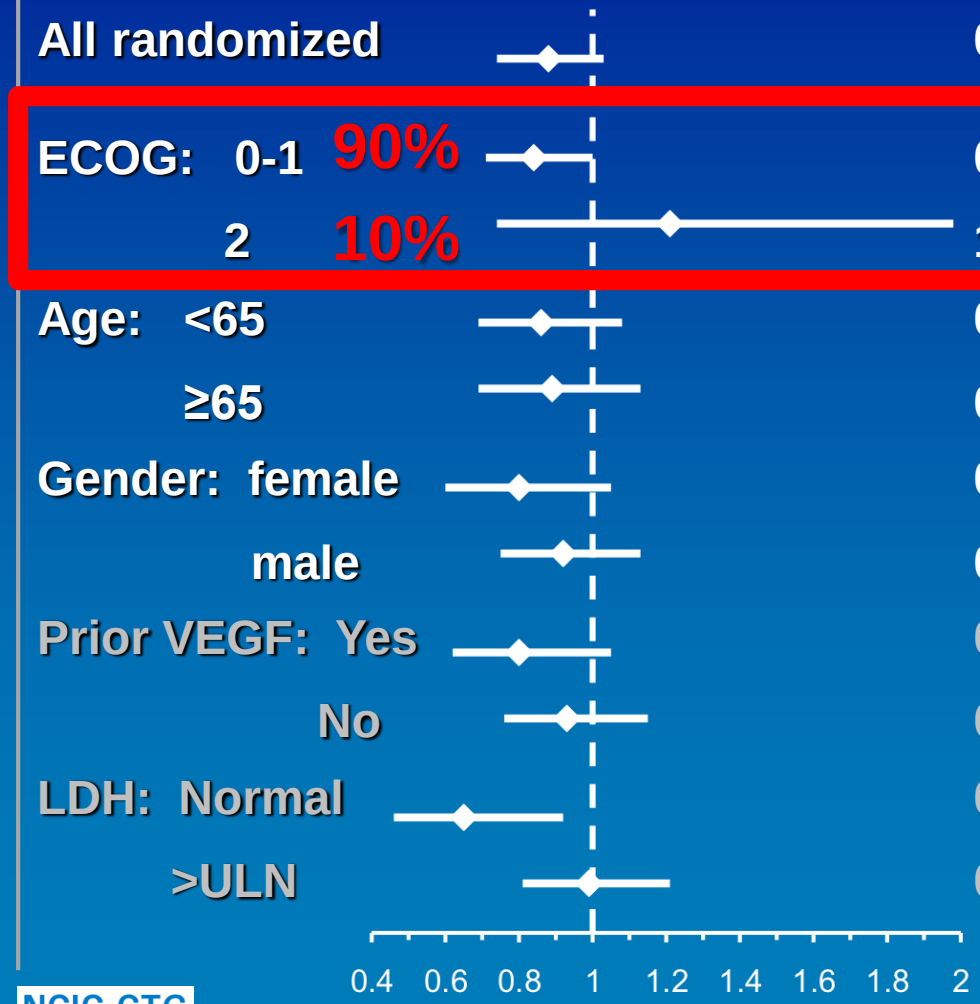


Study arm	Median (months)	95% CI
Brivanib + Cetuximab	8.8	7.9 – 9.6
Placebo + Cetuximab	8.1	7.4 – 9.0

HR 0.88 (95% CI = 0.74 – 1.03)
Stratified log rank p-value = 0.12

NCIC CTG
NCIC GEC

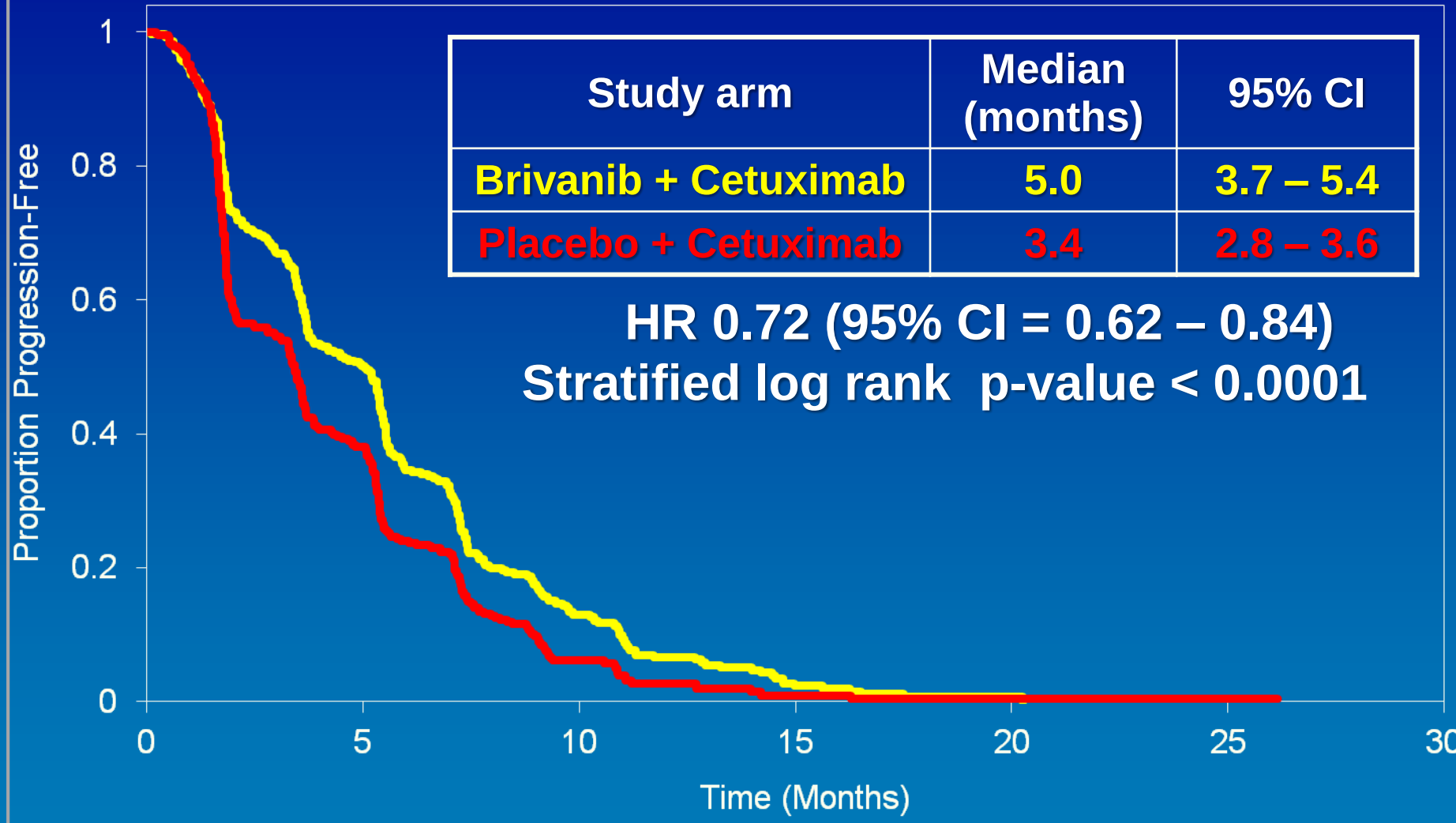
Survival Result by Subgroups



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

NCIC CTG
NCIC GEC

Progression Free Survival

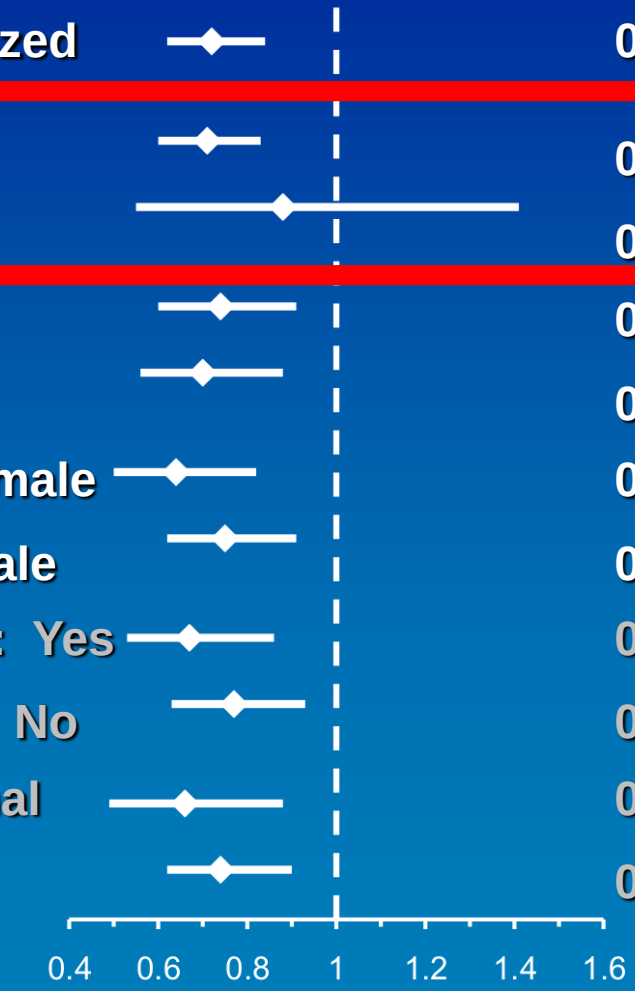


Study arm	Median (months)	95% CI
Brivanib + Cetuximab	5.0	3.7 – 5.4
Placebo + Cetuximab	3.4	2.8 – 3.6

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

NCIC CTG
NCIC GEC

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

NCIC CTG
NCIC GEC

Favours Brivanib Favours Placebo

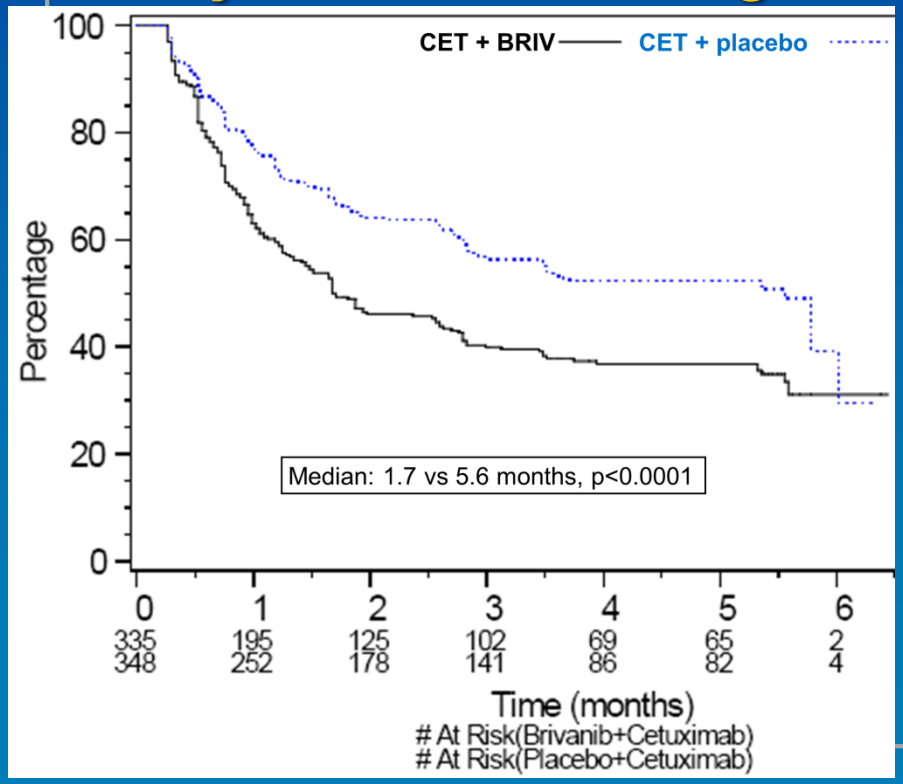
NCIC CTG CO.20: Treatment Response (RECIST 1.0)

Response Parameter	Brivanib + Cetuximab n = 376	Placebo + Cetuximab n = 374	p value
	No. of pts (%)	No. of pts (%)	
Complete Response (CR)	0 (0)	0 (0)	
Partial Response (PR)	51 (13.6)	27 (7.2)	
Stable Disease (SD)	188 (50)	163 (43.6)	0.004
Progressive Disease (PD)	81 (21.5)	142 (38)	
Not Evaluable (NE)	9 (2.4)	6 (1.6)	
Median Duration of Response in months (95% C.I.)	5.8 (4.7 – 7.4)	5.4 (3.7 – 5.5)	0.044

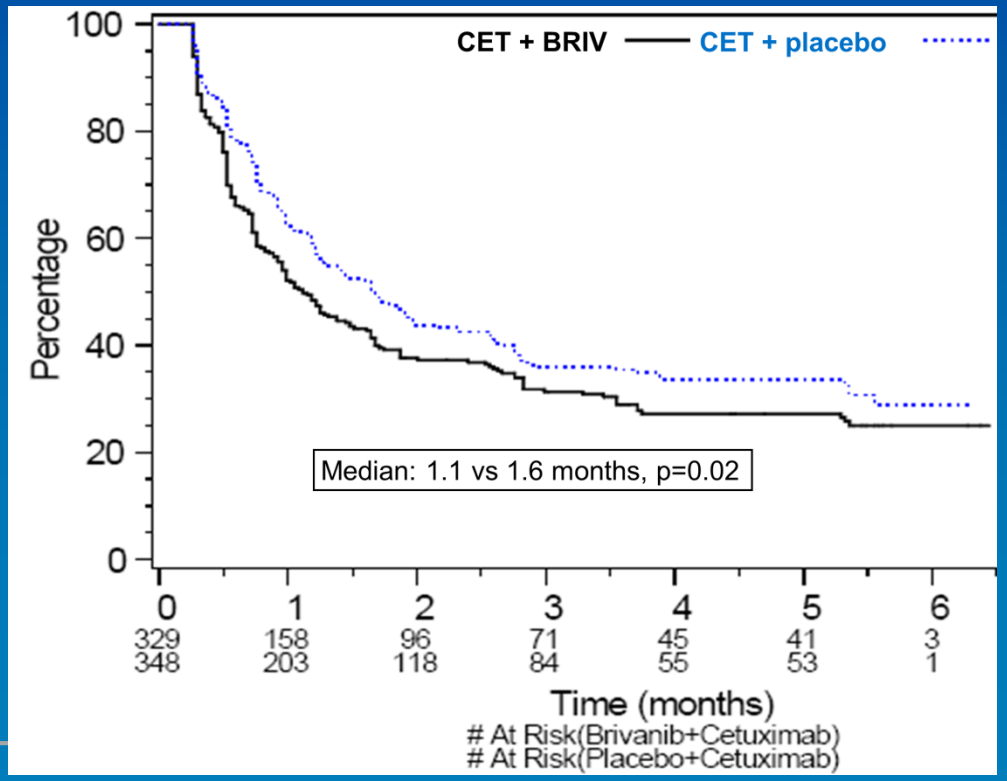
NCIC CTG CO.20: Quality of Life

- 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

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**

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Randomized, Placebo-Controlled Study of Cetuximab Plus Brivanib Alaninate Versus Cetuximab Plus Placebo in Patients With Metastatic, Chemotherapy-Refractory, Wild-Type *K-RAS* Colorectal Carcinoma: The NCIC Clinical Trials Group and AGITG CO.20 Trial

Lillian L. Siu, Jeremy D. Shapiro, Derek J. Jonker, Chris S. Karapetis, John R. Zalcberg, John Simes, Felix Couture, Malcolm J. Moore, Timothy J. Price, Jehan Siddiqui, Louise M. Nott, Danielle Charpentier, Winston Liauw, Michael B. Sawyer, Michael Jefford, Nadine M. Magoski, Andrew Haydon, Ian Walters, Jolie Ringash, Dongsheng Tu, and Chris J. O'Callaghan

QoL results 'under revision' with *Cancer*

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)

NCIC CTG
NCIC GEC

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

NCIC CTG
NCIC GEC

CO.23: A Phase III Randomized Study of BBI608 and Best Supporting Care versus Placebo and Best Supporting Care in Patients with Pretreated Advanced Colorectal Carcinoma

An NCIC Clinical Trials Group and AGITG Trial

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

AUSTRALASIAN GASTRO-INTESTINAL AGITG TRIALS GROUP

BBI608, an orally-administered first-in-class cancer stemness inhibitor blocks Cancer Stem Cells (CSC) self-renewal and induces cell death in CSC as well as non-stem cancer cells by inhibition of the Stat3, Nanog and B-catenin pathways, and has shown potent anti-tumour and anti-metastatic activities pre-clinically.

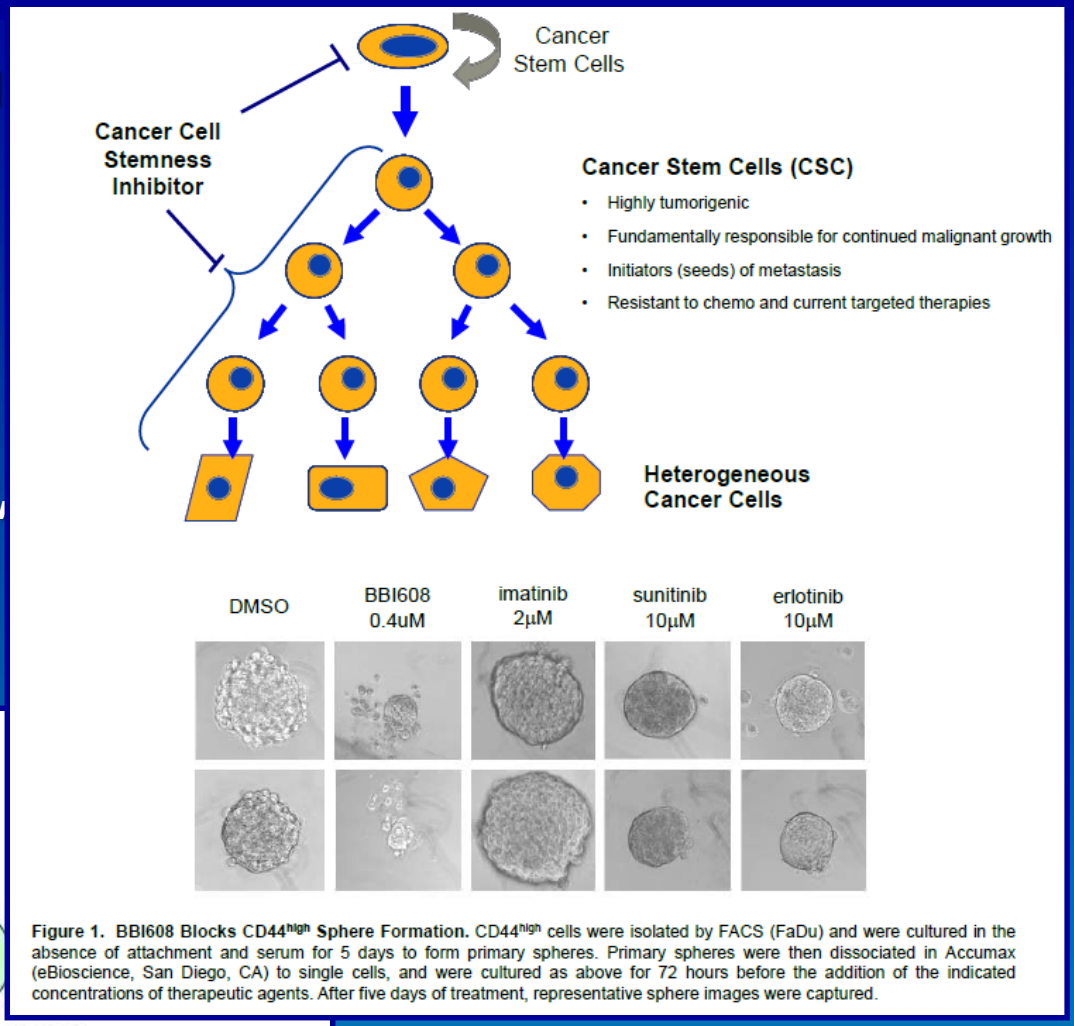


Figure 1. BBI608 Blocks CD44^{high} Sphere Formation. CD44^{high} cells were isolated by FACS (FaDu) and were cultured in the absence of attachment and serum for 5 days to form primary spheres. Primary spheres were then dissociated in Accumax (eBioscience, San Diego, CA) to single cells, and were cultured as above for 72 hours before the addition of the indicated concentrations of therapeutic agents. After five days of treatment, representative sphere images were captured.

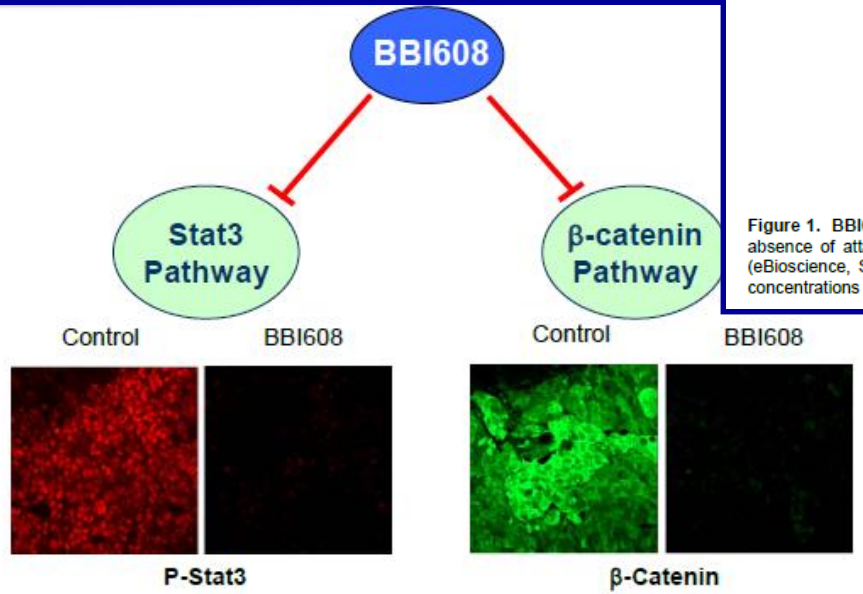
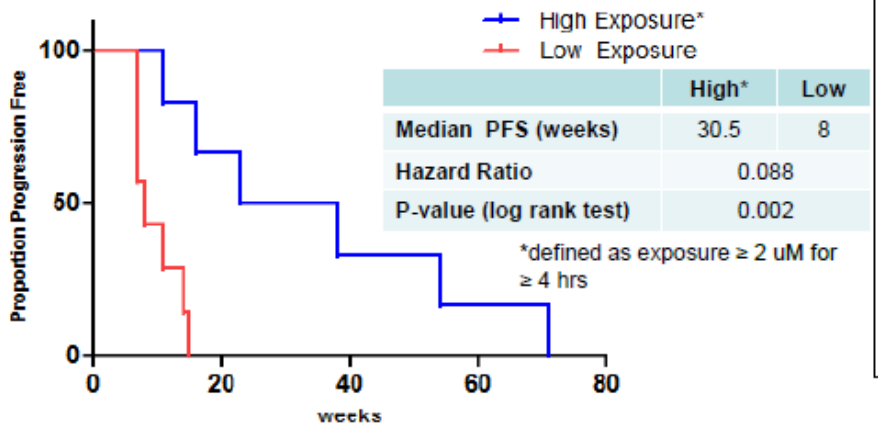


Figure 2. Effect of BBI608 Treatment on p-Stat3 and β-catenin Protein Levels in Human Colon Cancer Xenograft Tumor (SW480) in Nude Mice. Formaldehyde-fixed tumors from mice treated daily for 15 days with oral gavage of BBI608 or Vehicle (Control) were sectioned and analyzed by immunofluorescence staining using antibodies specific for human p-STAT3 and β-catenin.

Langleben et al., J Clin Oncol 31, 2013 (suppl; abstr 2542)

BBI608 – Early Efficacy

5A



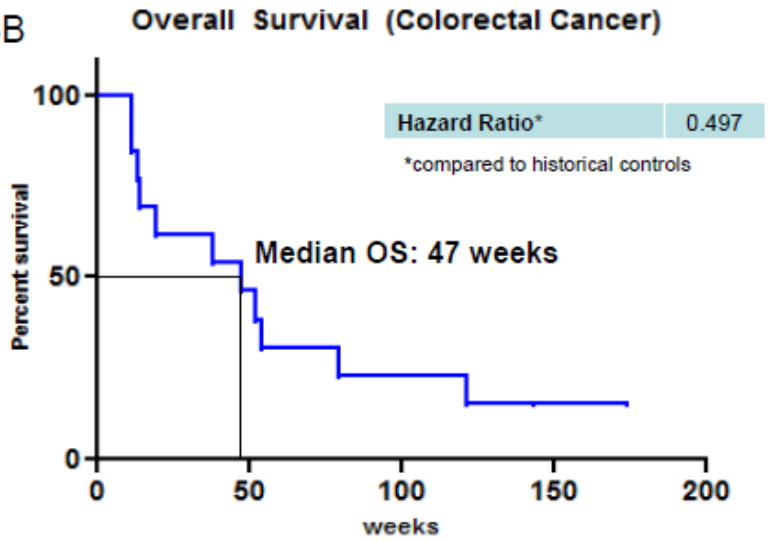
	High*	Low
Median PFS (weeks)	30.5	8
Hazard Ratio	0.088	
P-value (log rank test)	0.002	

*defined as exposure ≥ 2 uM for ≥ 4 hrs

Table 5. Disease Control Rate (DCR)*	
Colorectal	67% (8/12)
All Tumor Types	65% (17/26)

*DCR is defined as proportion of patients with SD + PR + CR by RECIST 1.1; evaluable patients had ≥4 weeks of BBI608, 80% compliance, and an on-study tumor assessment

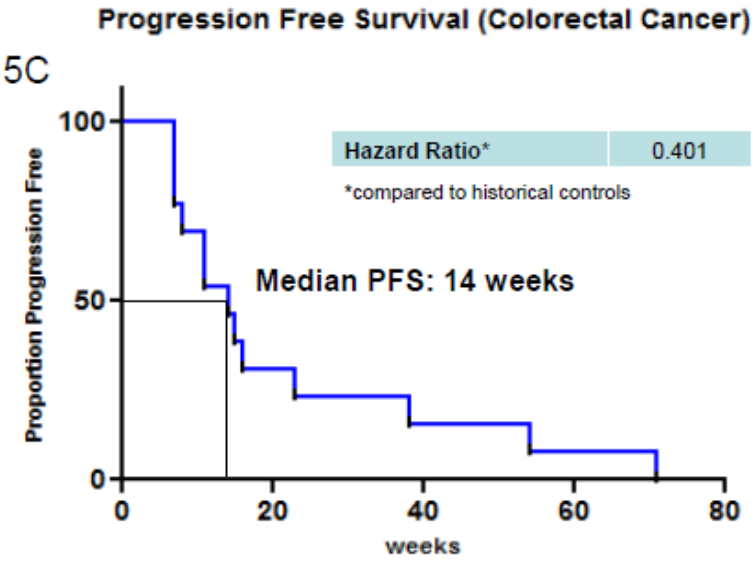
5B



Hazard Ratio*	0.497

*compared to historical controls

5C



Hazard Ratio*	0.401

*compared to historical controls

Figure 5A. Relationship Between PFS and Exposure of BBI608 in CRC Patients. In CRC patients, a statistically significant difference was seen in PFS between those with BBI608 plasma concentrations above 2.0 uM for greater than 4 hours and those who did not reach that level of exposure. **Figure 5B. Overall Survival (OS) in Evaluable CRC patients.** OS of evaluable CRC patients treated with BBI608 (defined as ≥4 weeks of BBI608, 80% compliance) compared with historical controls [Cetuximab for the treatment of colorectal cancer, 2007, N Engl J Med 357 2040-2048]. **Figure 5C. Progression Free Survival (PFS) in Evaluable CRC patients.** PFS of evaluable CRC patients treated with BBI608 (defined as ≥4 weeks of BBI608, 80% compliance) compared with historical controls [Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared with Best Supportive Care Alone in Patients with Chemotherapy-Refractory Metastatic Colorectal Cancer, 2007, J. Clin Onc 25 1658-1664].

BBI608 – Adverse Event Profile

Table 2. Subjects with Adverse Events Possibly Related to BBI608 (N=41)

Organ System	Adverse Event*	Any Grade		Grade 3	
		# Subjects	%	# Subjects	%
DIGESTIVE	Diarrhea	30	73.2%	2	4.9%
	Vomiting	20	48.8%	0	0.0%
	Nausea	20	48.8%	0	0.0%
	Abdominal cramps/pain	22	53.7%	0	0.0%
	Anorexia	14	34.1%	0	0.0%
	Loose/Soft Stools	8	19.5%	0	0.0%
	Dysgusia	5	12.2%	0	0.0%
	Reflux	4	9.8%	0	0.0%
CONSTITUTIONAL	Fatigue	18	43.9%	1	2.4%
	Weakness	6	14.6%	0	0.0%
	Weight loss	5	12.2%	0	0.0%
URINARY	Urine Color Change	10	24.4%	0	0.0%
METABOLIC	Dehydration	3	7.3%	0	0.0%
NEUROLOGIC	Dizziness	5	12.2%	0	0.0%

*observed in 10% or more of study subjects; adverse events graded using CTCAE v 3.0

Langleben et al., J Clin Oncol 31, 2013 (suppl; abstr 2542)

BBI608 – Potential Predictive Biomarkers

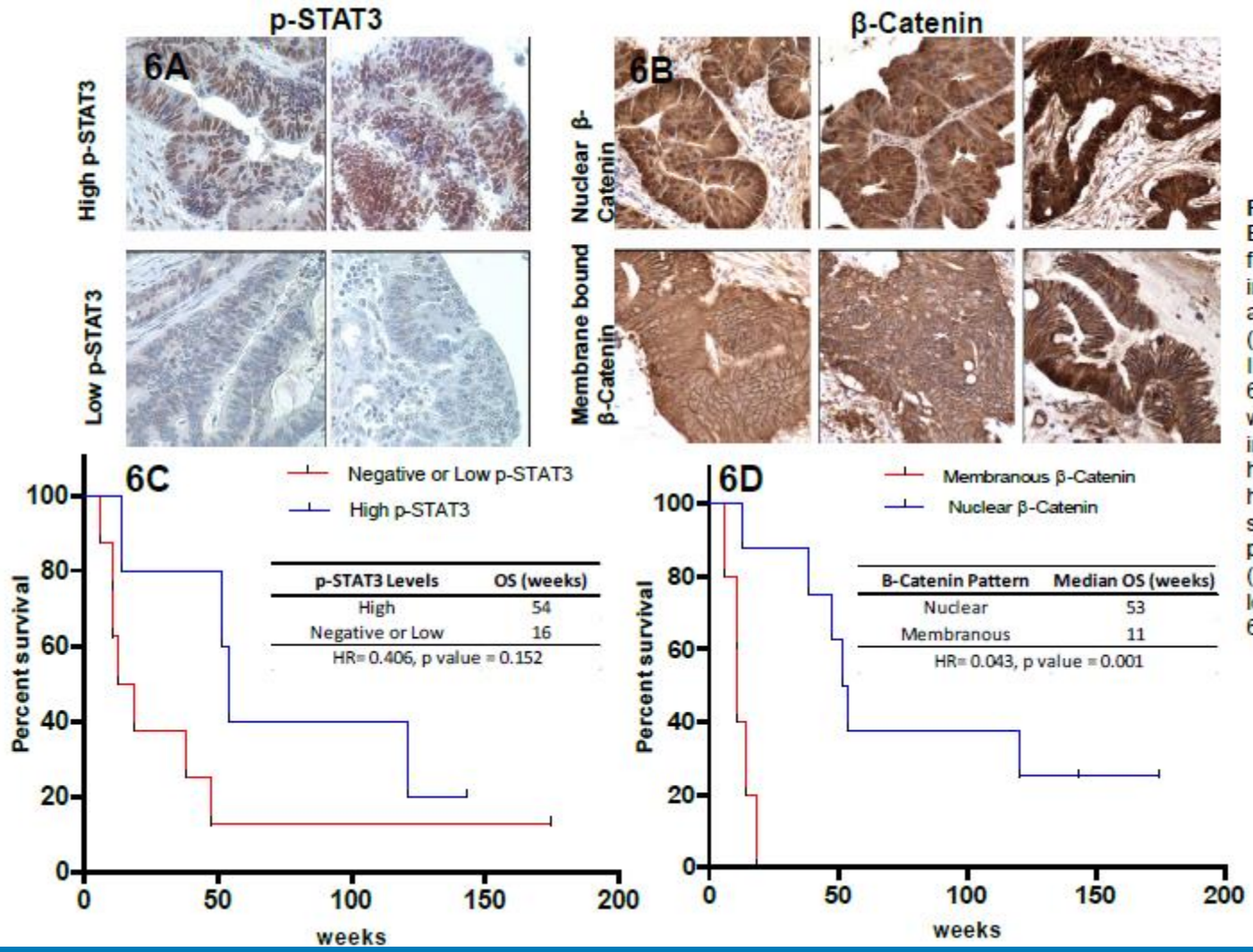


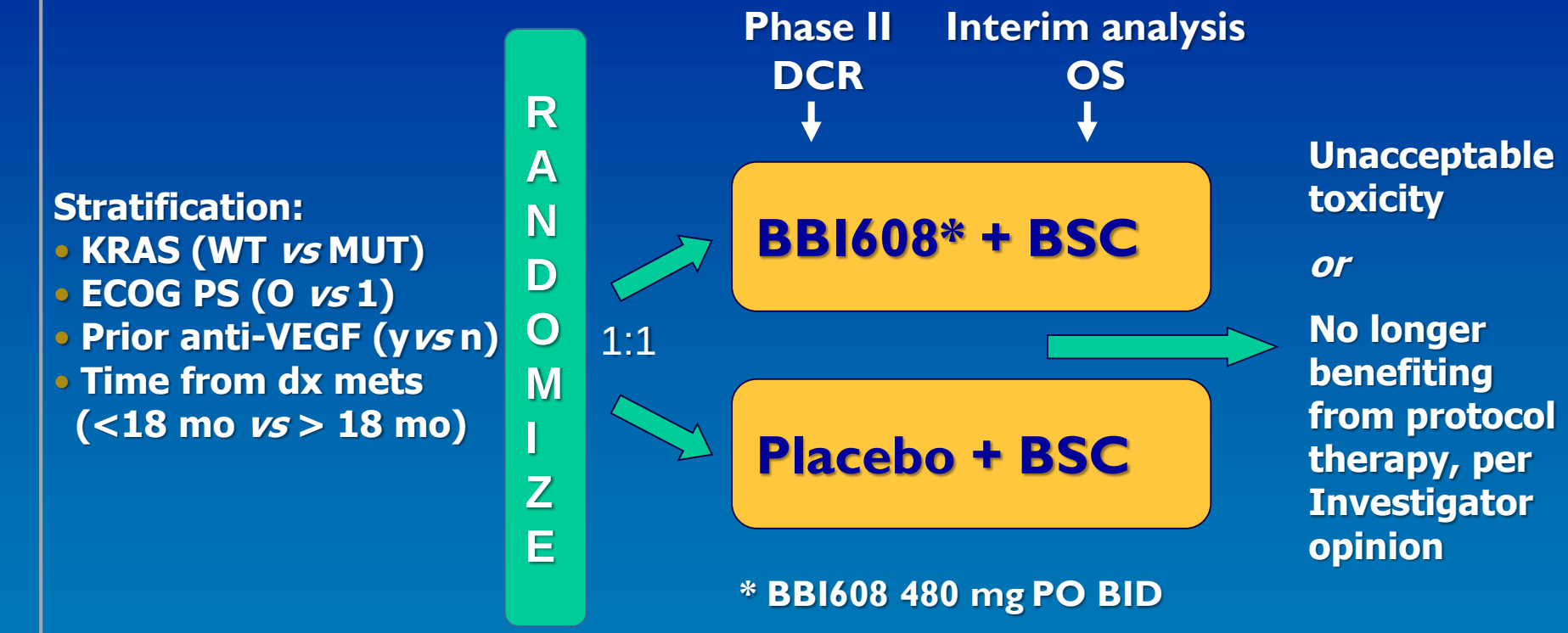
Figure 6A-D. Putative Predictive Biomarkers. Archival tissue samples from CRC patients were analyzed by immunohistochemistry (IHC) with antibodies against phosphorylated STAT3 (p-STAT3) and β-catenin. Representative IHC slides are shown [Figures 6A and 6B]. An analysis of CRC patients treated with BBI608 shows a trend towards improvement in survival for patients with high p-STAT3 (compared with patients having low or negative p-STAT3), and a significant improvement in survival for patients with nuclear β-catenin localization (compared with patient having β-catenin localized to the cell membrane) [Figures 6C and 6D].

Langleben et al., J Clin Oncol 31, 2013 (suppl; abstr 2542)

CO.23 Schema/Trial Design

Failed or intolerant to all recommended therapies

(TS inhibitor, Oxaliplatin, Irinotecan + EGFR inhibitor if KRAS WT)



- **Primary Objective: Overall Survival** (5% alpha, 90% power, HR=0.75)
- **Secondary: Progression Free Survival, Disease Control Rate, Safety, Quality of Life, Health Economics, PK, Correlative Biomarkers**

NCIC CTG
NCIC GEC

CO.23 Participants

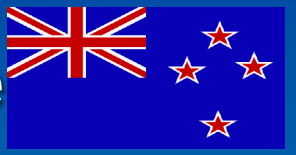
NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

Canada

– 275 patients from 40 sites

AUSTRALASIAN GASTRO-INTESTINAL AGITG TRIALS GROUP

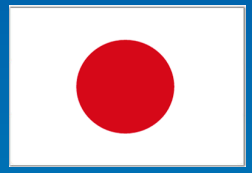
Australia, New Zealand & Singapore



– 275 patients from 40 sites

DAINIPPON SUMITOMO PHARMA

Japan



– 100 patients, ~10 sites

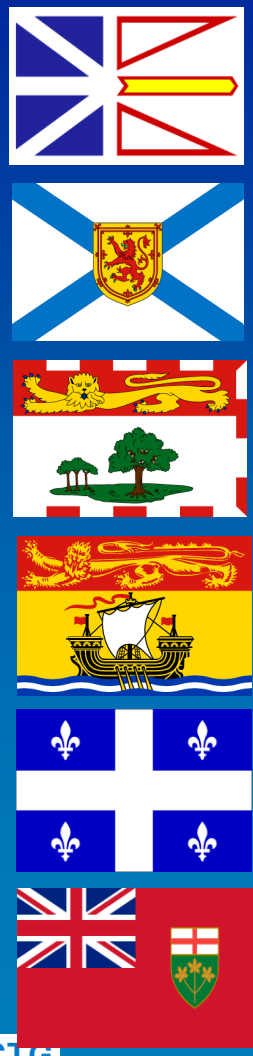
BOSTON BIOMEDICAL

United States of America

– 5 sites, accrual TBD

NCIC CTG
NCIC GEC

NCIC CTG Participating Centres



CAAJ	Dr. H. Bliss Murphy Cancer Centre, St. John's
CABN	QEII Centre for Clinical Research, Halifax
CACC	PEI Cancer Treatment Centre,Queen Elizabeth Hospital
CAEF	Horizon Health Network, Fredericton
CAEJ	Atlantic Health Sciences Corporation, Saint John
CAEM	The Moncton Hospital
CAER	The Vitalite Health Network - Dr. Leon Richard
CAGB	Hopital de la Cite-de-la-Sante
CAGH	Centre hospitalier universitaire de Sherbrooke
CAGT	Centre hospitalier regional de Trois-Rivieries
CAGQ	CHUQ - Hotel-Dieu de Quebec
CAGV	L'Hotel-Dieu de Levis
CAHA	Hopital Maisonneuve-Rosemont, Montreal
CAHC	McGill University - Dept. Oncology, Montreal
CAHN	CHUM - Hopital Notre-Dame, Montreal
CAKO	Ottawa Health Research Institute - General Division
CALC	Niagara Health System, St. Catharines
CALM	Juravinski Cancer Centre at Hamilton Health Sciences
CALO	Lakeridge Health Oshawa
CAME	Toronto East General Hospital

NCIC CTG Participating Centres

CAMM	Mount Sinai Hospital, Toronto
CAMN	Odette Cancer Centre, Toronto
CAMP	University Health Network-OCI/Princess Margaret Hospital, Toronto
CAMR	The Royal Victoria Hospital
CAMS	St. Michael's Hospital
CAMU	Credit Valley Hospital
CANL	London Regional Cancer Program
CAPN	Regional Cancer Program of the Hopital Regional de Sudbury
CAPS	Algoma District Cancer Program
CAPT	Thunder Bay Regional Health Science Centre
CARM	CancerCare Manitoba, St. Boniface General Hospital
CASA	Allan Blair Cancer Centre, Regina
CASS	Saskatoon Cancer Centre
CATC	Tom Baker Cancer Centre, Calgary
CATW	Cross Cancer Institute, Edmonton
CAVA	BCCA - Vancouver Cancer Centre
CAVF	BCCA - Fraser Valley Centre
CAVK	BCCA - Cancer Centre for the Southern Interior
CAVO	BCCA - Abbotsford Centre
CAVV	BCCA - Vancouver Island Cancer Centre, Victoria

CO.23 Timeline

- "First Contact" with Boston Biomedical Inc (BBI) = July 29, 2011
  - → Webcast to Investigators – October 7, 2011
  - → Survey of Interest – October 11, 2011
  - → Clinical Trials Committee Presentation – November 22, 2011
  - → CTC Approval "CO.23" – December 1, 2011
  - → Health Canada Pre-CTA Meeting – December 2, 2011
  - → Dainippon Sumitomo Pharma (DSP) announces their intention to acquire BBI – February 29, 2012
  - → FDA Special Protocol Assessment Meeting – March 5, 2012
  - → Contact with AGITG – April 11, 2012
  - → DSP acquires BBI – April 24, 2012
  - → CO.23 presented at Spring Meeting – April 28, 2012

CO.23 Timeline

- → AGITG Scientific Advisory Committee approve participation in CO.23 – May 5, 2012
- → FDA grant SPA approval – July 30, 2012
- → First CO.23 Newsletter – August 10, 2012
- → CO.23 presented at AGITG AGM – September 6, 2012
- → BBI and DSP visit NCIC CTG – September 18, 2012

- Protocol finalized – January 22, 2013 (18)
  - → CTA submitted to Health Canada – January 29, 2013
  - → CO.23 Website activated – February 14, 2013
  - → Second CO.23 Newsletter – February 14, 2013
  - → OCREB submission – February 22, 2013
  - → No Objection Letter received from HC – February 28, 2013

CO.23 Timeline

- Contract signed – April 1, 2013 (3)
  - → CO.23 registered on Clincialtrials.gov – April 10, 2013
  - → OCREB approval received – April 15, 2013
- Central Activation – April 15, 2013 (0.5)
- First NCIC CTG site activated – April 24, 2013 (0.25)
  - → Investigators/CRA Initiation Meeting – April 28, 2013
- First NCIC CTG patient randomized – May 10, 2013 (0.75)

Regorafenib compassionate release program

- First AGITG patient randomization projected – August 30, 2013

2 years and counting…

Will CO.23 be a "Success" ?

- ✓ 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
- X Limited therapeutic options – e.g. end stage settings (regorafenib)
- ✓ Good risk/benefit ratio (real or perceived)
- ✓ Unique - Not already planned, in progress… or complete!
- ✓ Well funded/resourced ($10,000 + $5,000 + $550 samples)

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

+

AUSTRALASIAN GASTRO-INTESTINAL AGITG TRIALS GROUP

Watch this space…

NCIC CTG
NCIC GEC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