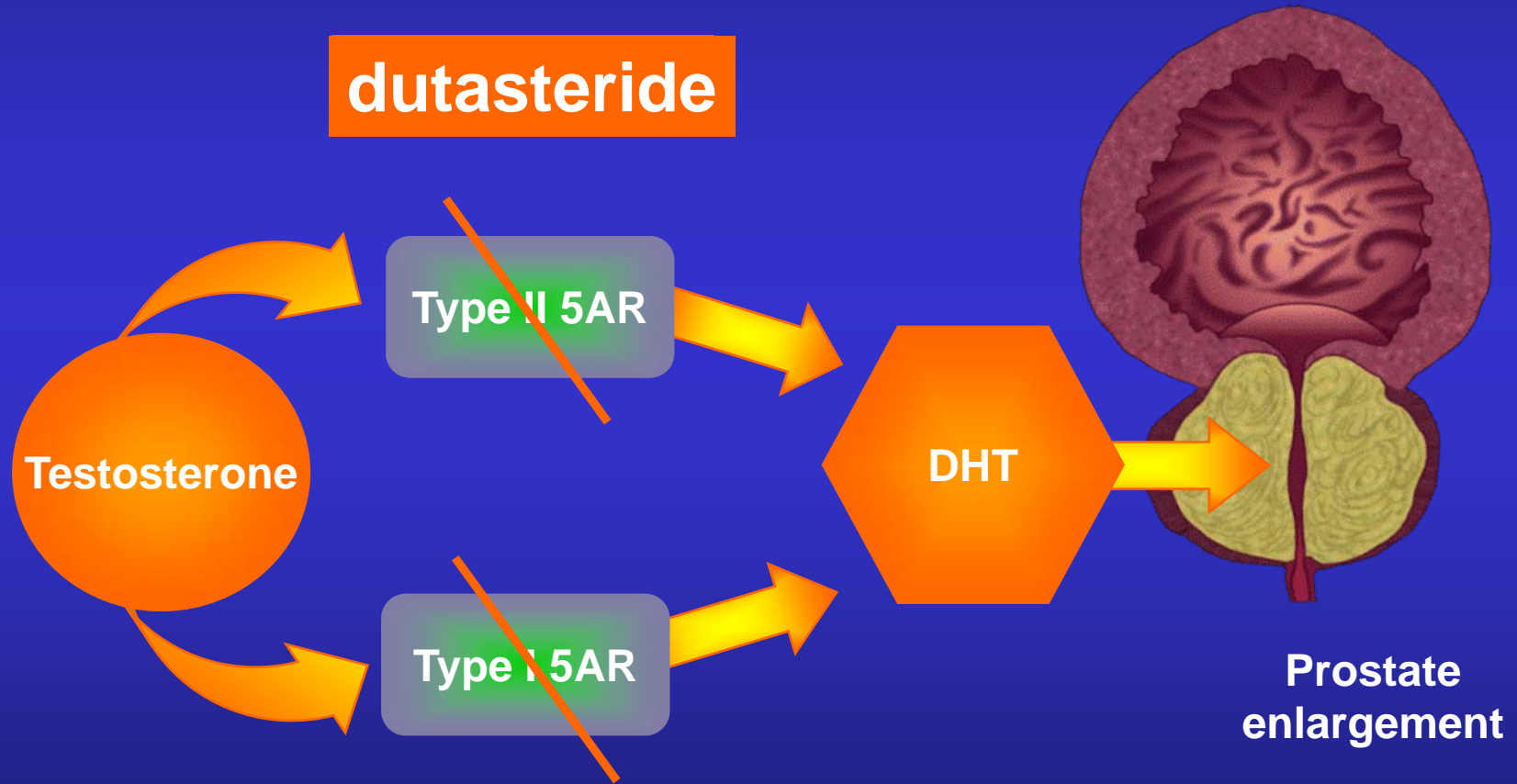


5 α -Reductase Inhibitors and Prostate Cancer Prevention

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Berlin, November 14, 2008

5 α -Reductase (5AR) and the Prostate



Outline

- 1) Finasteride (Proscar) and the Prostate Cancer Prevention Trial (PCPT)
- 2) Dutasteride (Avodart) and the REDUCE trial

PCPT trial design and inclusion criteria

- 18,882 men randomized, age ≥ 55
- “low risk” population for prostate cancer
 - PSA ≤ 3.0 ng/ml
- 7-year treatment with finasteride or placebo
- for-cause biopsies (≥ 6 cores) based on PSA ≥ 4 ng/ml or abnormal prostate examination; per protocol biopsy at year 7
- PSAs doubled in finasteride group
 - To preserve study blinding
 - To equalize number of for-cause biopsies

RESULTS

- Study terminated prematurely because study objectives were met.
- Prostate cancer detected in 24.4% of placebo group and 18.4% of finasteride group (24.8% reduction; $P < 0.001$)
- High grade cancer (Gleason grade 7-10) detected in 237 (5.1%) of placebo group and 280 (6.4%) of finasteride group ($P = 0.005$)

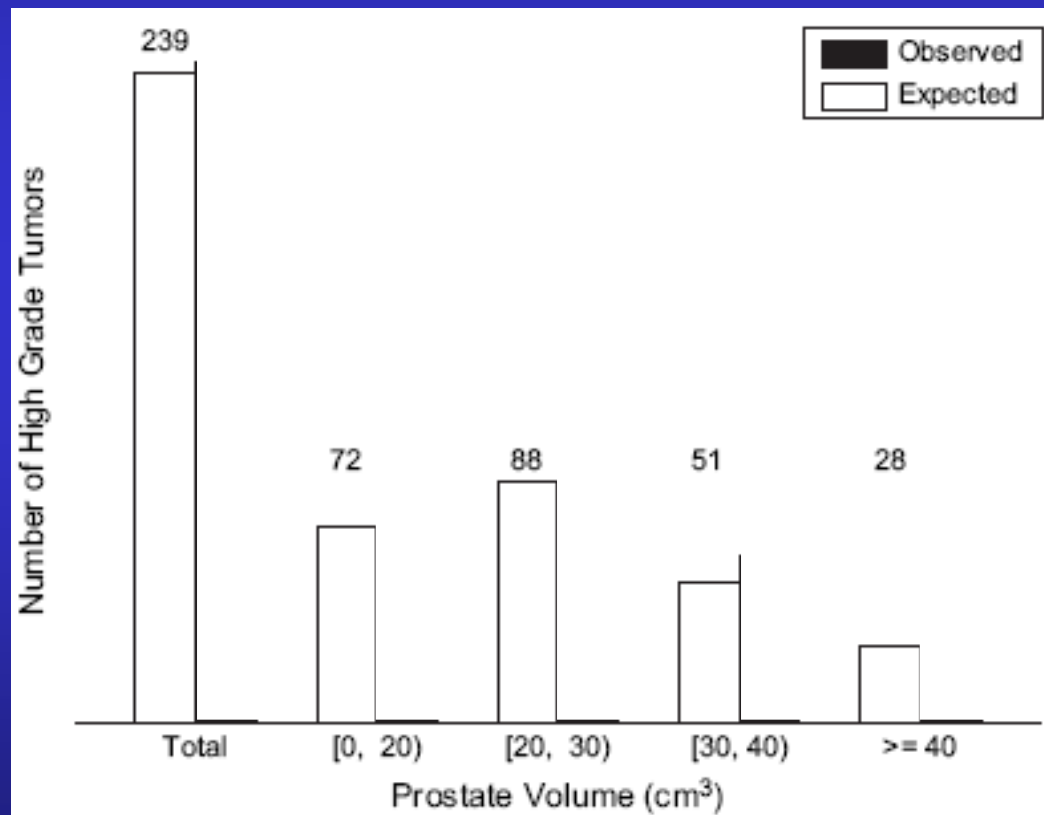
Editorial Conclusion

Finasteride prevents the
meaningless cancers and
increases the mean cancers.



PCPT: Effect of Prostate Volume Reduction Prediction of High Grade Cancer in Finasteride Arm Using Logistic Regression* Derived from Placebo Arm

*Includes age, race, FHx, PSA, PV and number of biopsy cores



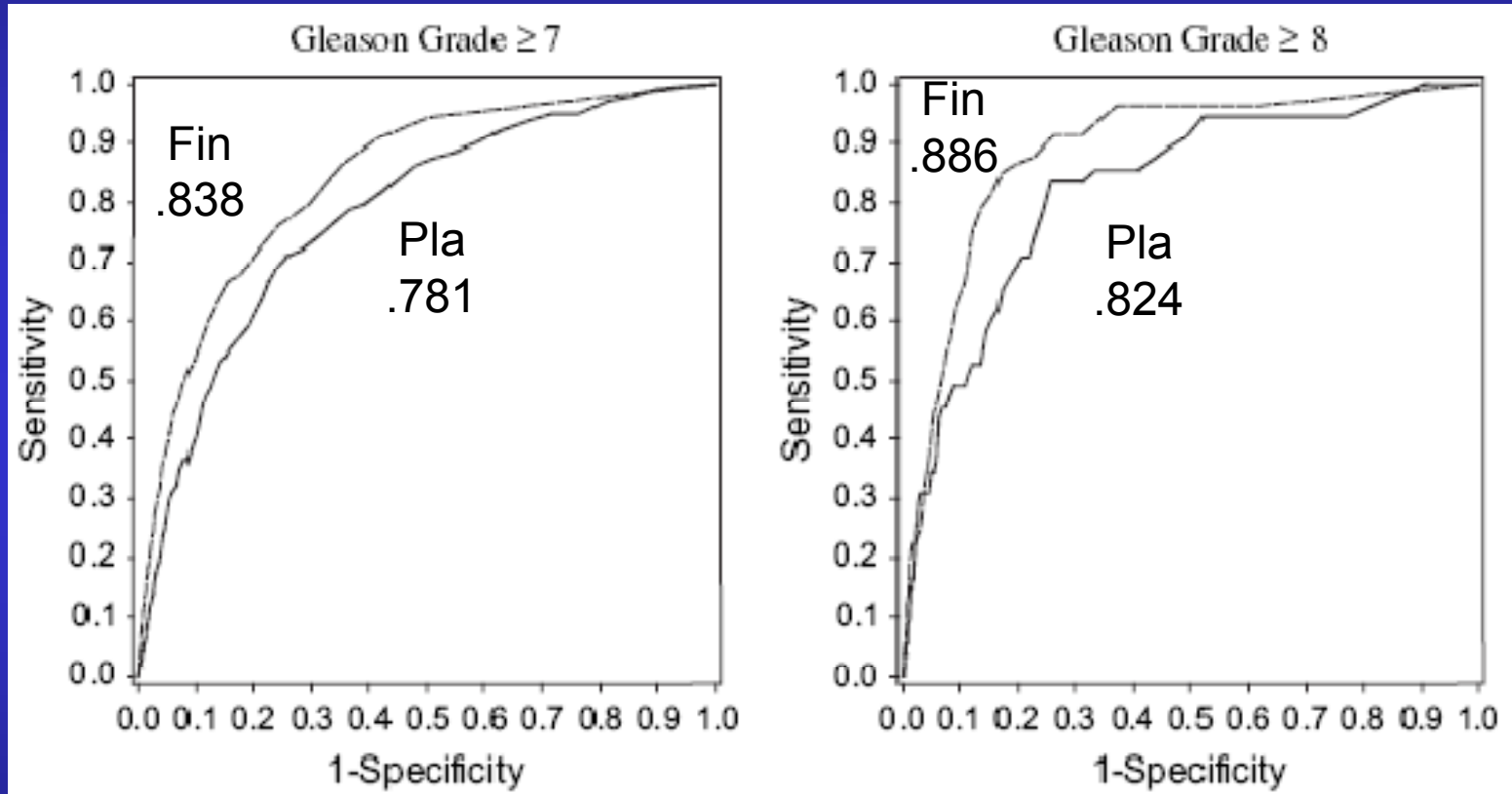
Cohen Y et al, JNCI 99:1366-74, 2007

Sources of Bias in PCPT

Low Number of Patients Biopsied and High Number of For-cause Biopsies

	Total	Finasteride	Placebo
Randomized	18,882	9423	9459
Included in analysis	9060 (48%)	4368 (46%)	4692 (50%)
For-cause biopsies	3573 (39%)	1639 (38%)	1934 (41%)
Total cancers	1950	803	1147
Cancers dx'ed for cause	1006 (52%)	435 (54%)	571 (50%)

PCPT: Effect of PSA on Detection of High Grade Cancer



40% of biopsies were for-cause and about half of those were PSA-driven

Thompson IM et al, JNCI 98:1128-33, 2006

PCPT: Higher Serum PSA in High Grade Cancer (Placebo Arm)

PSA Cut-off	Percent of low grade cancer with higher PSA	Percent of high grade cancer with higher PSA
2.1	33	76
3.1	18	58
4.1	10	40
6.1	2	13



Cut-off for biopsy recommendation

Effect of Finasteride on Incidence of High and Low Grade Cancer in PCPT

	Unadjusted Results	Results Adjusted for PV, PSA, age and race ¹	Results Based on Radical Prostatectomies ²
High Grade Cancer	+25%	- 12%	- 27%
Low Grade Cancer	-25%	- 53%	- 39%

¹Cohen Y et al, JNCI 99:1366-74, 2007

²Redman MW et al., Cancer Prevention Research 1:182-6, 2008.



PSA and High Grade Cancer in PCPT

- If high Gleason grade cancers release more PSA into the blood, PSA measurements would have selectively increased biopsies in men with high grade cancer.
- Finasteride appears to have shrunk high grade cancers less than low grade cancers. One might also assume that finasteride decreased PSA less from high grade cancers.
- The combination of the above two factors would lead to more high grade cancer diagnoses in situations where PSA drove biopsies.



Hypothesis

5-ARIs enhance the utility of PSA as a screen for clinically-significant prostate cancer by continually suppressing PSA production from benign tissue and non-aggressive prostate cancers.

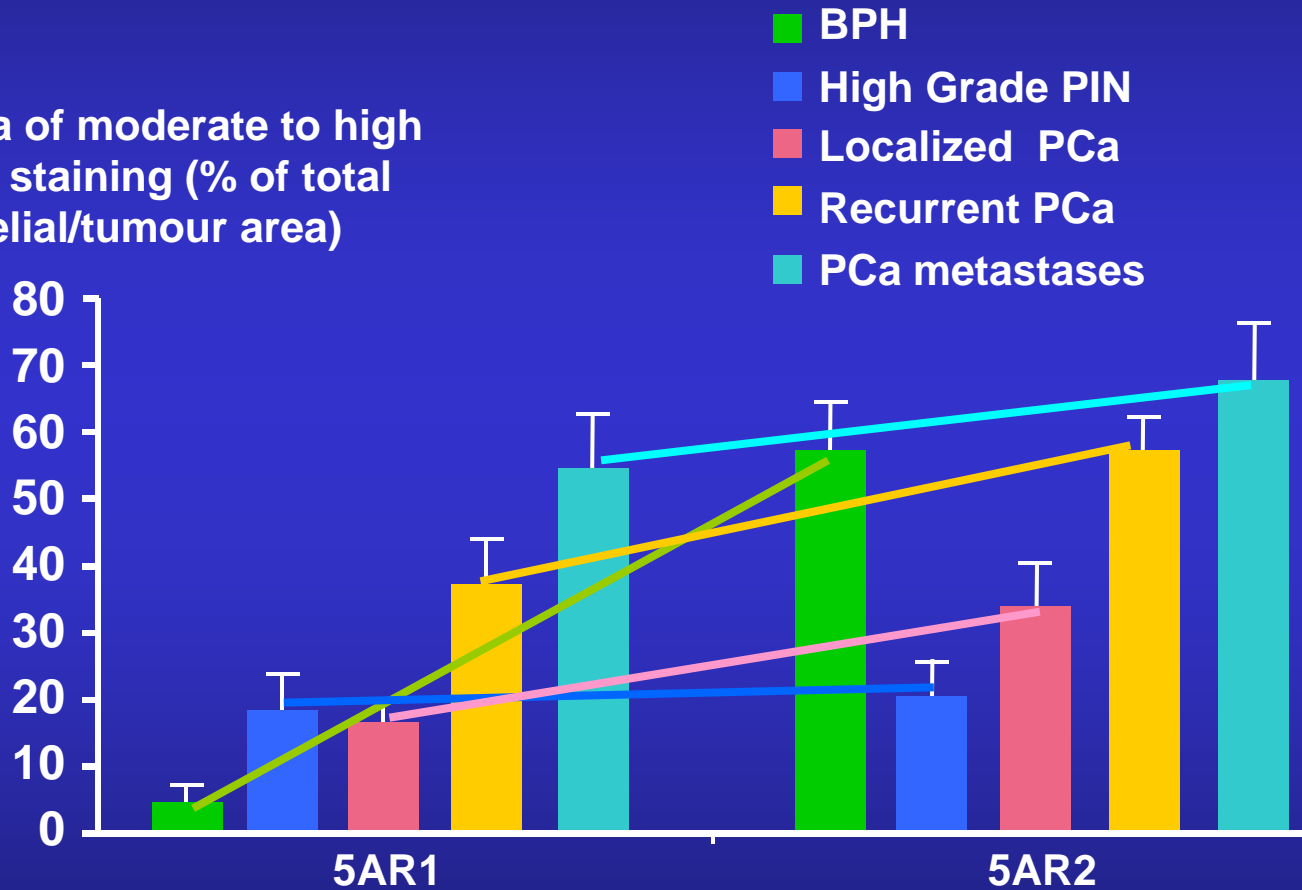
Dutasteride

A Dual 5α -Reductase Inhibitor

What is the evidence that justified developing dutasteride for prostate cancer prevention?

5AR -Type 1 increases in prostate cancer compared to BPH tissue

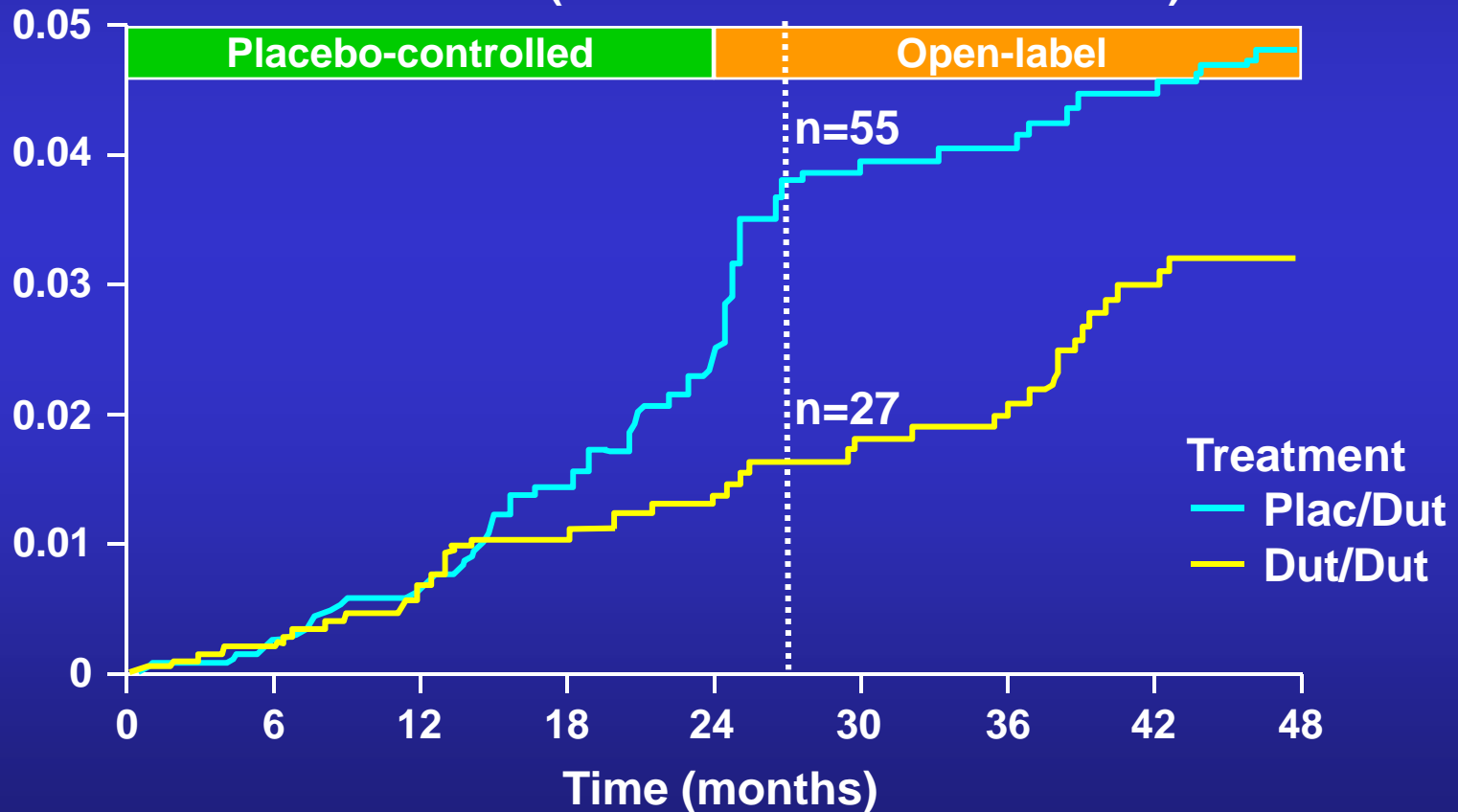
Mean area of moderate to high intensity staining (% of total epithelial/tumour area)



Dutasteride – Cancer Detection in Phase III BPH studies

Probability of prostate cancer

1.2% versus 2.5%, $p=0.002$
(men who reached month 27)



Andriole *et al.* Urology 2004; 64: 537–41, updated with data on file at GSK

REDUCE

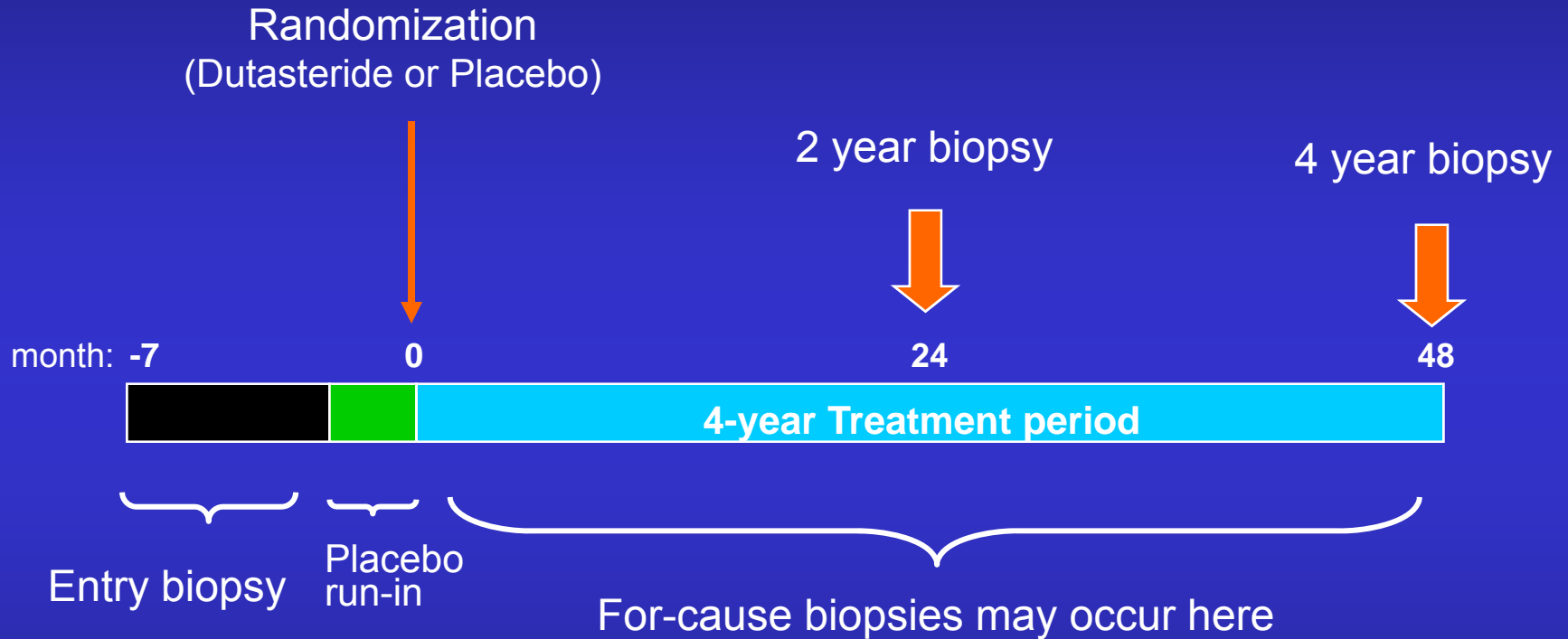
REduction by DUtasteride
of prostate Cancer Events



REDUCE Study Participants

- 8102 men worldwide
- Age 50-75
- PSA >2.5 and ≤ 10
- one negative prostate biopsy within 6 months of randomization
- No baseline characteristics that would mandate a biopsy before Year 2
- Phytotherapy, Vitamin E and selenium discouraged but not prohibited

REDUCE Study Design



Key Differences Between PCPT and REDUCE

	PCPT	REDUCE
Study Duration	7 years	4 years
No. of subjects	18,882	~ 8000
Location	U.S. only	International
Baseline biopsies	No	Yes (1 neg. bx.)
Follow-up biopsies	7 years	2 and 4 years
PSA entry criteria	< 3.0	2.5 – 10.0
Age	≥55	≥50
Enzymes inhibited	Type 2 5-AR	Types 1&2 5-AR

Prostate Cancer Risk Reduction

Prevention, prevention of
progression, or treatment?

Conclusions

- The PCPT demonstrated that finasteride reduces the risk of prostate cancer in men with low baseline PSAs. There is no evidence that finasteride caused high grade cancer; rather it appeared to enhance the ability of PSA to detect such cancers.
- Dutasteride is a dual 5α -reductase inhibitor being investigated for both prostate cancer prevention and treatment. Results of the REDUCE trial will be available in April, 2009.
- The hope exists that 5α -reductase inhibitors may decrease the diagnosis of cancers that don't need to be treated and enhance the diagnosis of cancers that warrant treatment.