

MRC

Clinical
Trials
Unit

Smarter studies
Global impact
Better health



UCL

Improving outcomes as rapidly as possible for patients

**Multi-arm, multi stage platform, umbrella
and basket protocols**

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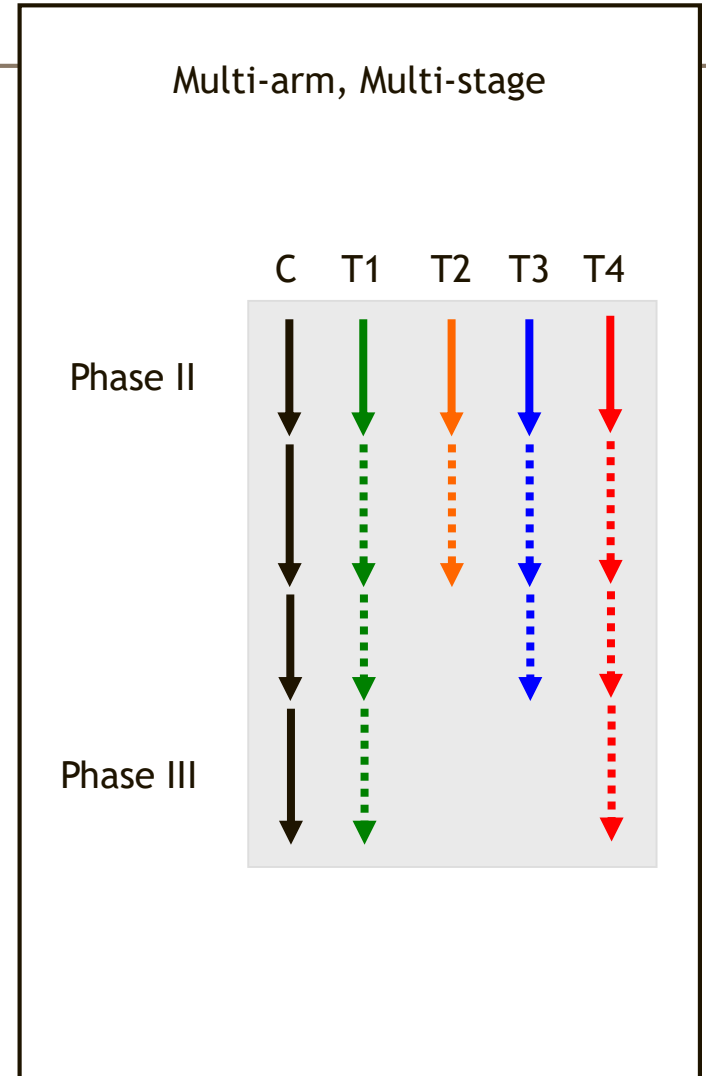
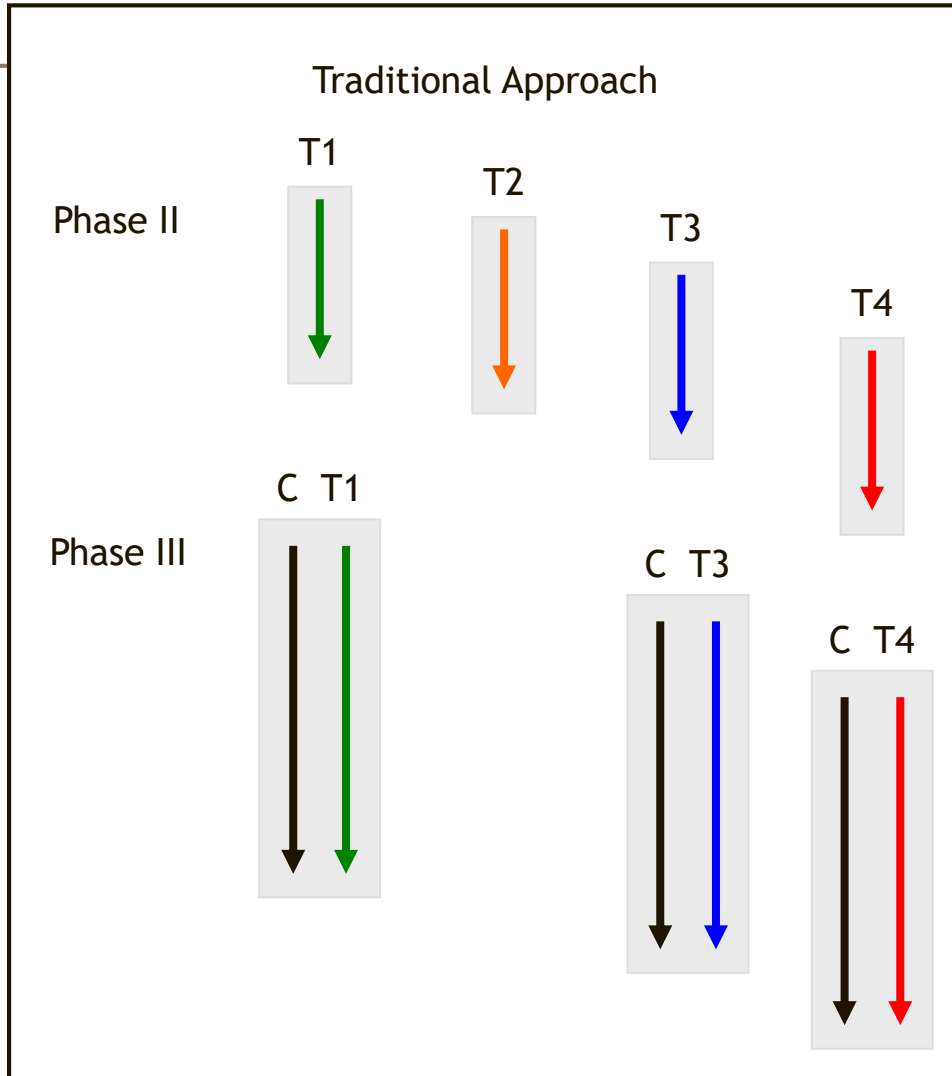
The need for speed and change

- Development and testing process too slow (>10 years)
- Too often shows new is not better than standard
- In some diseases number of new therapies demanding evaluation is large
- Some diseases are being classified to smaller subsets using molecular characterisation
- Process of developing and starting a new trial is very time consuming – often a long gap between trials
- Many solutions proposed have been for phase I and II trials
- Our emphasis is on Phase III trials – longest and most expensive part of evaluation process

Principles underlying solutions

- Evaluate many primary hypotheses/treatments in the same protocol
- If there is a pilot/feasibility/phase II
 - seamless run through to the phase III and
 - include all phase II information in the phase III
- Conduct an adaptive trial, with only major adaptations, e.g.
 - Dropping arms
 - Adding arms

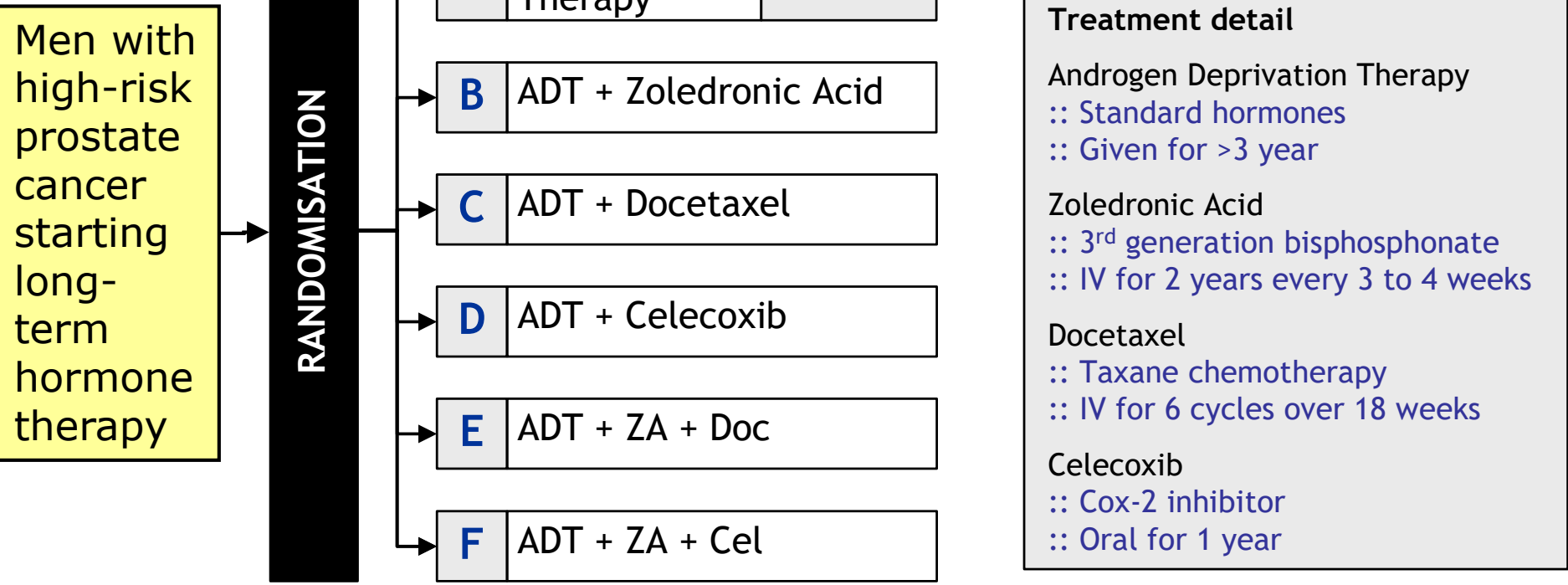
Multi-arm, multi-stage



Need in prostate cancer

- 900,000 new prostate cancers in early 2000s, globally
- Standard treatment for high risk disease = hormone therapy – no change for 40 years
 - Median survival: ~5 years
- Many promising agents to evaluate
 - Different classes, different modes of action
- Use MAMS design to test many agents
 - Focus towards active agents with lack-of-benefit analyses

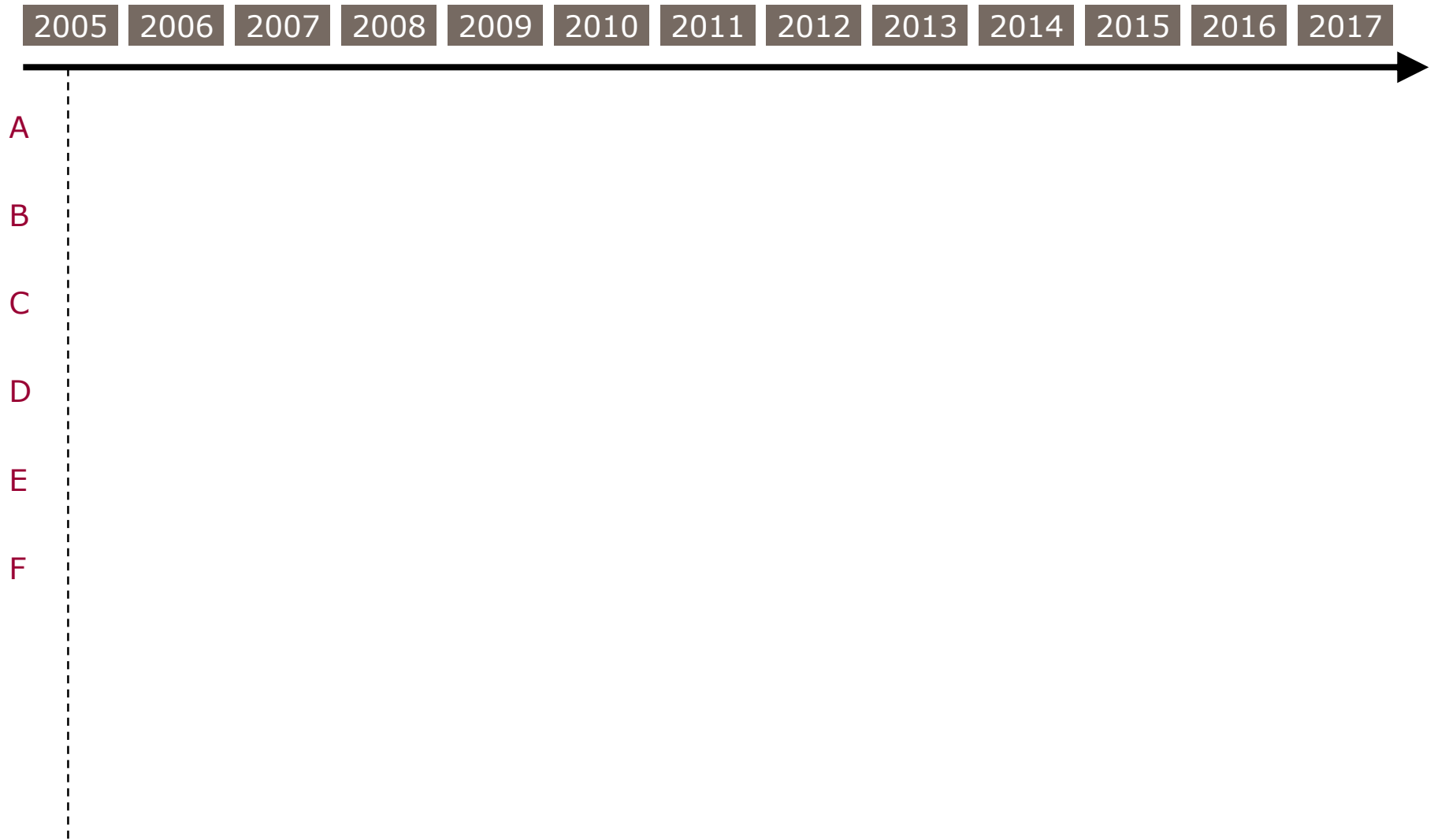
STAMPEDE design






STAMPEDE trial stages

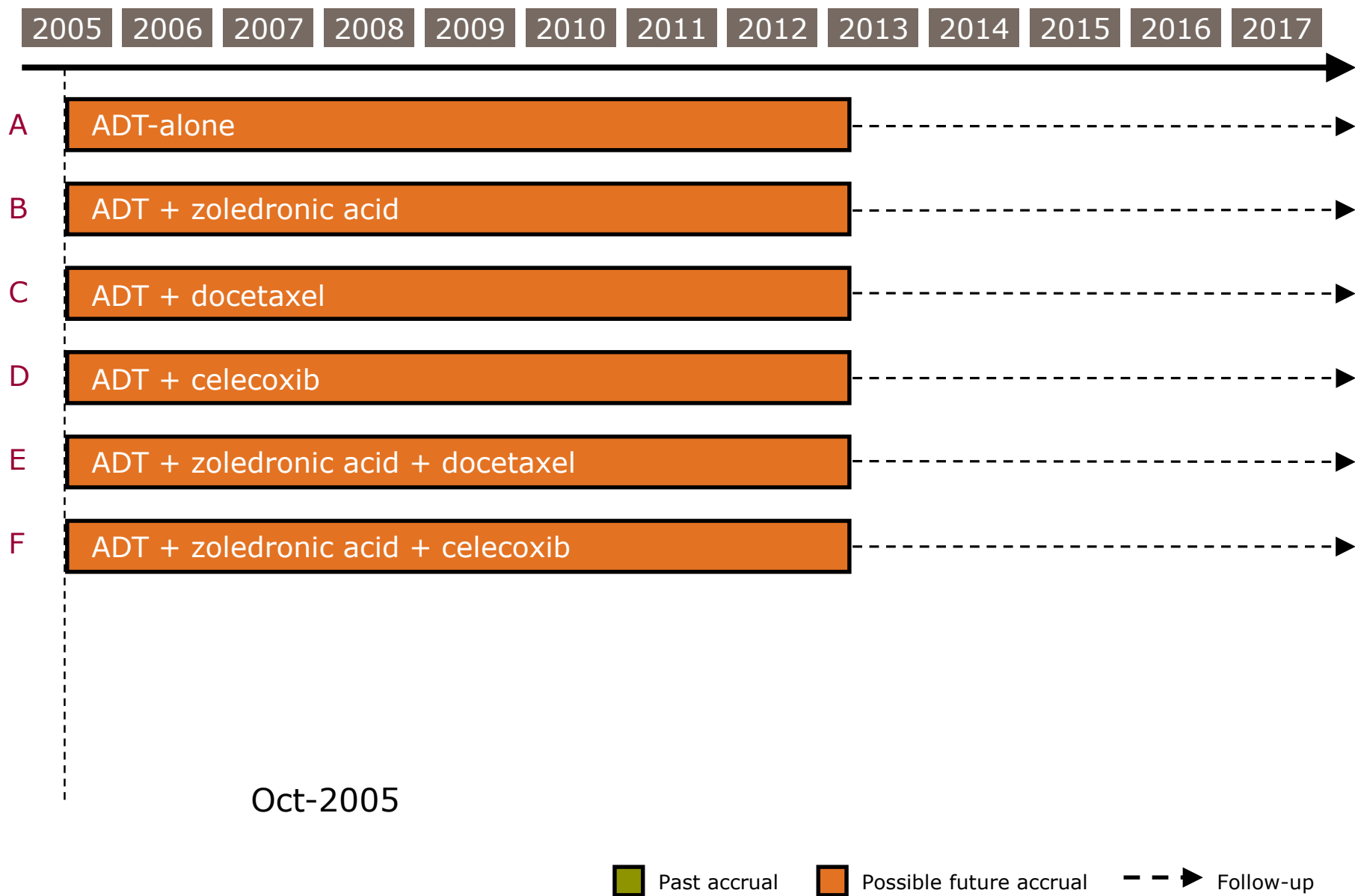
Stage	<u>Outcome Measures</u>	
	Primary	Secondary
(Pilot)	(Safety)	(Feasibility)
Activity I-III (phase II)	Failure-free survival	Overall survival Toxicity (safety) Skeletal-related events
Efficacy IV (phase III)	Overall survival	Failure-free survival Toxicity (safety) Skeletal-related events Quality of life

Accrual: initial plans

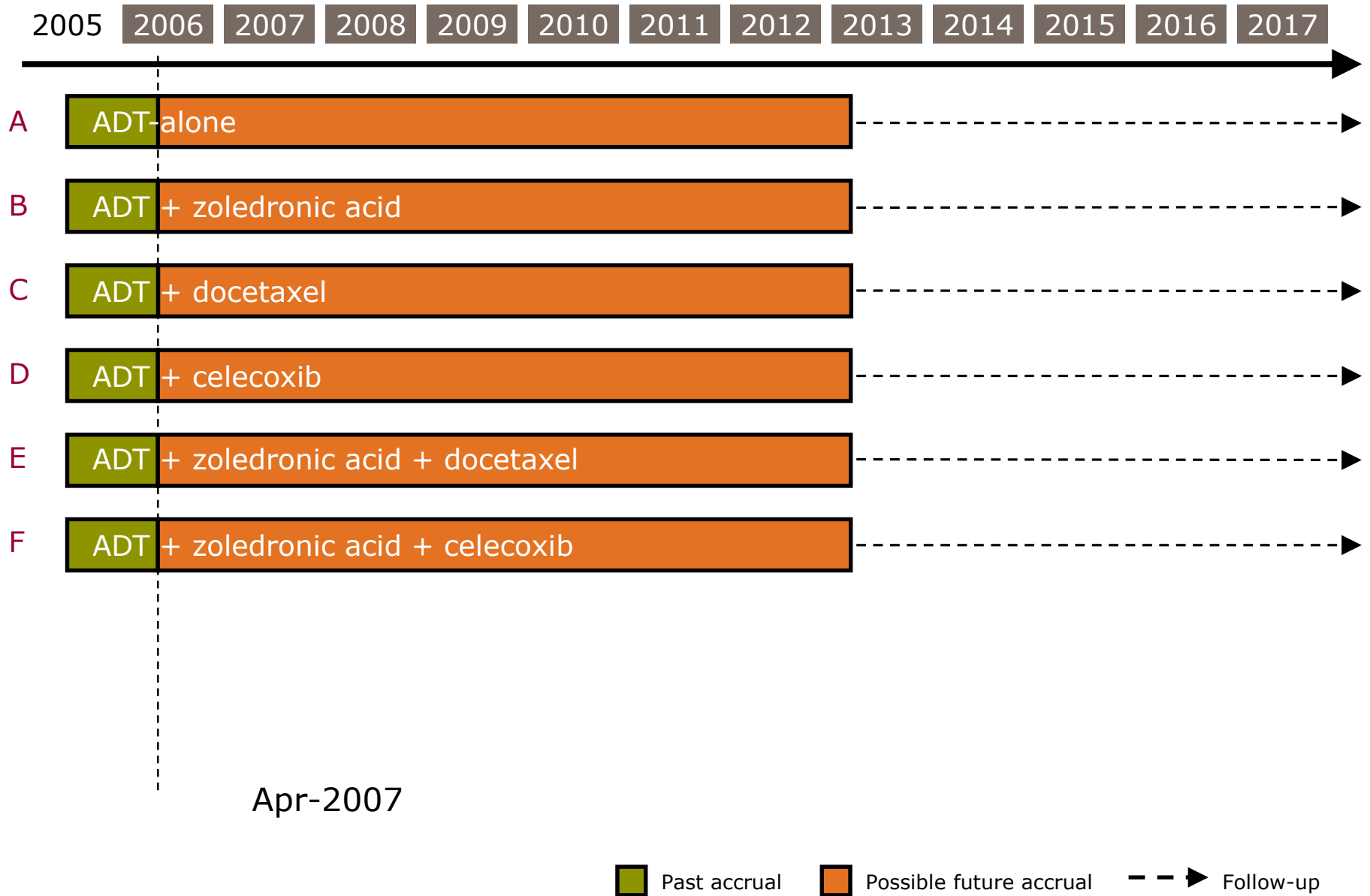


 Past accrual  Possible future accrual  Follow-up

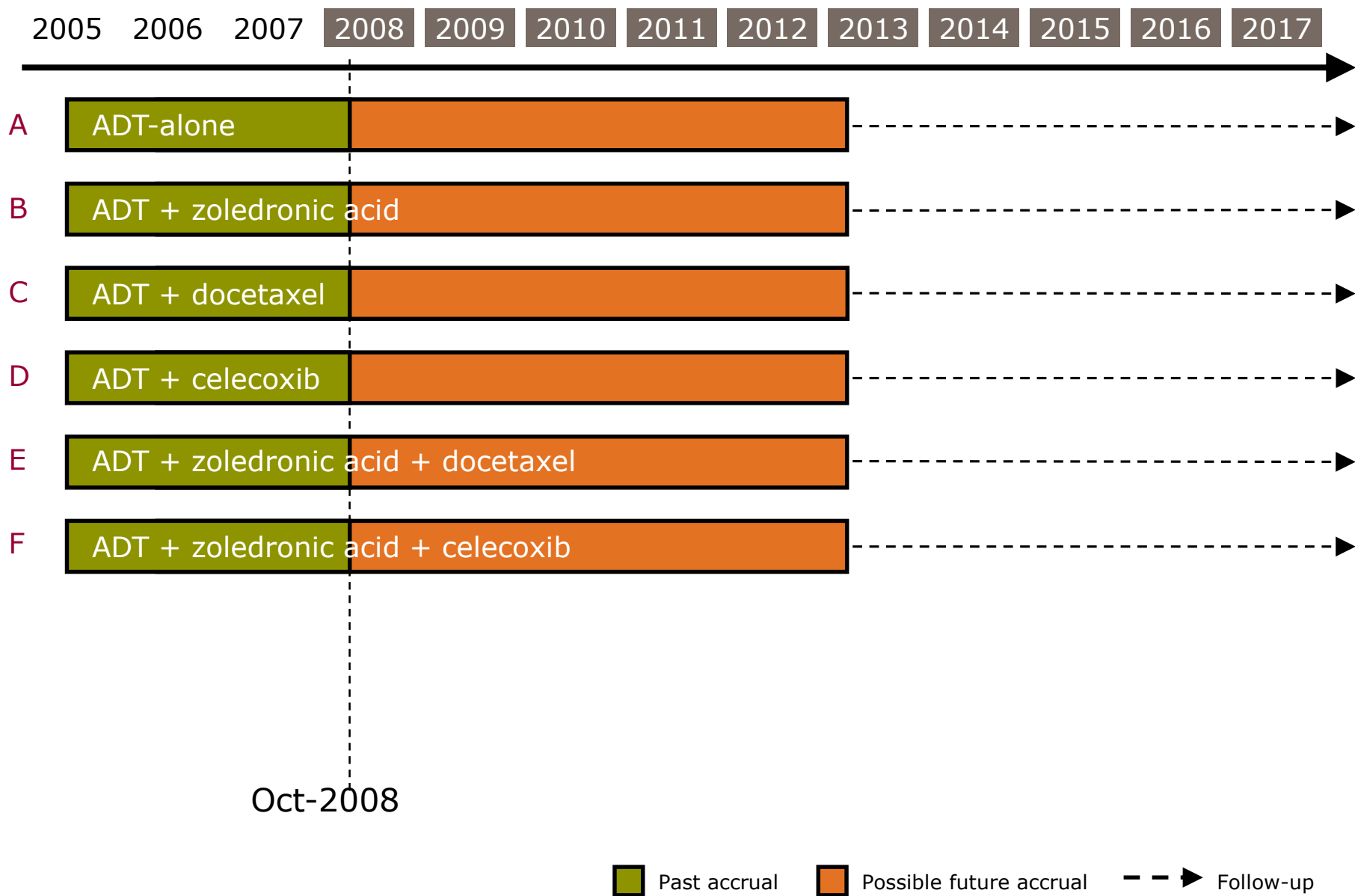
Accrual: initial plans



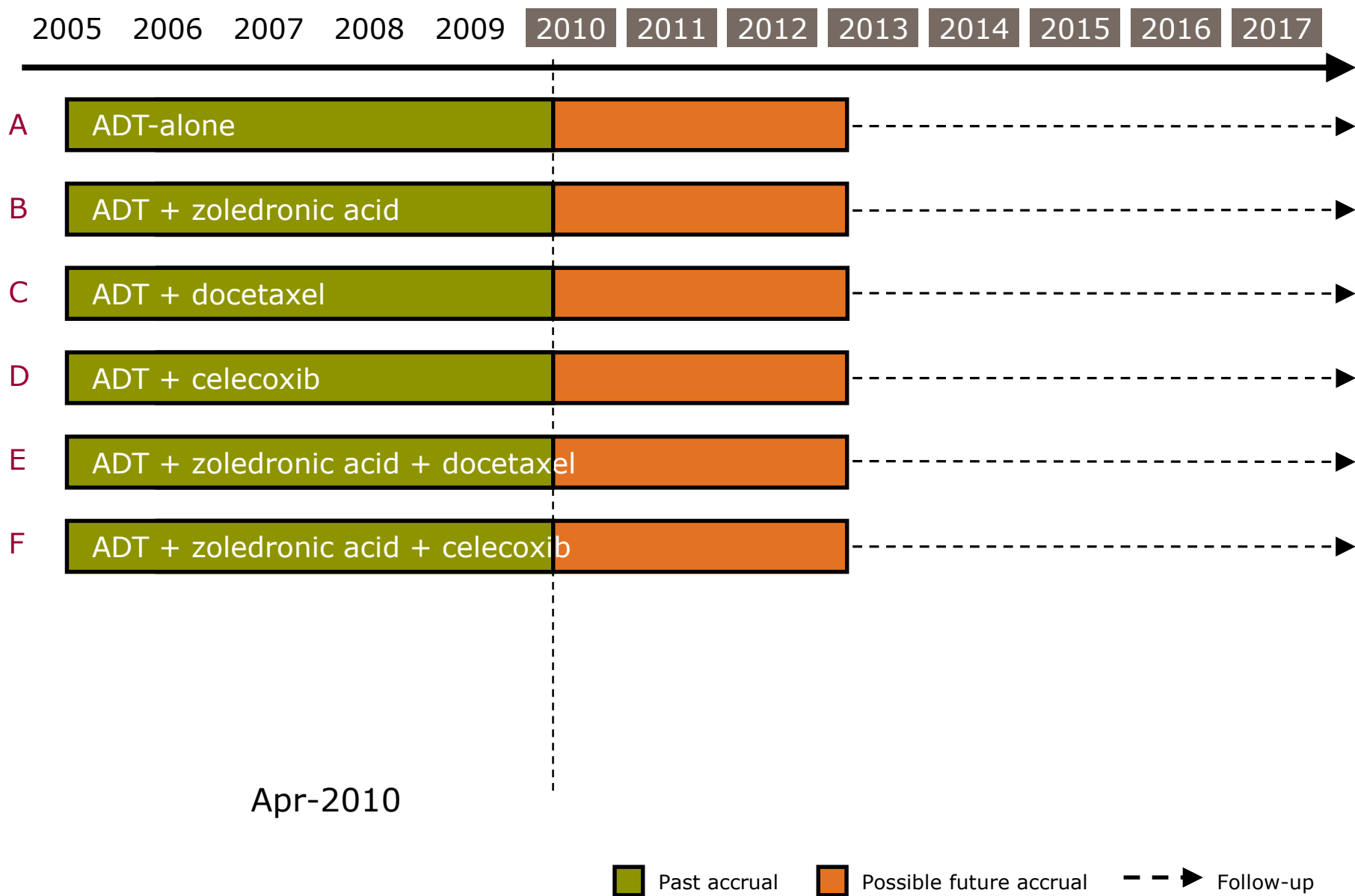
End of pilot phase (original arms)



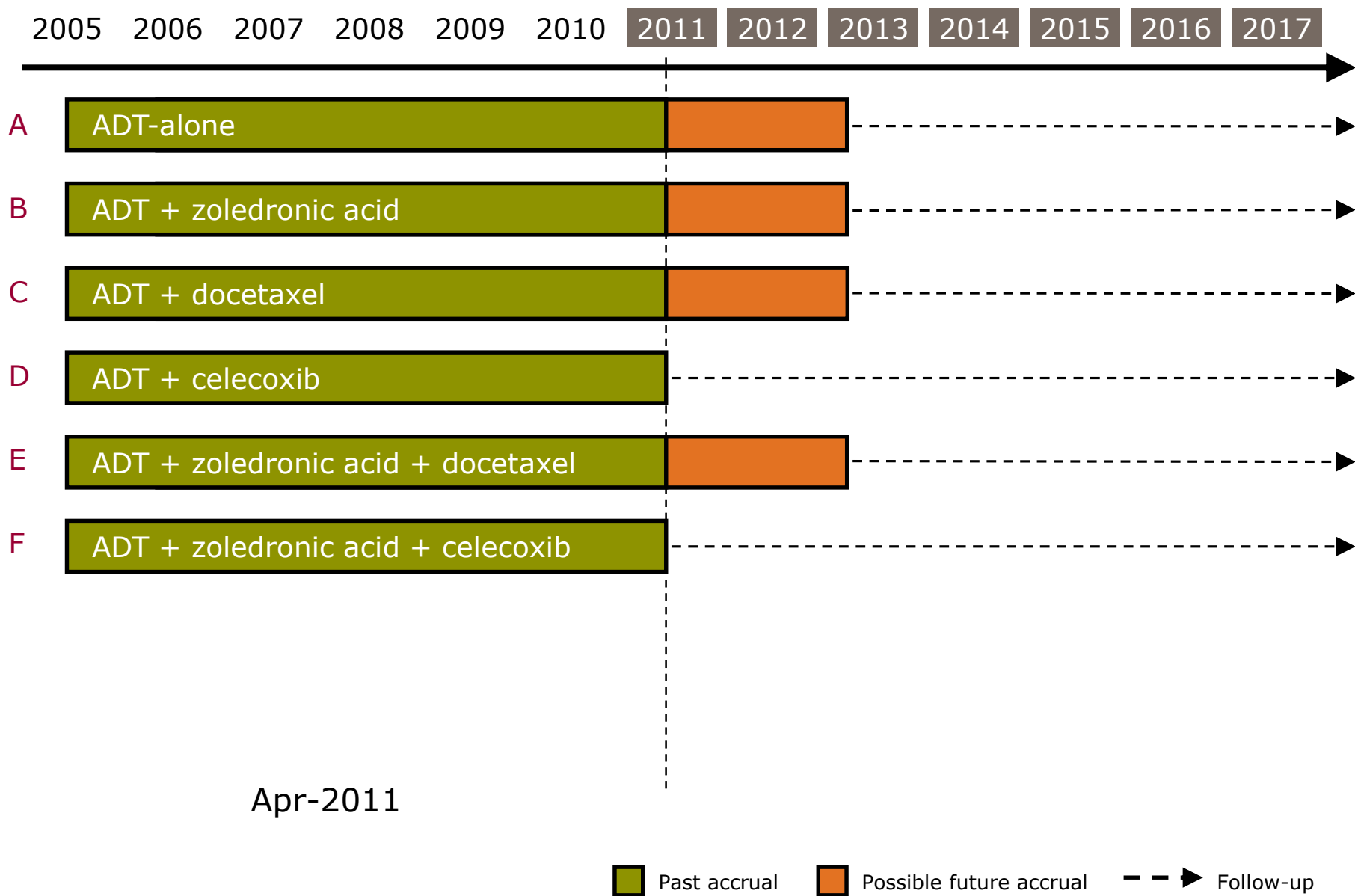
Milestone: 500 patients in trial



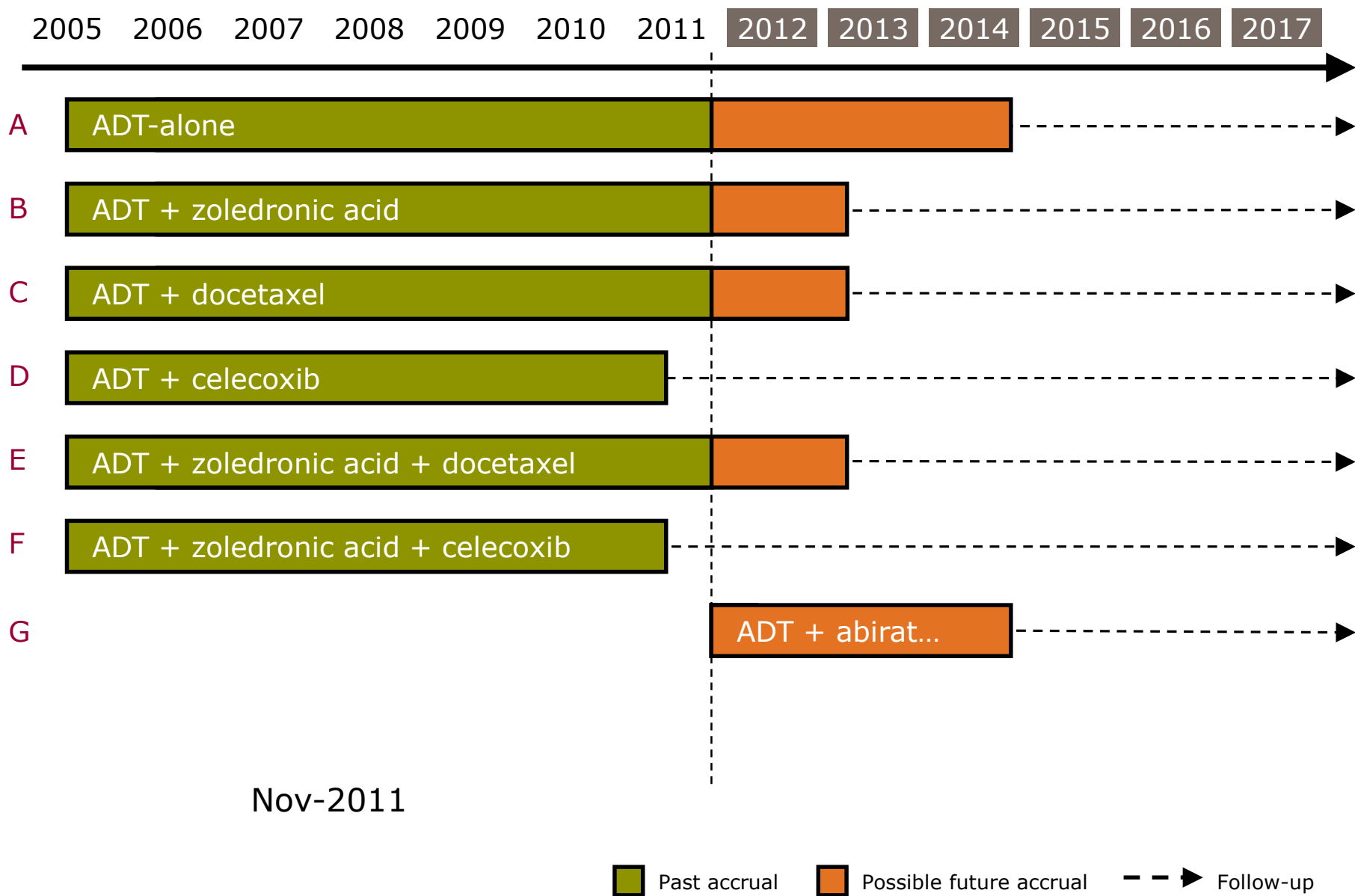
Activity Stage 1 analysis (original arms)



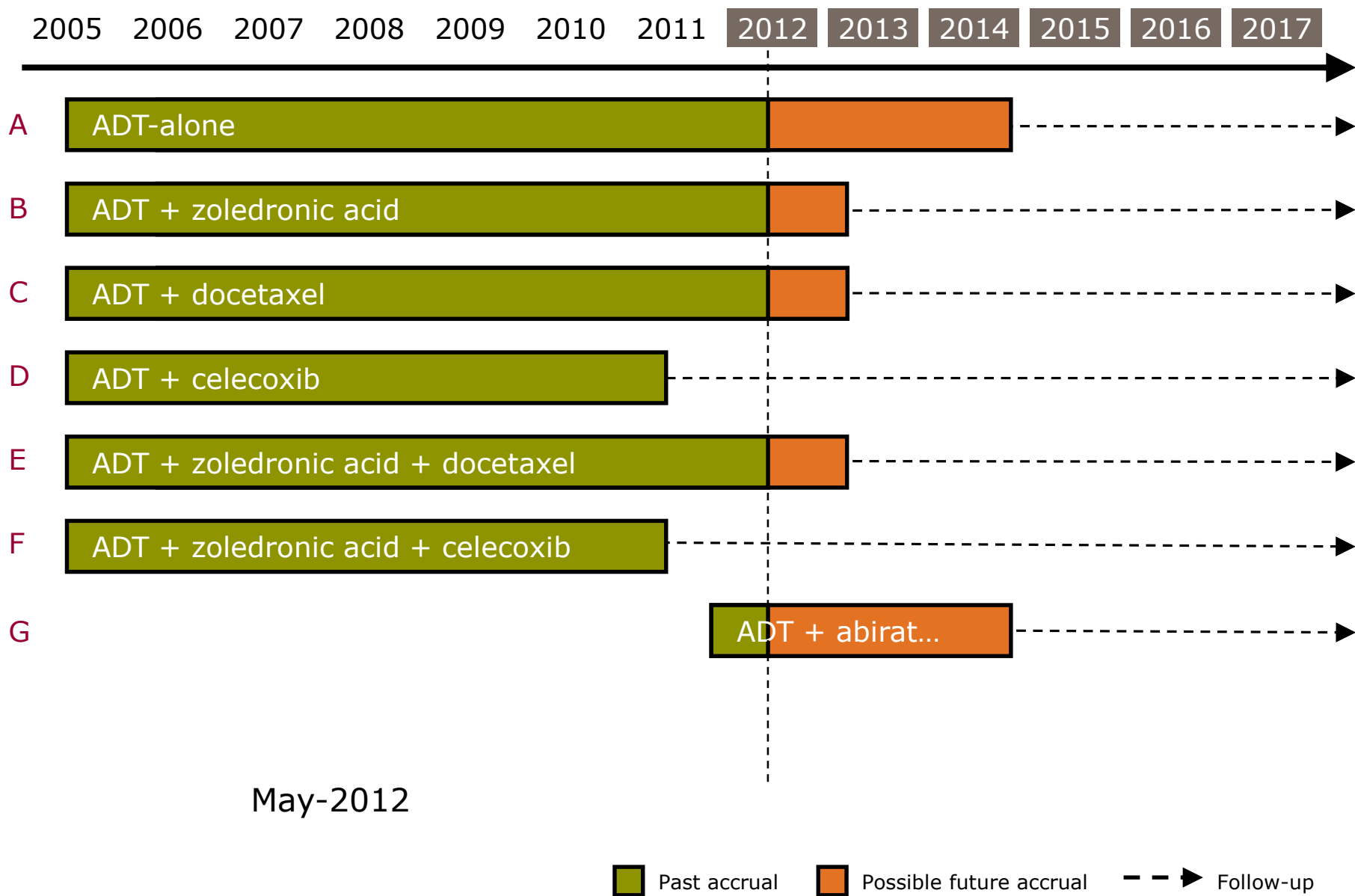
Activity Stage 2 analysis (original arms)



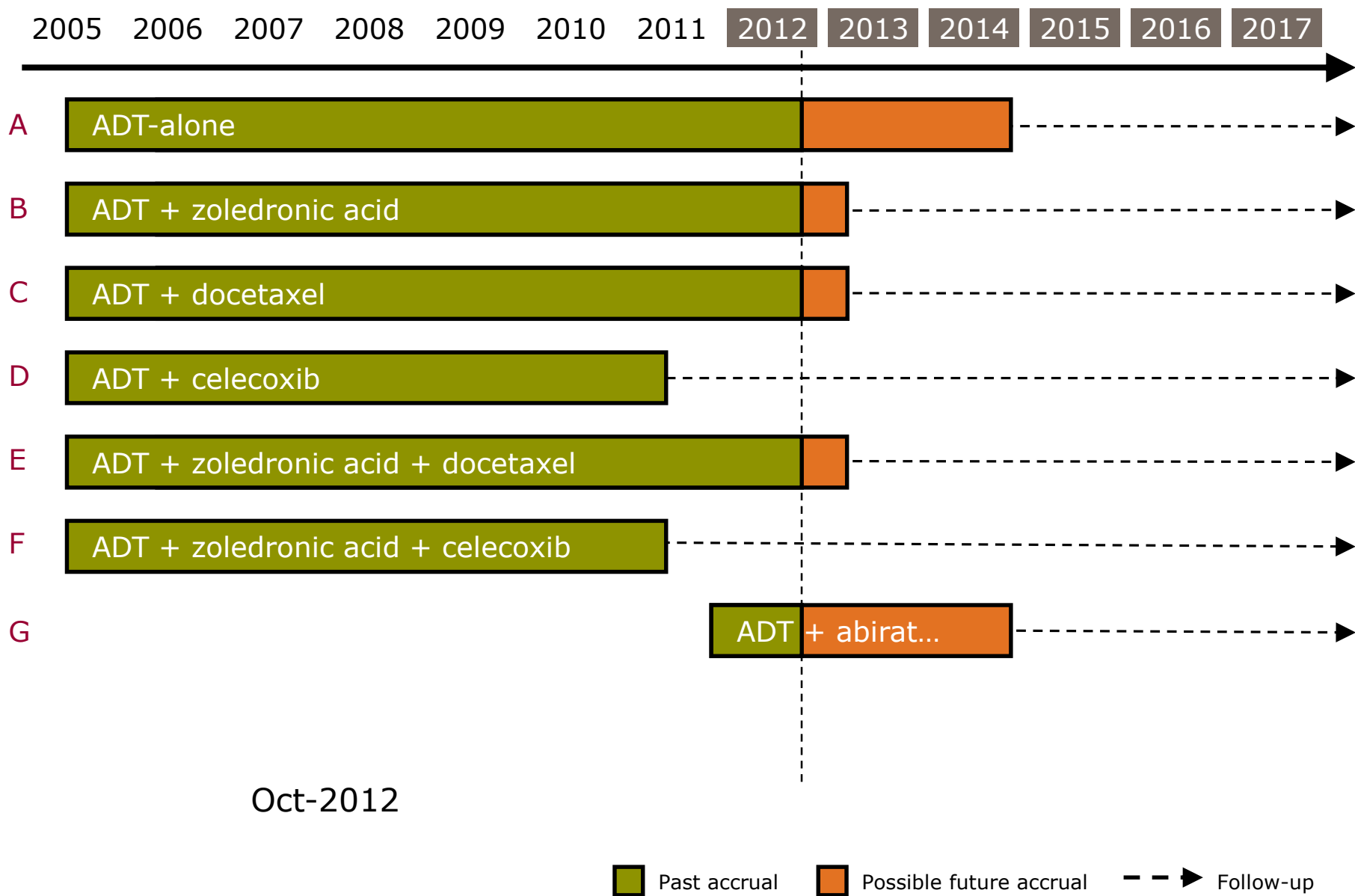
Abiraterone comparison activated



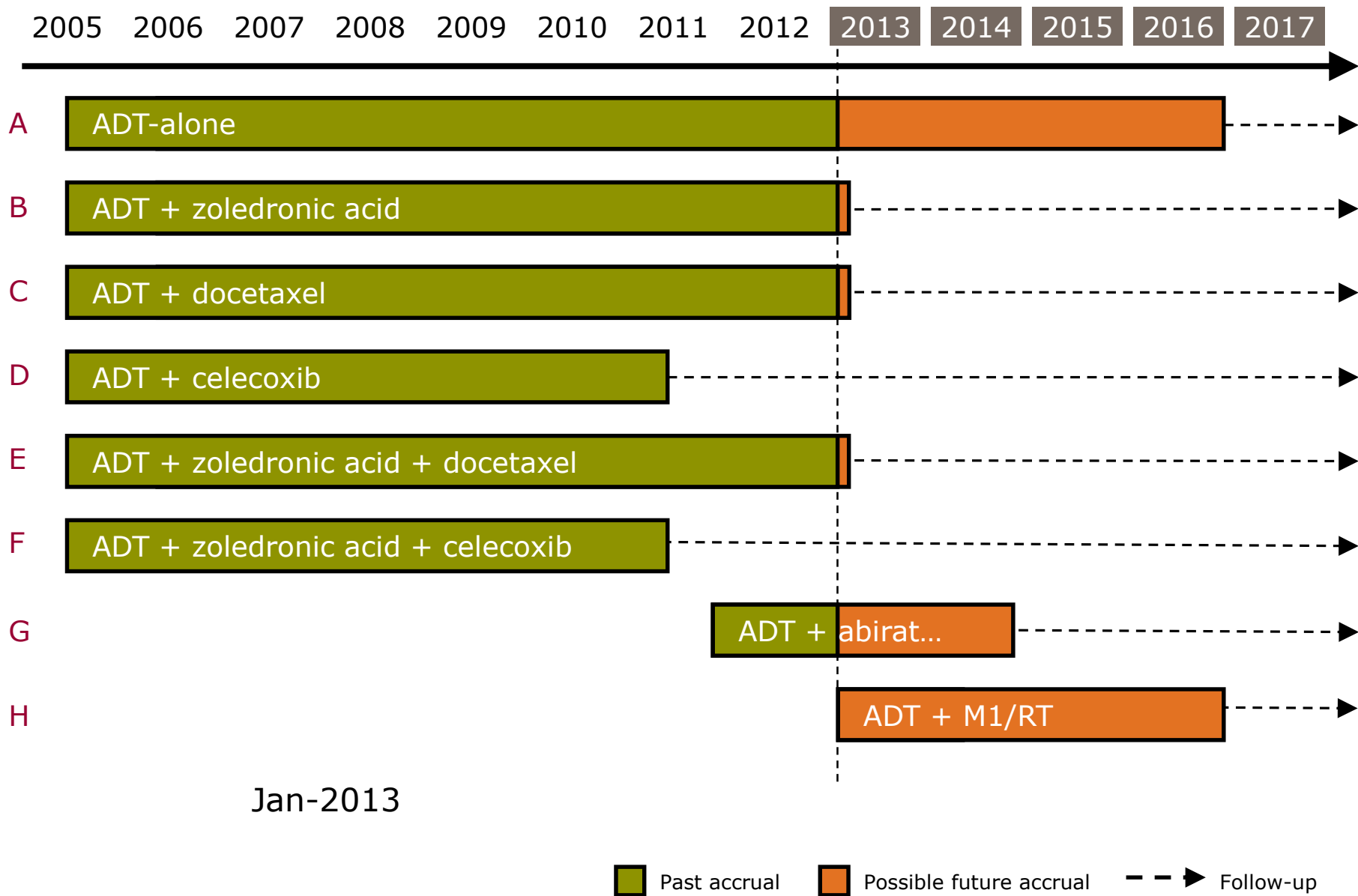
Activity Stage 3 analysis (original arms)



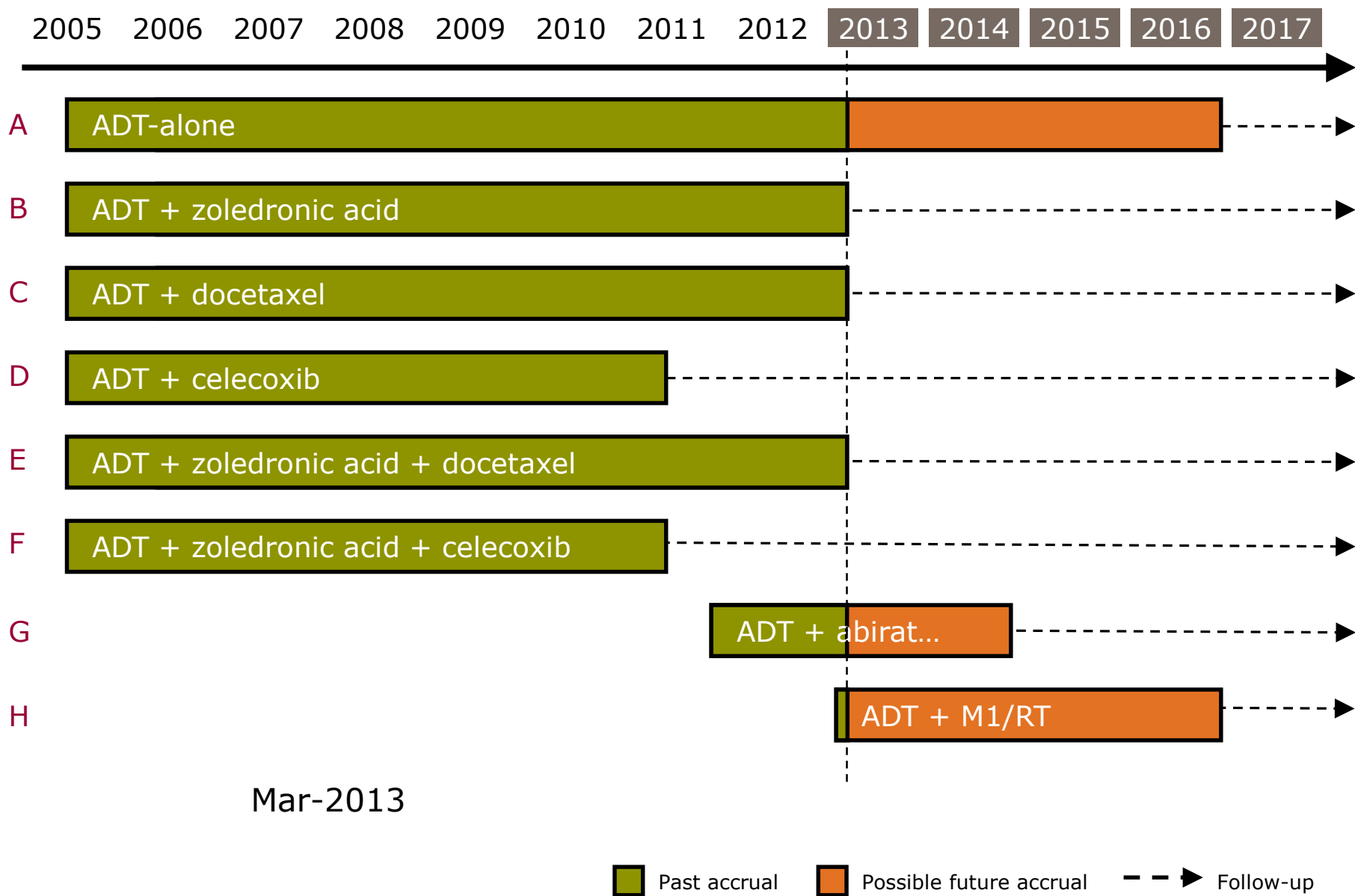
End of abiraterone pilot phase



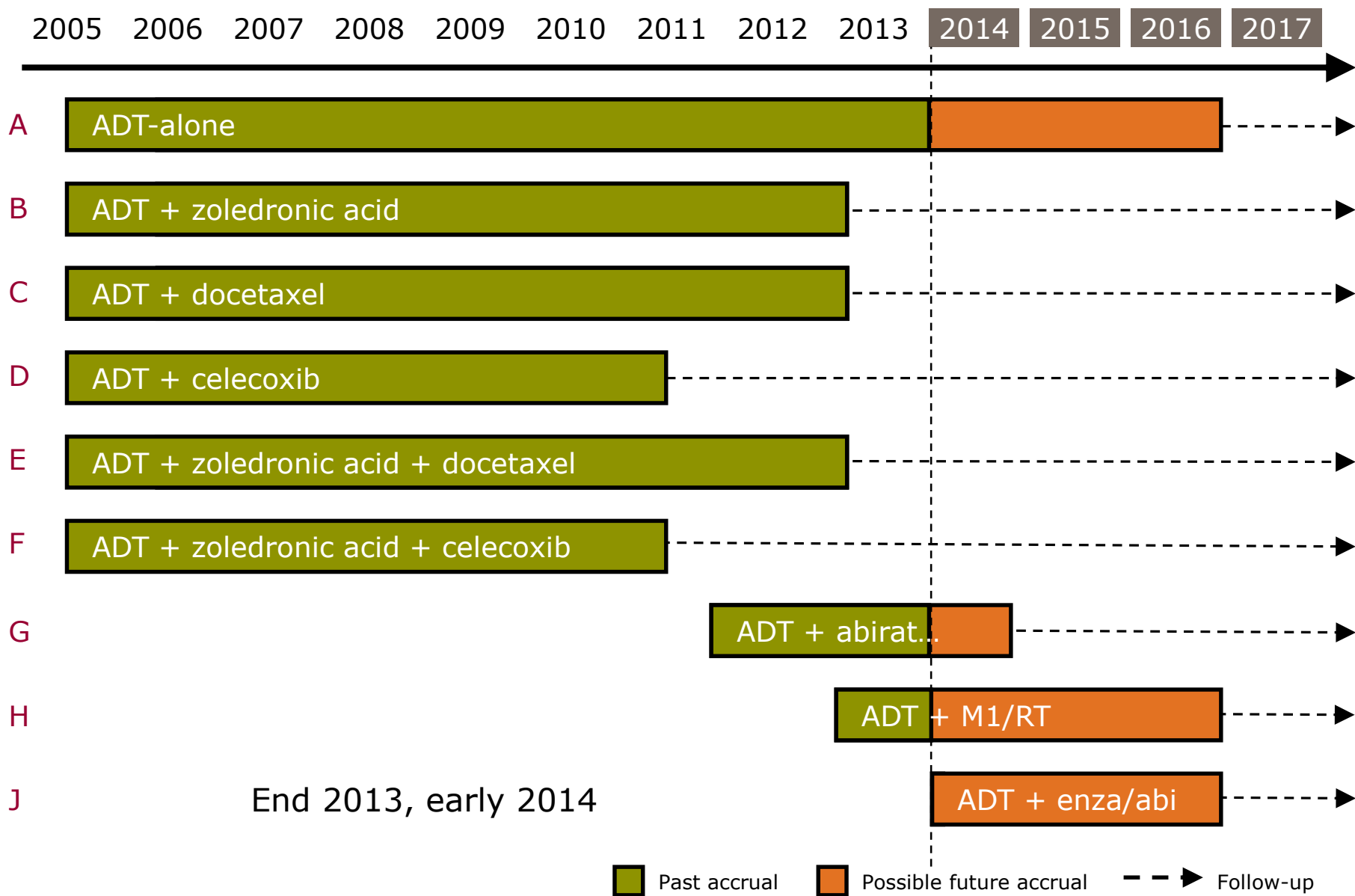
M1/RT comparison activated



Accrual completed (original comparisons)

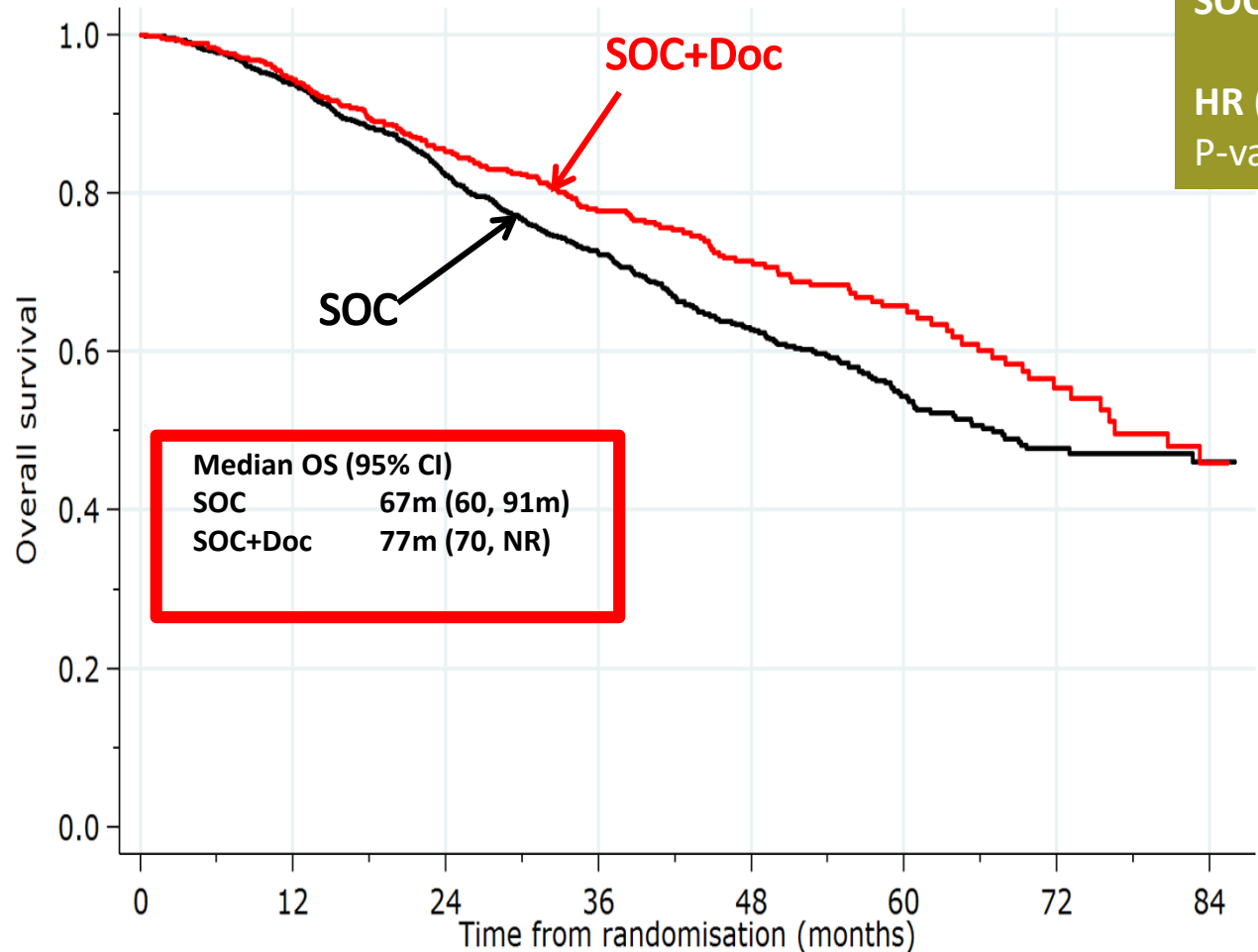


Enzalutamide comparison activated



2015: Docetaxel Survival Results

SOC	405 deaths
SOC+Doc	165 deaths
HR (95%CI)	0.76 (0.63, 0.91)
P-value	0.003



Non-PH p-value 0.51

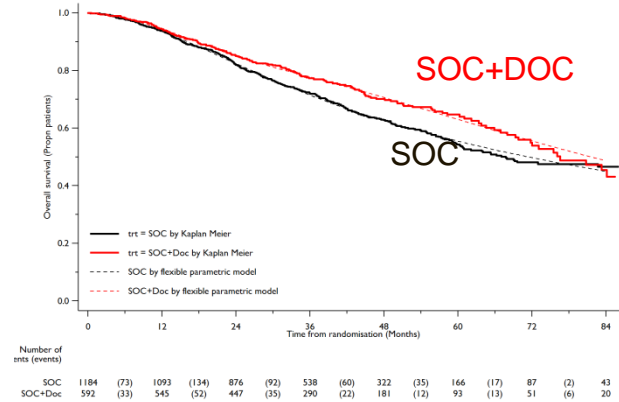
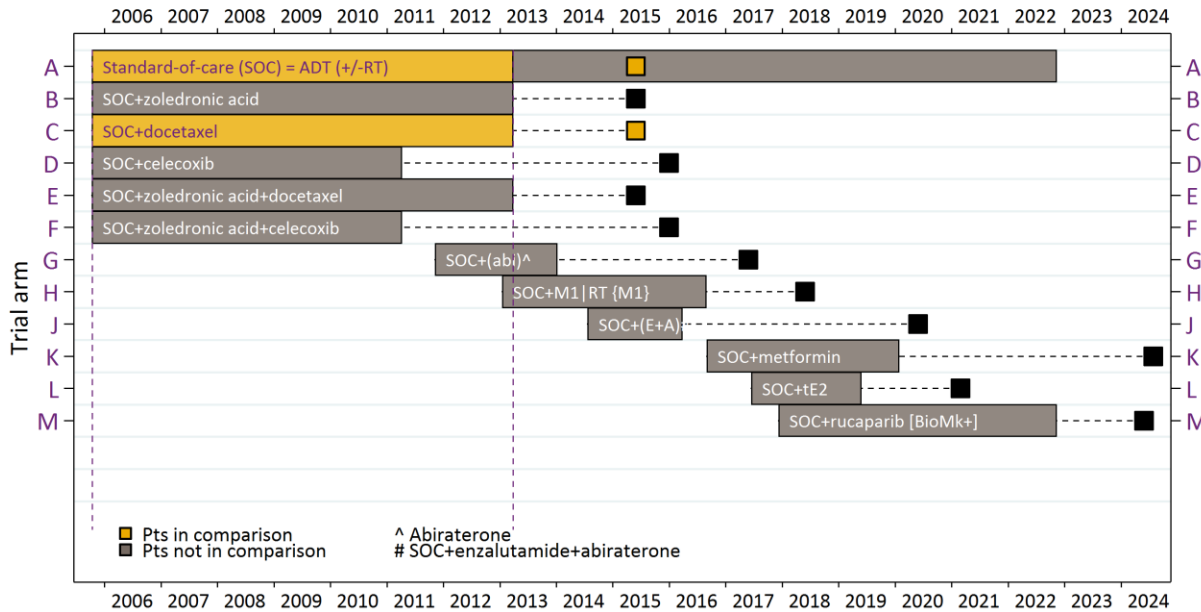
Restricted mean OS time	
SOC	58.8m
SOC+Doc	63.4m
Diff (95%CI)	4.6m (1.8, 7.3m)

Group
At risk (events)

SOC	1184	(73)	1092	(130)	860	(89)	521	(59)	310	(33)	156	(17)	81	(2)	36
SOC+Doc	592	(33)	545	(51)	437	(32)	283	(19)	180	(12)	91	(12)	48	(6)	18

STAMPEDE: SOC+DocP vs SOC

STAMPEDE: Docetaxel comparison



HR (95%CI) 0.78 (0.66, 0.93)
P-value 0.006

Recruitment: Oct-2005 to Mar-2013

Patients: 1184 SOC

592 SOC+DocP

Reported: ASCO 2015

Published: Lancet 2016

Allocation ratio: 2:1

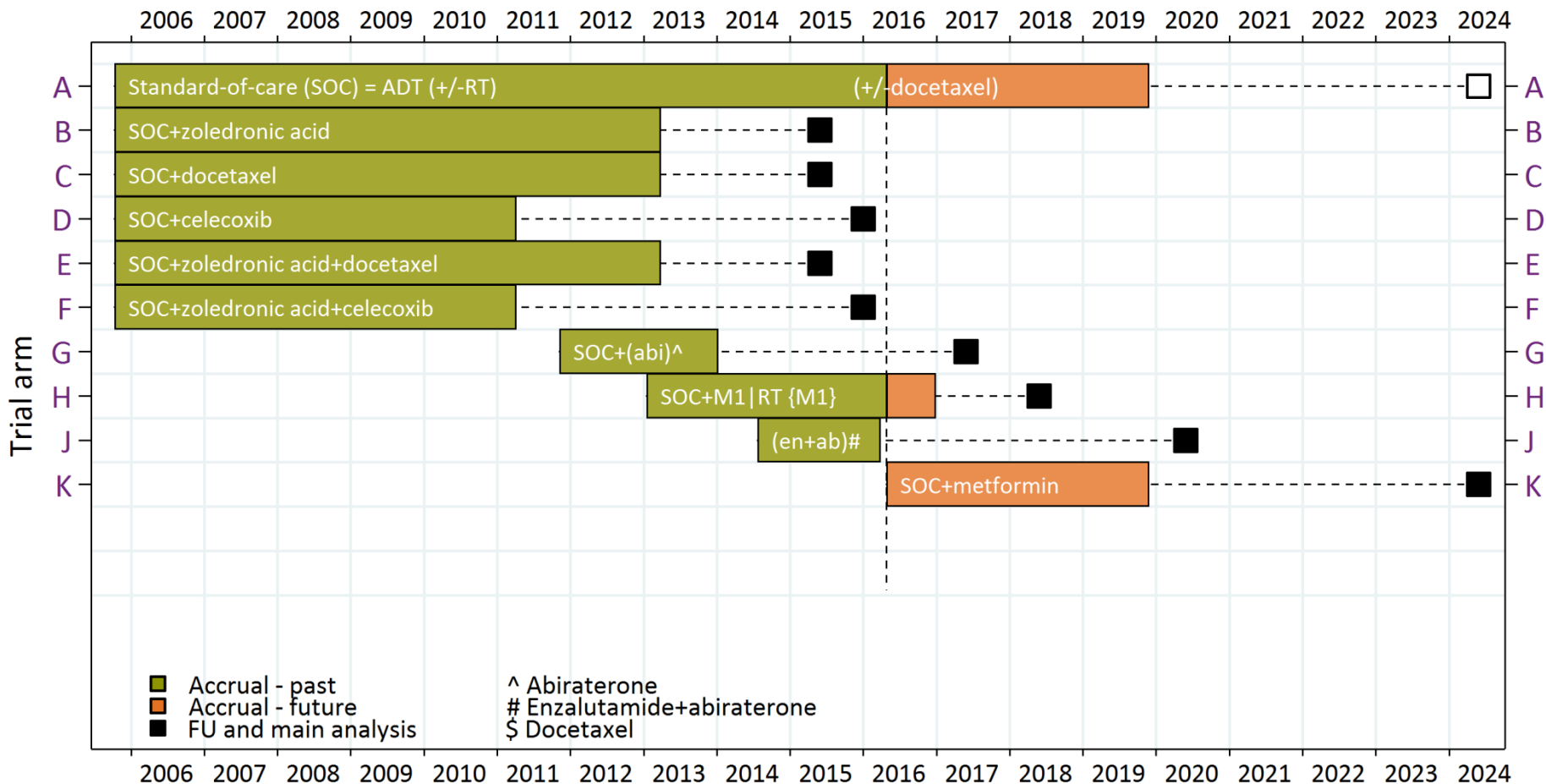


**Clinical Commissioning Policy
Statement: Docetaxel in
combination with androgen
deprivation therapy for the
treatment of hormone naïve
metastatic prostate cancer**

- Already changed clinical practice
- Shortlisted for BMJ UK Research Paper of the Year

Control arm changed and new arm added

STAMPEDE: Metformin comparison introduced

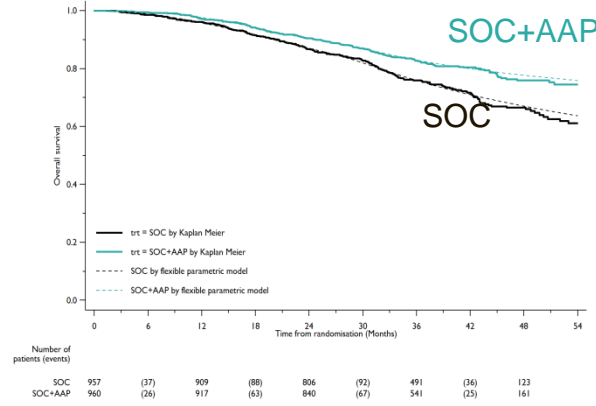
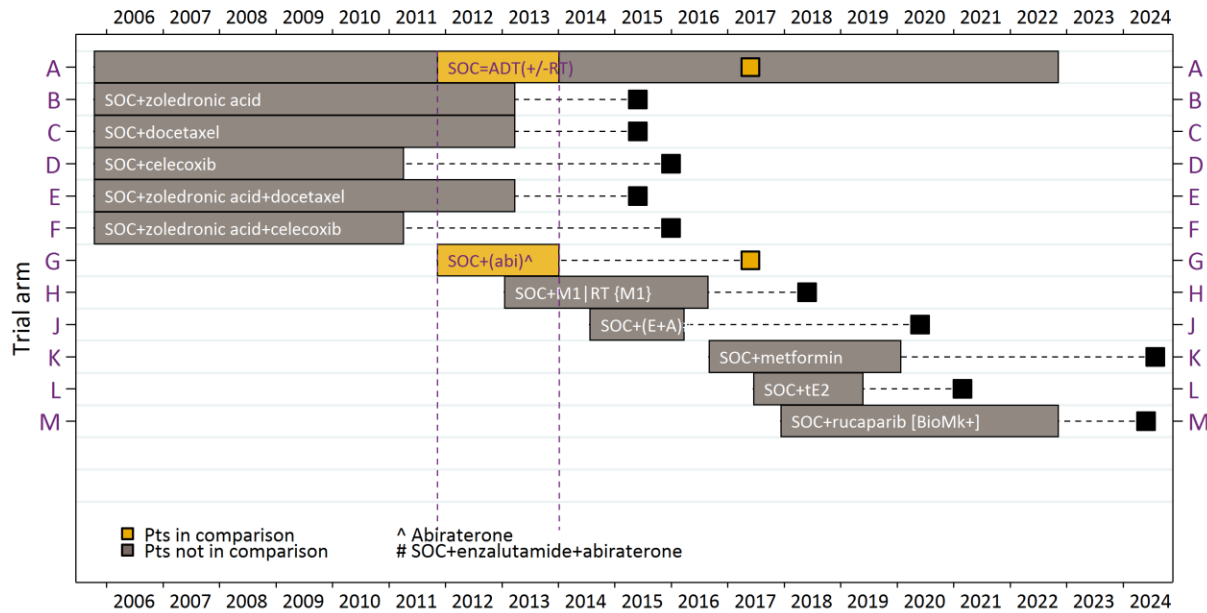


Q2-2015: launch of metformin comparison

--- Trial recruits from population; powered in M1

STAMPEDE: SOC+AAP vs SOC

STAMPEDE: Abiraterone comparisons



HR (95%CI) 0.63 (0.52, 0.76)
P-value 0.0000115

Recruitment: Nov-2011 to Jan-2014

Patients: 957 SOC
 960 SOC+AAP

Reported: ASCO 2017

Published: NEJM 2017

Allocation ratio: 1:1

ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Sporn, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.E. Arora, C. Gilson, R.J. Jones, D. Matheson, B. Millman, G. Attard, S. Chowdhury, W.P. Cross, S. Gillerson, C.C. Parker, J.M. Sargent, D.R. Berchuck, C. Bravinger, F. Adida, S. Kang, A.J. Griffin, J. Sella, S. Brock, P. Chakraborti, C. Ferguson, J. Galle, E. Grigg, M. Hingorani, P.J. Hosie, J.F. Lentin, Z.I. Malik, F. McArdina, M. McPhail, J. Monteyrie, J. O'Sullivan, D. Parkin, A. Proffers, A. Robinson, N.H. Squires, C. Thomas, J. Waggstaff, J. Wylie, A. Zelar, M.K.R. Parmar, and M.R. Sporn, for the STAMPEDE Investigators

ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Khalim Figueira, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fain, M.D., Roberto Matsuura, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Bruno T. Adelman, M.D., Mustafa Cengizoglu, M.D., Giuseppe Va, M.D., Susan Feyerscheid, M.D., Andrew Protherham, M.D., Ph.D., Peter De Perro, M.D., Thian Khoo, Ph.D., Isaac C. Park, Ph.D., Mary E. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators¹

ABSTRACT

BACKGROUND: Abiraterone acetate plus prednisone improves survival in men with advanced prostate cancer. We assessed the effect of this combination in men starting long-term androgen-deprivation therapy (ADT), using a multicenter, multicourse, double-blind, randomized, controlled, phase 3 trial.

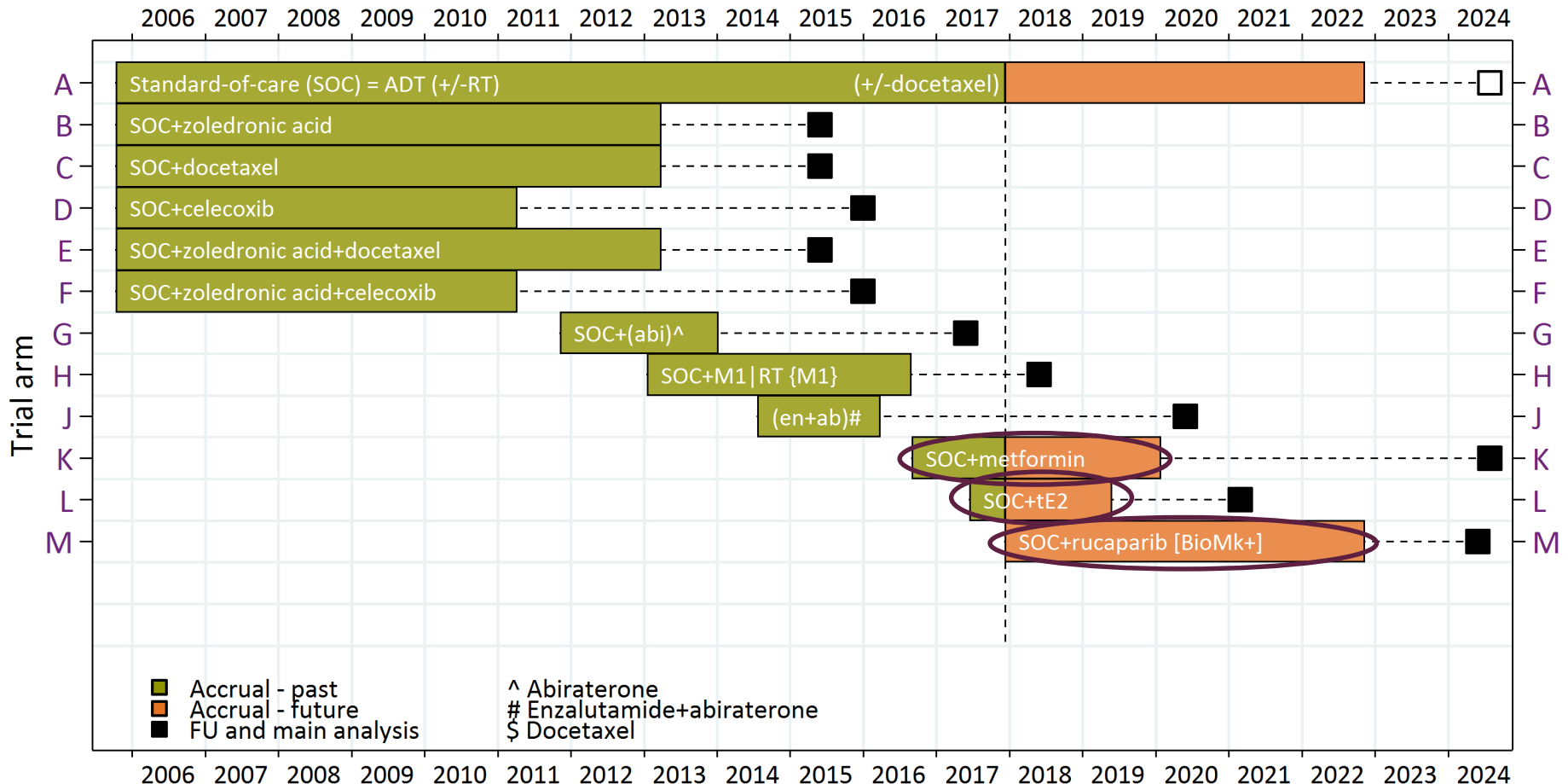
DESIGN: We randomly assigned patients in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate (1000 mg daily) and prednisone (5 mg daily) combination therapy. Local radiotherapy was mandated for patients with node-negative, nonmetastatic disease and encouraged for those with positive nodes. For patients with metastatic disease with no radiotherapy planned and for patients with metastatic disease, treatment continued until radiologic, clinical, or prespecified toxicity (PSA progression, edema, or other toxicity) was observed or until any type of progression, whichever came first. The primary outcome measure was overall survival. Secondary outcomes were failure-free survival, time to failure, time to failure as defined by radiologic, clinical, or PSA progression or death from prostate cancer causes.

RESULTS: A total of 1917 patients underwent randomization from November 2011 through January 2014. The median age was 67 years, and the median PSA level was 14.6 ng/mL. A total of 52% of the patients had metastatic disease, 20% had node-negative or node-intermediate nonmetastatic disease, and 28% had node-negative, nonmetastatic disease. 90% had newly diagnosed disease. The median follow-up was 36 months. There were 184 deaths in the combination group as compared with 214 in the ADT-alone group (hazard ratio, 0.63; 95% confidence interval [CI], 0.52 to 0.76; P<0.0001); the hazard ratio was 0.75 in patients with nonmetastatic disease and in those with metastatic disease. There were 260 treatment-related events in the combination group as compared with 335 in the ADT-alone group (hazard ratio, 0.29; 95% CI, 0.25 to 0.34; P<0.0001); the hazard ratio was 0.21 in patients with nonmetastatic disease and 0.31 in those with metastatic disease. Grade 3 or 4 adverse events occurred in 47% of the patients in the combination group (with nine fatal events) and in 37% of the patients in the ADT-alone group (with three grade 4 events).

CONCLUSIONS: Among men with newly diagnosed or metastatic prostate cancer, ADT plus abiraterone and prednisone was associated with significantly higher rates of overall failure-free survival than ADT alone. (Funded by Cancer Research UK, U.K., and STAMPEDE ClinicalTrials.gov number, NCT01270814).

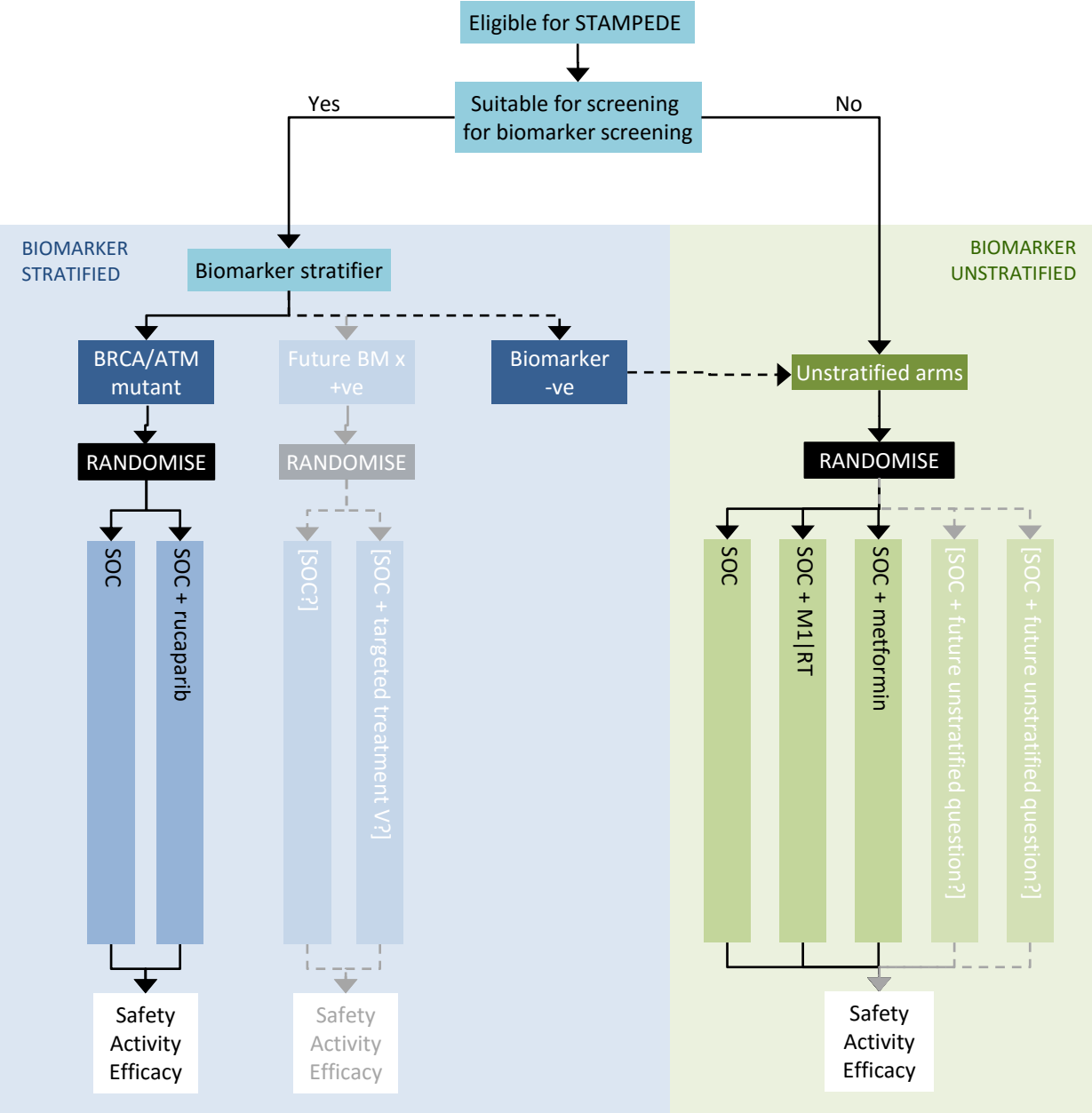
MAMS Platform: further developments in STAMPEDE

STAMPEDE: Rucaparib comparison introduced



First biomarker-stratified question for proportion of patients
 Launch Q4-2017

STAMPEDE overview with rucaparib comparison (and possible future comparisons)



Key
SOC: standard-of-care

STAMPEDE

- Will answer 12 major questions in 20 years (inc. phase II and phase III components)
- Has shown that Adaptive trials are
 - Feasible & practicable
 - Recruit well enough to overcome more arms
 - Efficient
 - Supported by patients, clinicians, funders, companies

MAMS platform

- EMA and FDA review & approval of MAMS platform design for RAMPART (about to be initiated)
- RAMPART – 4 arm randomised trial of immunotherapies in early renal cancer
 - 4th arm, blank at the moment

RAMPART – about to open

- International MAMS trial for renal cancer

Patients who have had their primary
RCC resected and are at intermediate or
high risk of relapse
n=1750

Arm A
Active Monitoring
for 1 year

Arm B
Durvalumab
1500mg q4w for 1
year

Arm C
Durvalumab
1500mg q4w for 1
year
Tremelimumab
75 mg at day 1
and w4

Arm D
*New agent/
Combination of
agents*

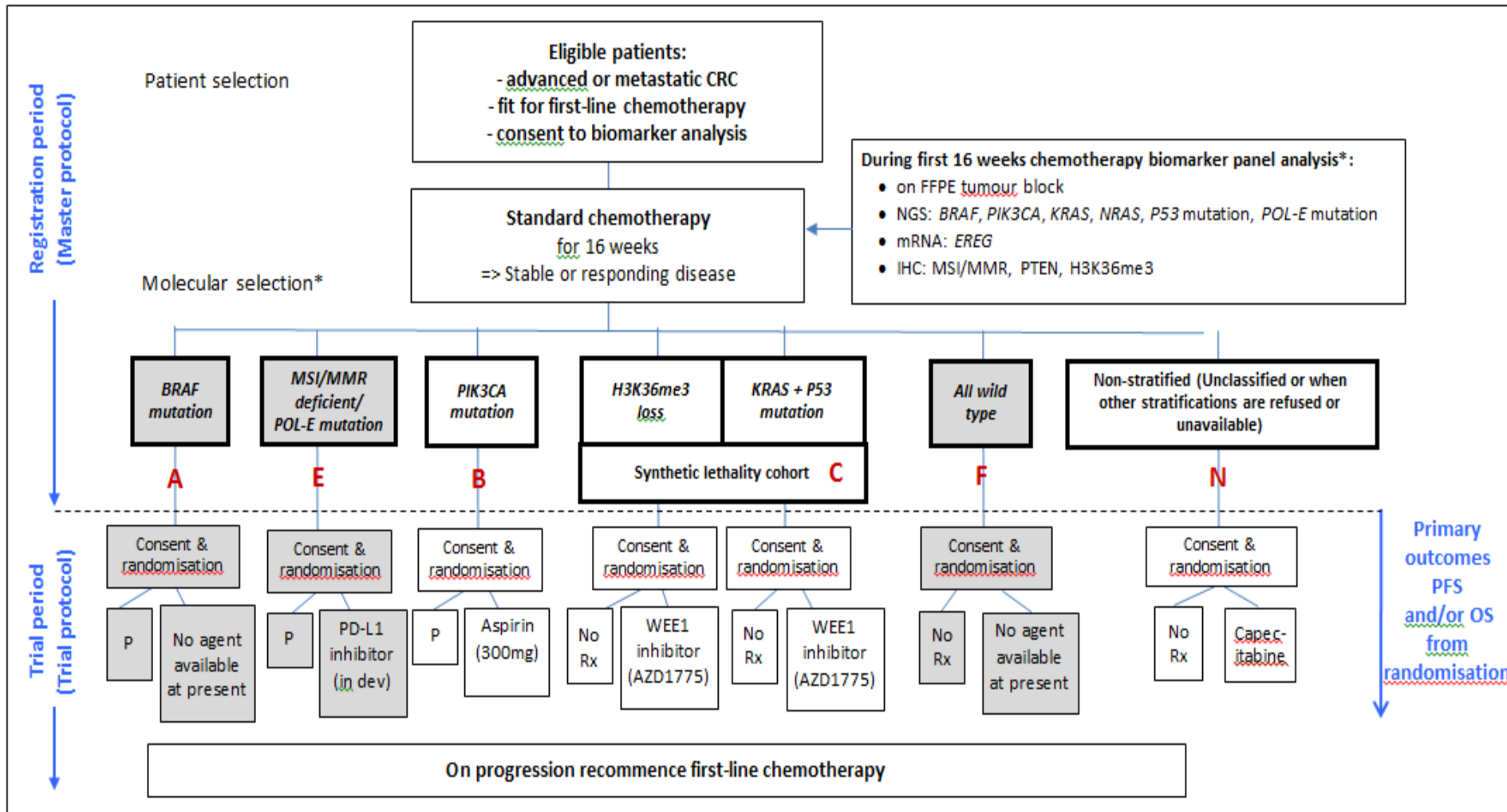
Principles for trial design for biomarker defined subgroups of a specific disease:

Umbrella Trial

Aim to include questions testing new treatments in all (or most) subgroups, using an adaptive approach and incorporate:

- (i) refinement of the subgroups
- (ii) introduction of new subgroups
- (iii) ability to stop testing specific treatments and introduce new treatments
- (iv) evaluation of the link between the biomarker and that treatment

FOCUS4 –umbrella trial design



Add-Aspirin basket design

FOUR PARALLEL COHORTS WITHIN AN OVER-ARCHING PROTOCOL

Participants will have undergone primary treatment with curative intent

BREAST

COLORECTAL

**GASTRO-
OESOPHAGEAL**

PROSTATE

REGISTRATION AND RUN-IN PERIOD

All participants take 100mg aspirin for 8 wks to assess adherence and tolerability

RANDOMISATION

Performed separately within each tumour cohort, double-blind

100mg ASPIRIN

300mg ASPIRIN

PLACEBO

FOLLOW-UP

≥ 5 years, including long-term follow-up via routine health databases in the UK

**Breast primary
outcome: Disease-
free survival**

n=3100

**Colorectal primary
outcome: Disease-
free survival**

n=2600

**Gastro-oesophageal
primary outcome:
Overall survival**

n=2100

**Prostate primary
outcome: Biochem
recurrence-free
survival**

n=2120

Add-Aspirin

- Recruited >3,500 patients in 2 year
- Recruitment has started in India, alongside capacity building work
- 150 recruiting centres in UK, with plans to expand that to more sites

Add Aspirin: basket protocol

- Looking to add further randomisations after 5 years of Aspirin

Applying these designs to infectious diseases

- Truncate-TB: funded
 - MAMS platform trial to shorten drug sensitive TB treatment to 2-3 months (starting with 5 arms)
 - Coordinated in Singapore, conducted in Asia
- Vietnarms: funded
 - Multi-arm trial assessing short courses of direct-acting antivirals to cure hepatitis C
 - Coordinated and conducted in Vietnam
- HCV AVERT: being developed
 - A stratified umbrella trial on how to prevent mother to child transmission of hepatitis C
 - Application for a development grant currently being considered by the MRC, for preparatory work in Egypt and Ukraine

Expanding to other diseases

- Working with a number of other groups nationally and internationally to design and deliver MAMS platform, umbrella and basket trials
- Major need to make progress in number of neurological diseases
 - Alzheimers
 - Motor Neurone Disease
 - Progressive Multiple Sclerosis
 - Parkinsons

Conclusions

- There is a real need to change how we do trials
 - To make faster progress
 - To respond the many new opportunities

