Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

Plenary Session 2:

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

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 permitted 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?

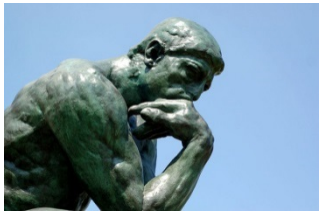
- A poorly designed or executed trial that, even if ‘completed’, fails to answer the question
  - biased, uninterpretable, inconclusive, underpowered, flawed, fraudulent

- 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

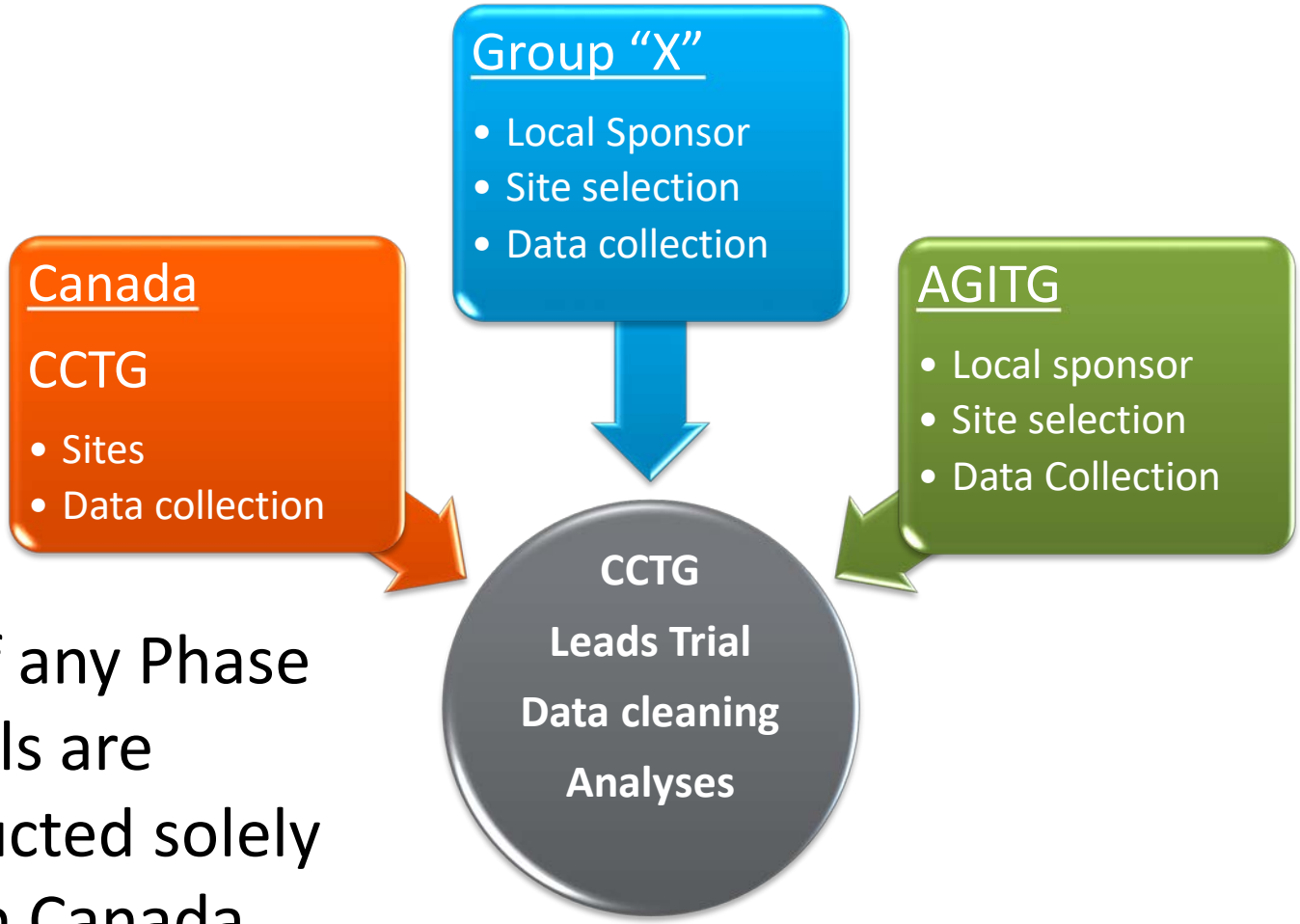
Patient preference
Investigator preference
"Red Tape"/Costs
Intangibles

Eligiblity Criterion*

Design, Data & Analysis: The CCTG Mantra

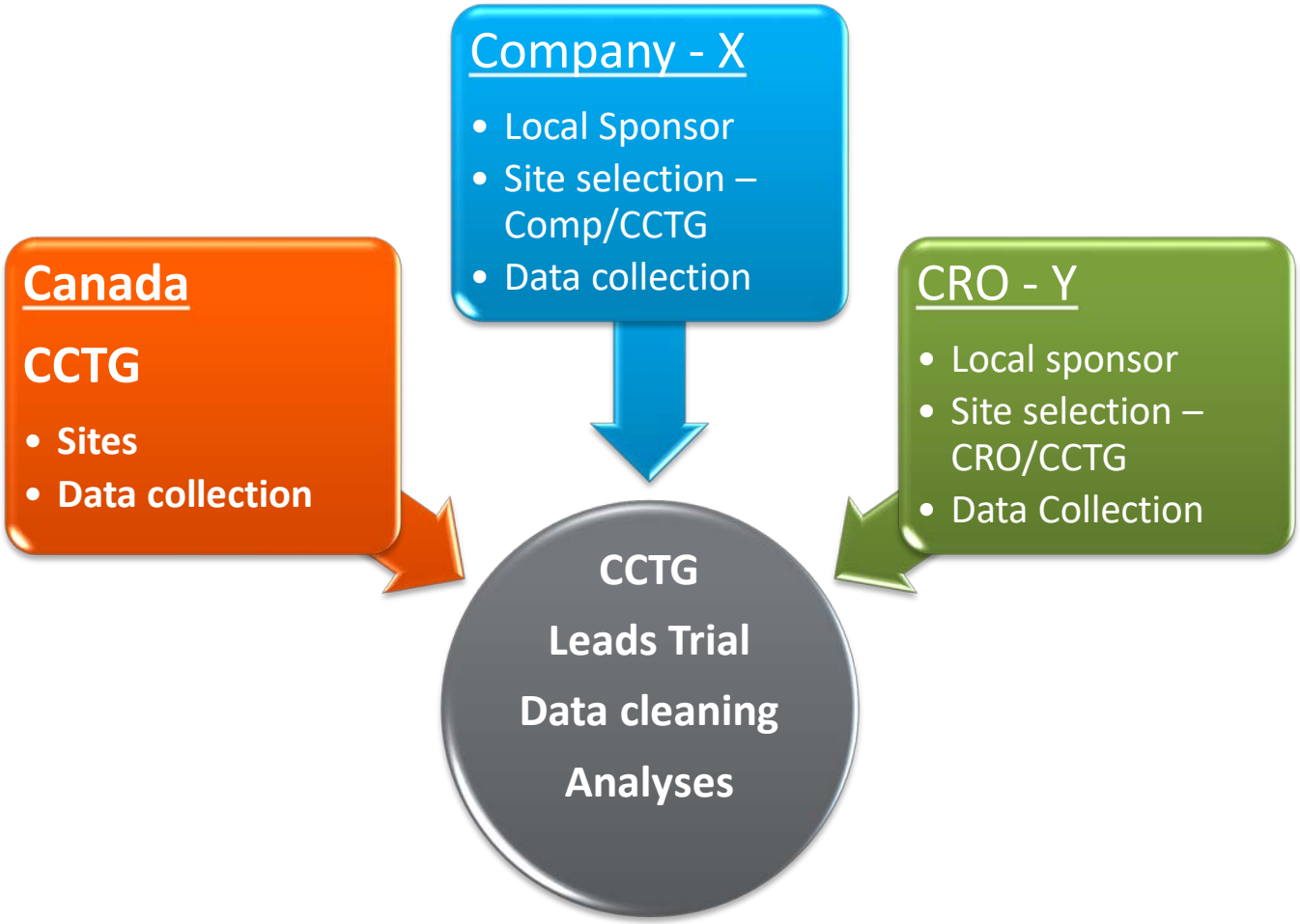
- Hypothesis robust and well supported
- Valid design
  - Statistical components of design critical
- Consensus (collaborators, pharma) needed
  - Comparators / standard of care, placebo control
  - "Access" to IMP
    - regulatory status, funding status, availability of placebo, distribution, storage, 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

Creating Collaborators: The 'Intergroup' Trial Model



Few if any Phase III trials are conducted solely within Canada

Creating Accrual: The 'International' Trial Model



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

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

Is this patient eligible?

Again, it sounds simple = Be sure patients…

1) Meet the eligibility criteria
2) 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, 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")

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

ASIDE: Funding and Resource

1. Fund yourself ('local' funding)
   - not feasible for phase III
2. Apply for a peer-reviewed grant
   - e.g. 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…

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BR.31

A Trial of the Lung Immunotherapy Non Small Cell Lung Cancer Consortium

IFCT

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

NEDERLANDSE VERENIGING VAN ARTSEN VOOR LONGZIEKTEN EN TUBERCULOSE

NHMRC Clinical Trials Centre

CEEOG Central and East European Oncology Group

GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

WJOG

LINC

NSCLC CONSORTIUM

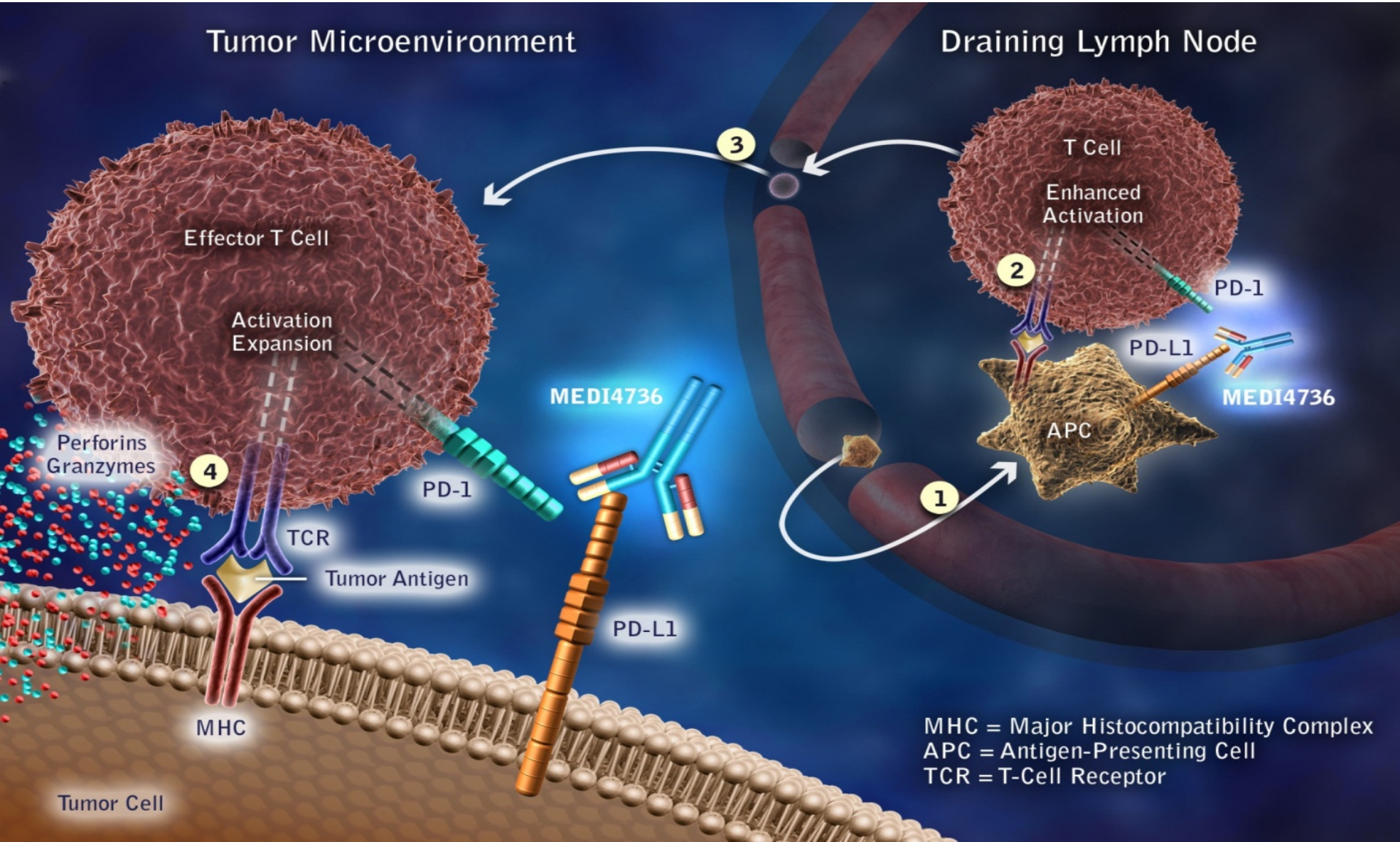
LUNG IMMUNOTHERAPY

ALTG Australasian Lung Cancer Trials Group

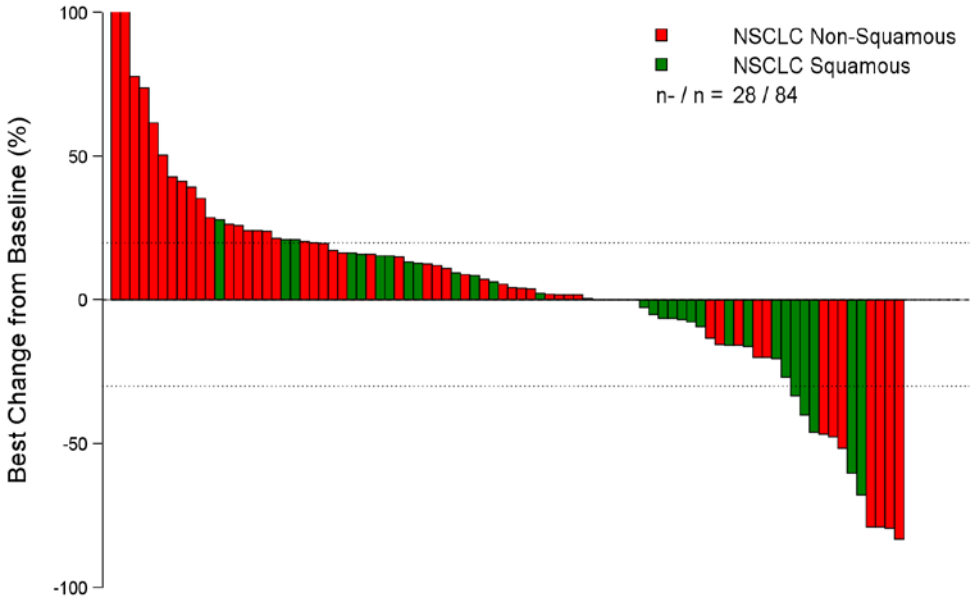
대한임상암연구회 Since 1998 KCSG

Chinese Thoracic Oncology Group(CTONG)

Durvalumab is a Human IgG1κ Triple Mutant mAb Directed Against PD-L1



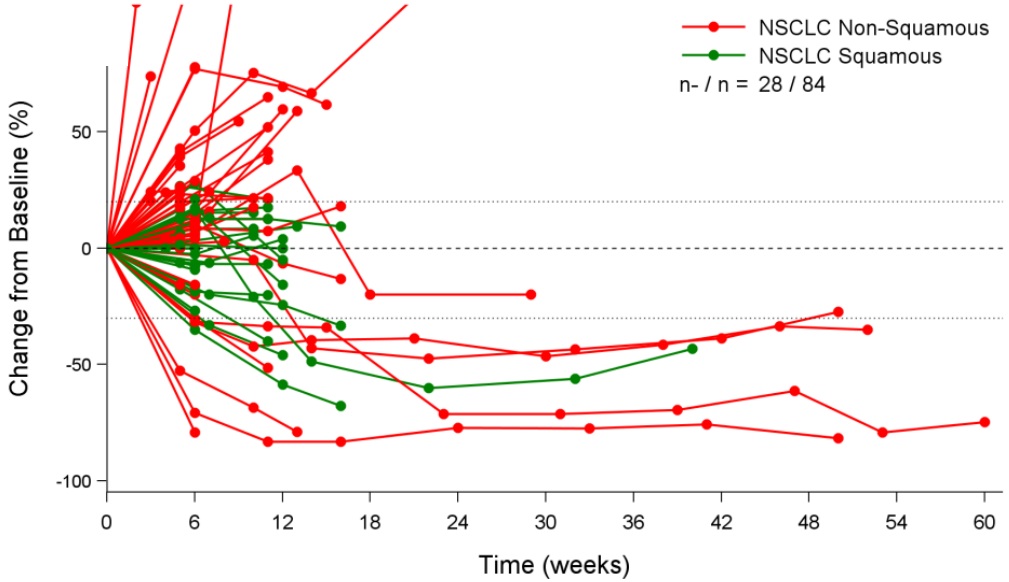
Durvalumab - Early and Durable Activity Observed in Squamous and Non-Squamous NSCLC



All patients with ≥1 follow-up scan (n=84)

Durvalumab monotherapy was well tolerated

Majority of patients had limited follow-up and had not reached Week 12 tumor assessment



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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**

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

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

Primary Endpoint = DFS (PDL1+)

Secondary Endpoints = DFS (all), OS, QoL

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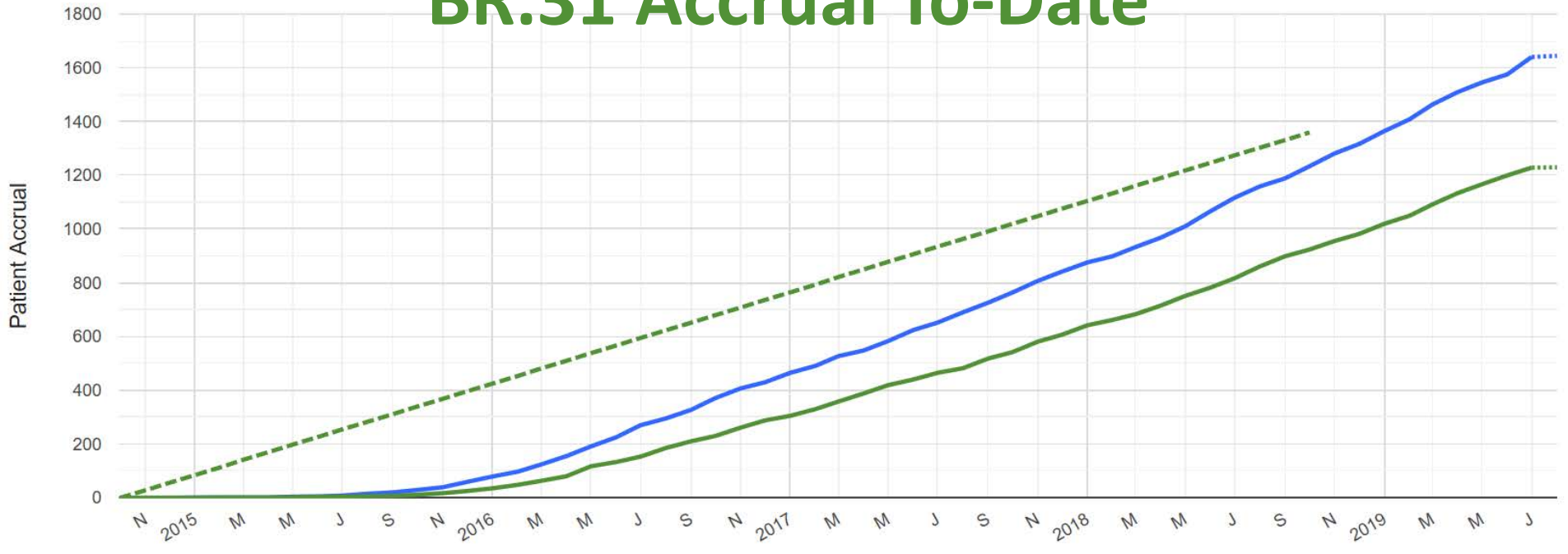
Interesting?

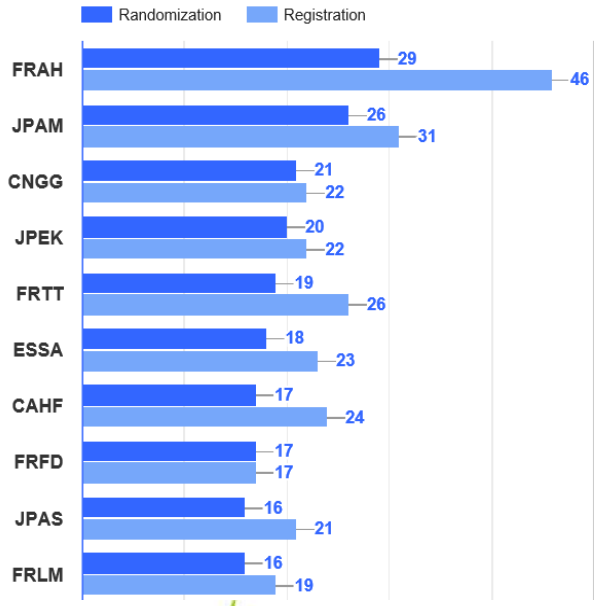
- ✓ Relevant question that will change practice, NOT superseded by changing practice (equipoise)
- ✓✓ Promising data from earlier stage trials, other disease sites
- ✓✓ New, particularly ‘novel’, drugs or treatments always of interest
- ✗ Simple is more attractive – i.e. complexity as scientifically 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 (CDN$15,250 PCF)

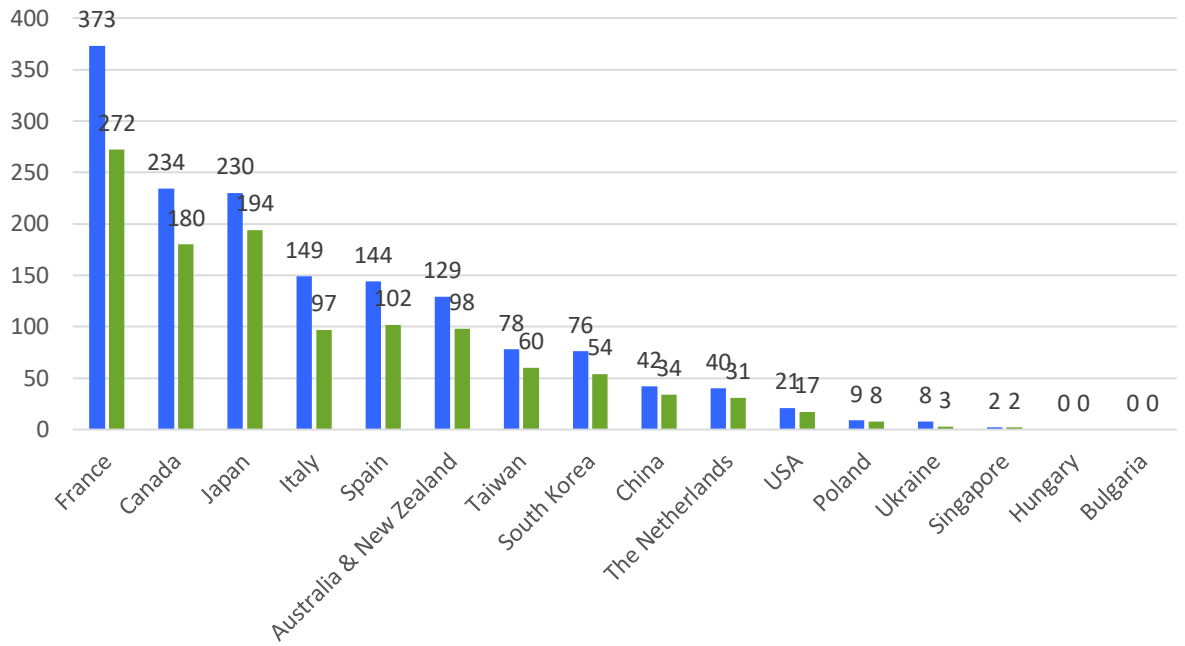
How's it going so far?

- CTA submitted to Health Canada = September 4, 2014
- Centrally activated = October 9, 2014 **(35 days)**
- First site locally activated = November 25, 2014 **(82 days)**
- First patient registered = January 29, 2015 **(147 days)**
- First patient randomized = February 24, 2015 **(173 days)**
- To-date… **(1,798 days from CTA submission)**
- 19 countries: 264 of 277 sites are locally activated
- 1645 patients registered (68 in past 30 days, 134 in past 90 days)
- 1230 patients randomized (**75% of expected;** 29 in past 30 days, 92 in past 90 days)

BR.31 Accrual To-Date







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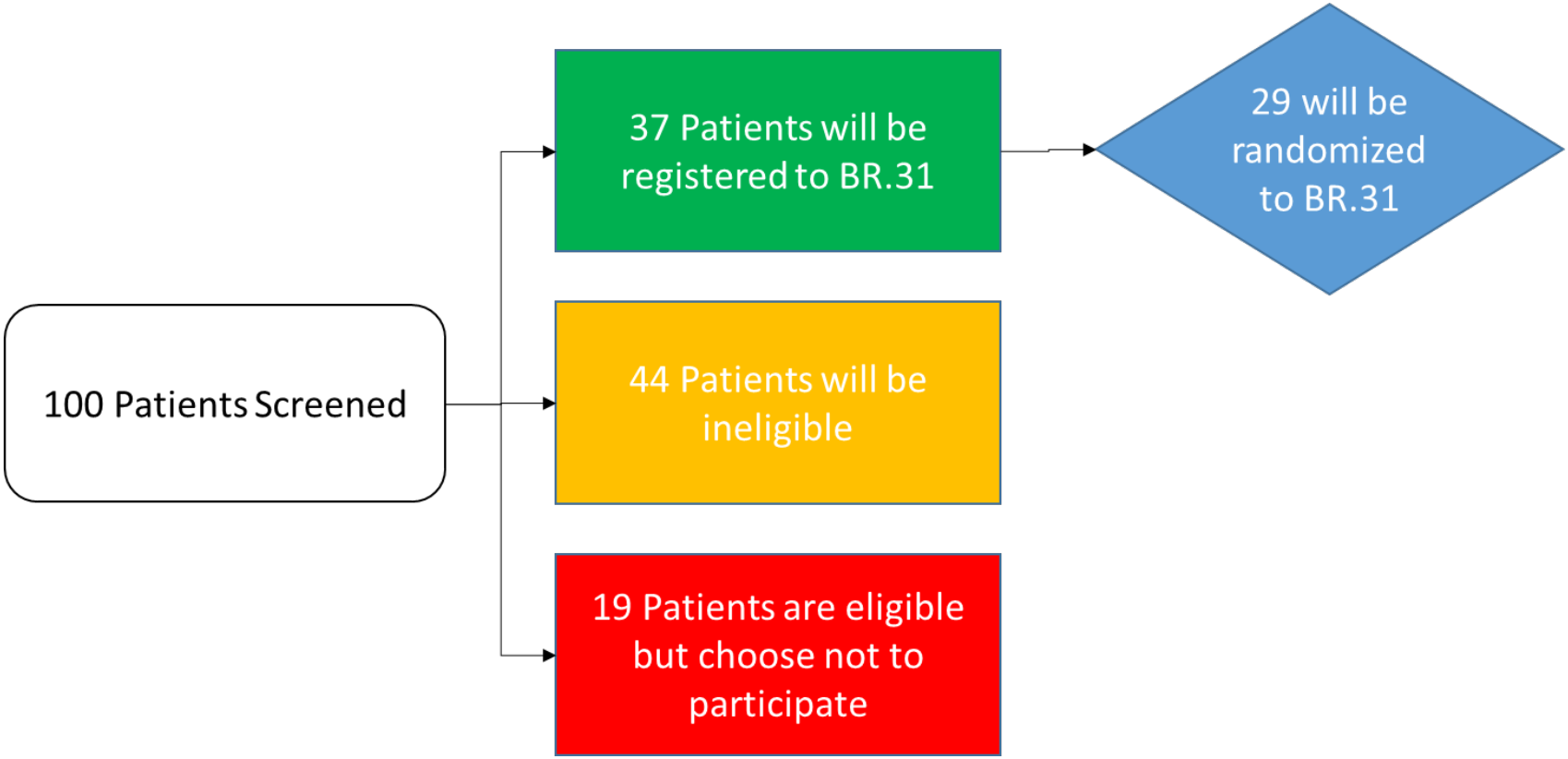
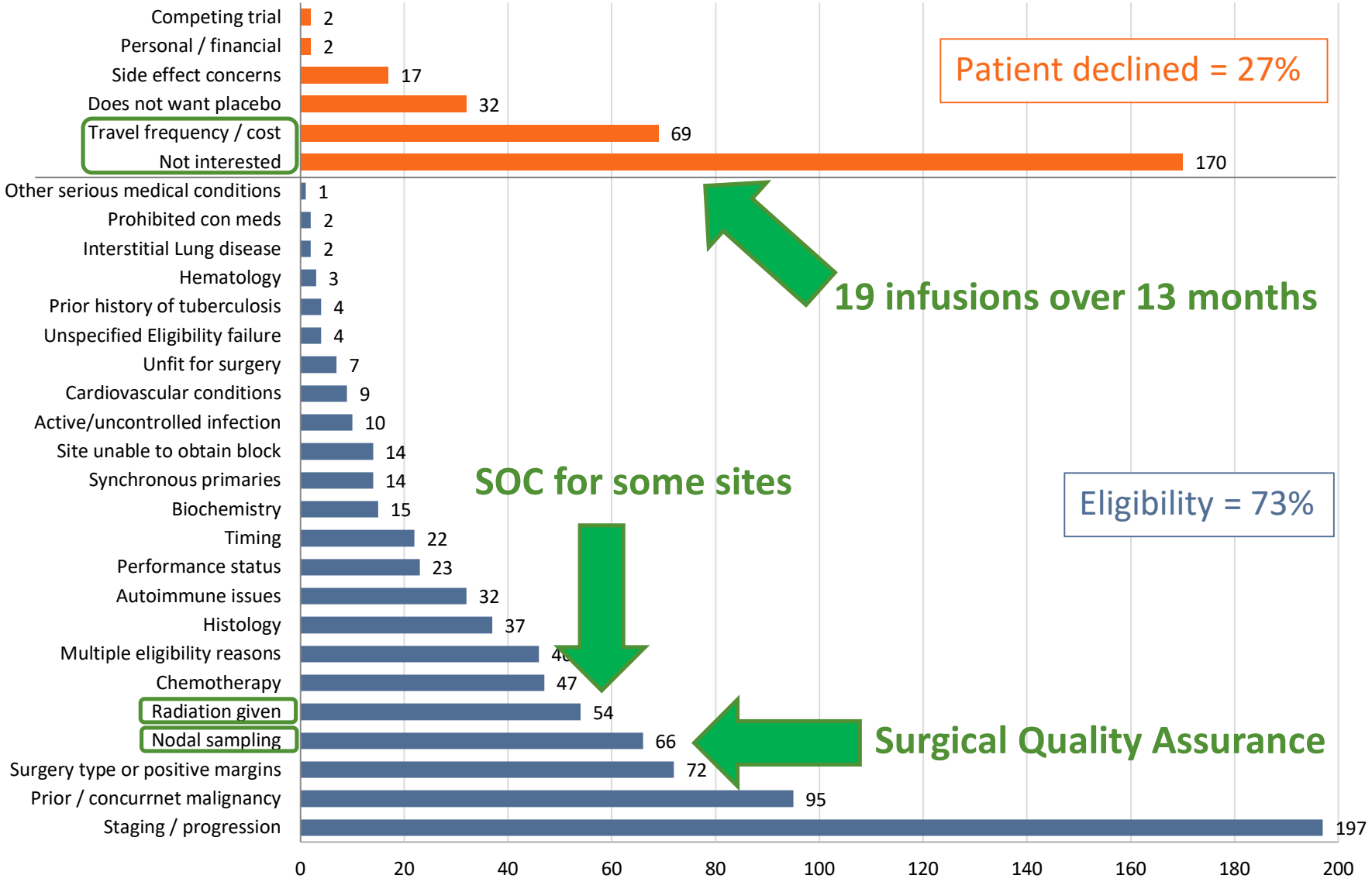
Web-based Screen Failure Log



29% successful enrollment

~ 30 patients/month

Reasons patients have not been registered



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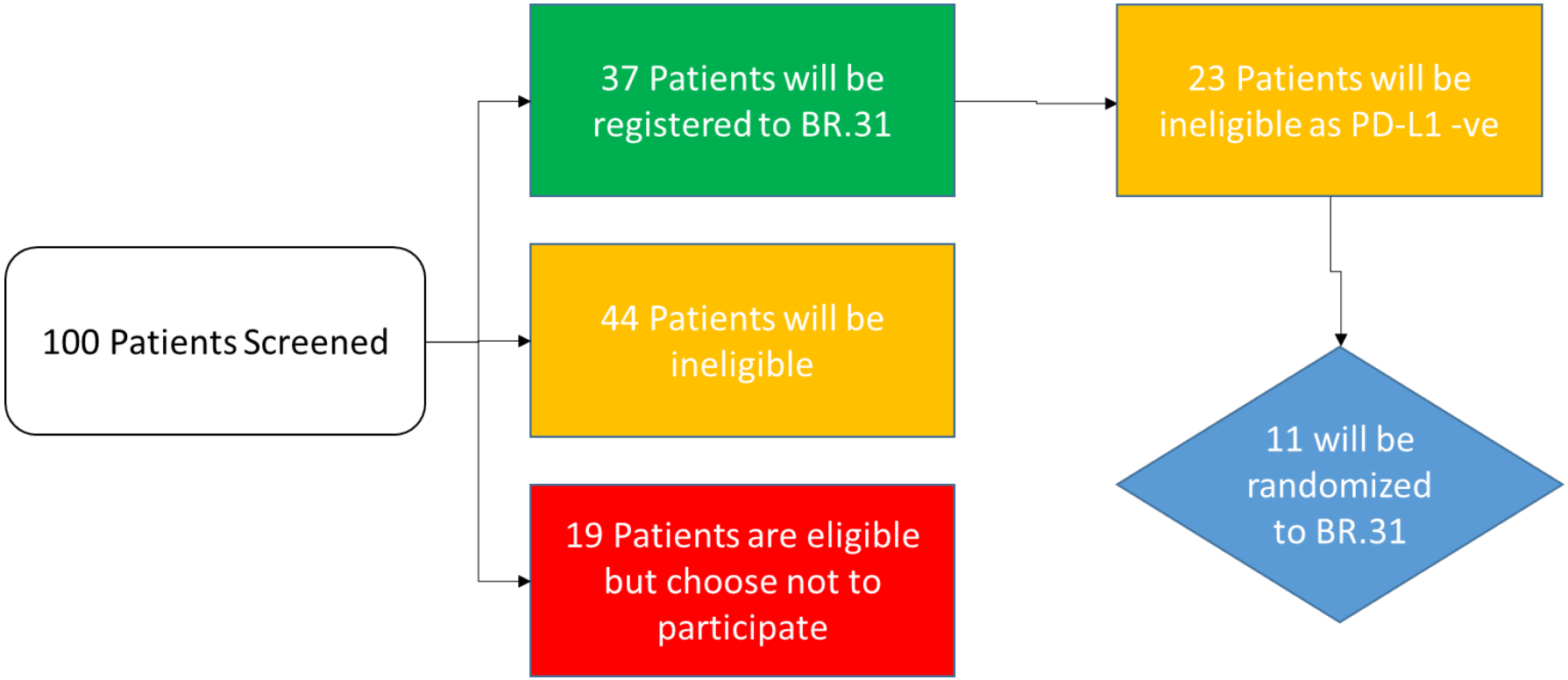
web-based screen failure log

After Switch to PD-L1 positive patients



11% successful enrollment

~ 10 patients/month

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

- The PACIFIC trial was a randomized double-blind placebo controlled trial of durvalumab as sequential treatment in patients with locally advanced unresectable (Stage III) NSCLC who had not progressed on platinum-based chemotherapy concurrent with radiation therapy,

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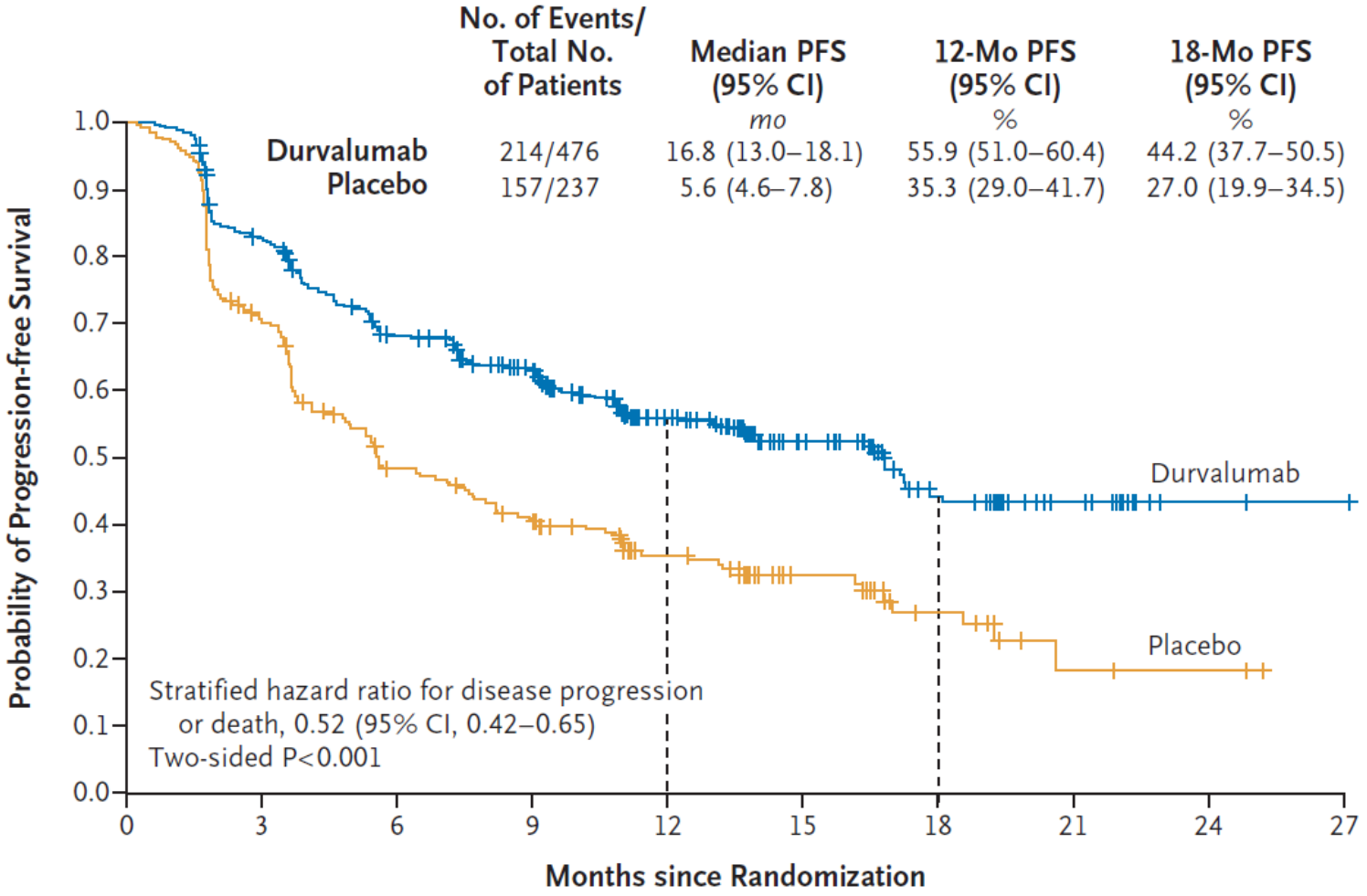
Impact of PACIFIC results on BR.31

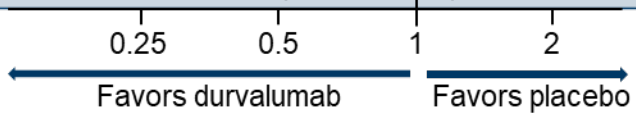
- A planned interim analysis of PFS at 80% data maturity (371 vs 458 events) met criteria for declaring superiority:



Impact of PACIFIC results on BR.31

- The PACIFIC trial demonstrated high efficacy of durvalumab monotherapy in patients with PD-L1 positive tumours:
  - PD-L1 positives (n=115): HR = 0.41 [0.26-0.65]
- …but perhaps most interestingly, subgroup analysis by PD-L1 status showed benefits in all comers:
  - PD-L1 negatives (n=187): HR = 0.59 [0.43-0.82]
  - PD-L1 unknown (n=174): HR = 0.59 [0.42-0.83]

		Durvalumab	Placebo	Unstratified HR* (95% CI)
		No. of patients		
	All patients	476	237	0.55 (0.45–0.68)
Sex	Male	334	166	0.56 (0.44–0.71)
	Female	142	71	0.54 (0.37–0.79)
Age at randomization	<65 years	261	130	0.43 (0.32–0.57)
	≥65 years	215	107	0.74 (0.54–1.01)
Smoking status	Smoker	433	216	0.59 (0.47–0.73)
	Non-smoker	43	21	0.29 (0.15–0.57)
Disease stage	Stage IIIA	252	125	0.53 (0.40–0.71)
	Stage IIIB	212	107	0.59 (0.44–0.80)
Histology	Squamous	224	102	0.68 (0.50–0.92)
	Non-squamous	252	135	0.45 (0.33–0.59)
Best response to cCRT	CR	9	7	–
	PR	232	111	0.55 (0.41–0.75)
	SD	222	114	0.55 (0.41–0.74)
PD-L1 status	≥25%	115	44	0.41 (0.26–0.65)
	<25%	187	105	0.59 (0.43–0.82)
	Unknown	174	88	0.59 (0.42–0.83)
EGFR status	Mutant	29	14	0.76 (0.35–1.64)
	Wild-type	315	165	0.47 (0.36–0.60)
	Unknown	132	58	0.79 (0.52–1.20)



*Hazard ratio and 95% CI not calculated if the subgroup has less than 20 events.

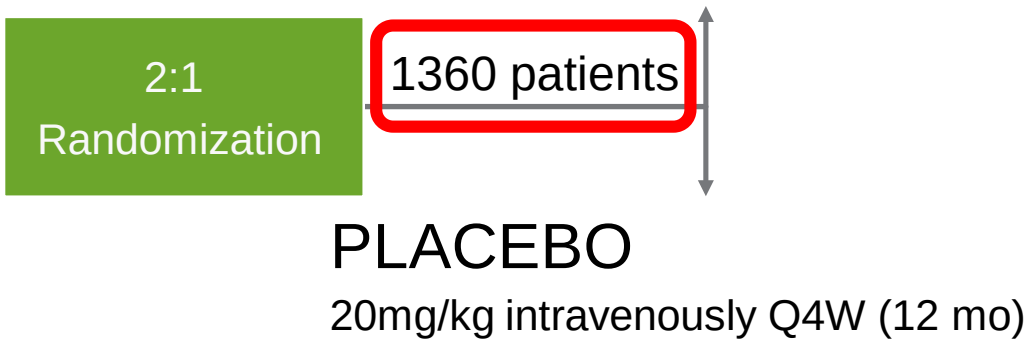
BICR, blinded independent central review; CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intention-to-treat; EGFR, epidermal growth factor receptor

Impact of PACIFIC results on BR.31

- Indicates that durvalumab has activity in NSCLC that is not limited to patients with PD-L1 positive tumours.
- No safety signal of durvalumab monotherapy in NSCLC patients that have received prior radiation.
- Prompted consideration that BR.31 could/should be amended to slightly more optimistic efficacy target w.r.t. PD-L1 positives + include additional PD-L1 negatives to permit more accurate efficacy determination in this subgroup + to ensure “all-comers” study population is more representative of actual distribution of PD-L1 expression in incident population – Dual Primary Outcomes

BR.31 Schema

- Stage IB (≥ 4cm) ,II,IIIA NSCLC
- Completely resected
- ECOG PS 0-1
- Stratified by:
  - i. Stage,
  - ii. Pre-tx PD-L1 (high/int/low/neg),
  - iii. prior adj chemo,
  - iv. centre,
  - v. ESTS nodal dissection (y/n)



- Primary Objective:
  - a) DFS in PD-L1 positive patients,
  - b) DFS in all patients
- Secondary Objectives: OS in PD-L1 positive patients, OS in all patients, Toxicity, Prognostic Significance of PD-L1 expression, Exploratory correlative biomarker analyses

Will BR.31 be a "Success" ?

YES! ⟹ **WHY?**

- Although target sample size of 1360:
  - 264 sites activate in 19 countries
  - Added Japan(28), China(17+11), Brazil(8+2), Romania(6), Ukraine(3), Bulgaria(3)

- Amendments to promote accrual:

  Amended to remove PD-L1 enrichment phase → **accrual**

  Amended eligibility criteria w.r.t. lymph node sampling ↑ **accrual**

  Amended infusion frequency to monthly throughout ↑ **accrual**

  Amend to permit prior radiation treatment ↑ **accrual**

- 1230/1360 accrued

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

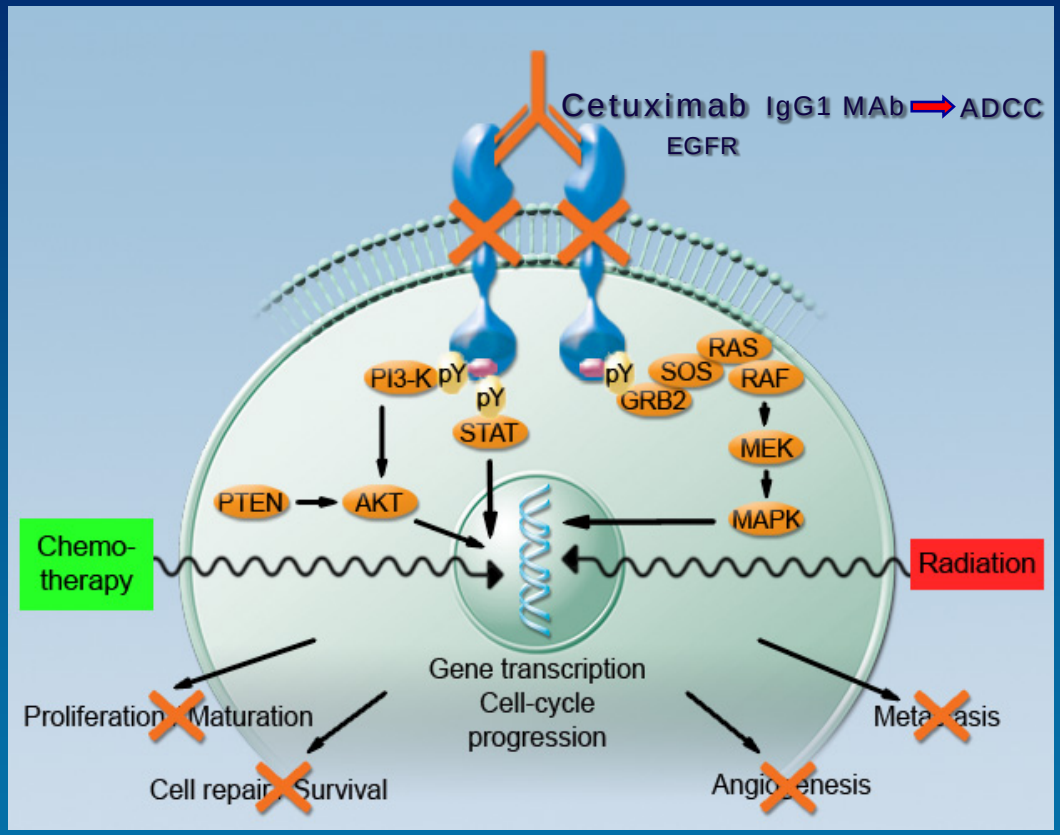
Australasian Gastro-Intestinal Trials Group (AGITG)

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

AUSTRALASIAN GASTRO-INTESTINAL AGITG TRIALS GROUP

Cetuximab: Multiple Mechanisms of Action

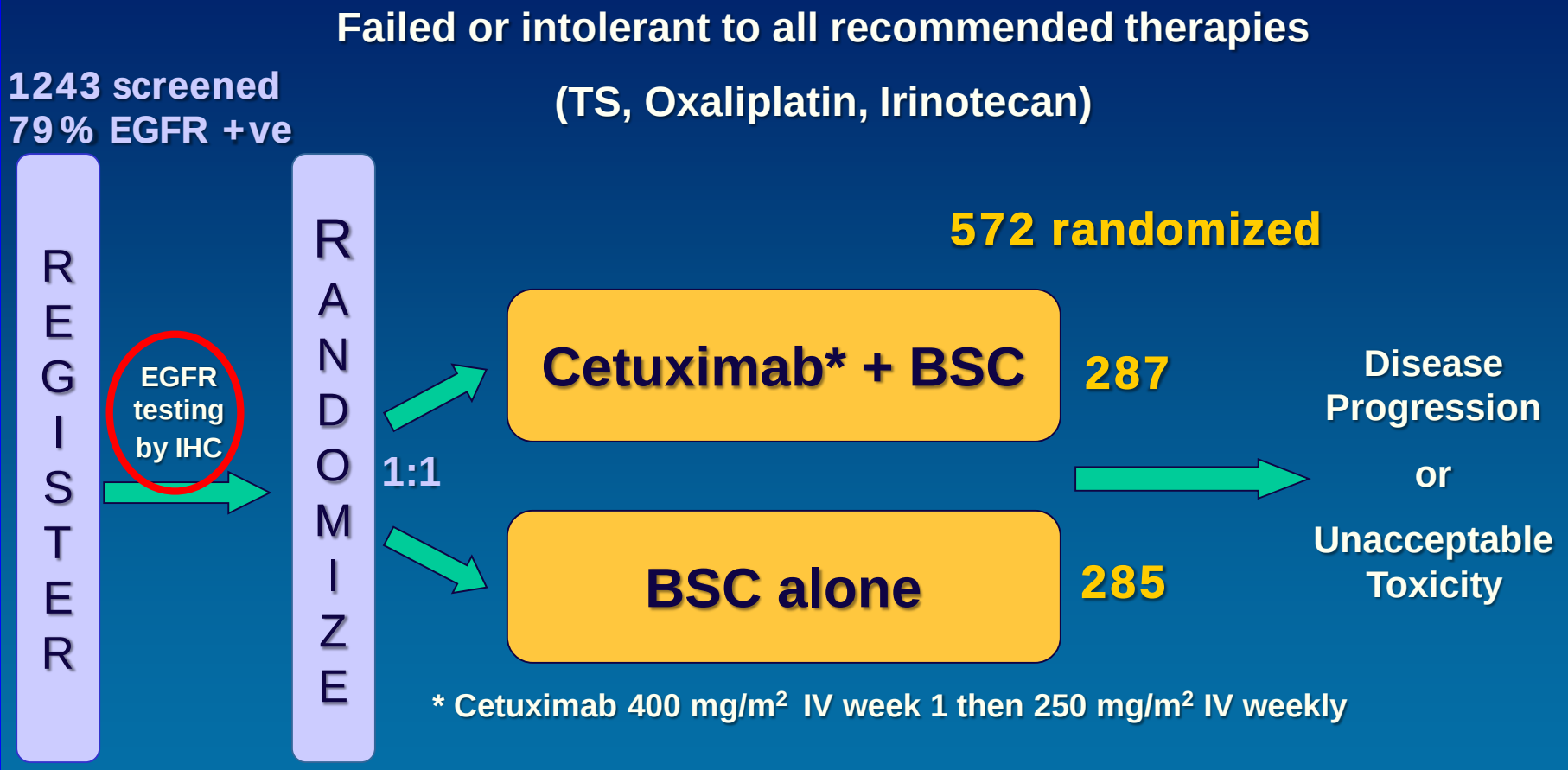
- IgG1 monoclonal antibody
- Binds to EGFR and competitively inhibits ligand binding (e.g. EGF)
- Blocks receptor dimerization, tyrosine kinase phosphorylation, and signal transduction
- IgG1-induced Antibody-Dependent Cell Cytotoxicity (ADCC)



Cetuximab: Phase II Clinical Data

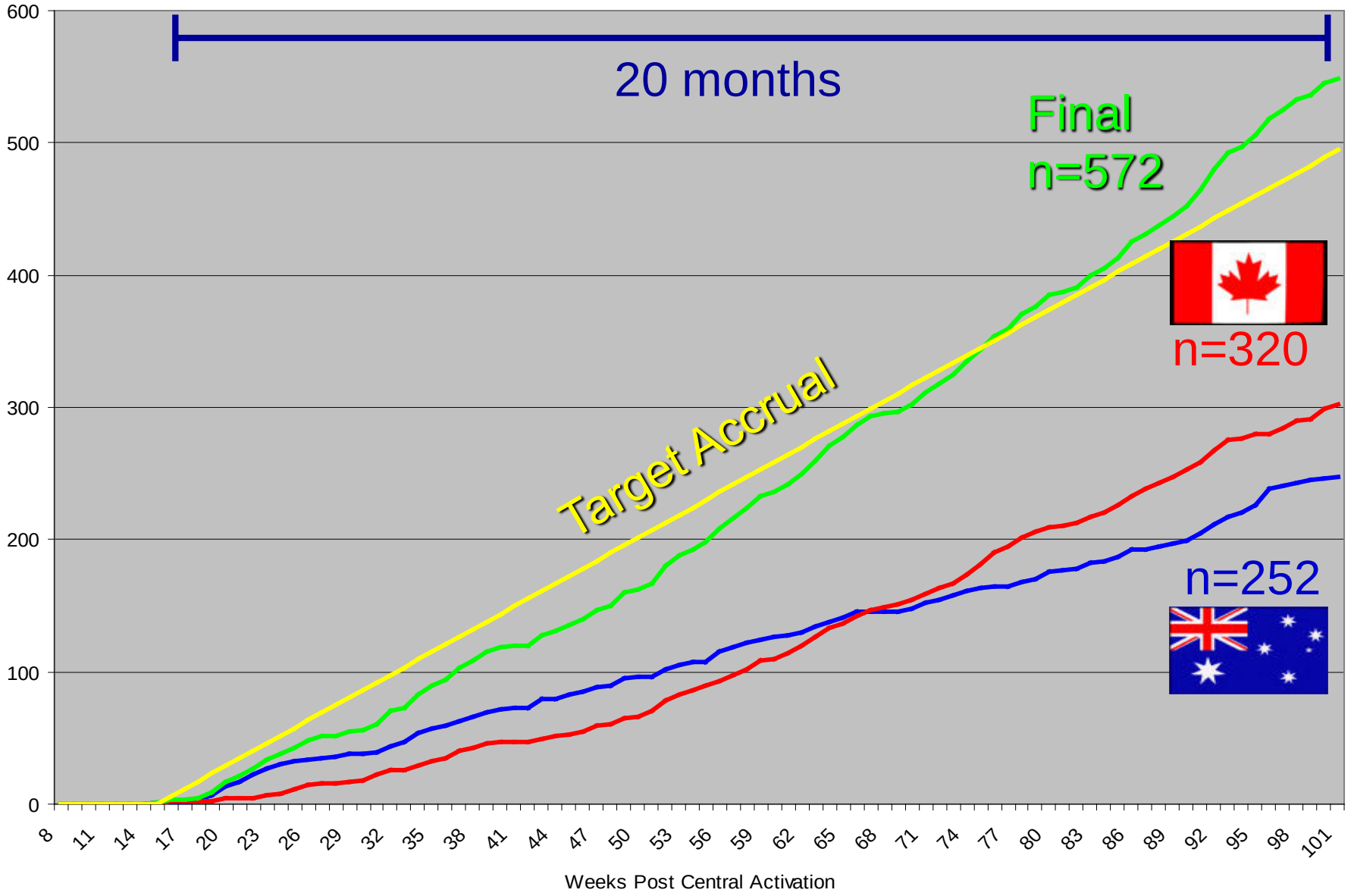
Study	Treatment	N	Efficacy	
			ORR	TTP
Irinotecan Failure				
Saltz L. *J Clin Oncol* 2004 (IMC 0141)	Cetuximab	57	8.8%	1.4 mo
Cunningham D. *N Eng J Med* 2004 (EMR 007 / BOND)	Cetuximab	111	10.8%	1.5 mo
	Cetuximab + Irinotecan	218	22.9%	4.1 mo
Irinotecan, Oxaliplatin, Fluoropyrimidine Failure				
Lenz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

CO.17: Randomized Phase III Trial in mCRC



- **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)

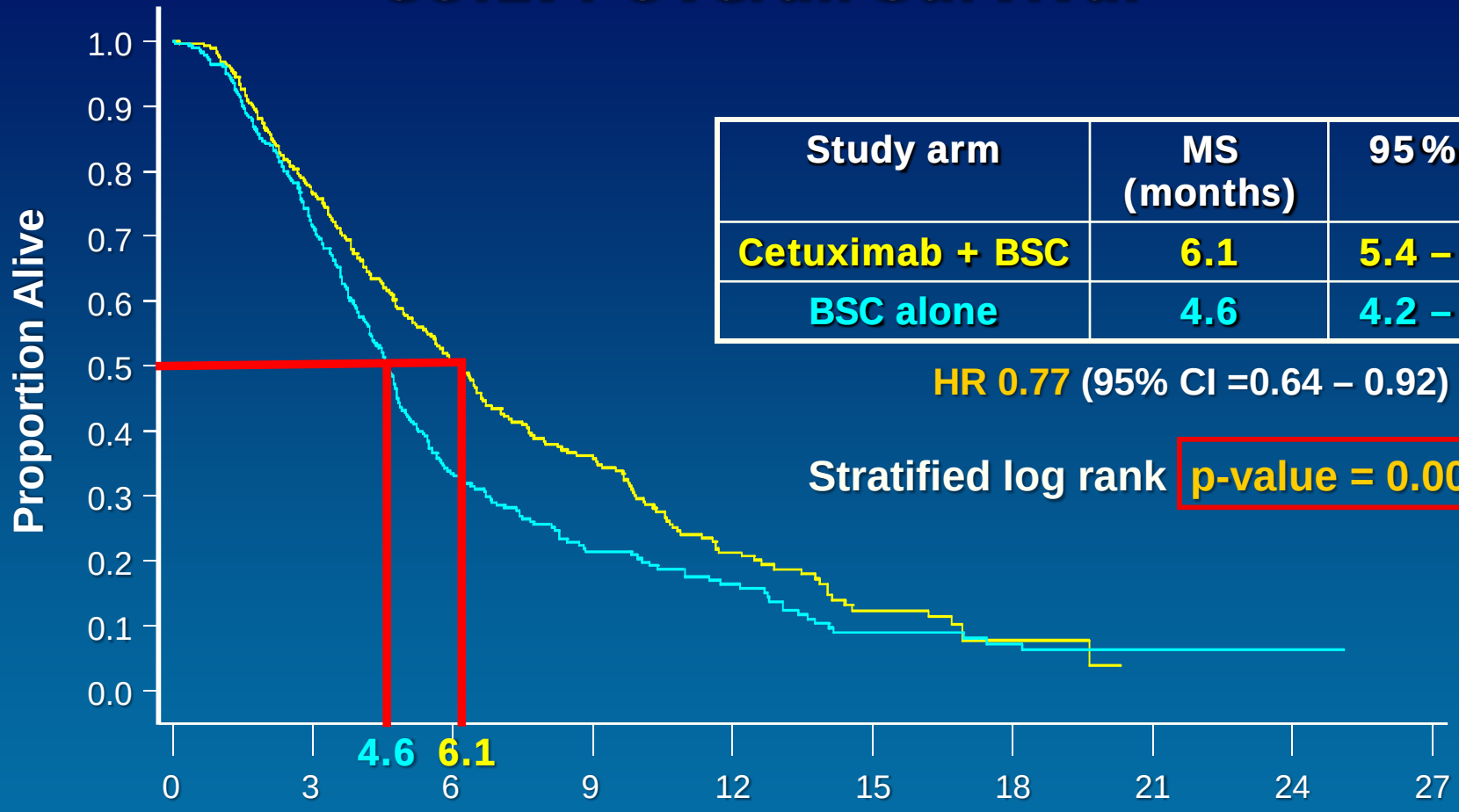
CO.17: Accrual



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



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

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/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

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
- 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

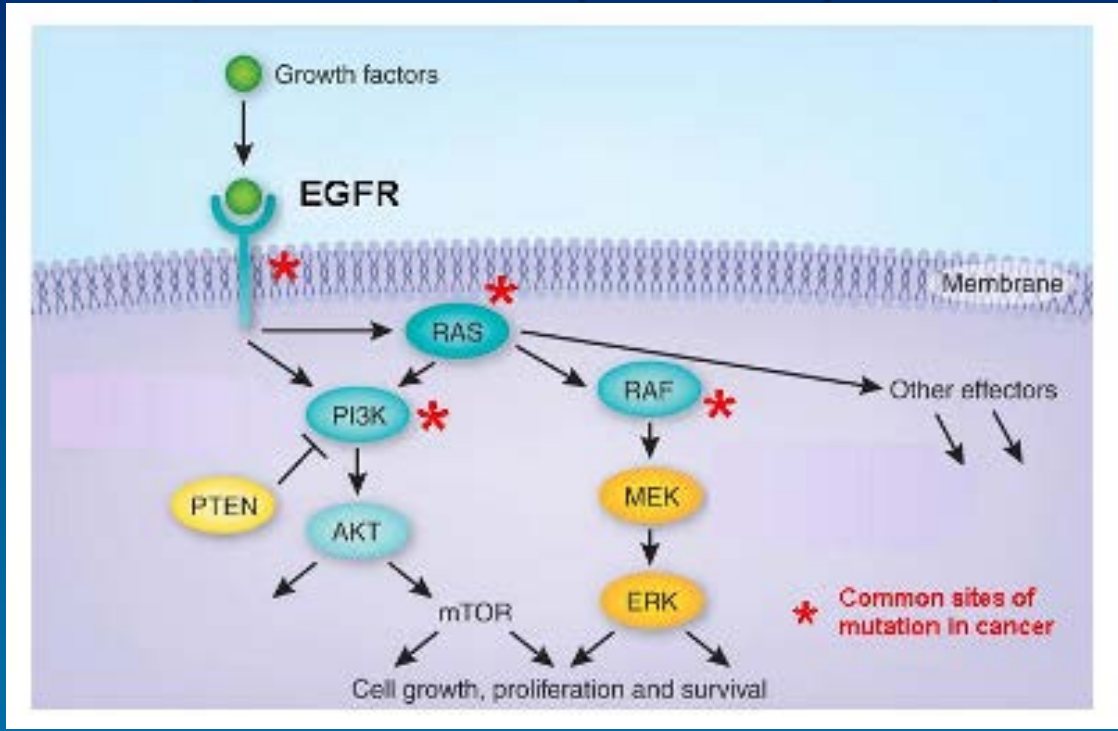
The *KRAS* mutation status of the tumour was proposed as a potential marker of response and a predictor of benefit

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

“Luckily” we had collected tumour samples!

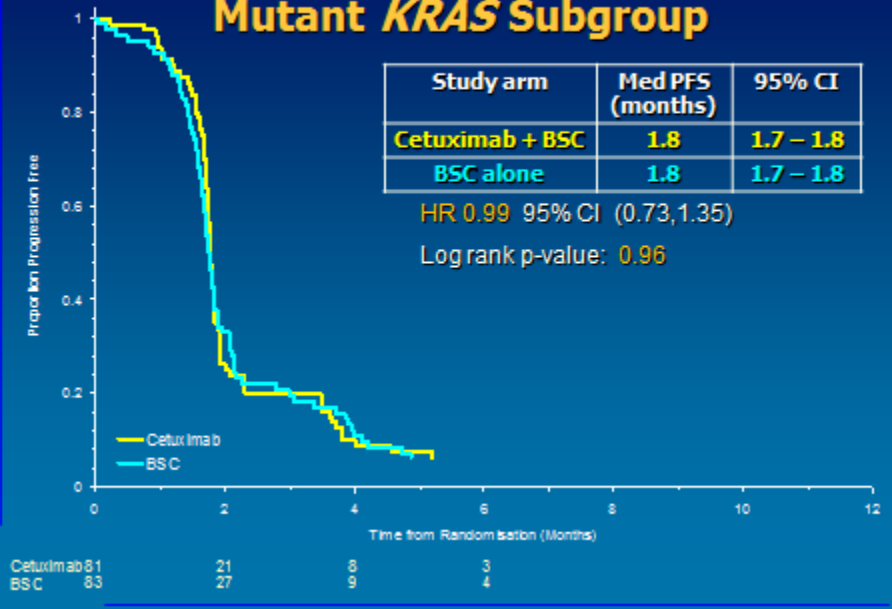
The *KRAS* Oncogene

- KRAS is a small G-protein downstream of EGFR and is an essential self-inactivating component of the EGFR signalling cascade, normally cycling from 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

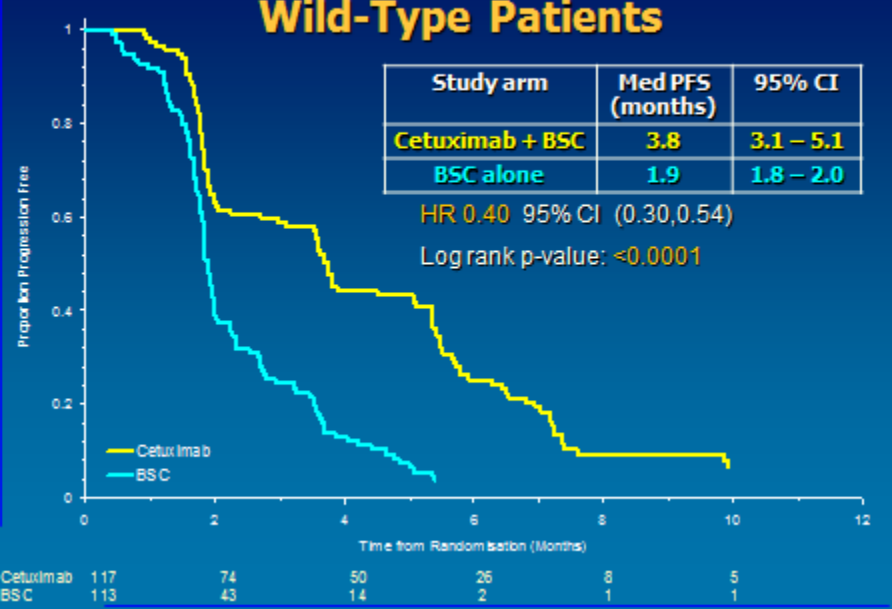


Study arm	Med PFS (months)	95% CI
Cetuximab + BSC	1.8	1.7 – 1.8
BSC alone	1.8	1.7 – 1.8

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

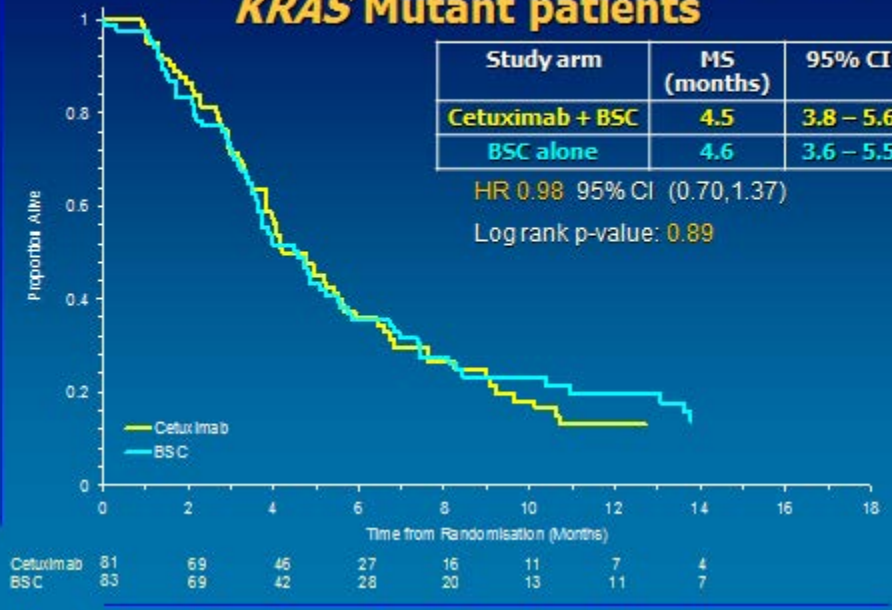


Study arm	Med PFS (months)	95% CI
Cetuximab + BSC	3.8	3.1 – 5.1
BSC alone	1.9	1.8 – 2.0

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

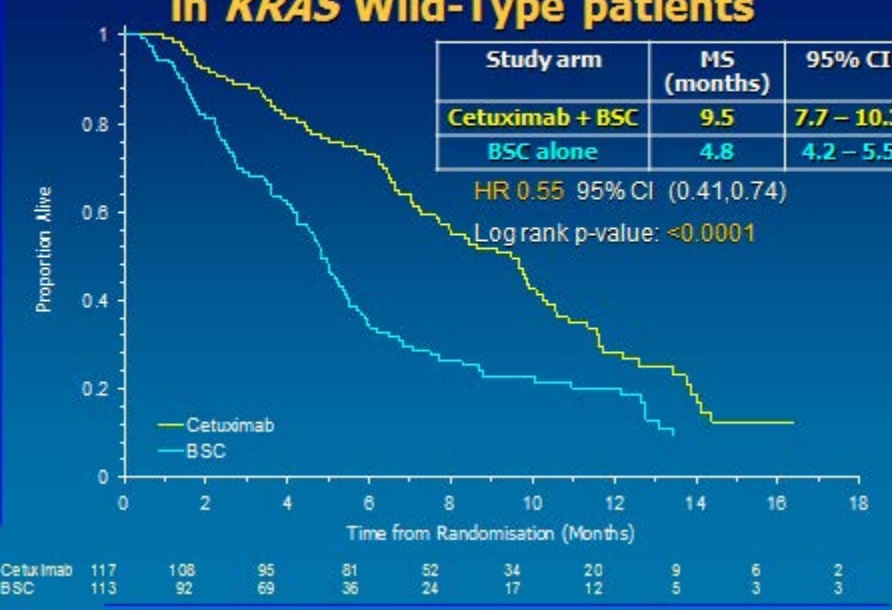


Study arm	MS (months)	95% CI
Cetuximab + BSC	4.5	3.8 – 5.6
BSC alone	4.6	3.6 – 5.5

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

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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

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 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

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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

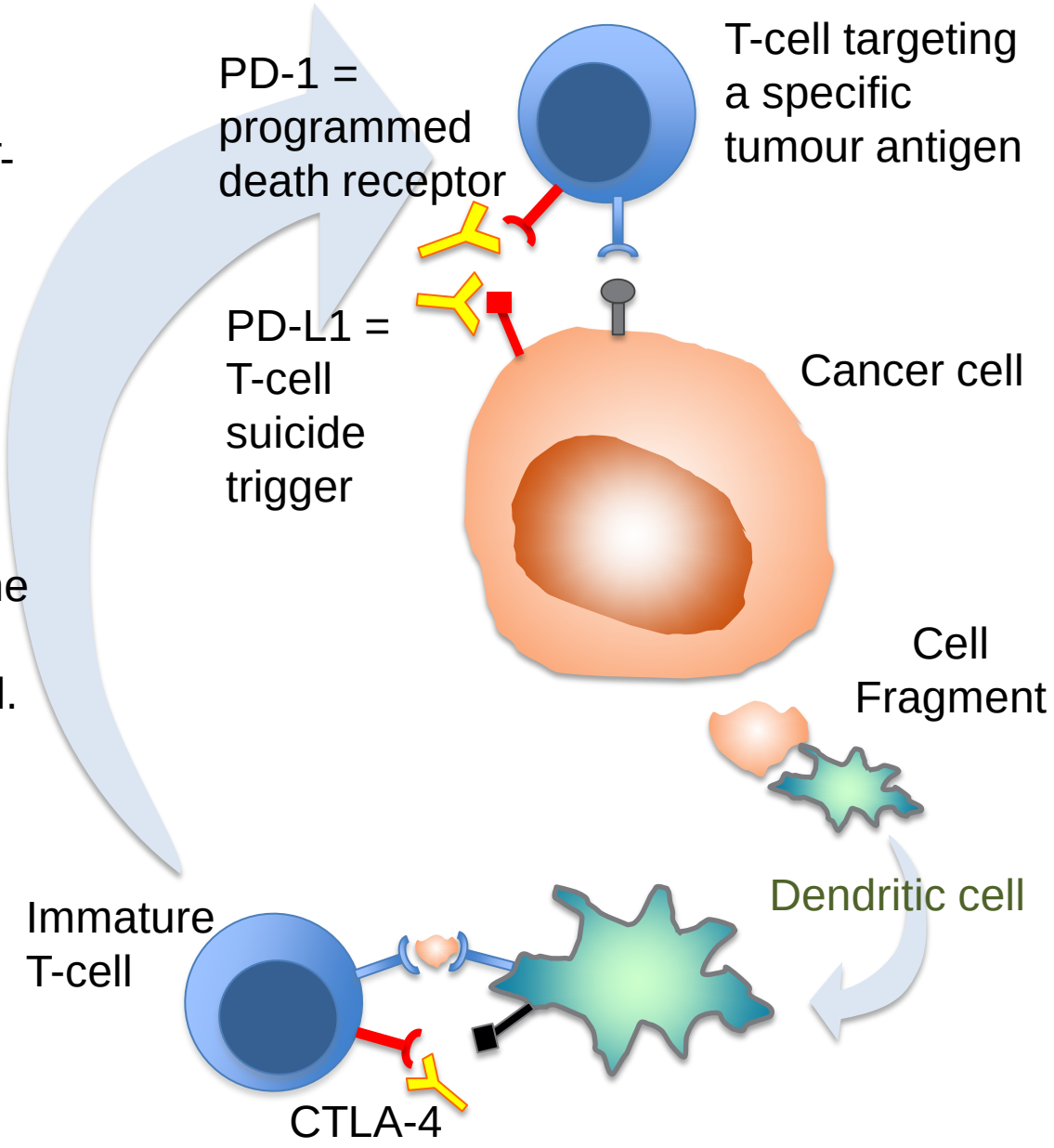
Anti Tumour Immunity

- 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:

- **PD1** – nivolumumab, pembrolizumab
- **PD-L1** – durvalumab, BMS-936559
- **CTLA-4** – ipilumumab, tremelimumab



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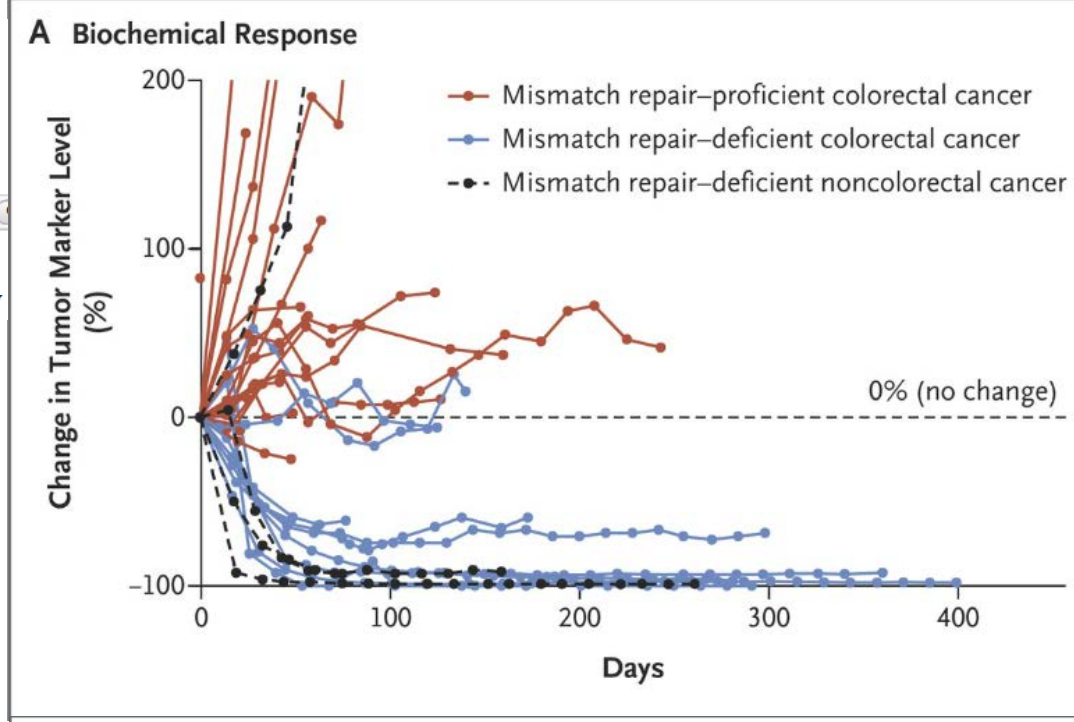
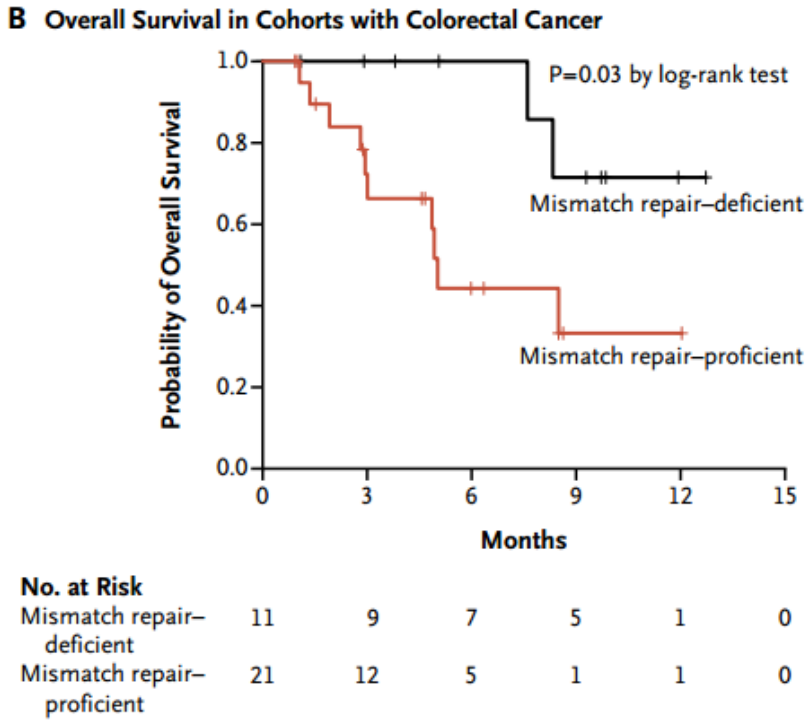
HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS

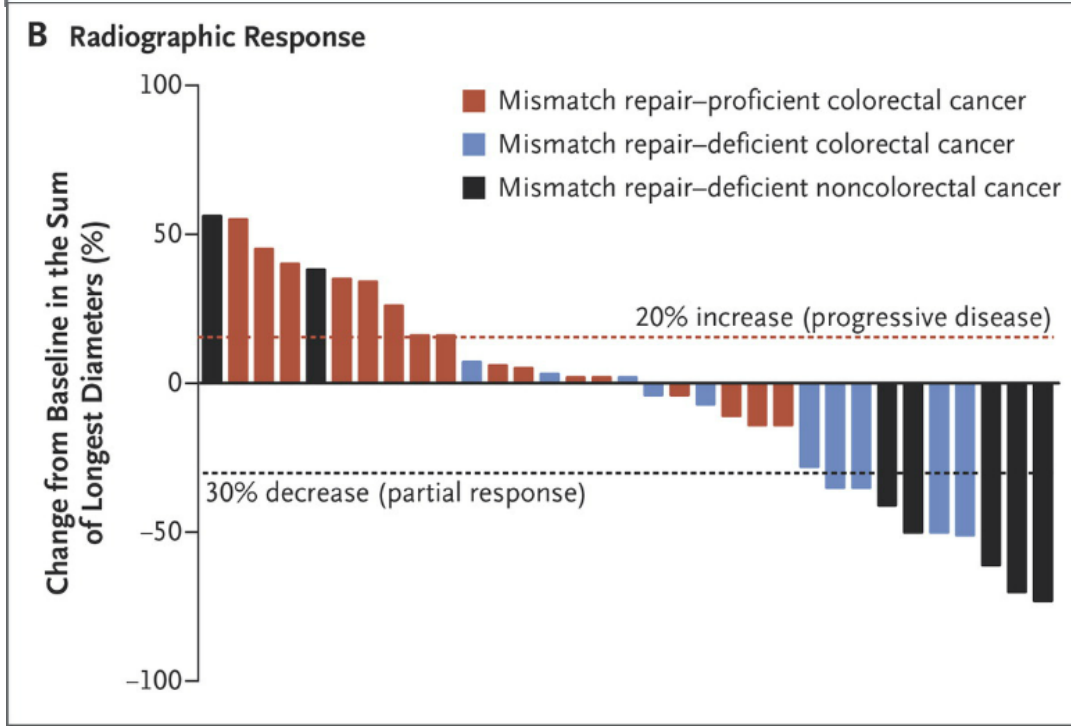
ORIGINAL ARTICLE

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







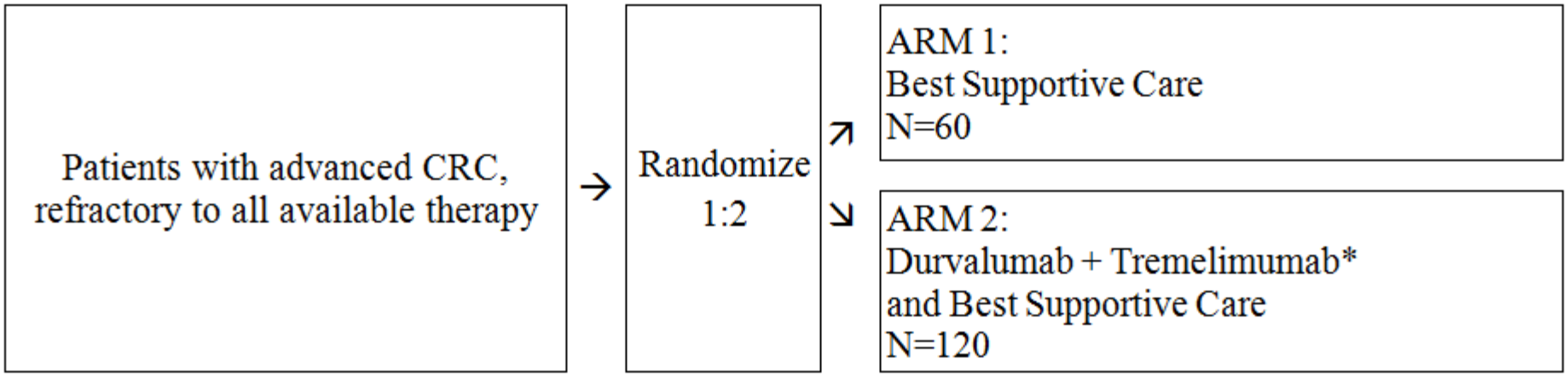
Immune therapy for CRC: Beyond anti PD-1/PD-L1 in MSI-H?

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

  "August 1st 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



Sample Size: 180
Primary Endpoint: Overall Survival

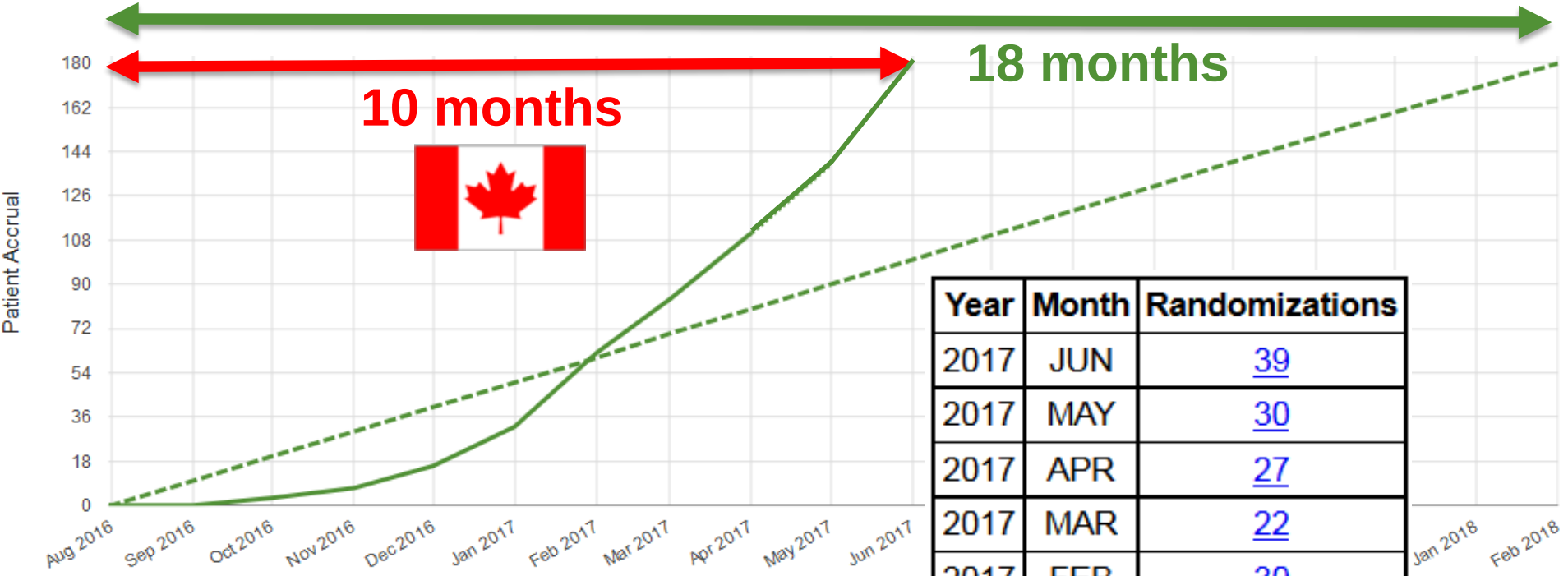
* *Tremelimumab and Durvalumab every 4 weeks for 4 cycles (1 cycle = 4 weeks (28 days), followed by Durvalumab monotherapy to objective disease progression. See Section 7 for details.*

Stratified by:

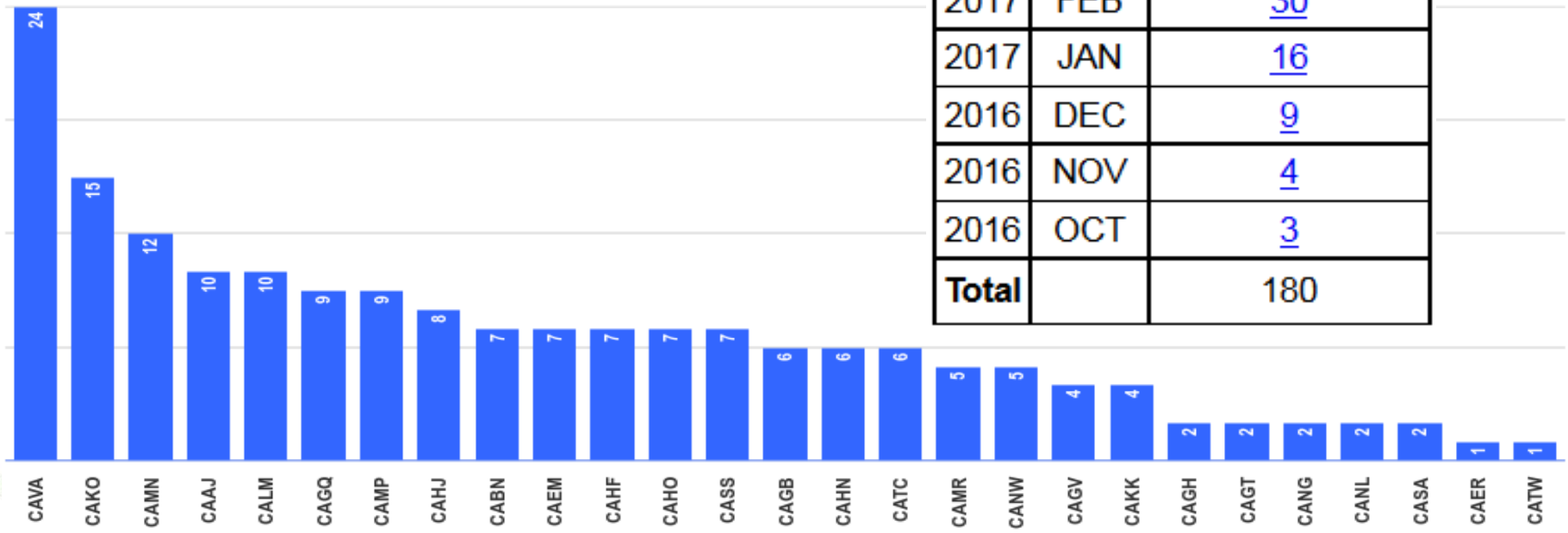
- ECOG Performance Status: 0 *vs* 1
- Site of tumour

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

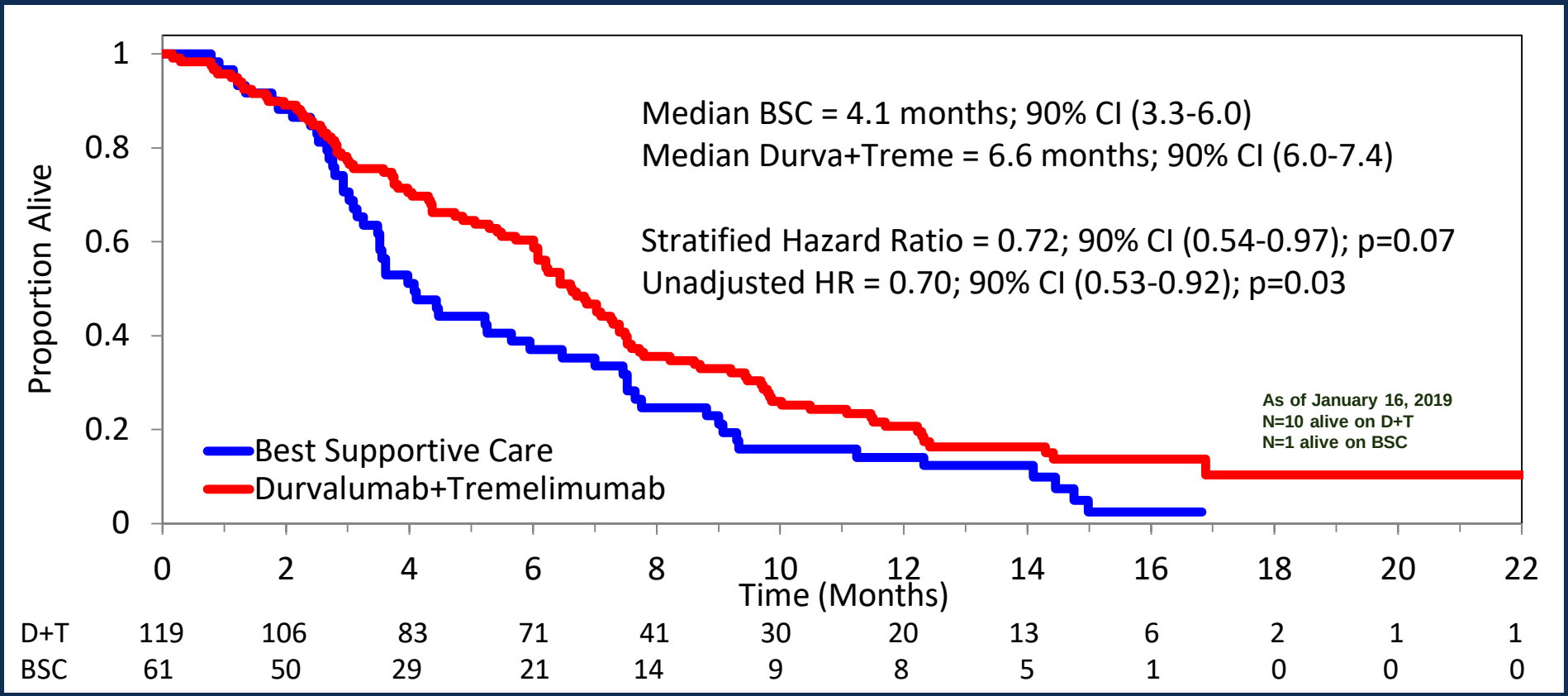
CO.26 Accrual



Year	Month	Randomizations
2017	JUN	39
2017	MAY	30
2017	APR	27
2017	MAR	22
2017	FEB	30
2017	JAN	16
2016	DEC	9
2016	NOV	4
2016	OCT	3
Total		180

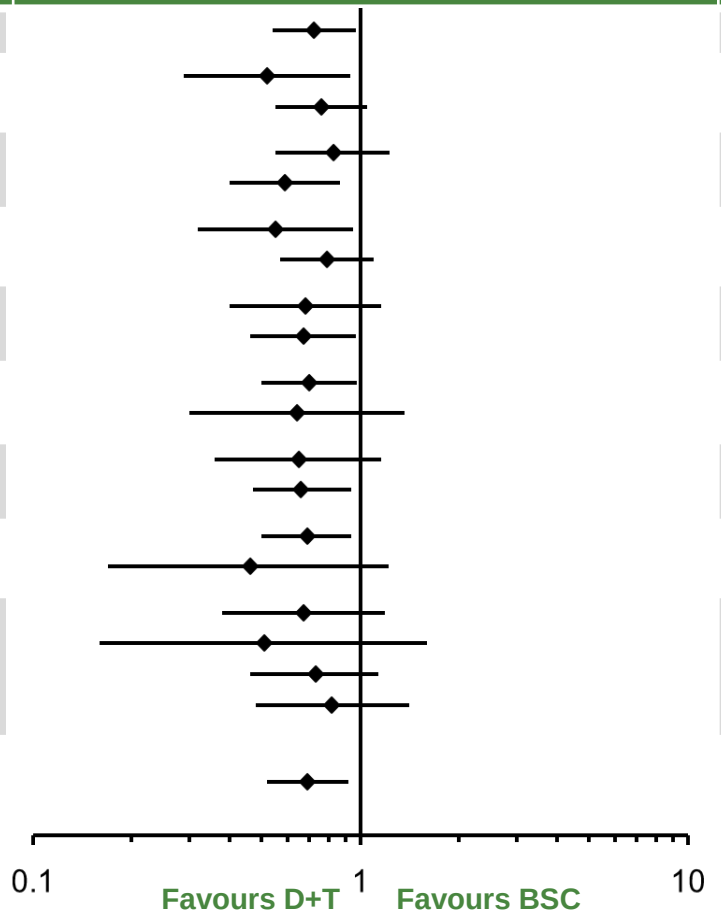


CO.26: Overall Survival



CO.26: Overall Survival

Subset		N	Hazard Ratio (95% CI)	HR (90% CI)
All patients		180		0.72 (0.54-0.97)
Performance status	ECOG 0	50		0.52 (0.29-0.93)
	ECOG 1	130		0.76 (0.55-1.05)
Age	<65	87		0.83 (0.55-1.23)
	≥ 65	93		0.59 (0.40-0.87)
Gender	Female	59		0.55 (0.32-0.95)
	Male	121		0.79 (0.57-1.10)
KRAS	Wild	45		0.68 (0.40-1.16)
	Mutant	123		0.67 (0.46-0.97)
NRAS	Wild	147		0.70 (0.46-0.98)
	Mutant	21		0.64 (0.30-1.37)
RAS (KRAS/NRAS)	Wild	38		0.65 (0.36-1.16)
	Mutant	130		0.66 (0.47-0.94)
BRAF	Wild	153		0.69 (0.50-0.94)
	Mutant	15		0.46 (0.17-1.22)
Tumour primary	Right	40		0.67 (0.38-1.19)
	Transverse	10		0.51 (0.16-1.60)
	Left	68		0.73 (0.46-1.14)
	Rectum	60		0.82 (0.48-1.41)
Microsatellite status	MSI-H / dMMR	2		NA
	MSS / pMMR	166		0.66 (0.49-0.89)*
	Unknown	12		NA



*p=0.024

Presented by:
Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

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:

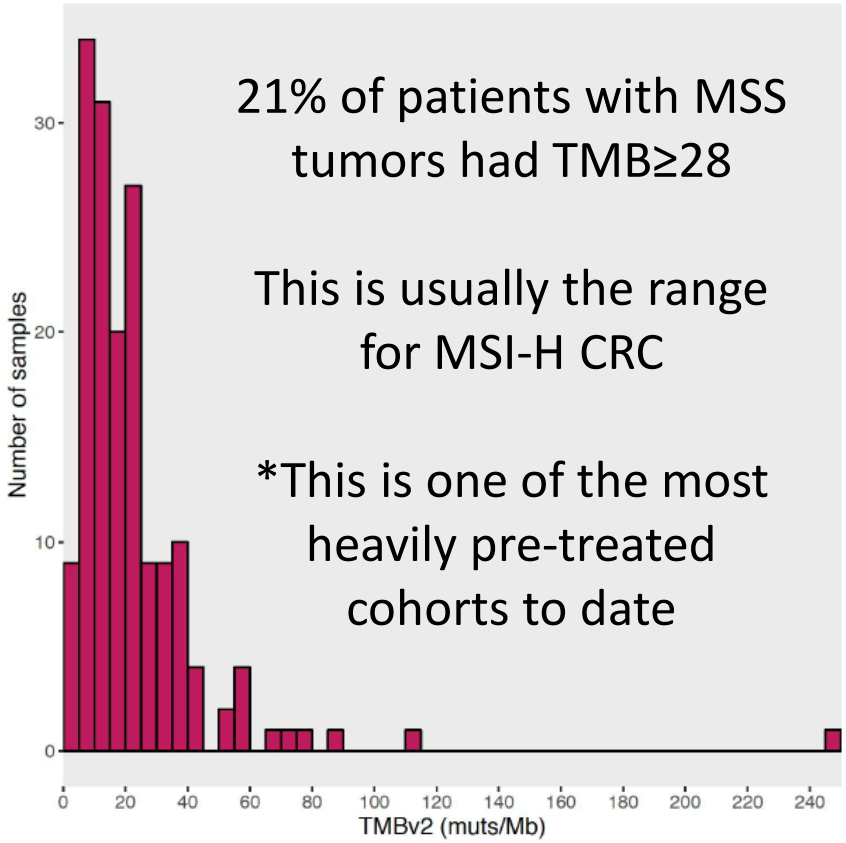
cfDNA analysis

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

Tissue correlatives ongoing

1 Artyomenko *et al* ESMO 2018
2 Quinn *et al* ESMO

CO.26: Tumour Mutation Burden (TMB):

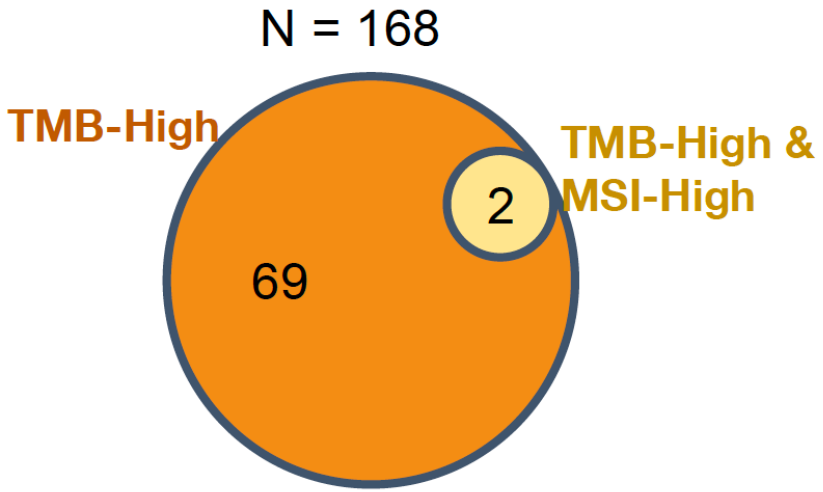


21% of patients with MSS tumors had TMB≥28

This is usually the range for MSI-H CRC

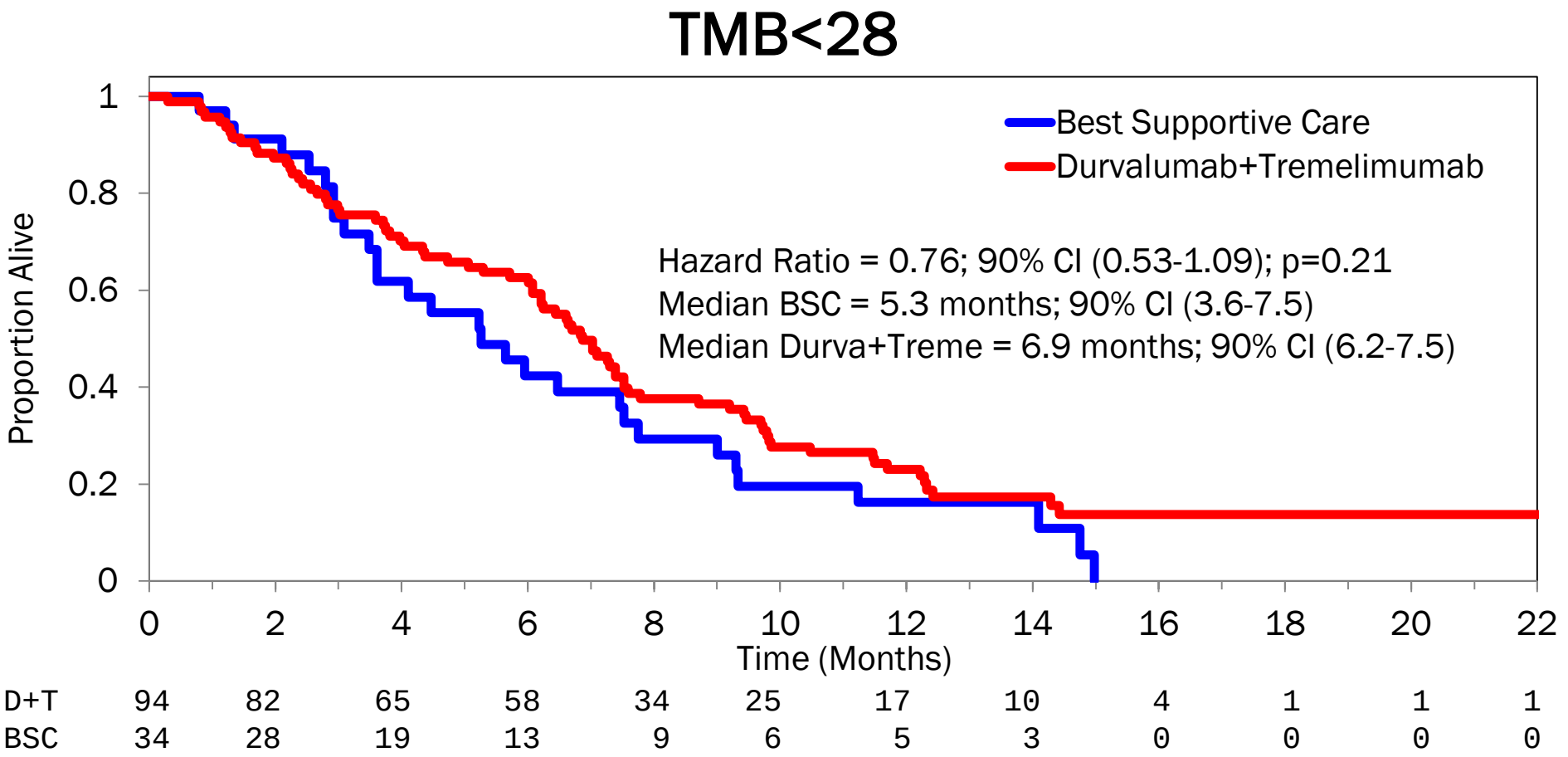
*This is one of the most heavily pre-treated cohorts to date

MSI-High samples are also TMB-High:

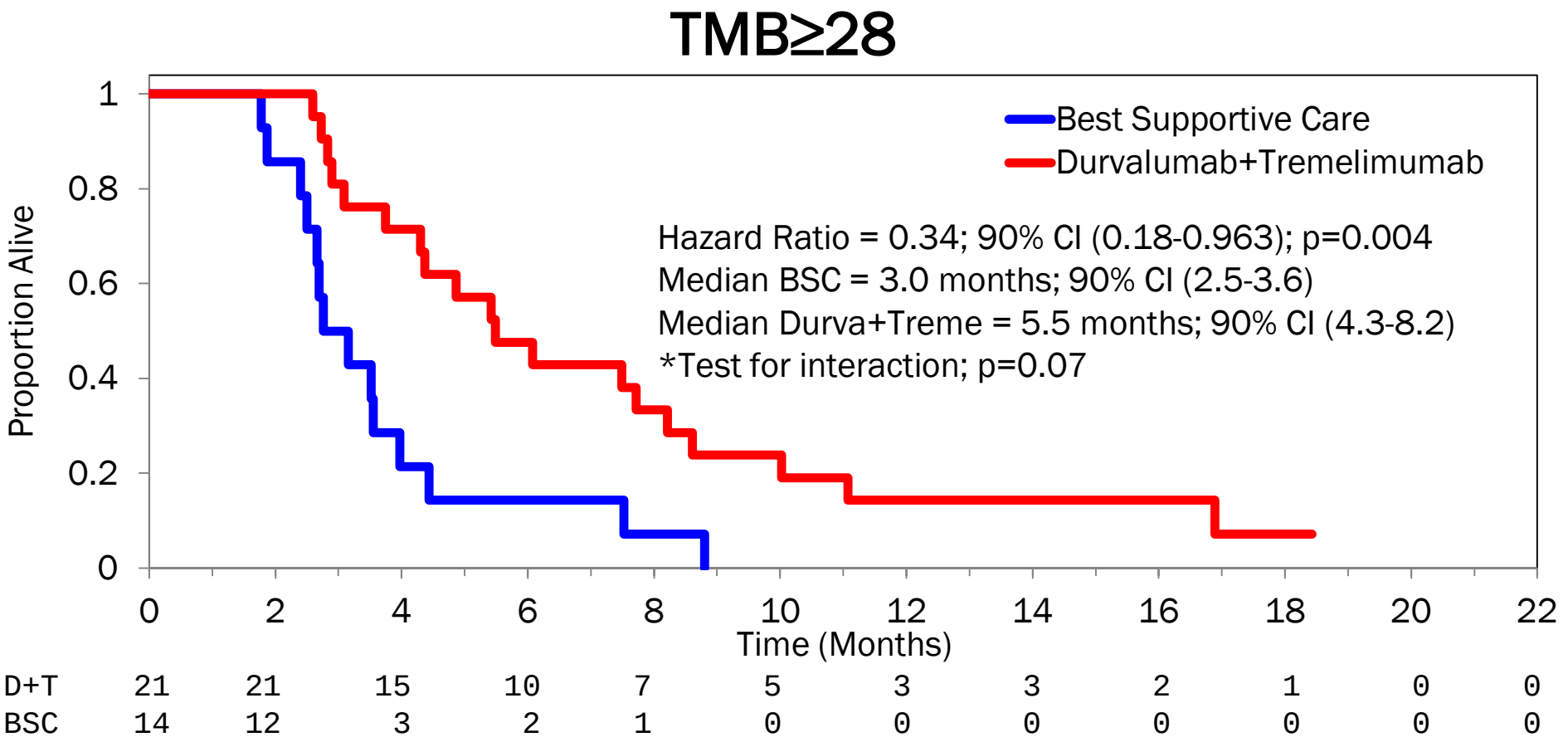


- Excluding 2 patients with MSI-H
- TMB in MSS patients:
  - Mean: 20.4 ± 16.3 mts/Mb
  - Range: 0.96 – 114.0

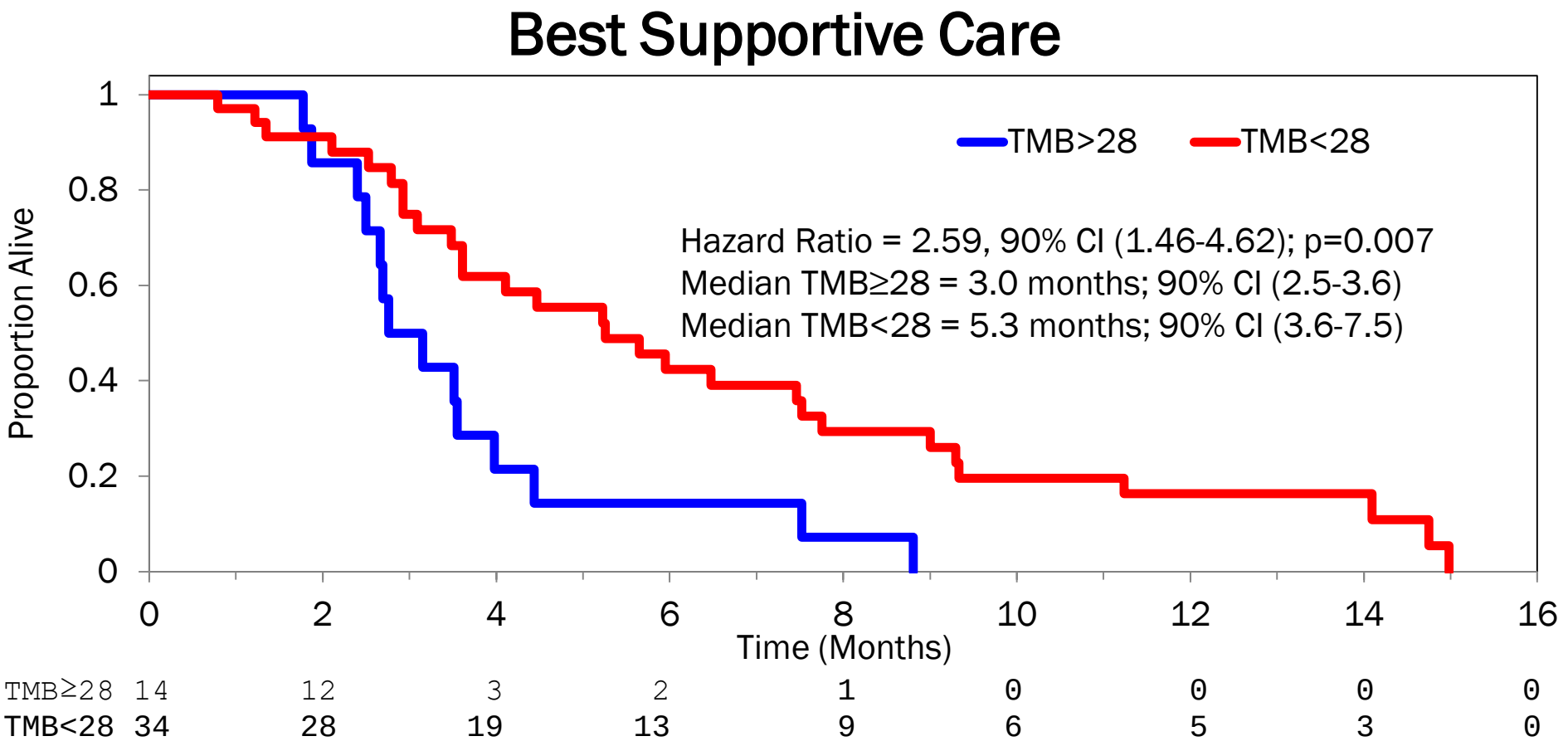
TMB predictive for OS:



TMB predictive for OS:



TMB prognostic for OS:



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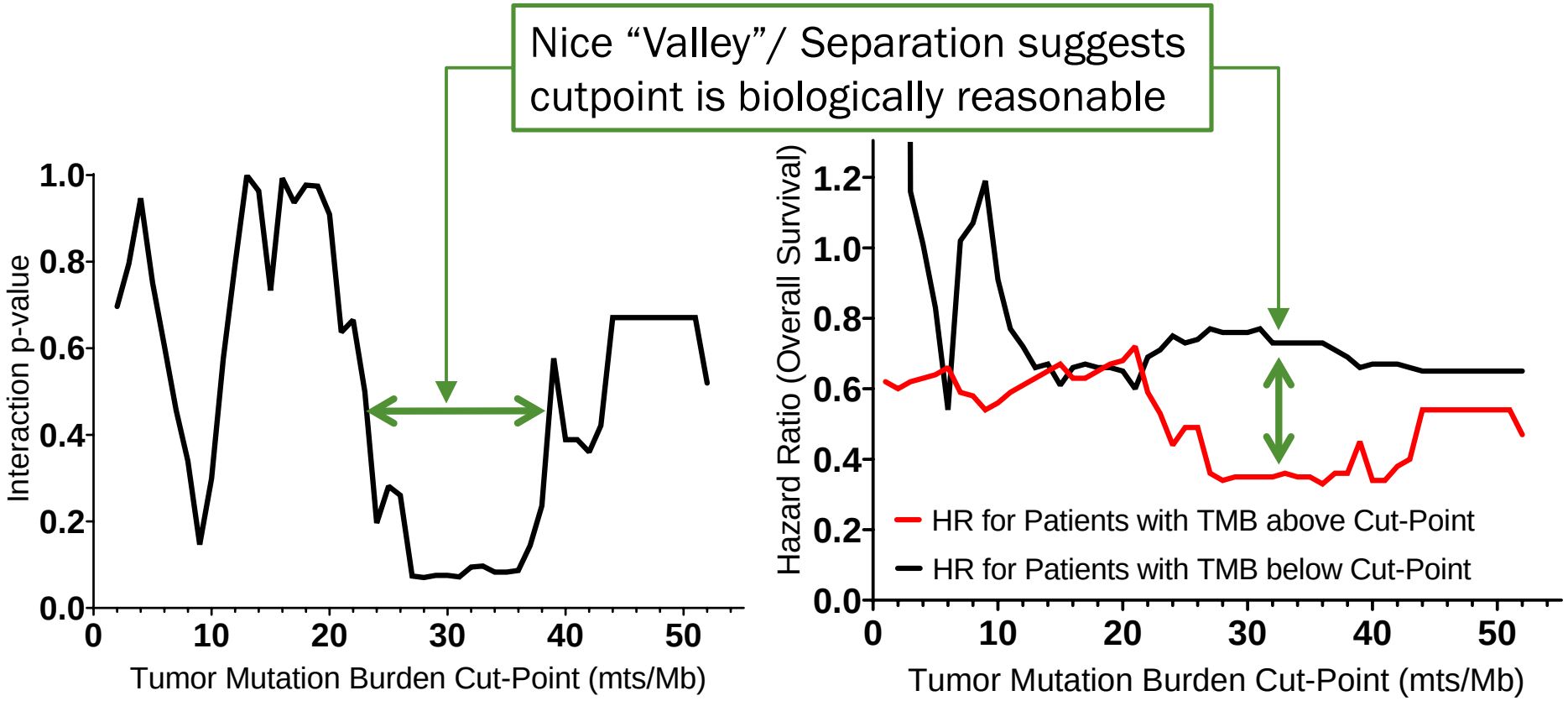
Minimum p-value method:



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.

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 ~10 vs 18 months - **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
- GI ASCO Oral Presentation; ASCO Poster Discussion

Thank You