A Multicenter, Placebo-controlled, Double-blind, Randomized Clinical Trial with Aspirin in Patients Undergoing Resection of Colorectal Liver Metastases

Are we ready to recommend aspirin for cancer prevention?

Aspirin to prevent colorectal cancer: time to act?

Effect of daily aspirin on risk of cancer metastasis: a study of

Summary

Long-Term Effects of Aspirin on Colorectal Cancer

Carl J Brown, MD, Steven Gallinger, MD, James Church, MD, for Members of the Evidence-Based Reviews in Surgery Group

ue to *Lancet* 2012; 379: 1591–601

Peter M Rothwell, Michelle Wilson, Carl-Eric Elwin, Bo Norrving, Ale Algra, Charles P Warlow, T

Summary

Background High-dose aspirin (≥500 mg daily) reduce

Colon cancer

PRESS RELEASE

The impact of aspirin, st ACE-inhibitors on the pr colorectal neoplasia in a screening programme

D Mansouri*,[1], D C McMillan[1], C S D Roxburgh[1], E M Crighton[2] and P G Horga

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Gastroenterology

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Aspirin and the prevention of colorectal cancer

us,[4]

Ángel Ferrández, MD, PhD, Investigator[a,1], Elena Piazuelo, MD, PhD, Investigator[b,1], Antoni Castells, MD, PhD, Investigator[c,*]

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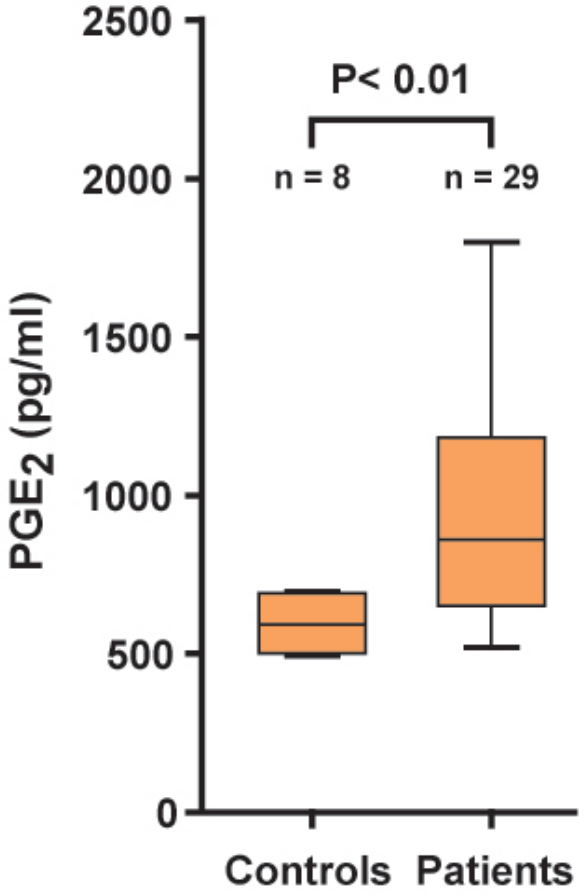
Increased plasma-levels of PGE_2 in patients with colorectal cancer



Yaqub S. et al, Cancer Immunol Immunother, 2008

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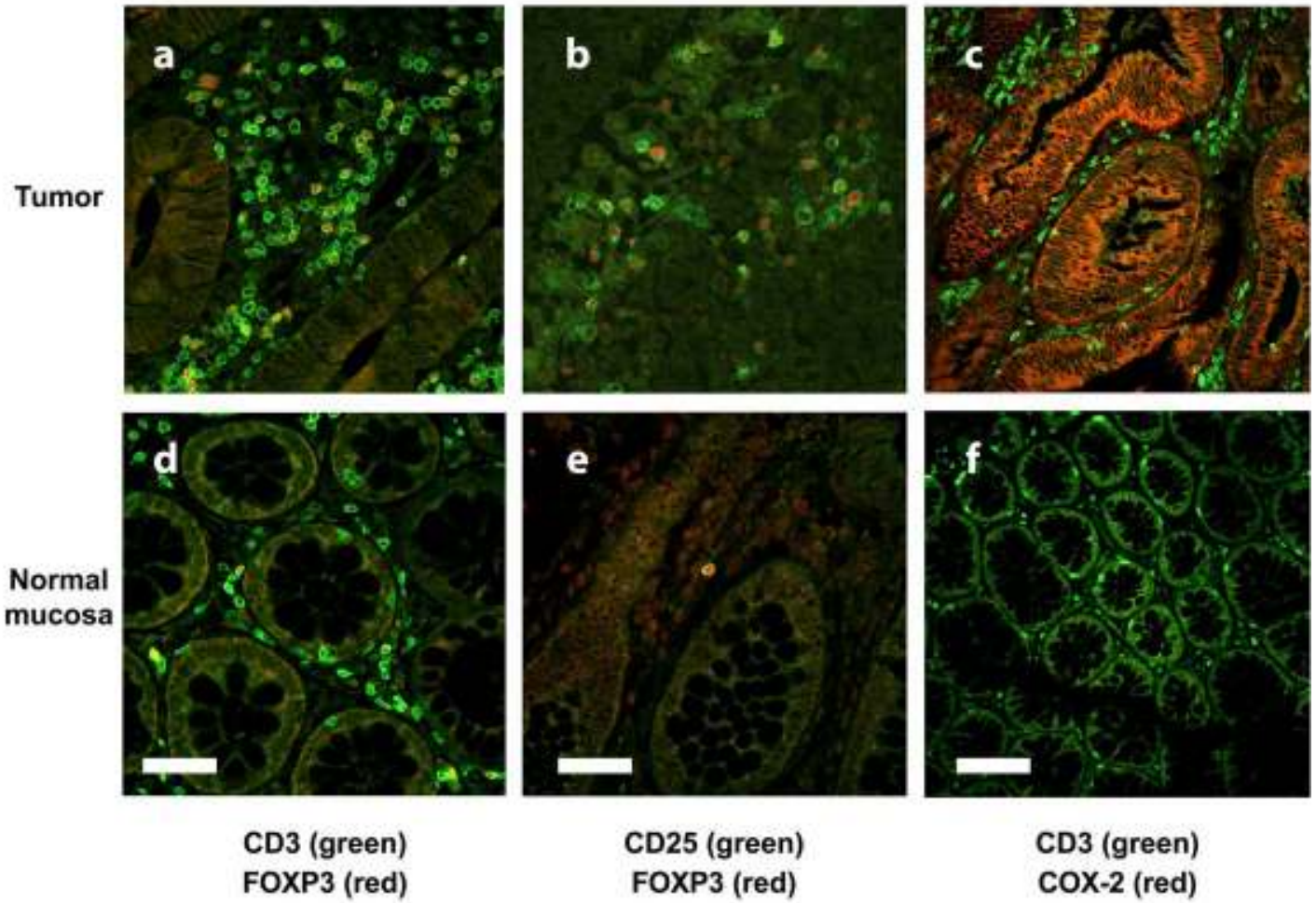
T regulatory cells accumulate within colorectal cancer



Yaqub S. et al, Cancer Immunol Immunother, 2008

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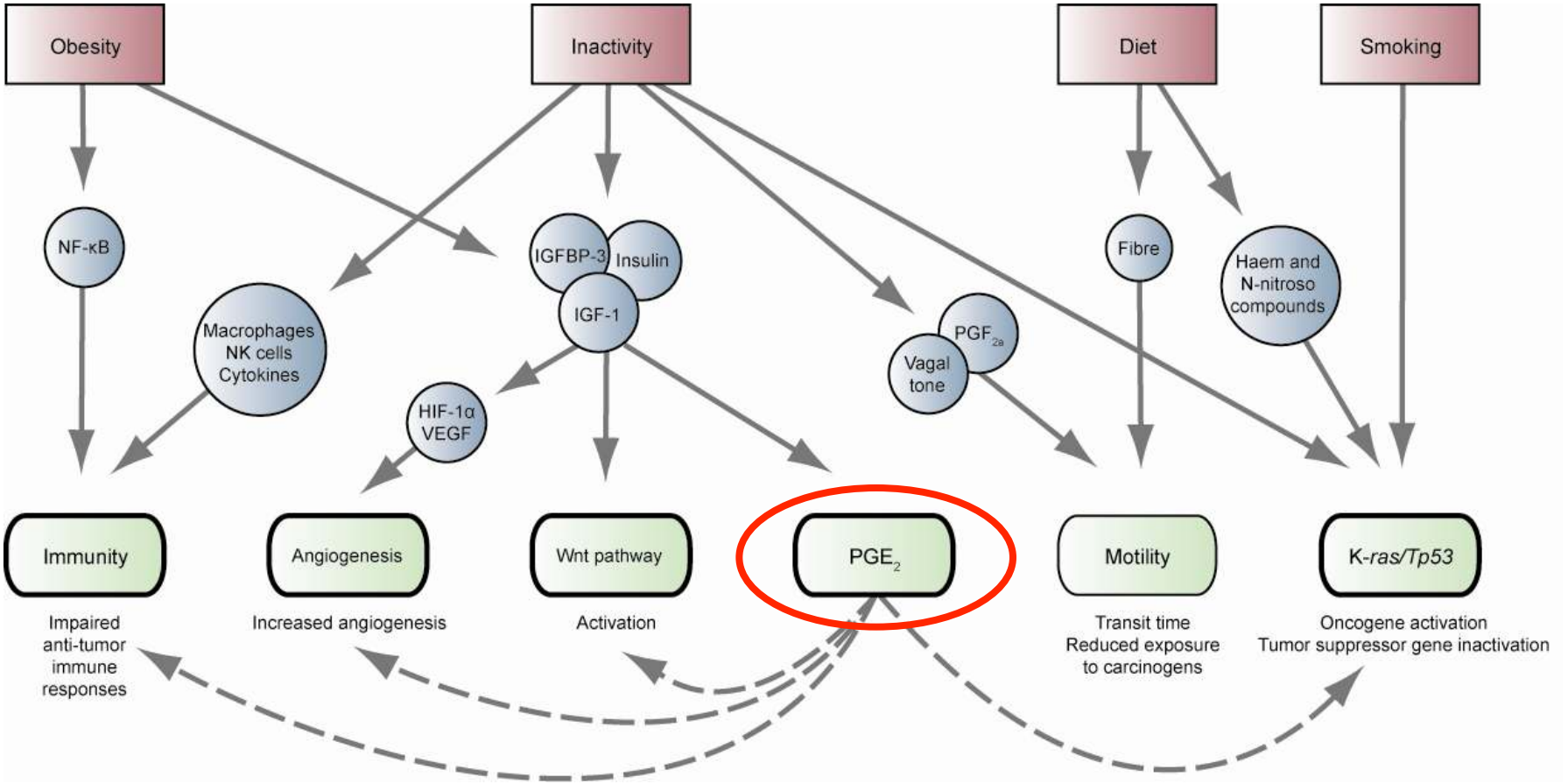
How Does Cyclooxygenase Inhibition Work in Colorectal Cancer Cyclooxygenase - A Main Regulator of Prostaglandin



Prostaglandin 2 (PGE_2) is Upregulated in CRC and Interacts with Several Pathways
Inhibition May Have Several Potential Benefits on CRC Development and Progression

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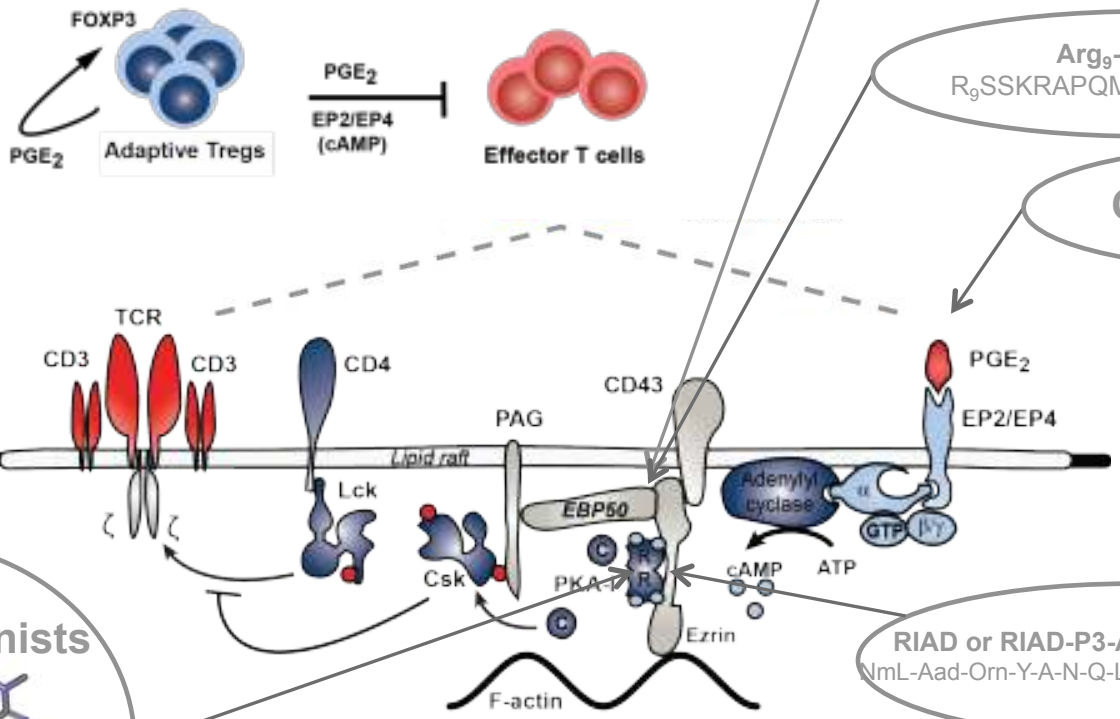
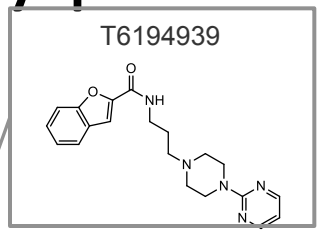
The PGE_2-cAMP-PKA inhibitory pathway – preclinical and clinical studies



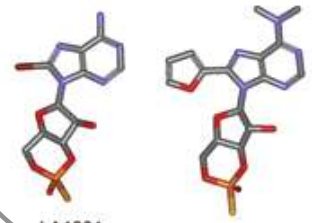


Arg_9-$EBP50_{pep}$
R_9SSKRAPQMDWSKKNELFSNL

COX-2 inhibitor

HIV: patent 2000,
AIDS, 2004 &2006;
J. Virol, 2011

cAMP antagonists



Patents 1997, 2006, 2007
HIV: FASEB J., 1998 AIDS, 1999,
J. Immunol. 2002
Compounds: J. Biomol. Chem., 2008,
Eur.J. Med. Chem. 2011, Mol. Cancer 2012…

RIAD or RIAD-P3-Arg_9 peptidomimetic
NmL-Aad-Orn-Y-A-N-Q-L-A-Aad-Q-I-I-K-E-A-T-E-R_9

Patent 2004, J. Biol. Chem. 2006,
J. Immunol. 2007, Biochem. J. 2009
J. Immunol. 2011

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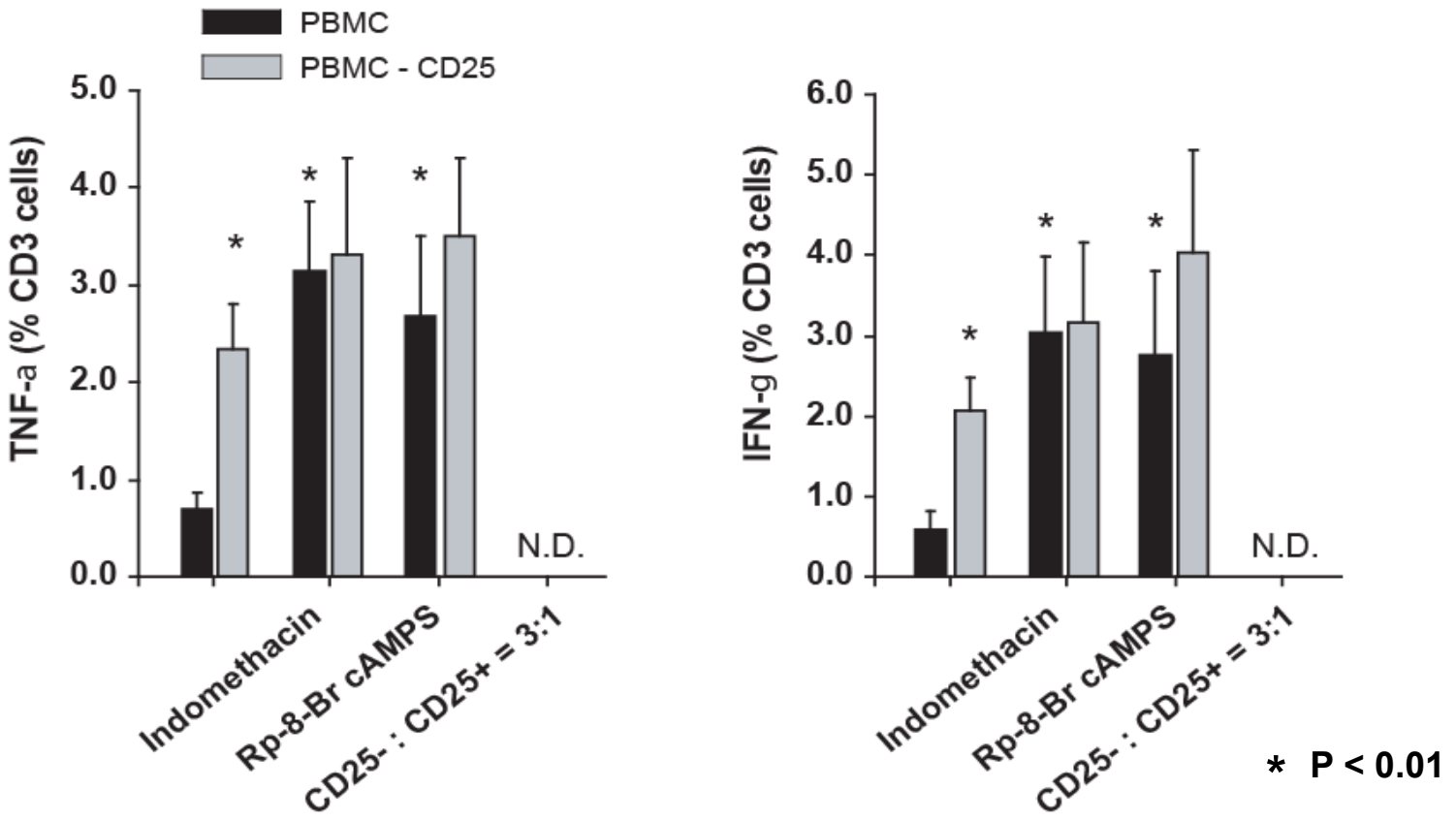
Pharmacological intervention increases anti-CEA immune responses in colorectal cancer patients



Yaqub S. et al, Cancer Immunol Immunother, 2008

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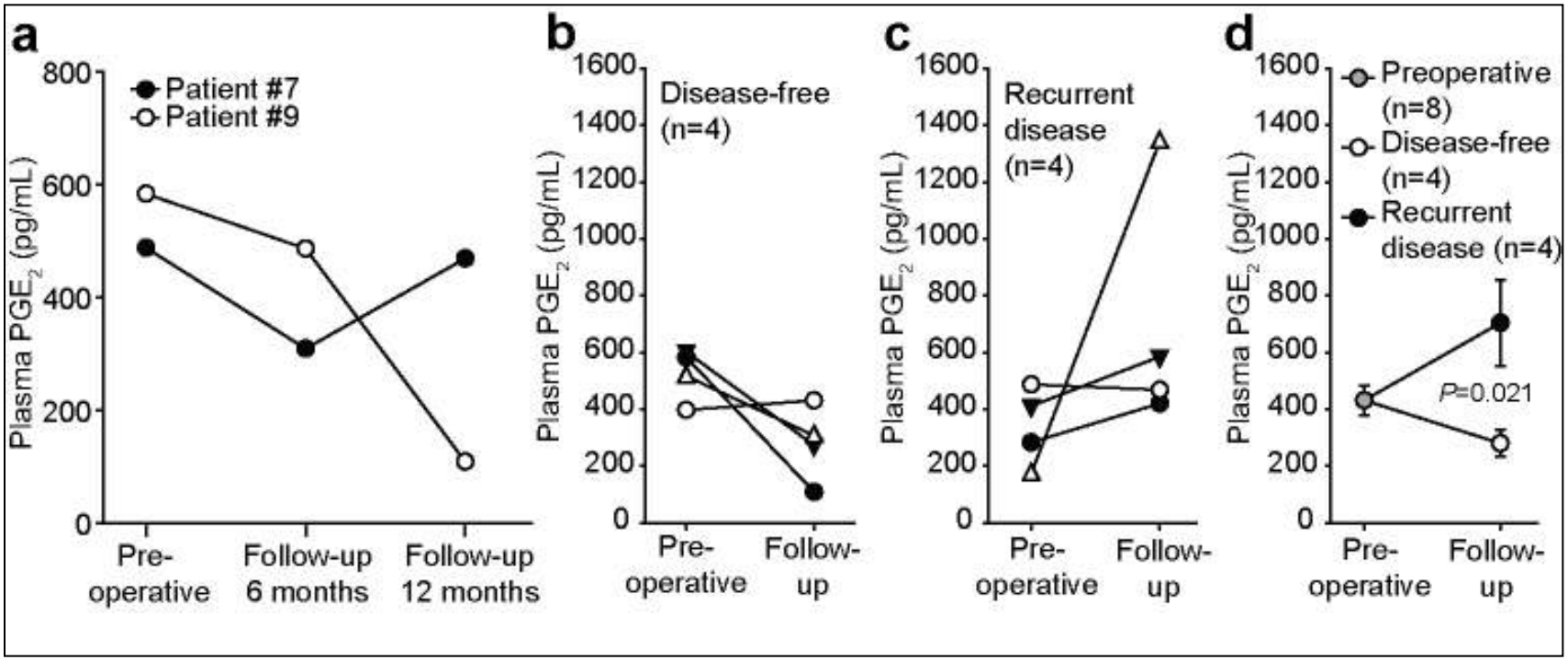
PGE_2 levels post-surgery for colorectal cancer liver metastasis (CRCLM)



Brudvik KW. et al, Cancer Immunol Immunother, 2012

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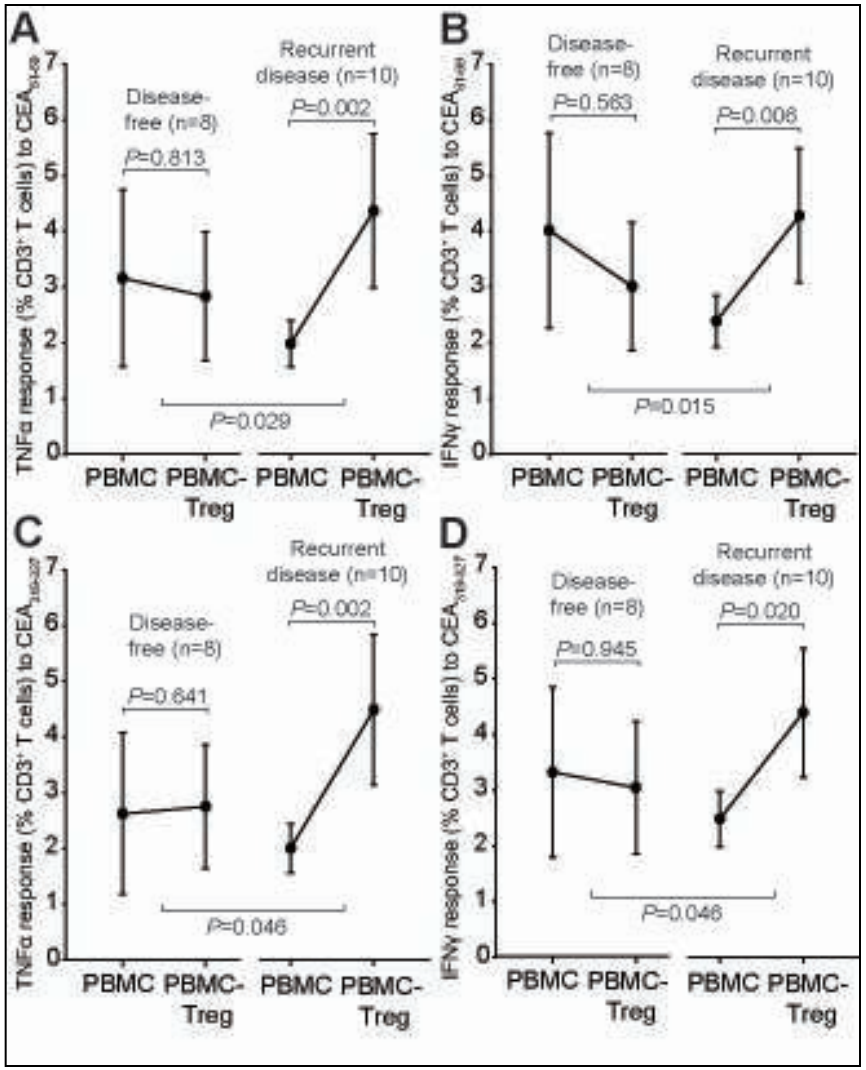
Anti-tumor immune responses in CRCLM patients at time of surgery predict clinical outcome



Brudvik KW. et al, Cancer Immunol Immunother, 2012

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"Kinderegg" effect of perturbation of prostaglandin E_2 signaling in CRC

- PGE_2 in colorectal cancer:
  1) Stimulates tumor formation and growth
  2) Stimulates angiogenesis
  3) Stimulates formation of regulatory T cells and inhibits anti-tumor immunity (our findings)
  - Cox2 inhibitors, NSAIDs and ASA:
  1) Inhibits tumor formation – primary cancer / primary prophylaxis
  2) Blocks effect on angiogenesis – primary cancer / primary prophylaxis
  3) Blocks tumor imune evasion – established cancer / metastasis secondary prophylaxis

Yaqub S. et al, Cancer Immunol Immunother, 2008
Budvik KW. et al, Cancer Immunol Immunother, 2012
Bains, SJ. Et al. J Clin Oncol, 2016.

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Background: CRC and Aspirin

- CRC incidence
  - Worldwide: 1.3 million cases/year
  - Norway: 4300 cases/year
- Aspirin primary prevention – well documented, but debated due to risks
- Aspirin as secondary prevention?

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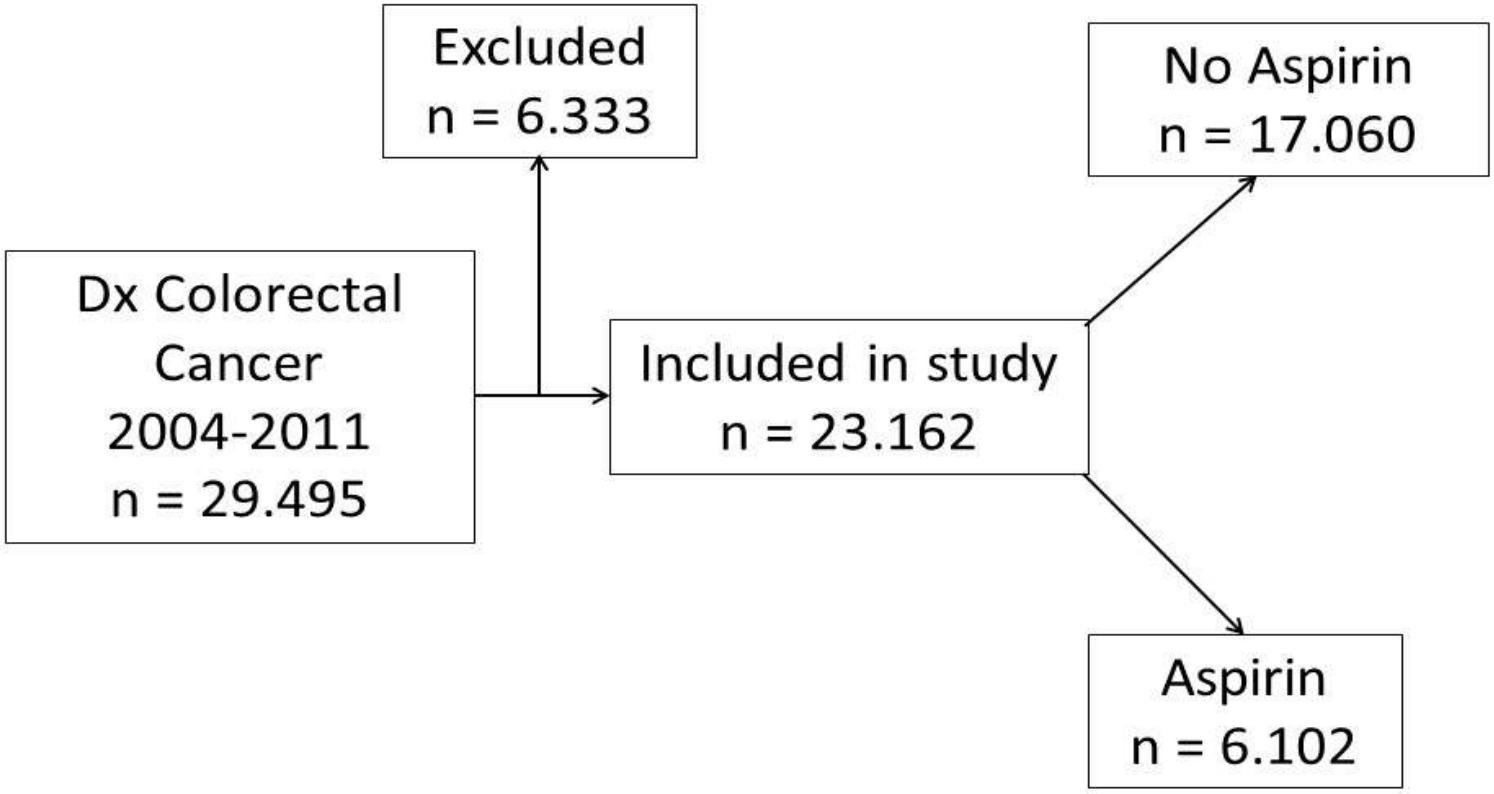
Registry study design



Bains, SJ. Et al. J Clin Oncol, 2016

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Overall and CRC-specific Survival

- 23,162 patients with CRC, 6,102 of whom were exposed to aspirin after the diagnosis of CRC (26.3%)
- Median follow-up was 3.0 years
- Mortality: ASA users: 32.9% (all causes) / 19.0% (CRC-specific). Non-exposed cases: 42.3% (all causes) / 31.5% (CRC-specific)
- Multivariate analysis, ASA exposure after the diagnosis of CRC was independently associated with improved CCS (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.79-0.92) and OS (HR, 0.95; 95% CI, 0.90-1.01)
- ASA use both before and after CRC diagnosis reduced HR to 0.76
- **Conclusion:** Aspirin use after the diagnosis of CRC is independently associated with improved CCS and OS

Bains, SJ. Et al. J Clin Oncol, 2016

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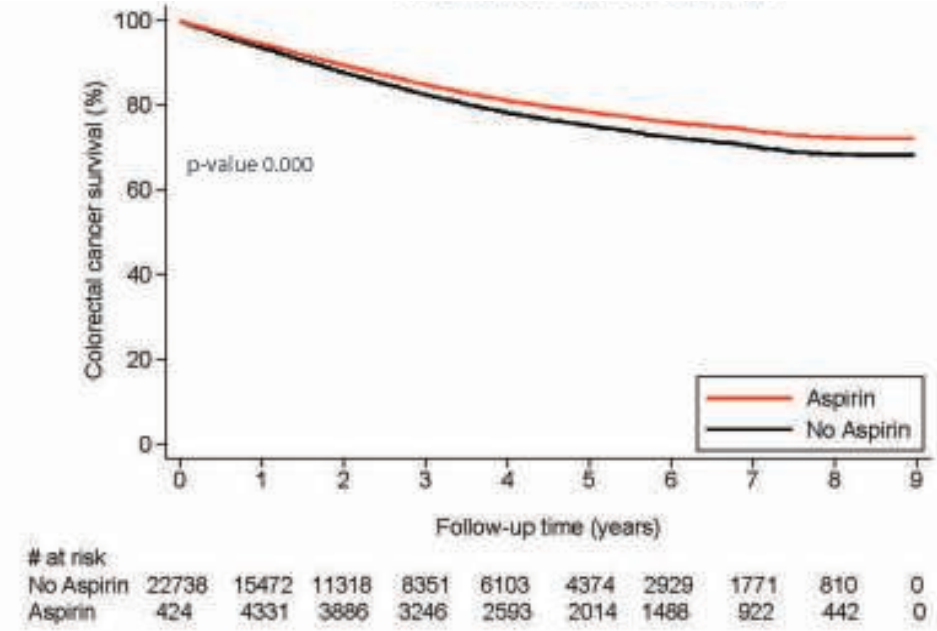
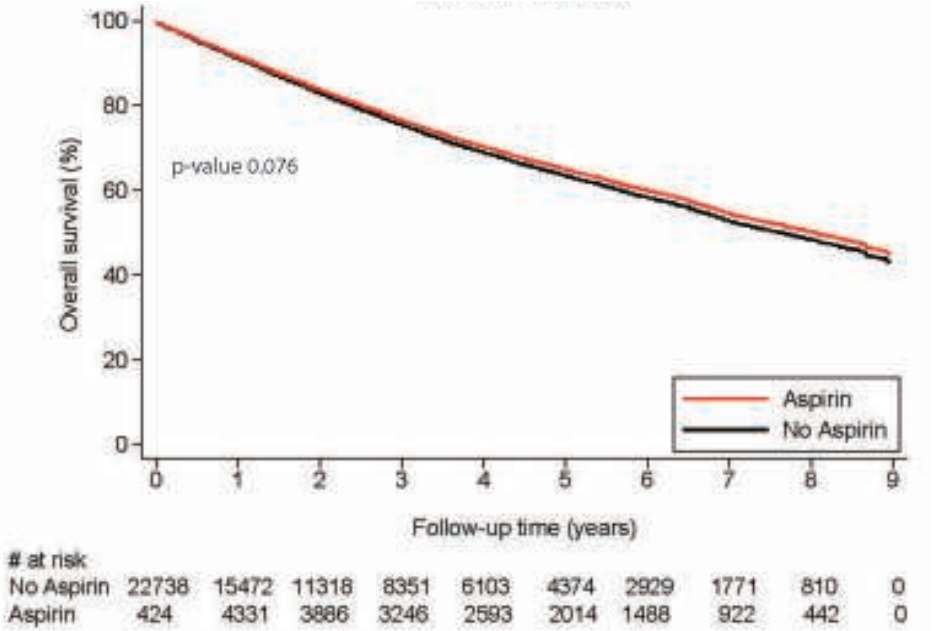
Aspirin as Secondary Prevention in 23,162 Patients with Colorectal Cancer – An Unselected Population-Based Study

CRC survival



Overall survival



Bains, SJ. Et al. J Clin Oncol, 2016

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Aspirin As Secondary Prevention in Patients With Colorectal Cancer: An Unselected Population-Based Study

Simer J. Bains, Milada Mahic, Tor Åge Myklebust, Milada Cvancarova Småstuen, Sheraz Yaqub, Liv Marit Dørum, Bjørn Atle Bjørnbeth, Bjørn Møller, Kristoffer Watten Brudvik, and Kjetil Taskén

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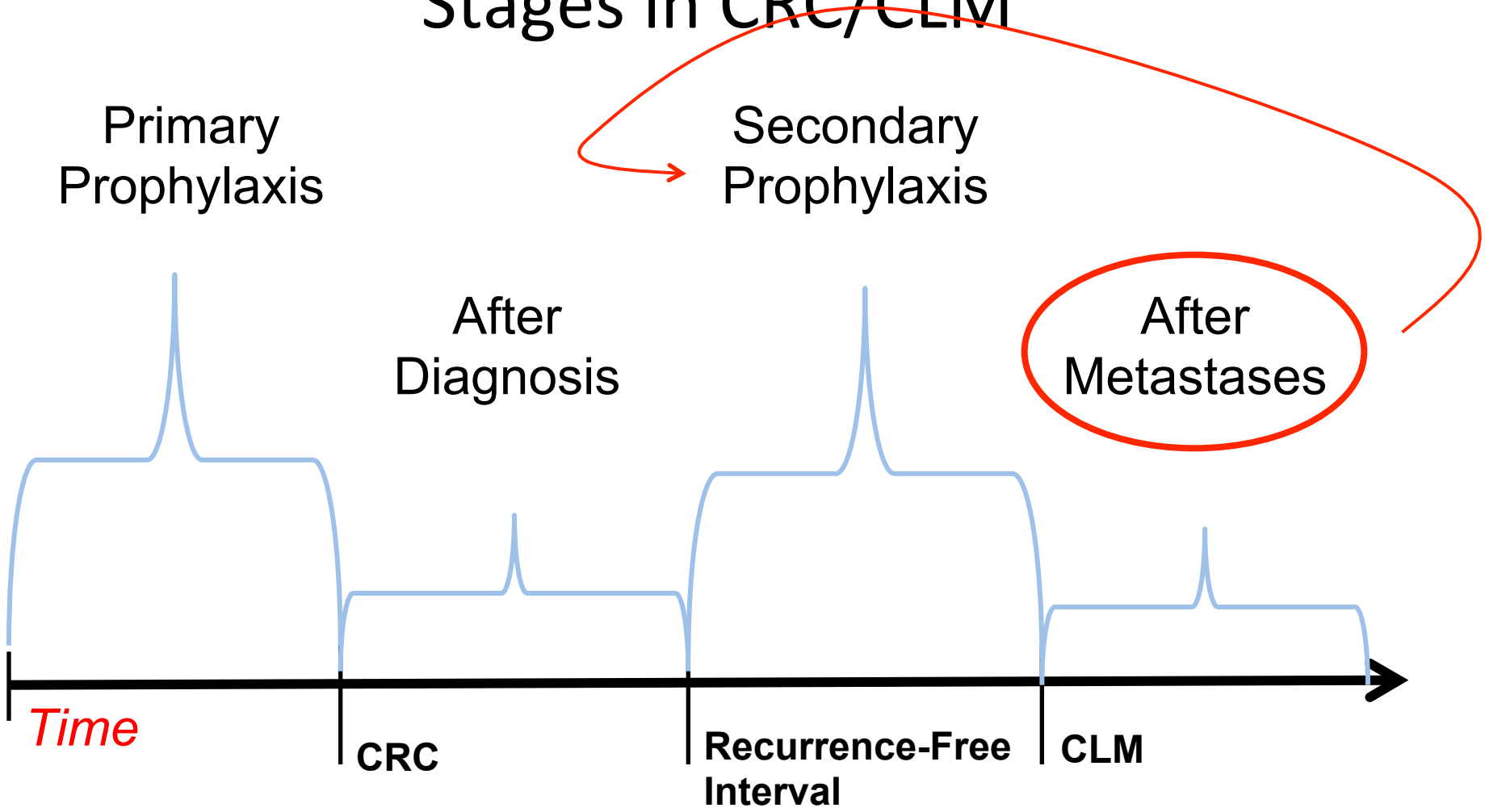
Cyclooxygenase Inhibition at Different Stages in CRC/CLM



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ASAC-trial

- A multicenter, randomized, double-blind, placebo-controlled clinical trial
- 5 sites in Norway, 6 sites in Sweden, 3 sites in Denmark
- 400 pt each arm, Drug ASA (Trombyl®) 160 mg x 1, treatment 36 months
- **Primary endpoint**: Disease free survival (DFS) increased by 6 months for at least 10 % of the patients in the intervention group

ASAC TRIAL
Scandinavian Livermet Study

Participating sites*

Norway

Oslo University Hospital
Bjørn A Bjørnbeth, MD PhD
Sheraz Yaqub, MD PhD
Haukeland University Hospital
Arild Horn, MD PhD
Jon Helge Angelsen, MD PhD
Stavanger University Hospital
Jon Arne Søreide, MD PhD
University Hospital of North-Norway, Tromsø
Kim E Mortensen, MD PhD
St Olavs Hospital
Jon Erik Grønbech, MD PhD

Sweden

Karolinska University Hospital
Ernesto Sparelid, MD PhD
Sahlgrenska University Hospital Gothenburg
Magnus Rizell, MD PhD
Linköping University Hospital
Per Sandström, MD PhD
Lund University, Skåne Hospital
Gert Lindell, MD PhD
Uppsala University Hospital
Bengt Isaksson, MD PhD
University Hospital of Umeå
Oskar Hemmingsson, MD PhD

Denmark

Rigshospitalet, Copenhagen
Peter Larsen, MD PhD
Aarhus University Hospital
Frank V Mortensen, MD PhD
Odense University Hospital
Claus W Fristrup, MD PhD

** Signed project collaboration form, 17th November 2017*

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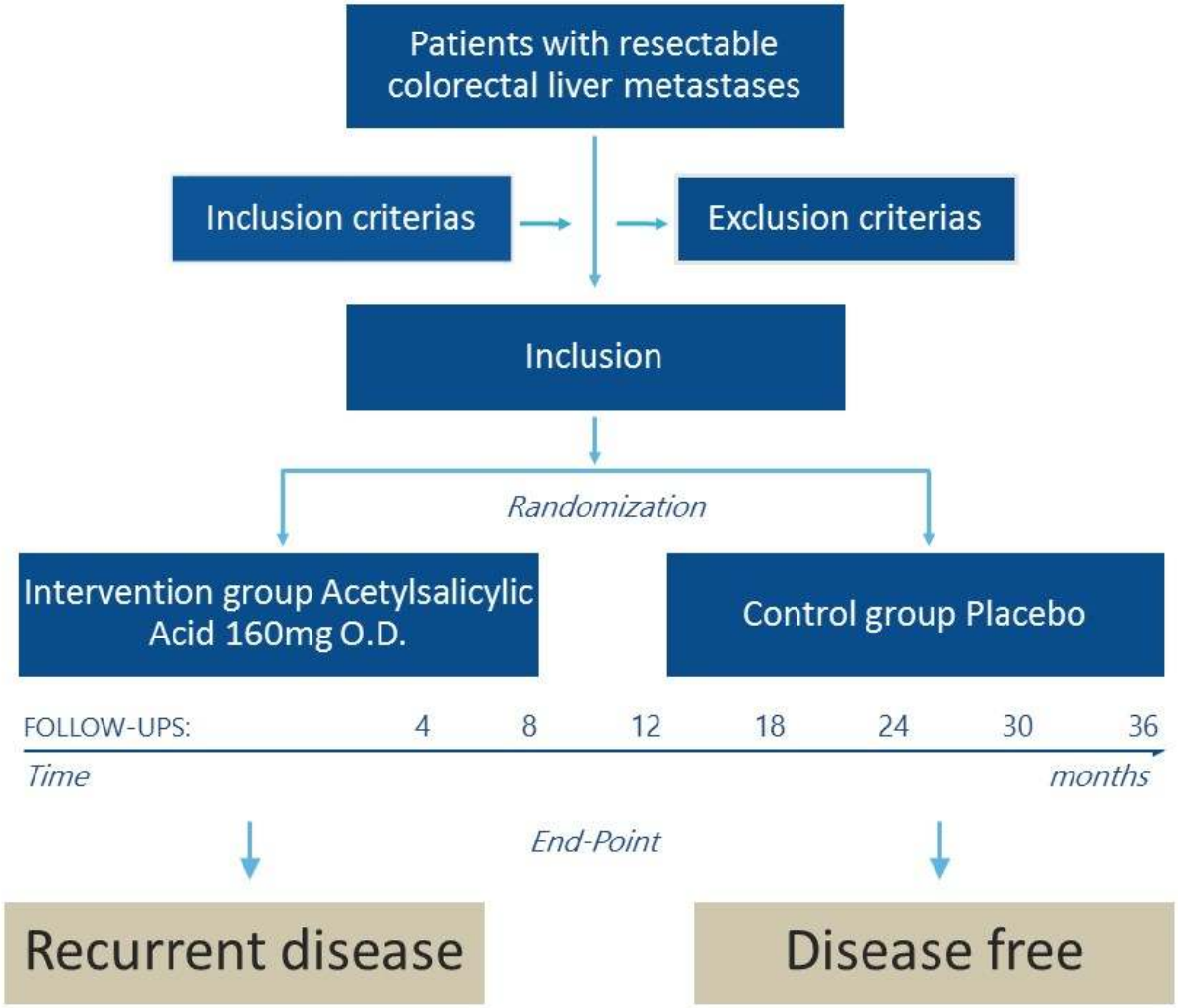
ASAC-trial



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Inclusion criteria

- All patients undergoing radical liver resection for CRCLM as part of a curative intent (macroscopic surgical free resection margin, R0 or R1) or combined with radiofrequency or microwave ablation technique
- Synchronous, metachronous, or recurrence of CRCLM (not previously included in this trial)

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Exclusion criteria

- Concomitant use of ASA or other anticoagulants or platelet inhibitors such as warfarin or klopidogrel
- Inherited or acquired coagulopathy (hemophilia)
- Blood platelets < 100 x 10^9/L
- Severe heart failure, NYHA class III
- Kidney failure
- Pregnancy
- Ongoing regular use of corticosteroids and/or NSAIDs

ASA TRIAL
Scandinavian Livermet Study

Exclusion criteria

- Active peptic ulcer
- Previous severe gastrointestinal hemorrhage/peptic ulcer due to ASA/NSAIDs
- Hypersensitivity/allergies to ASA or NSAIDs

- Need to use medications contraindicated according to SmPC of Trombyl® from Swedish Medicines Agency

ASAC TRIAL
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Logistics

- Before surgery
  - Informed consent
  - Screening data register – eCRF (doctor)
- After surgery
  - Baseline data register – eCRF and randomization (study nurse)
  - Dispensing study drug for 12 months (4 bottles á 100 tablets)
- Starting study medicine 4 weeks after surgery
  - discontinued lmw heparin (Fragmin®), call from study nurse
- Data collection at every control (4,8,12*,18,24*,30,36* months)
  - CT liver and chest, quality of life (SF-36 & EQ-5D), Adverse Events
- Control every 12 months (maximum 3 years) at study site
  - Drug accountability and dispense new batch with study drug (next 12 months) – study nurse

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Interim analysis

- An interim analysis will be performed when approximately half of the planned primary events (135) have occurred and the primary endpoint has been entered
- A Data Monitoring Committee will perform the interim analysis

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Adverse Events (AE) and Severe Adverse Events (SAE)

- All AEs and SAEs will be registered in the eCRF at each visit
- SAEs must be reported by the investigator to the Head of Surgical Clinic Dr Morten Tandberg Eriksen (OUH) within 24 hours after the site has gained knowledge of the SAE
- Every SAE must be documented by the investigator in the eCRF
- In case of SUSARs the report will be sent to Martha Colban, OUH, Clinical Trial Unit. The initial report shall promptly be followed by detailed, written report if necessary

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Emergency Unblinding

- Contact study nurse at Oslo University Hospital

Victoria Bringsjord
E-mail: vicbri@ous-hf.no

Gyda G Christiansen
E-mail: gydchr@ous-hf.no

- 24/7/365: Contact on-call HPB surgeon at Oslo University Hospital (+47-23070000)

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Trial webpage: www.asac.no

- All the information you need
- Log in to e-CRF (VieDoc)
- Patient report forms (QoL)
- Protocol
- Contact information

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www.asac.no


ASAC TRIAL
Scandinavian Livermet Study
Home
Recruiting sites
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Unblinding
Downloads
Contact
Aspirin vs Placebo
after Resection of Colorectal Liver Metastases
The ASAC study will try to answer this

Written information

- All participating sites get one binder with all information about the trial (Investigator Site File)

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Molecular profiling

- Biobanking in Oslo for molecular and genetic analysis
  - KRAS, BRAF, PIK3CA etc
- Other sites are recommended to biobank for future analysis and stratification of data (not compulsory to participate)

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Academic teambuilding

ASAC will try to provide a Scandinavian Surgical Research milieu that will stimulate future prospective clinical and translational research projects

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ASAC TRIAL

Scandinavian Livermet Study

B.A Bjørnbeth, OUH

K. Taskén, UoO

S. Yaqub, OUH

Oslo University Hospital

NCMM

UNIVERSITAS OSLOENSIS MDCCCXI

NORWEGIAN CANCER SOCIETY

The Research Council of Norway

KLINBEFORSK