




## Plenary Session 2:

# Key Elements of a Successful Phase III Trial: Examples from the CCTG

A photograph showing a hand pulling back a heavy red curtain. The curtain is split down the middle, revealing a plain white background behind it. The text 'A Look Behind the Curtain' is overlaid on the left side of the red curtain.

**A Look  
Behind  
the  
Curtain**

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

# 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 permitting future decision-making.
- NOT necessarily a positive trial...
  - a negative trial can be as important and may also change or inform practice

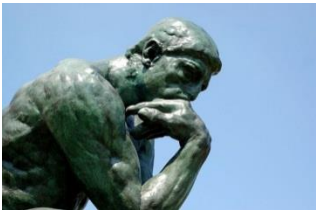
# What is a “Failed” Trial?

- 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 = a waste of time, effort & resources as well as a huge opportunity cost (... could be doing another trial)

# Surely its simple?

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



Smart people  
Careful planning  
Peer review  
Monitoring  
**Science**

***The Proof***



Patient preference  
Investigator preference  
“Red Tape”/Costs  
**Intangibles**

**Eligibility Criterion\***



# Design, Data & Analysis: The CCTG 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
  - 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

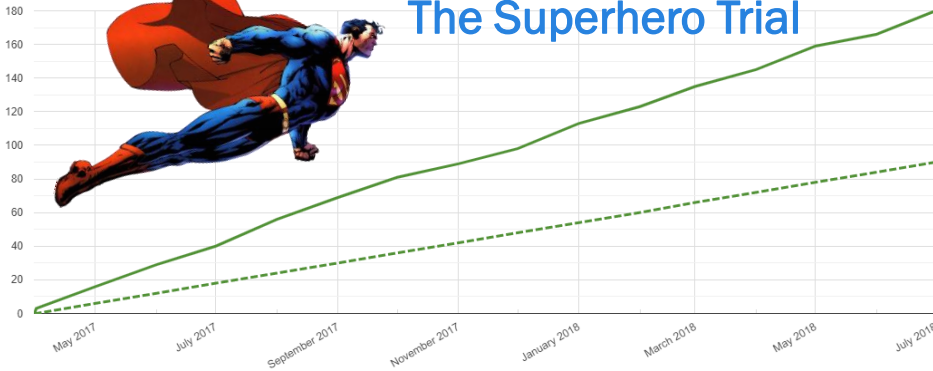
# The Absolute Truths: Death, Taxes and ...



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

# The Good, The Bad & The Ugly

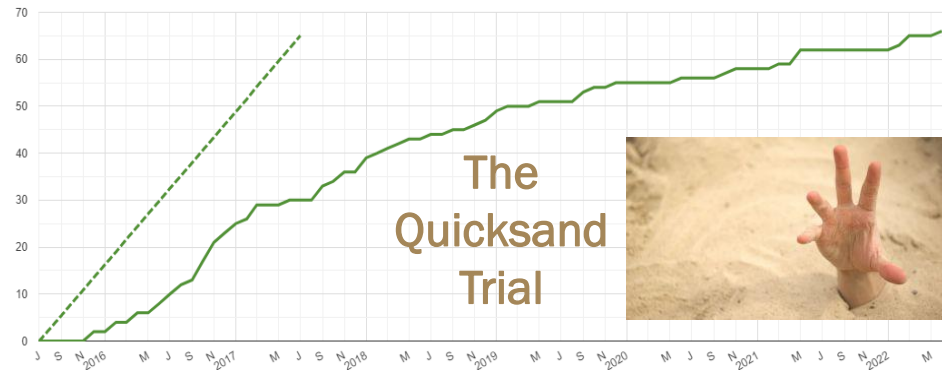
## The Superhero Trial



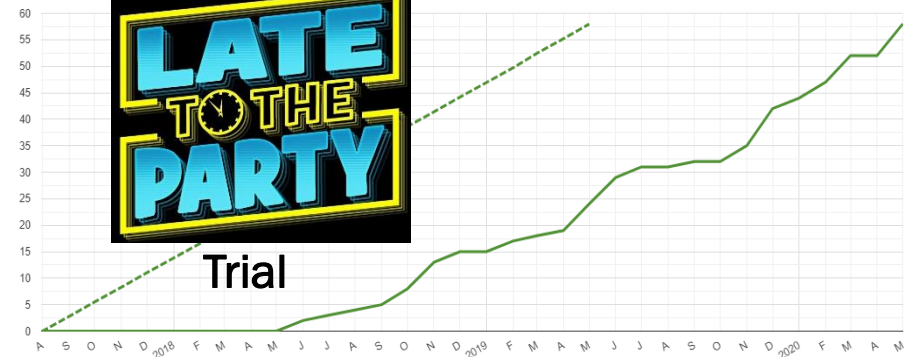
## The Hockey Stick Effect Trial



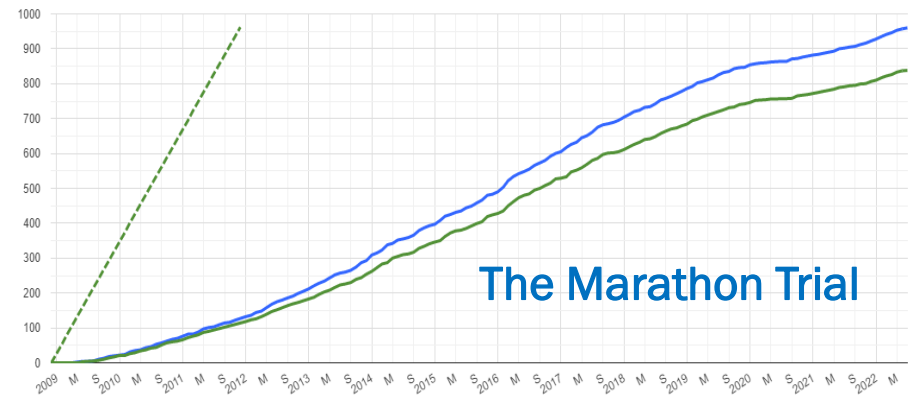
## The Quicksand Trial



## The Late To The Party Trial



## The Marathon Trial



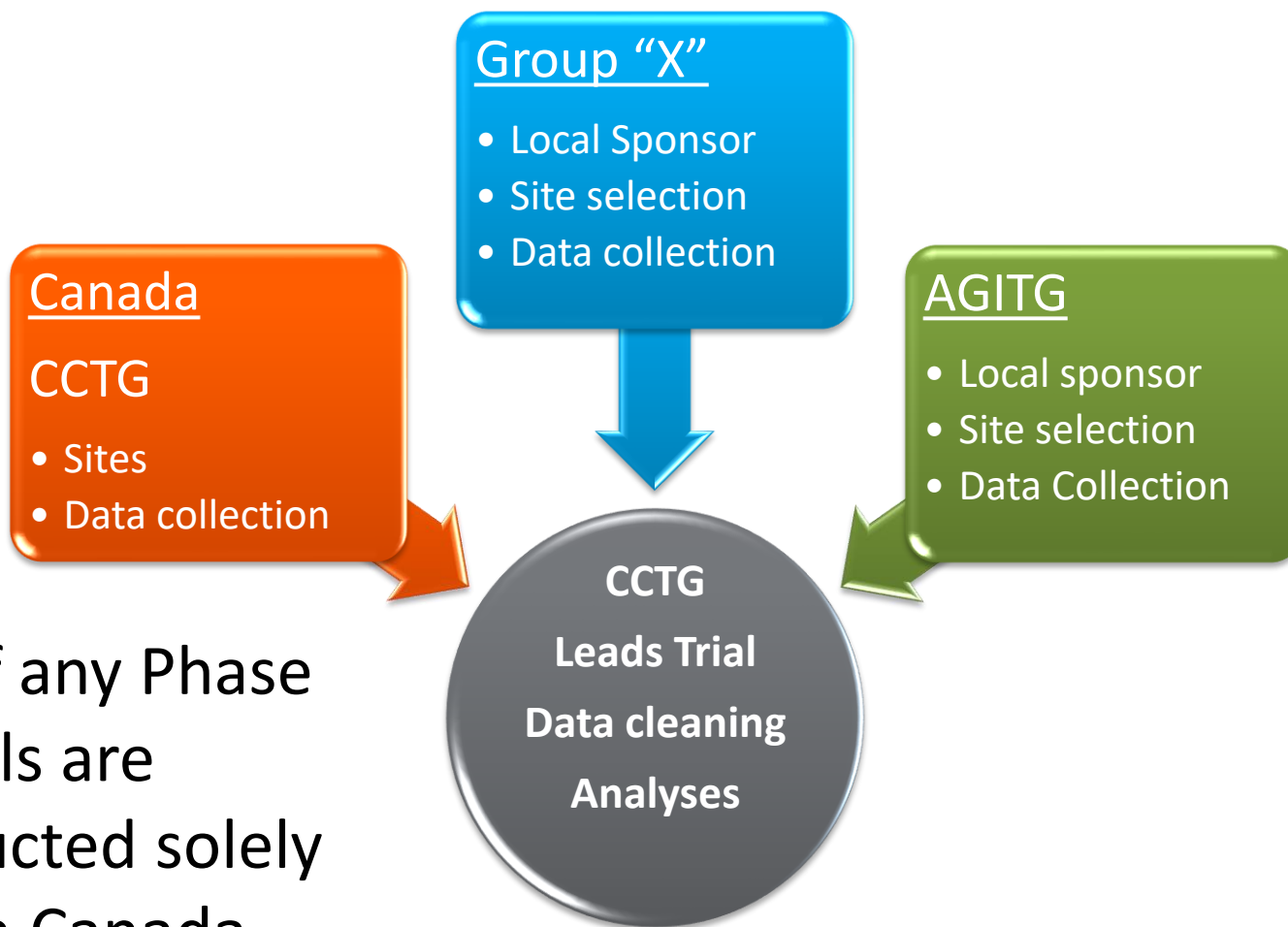
# Determinants of Good Accrual

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

= rapid activation and timely accrual

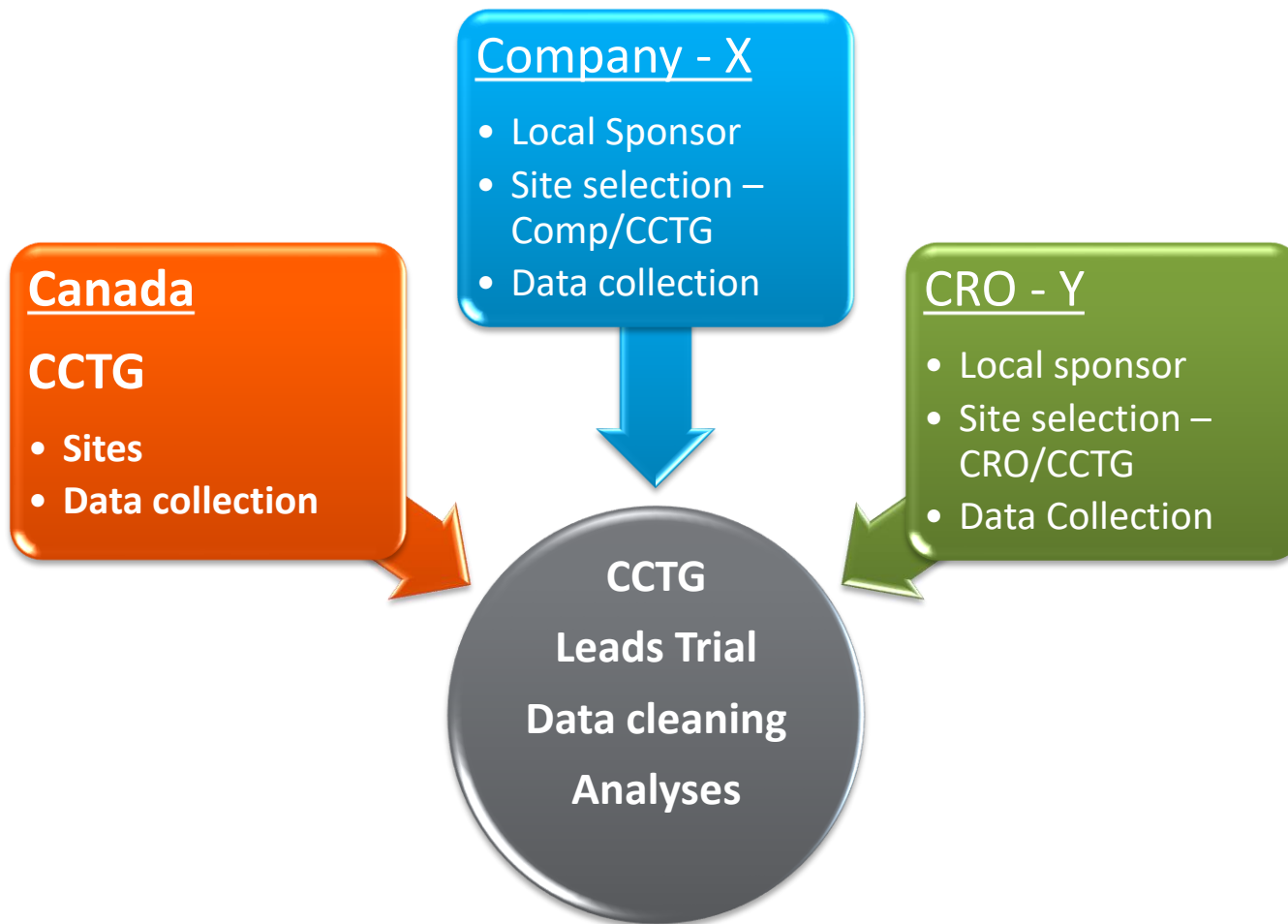
= minimized cost and timely answer

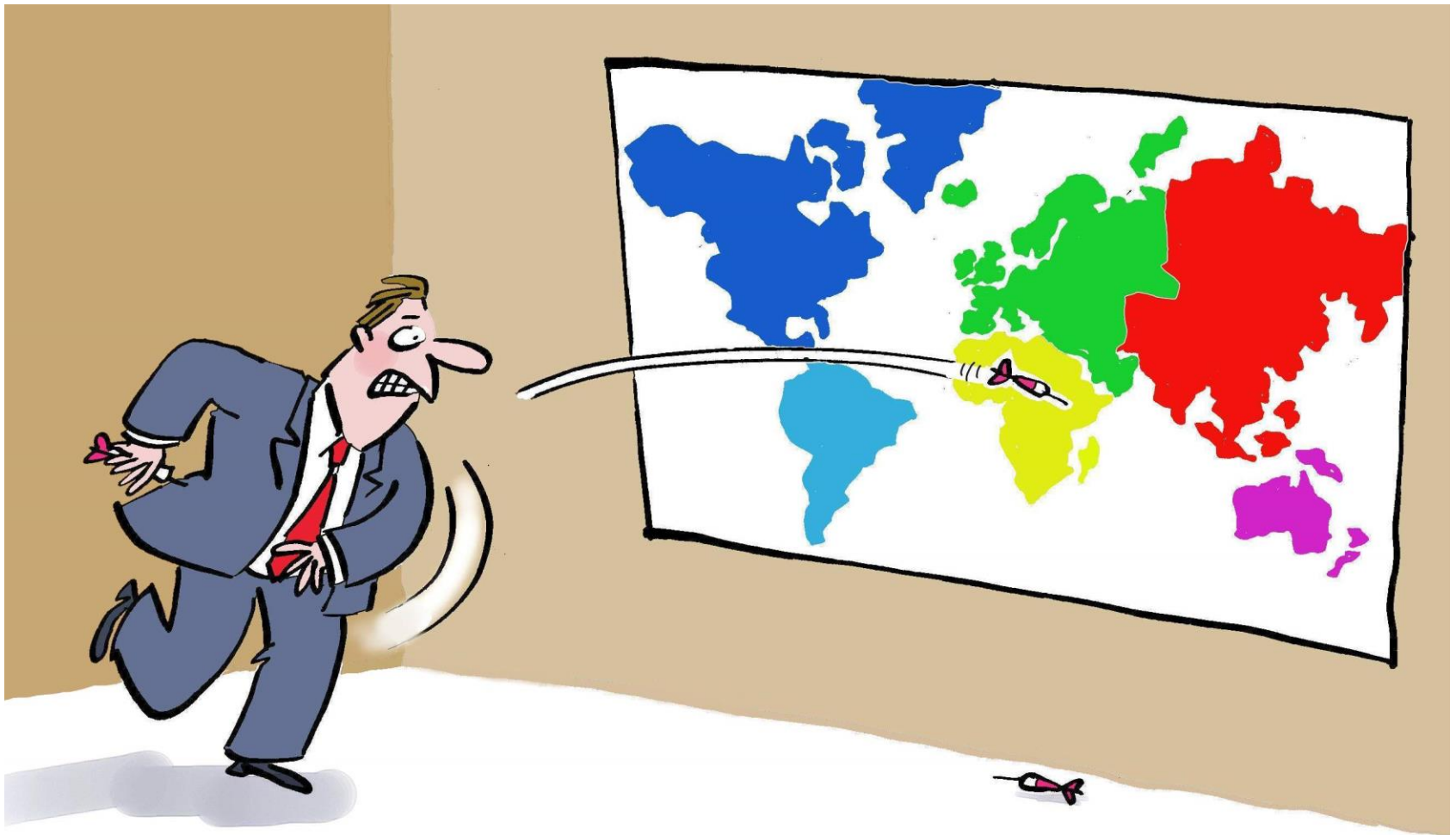
# ASIDE: Creating Collaborators: The 'Intergroup' Trial Model



Few if any Phase  
III trials are  
conducted solely  
within Canada

# Creating Accrual: The 'International' Trial Model





PROTHERO DIDN'T BELIEVE IN THESE NEW-FANGLED FEASIBILITY STUDIES  
AND RANKINGS TO DECIDE WHERE TO SITE STUDIES ...

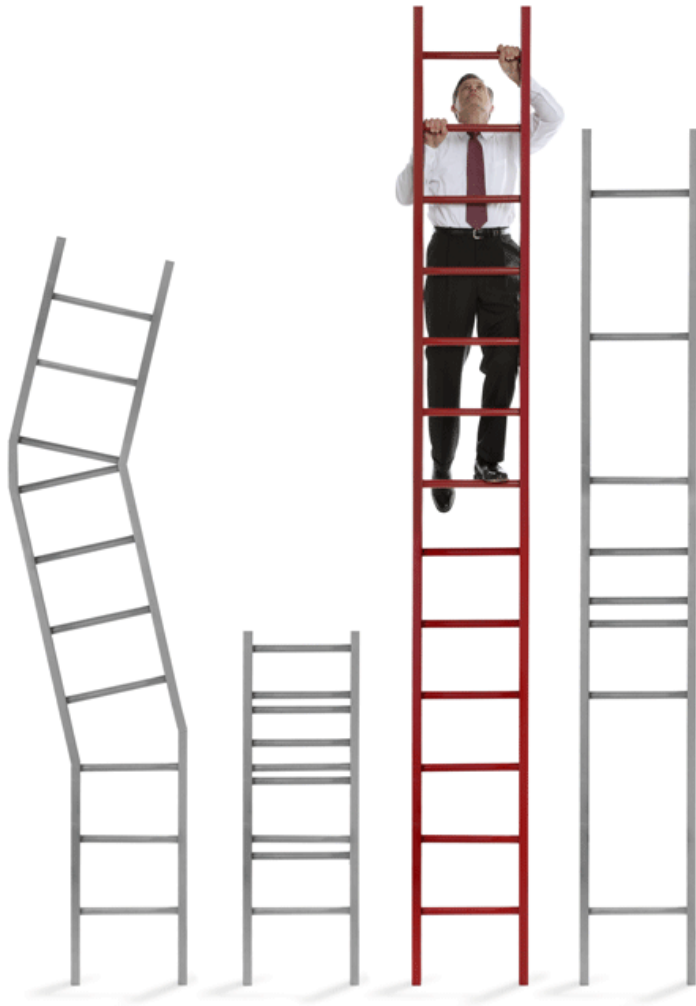
# Choose your friends wisely!



# 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

# Like rungs in a ladder...



Not all are  
absolutely  
essential...  
but the more  
that are  
missing....



# Is this patient eligible?

Again, it sounds simple = Be sure patients...

- 1) Meet the eligibility criteria
- 2) Do not meet the ineligibility 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, principle may be to “optimize potential” vs generalizability
- Quality – e.g. surgical/RT QA, SOC

# 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 (“Catch 22”)

# ASIDE: Funding and Resource

1. Fund yourself ('local' funding)
  - not feasible for phase III
2. Apply for a peer-reviewed grant
  - CIHR = ↓ 10% success rate, bias against clinical trials?
3. Submit proposal to a Group (e.g. CCTG)
  - may still need #2 ± #4
4. Submit proposal to a company
  - Supported proportionate to interest
  - Investigator/Sponsor independence?
  - Faster!, more oversight, more demands...



**Working with pharma can be like  
being pecked to death by chickens...**



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

# SPOILER ALERT

**What follows is  
often shameless  
CCTG  
self-promotion...**

# **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)**

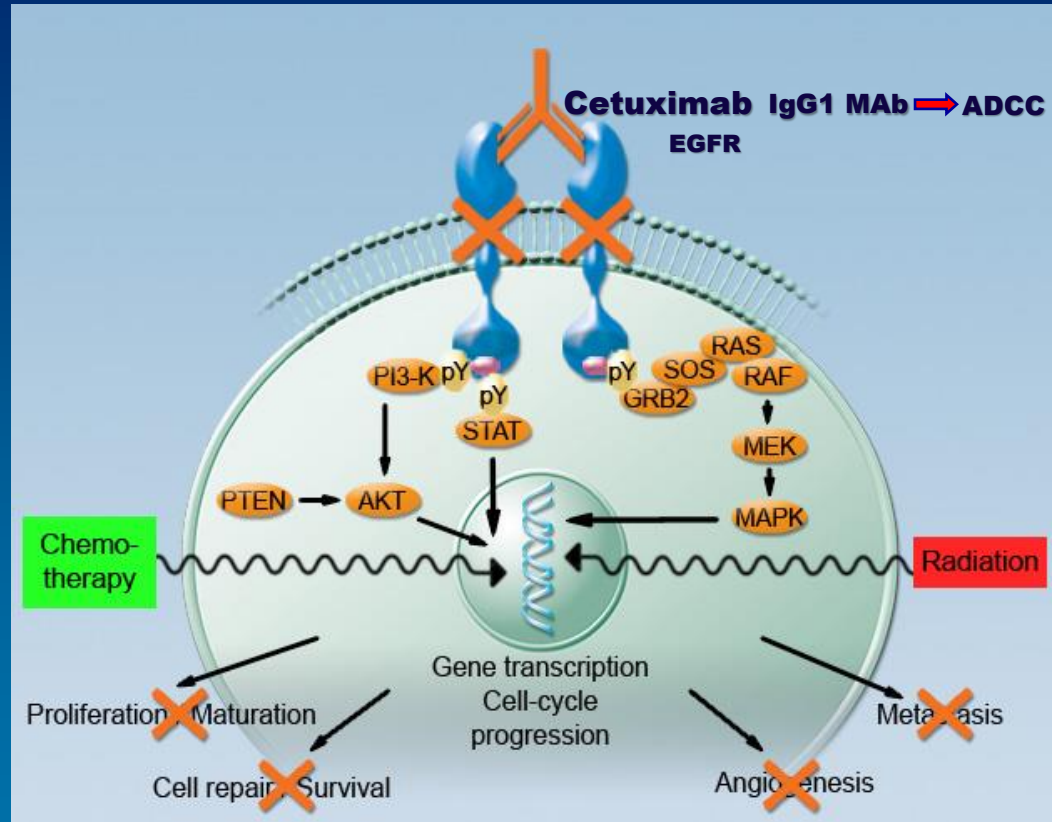
**A trial of the  
NCIC Clinical Trials Group  
(NCIC CTG)  
and the  
Australasian Gastro-Intestinal Trials Group  
(AGITG)**

**NCIC Clinical Trials Group  
NCIC Groupe des essais cliniques**



# 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
<u>Irinotecan Failure</u>				
<b>Saltz L.</b> <i>J Clin Oncol</i> 2004 (IMC 0141)	<b>Cetuximab</b>	<b>57</b>	<b>8.8%</b>	<b>1.4 mo</b>
<b>Cunningham D.</b> <i>N Eng J Med</i> 2004 (EMR 007 / BOND)	<b>Cetuximab</b>	<b>111</b>	<b>10.8%</b>	<b>1.5 mo</b>
	<b>Cetuximab + Irinotecan</b>	<b>218</b>	<b>22.9%</b>	<b>4.1 mo</b>
<u>Irinotecan, Oxaliplatin, Fluoropyrimidine Failure</u>				
<b>Lenz H-J.</b> <i>J Clin Oncol</i> 2006 (IMC 0144)	<b>Cetuximab</b>	<b>346</b>	<b>12.4%</b>	<b>1.4 mo</b>

# CO.17: Randomized Phase III Trial in mCRC

Failed or intolerant to all recommended therapies  
(TS, Oxaliplatin, Irinotecan)

1243 screened  
79% EGFR +ve

R  
E  
G  
I  
S  
T  
E  
R

EGFR  
testing  
by IHC

R  
A  
N  
D  
O  
M  
I  
Z  
E

1:1

**Cetuximab\* + BSC**

**287**

**BSC alone**

**285**

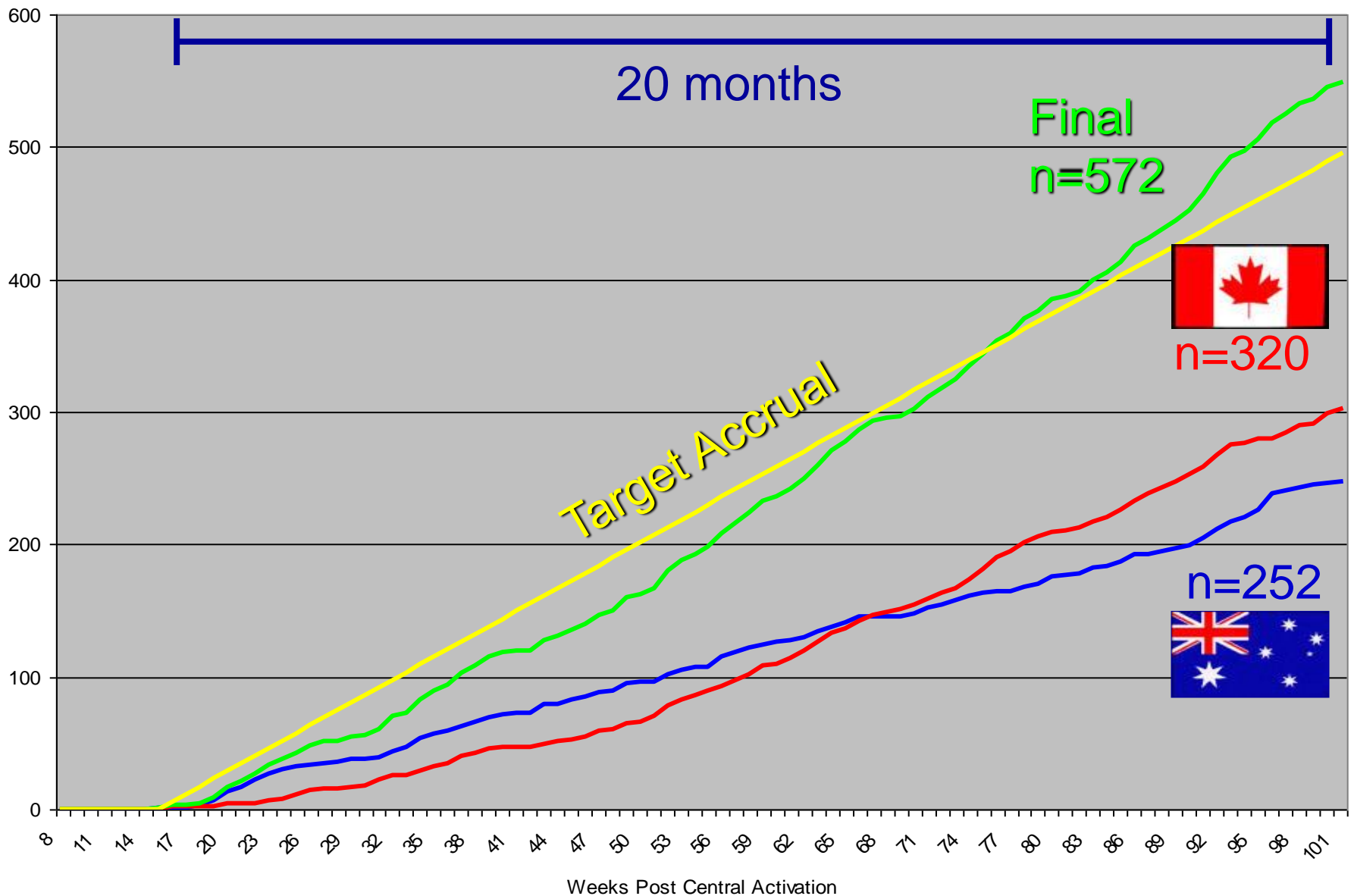
Disease  
Progression  
or  
Unacceptable  
Toxicity

**572 randomized**

\* Cetuximab 400 mg/m<sup>2</sup> IV week 1 then 250 mg/m<sup>2</sup> 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)**

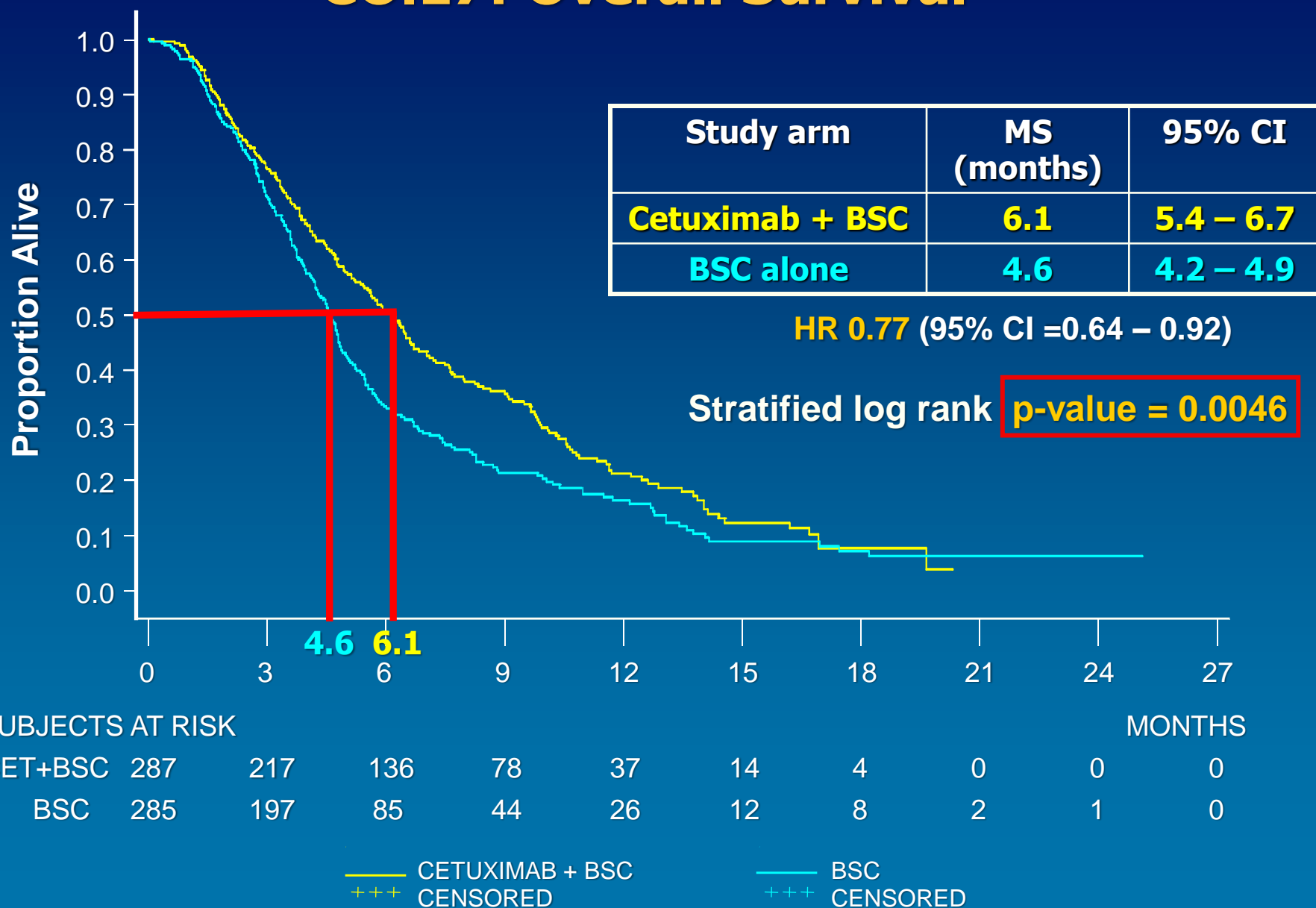
# CO.17: Accrual



## CO.17 Top Accruing Canadian 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

# CO.17: Overall Survival



# 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.

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*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/CTA submission = July 2003 (3)
- Central activation = Aug 2003 (1)
- First site activated = Nov 2003 (AGITG) , Dec 2003 (CCTG) (3)
- First patient randomized = Dec 2003 (AGITG & CCTG) (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**

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# 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 (**weekly infusions**)
  - ✓ Limited therapeutic options – e.g. end stage settings
  - ✗ 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

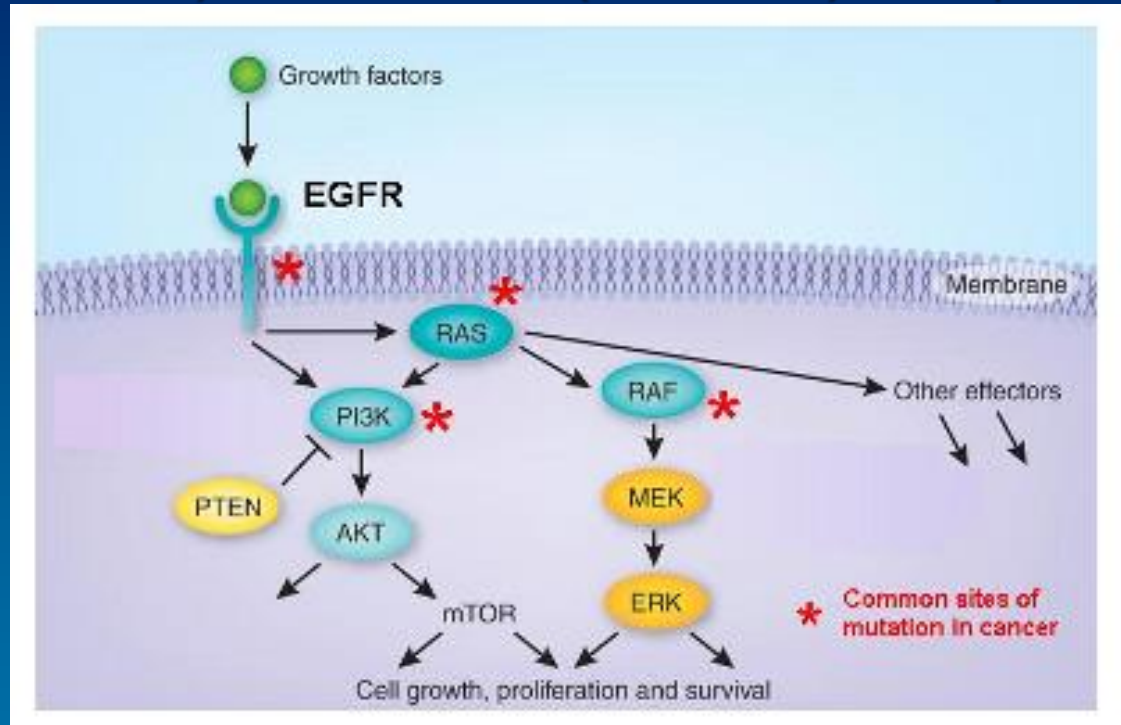
The *KRAS* mutation status of the tumour was proposed as a potential marker of response and a predictor of benefit

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

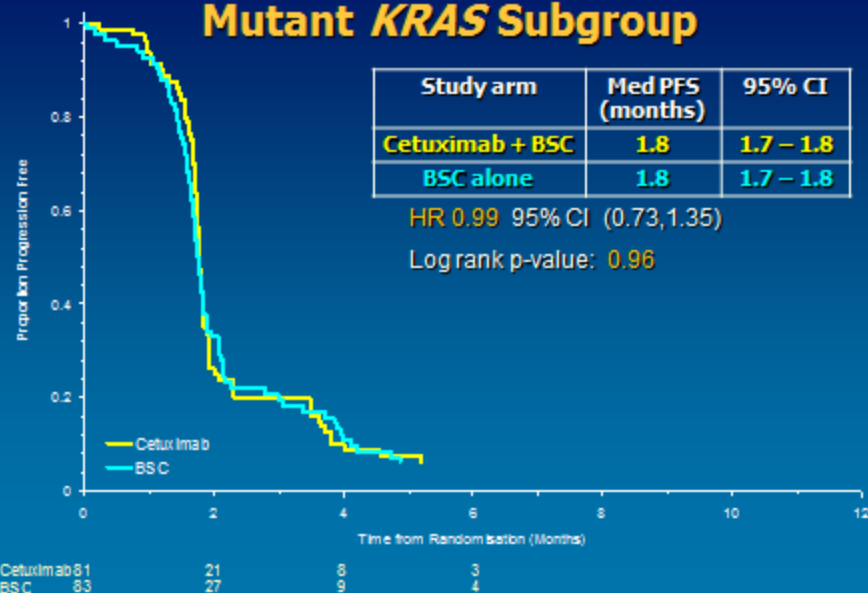
# “Luckily” we had collected tumour samples!

# The *KRAS* Oncogene

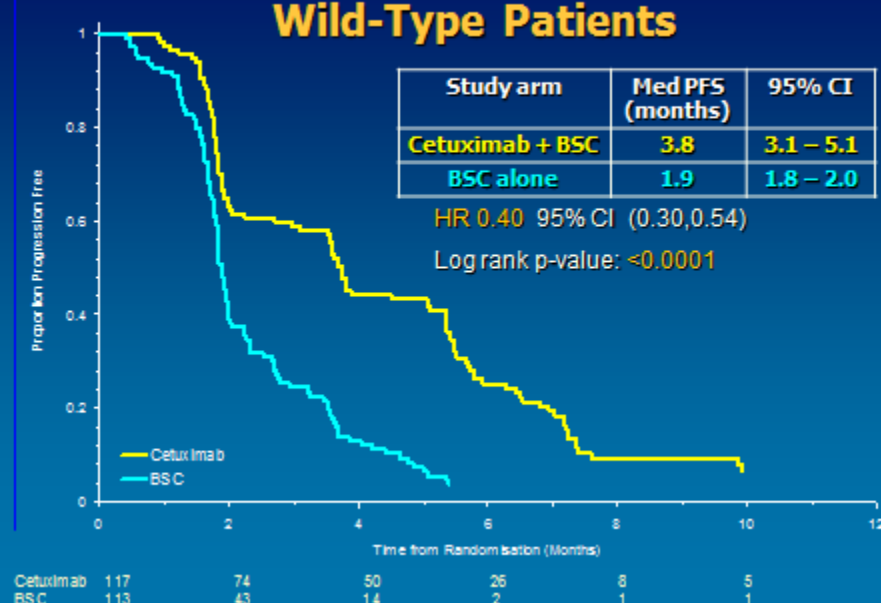
- KRAS is a small G-protein downstream of EGFR and is an essential self-inactivating component of the EGFR signalling cascade, normally cycling from GDP bound ("off" state) to GTP bound ("on" state) in response to receptor activation
- Mutations in the *KRAS* gene can lead to constitutive activation 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



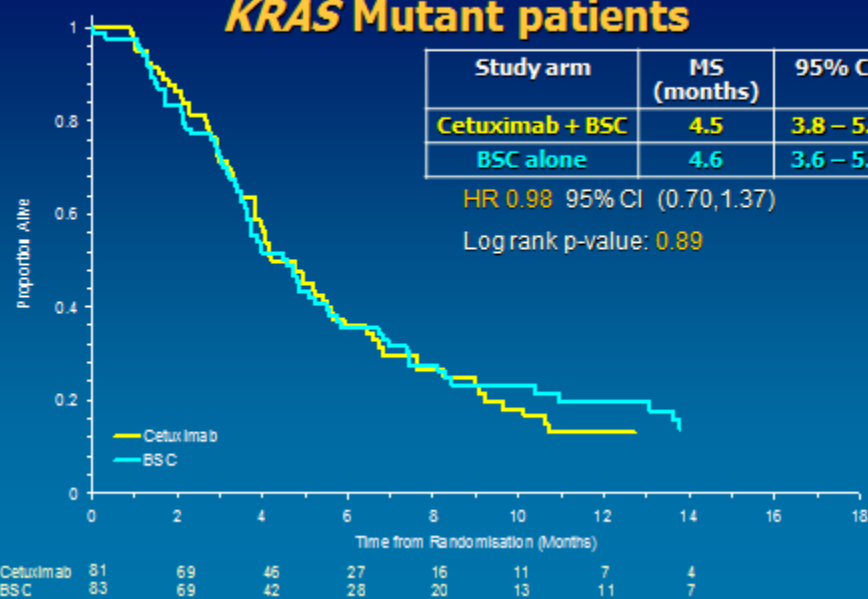
## NCIC CTG C0.17: PFS in the Mutant *KRAS* Subgroup



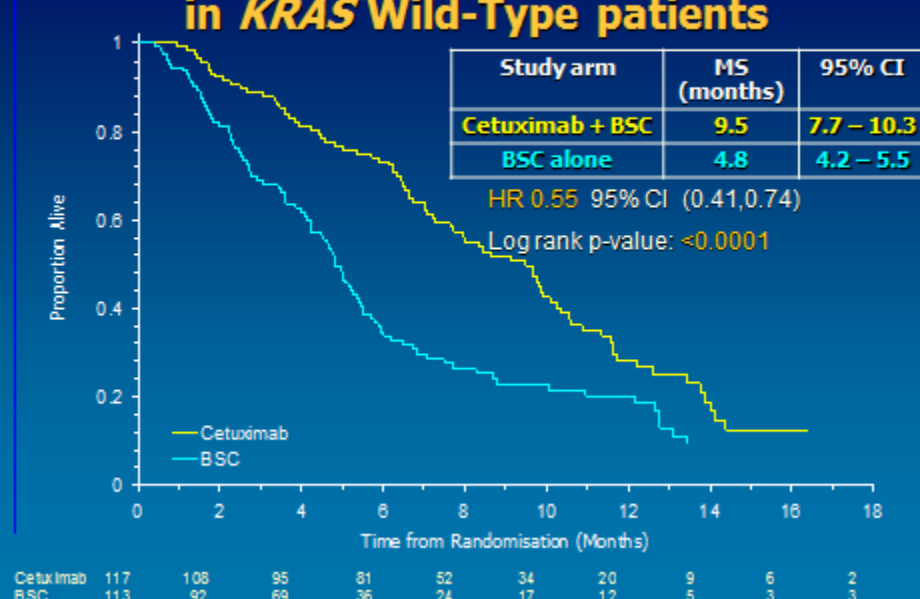
## NCIC CTG C0.17: PFS in the *KRAS* Wild-Type Patients



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



## NCIC CTG C0.17: Overall survival in *KRAS* Wild-Type patients



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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

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

*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*

ARTICLE

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**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 Other Metrics of “Success”

- Multiple (10+) peer-reviewed scientific presentations and publications in high-impact journals
  - Primary, secondary and unplanned post-hoc analyses of trial data and biological samples
- Multiple authorship positions for CCTG investigators & fellows (... virtually every PI)
- Establish collaborative academic cooperative group partnership with AGITG (NHMRC CTC)
  - 8 GI trials (CO.20, CO.23, etc) + lung, brain, prostate
- Demonstrate CCTG capability to run international multi-centre registrational phase III trials via academic cooperative groups
- Correlative biomarker studies STILL ongoing



## CO.26

# **A Phase II Randomized Study of Durvalumab and Tremelimumab and Best Supportive Care vs Best Supportive Care Alone in Patients with Advanced Colorectal Adenocarcinoma Refractory to Standard Therapies**

Study Chair: Eric Chen  
Senior Investigator (SI): Chris O'Callaghan  
Senior Biostatistician: Dongsheng Tu  
Study Coordinator (SC): Nadine Magoski  
Supported by: AstraZeneca

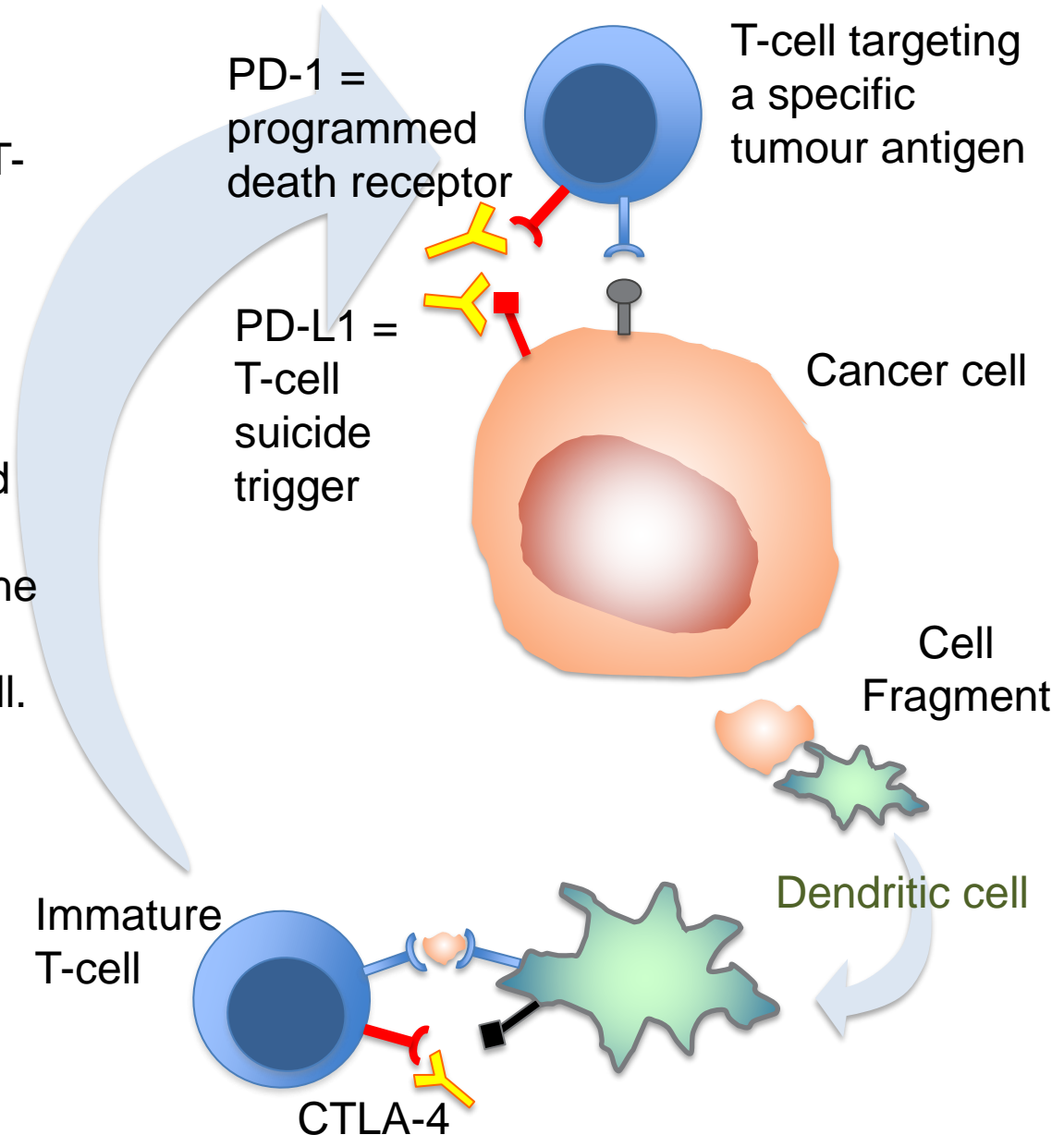
## Anti Tumour Immunity

- Tumour cell antigens /fragments are delivered by dendritic cells to immature T-cells
- T-cells mature and multiply until triggered to shut off by CTLA-4
- Mature T-cells targeting specific tumour antigen bind to and attack cancer cells
- In the presence of PD-L1, the PD-1 receptor is triggered leading to death of the T-cell.

### Opportunity to enhance?

• Inhibition of:

- Y ■ **PD1** – nivolumumab, pembrolizumab
- Y ■ **PD-L1** – durvalumab, BMS-936559
- Y ■ **CTLA-4** – ipilimumab, tremelimumab



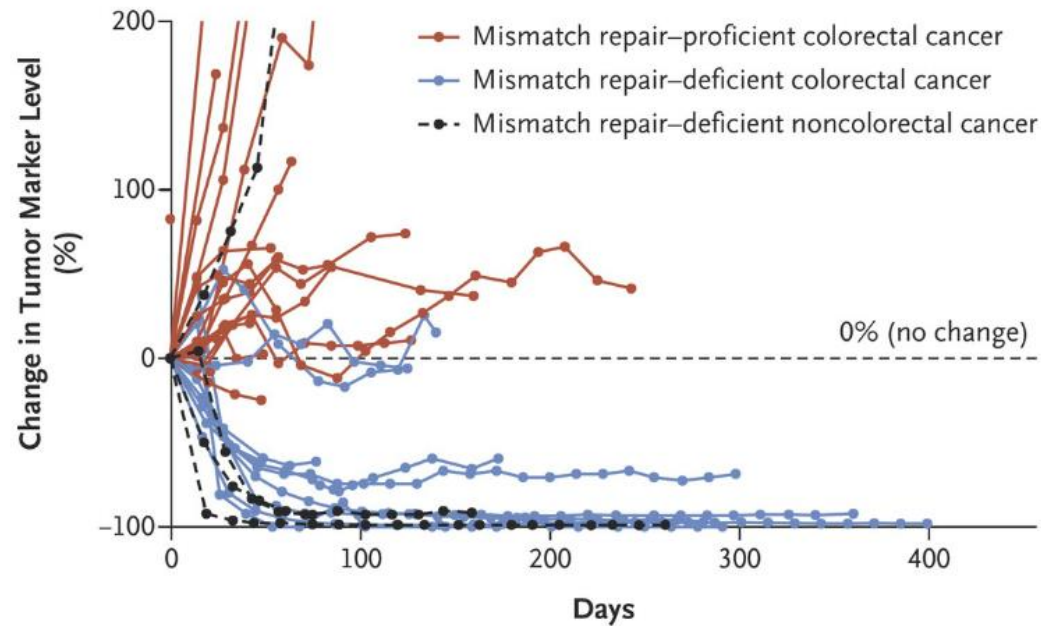


ORIGINAL ARTICLE

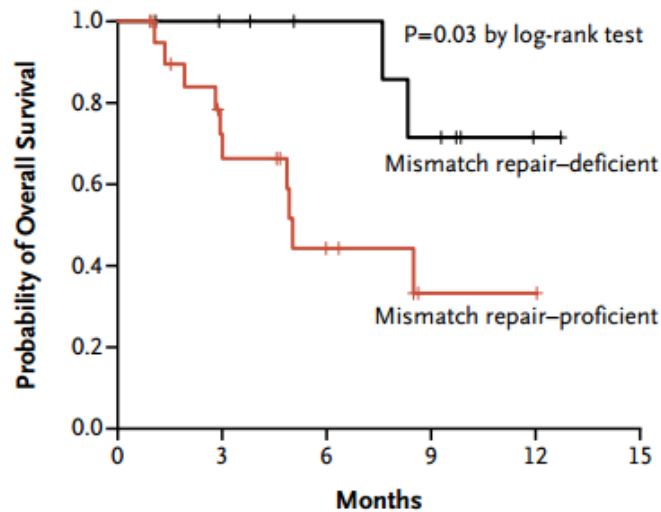
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

- 78% of MSI-H patients had disease control
- Superior OS (HR 0.22) and PFS (HR 0.10) in the MSI vs MSS patient

A Biochemical Response



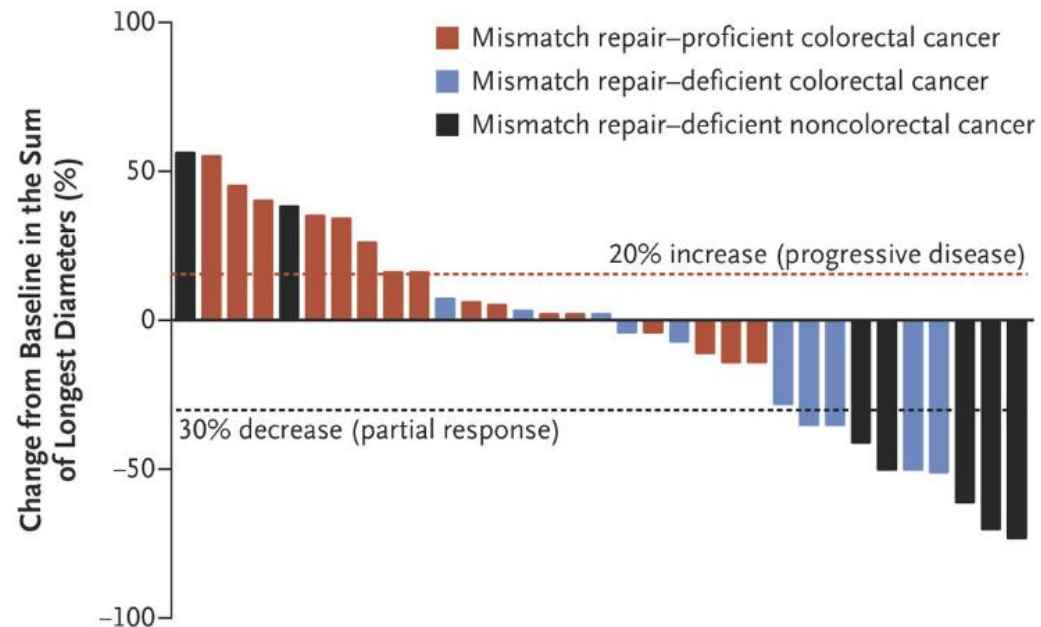
B Overall Survival in Cohorts with Colorectal Cancer



No. at Risk

Mismatch repair-deficient	11	9	7	5	1	0
Mismatch repair-proficient	21	12	5	1	1	0

B Radiographic Response

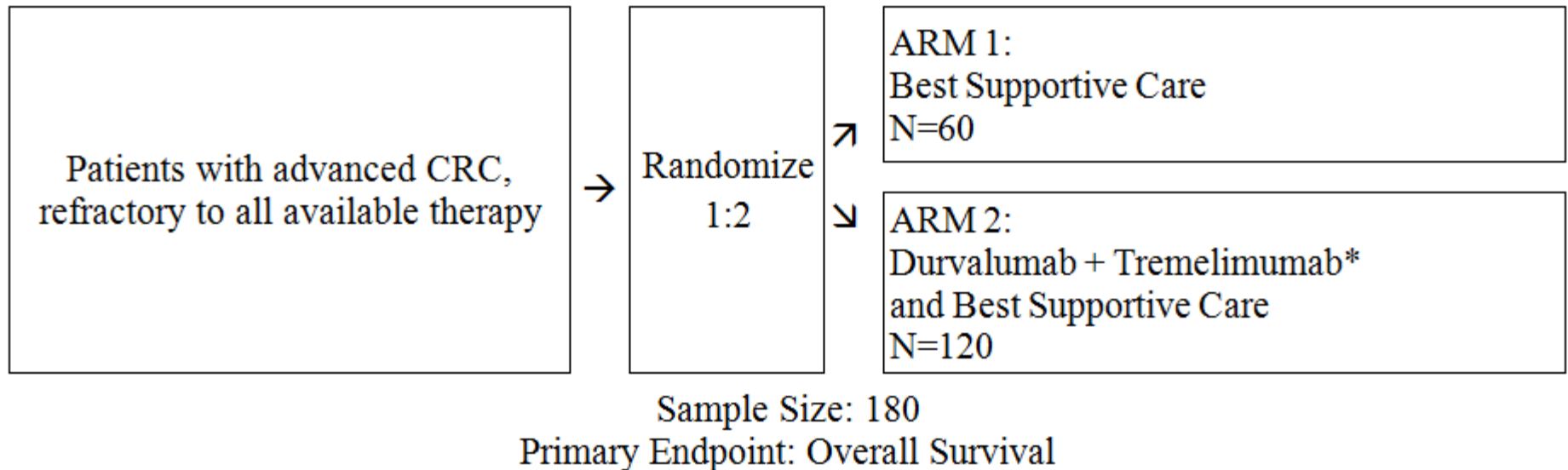


# Immune therapy for CRC: Beyond anti PD-1/PD-L1 in MSI-H?

- Promising results for efficacy of PD-1/PD-L1 inhibition in MSI-H CRC

*“August 1<sup>st</sup> the U.S. Food and Drug Administration (FDA) approved nivolumab for the treatment of adult and pediatric (12 years and older) patients with microsatellite instability–high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Approval for this indication has been granted under accelerated approval based on overall response rate and duration of response found in the CheckMate 142 trial.”*
- Subset of MSS have hypermutation, may be more amenable to immune therapy
- Dual PD-L1 / CTLA-4 inhibition may have additive or synergistic activity because the mechanisms of action of CTLA-4 and PD-1 are non-redundant.

# CO.26 Schema



\* *Tremelimumab and Durvalumab every 4 weeks for 4 cycles (1 cycle = 4 weeks (28 days)), followed by Durvalumab monotherapy to objective disease progression. See Section 7 for details.*

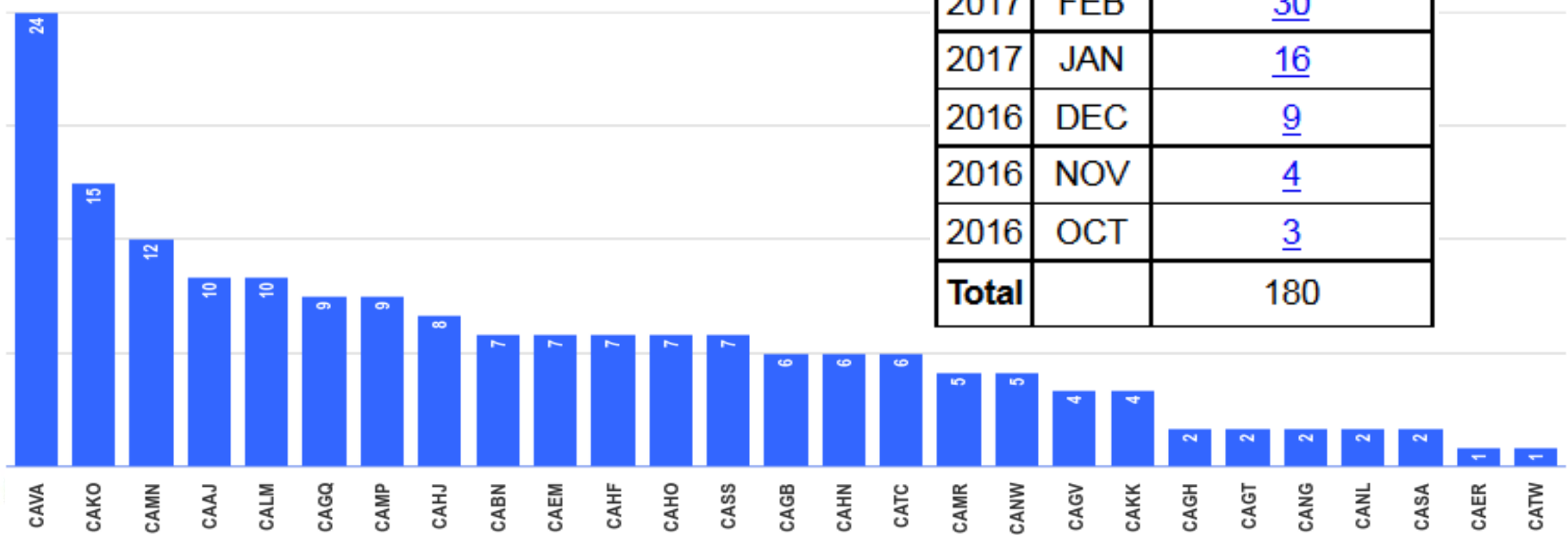
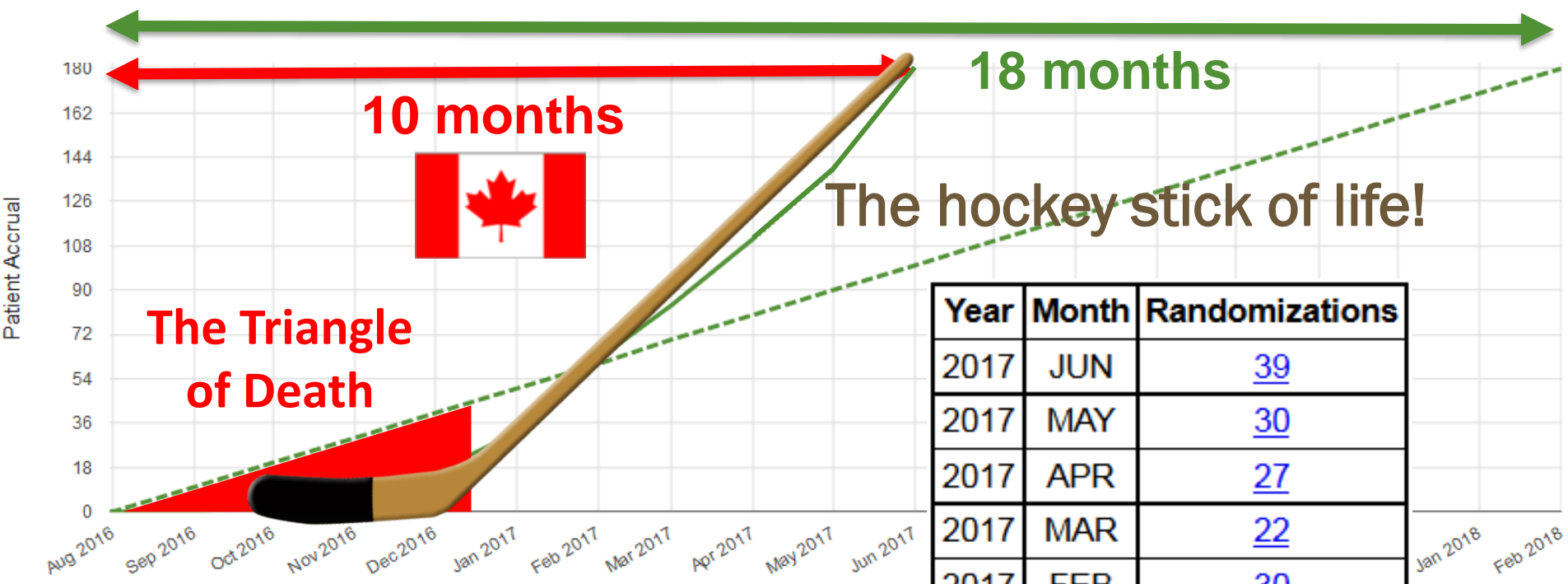
Stratified by:

- ECOG Performance Status: 0 vs 1
- Site of tumour

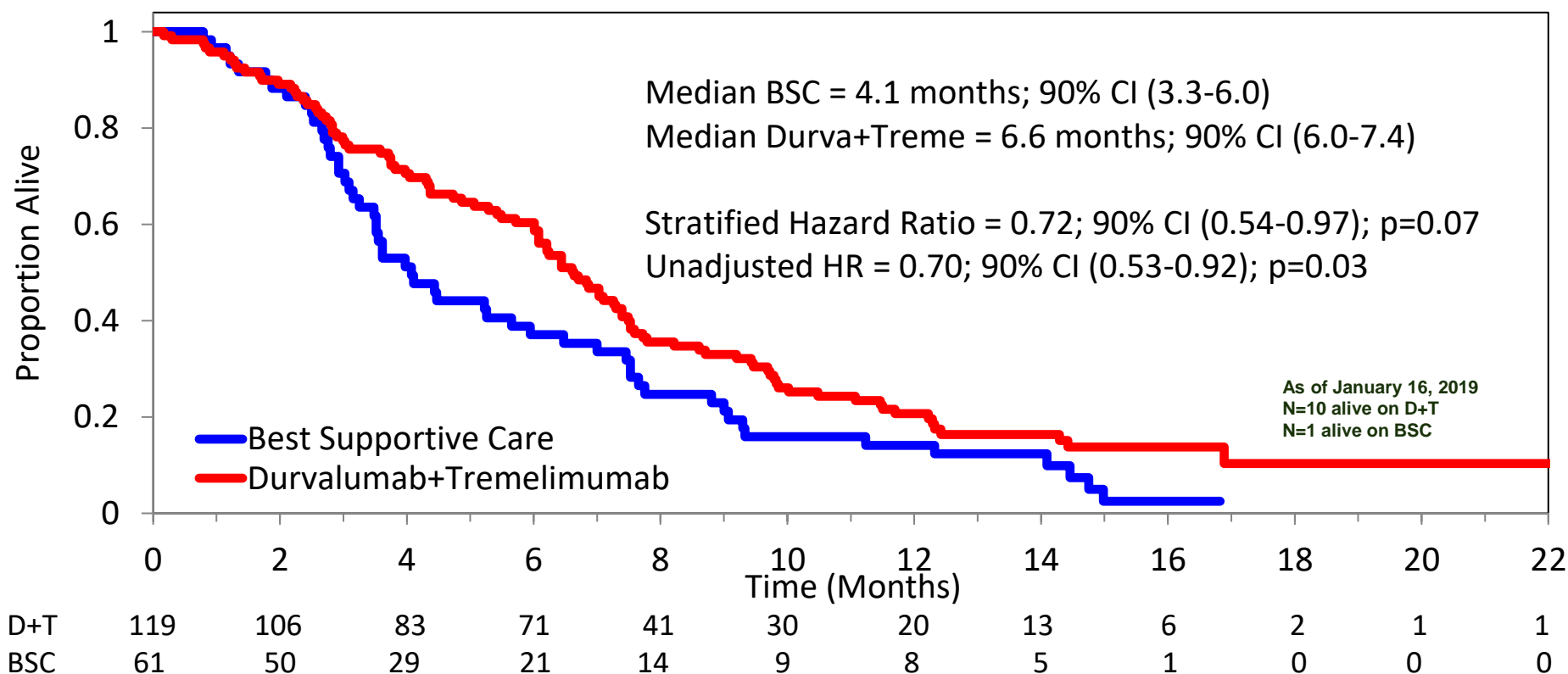
Primary Objective: Overall Survival

Secondary Objectives: Progression-free survival (PFS), Objective response rate (ORR), Toxicity and Safety

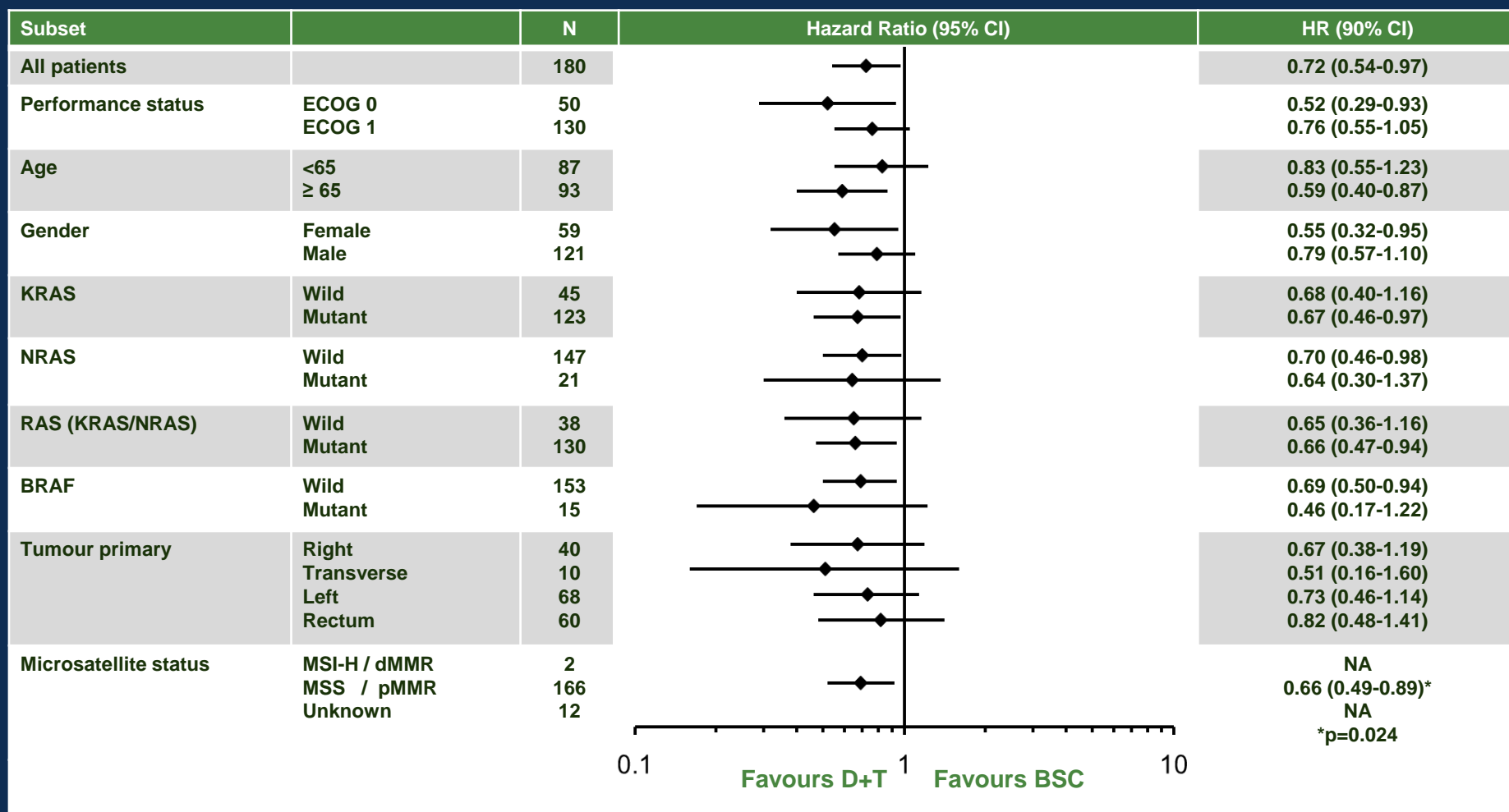
# CO.26 Accrual



# CO.26: Overall Survival



# CO.26: Overall Survival



# Conclusions:

- Results from this study suggest that the combination of Durvalumab and Tremelimumab prolongs overall survival of patients with refractory colorectal cancer, compared to best supportive care.
- Adverse events are consistent with prior experiences and quality of life is not adversely affected in patients treated with Durvalumab and Tremelimumab.
- This is the first study demonstrating immune checkpoint blockade effectiveness in colorectal cancer patients unselected for mismatch repair deficiency – phase III confirmation is warranted.
- Correlative studies are ongoing
  - Is intermediate tumor mutational burden a biomarker of benefit from immune checkpoint blockade in MSS advanced colorectal cancer?
  - Results will be submitted to ASCO Annual Meeting

# CO.26: Molecular Characteristics:

## cfDNA analysis

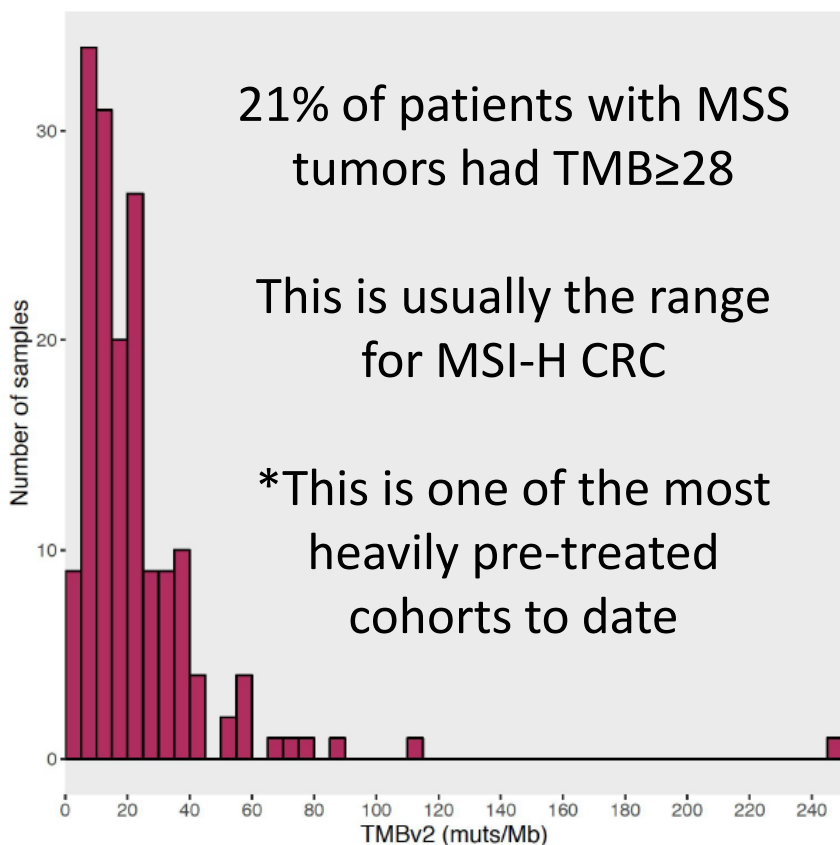
- 169/180 patients with baseline blood samples available
- 168/169 (99%) patients had successful cfDNA assessment based on baseline blood
- Sequenced with GuardantOMNI™ Panel<sup>1-2</sup>
  - 500 gene, 2.1 MB panel with 93.7% sensitivity and 99.2% specificity for detecting MSI<sup>1-2</sup>
  - cfDNA results used for subgroup analysis

Tissue correlatives ongoing

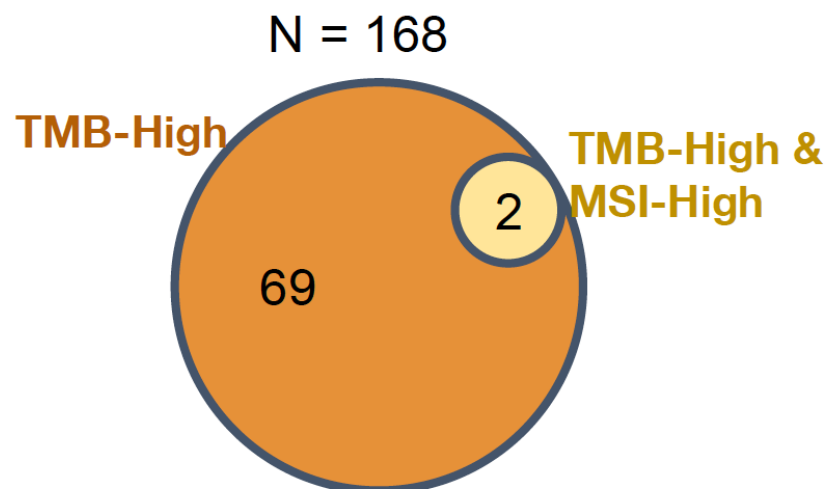
<sup>1</sup> Artyomenko *et al* ESMO 2018

<sup>2</sup> Quinn *et al* ESMO

# CO.26: Tumour Mutation Burden (TMB):



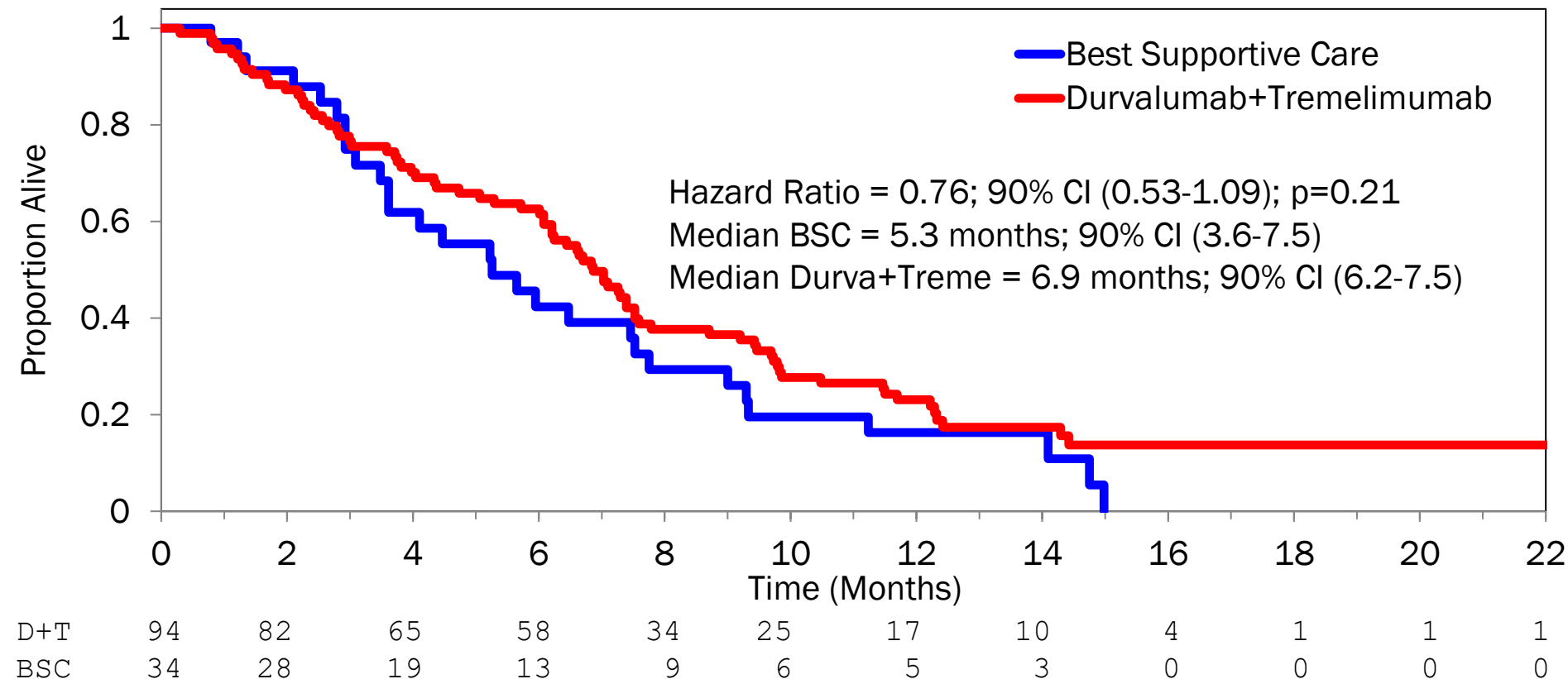
MSI-High samples are also TMB-High:



- Excluding 2 patients with MSI-H
- TMB in MSS patients:
  - Mean:  $20.4 \pm 16.3$  mts/Mb
  - Range: 0.96 – 114.0

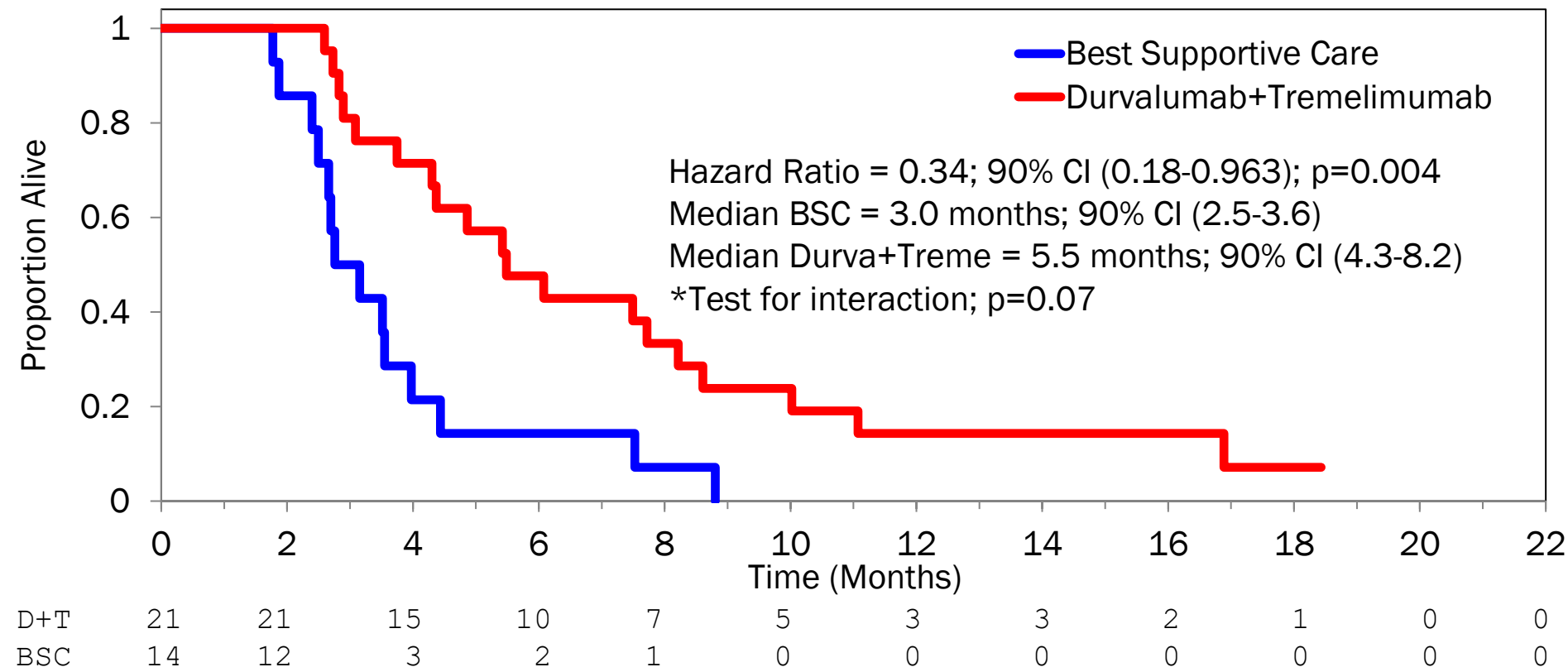
# TMB predictive for OS:

TMB<28



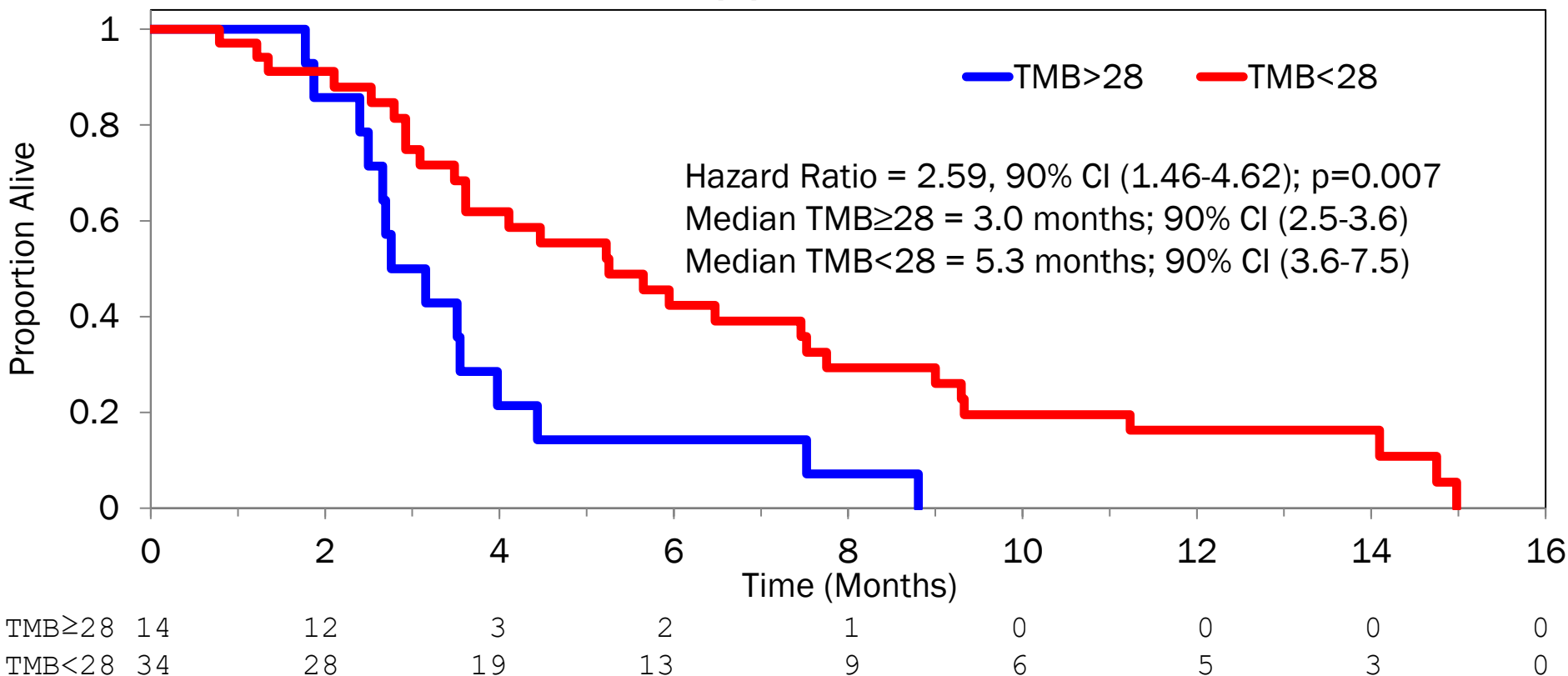
# TMB predictive for OS:

**TMB $\geq$ 28**

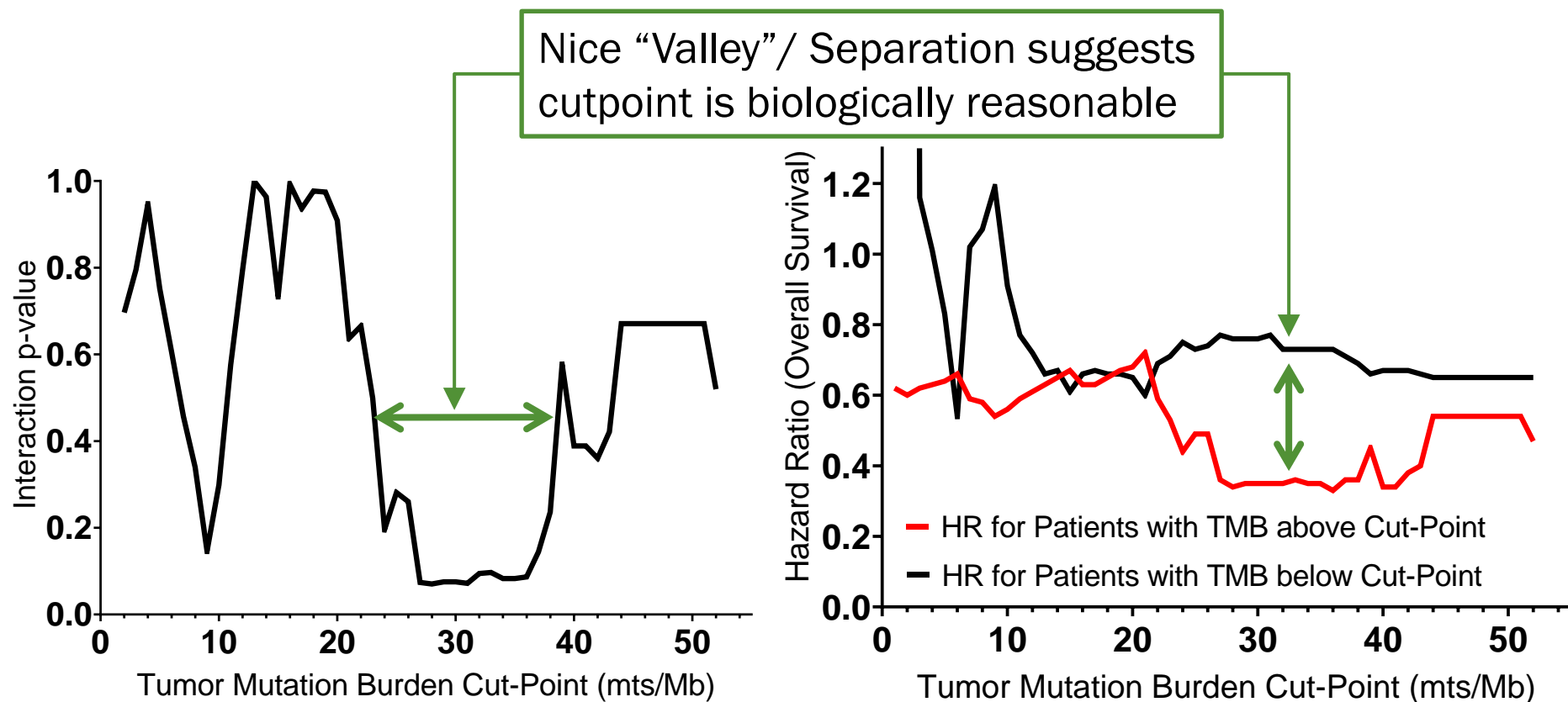


# TMB prognostic for OS:

## Best Supportive Care



# Minimum p-value method:



# Conclusions:

- Results from this study suggest that the combination of Durvalumab and Tremelimumab prolongs overall survival of patients with refractory colorectal cancer, compared to best supportive care.
- Tumour Mutation Burden (TMB) appeared prognostic in the BSC arm.
- High TMB selects a group of MSS patients who benefit from Durvalumab and Tremelimumab.
- This is the first study demonstrating immune checkpoint blockade effectiveness in colorectal cancer patients unselected for mismatch repair deficiency – phase III confirmation is warranted.
- D+T improves OS vs sorafenib [HR=0.78] in advanced HCC (without PFS benefit and only modest ORR benefit) in phase III HIMALAYA trial.

# Was CO.26 likely to be 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?”*

± 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 (doublet immunotherapy)

✓ Simple is more attractive – i.e. complexity as scientifically necessary

✓ Limited therapeutic options – e.g. end stage settings

XXX Good risk/benefit ratio (real or perceived) (BSC arm)

✓ Unique - Not already planned, in progress... or complete!

✓ Well funded/resourced (\$8,000)

# Is CO.26 a Success?

- Study dramatically exceeded accrual expectations with sample size reached in ~16 weeks - **50% faster than expected!**
- Doublet durvalumab and tremelimumab therapy met primary endpoint of improved overall survival in advanced, refractory CRC patients
- Toxicity consistent with known adverse events
- Pre-planned correlative studies confirmed benefit in MSS patients
- Exploratory analysis identified predictive marker for biologically consistent target subgroup
- Multiple publications in high-impact journals, including similar results in other tumours (HCC)



# FAIL

Just when you thought you had it all figured out.

# Thank You

