AVODART® (dutasteride) for Reduction of Risk of Prostate Cancer (PCa)

NDA 21-319/S-024

GlaxoSmithKline Presentation

Oncologic Drugs Advisory Committee

01 December 2010

Presentation Overview

Introduction	**Paolo Paoletti, MD** SVP Oncology R&D, GSK
Summary of Efficacy & Safety	**Gerald L. Andriole, MD** Chief, Division of Urologic Surgery Washington University
High Grade Cancers and PSA	**Christopher Logothetis, MD** Chair, Department of GU Medical Oncology MD Anderson Cancer Center, Houston, TX
Clinical Perspective	**Claus Roehrborn, MD** Professor and Chairman of Urology UT Southwestern Medical Center
Risk Management & Concluding Remarks	**Anne M. Phillips, MD** VP, Medicine Development Leader, GSK

Additional Participants

- **David Bostwick, MD, MBA**
  Pathologist, CEO, Bostwick Laboratories
- **Gary Koch, PhD**
  Professor of Biostatistics
  University of North Carolina, Chapel Hill
- **Peter Kowey, MD**
  Professor of Medicine, Jefferson University
- **Scott Lucia, MD**
  Associate Professor, Chief of Genitourinary and Renal Pathology, University of Colorado School of Medicine

Financial Disclosure:
The participants noted above are paid consultants of GSK

Prostate Cancer in the U.S.

- US incidence of PCa is expected to increase*
  - Approximately 217,000 in 2010
  - More than 344,000 in 2025
- Most cancers diagnosed are low grade & early stage*
- 90% of patients will receive surgery, drug therapy or radiotherapy**
  - Interventions associated with complications & morbidities

* American Cancer Society. Cancer Facts & Figures 2010. Atlanta: American Cancer Society; 2010.

** Andriole GL, Grubb RL, Buys SS, et al. Mortality Results From A Randomized Prostate Cancer Screening Trial. NEJM 2009; 360: 1310-19

Medical Need in Prostate Cancer

- Reduce overall numbers of prostate cancers
- Reduce burden associated with low grade cancers
- Preserve ability to diagnose high grade cancers

Sources of Clinical Data

sNDA Data Package

Study / Duration	Patient Numbers	Population
REDUCE / 4 Yr	N = 8,231	Increased Risk Prostate Cancer
CombAT / 4 Yr	N = 4,844	Benign Prostatic Hyperplasia
ARI103094 / 2 Yr *	N = 2,775	Increased Risk Prostate Cancer

Other Clinical Data

Study / Duration	Patient Numbers	Population
REDUCE Pathology Review	N = 1472	Biopsies Positive for Prostate Cancer
REDEEM / 3 Yr	N = 302	Low Grade Prostate Cancer

*Ongoing study

AVODART® (dutasteride)

- Approved in over 90 countries for the treatment of Benign Prostate Hyperplasia (BPH)
- Launched in US in 2003
- Over 5.5 million patient years of exposure

Avodart: An Important Option for Men at Increased Risk of Prostate Cancer

- Reduced overall incidence of biopsy detectable prostate cancer
  - Preferentially low grade cancers
- Reduced interventions associated with a prostate cancer diagnosis
- Reduced number of biopsy-associated complications
- Preserved ability to detect high grade cancers with PSA

Presentations Will Also Address Important Issues

- Difference in number of Gleason 8-10 cancers seen with Avodart vs. placebo
- Relevance of protocol-dependent biopsies to clinical practice
- Importance of reducing low grade cancers

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Use of a 5-α-Reductase Inhibitors for Prostate Cancer Chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline

BS Kramer, KL Hagerty, S Justman, MR Somerfield, PC Albertson, WJ Blot, H Ballentine Carter, JP Constantino, J Epstien*, PA Godley, RP Harris, TJ Wilt, J Wittes, R Zon, and P Schellhammer*

"…even if 5-ARI treatment never translates into reduced overall or prostate cancer-specific mortality, reduction in risk of prostate cancer diagnosis with the consequent morbidity of treatment is a clinically beneficial end point in and of itself."

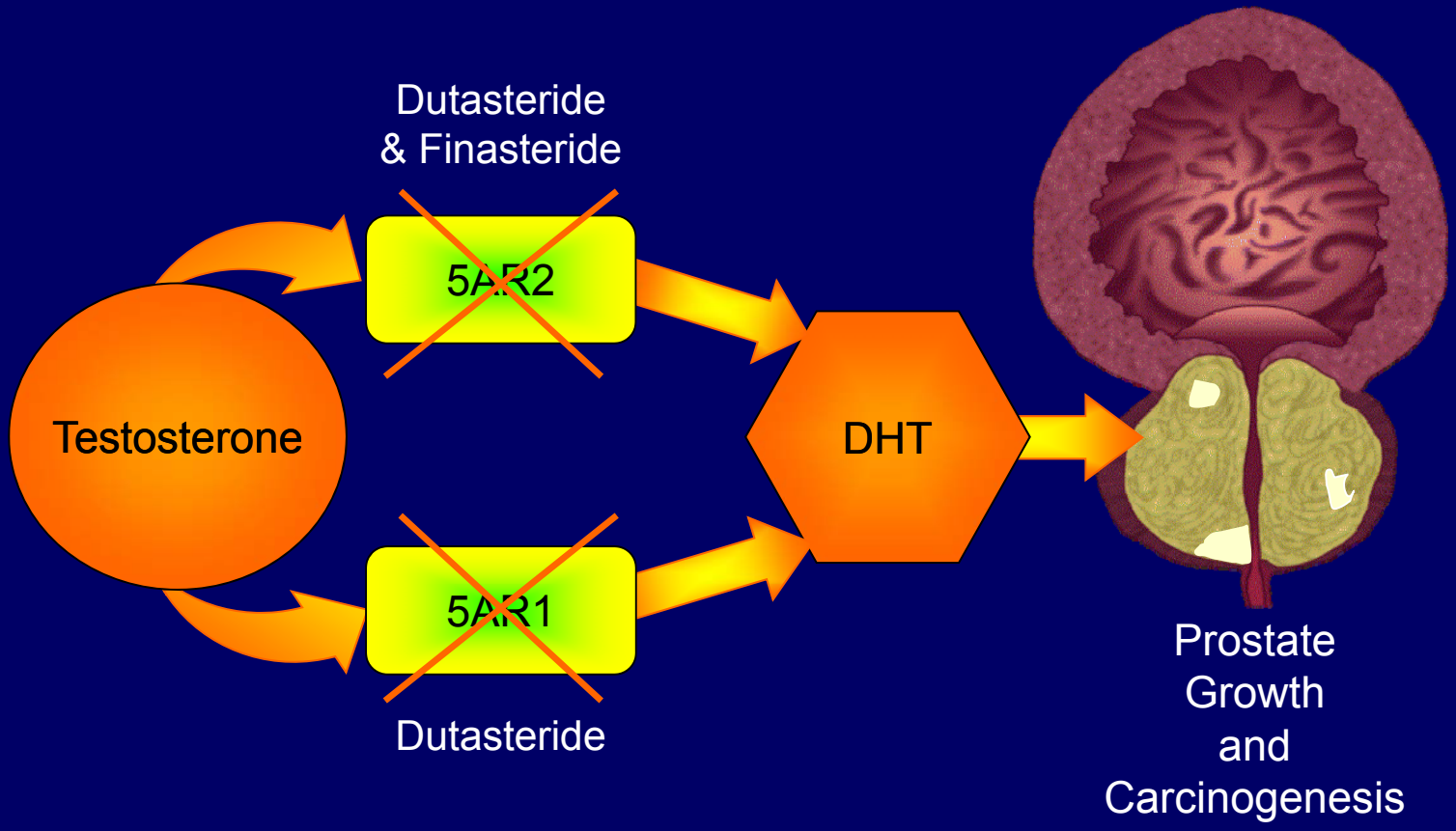
Proposed Indication

AVODART® (dutasteride) is indicated for reduction in the risk of prostate cancer in men at increased risk of developing the disease, defined as those who have had a prior negative biopsy due to clinical concern and have an elevated serum prostate-specific antigen (PSA).

Summary of Clinical Efficacy and Safety
REDUCE Study

Gerald L. Andriole, MD
Chief, Division of Urologic Surgery
Washington University
St. Louis, MO

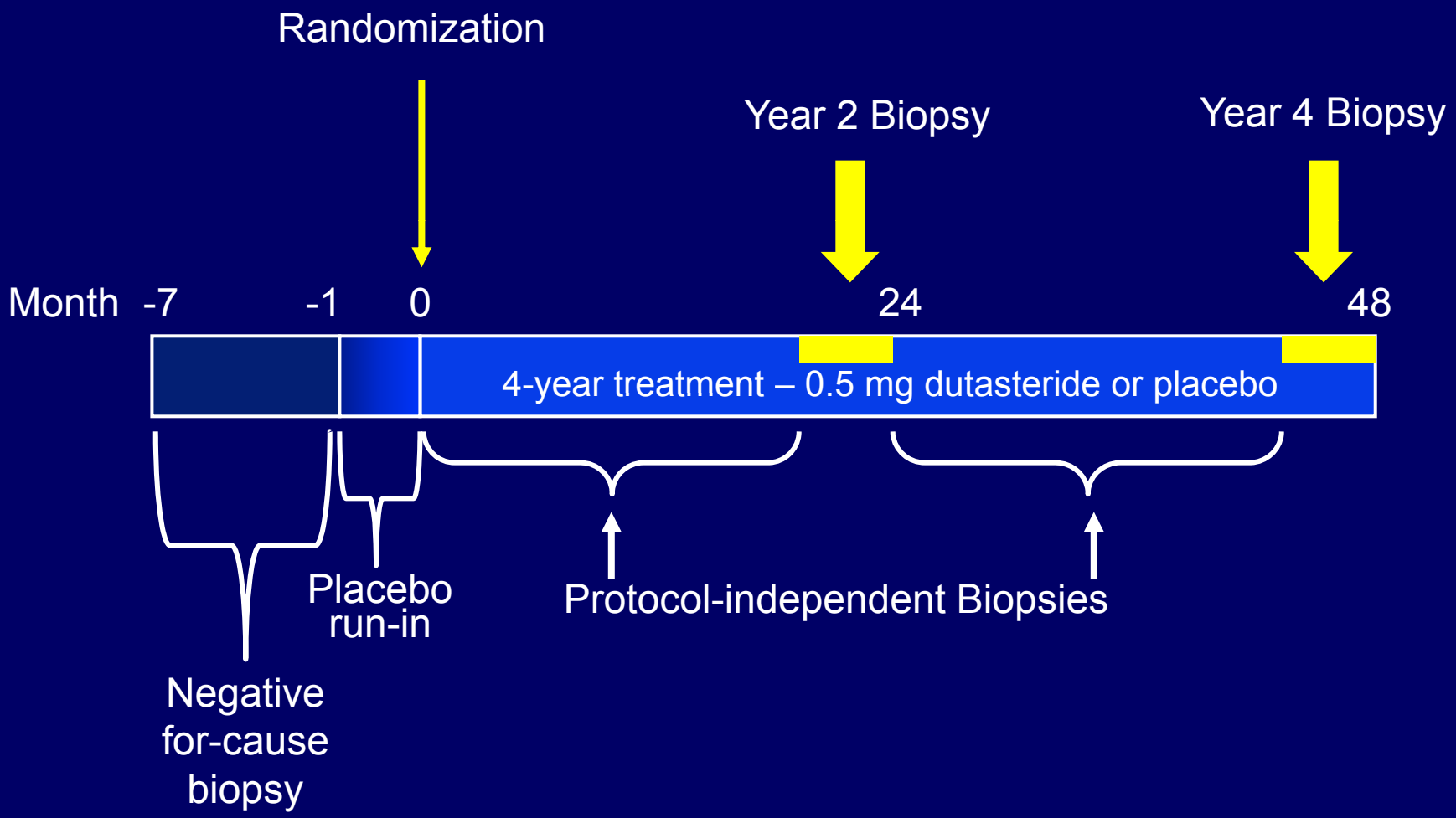
Dutasteride Inhibits Both Type 1 and 2 5AR



REDUCE Investigated Impact of Dutasteride on Prostate Cancer Over 4 Years

- Enrolled men at increased risk of prostate cancer
  - ≥50 and ≤75 yrs
  - PSA 2.5 - 10 ng/mL (≤60 yrs) or 3.0 - 10 ng/mL (>60 yrs)
  - Single, negative for-cause biopsy (6 - 12 cores) independent of the study within 6 months of randomization

REDUCE Designed to Provide Equal Opportunity for Prostate Cancer Diagnosis



Some Comments on Protocol-Dependent Biopsies in REDUCE

- The FDA has raised concern that the protocol-dependent biopsies in REDUCE do not reflect clinical practice
- In clinical practice patients are biopsied for clinical concern
- Biopsies may miss prostate cancer
- Such patients are often repeatedly re-biopsied
- The repeat biopsies in REDUCE often reflect standard clinical practice

Study Endpoints

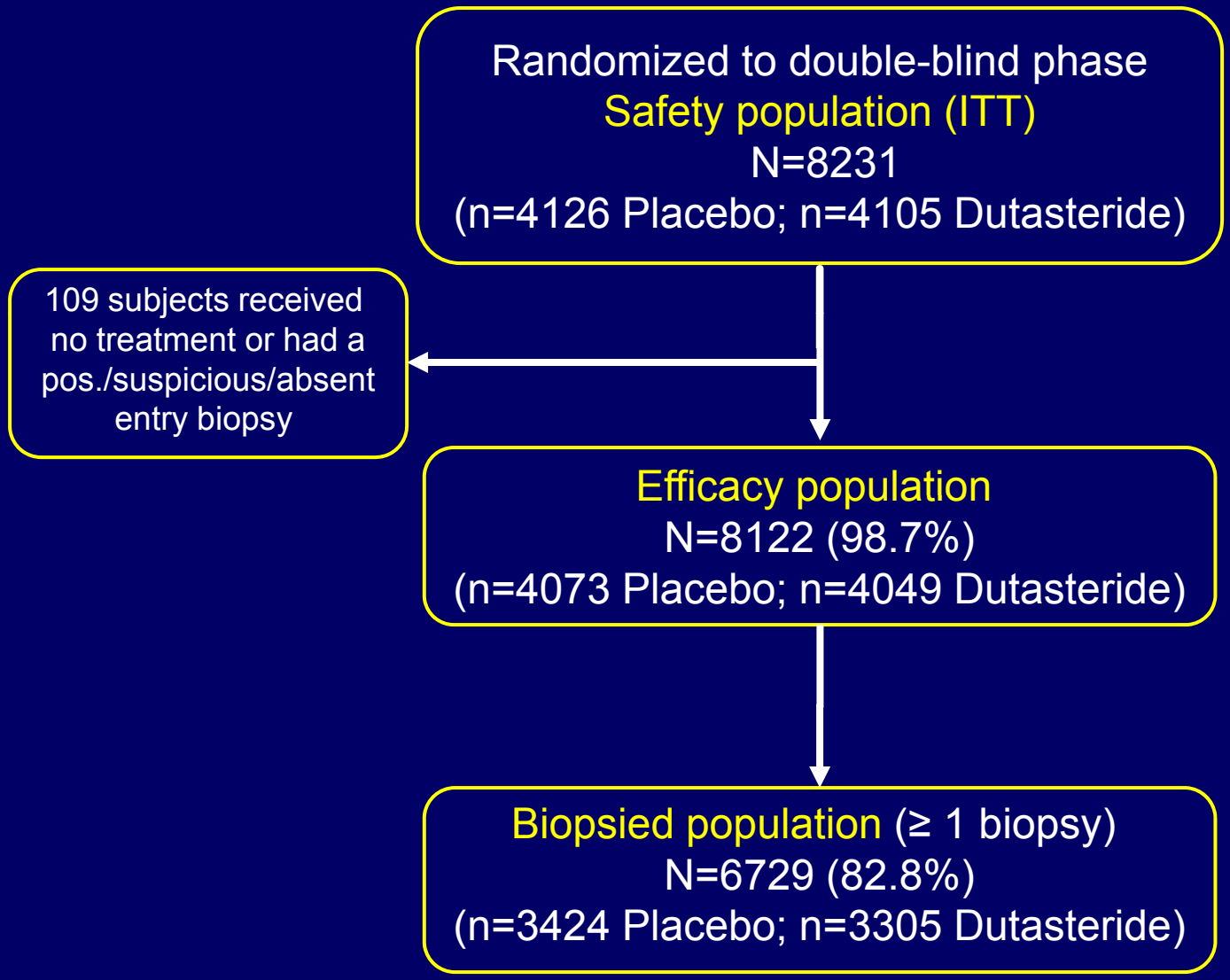
Primary endpoint:

- Biopsy-detectable prostate cancer at 2 and 4 years

Additional Key Endpoints:

- Prostate cancer (PCa) interventions
- Cancer associated lesions
  - High grade prostatic intraepithelial neoplasia (HGPIN)
  - Atypical small acinar proliferation (ASAP)
- BPH-related complications
- Gleason score at diagnosis
- Safety and tolerability

Study Populations

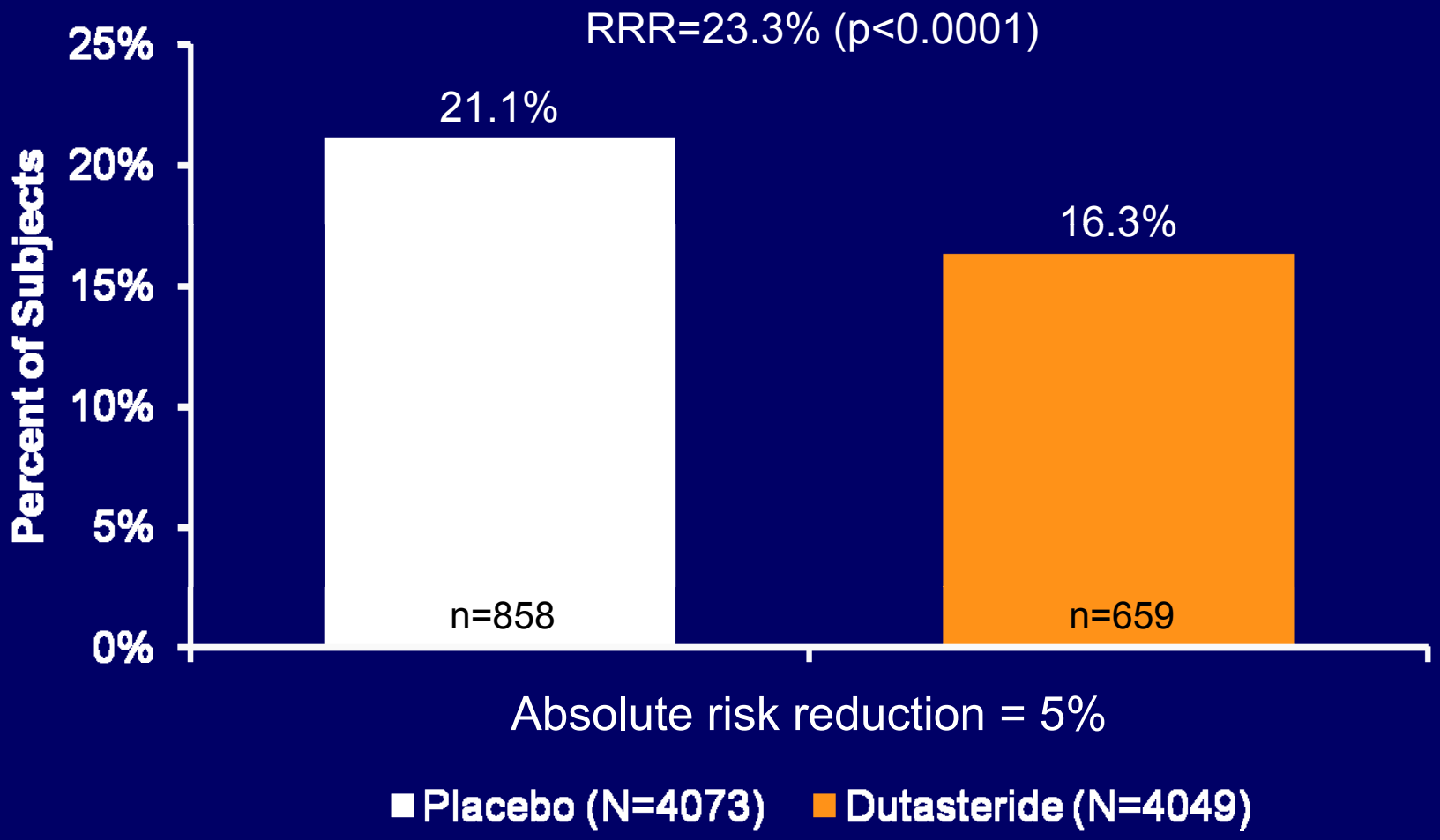


Baseline Demographics Balanced Between Treatment Groups

	Placebo (N=4126)	Dutasteride (N=4105)
Age (years)	62.7 ± 6.08	62.8 ± 6.04
White	91%	91%
Family history of PCa	13%	13%
Total PSA (ng/mL)	5.9 ± 2.00	5.9 ± 1.97
Prostate volume (cc)	45.7 ± 18.78	45.7 ± 18.20
IPSS (≥8 = mod-severe BPH symptoms)	8.6 ± 5.62	8.7 ± 5.70

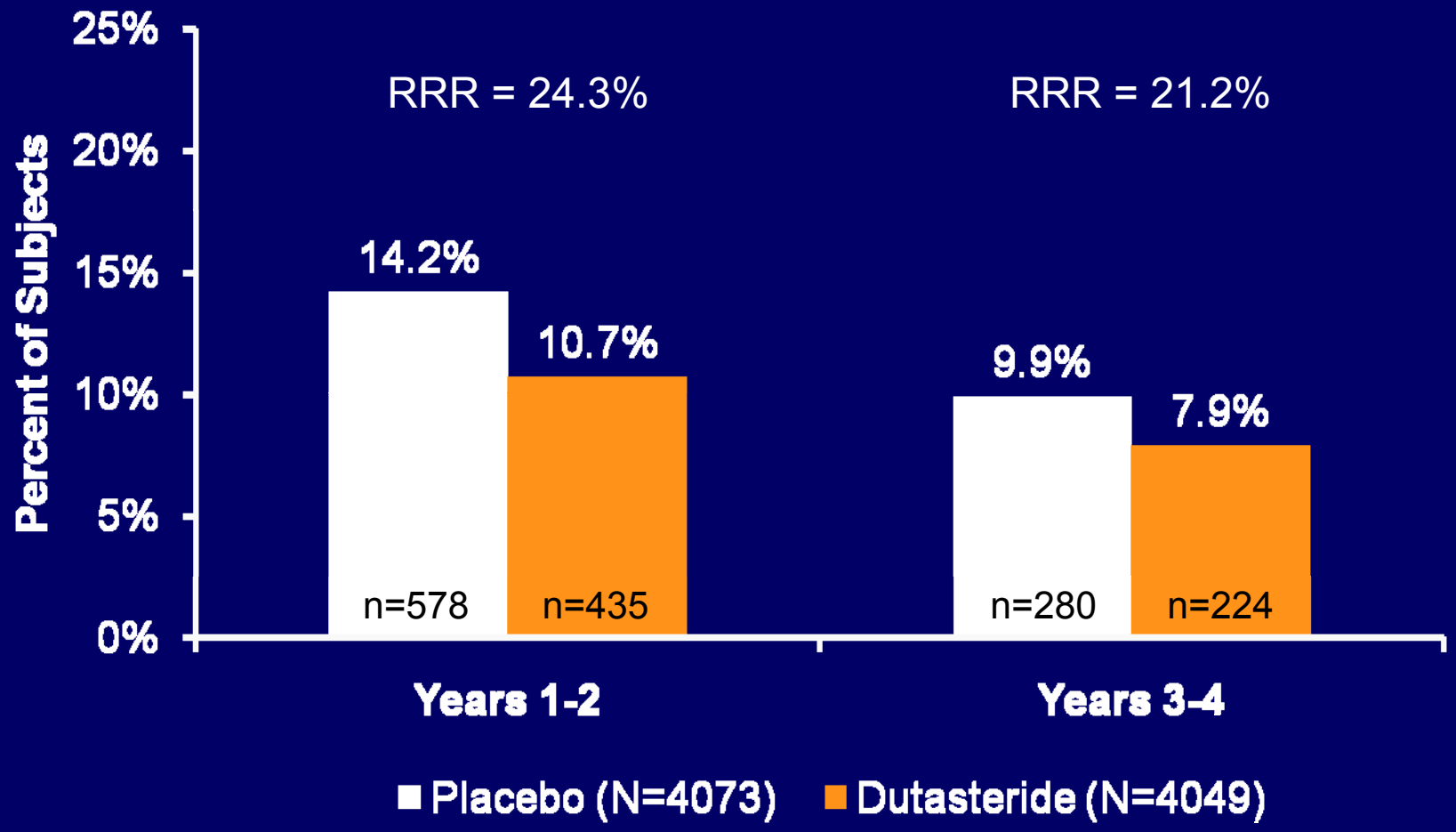
Mean ± standard deviation
Safety Population

REDUCE Primary Endpoint: Dutasteride Reduced Risk of Prostate Cancer Over 4 Years



Efficacy Population

Consistent Risk Reduction in Each Time Period

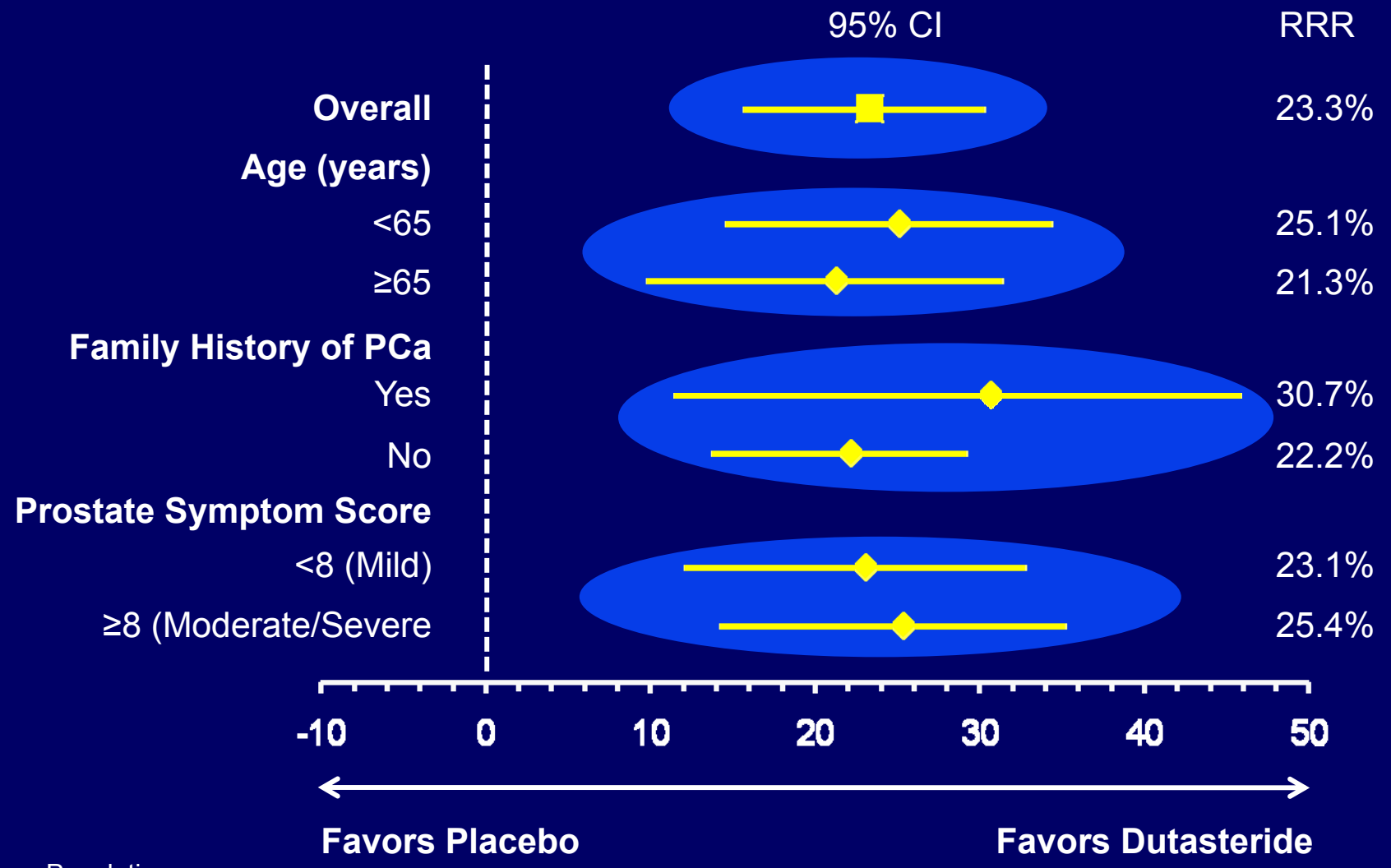


Efficacy Population

Potential Biases in Years 3 and 4 of REDUCE

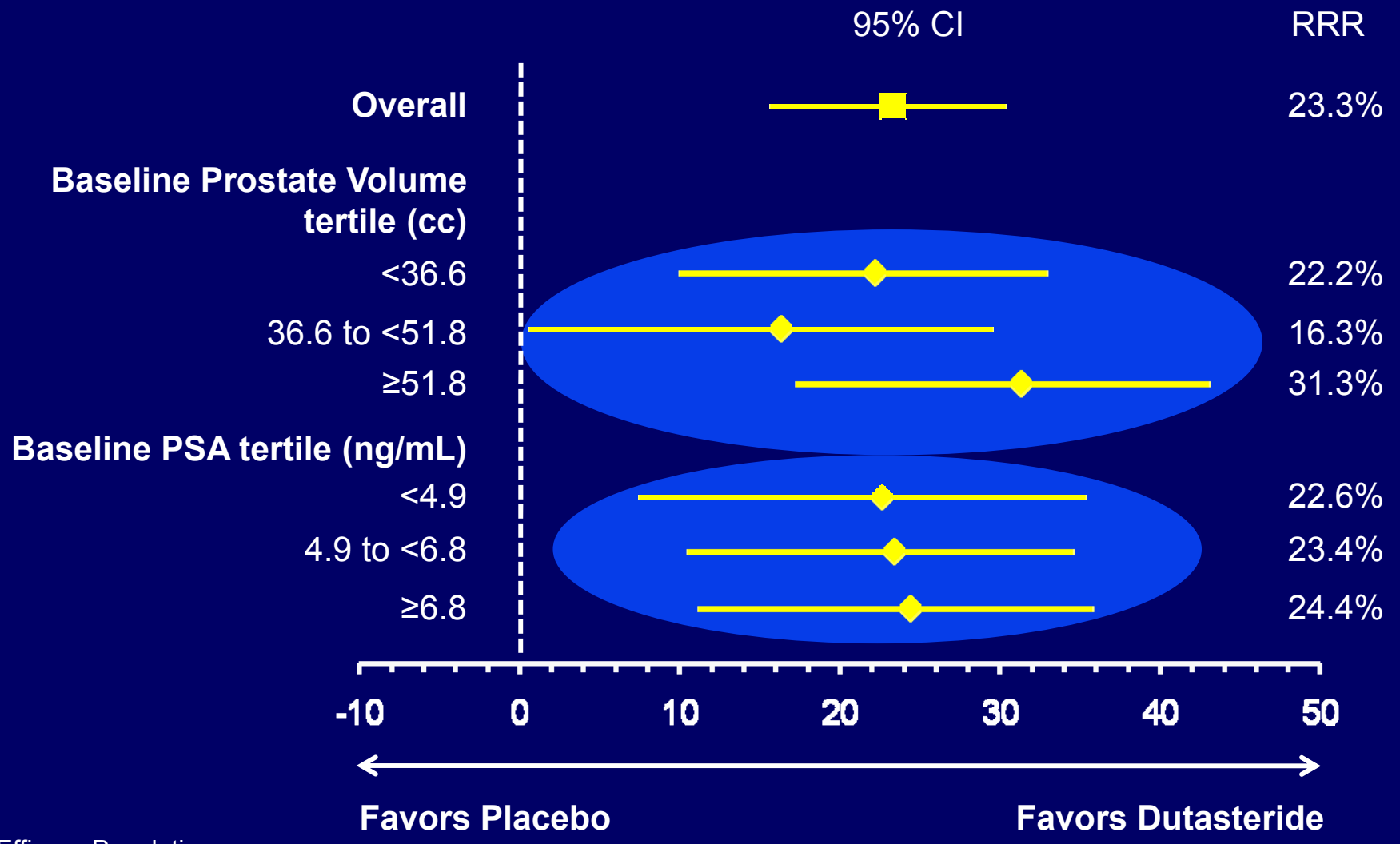
- 143 more cancers diagnosed in the placebo group during Years 1-2 were not available during Years 3-4
- In REDUCE, prostate volume decreased by 17.5 % in the dutasteride group, compared to a 19.7% increase in the placebo group, which could result in a greater likelihood of cancer detection by biopsy in the dutasteride group
- Despite these potential biases, the finding of 56 fewer cancer cases in dutasteride arm in Years 3-4 suggests continued cancer growth suppression by dutasteride

Consistent Relative Risk Reduction Across Key Baseline Characteristics



Efficacy Population

Consistent Relative Risk Reduction Across Key Baseline Characteristics

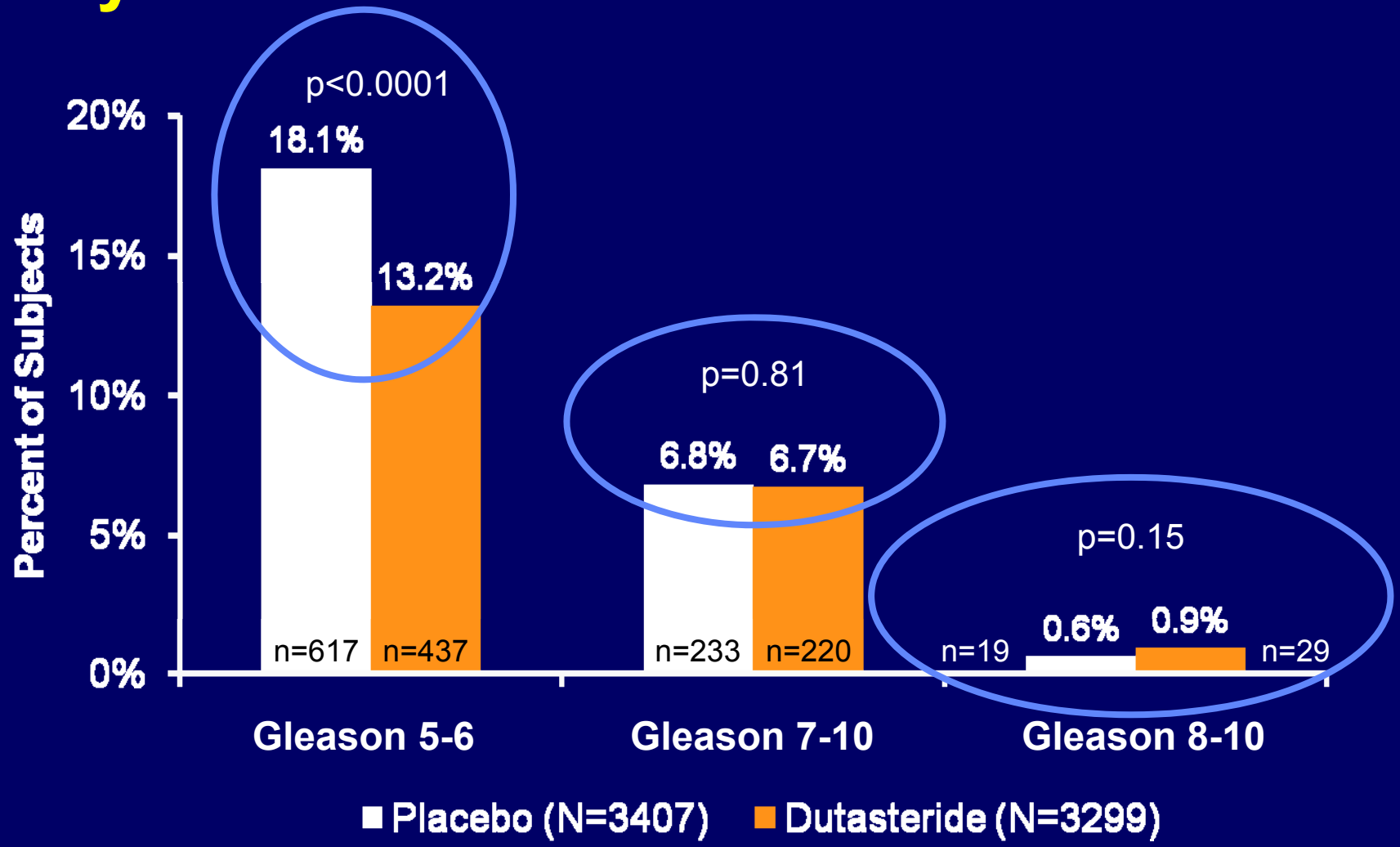


Efficacy Population

African Americans in REDUCE

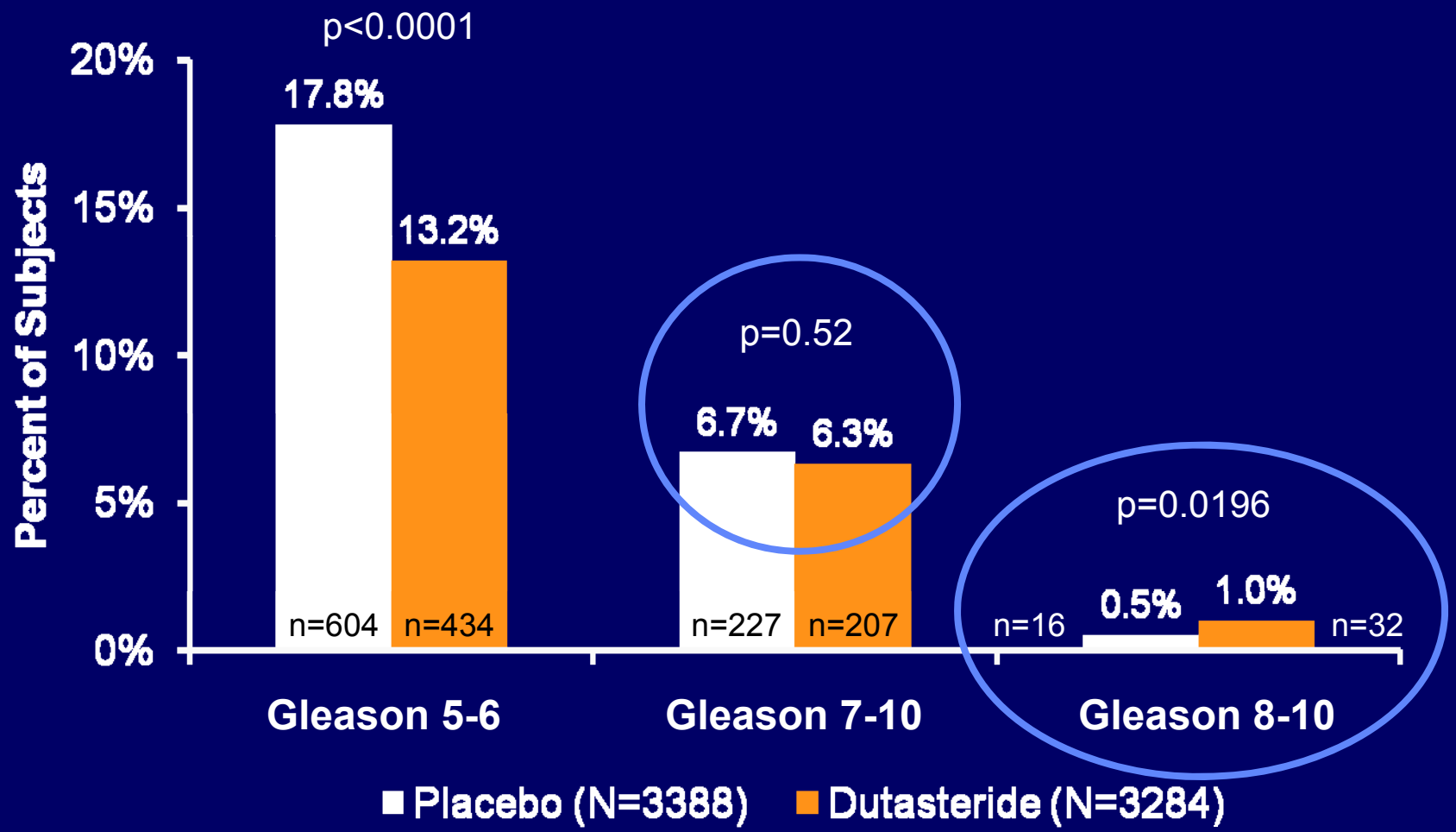
- Small proportion enrolled in REDUCE overall
- In the US, 138 (8%) of subjects African American
- Similar to proportion of African American men in US population aged 50-74 years (9.5%)
- Small number of cancers make subgroup analysis uninformative

Proportion of Men with Prostate Cancer by Classic Gleason Score Over 4 Years



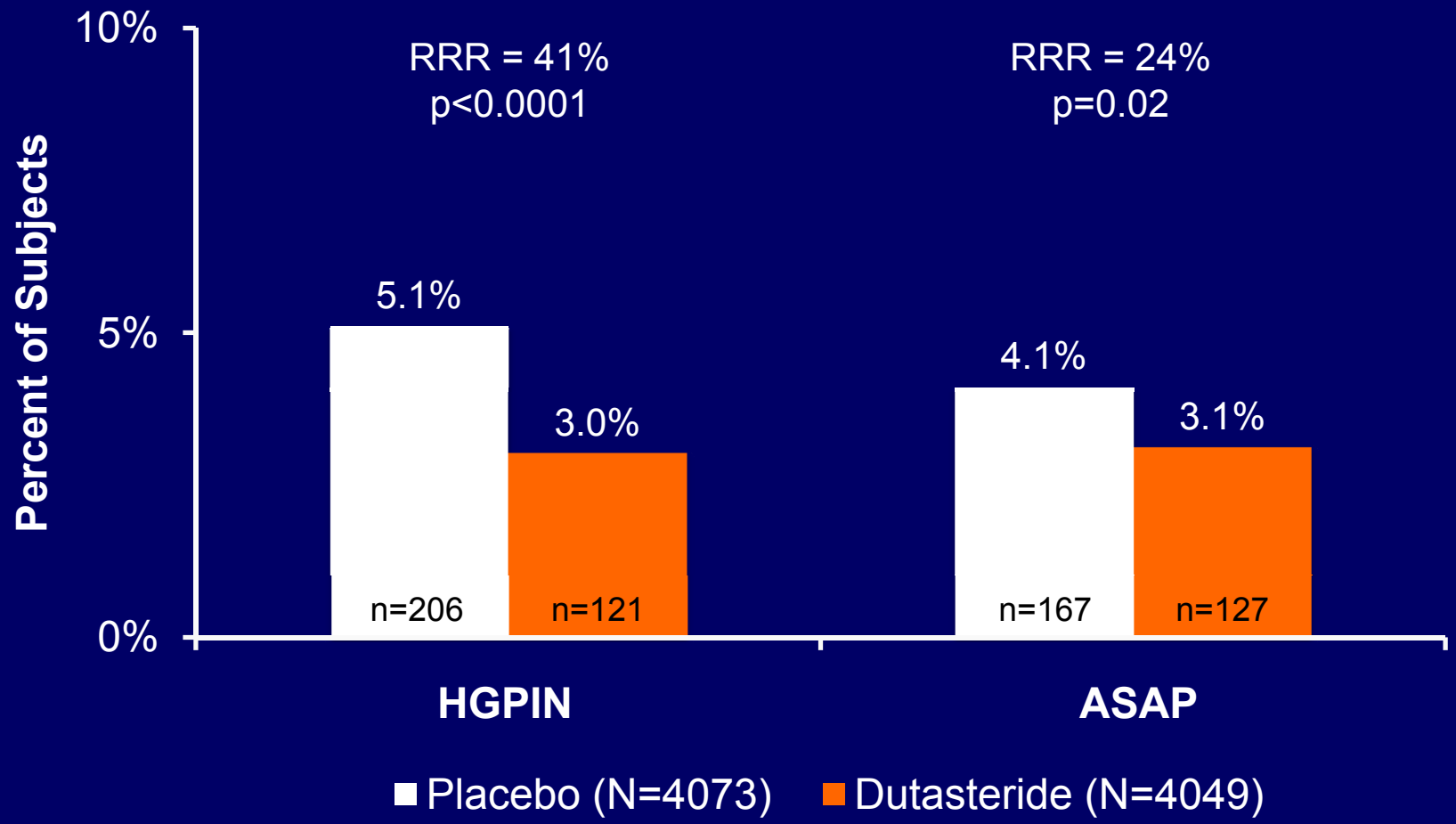
Biopsied Population

Proportion of Men with Prostate Cancer by Modified Gleason Score Over 4 Years



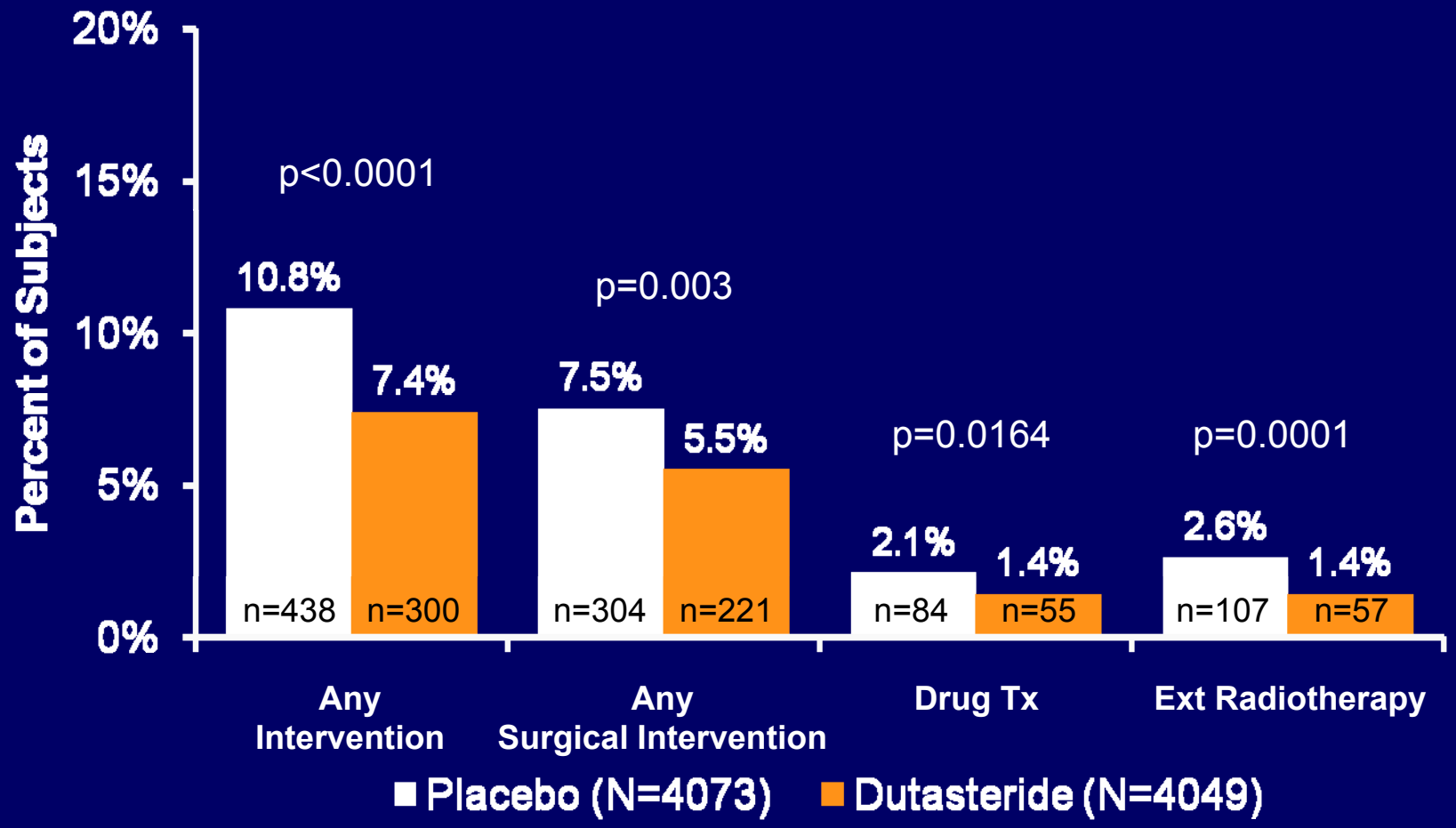
Reassessment Population

Dutasteride Significantly Decreased Prostate Cancer-Associated Lesions



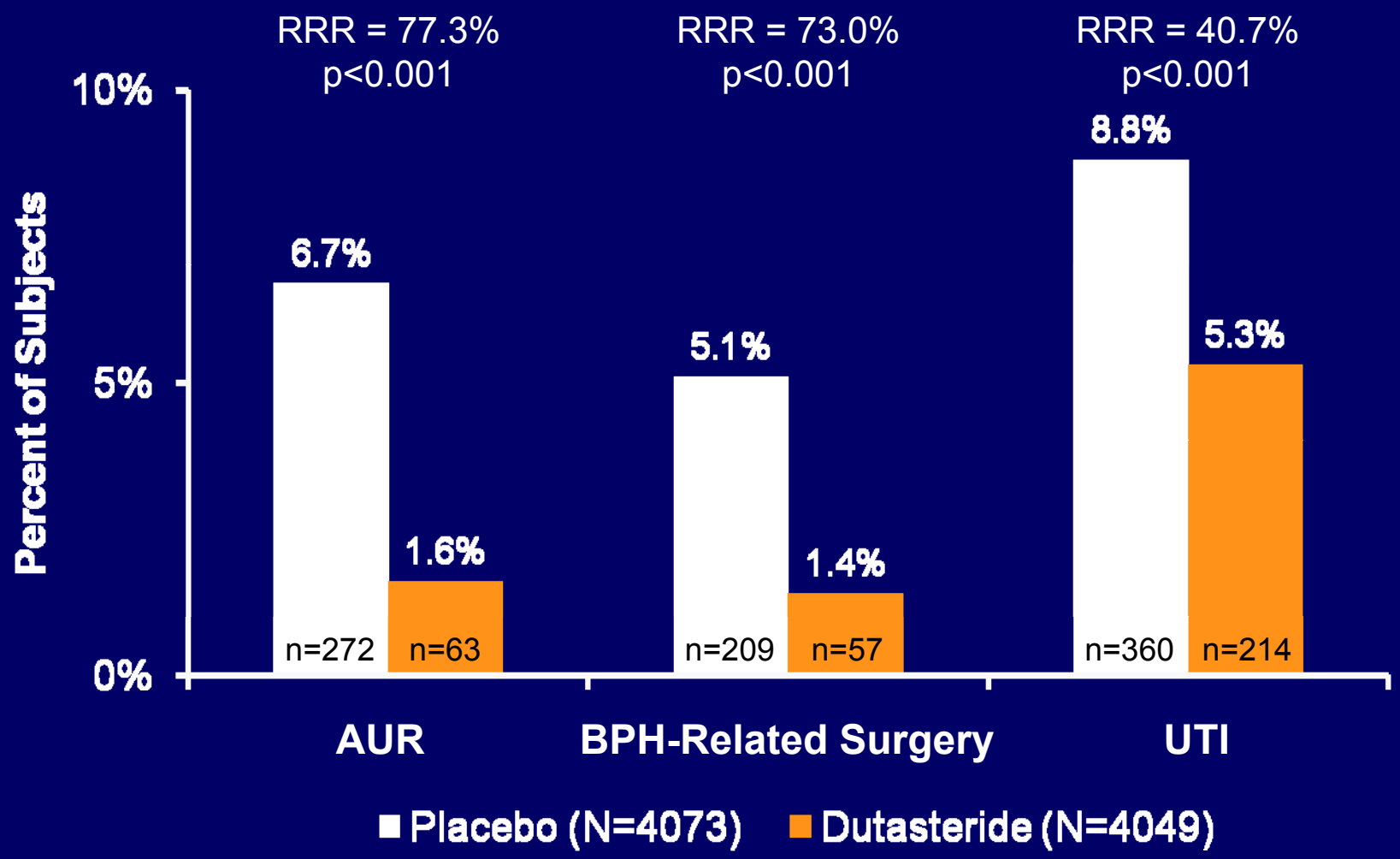
Efficacy Population

Dutasteride Significantly Reduced Prostate Cancer Interventions Over 4 Years



Efficacy Population

Dutasteride Significantly Reduced BPH-Related Complications



Efficacy Population

Most Common* Treatment-Emergent Drug-Related** AEs Consistent with Known Safety Profile and Labeling

	Number (%) of Subjects		
	Placebo (N=4126)	Dutasteride (N=4105)	P value
Any drug-related event	604 (15)	904 (22)	< 0.0001
Erectile dysfunction	237 (6)	369 (9)	< 0.0001
Libido decreased	65 (2)	137 (3)	< 0.0001
Loss of libido	54 (1)	79 (2)	0.03
Gynecomastia	43 (1)	76 (2)	0.002
Semen volume decreased	9 (<1)	56 (1)	< 0.0001

Safety Population
*≥1% of Subjects
**Relationship to drug is based on investigator assessment

Cardiovascular Adverse Events in REDUCE

Composite AE Term	Number (%) of Subjects		Relative Risk (95% CI)
	Placebo N = 4126	Dutasteride N = 4105	
Any CV AE of Special Interest	212 (5.1)	223 (5.4)	1.06 (0.88,1.28)
Ischemic Coronary Artery Disorders/ Atherosclerosis	68 (1.6)	78 (1.9)	1.15 (0.83,1.60)
Acute Coronary Syndrome	73 (1.8)	61 (1.5)	0.83 (0.59,1.17)
Ischemic Cerebrovascular Event	53 (1.3)	58 (1.4)	1.11 (0.77,1.61)
Cardiac Failure	16 (0.4)	30 (0.7)	1.91 (1.04, 3.50)
Peripheral Vascular Disease	11 (0.3)	11 (0.3)	1.02 (0.44, 2.35)
Cardiac Arrhythmias	9 (0.2)	7 (0.2)	0.78 (0.29, 2.10)

Safety Population

Efficacy and Safety Summary

- Clinically significant reduction in biopsy-detectable prostate cancers and decreased need for interventions
- Reduction in prostate cancer-associated lesions
  - HGPIN and ASAP
- Reduction in BPH-associated complications
- Safety and tolerability profile generally consistent with known profile of dutasteride, with the exception of:
  - Cardiac failure
  - Gleason 8-10 cancers

High Grade Cancers in Dutasteride Studies

Christopher Logothetis, MD
MD Anderson Cancer Center

Overview

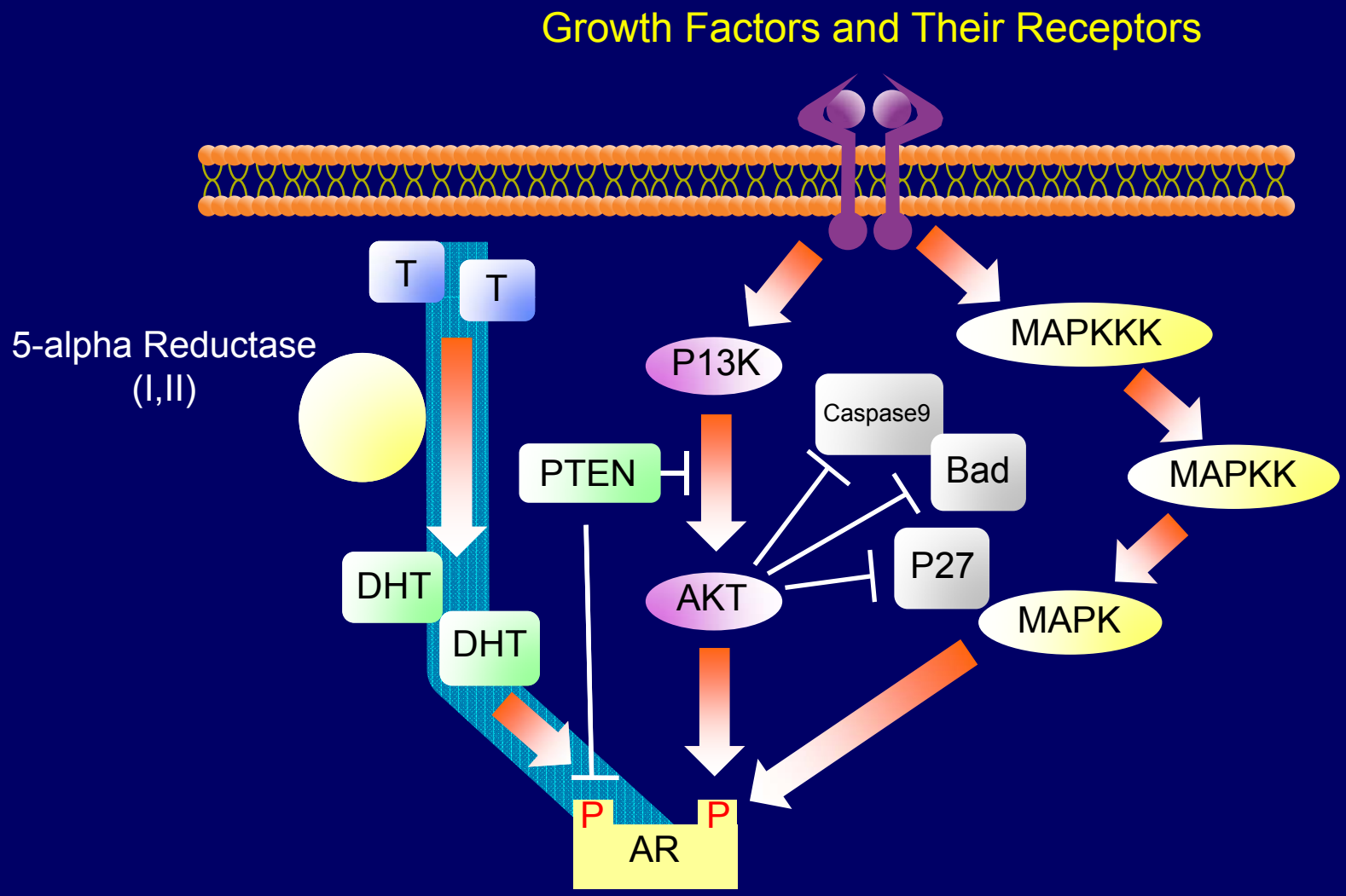
- High-grade cancers in REDUCE
- Biologic and trial design rationale to account for numerical difference
- Review of dutasteride's effect on prostate cancer in other studies
- Absence of interference of dutasteride on PSA predictive value
- Conclusions and recommendations

Cancer Detection in REDUCE by Time, Treatment and Gleason Score

	Years 1-2		Years 3-4	
	Placebo	Dutasteride	Placebo	Dutasteride
No. Subjects Biopsied	3346	3239	2343	2447
Gleason 5-6	401	290	216	147
Gleason 7	157	127	57	64
Gleason 8-10	18 (0.5%)	17 (0.5%)	1 (0.04%)	12 (0.5%)

Biopsied Population

AR Signaling in Prostate Cancer

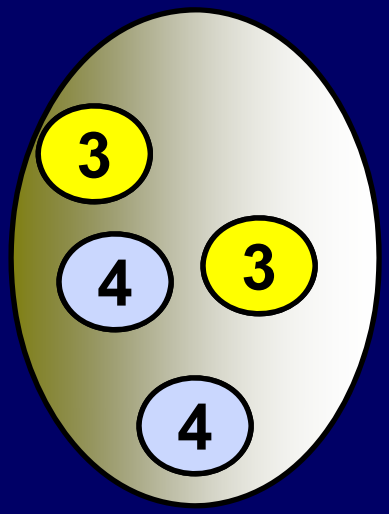


Li J. and Kim J., 2009

Potential Effect of Dutasteride on Gleason Score and Prostate Volume

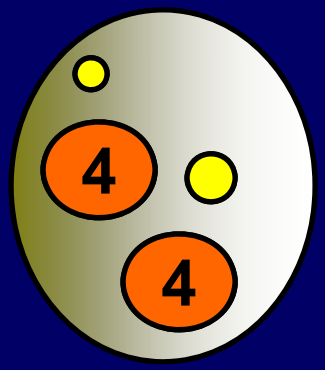
Baseline

- Pattern 3 and 4 Present but Undetected



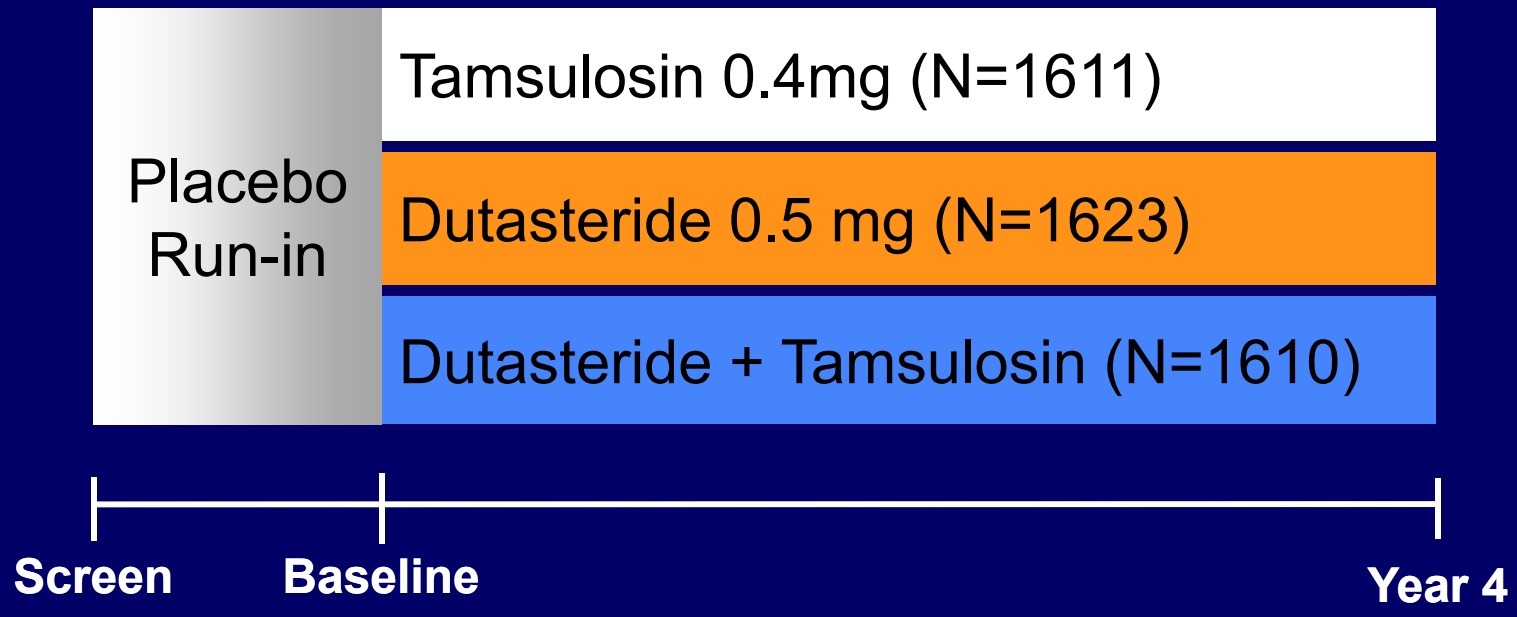
Dutasteride

- Reduced Prostate Volume
- Suppression of Pattern 3
- Less Effect on Pattern 4



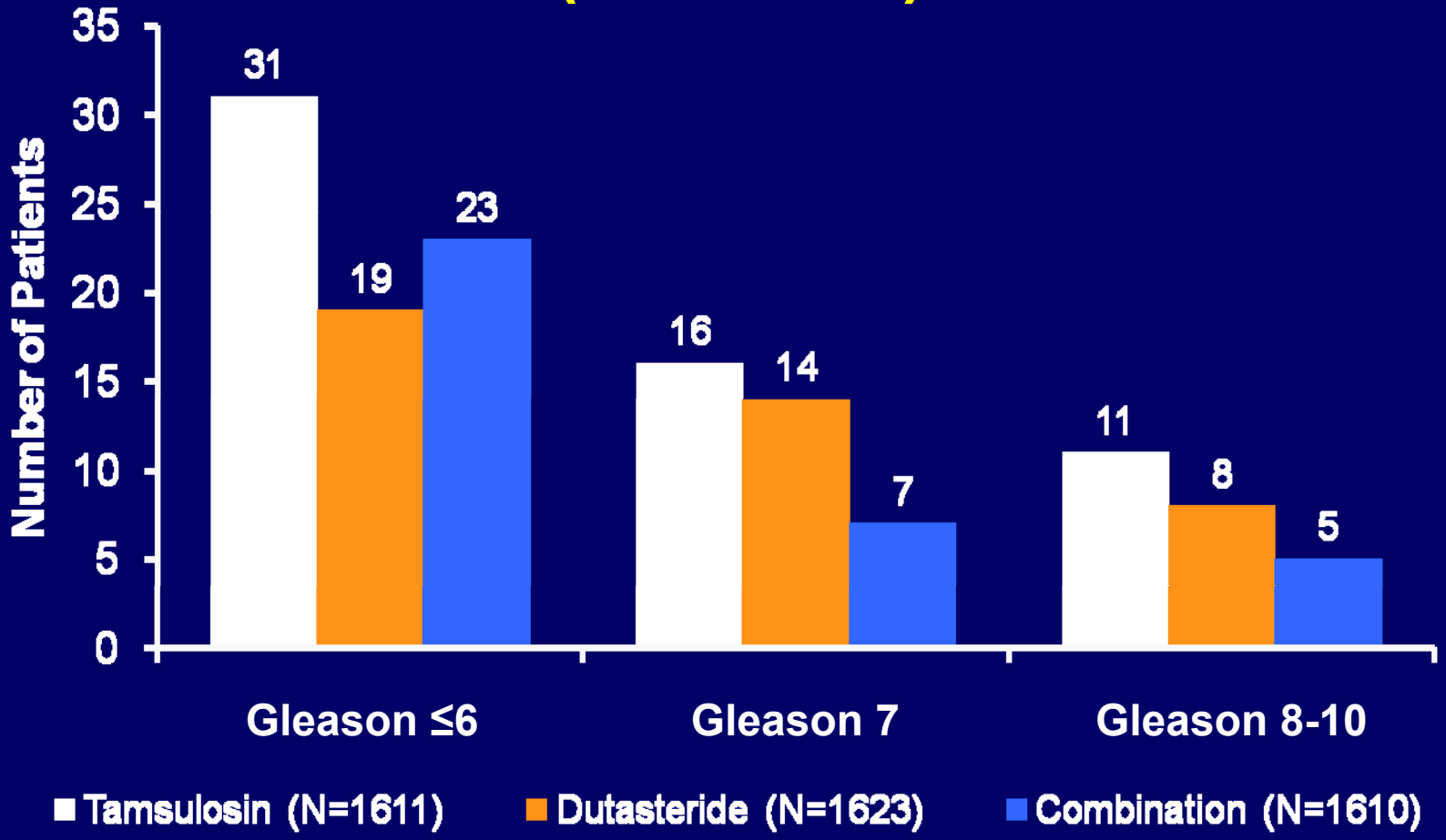
Gleason Score On Biopsy 4 + 4 = 8

Effect of Dutasteride on PCa in BPH population (CombAT)

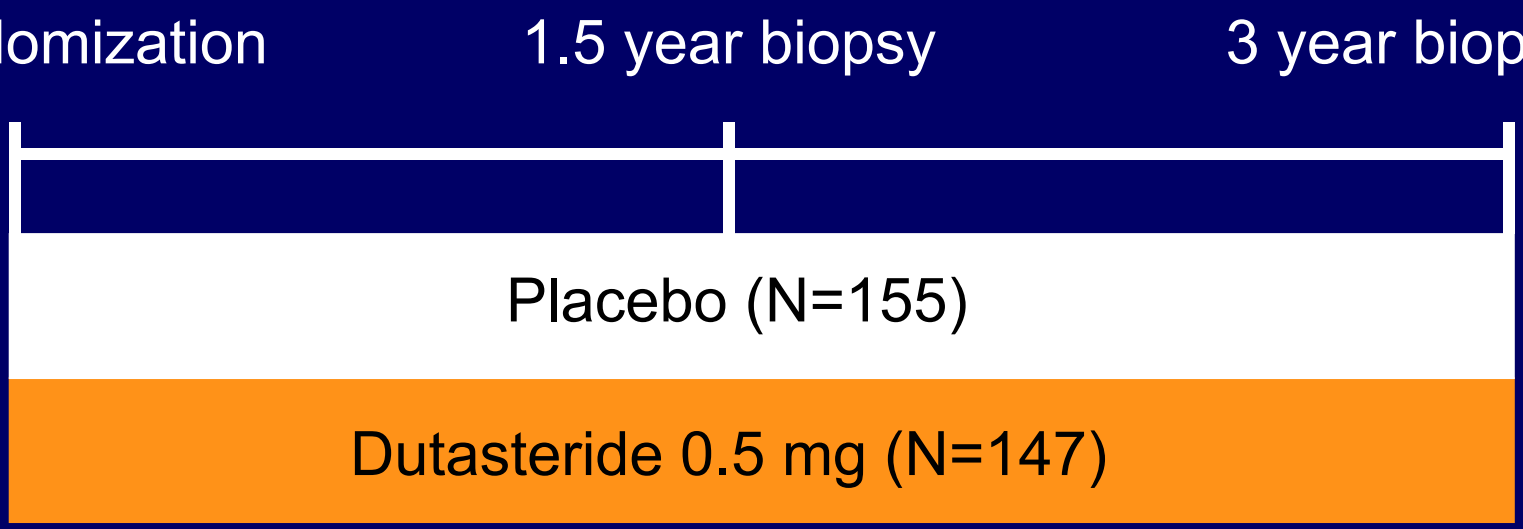


PSA and digital rectal examination annually.
Biopsies conducted for-cause.

Reduction in All Grades of Prostate Cancers in Dutasteride Treated Patients (CombAT)

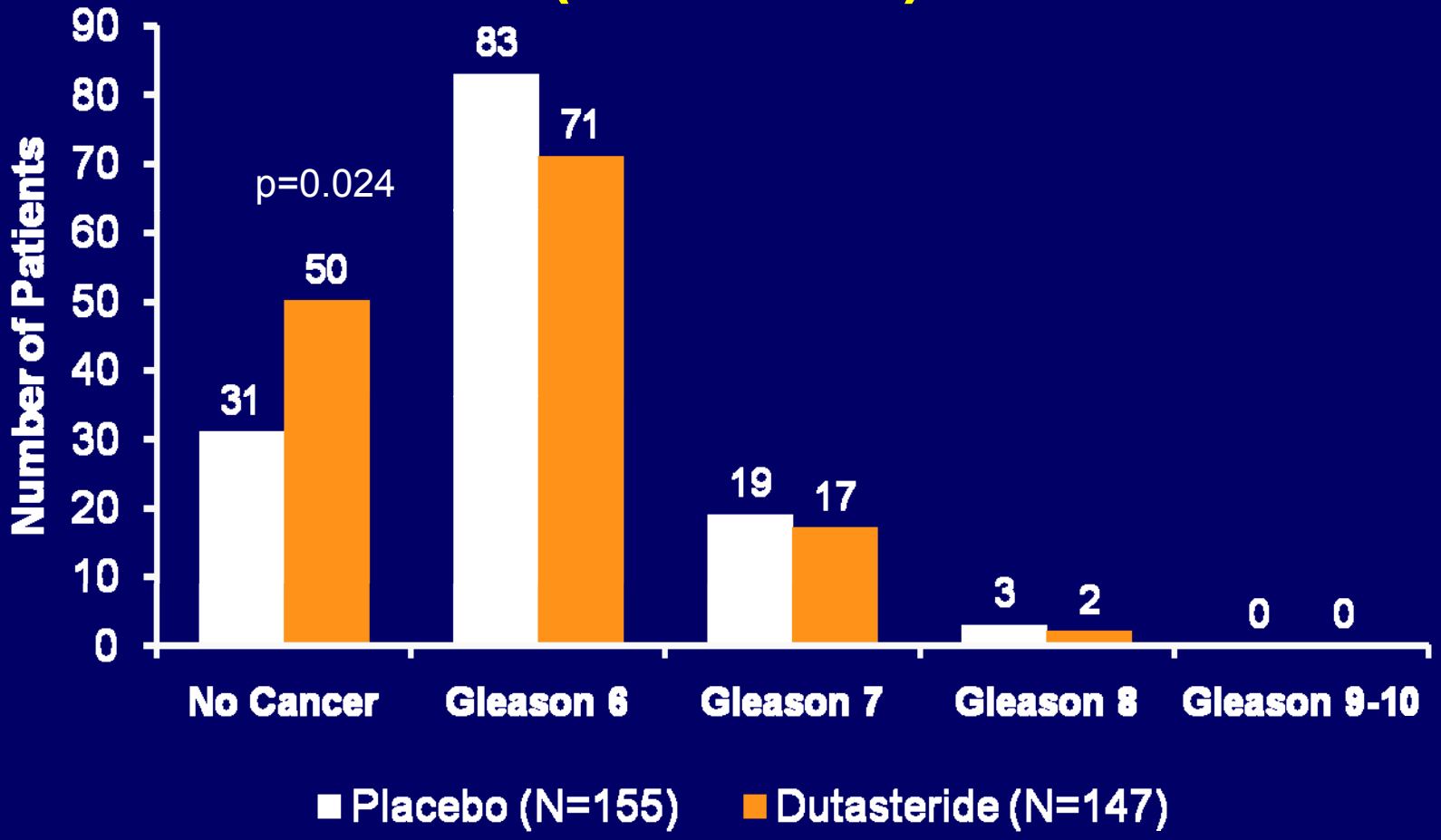


Effect of Dutasteride on Low Grade Cancers (REDEEM)

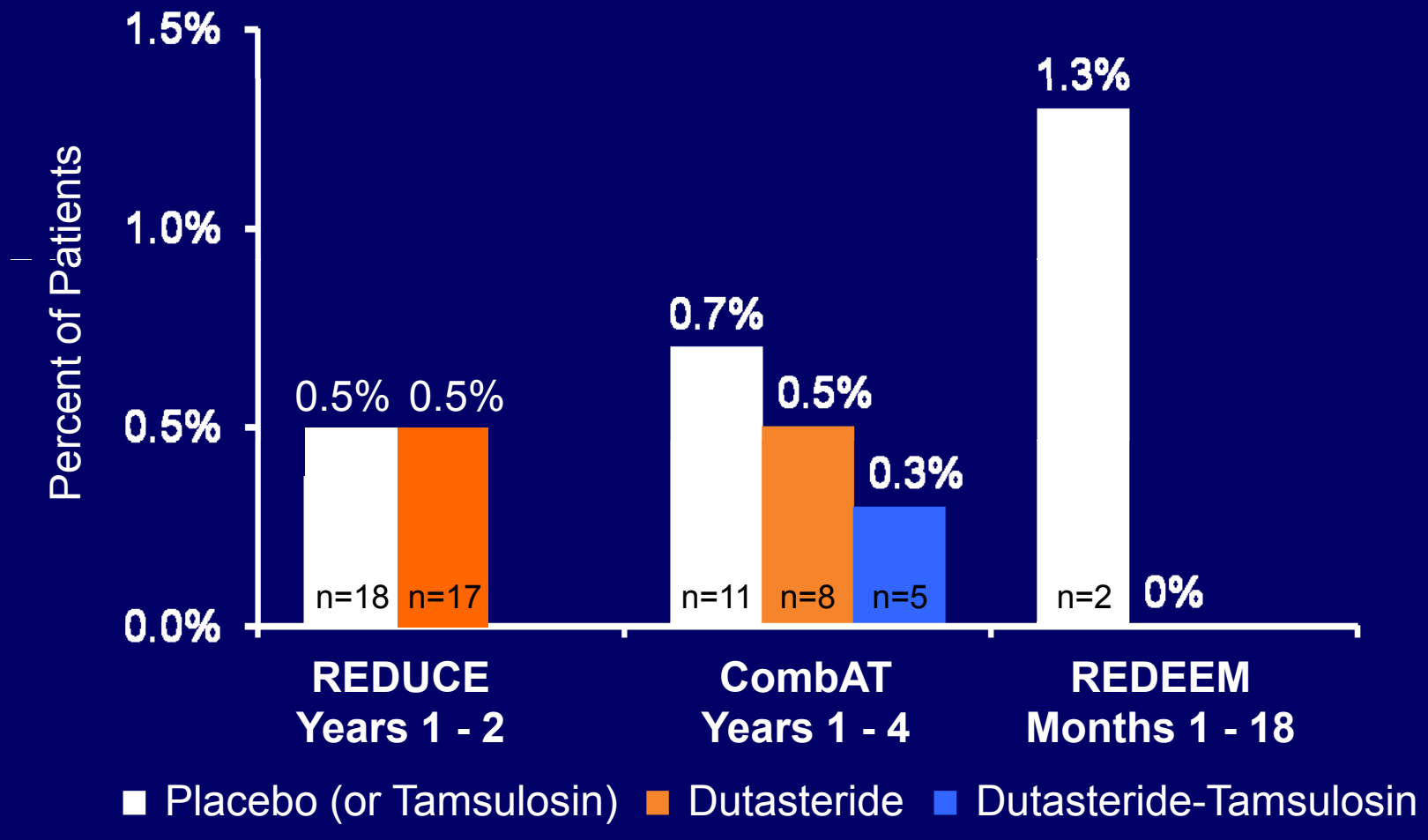


Enrolled men with low grade, low risk prostate cancer
Gleason ≤ 6

Similar Rates of Gleason 7-8 Cancers in Dutasteride and Placebo Groups (REDEEM)



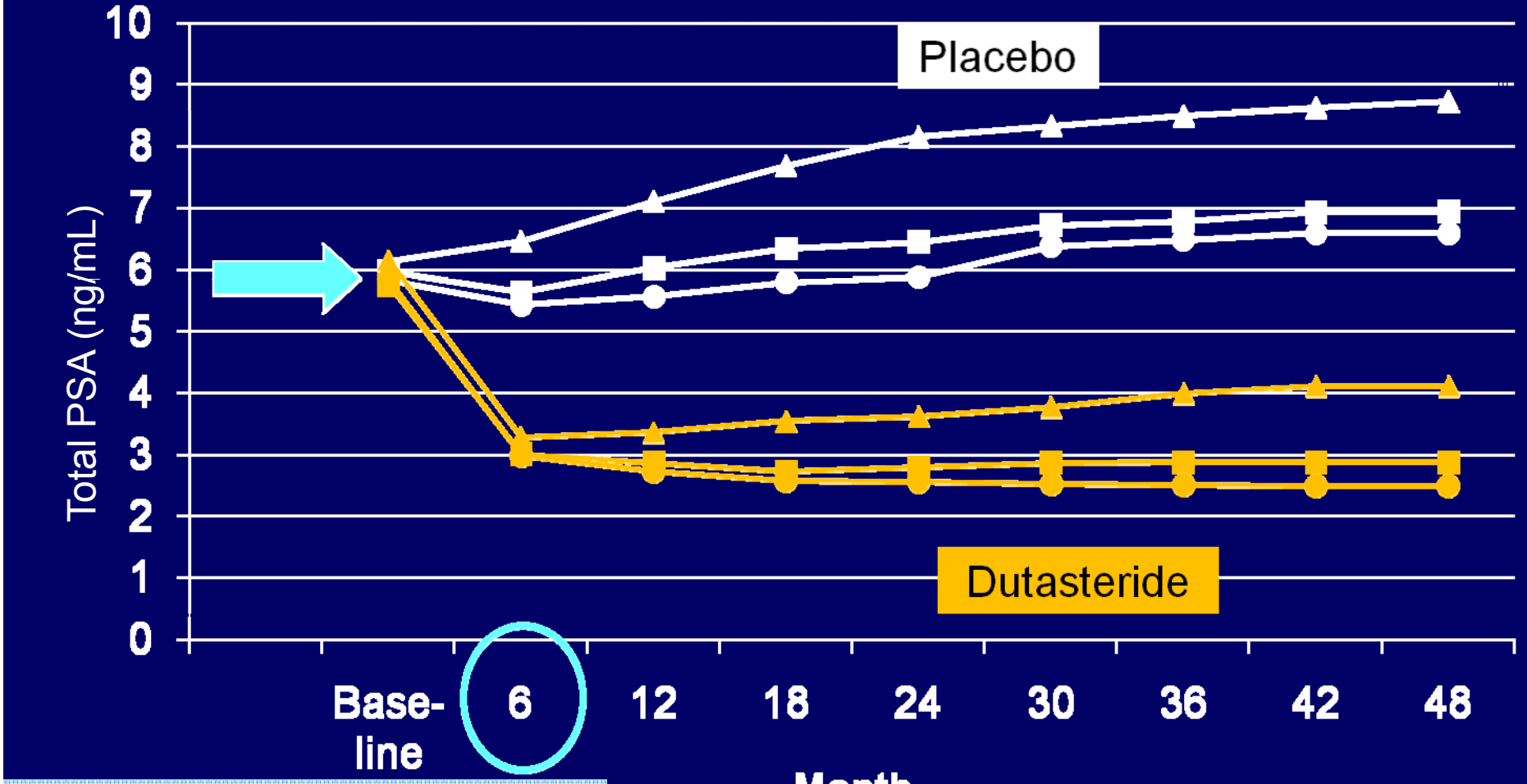
No Increase in Gleason 8-10 Cancers in the Randomized Periods of Dutasteride Trials



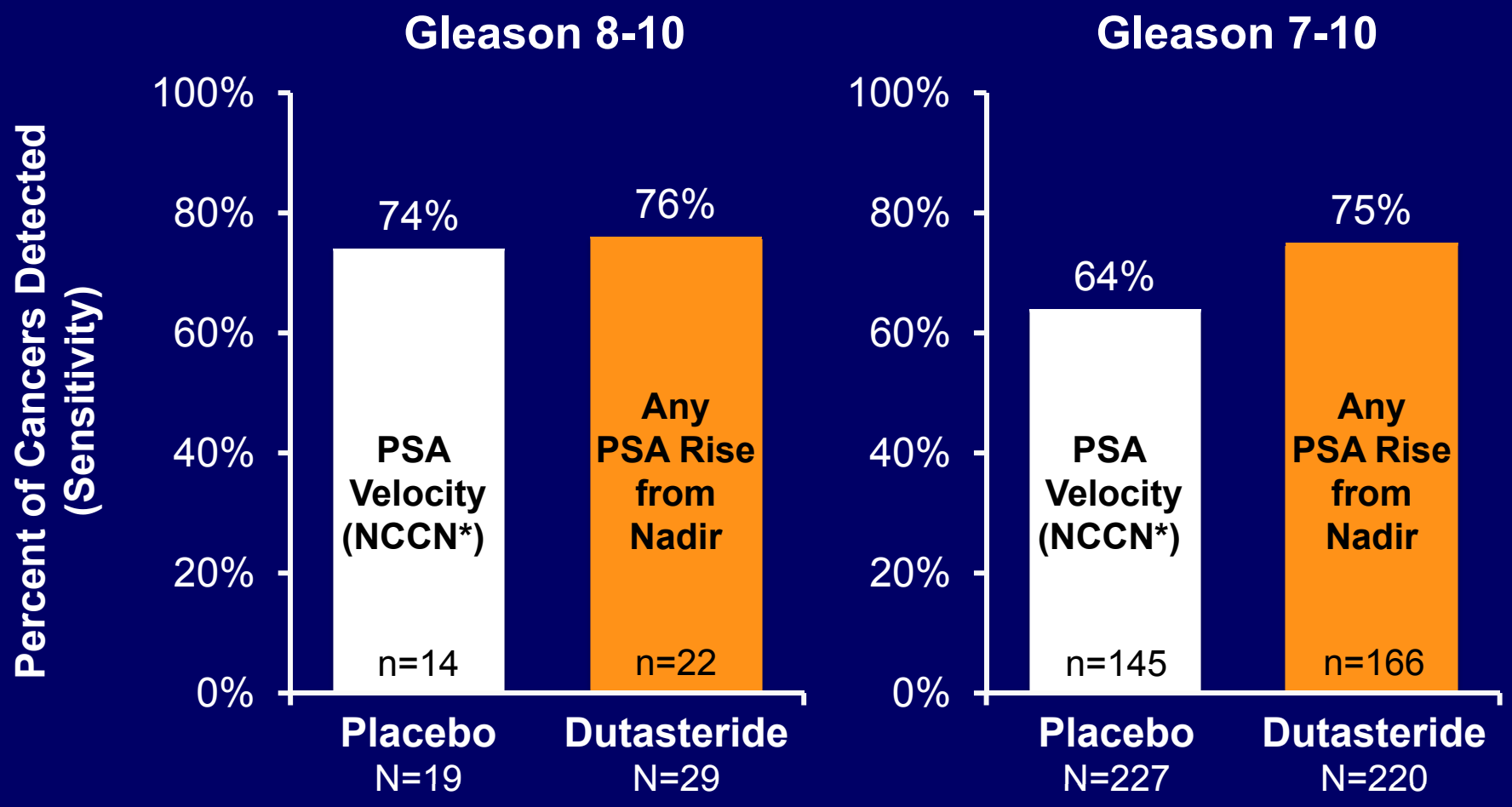
Cancer Diagnoses in REDUCE by Time, Treatment and Gleason Score

	Years 1-2		Years 3-4	
	Placebo	**Dutasteride**	**Placebo**	**Dutasteride**
Number of Biopsies	3345	3239	2342	2446
Gleason 5-7	558	417	273	211
Gleason 8-10	18 (0.5%)	17 (0.5%)	1 (0.04%)	12 (0.5%)
Imputed Gleason 8-10	*-*	*-*	*28*	*21*
Total Gleason 8-10	*-*	*-*	*29*	*33*

Serial Mean PSAs by Treatment and Cancer Status in REDUCE



Dutasteride Does Not Interfere With the Detection of High Grade Cancers Using PSA



*PSA change of 0.75 ng/mL/year or 0.35 ng/mL/year, dependent on baseline PSA

Conclusions

- Benefit seen in low grade cancers
- Difference in number of high grade cancers in Years 3-4 in REDUCE, not seen in other studies- CombAT & REDEEM
- Dutasteride does not interfere with diagnostic performance of PSA

Recommendations

- Men at risk with an elevated PSA and a baseline negative biopsy should be treated with dutasteride to reduce risk of prostate cancer

- Men on dutasteride should be closely monitored with PSA to assure safety and the rapid detection of cancer

Claus G. Roehrborn
Professor and Chairman
Department of Urology
UT Southwestern Medical Center
Dallas, TX

Clinician's Perspective

Promises and hopes of 5 alpha reductase inhibitors

- Promises:
  - Reduction in the number of TRUS biopsies and associated morbidity
  - Reduction in the number of prostate cancer diagnoses
  - Maintain ability to identify men with significant high grade cancers
  - Improvement in LUTS/ BPH symptoms and outcomes
- Hopes:
  - Reduction in the cost, morbidity and mortality associated with prostate cancer care in the US

The clinical challenges I face in managing men at risk for prostate cancer

- High number of ultrasound guided biopsies with associated morbidity
- Over-diagnosis and over-treatment of low grade prostate cancer
- Difficulties in using PSA or any other marker to identify Gleason score 7-10 prostate cancer
- Managing the coexisting lower urinary tract symptoms and BPH in patients at risk for prostate cancer

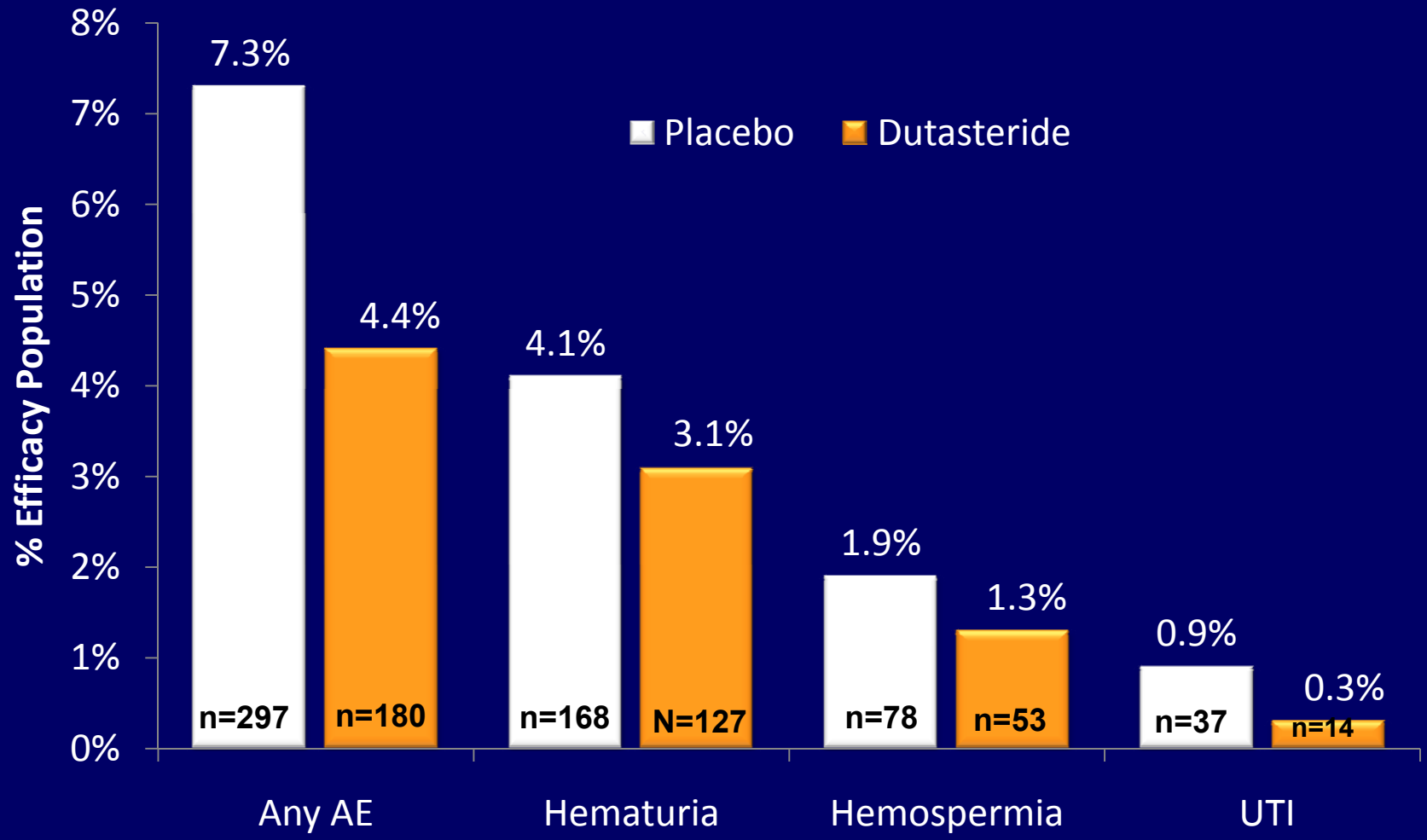
High number of ultrasound guided biopsies with associated morbidity

- More than 650,000 transrectal ultrasound guided biopsies (TRUS) done in 2010 in the US.[1]
- About 217,000 new cases diagnosed
- Minor biopsy complications are common
- Severe complications (<1%) or even death (0.09%) occur rarely[2,3,4,5]
  - Increasing rates of infection due to quinolone resistant E coli strains

[1] Estimation based on 1 out 3 bx done positive for Prostate Cancer (Welch JNCI 2007) and 217000 dx of Prostate Cancer in US in American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta: American Cancer Society; 2010.

[2]Urol Oncol. 2008; 26: 474-478 [3] Int J Urol. 2008; 15: 997-1001 [4]EAU Prostate Cancer guidelines [5] Nam J Urol. 2010 ;183: 963-969

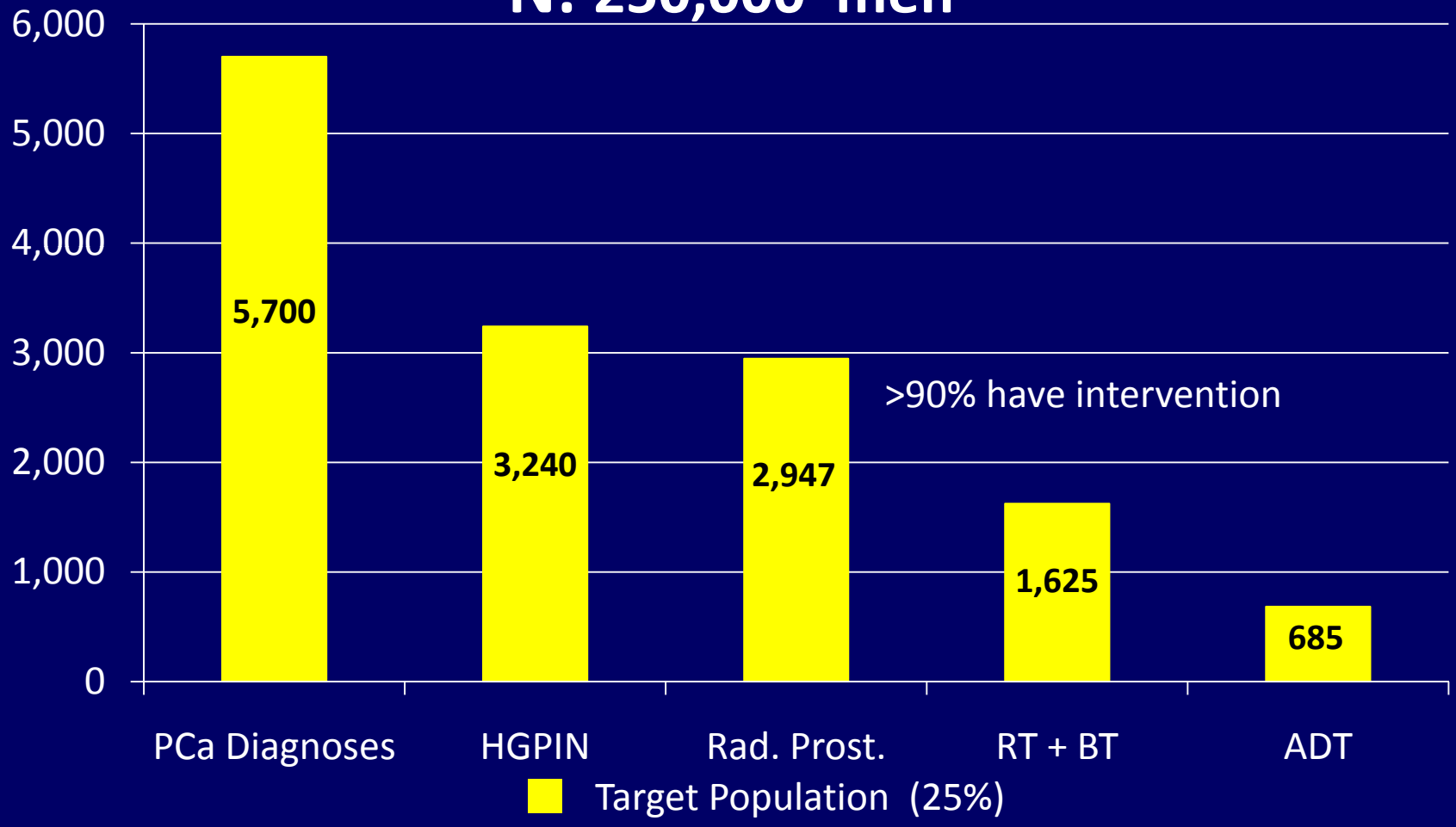
Biopsy related adverse events in REDUCE are significantly less common in Dutasteride treated patients



All p-values < 0.05

Prostate cancer diagnosis and treatment in 25% of the US at risk population

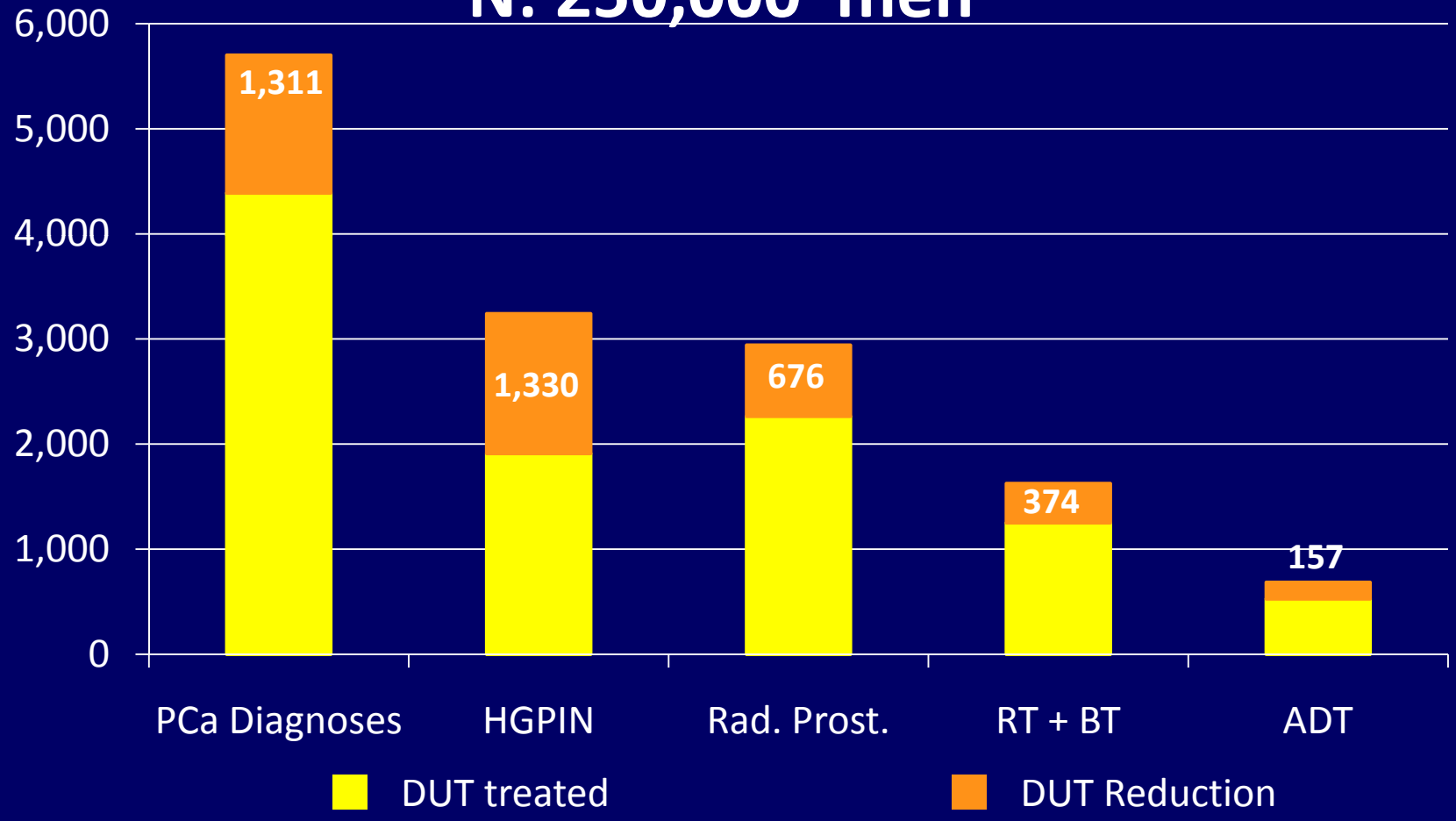
N: 250,000 men*



* Assumptions based on : Population at risk and screening practices from NHANES database . Treatment distribution from CAPSURE database in Barocas et al J. Urol 2008 ; 180: 1330-1335. Pca Diagnoses from SEER database in Walsh JNCI 2007; 99: 1395 – 400

Dutasteride reduced prostate cancer diagnoses and treatments in 25% of the US at risk population

N: 250,000 men



Interventions: CAPSURE, J. Clin. Onc (2004); Pca Diagnoses: SEER database from Walsh JNCI (2007)

Relevance of the cancers avoided using Epstein Criteria

- **Epstein Criteria:**
  - Used to differentiate low risk patients that may be followed with active surveillance without immediate treatment intervention
- **FDA Briefing Document:**
  - "As assessed by the Epstein criteria, approximately 80% of patients who had Gleason score ≤ 6 prostate cancers that were confirmed in both the reread and the initial read had very low or low risk prostate cancer"

Gleason score ≤ 6 cancers do not always have a benign course

- Up to 50% of patients with low grade cancer in active surveillance protocols switch to active interventions, not infrequently because of their anxieties [Klotz Curr Oncol. 2010 Sep;17 Suppl 2:S11-7]
- 40-60% of biopsy Gleason score 6 cancers are upgraded to Gleason score 7 or higher cancers on prostatectomy [Pinthus et al J Urol 2006; 176: 979–984] “
- *“the Epstein criteria are insufficiently robust to predict biologically insignificant disease” [Lee et al, Eur Urol 58:90, 2010]*

Relevance of REDUCE to clinical practice & CombAT biopsy methodology

- "questionable relevance of the results of REDUCE to clinical practice, where only "for-cause biopsies" are performed"
- The CombAT (BPH treatment study) protocol "did not specify criteria for when to biopsy the prostate or for how the biopsies would be performed"

The dilemma of study design

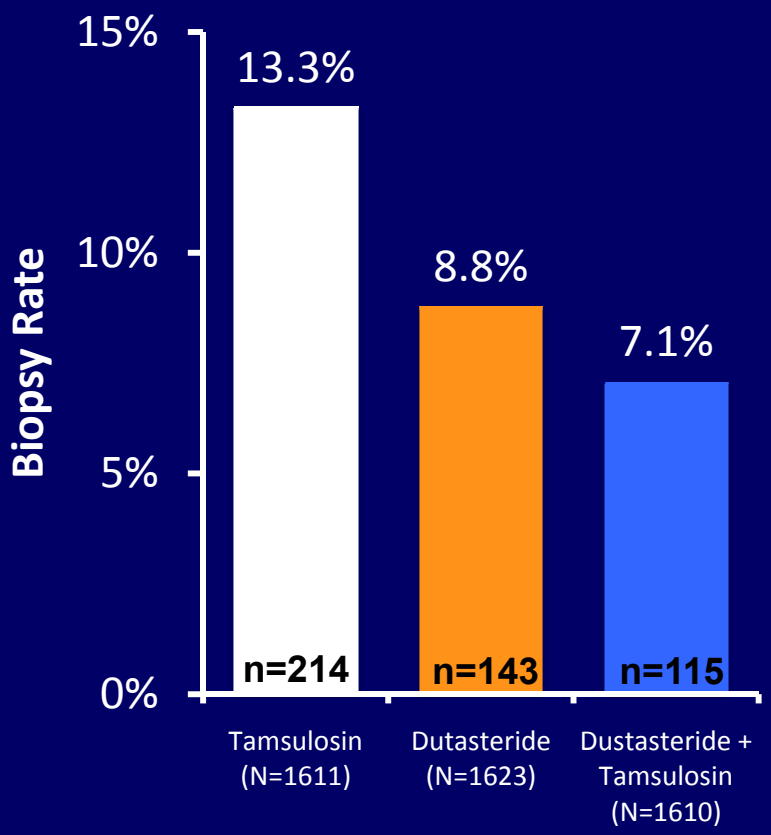
- As Dr. Walsh pointed out in his NEJM editorial:
  - Protocol driven, end of study, random biopsies are not relevant for a real life practice situation
  - For cause biopsies in patients on 5 alpha reductase inhibitors are confounded by the PSA kinetics
- Protocol-dependent biopsies aimed to ensure equal opportunity of assessment (ascertainment bias)
- Some 'protocol-dependent' biopsies may have had a 'cause' but were done at the 24 / 48 mo time points
- Bias is ubiquitous in all of medicine

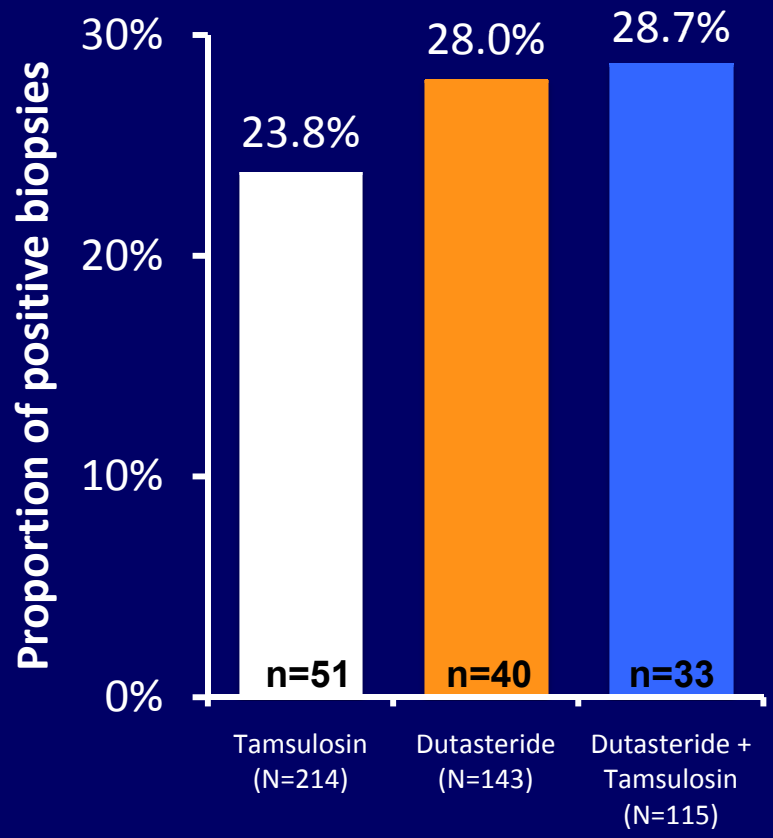
N Engl J Med 362;13 nejm.org April 1, 2010

Considerations and insights

- A cohort of patients on 5 ARIs unencumbered by protocol driven biopsies, presence or absence of criteria, thus representing true real life practice
- In lieu of such:
  - Consider the for cause biopsies in CombAT
  - Compare to the truly randomized phase of REDUCE, the 'for cause' biopsies in the first 24 mo before 143 excess cancers were removed from the placebo arm
  - Learn from the results of the end of study protocol-dependent biopsies how to interpret the PSA changes during treatment and decide when to do for cause biopsies

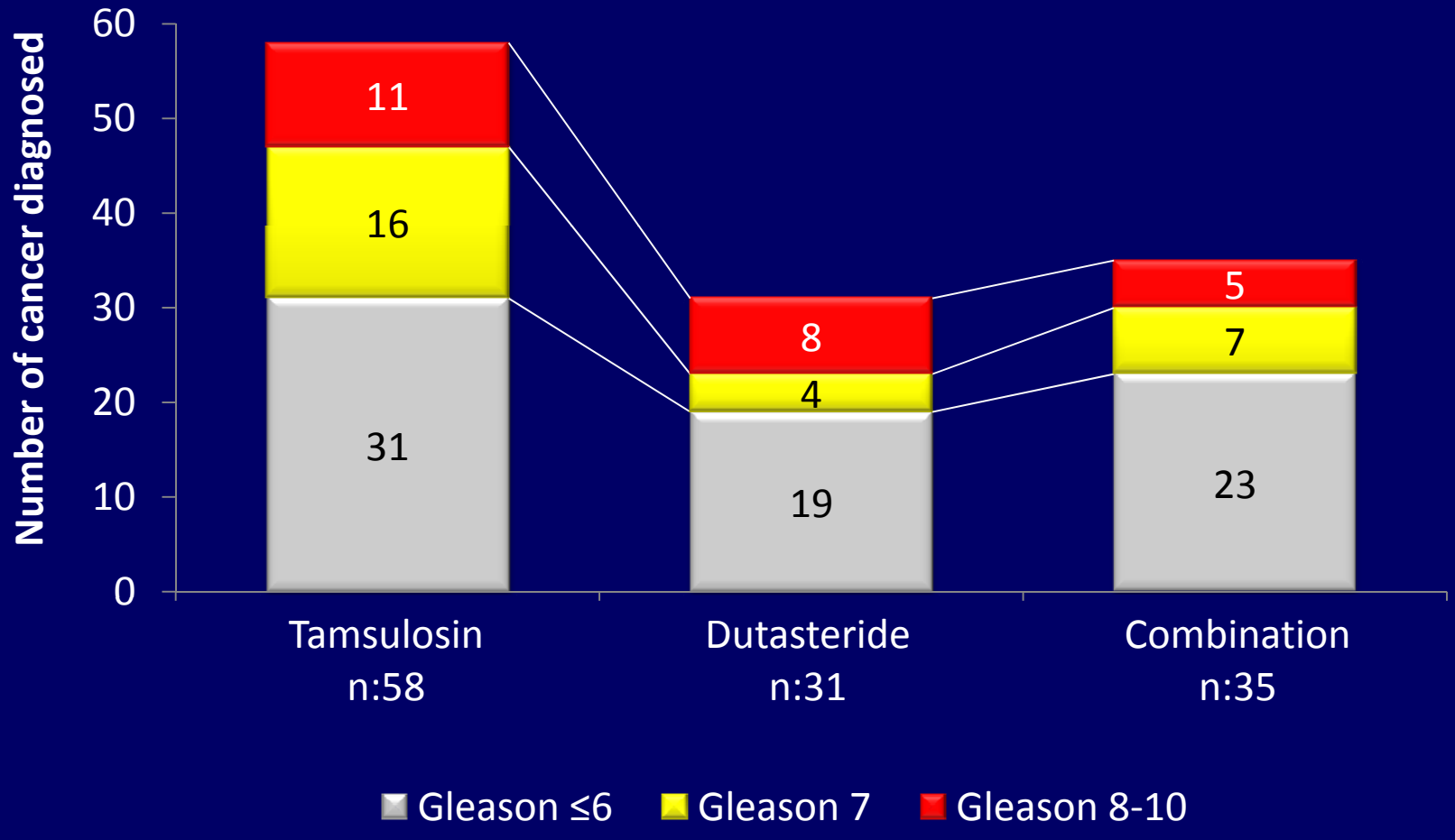
CombAT - BPH :
Dutasteride reduces post-baseline biopsy rate and is associated with an increased diagnostic yield





The majority of men were referred for biopsy based on elevated PSA, others reasons included transrectal ultrasound, digital rectal examination

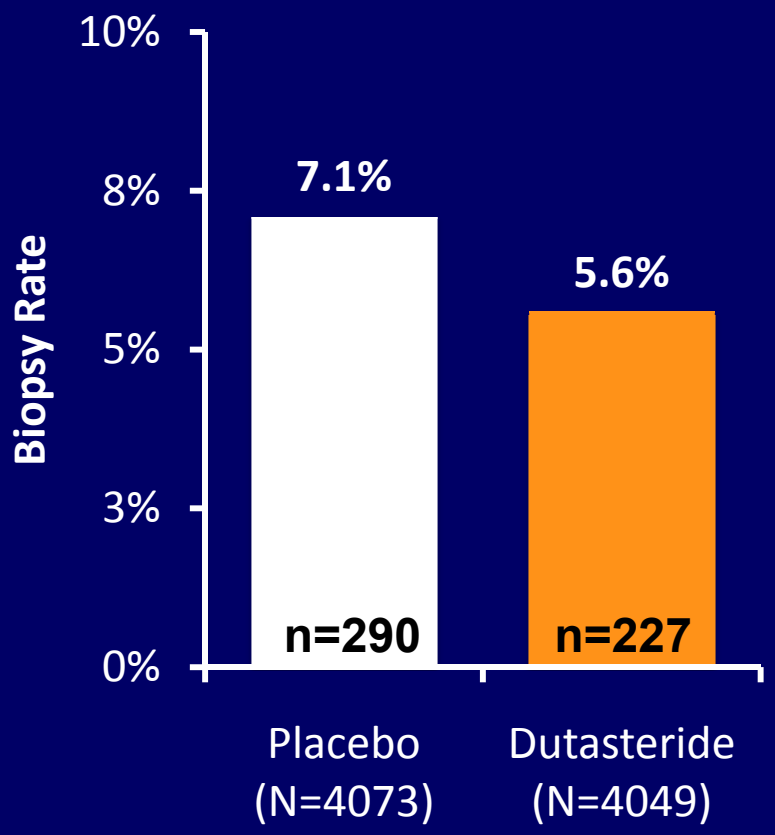
CombAT BPH:
Reduction in prostate cancer with Dutasteride treatment is evident across all Gleason scores

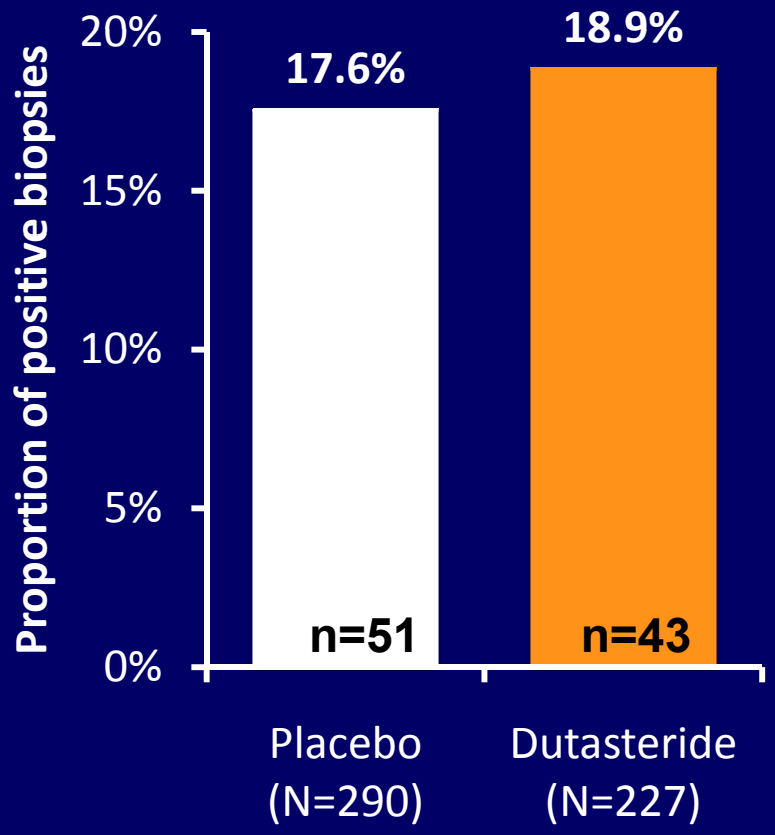


Numbers include prostate cancer diagnosed on biopsy or BPH-related surgery

REDUCE:

Dutasteride reduces for-cause biopsy rate and is associated with an increased diagnostic yield in Years 1-2

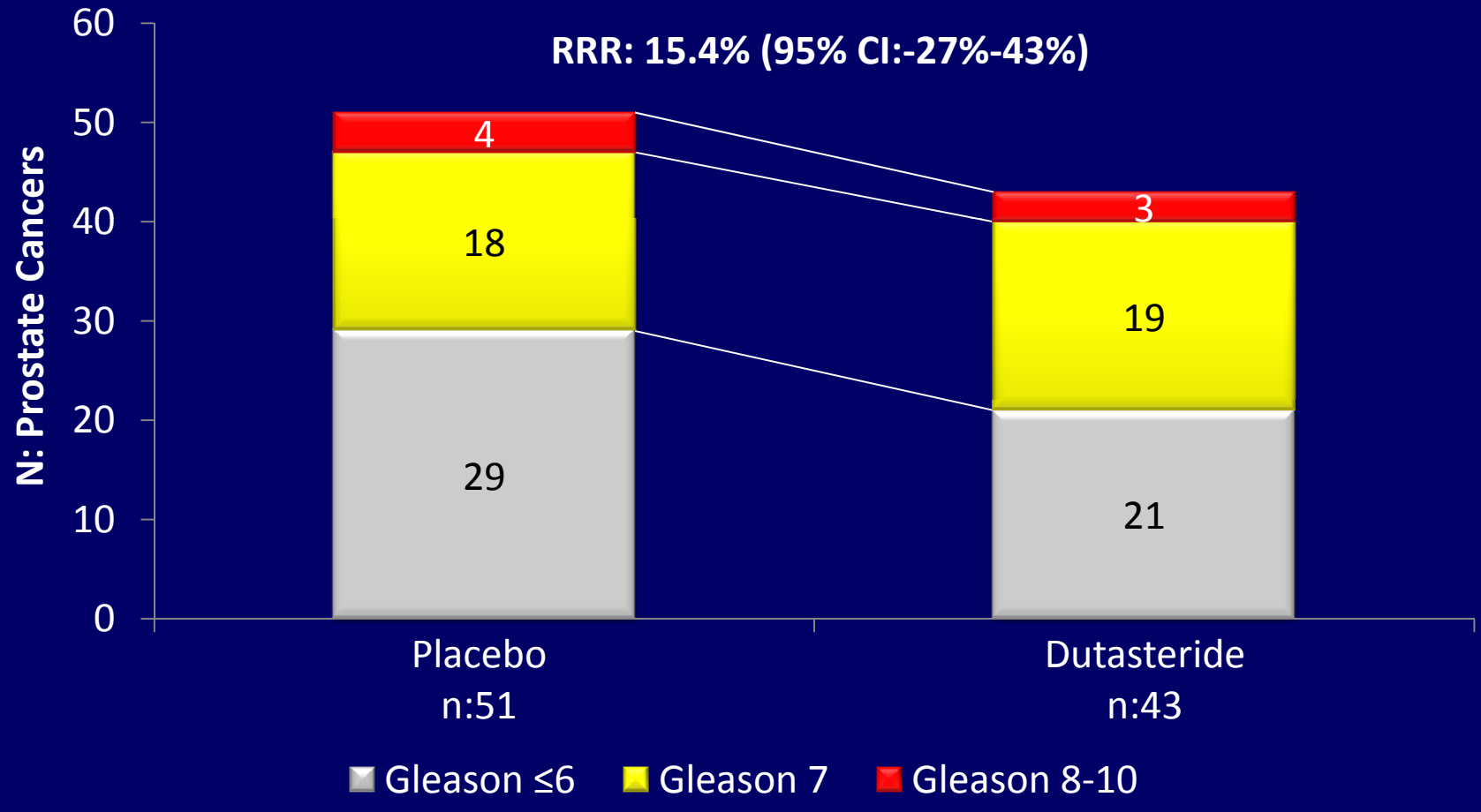




The majority of men were referred for biopsy based on elevated PSA, others reasons included transrectal ultrasound, digital rectal examination

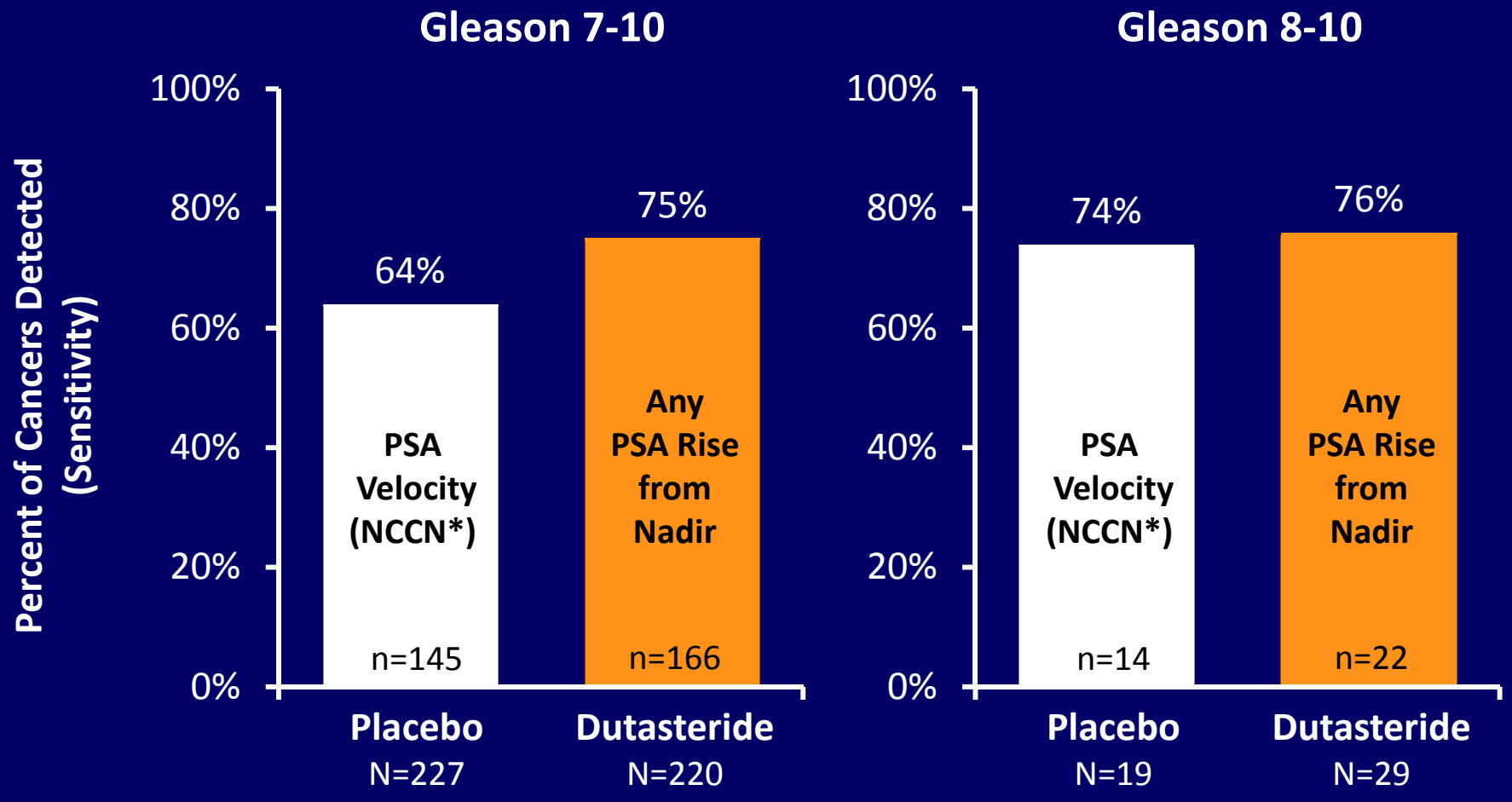
REDUCE:

Reduction in for-cause biopsies in prostate cancer with Dutasteride treatment by Gleason score group, years 1-2



Numbers include prostate cancer diagnosed on biopsy or BPH-related surgery

Dutasteride does not interfere with the detection of Gleason 7-10 or 8-10 cancers using PSA



*PSA change of 0.75 ng/mL/year or 0.35 ng/mL/year, dependent on baseline PSA

Conclusions

- Dutasteride has proven long term safety and efficacy for men with LUTS and BPH
- High Grade Prostate Cancer
  - Patient and health care provider information and education
  - Regular PSA monitoring
  - Appropriately responding to PSA changes from nadir
- Benefits outweigh the risks for reduction in the risk of prostate cancer in men with a prior negative biopsy and a PSA ≥ 2.5 ng/ml

Concluding Remarks

Anne M. Phillips, MD
VP, Medicine Development Leader
Oncology R&D, GlaxoSmithKline

Our Purpose

- Evaluate dutasteride for prostate cancer risk reduction in men at increased risk
  - Important medical need
  - Prevalent, serious and complex disease
- Exercise caution
  - Benefits – risks – uncertainties
  - Specific target population

Target Population

- Men at increased risk for prostate cancer, defined as:
  - Negative, for-cause biopsy
  - Elevated PSA
- Approximately 1 million U.S. men in 2010

Challenges and Medical Need

- 70 percent of cancers detected are low grade
- 90 percent of men with positive biopsies are actively treated
- Reduce diagnosis and unnecessary treatment of low grade, indolent cancers
- Detect cancers with greatest risk of morbidity and mortality

Benefits

- Significant reduction relative to placebo in:
  - Prostate cancer 23%
  - Prostate cancer associated lesions
    - HGPIN reduction (41%)
    - ASAP reduction (24%)
  - Surgical and non-surgical interventions (32%)
  - BPH symptoms and complications (73%)
- High grade cancer detection maintained with PSA
- Long history of use in BPH (5.5 million p.y.e.) with established safety profile

Risks

- Potential for sexual dysfunction
- Potential for breast disorders

Uncertainties

- Effect on prostate cancer associated mortality
- Optimal duration of treatment
- Difference in numbers of high grade cancers
  - 0.9% dutasteride and 0.6% in placebo

Risk Management

- Knowledge
  - Commitment to advancing the science for prostate cancer including high grade cancers
    - Genetics, epidemiology, pharmacoepidemiology
  - Pharmacovigilance
- Education
  - PSA, high grade cancers, risk not reduced to zero
- Labeling
  - Targeted population
  - Uncertainties about high grade cancer
  - Guidance around PSA monitoring

Conclusion

- 23% relative risk reduction of biopsy-detected prostate cancer
- Reduction in BPH symptoms and complications
- Maintained ability to identify high grade cancer
- Comprehensive risk management plan
- Benefit:risk profile for dutasteride in men at risk of developing prostate cancer is favorable

Proposed Indication

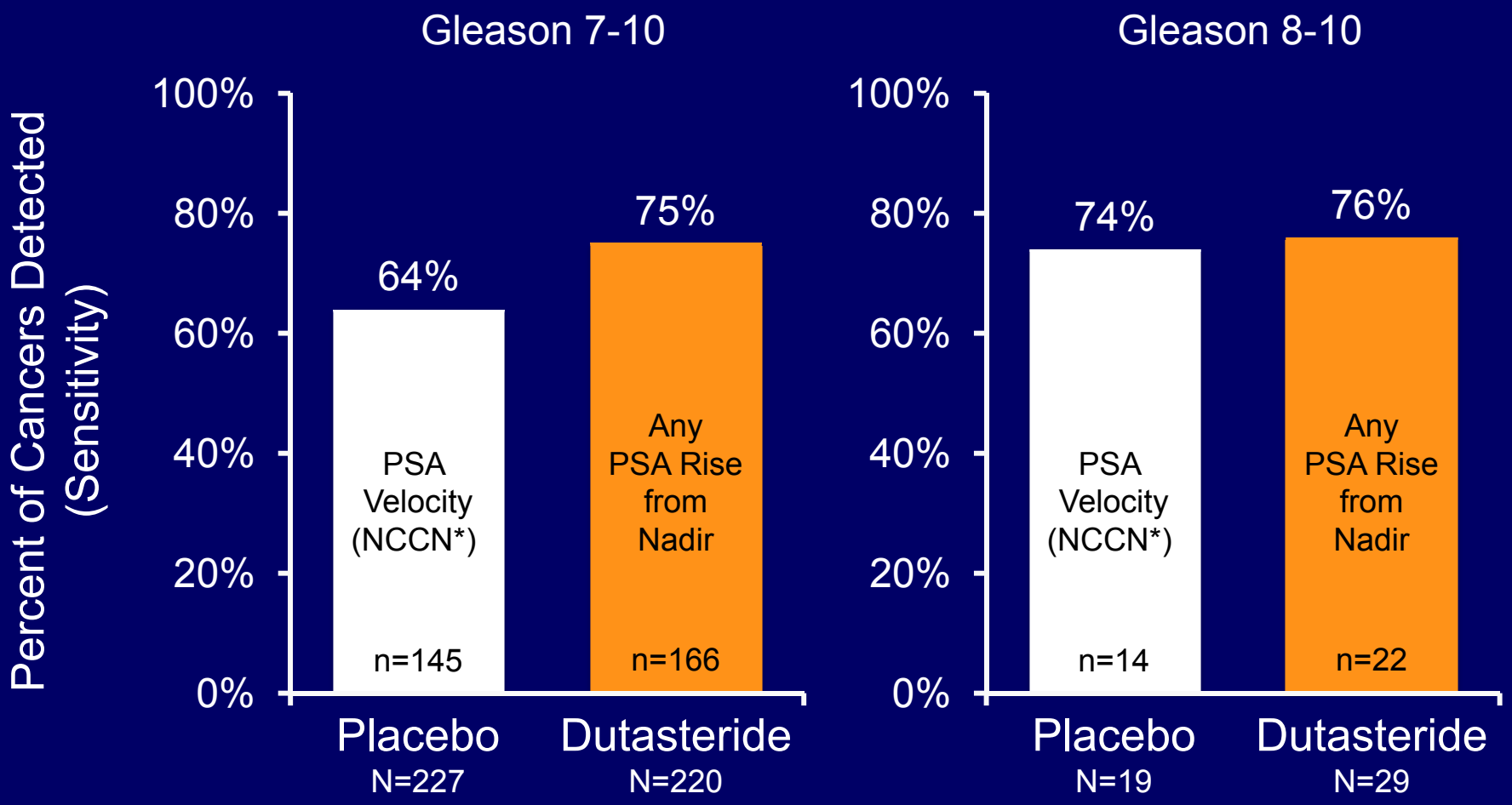
AVODART® (dutasteride) is indicated for reduction in the risk of prostate cancer in men at increased risk of developing the disease, defined as those who have had a prior negative biopsy due to clinical concern and have an elevated serum prostate-specific antigen (PSA).

Backups

REDUCE Number Needed to Treat

Time Period	Number Needed to Treat	
	Per Time Period	Per Year
Years 1-2	27.7	55.4
Overall (Years 1-4)	19.1	76.4

Dutasteride does not interfere with the detection of Gleason 7-10 or 8-10 cancers using PSA



*PSA change of 0.75 ng/mL/year or 0.35 ng/mL/year, dependent on baseline PSA

Study Results: Odds Ratios For Gleason 8-10 REDUCE, CombAT and REDEEM

Study	Odds Ratio (95% CI)
REDUCE Years 1-2	0.950 (0.459, 1.956)
REDUCE Years 3-4	11.924 (1.762, 509.889)
COMBAT	0.587 (0.242,1.451)
REDEEM Months 1-18	0 (0, 3.656)
REDEEM Months 19-36	1.592 (0.081, 95.100)

COMBAT Odds ratio is Dutasteride/Dutasteride+Tamsulosin vs Placebo/Tamsulosin

Stratified Mantel-Haenszel Meta-analysis For Gleason 8-10 REDUCE, CombAT and REDEEM

	Odds Ratio (95% CI)
Randomized phases of studies	0.742 (0.447, 1.232)
All phases of studies	1.074 (0.684, 1.687)

Odds ratio is Dutasteride/Dutasteride+Tamsulosin vs Placebo/Tamsulosin