cancer trials ireland

Together, we're finding answers to cancer.

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AGENDA

Cancer Trials Ireland Stakeholder Engagement meeting

Gibson Hotel, Dublin, June 23rd 2017

9.00 am	Welcome	***Eibhlin Mulroe,*** CEO, Cancer Trials Ireland	5 mins
9.05 am	Patient Advocate Advisory Group Session: 'Crowdsourcing Biomarkers – Opening the Lab doors'	***Professor Amanda McCann*** Head of Pathology, The Conway Institute, UCD	55 mins
10.00 am	Introduction to Stakeholder Session 'From Biomarker to Basket Studies'	***Professor William Watson*** The Conway Institute, UCD	5 mins
10.05 am	The Cancer Trials Ireland Bio-resources - Opportunities for Research	***Verena Amberger-Murphy PhD*** Translational Research Leader, Cancer Trials Ireland	20 mins
10.25 am	"Molecular pathology and biomarker assessment, a vital part of modern cancer therapy".	***Dr Brendan Doyle*** Clinical Director for Molecular Histopathology Beaumont Hospital / RCSI	20 mins
10.45 am	Add Aspirin Basket Study	***Professor Ruth Langley,*** MRC Programme Leader & Chair, Cancer Group, Medical Research Council Clinical Trials Unit, University College London	25 mins
11.10 am	Q&A	***Professor William Watson*** The Conway Institute, UCD	20 mins

Welcome to the Cancer Trials Ireland, June Stakeholder Meeting

Eibhlin Mulroe,
CEO,
Cancer Trials Ireland

Patient Advocate Advisory Group Session:

‘Crowdsourcing Biomarkers – Opening the Laboratory doors’

Facilitator:
Professor Amanda McCann,
Head of Pathology,
Conway Institute,
University College Dublin

Thank you

‘From Biomarkers to Basket Studies’

Facilitator,
William Watson,
Professor of Cancer Biology,
Conway Institute,
University College Dublin

Biomarkers

"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmaceutical responses to a therapeutic intervention"

Types:

Detection/screening: evaluating patients with either risk factors for or symptoms of cancer

Diagnostic: assessing presence or absence of cancer

Prognostic: predict the outcome of patients allowing individualized management

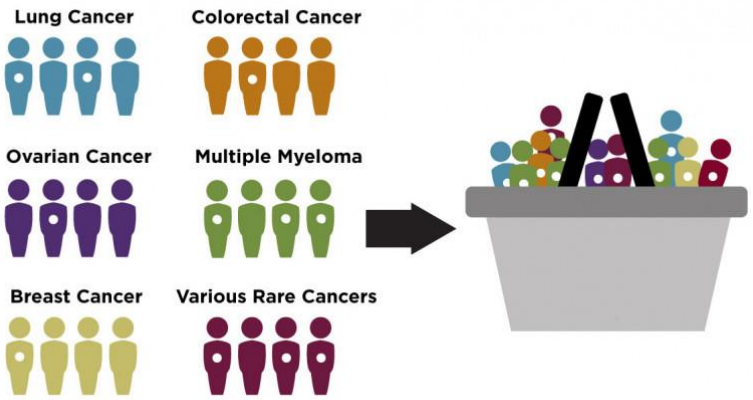
Predictive: predict response to the treatment and/or to monitor the effectiveness of the treatment

Therapeutic target: molecular targets of novel therapies and is affected by therapy.

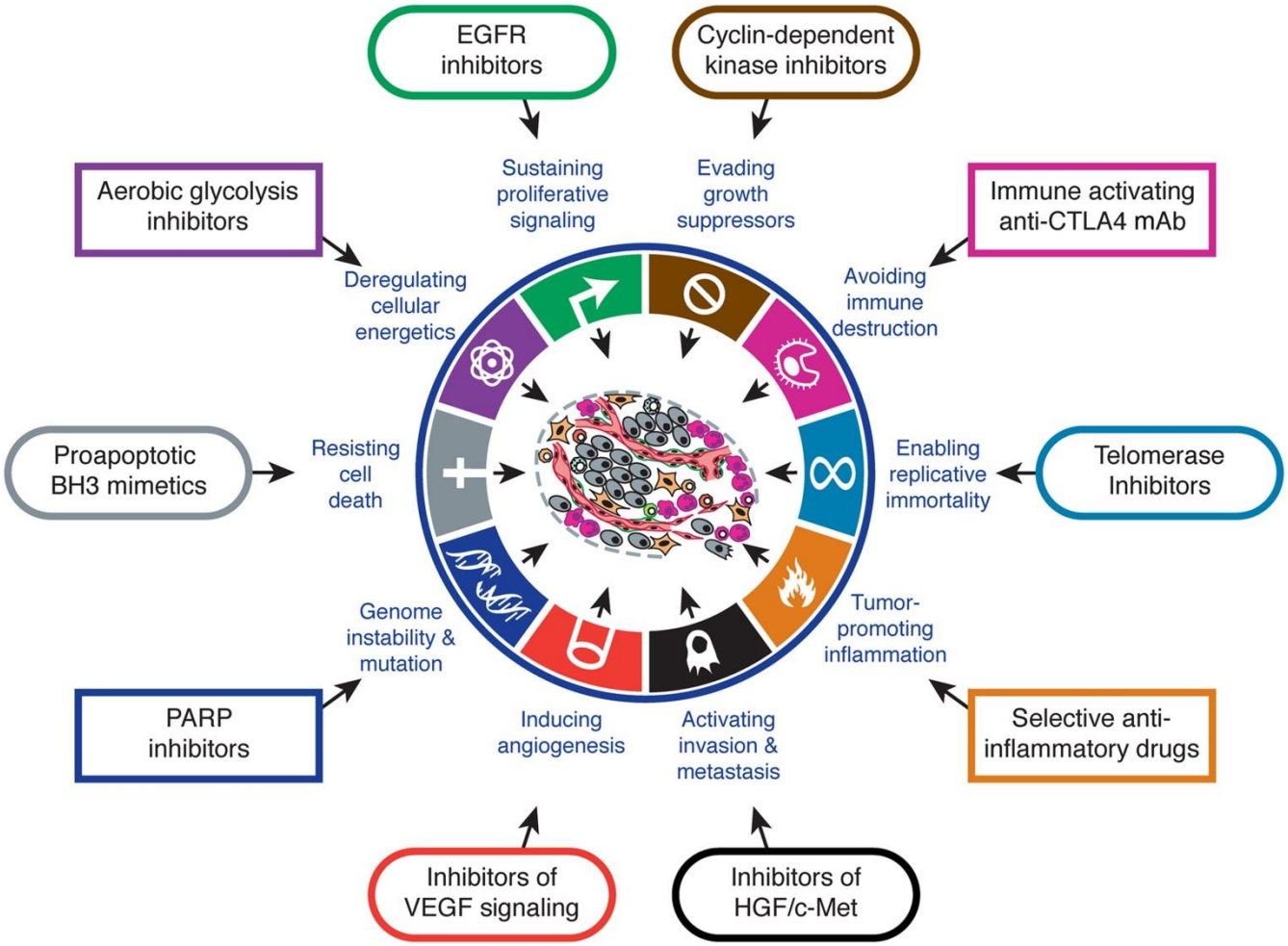
Basket Study

"Matching the **right drug** to the **right subgroup of patients** through **biomarkers**"

One molecular biomarker abnormality targeted across multiple tumour types



Hallmarks of Cancer



Cell 2011 144, 646-674DOI: (10.1016/j.cell.2011.02.013)

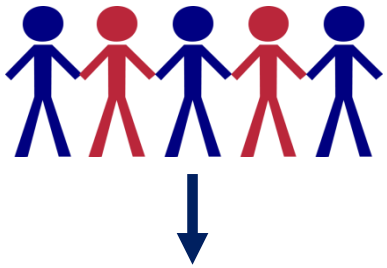
Cancer Trials Ireland Bio-resources: Opportunities for Research Projects

Verena Amberger-Murphy PhD
Translational Research Leader,
Cancer Trials Ireland

Overview

- Definitions and Explanations of commonly used concepts and words
- Biological samples collected through ICORG/Cancer Trials Ireland studies
- SOPs
- New Proposal Workflow

Why collecting biological samples?

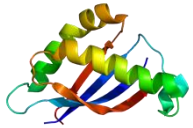


Blood /Tissue sample

Translational Research

Biomarkers

Proteins



DNA

Personalised Therapy

Treatment Plan A Treatment Plan B

Translational Research

Definition (Wikipedia):

Translational Research applies findings from basic science to enhance human health and well-being.

In a medical research context, it aims to "translate" findings in fundamental research into medical practice and meaningful health outcomes.

Bench  *Bedside*

Biomarker

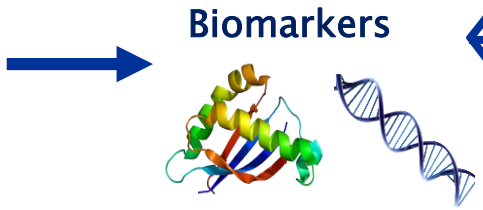
Definition in the context of Cancer:

A Biomarker is a characteristic of a particular cancer, which can be either

- expressed by the cancer
  - on the cell membrane, e.g. HER2/neu Receptor *(as you might have seen in the PAAG workshop)*
  - within the cell, e.g. K-ras Oncogen
  - or mutations thereof, e.g. K-ras mut
- produced and released (into the blood stream) by the cancer, e.g. Circulating Tumour Cells (CTCs) or Tumour DNA
- produced by the host organism as a reaction to the cancer, e.g. PSA increase as a reaction to prostate cancer

Predictive and/or Prognostic Biomarker

Blood /Tissue sample



Prognostic:

CEA and CRC → poor prognosis

CTCs and BC → shorter PFS and OS

Worse Prognosis

Prognostic and Predictive

BRCA1 in BC

Responsive to Chemo

Predictive:

Progesterone Receptor on BC

→ benefit of Tamoxifen

MGMT methylation in Glioblastoma

→ benefit of Temozoloamide T

Targeted Therapy

Targeted Therapy

Biomarker	Small Molecule Inhibitors	Antibodies
Bcr-Able	Imatinib	
ALK	Crizotinib	
EGFR	Erlotinib	Cetuximab
HER2neu / EGFR	Lapatinib	
VEGF		Bevacizumab
PDL-1		Atezolizumab
Braf		Vemurafenib, Dabrafenib

Trial Types

Non-interventional

1. Collection of biological samples (and clinical information)
2. Questionnaires
3. Biobanking
4. Registries (collection of disease/clinical data)

'Translational Trials'

Interventional

1. Test of Investigational medicinal product(s) (IMP) or combinations thereof
2. Radiotherapy Trials (RT)
3. Combination Trials of RT and IMP

(Collection of clinical information is always part of these trials, Collection of biological samples optional)

'Clinical Trials'

Basket Trial (IMP trial)

'Conventional' trial:

- Targets **a** particular Cancer Type, e.g. CRC **or** Lung **or** Breast
- ≥ 1 **Biomarker**, e.g. HER2
- Cancer at a specific stage, e.g. advanced/metastatic, or grade 2,3, etc

Basket Study:

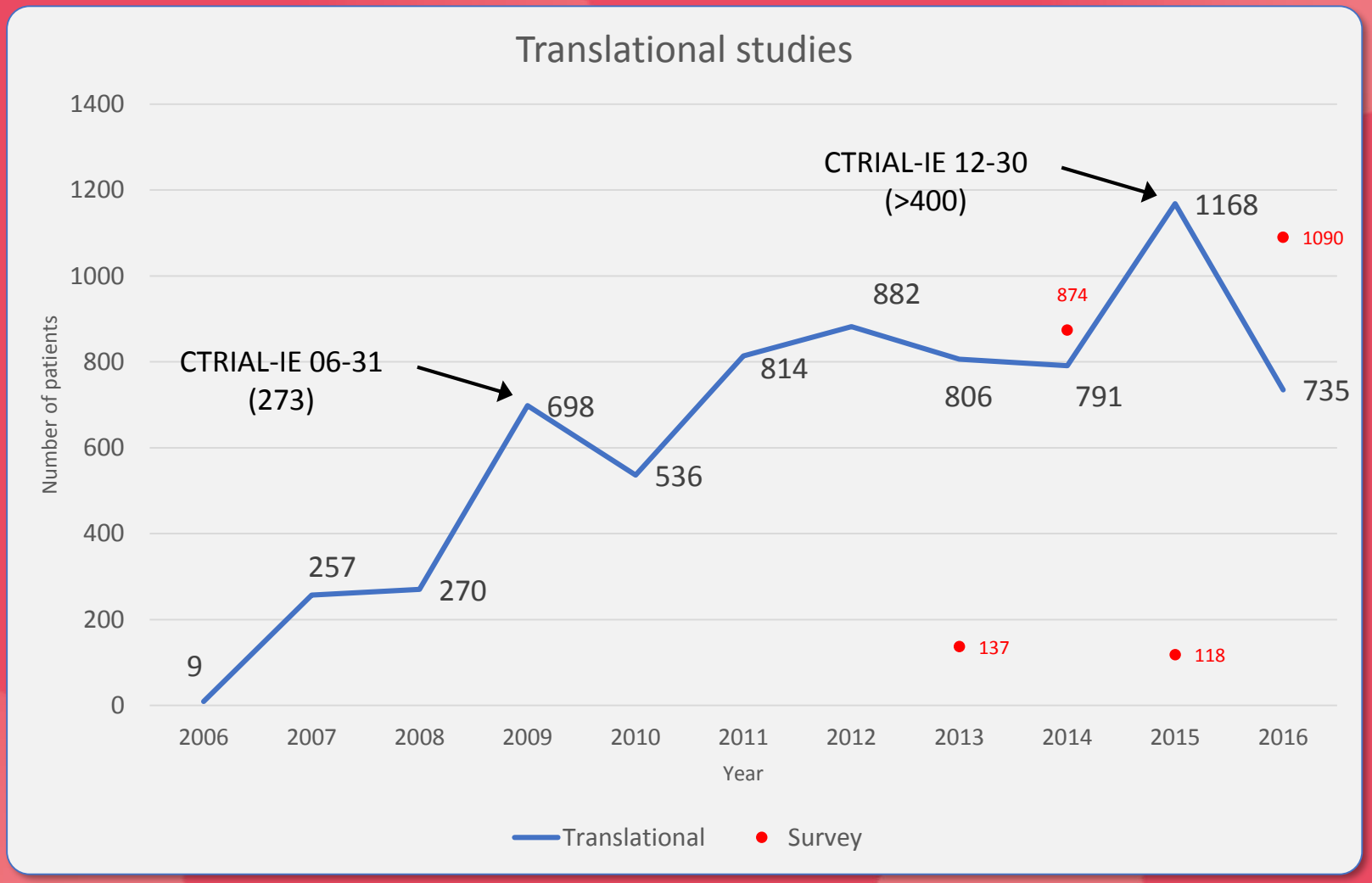
- Targets **various** Cancer Types
- ≥ 1 **common Biomarker** **or** a common/comparable stage (Add-Aspirin)

‘Translational’ History in ICORG/Cancer Trials Ireland

- 1996 - 2006 very few translational studies
- 2009: Strategic decisions
  - All in-house clinical studies need to have a translational arm
  - Create the position for a Translational Research Coordinator

Translational Studies		
Study Status	**2009**	**2017**
Open	2	21 (11)
In Development	1	8 (3)
Proposals	2	6 (1)

Patient Accrual 2006 - 2016



Cancer Trials Bioresources

In-house Studies: Translational and Clinical

Cancer Type	Number of Studies	Sub-types
Breast Cancer	9	Biobank, newly diagnosed, metastatic, recurrent
Colorectal Cancer	3	stage II, stage II-III
Pancreatic Cancer	1	resectable, unresectable, metastatic, pancreatitis
Oesophageal Cancer	1	newly diagnosed
Brain Tumour	2	Glioma II, Glioma III/IV, Biobank (various types)
Prostate Cancer	6	metastatic, hormone responsive, hormon refractory
Melanoma	2	advanced/metastatic
Rectal Cancer	1	locally advanced
Lung	2	NSCLC, various other sub-types
Paediatric	2	Biobanks (various types)

Cancer Trials Bioresources

Sample Types

Cancer Type	Tissue	Blood	Other samples	Longitudinal samples
Breast Cancer	FFPE, Fresh Frozen, RNA later	Whole Blood. Serum	-	YES
Colorectal Cancer	FFPE, Fresh Frozen	Plasma, Serum, Cellular Components	-	YES
Pancreatic Cancer	FFPE	Plasma	-	YES
Oesophageal Cancer	Fresh Frozen, RNA later	Whole Blood, Serum, Plasma	-	NO
Brain Tumour	-	Serum	-	YES
Prostate Cancer	FFPE	Plasma, Serum, Whole Blood (Tempus Tubes, CTC)	Urine, Bone Biopsies	YES
Melanoma	FFPE, RNA later	-	-	NO
Rectal Cancer	FFPE, Fresh Frozen	Plasma, Serum, Whole Blood (CTC)	-	YES
Lung	-	Whole Blood, Serum	-	YES
Paediatric	FFPE	?	-	NO

SOPs

Standard Operating Procedures

SOPs for Sample Processing

SOP 45 Blood Sampling-Serum:

30-60 min clotting, centrifugation at 1000g, 10 min, storage at -80°C

SOP 46 Blood Sampling-Plasma:

Collection in EDTA (Citrate, Heparin, EDTA + protein stabilizer) tubes, centrifugation 1000 or 2000xg, 15 min, optional 2nd centrifugation 20,800g, 10 min, storage -80°C (Buffy Coat, Cellular Components)

SOP 47 Fresh Tissue Processing:

Cut into 0.5x0.5x0.5cm pieces, place directly into cryo tubes (empty, Allprotect Reagent), storage -80°C

FFPE according to local Pathology Lab SOPs

How can I get my scientific idea translated into a trial/study?

From Idea to Proposal

Contact Cancer Trials Ireland and discuss your idea

- Clinical Trial (including an IMP): Dr Kathleen Scott, Head of Operation and Clinical Programs
  kathleen.scott@cancertrials.ie
- Any other study (translational and basket): Dr Verena Murphy, Translational Research Leader
  verena.murphy@cancertrials.ie

The earlier the better!

Proposal Workflow – Inhouse Studies

DSSG meeting

Scientific Management Group

Feasibility Outcome
Resource Requirement from GCO
Availability/Requirement of Funding

Thank you

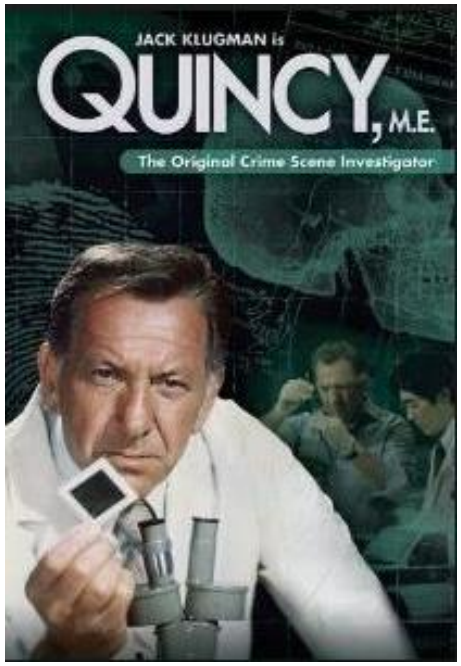
"Molecular pathology and biomarker assessment, a vital part of modern cancer therapy"

Dr Brendan Doyle
Clinical Director for Molecular Histopathology
Beaumont Hospital / RCSI

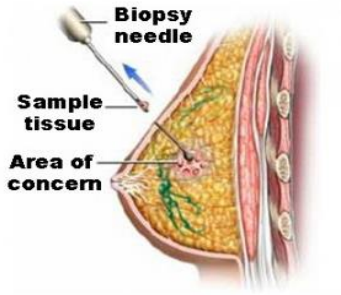
Overview

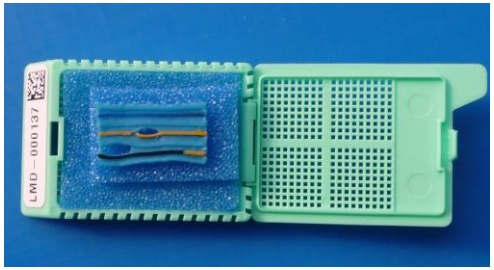
- What does a pathologist actually do?
- What is molecular pathology?
- What's going to happen in the future?

What does a pathologist actually do?



Surgical pathology and its role in cancer care

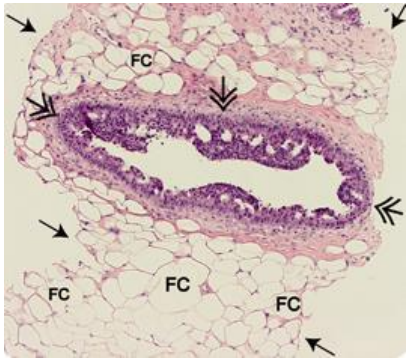




Biopsy taken

Biopsy processed

Slides generated and interpreted



Surgical pathology and its role in cancer care

- Diagnosis

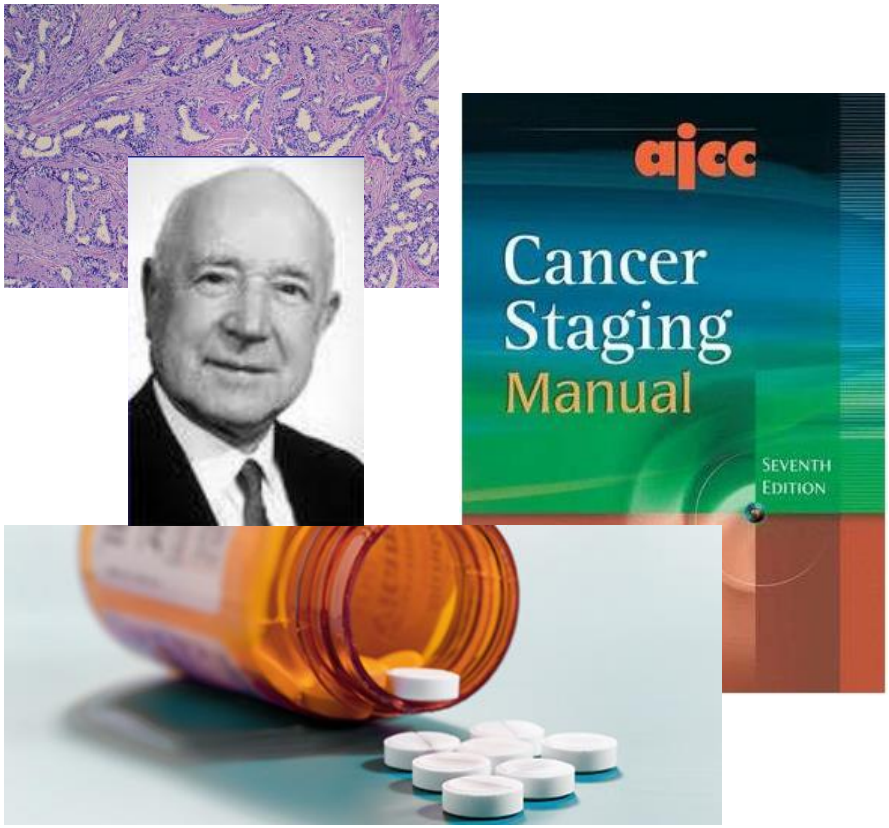
1800- 1960s

- Prognosis

1970s – 1990s

- Prediction

1990s till now



What about molecular pathology?

What is molecular pathology?

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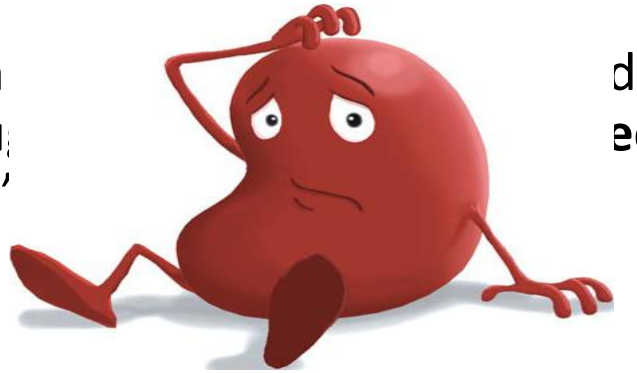

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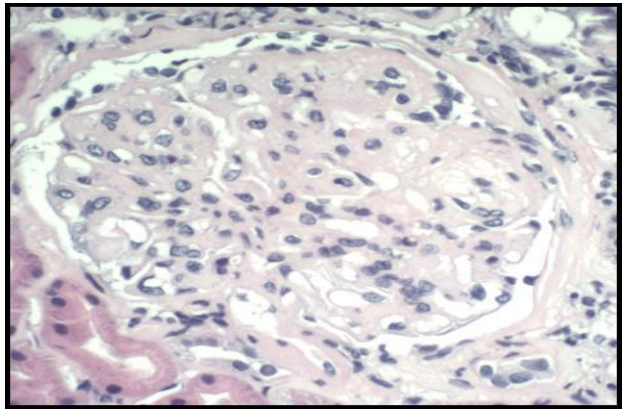

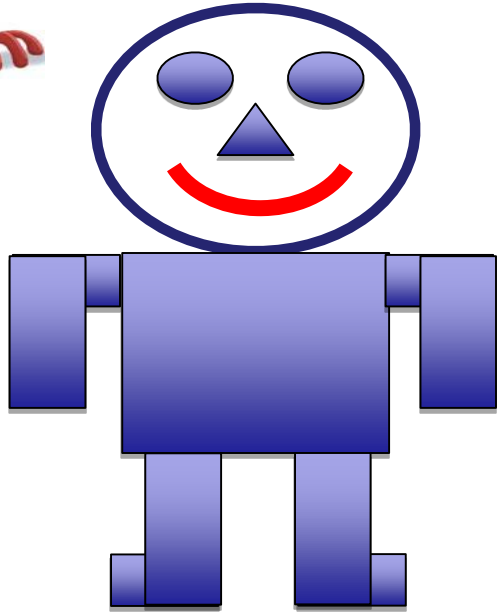

What is molecular pathology?

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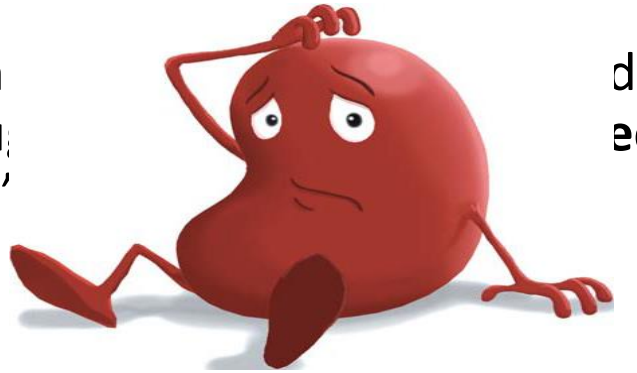

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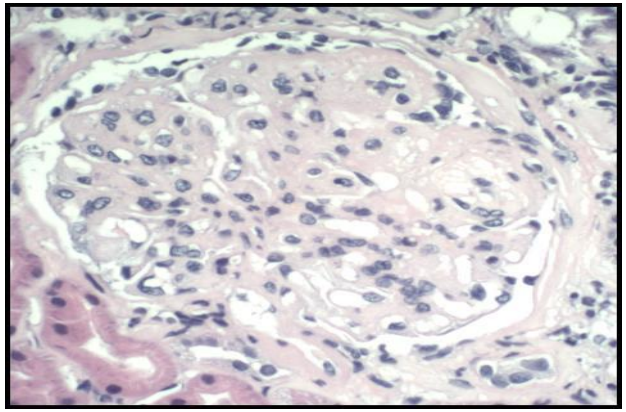
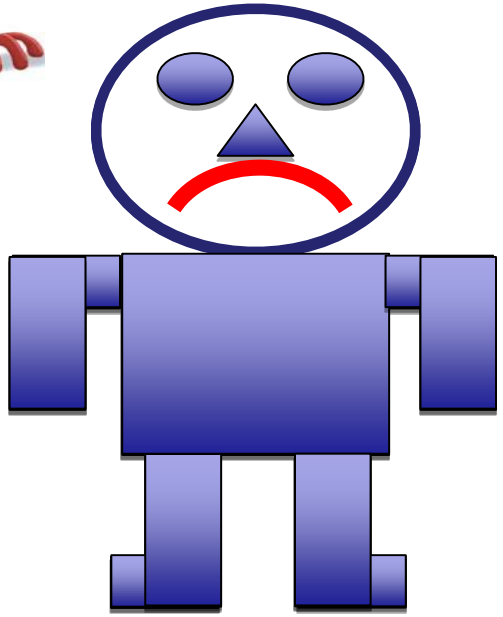
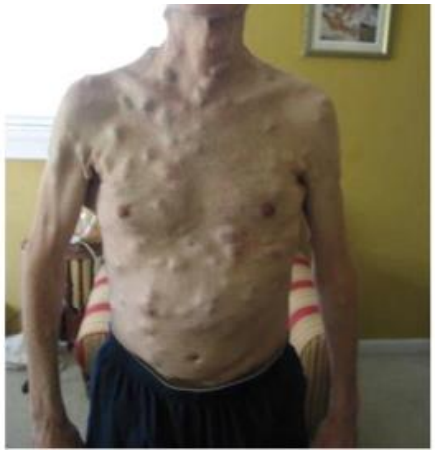
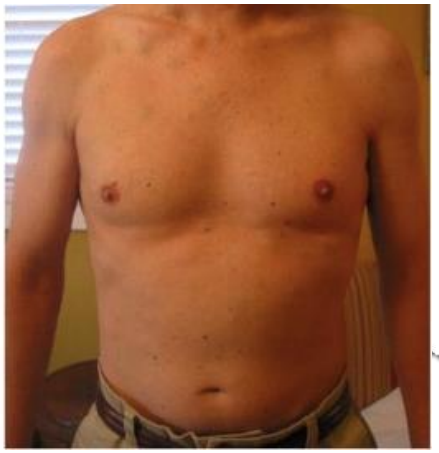




Why is Molecular Pathology Important in Cancer Care?





Wagle et al J Clin Oncol, 29 (2011), pp. 3085–3096

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

ABSTRACT

BACKGROUND

Phase 1 and 2 clinical trials of the BRAF kinase inhibitor vemurafenib (PLX4032) have shown response rates of more than 50% in patients with metastatic melanoma with the BRAF V600E mutation.

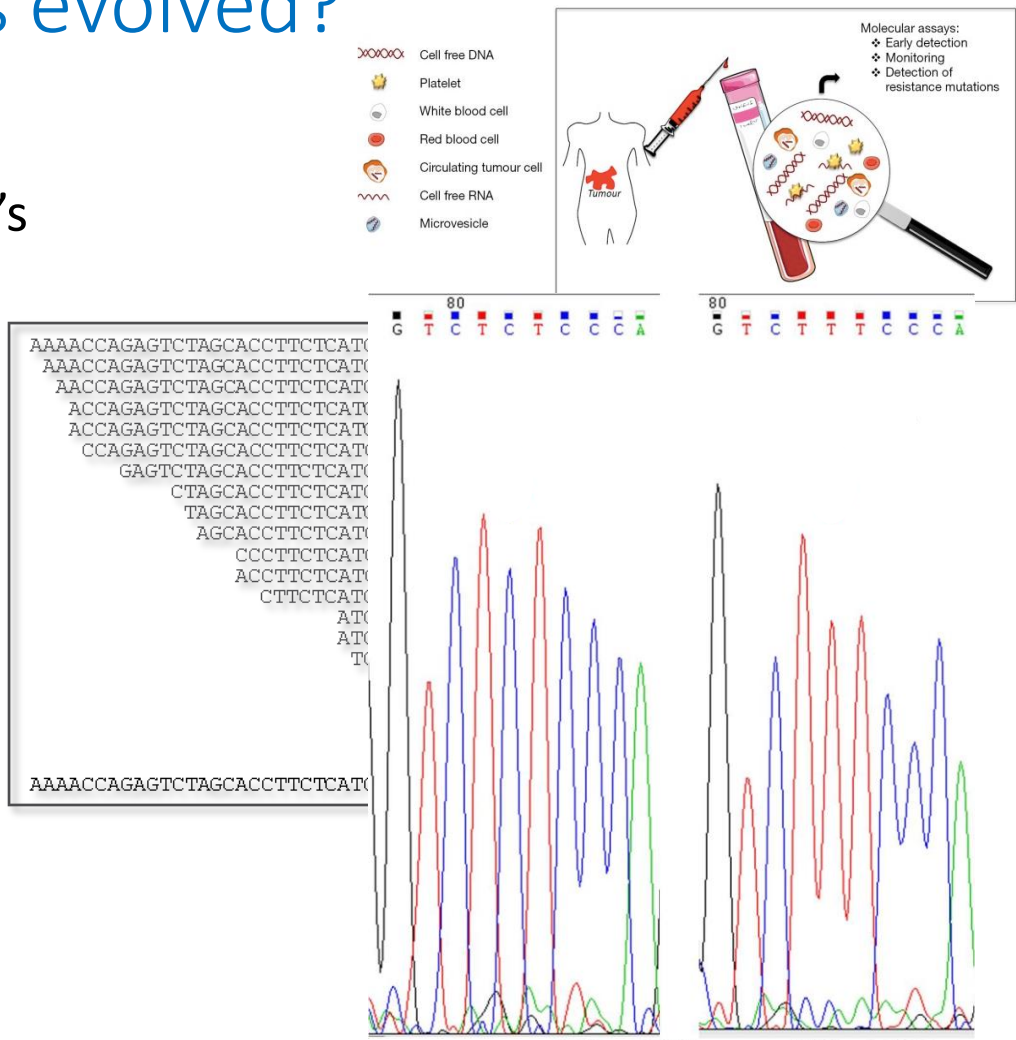
METHODS

We conducted a phase 3 randomized clinical trial comparing vemurafenib with

The authors' affiliations
Appendix. Address rep
Dr. Chapman at the Depa
cine, Memorial Sloan-K
Center, 1275 York Ave.,
10065, or at chapmanp@

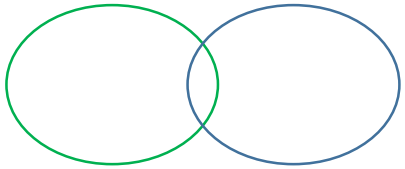
How have biomarkers evolved?

- Tamoxifen, used since the 1970's
- PCR and traditional sequencing
- Next generation sequencing
- Tumour mutational burden, Liqu



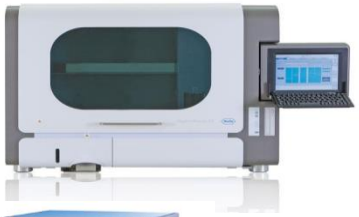
Molecular Pathology at Beaumont/RCSI

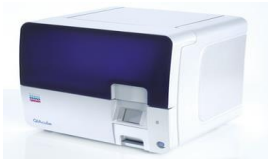
Beaumont Molecular Pathology



RCSI Beaumont Molecular Histopathology

Automated DNA/RNA extraction





PCR / qPCR

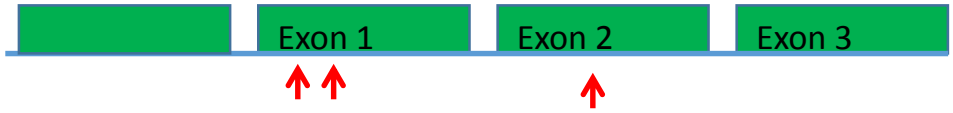
x3

Microarray

Sequencing
Next-generation sequencing

Biomarker detection PCR to NGS

PCR

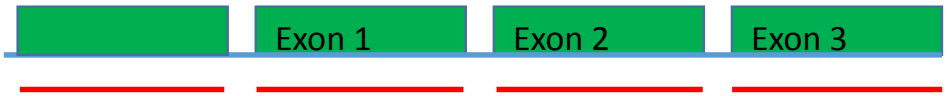


Single base variant detection

Traditional Sequencing

Variant detection across 500-600bp (max 800bp)

Next Generation Sequencing



Whole exon coverage to detect common, rare and novel variants

2005
HER2 FISH Testing

2008
KRAS testing

2012
Sequenome testing

2013
First ISO15189 accredited laboratory for molecular testing in Ireland

2014
Microarray-CGH for FFPE tissue

2017
MiSeq NGS platform

Multiplicom
A part of Agilent Technologies

Cancer hotspot NGS panel

Genes included			
AKT	*ERBB2 (HER2)*	*IDH1*	*PDGFRA*
ALK	*ERBB4*	*IDH2*	*PIK3R1*
BRAF	*FGFR2*	*KIT*	*PIK3CA*
CDKN2A (p16-INK4A, p14-ARF)	*FGFR3*	*KRAS*	*PTEN*
CTNNB1 (ß-catenin)	*H3F3A (Histone H3, F3A)*	*MEK1 (MAP2K1)*	*STK11 (LKB1)*
DDR2	*HIST1H3B (Histone H1, 3B)*	*MET*	
EGFR	*HRAS*	*NRAS*	

ALK, ROS1, RET, NTRK

TUMOUR BRCA

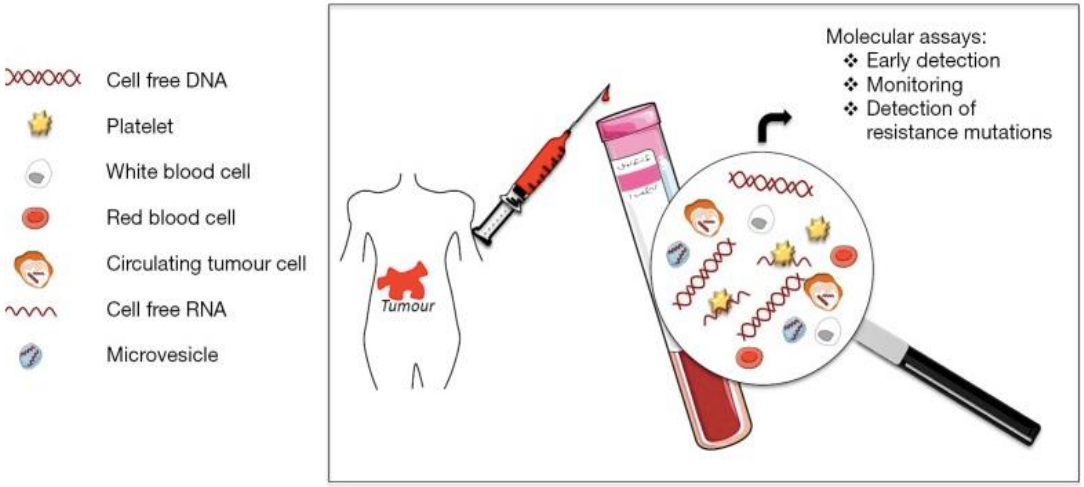
Why are we working with Cancer Trials Ireland?

Genes included			
AKT	*ERBB2 (HER2)*	*IDH1*	*PDGFRA*
ALK	*ERBB4*	*IDH2*	*PIK3R1*
BRAF	*FGFR2*	*KIT*	*PIK3CA*
CDKN2A (p16-INK4A, p14-ARF)	*FGFR3*	*KRAS*	*PTEN*
CTNNB1 (ß-catenin)	*H3F3A (Histone H3, F3A)*	*MEK1 (MAP2K1)*	*STK11 (LKB1)*
DDR2	*HIST1H3B (Histone H1, 3B)*	*MET*	
EGFR	*HRAS*	*NRAS*	
			ALK, ROS1, RET, NTRK
			TUMOUR BRCA

What’s coming in the future?

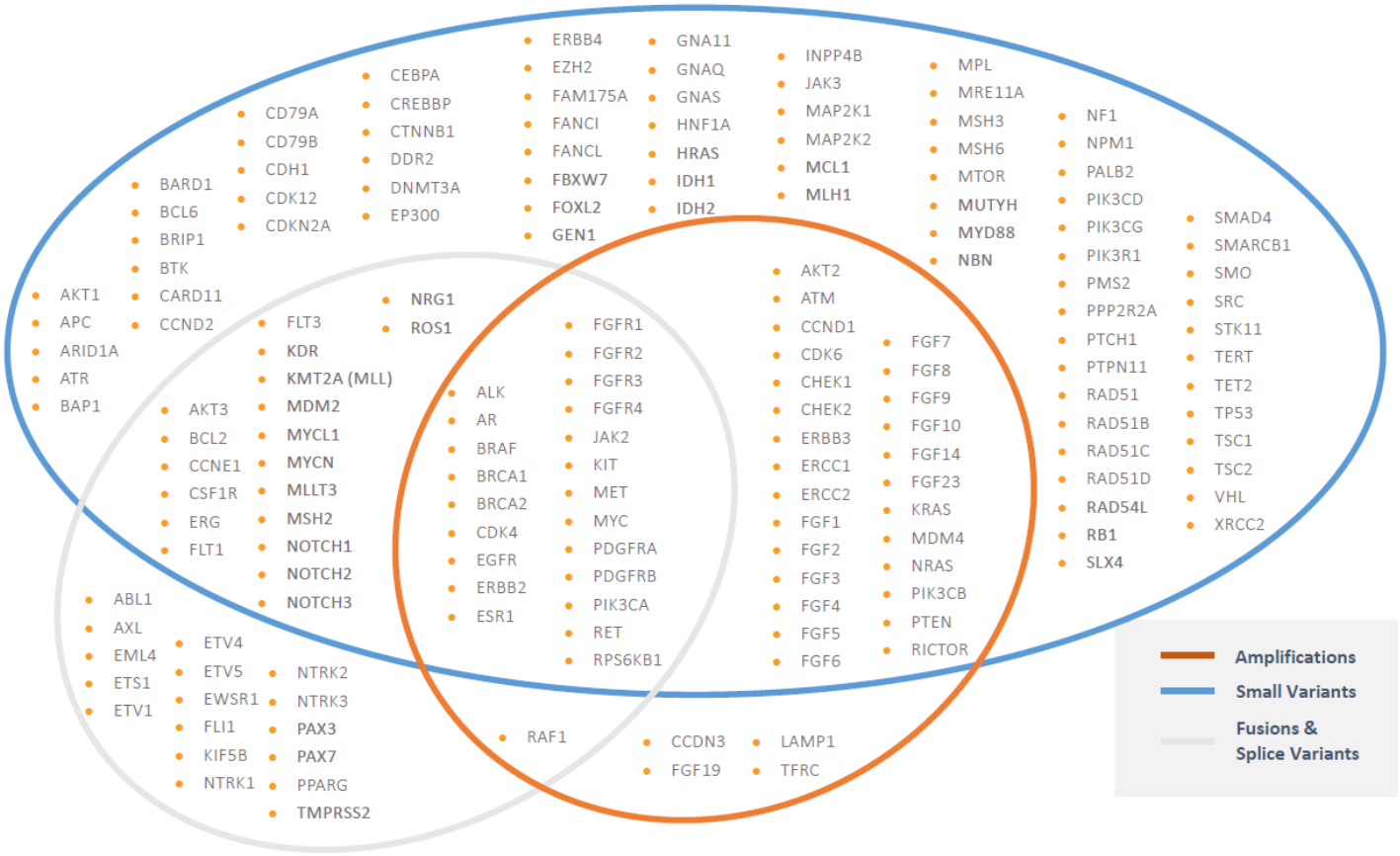
What's coming in the future?

- Liquid biopsies
- Many more biomarkers



TruSight Tumor 170

Gene List and Variant Classification



For Research Use Only. Not for use in diagnostic procedures.

What if we were to combine these two developments?

nature Accelerated Article Preview

ARTICLE
doi:10.1038/nature22364

Phylogenetic ctDNA analysis depicts early stage lung cancer evolution

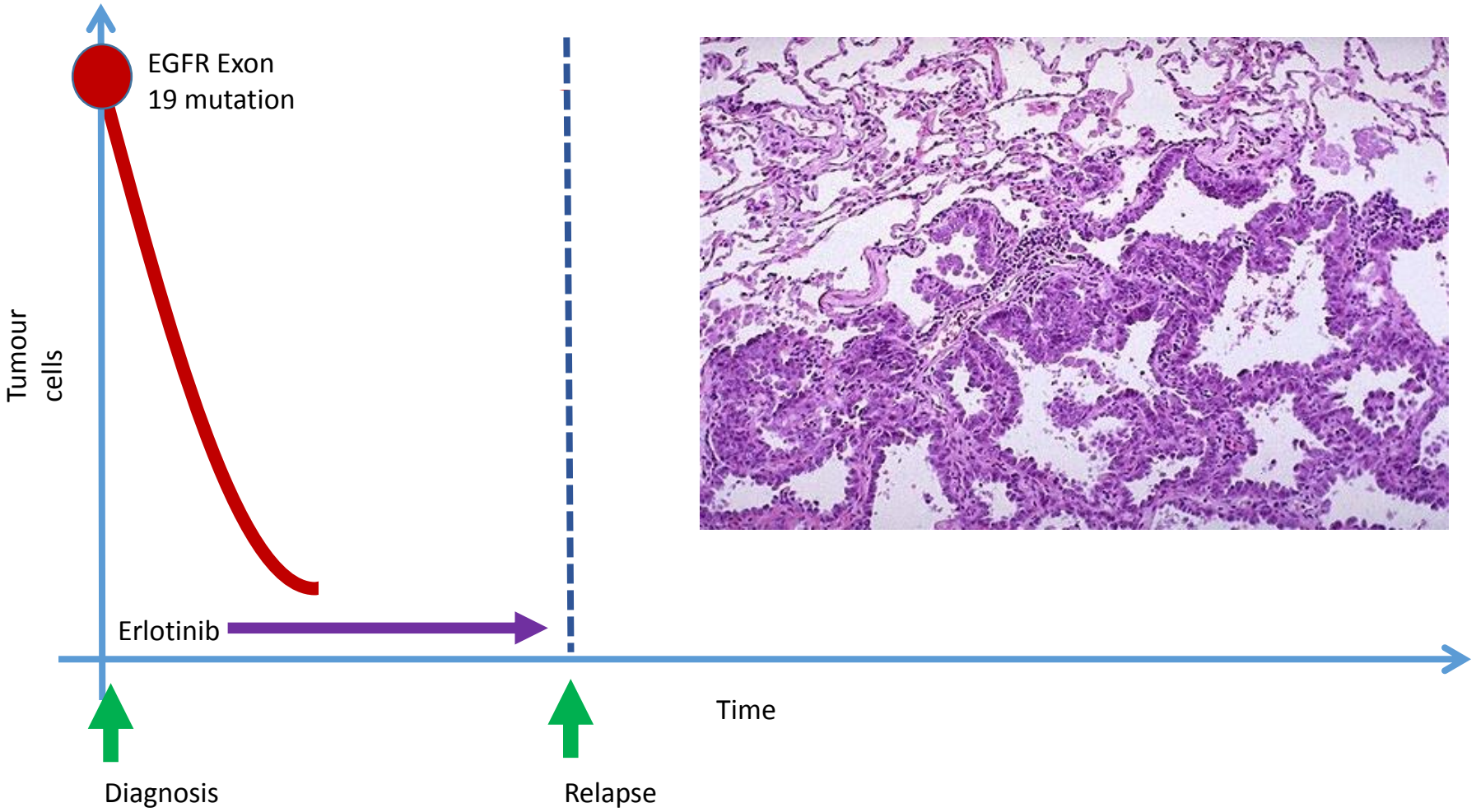
Christopher Abbosh, Nicolai J. Birkbak, Gareth A. Wilson, Mariam Jamal-Hanjani, Tudor Constantin, Raheleh Salari, John Le Quesne, David A Moore, Selvaraju Veeriah, Rachel Rosenthal, Teresa Marafioti, Eser Kirkizlar, Thomas B K Watkins, Nicholas McGranahan, Sophia Ward, Luke Martinson, Joan Riley, Francesco Fraioli, Maise Al Bakir, Eva GrÖnroos, Francisco Zambrana, Raymondo Endozo, Wenya Linda Bi, Fiona, Seema Shafi, Justyna Czyzewska-Khan, Andrew Rowan, Tim C, Siow Ming Lee, Martin D. Forster, Tanya Ahmad, Mary Falzon, E, Nikolaos Panagiotopoulos, Sam M Janes, Ricky Thakrar, Asia Ah, Ashwini Naik, Apratim Ganguly, Stephanie Kareht, Rajesh Shah, Gary Middleton, Gerald Langman, Simon Trotter, Marianne Nic, Lesley Gomersall, Dean A. Fennell, Apostolos Nakas, Sridhar Ra, Babikir Ismail, Melanie Irvin-sellers, Vineet Prakash, Jason F. L, Haydn Adams, Helen Davies, Dahmane Oukrif, Ayse U Akarca, Harriet Bell, Yenti, Ngai, Greg Elgar, Zoltan S, si-Rolar

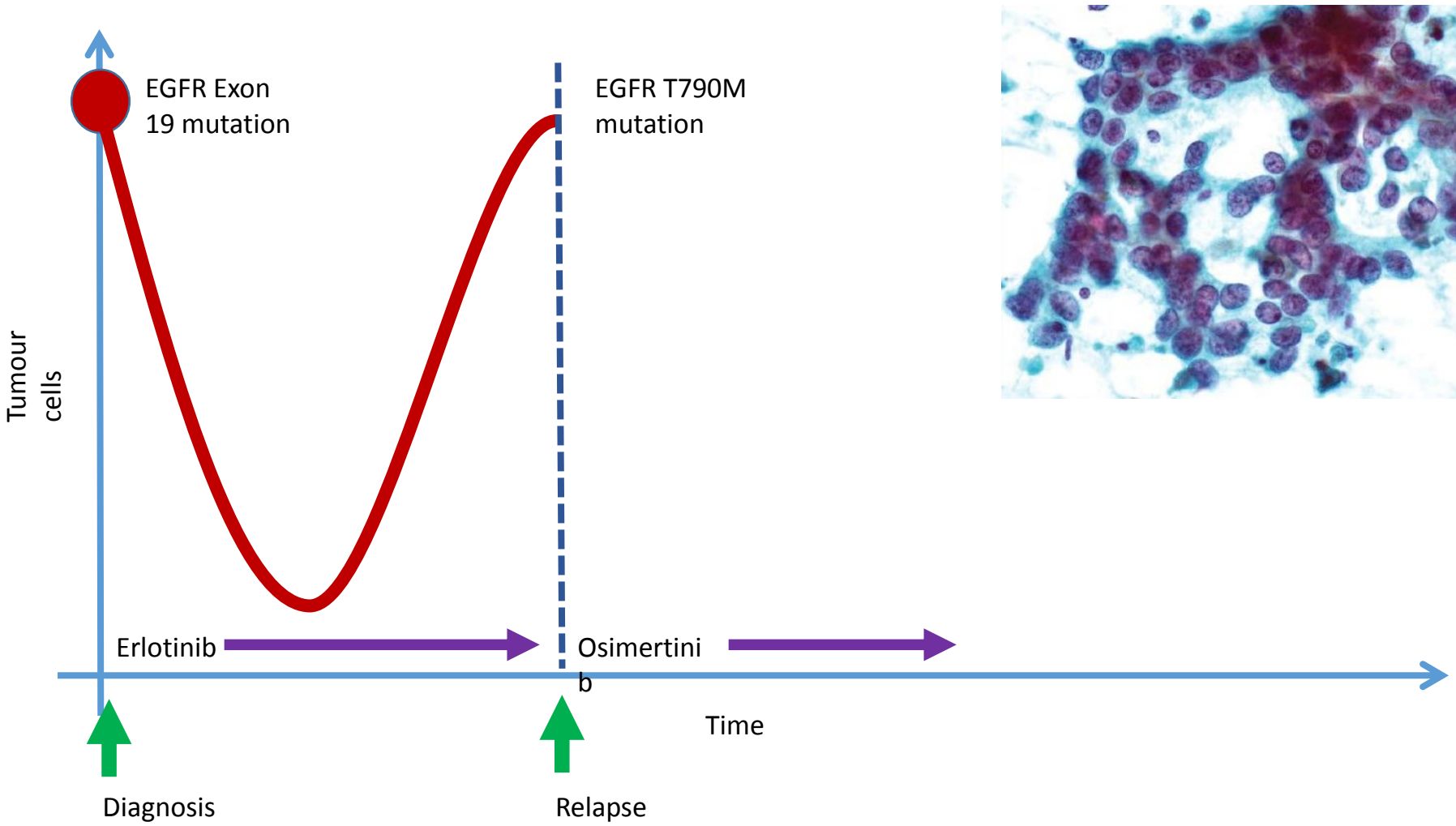
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tracking the Evolution of Non–Small-Cell Lung Cancer

M. Jamal-Hanjani, G.A. Wilson, N. McGranahan, N.J. Birkbak, T.B.K. Watkins, S. Veeriah, S. Shafi, D.H. Johnson, R. Mitter, R. Rosenthal, M. Salm, S. Horswell, M. Escudero, N. Matthews, A. Rowan, T. Chambers, D.A. Moore, S. Turajlic, H. Xu, S.-M. Lee, M.D. Forster, T. Ahmad, C.T. Hiley, C. Abbosh, M. Falzon, E. Borg, T. Marafioti, D. Lawrence, M. Hayward, S. Kolvekar, N. Panagiotopoulos, S.M. Janes, R. Thakrar, A. Ahmed, F. Blackhall, Y. Summers, R. Shah, L. Joseph, A.M. Quinn, P.A. Crosbie, B. Naidu, G. Middleton, G. Langman, S. Trotter, M. Nicolson, H. Remmen, K. Kerr, M. Chetty, L. Gomersall, D.A. Fennell, A. Nakas, S. Rathinam,


EGFR Exon
19 mutation
Tumour
cells
Erlotinib
Time
Diagnosis
Relapse


EGFR Exon
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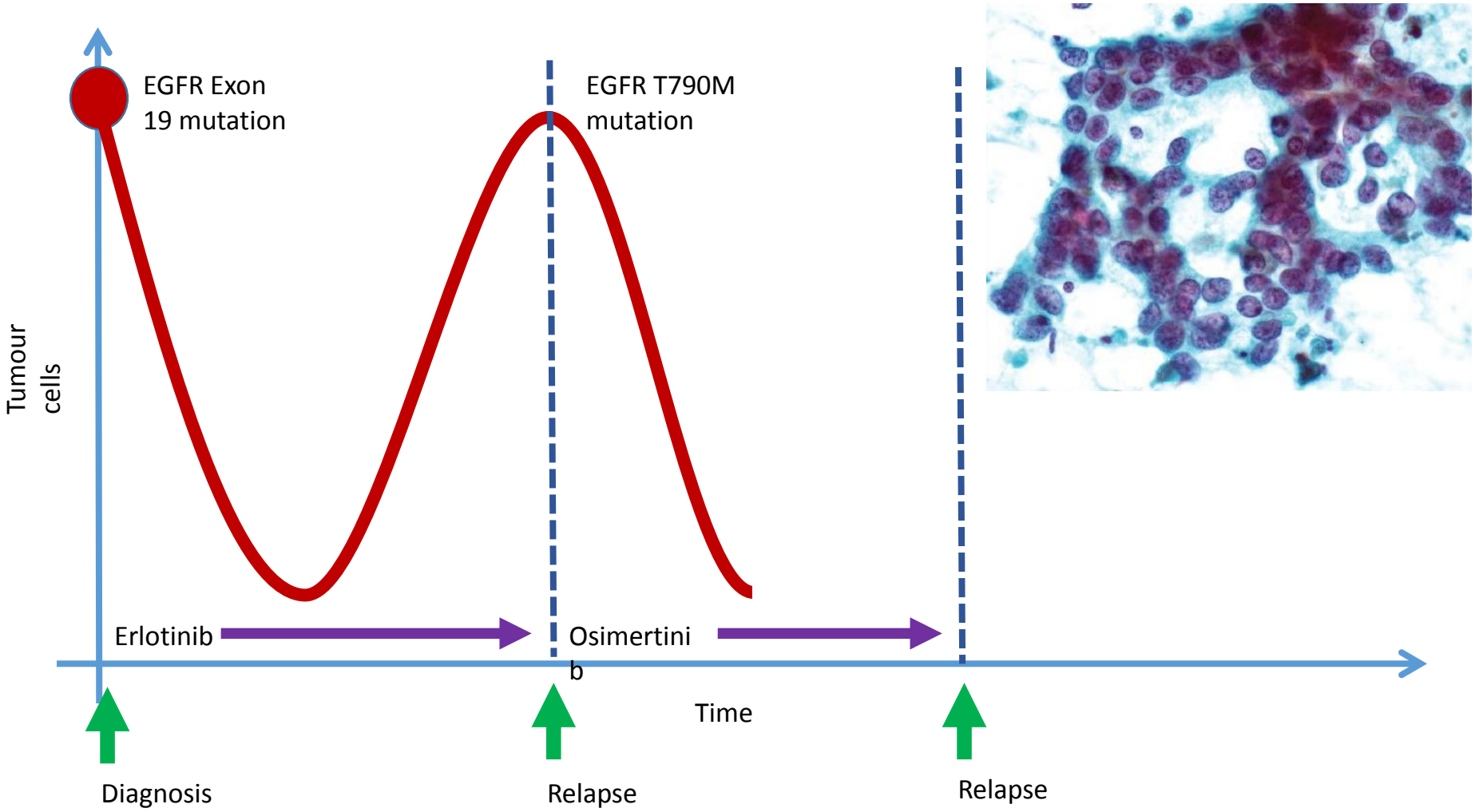
EGFR T790M
mutation
Tumour
cells
Erlotinib
Osimertini
b
Time
Diagnosis
Relapse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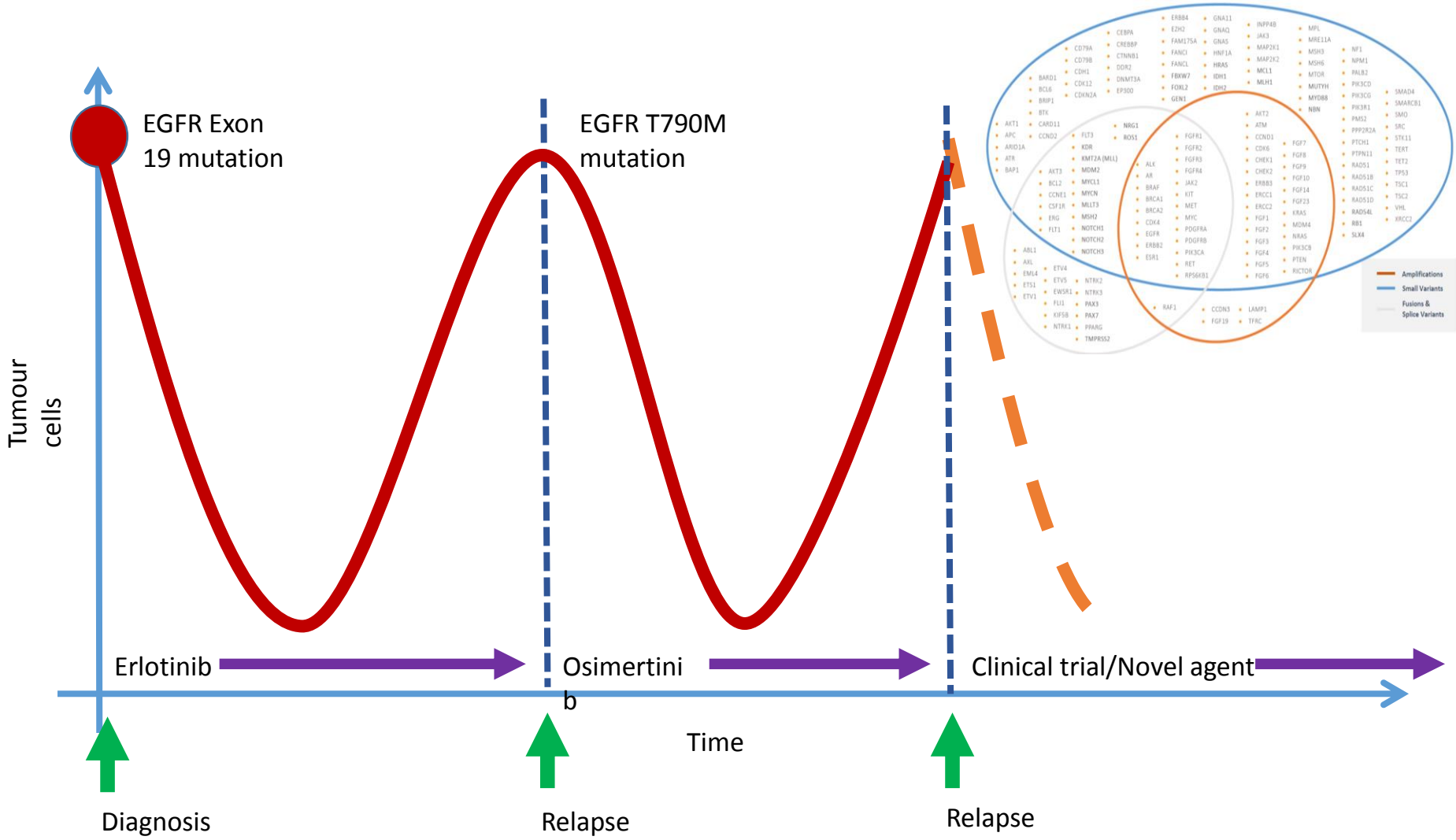
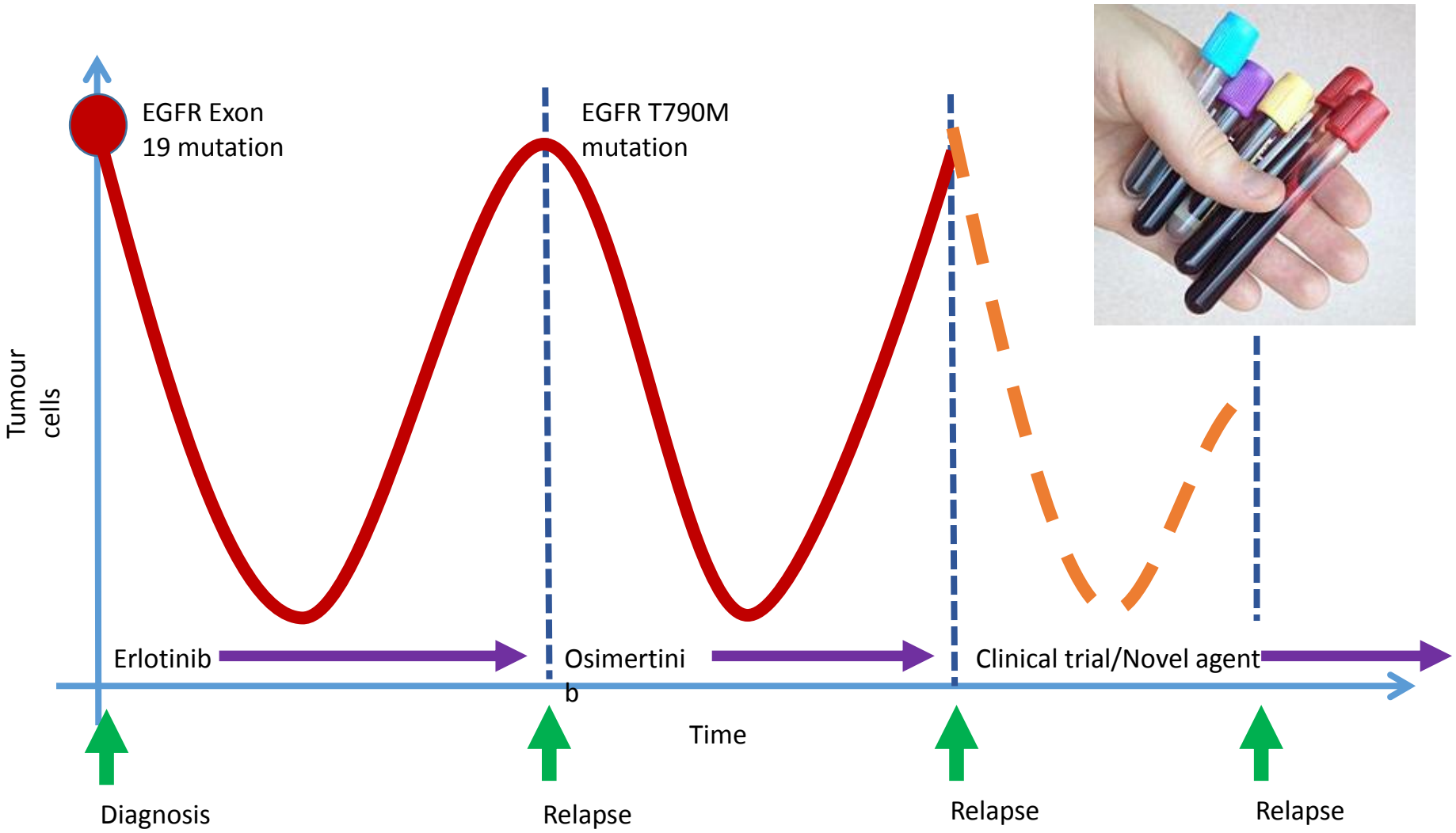

EGFR Exon 19 mutation
EGFR T790M mutation
Tumour cells
Erlotinib
Osimertinib
Clinical trial/Novel agent
Time
Diagnosis
Relapse
Relapse
Amplifications
Small Variants
Fusions & Splice Variants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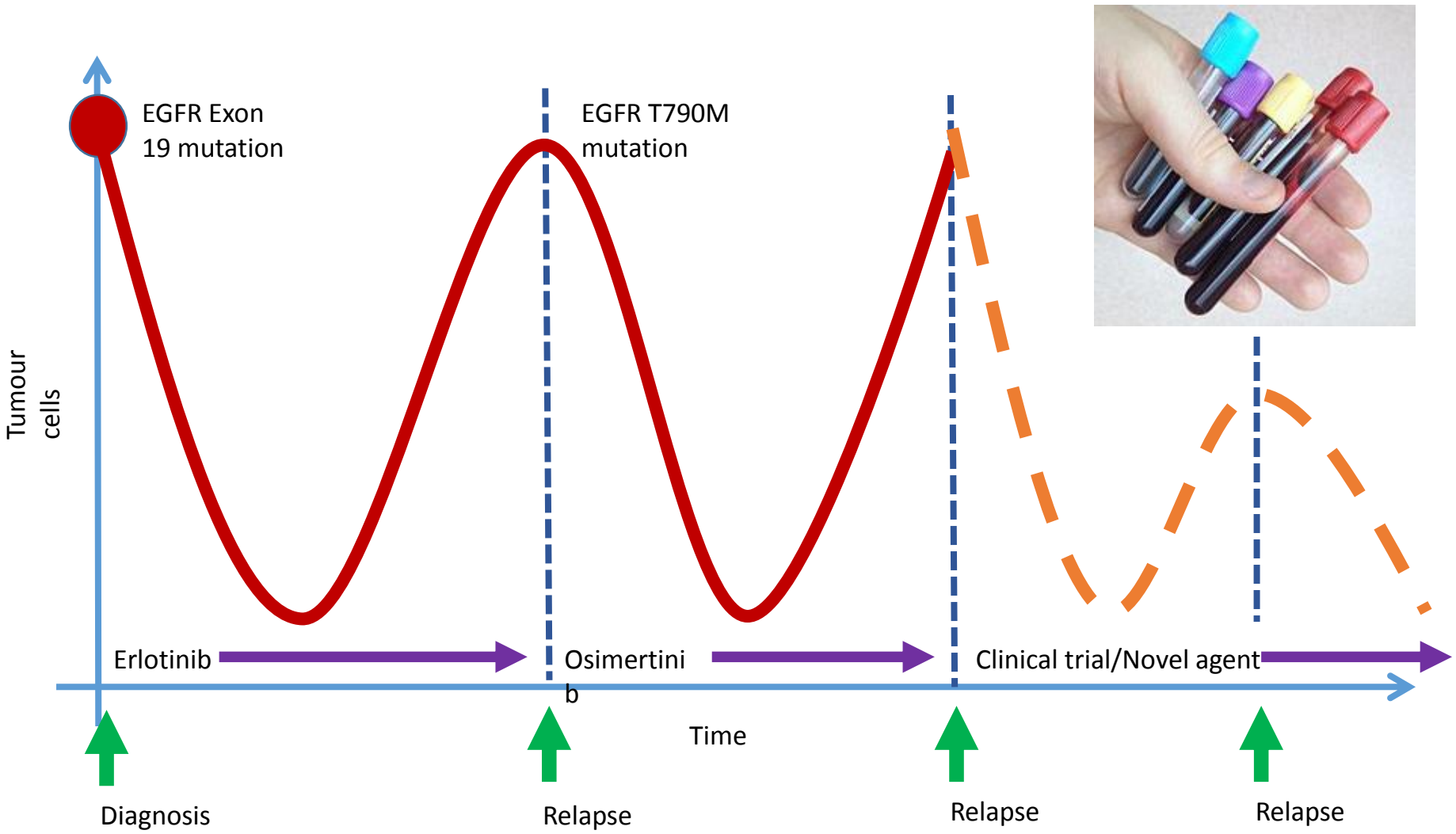
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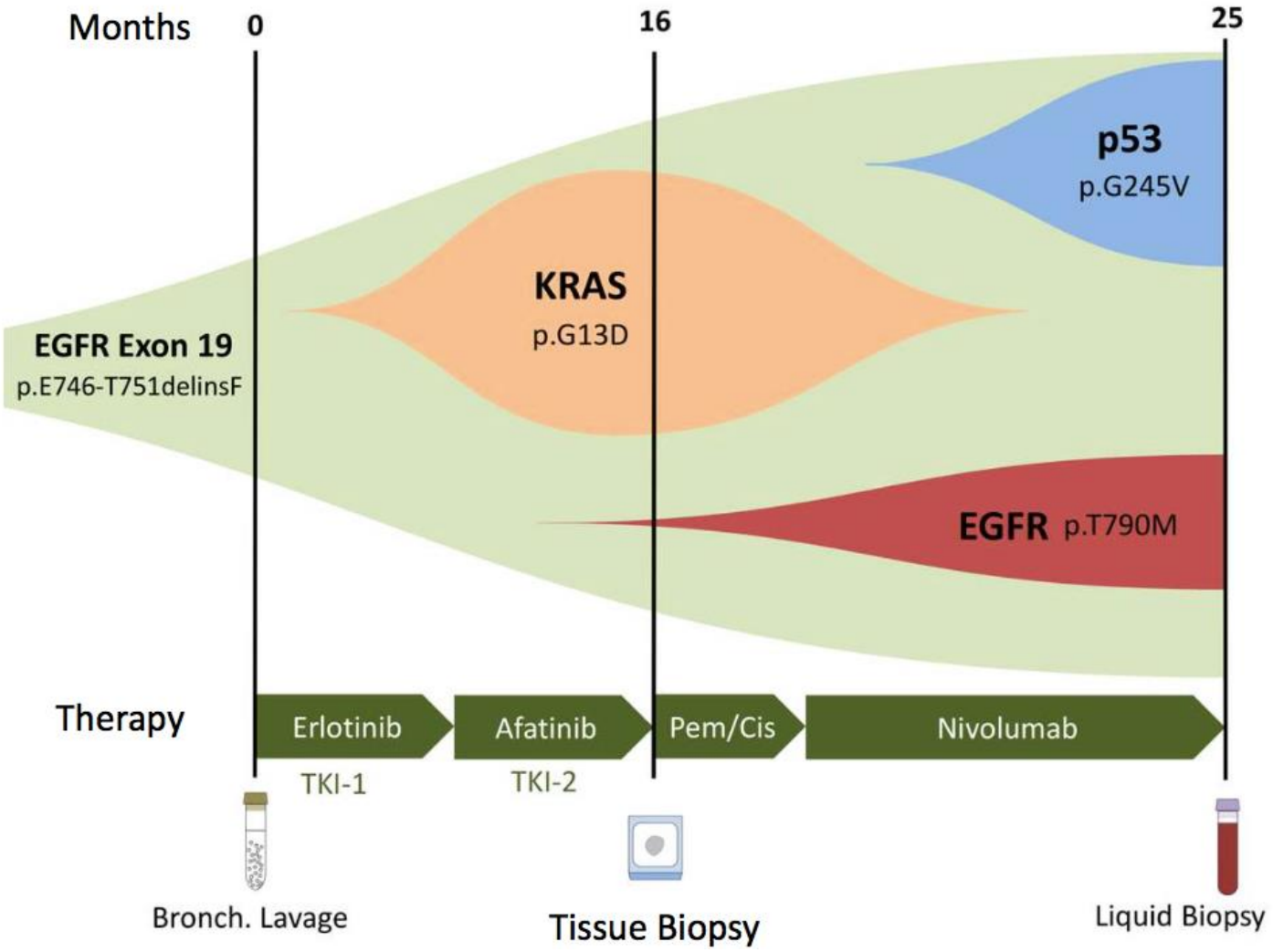

Months
0
16
25
p53
p.G245V
KRAS
p.G13D
EGFR Exon 19
p.E746-T751delinsF
EGFR p.T790M
Therapy
Erlotinib
Afatinib
Pem/Cis
Nivolumab
TKI-1
TKI-2
Bronch. Lavage
Tissue Biopsy
Liquid Biopsy

Summary

- Role of Pathology in cancer care
- Molecular Pathology and Personalised Medicine
- Potential for a paradigm shift in the way we think about cancer

Acknowledgments

- Elaine Kay
- Tony O’Grady
- Patrick Buckley
- Robert Cummins
- Etain Daly
- Teresa Loftus
- Julie Moran
- Carl O’Regan
- Sarah Curry

RCSI HOSPITALS
OSPIDÉIL RCSI

Thank you

The Add Aspirin Basket Study

Professor Ruth Langley,
MRC Programme Leader & Chair of the Cancer Group,
Medical Research Council Clinical Trials Unit,
University College London

ADD-ASPIRIN

MRC Clinical Trials Unit

Smarter studies
Global impact
Better health

UCL

TATA MEMORIAL CENTRE

Aspirin and Cancer

Ruth Langley

Introduction

- Brief overview of the use of aspirin for the primary prevention of cancer
- Evidence supporting the use of aspirin as a possible treatment for cancer
- Add-Aspirin trial and other relevant studies

Early Data – Inhibition of Metastases

Fibrosarcoma cells injected into tail vein of mice (group 1-4) and a hindleg innoculation (group 5-6). Aspirin (ASA) 2.5 mg per 4 ml drinking water

Group	Treatment	Tumour	lung metastases* mean ± se	p
1	Control	MCA2	245 ± 13	
2	ASA, 6 days	MCA2	143 ± 12	<0.01
3	Control	T241	24 ± 3	
4	ASA, 13 days	T241	17 ± 3	<0.2
5	Control	T241	24 ± 5	
6	ASA, 13 days	T241	9 ± 2	<0.01

Gasic *et al.* Lancet 1972, 2(7783):932-3

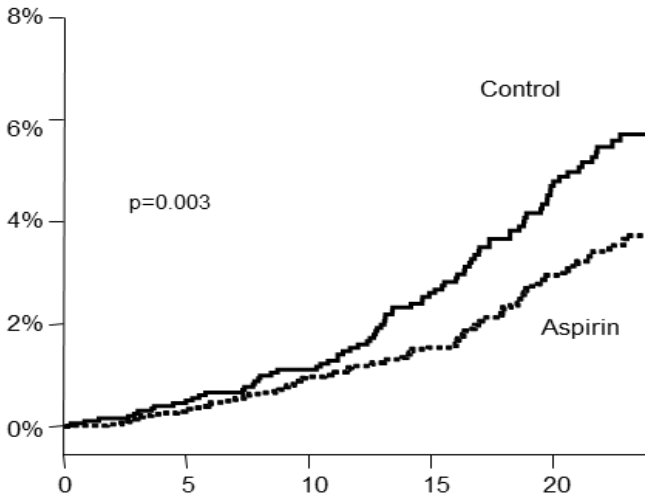
Epidemiological Studies: Primary Prevention

Cancer/Study	No of Studies	No of Cases	RR (95% CI)
Colorectal Cancer			
Case-control	15	21,414	0.63 (0.56-0.70)
Cohort	15	16,105	0.82 (0.75-0.89)
Overall	30	37,519	**0.73 (0.67-0.79)**
Gastric Cancer			
Case-control	7	2411	0.60 (0.44-0.82)
Cohort	6	2108	0.77 (0.58-1.04)
Overall	13	4519	**0.67 (0.54-0.83)**
Breast Cancer			
Case-control	10	28.835	0.83 (0.76-0.91)
Cohort	22	27,091	0.93 (0.87-1.00)
Overall	32	52,926	**0.90 (0.85-0.95)**
Prostate Cancer			
Case-control	9	5795	0.87 (0.74-1.02)
Cohort	15	31,657	0.91 (0.85-0.97)
Overall	24	37,452	**0.90 (0.85- 0.96)**

Bosetti *et al.* Annals of Oncology 2012

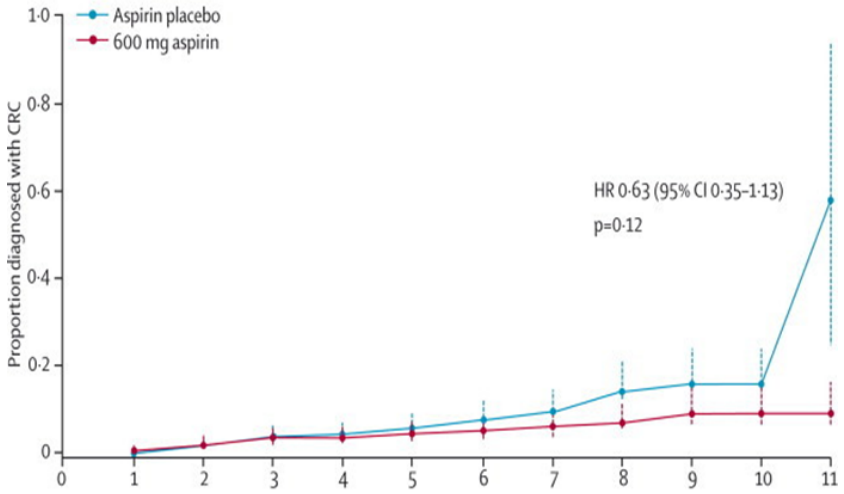
Effect of aspirin on risk of colorectal cancer

BDAT & UK-TIA



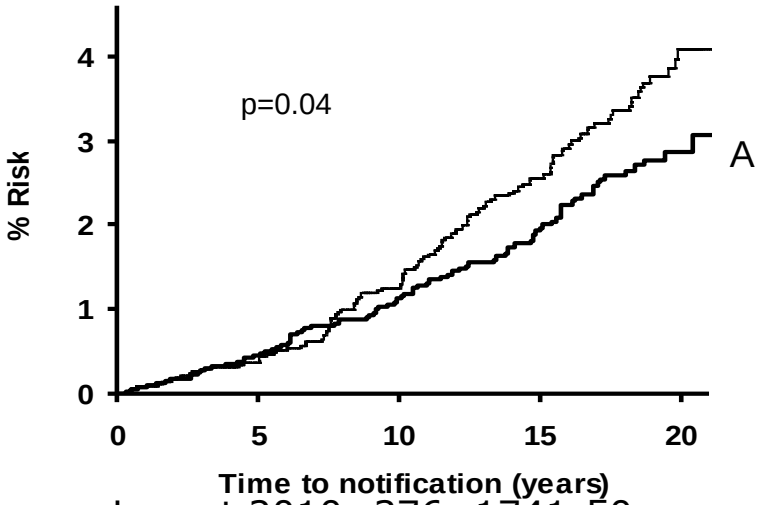
Lancet 2007; 369:1603-13

CAPP2



Lancet 2011; 378:2081-2087

TPT & SALT



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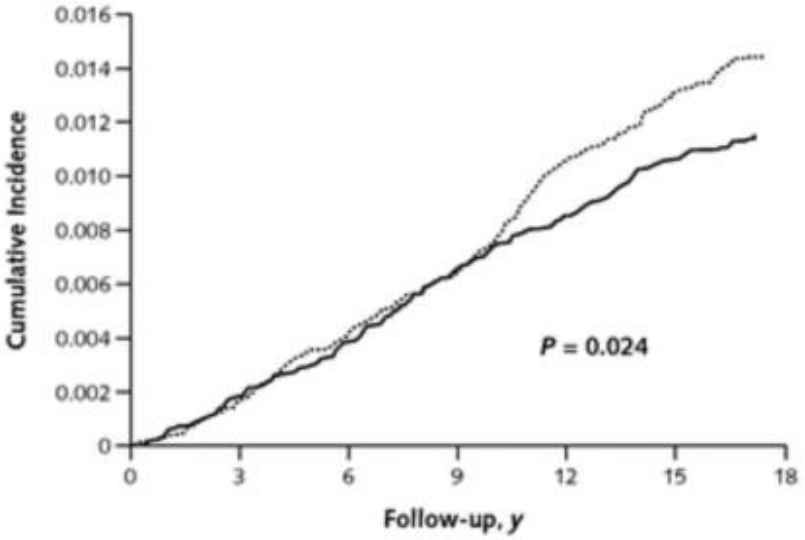
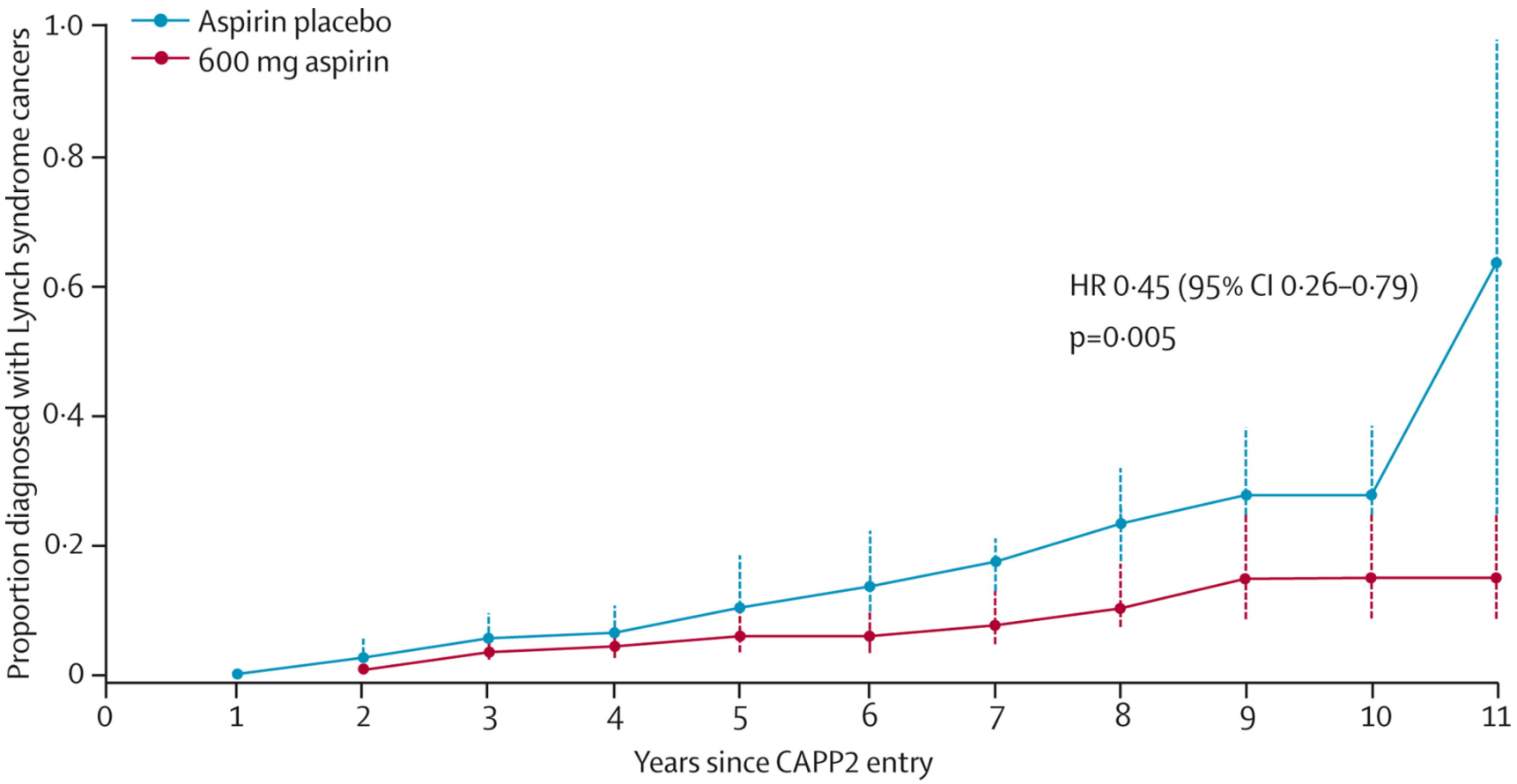
Lancet 2010; 376: 1741-50

WHS



Ann Intern Med 2013

CAPP-2 -Time to 1st Lynch syndrome cancer in participants assigned to aspirin vs placebo

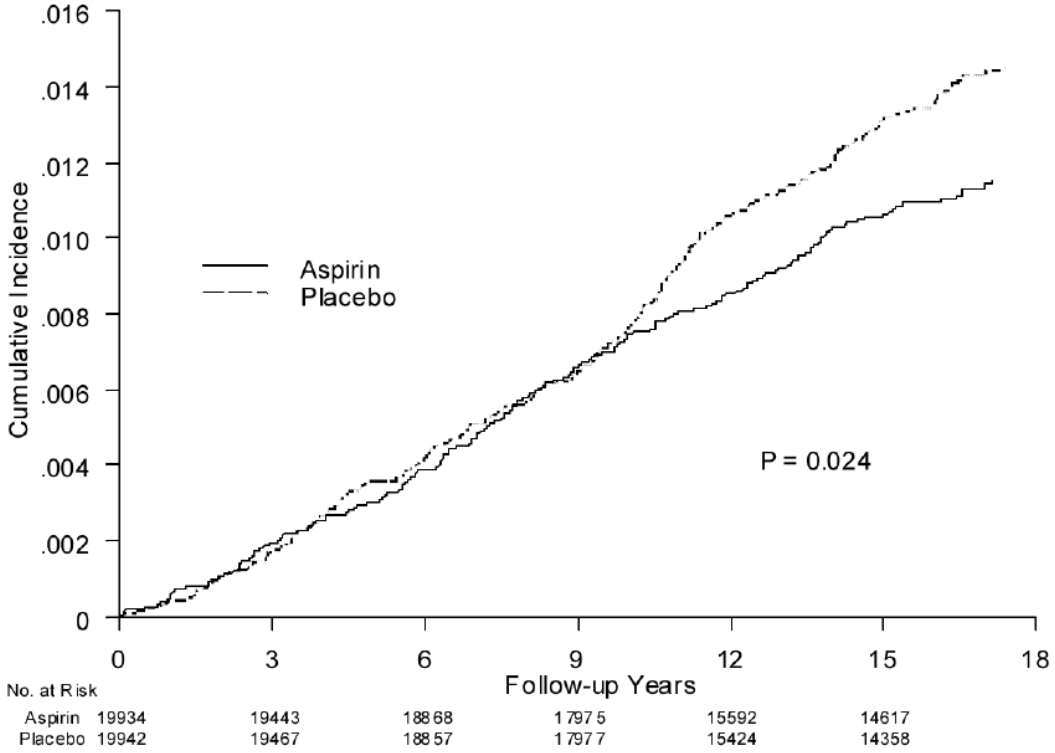


restricted to participants who had taken the intervention for ≥ 2 years

Burn et al, Lancet 2011

Women's Health Study: Incidence of Colorectal Cancer

- 40,000 US female health professionals
- Randomised 1:1 to receive 100mg aspirin or placebo every other day
- Collected information on diagnosis of various cancers, including colorectal



Cook et al. 2013

Serious Haemorrhage

- Aspirin increases bleeding risk, however this increase is small

Bleeding site	Estimated risk* in control group	Estimated risk* on aspirin
Serious bleeding** gastrointestinal or other extracranial site	0.07% per year	0.1% per year
Intracranial bleed	0.03% per year	0.04% per year

*Based on the Antithrombotic Trialists Collaboration (ATTC) meta-analysis of 6 primary prevention studies ~95,000 participants, (mean age 56 years, 46% men) published 2009

**Serious bleeding is defined as requiring a hospital admission or blood transfusion

US preventative recommendations on primary prevention

Population	Recommendation	Grade
Adults 50 to 59 with a ≥10% 10-year CVD risk	Low-dose aspirin recommended for prevention of cardiovascular disease and colorectal cancer (provided no risk of bleeding)	Recommendation with moderate certainty
Adults 60 to 69 with a ≥10% 10-year CVD risk	Benefits vs. harms of low-dose aspirin should be considered on a case-by-case basis.	Selective recommendation: physician judgement / patient preference
Adults <50	Insufficient evidence to recommend aspirin use	Insufficient evidence
Adults ≥70	Insufficient evidence to recommend aspirin use	Insufficient evidence

Usual drug development pathway

Promising pre-clinical data - aspirin √

Phase I	First human use/MTD	- aspirin √
Phase II	Initial activity – dose and efficacy Advanced disease, small, non-randomised, response rate (tumour shrinkage)	- aspirin X
Phase III	Comparison with standard therapy Start with metastatic disease	- aspirin X

Issues not unique to aspirin – Cox-2 inhibitors, statins, metformin – rethink approach to testing other potential anti-cancer drugs

Vascular trials

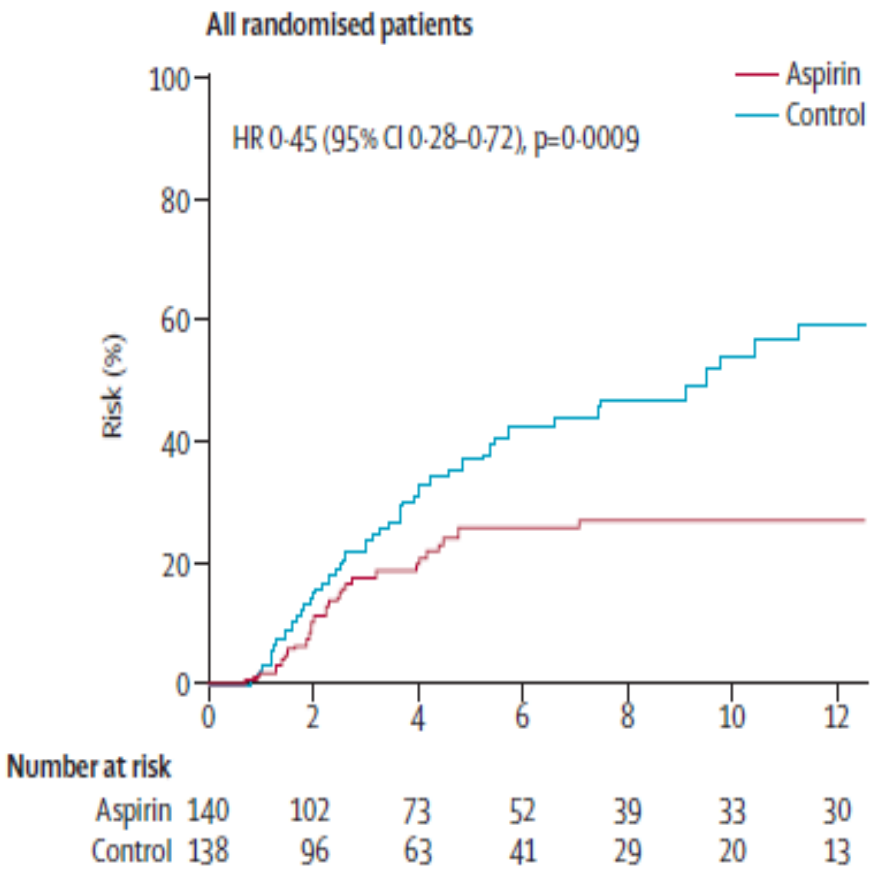
- A major part of the evidence base relating to the anti-cancer effects of aspirin has emerged from RCT's primarily designed to evaluate the vascular effect of aspirin. *(Rothwell, Lancet 2010, 2011, 2012)*

- 51 randomised trials, aspirin vs no aspirin or other anti-platelet drug ~77,000 participants

- Decreased incidence cancer HR 0.81 (0.7-0.93) Rx > 5yrs and reduced cancer deaths by ~ 15% with effects seen across tumour types – gastrointestinal tract, breast, prostate and lung (particularly adenocarcinomas)

- Potentially most relevant to the treatment of cancer was the observation that within a few years of allocation to aspirin beneficial effects on cancer outcomes were seen

Prevention of metastasis

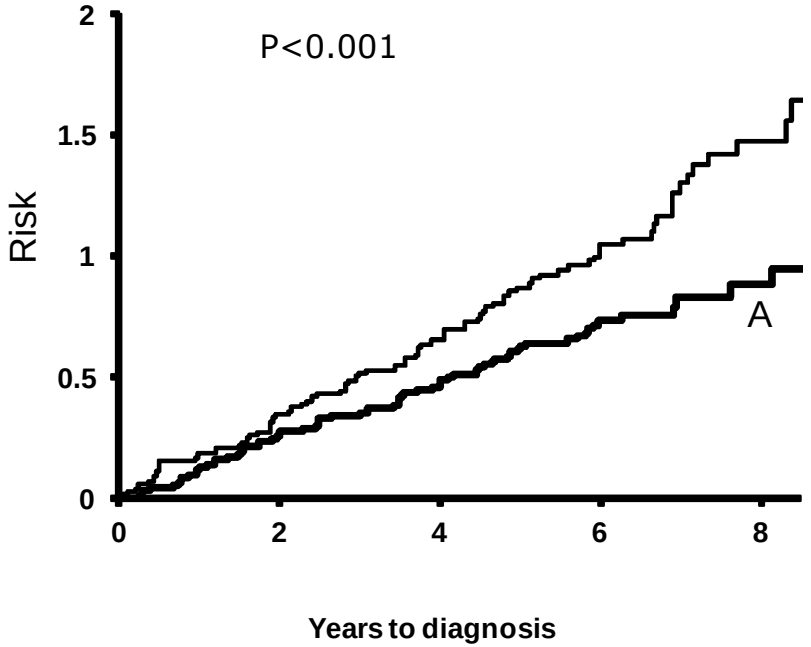


- Risk of developing metastasis (not present at dx). 5 randomised studies (~ 17,000 participants). Effect > if on aspirin at time of dx.
- Effects seen across tumour types particularly adenocarcinomas, and across sites of metastasis (lung, liver, brain)

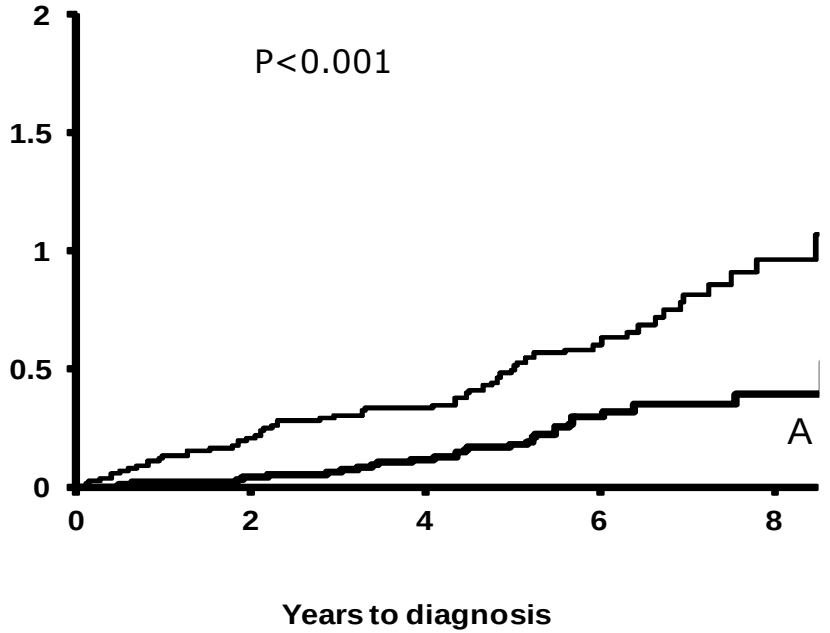
Rothwell et al. 2012

Effect of aspirin on risk of cancer with distant metastasis: 5 large UK aspirin trials

Cancer with metastasis at presentation

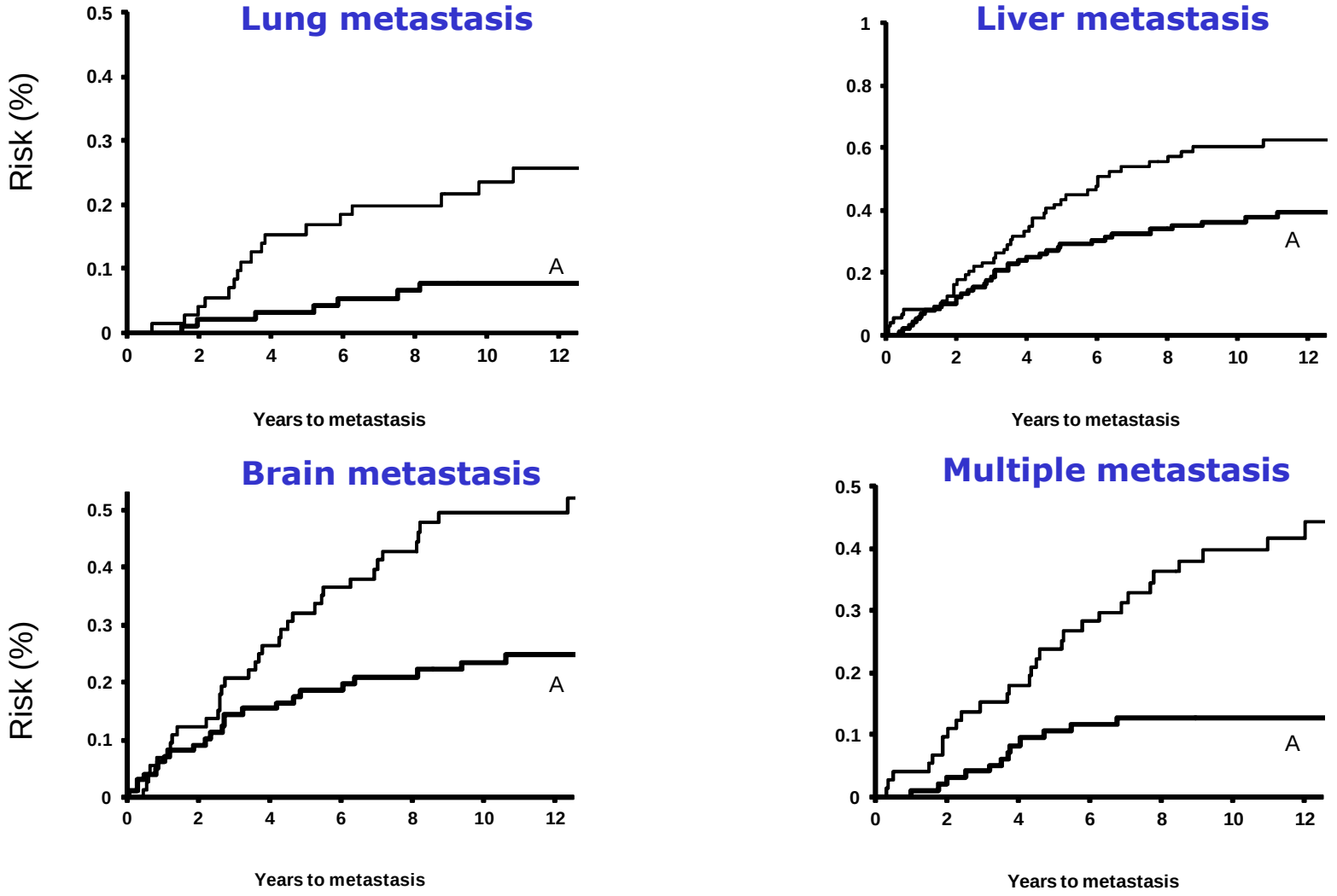


Cancer with no metastasis at presentation in which metastasis developed on follow-up



Lancet 2012; 379:1591-601

Effect of aspirin on risk of distant metastasis: time from randomisation to presentation of metastasis



Lancet 2012; 379:1591-601

Short-term effect of daily aspirin versus control on cancer deaths during 51 eligible trials

Years to death	Number of deaths: Aspirin	Control	Odds ratio (95%CI)	P
Cancer death only[1]				
0-2.99	292	325	0.90 (0.76-1.06)	0.18
3-4.99	161	173	0.93 (0.75-1.16)	0.51
≥5	92	145	0.63 (0.49-0.82)	0.0005
Unknown	17	21		
Total	562	664	0.85 (0.76-0.96)	0.008
Cancer death or non-vascular deaths if cancer data were unavailable[2]				
0-2.99	322	364	0.88 (0.76-1.03)	0.10
3-4.99	161	173	0.93 (0.75-1.16)	0.51
≥5	92	145	0.63 (0.49-0.82)	0.0005
Unknown	39	46		
Total	614	728	0.85 (0.76-0.95)	0.005

1. Cancer deaths available from 34 trials of aspirin versus control (n=69,224)
2. Cancer deaths unavailable from 17 smaller trials (n=8325) so non-vascular deaths were therefore added to cancer deaths

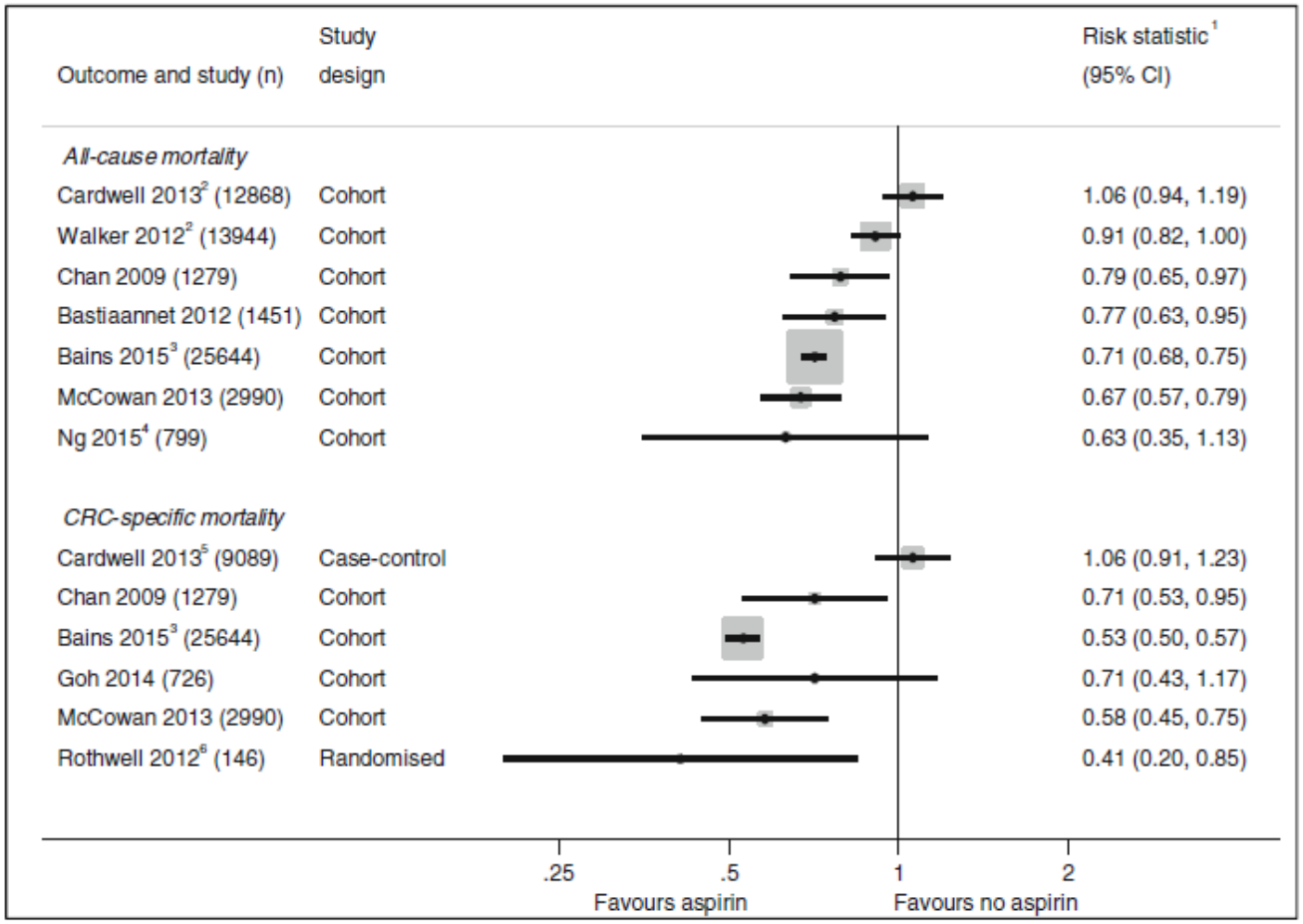
Rothwell Lancet 2012 ;379:1602-12

Effects of aspirin use after colorectal cancer diagnosis

Study (n)	Cohort	Aspirin exposure	Risk reduction with aspirin* (95% CI)
Chan 2009 (n=1279)	Population (NHS and HPFS, stage I-III CRC)	Regular aspirin use after diagnosis (self-report)	CRC mortality HR=0.71 (0.53-0.95) All-cause mortality HR=0.79 (0.65-0.97)
Walker 2012 (n=13,944)	Population (UK GPRD)	≥2 prescriptions in year after diagnosis	All-cause mortality HR=0.91 (0.82, 1.00)
Bastiaannet 2012 (n=4481)	Population (Eindhoven registry)	Prescription for >14 days after diagnosis (prescription data)	Survival risk ratio (RR)=0.77 (0.63-0.95)
McCowan 2013 (n=2990)	Population (Tayside registry data)	Prescription after diagnosis	CRC mortality HR=0.67 (0.57-0.79) All-cause mortality RR=0.58 (0.45-0.75)
Ng 2015 (n=799)	Clinical trial cohort (CALGB 89803, stage III colon cancer)	Consistent use midway through and 6 months after chemo (trial data)	Disease-free survival HR=0.68 (0.42, 1.11) Overall survival HR=0.63 (0.35, 1.12)
Bains 2015** (n=25644)	Population (Norwegian registry data)	Prescription for ≥6 months after diagnosis	CRC-specific survival HR=0.53 (0.50, 0.57) Overall survival HR=0.71 (0.68, 0.75)

* Multivariate estimates (adjusted for other factors) are presented where available; ** Results only available in abstract form
CRC = Colorectal cancer; HR = Hazard ratio; NHS = Nurses' Health Study; HPFS = Health Professionals Follow-up Study; GPRD = General Practice Research Database

Aspirin use after colorectal cancer diagnosis



Coyle *et al,* 2016

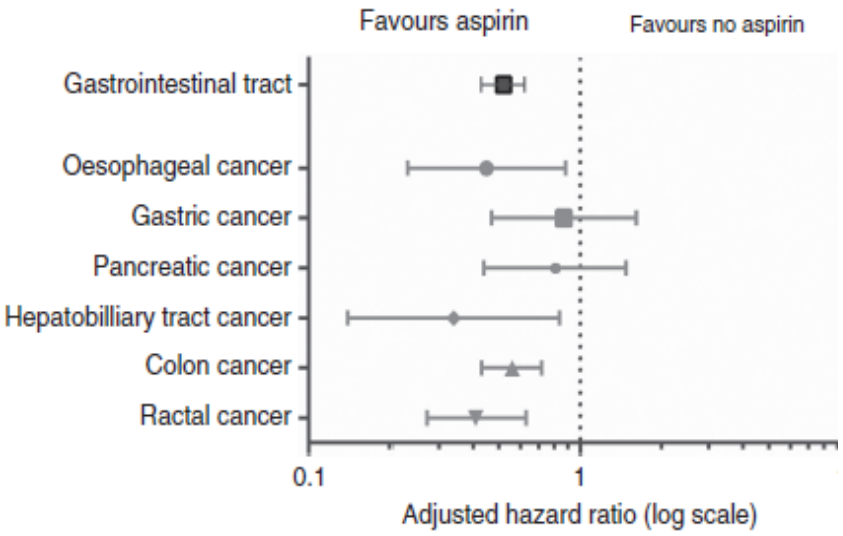
Adjuvant setting: non-randomised data for the use of aspirin

Tumour	Study/Year	Result (in favour of aspirin)
Breast	Holmes 2010	BC mortality: RR=0.36 (0.24 – 0.65) Overall Survival: RR=0.54 (0.41 - 0.70)
	Fraser 2014	All-cause mortality: HR=0.53 (0.45 – 0.63) BC mortality: HR=0.42 (0.31 – 0.55)
Gastro-oesophageal	Liu 2009	5 year Overall Survival Aspirin 51.2%, placebo 41%, no tablet 42.3%
	Staalduinen 2016	OS adjusted RR=0.42 (0.30-0.57)
Prostate	Zaorsky 2012	Reduced interval to biochemical failure Aspirin non-use OR=2.05 (1.33 – 3.17)
	Choe 2012	PC mortality: HR=0.43 (0.21 – 0.87)
	Jacobs 2014	PC mortality: HR=0.60 (0.37 – 0.97)

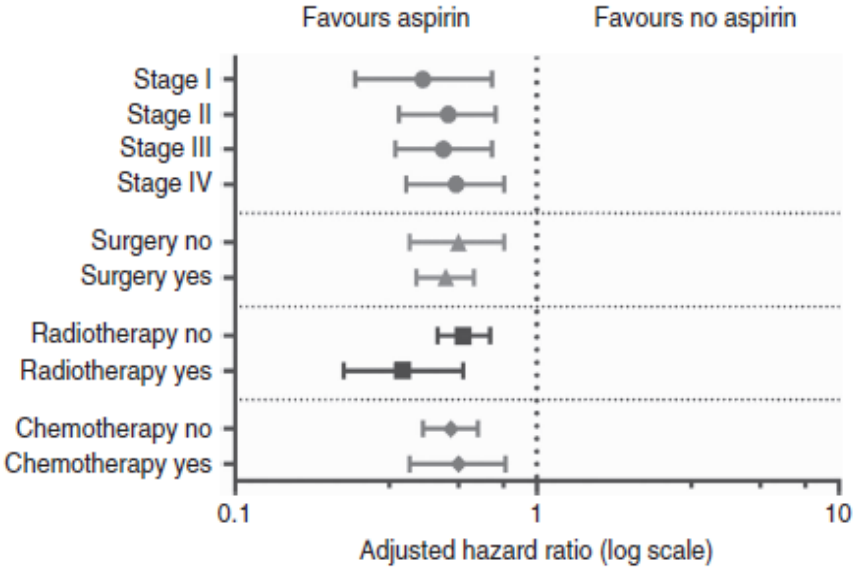
Eindhoven Cancer Registry data

- Included 13,715 patients with gastrointestinal cancers
- 1,008 (7%) were aspirin users (prescribed for >30 days)
- Overall Survival adjusted HR=0.52 (0.44 – 0.63)

Overall survival by tumour type

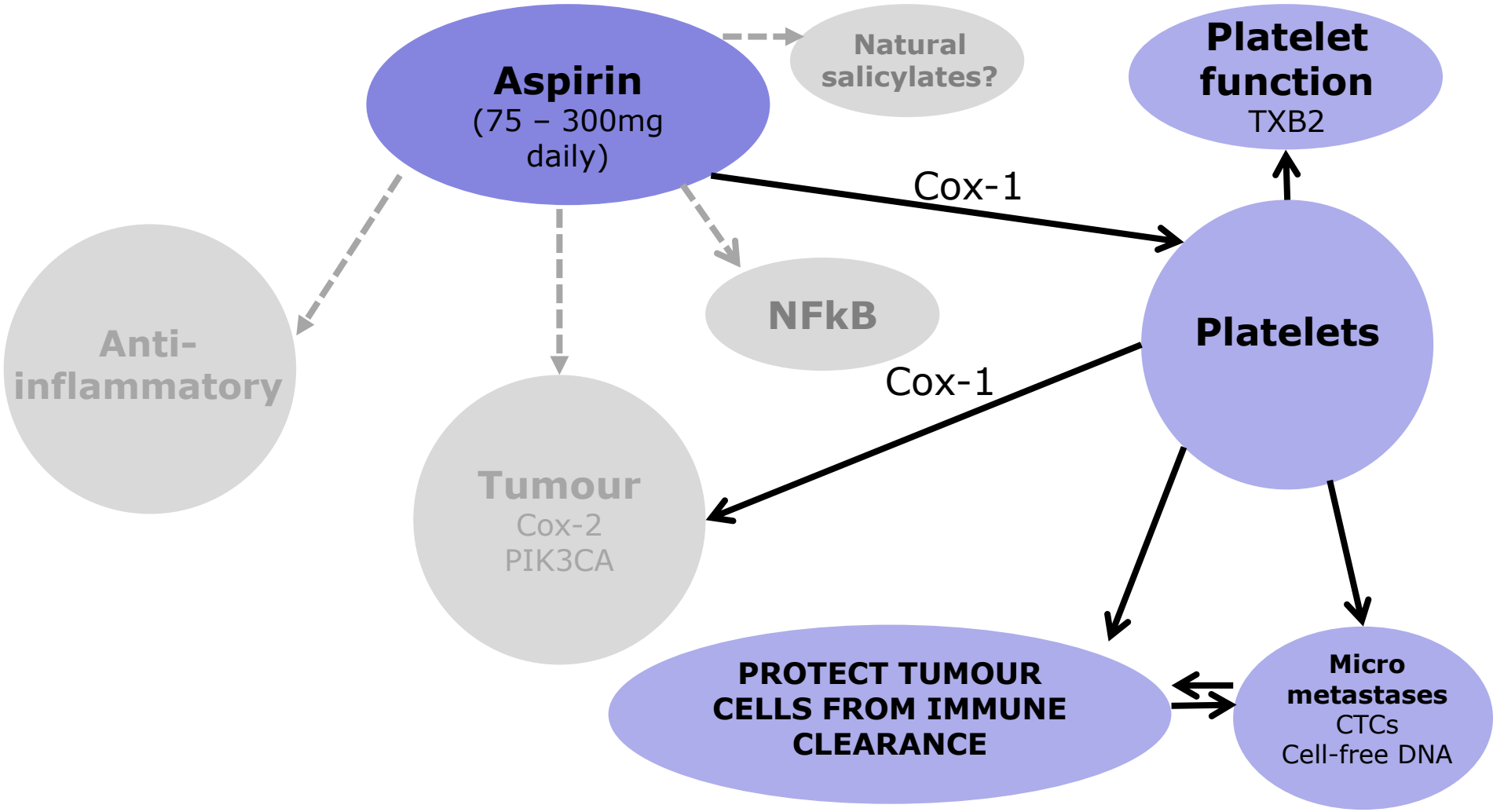


Overall survival by stage and treatment

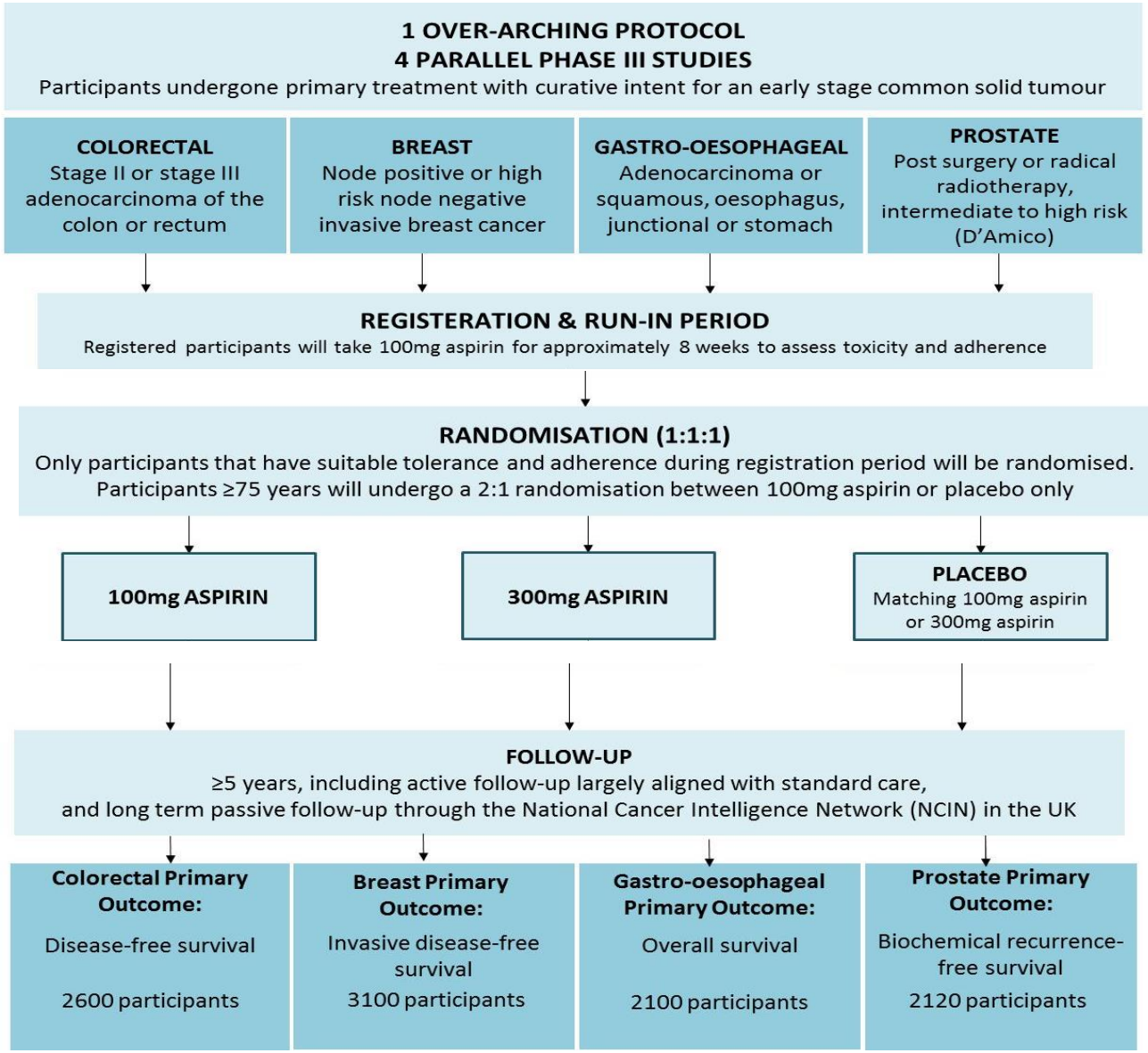


Frouws et al, 2017; BJC

Aspirin Anti-Cancer Mechanisms of Action

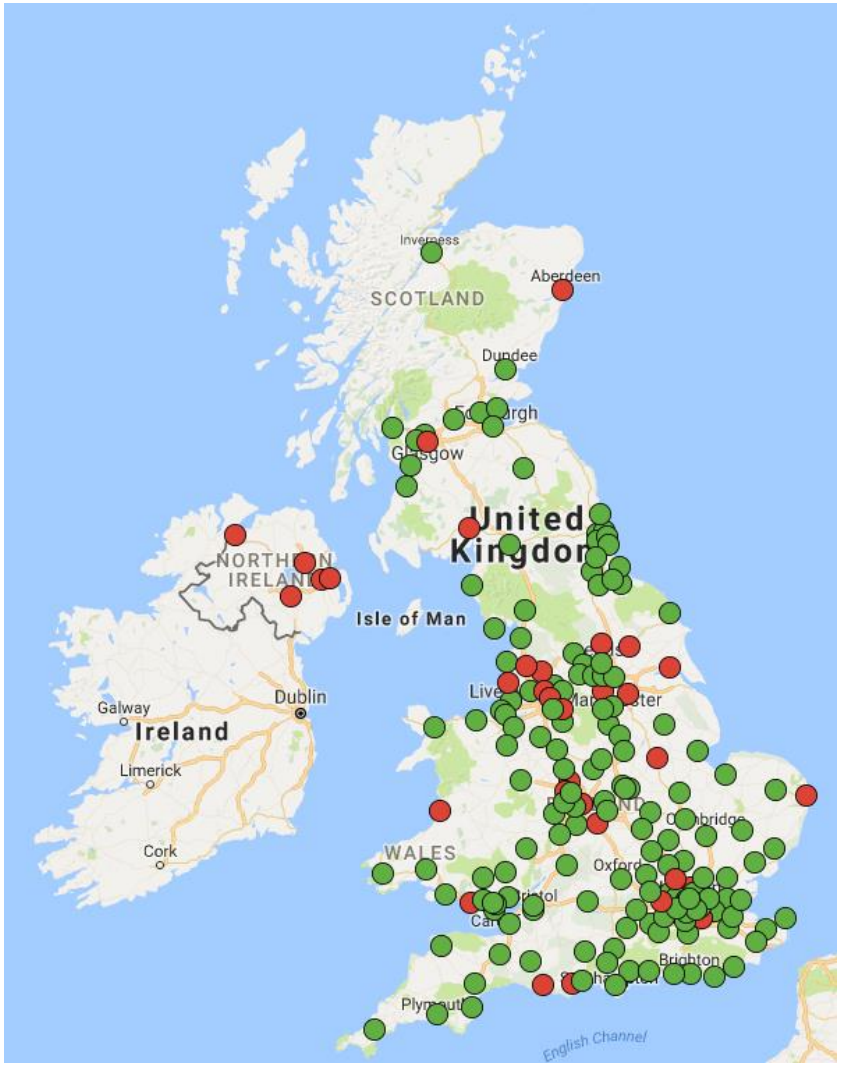


Trial design of Add-Aspirin



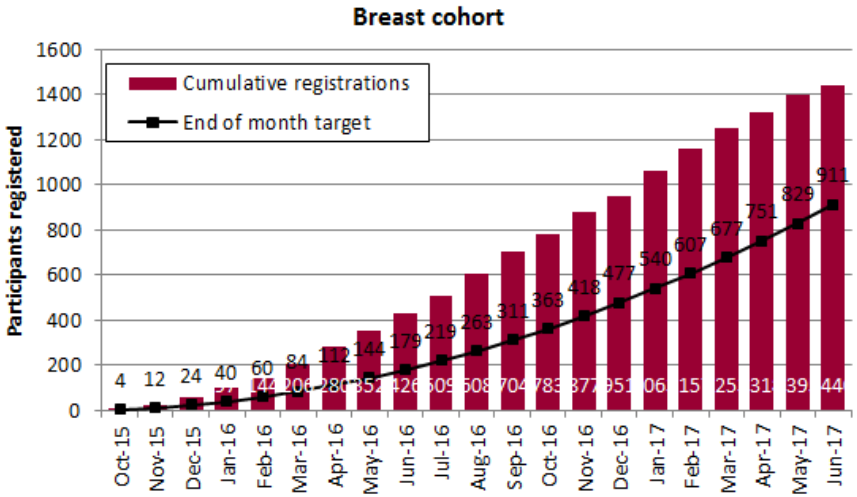
Trial Update

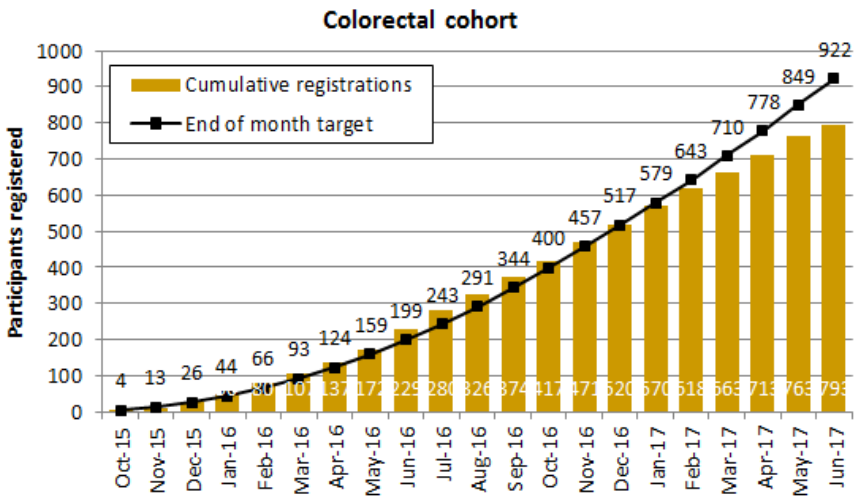
- Add-Aspirin opened to recruitment in October 2015
- It is planned to open across all CRNs
- To date (20/06/2017):
  - 162 sites are open across all cohorts
  - 2945 patients recruited overall

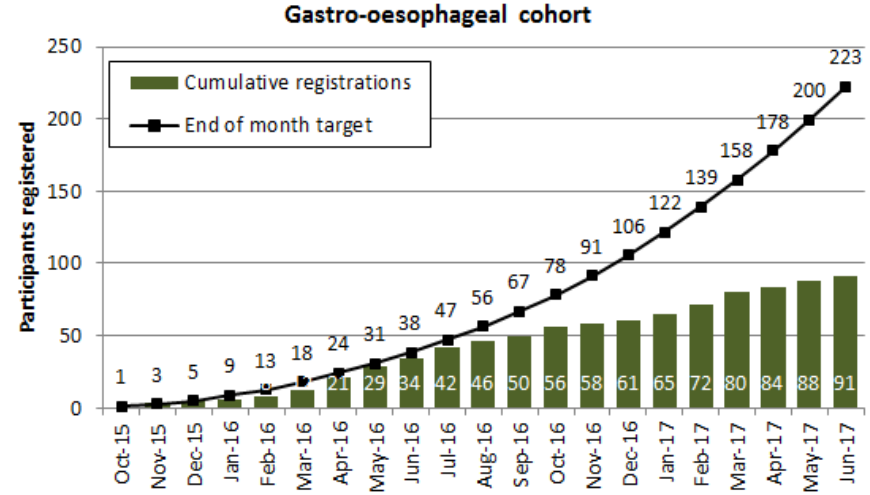


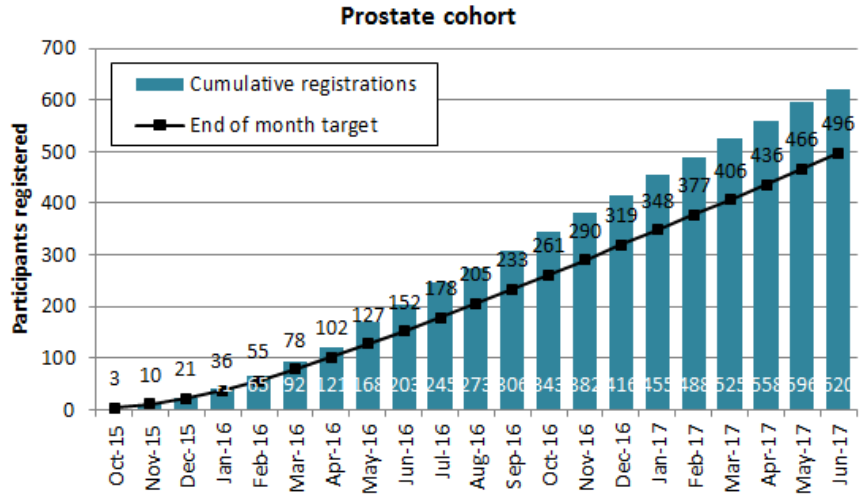
Trial Recruitment Update

to 20/06/2017









Add-Aspirin:
Trial Management Group

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Aspirin
Professor Peter Rothwell
Professor Sir John Burn
Professor Carlo Patrono
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Translational Group Chair
Professor David Cameron

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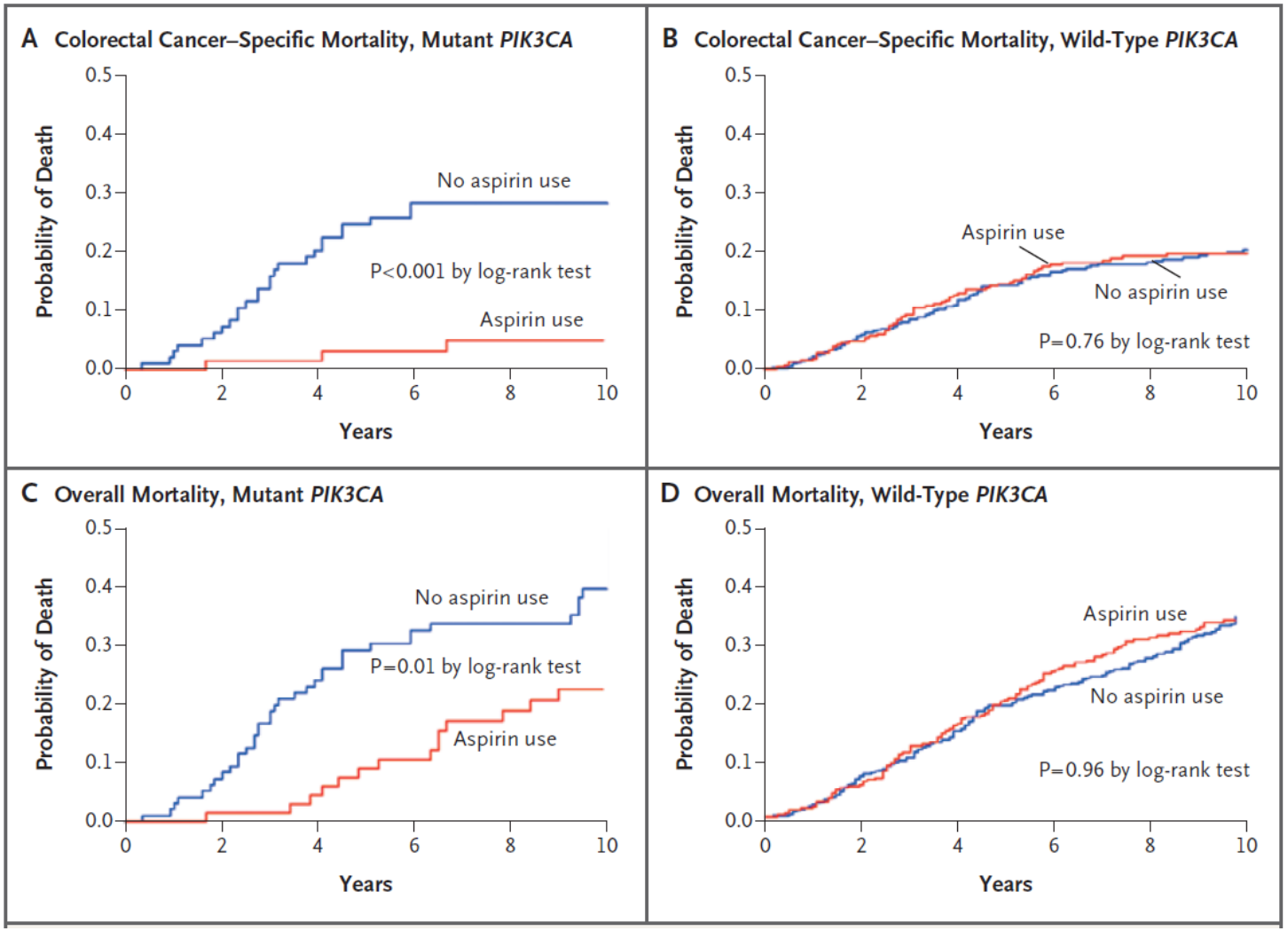
Sue Campbell, Yvonne Carse, Vandana Gupta

Questions ?

Colorectal-specific and overall mortality PIK3CA mutation and aspirin use



Liao *et al*, NEJM 2012

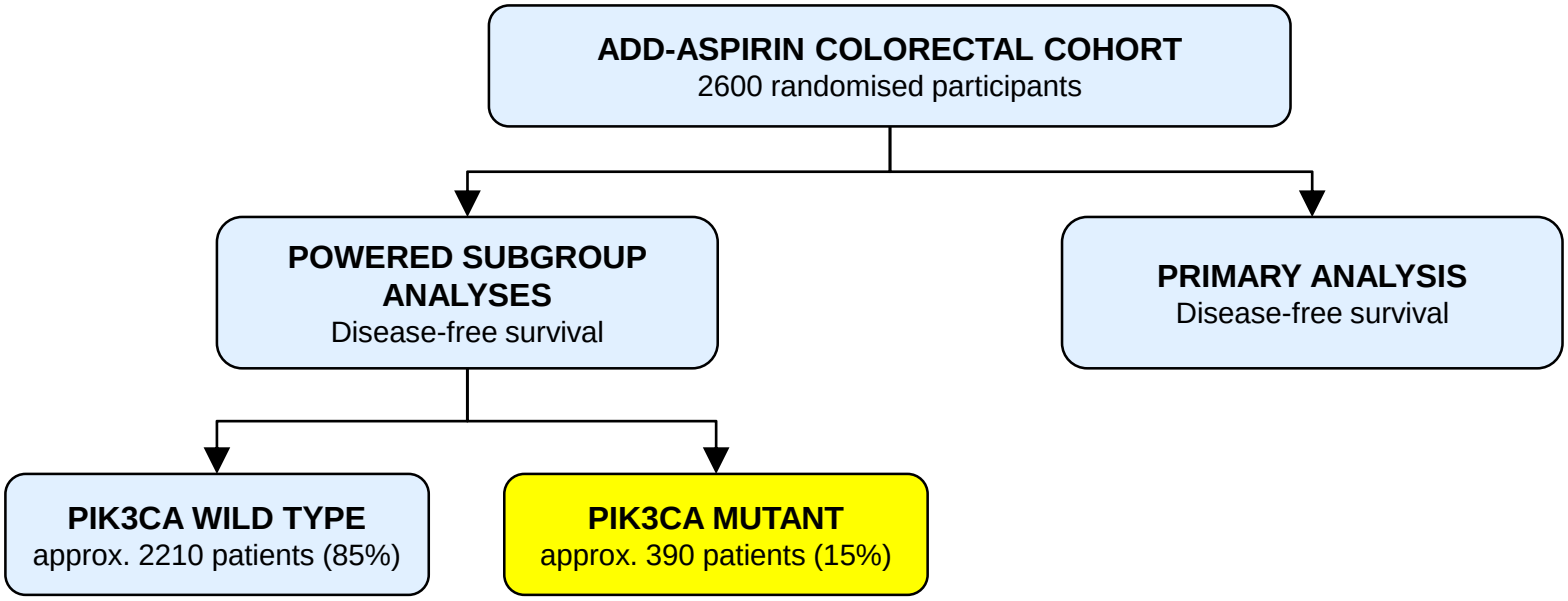
Outcomes:
PIK3CA mutant vs. wild-type

Study	PIK3CA mutation (%)	Endpoint	PIK3CA Mutant				PIK3CA Wild-Type			
			No aspirin	Aspirin	HR	95% CI, p value	No aspirin	Aspirin	HR	95% CI p value
NHS &HPFS(37)	16.7%	OS	95	66	0.54	0.31-0.94 p=0.01	466	337	0.94	0.75-1.17 p=0.96
		CSS	-	-	0.18	0.06-0.61 P<0.001	-	-	0.96	0.69-1.32 p=0.76
VICTOR trial(38)	11.6%	OS	90	14	0.29	0.04-2.33 P=0.19	681	111	0.95	0.56-1.61 p=0.26
		RFS	-	-	0.11	0.001-0.83 p=0.027	-	-	0.94	0.59-1.49 p=0.79
MCS& RMH(39)	12.4%	OS	136	49	0.96	0.58-1.57 p=0.86	-	-	-	-
		CSS	-	-	0.60	0.34-1.16 p=0.14	-	-	-	-
ECR(35)	15.8%	OS	73	27	0.73*	0.33-1.63 p=0.4	348	147	0.55	0.40-0.75 P<0.001

*=Adjusted rate ratio, OS=overall survival, CSS=colorectal cancer-specific survival, RFS=recurrence-free survival, NHS= Nurses' Health Study, HPFS=Health Professionals Follow-up Study, MCS=Moffitt Cancer Centre, RMH=Royal Melbourne Hospital, ECR=Eindhoven Cancer Registry, HR=multivariate hazard ratio

Add-Aspirin trial
Colorectal cohort analysis

Primary analysis (n=2600) - 90% power, 5% 2 sided significance level - 5% improvement in 5 year disease-free survival (DFS) (HR 0.80)



- Planned subgroup (n=390 (15%) with the PIK3CA mutation) - 90% power to detect a HR of **0.5** at a 5% significance level
- Accounts for multiple testing

Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study

- Data relates to those with established vascular disease (secondary prevention)
- Bleeding from aspirin and other anti-platelet agents increases with age (particularly over the age of 75)
- Encourages co-prescription of a proton-pump inhibitor (PPI) for patients over 75 years.
- Risks may be different for those without established vascular disease.

Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study

- Add-Aspirin trial already designed to exclude those at higher risk of bleeding:
  - Mandates a PPI for those undergoing oesophagectomy or partial gastrectomy
  - Restricts randomisation to those over 70 years to placebo or lower dose of aspirin (100mg)
  - Permits a PPI to be co-prescribed

- TMG have recommended to sites that results of this recent research are discussed with all patients $\geq$ 75 years participating in the trial and co-prescription of a PPI is considered (if not already prescribed).

- PPI can be co-prescribed for younger patients that are worried or have any symptoms

Cohort Specific Slides

Eligibility: Breast Cohort

- Histologically confirmed invasive breast cancer
- Node positive or node negative with high risk features
- Undergone complete primary invasive tumour excision (R0 resection) with standard neo-adjuvant and/or adjuvant therapy where indicated
- Known HER2 and ER status
- No current, regular use of aspirin, NSAIDs or anti-coagulants, and no pre-disposition to aspirin toxicity (e.g. active ulceration)

Please see protocol for full eligibility criteria

Eligibility: Colorectal Cohort

- Stage II or III colon or rectum adenocarcinoma
- No clinical or radiological evidence of residual or distant disease

  **Patients who have undergone resection of liver metastases with clear margins are eligible*
- Surgery (R0 resection) with standard neo-adjuvant/adjuvant therapy where indicated
- CEA and LFT's ideally ≤1.5 X upper limit of normal
  (Values outside this range can be discussed with MRC CTU at UCL)
- No current, regular use of aspirin, NSAIDs or anti-coagulants, and no pre-disposition to aspirin toxicity (e.g. active ulceration)

Please see protocol for full eligibility criteria

Eligibility: Gastro-Oesophageal Cohort

- Oesophageal, Gastro-oesophageal junction or gastric cancer
- Adenocarcinoma or squamous cell carcinoma
- No clinical or radiological evidence of residual or distant disease
- Previous therapy with curative intent
  - Surgery (R0 resection with clear margins *or* R1 resection with circumferential margin microscopically positive within 1mm) with standard neo-adjuvant +/- adjuvant therapy

    OR
  - Primary chemoradiotherapy with curative intent
- If underwent partial gastrectomy or oesophagectomy, a proton pump inhibitor should be prescribed for the duration of the trial
- No current, regular use of aspirin, NSAIDs or anti-coagulants, and no pre-disposition to aspirin toxicity (e.g. active ulceration)

Please see protocol for full eligibility criteria

Eligibility: Prostate Cohort

- Histologically confirmed non-metastatic prostate adenocarcinoma (T1-3a, N0)
- Intermediate or high risk according to D'Amico classification
- Previous therapy with curative intent:

  Either:
  - radical radiotherapy
  - radical prostatectomy (+/- adjuvant radiotherapy)
  - radical prostatectomy followed by salvage radiotherapy
- No current regular use of aspirin, NSAIDs, anti-coagulants or pre-disposition to aspirin toxicity (e.g. active ulceration)

Please see protocol for full eligibility criteria

Outcome measures

- Four separate, tumour-specific primary outcomes
- A long-term, combined analysis of overall survival in all participants is also planned

Cohort	Primary outcome measure
Breast	Invasive Disease-Free Survival
Colorectal	Disease-Free Survival
Gastro-oesophageal	Overall Survival
Prostate	Biochemical Recurrence-Free Survival
All participants	Overall Survival

- Secondary outcomes: toxicity (including major haemorrhage), adherence, cardiovascular events and tumour-specific outcomes

Sample Size Assumptions

- Each cohort is individually powered to detect the effect of aspirin on survival

Cohort	5yr control group survival	Detectable difference with aspirin	Hazard ratio	Expected recruitment	N
Breast	80%	4%	0.78	3.5 years	3100
Colorectal	70%	5%	0.80	3.5 years	2600
Gastro-oesophageal*	45%	6%	0.84	6 years	2100
Prostate	69%	6%	0.78	5 years	2120
Total					**9920**

* The gastro-oesophageal cohort has 80% power. All other cohorts have 90% power.

- We anticipate 90% of registered participants will go on to be randomised following the run-in
- Therefore, approximately 11,000 patients will be registered

Breast Cohort Eligibility - detail

4. In those patients with a positive sentinel node biopsy:
    a. If 1, 2 or 3 nodes are positive, subsequent management of the axilla (with surgery, radiotherapy or no further intervention) should follow institutional policy. If axillary surgery is to be undertaken, this should be completed prior to registration.
    b. If 4 or more nodes are involved, patients must have undergone completion axillary node dissection.
5. Radiotherapy:
    a. Patients who have undergone breast-conserving surgery should receive adjuvant radiotherapy.
    b. Patients who have undergone mastectomy should receive radiotherapy if they have more than 3 axillary lymph nodes involved.
    c. Patients who have undergone mastectomy and have T3 tumours and/or 1, 2 or 3 involved lymph nodes may (or not) receive radiation as per institutional practice.

Breast Cohort Eligibility – detail

6. Final histology must fall within at least one of these groups:
    a. For patients *not* receiving neoadjuvant chemotherapy:
        i. Node positive, or,
        ii. Node negative with high-risk features, defined as two or more of:
            - ER negative (Allred score <3/8 or negative according to institutional criteria)
            - HER2 positive
            - Grade 3
            - Lymphovascular invasion present
            - Age less than 35
            - Oncotype Dx score of >25
            - Prosignia score (PAM50) of >60

        -Patients are permitted to have had neoadjuvant endocrine therapy for up to 6 months, as long as final surgical pathology falls within one of the above two groups.
        -In the above definitions patients with micrometastases should be regarded as node positive. Patients with isolated tumour cells should be regarded as node negative.
    b. Patients who *have* received neo-adjuvant chemotherapy must fall into one of the following 3 categories:
        i. Hormone receptor negative and HER2 negative tumour AND has not achieved a complete pathological response, or,
        ii. A HER2 positive tumour (any hormone receptor status) AND not achieved a pathological complete response, or,
        iii. A hormone receptor positive, HER2 negative tumour which is grade 3 AND has not achieved a pathological complete response.

Prostate Cohort – eligibility details

Table 3. D'Amico Classification[88]

RISK CLASSIFICATION	
Low	▪ PSA less than or equal to 10 ▪ **And** Gleason score less than or equal to 6 ▪ **Or** clinical stage T1-2a
Intermediate	▪ PSA between 10 and 20 ▪ **Or**Gleason score of 7 ▪ **Or** clinical stage T2b
High	▪ PSAmore than 20 ▪ **Or** Gleason score equal or larger than 8 ▪ **Or**clinical stage T2c-3a

Adjuvant Aspirin Trials

Trial Acronym	Phase	Status (Location)	Tumour site
ASCOLT Aspirin for Dukes C and High Risk Dukes B Colorectal Cancer (200mg)	III	Recruiting (12 Countries, Asia and Australasia)	Colorectal
ASPIRIN A Trial of Aspirin on Recurrence and Survival in Elderly Colon Cancer Patients (100mg)	III	Recruiting (Netherlands)	Colon
US Breast Cancer Trial Randomized trial of aspirin as adjuvant therapy for node-positive breast cancer (325mg)	III	In set-up (US)	Breast
ALASCCA Adjuvant Low dose Aspirin in Colorectal Cancer – PIK3CA mutated patients only (160mg)	III	In set-up (Sweden)	Colorectal
Add-Aspirin A phase III double-blind placebo-controlled randomized trial assessing the addition of aspirin after standard primary therapy in early stage common solid tumours (100 and 300mg)	III	Recruiting (Oct 2015) (UK and India)	Breast, colorectal, gastro-oesophageal and prostate

Other Aspirin Treatment Trials

Trial Acronym	Phase	Status (Location)	Tumour site
PROVENT A randomised, double blind, placebo controlled feasibility study to examine the clinical effectiveness of aspirin and/or Vitamin D to prevent disease progression in men on active surveillance for prostate cancer	Feasibility study prior to phase III	In set-up (UK)	Prostate
FOCUS 4-B A randomised controlled comparison of aspirin versus placebo in patients with PIK3CA exon 9 or 20 mutant, metastatic colorectal cancer, stable or responding to first-line treatment	II/III	In set-up (UK)	Colorectal
Lung Cancer Trial High-Risk Individuals (heavy smokers, > 50yrs) with CT Screen Detected Subsolid Lung Nodules	II	Recruiting	Lung cancer
ASAMET Trial Colorectal Cancer Adjuvant – aspirin and metformin 2x2 factorial Primary outcome - NFκB IHC expression at 12 months	II		Colorectal

Thank you

Q&A

The Stakeholder Meeting is now closed

The DSSG meetings will commence shortly

These are closed sessions
Strictly Members only