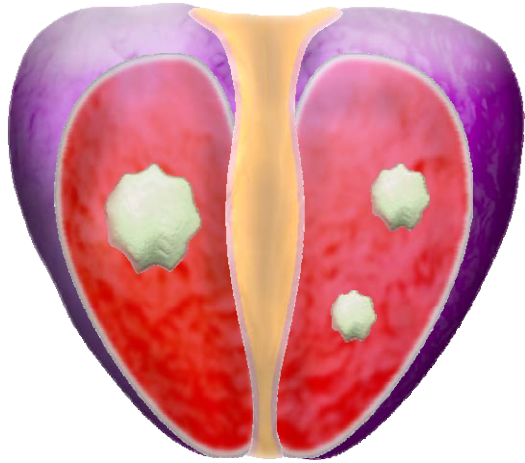


New Treatment Options for Advanced Prostate Cancer

William K. Oh, M.D.

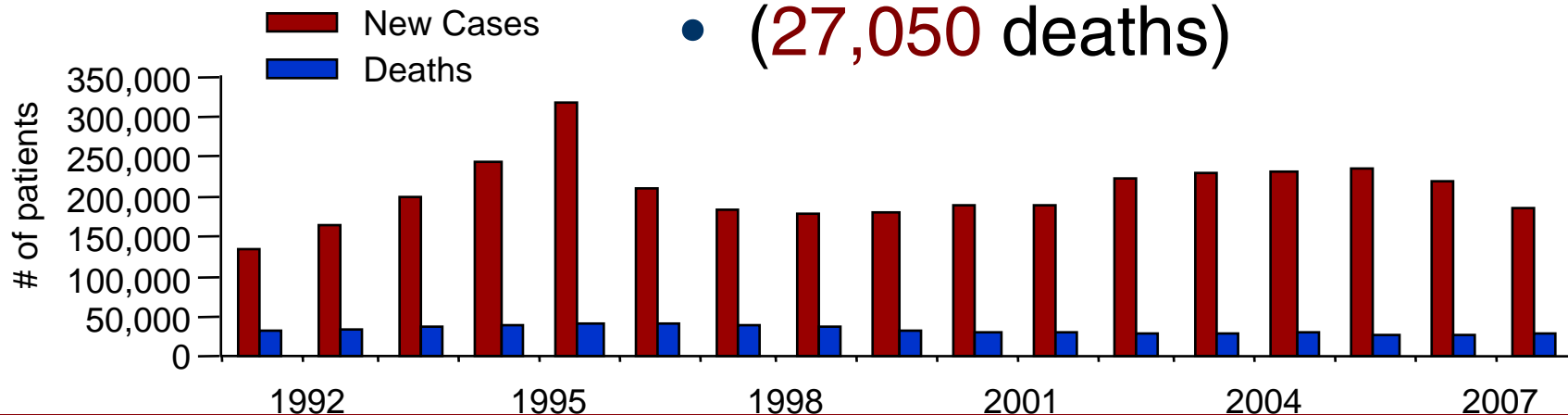
Clinical Director, Lank Center for Genitourinary Oncology
Dana-Farber Cancer Institute
Associate Professor, Harvard Medical School

Prostate Cancer 2009

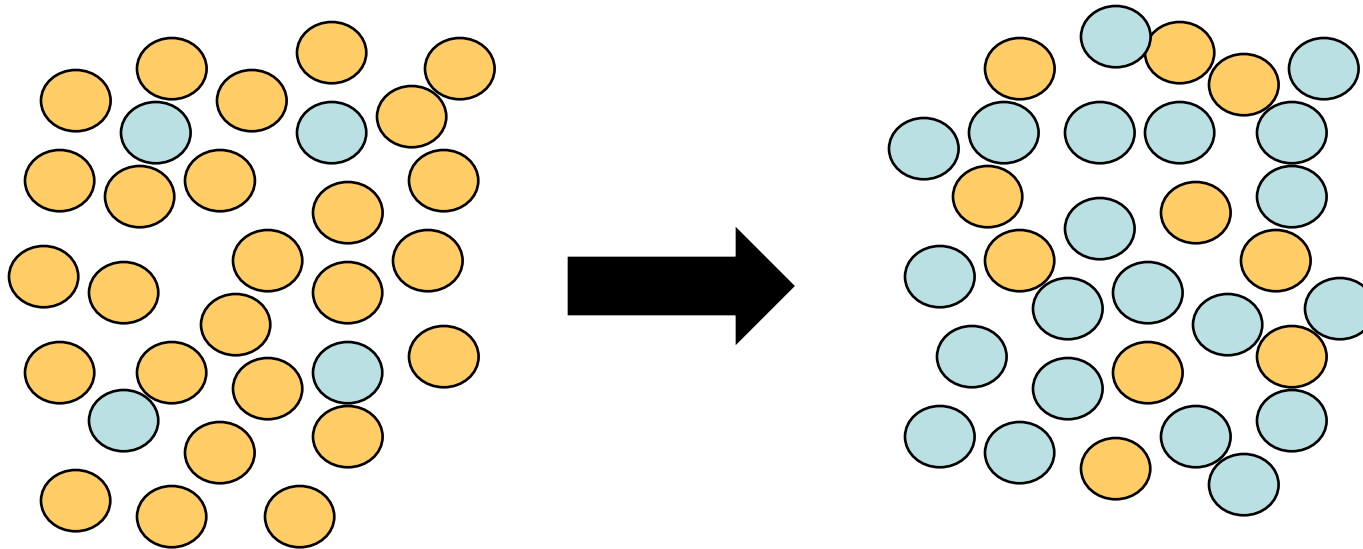


Prostate With Tumors

- **Leading** cause of cancer in men
- **(218,890 cases, 29%)**
- **Second leading** cause of cancer death in men, after lung cancer
- **(27,050 deaths)**

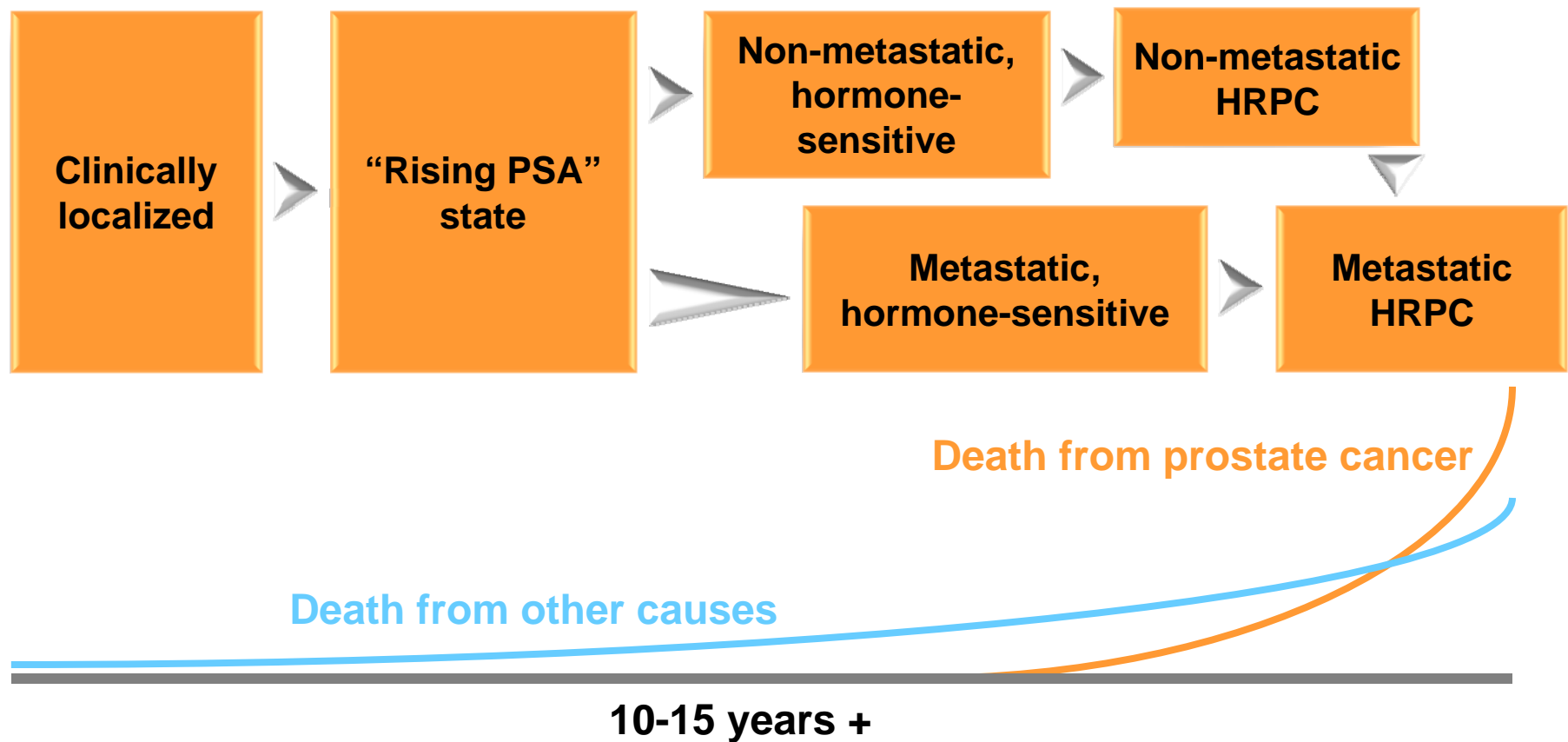


Hormone-Refractory Prostate Cancer (HRPC)*

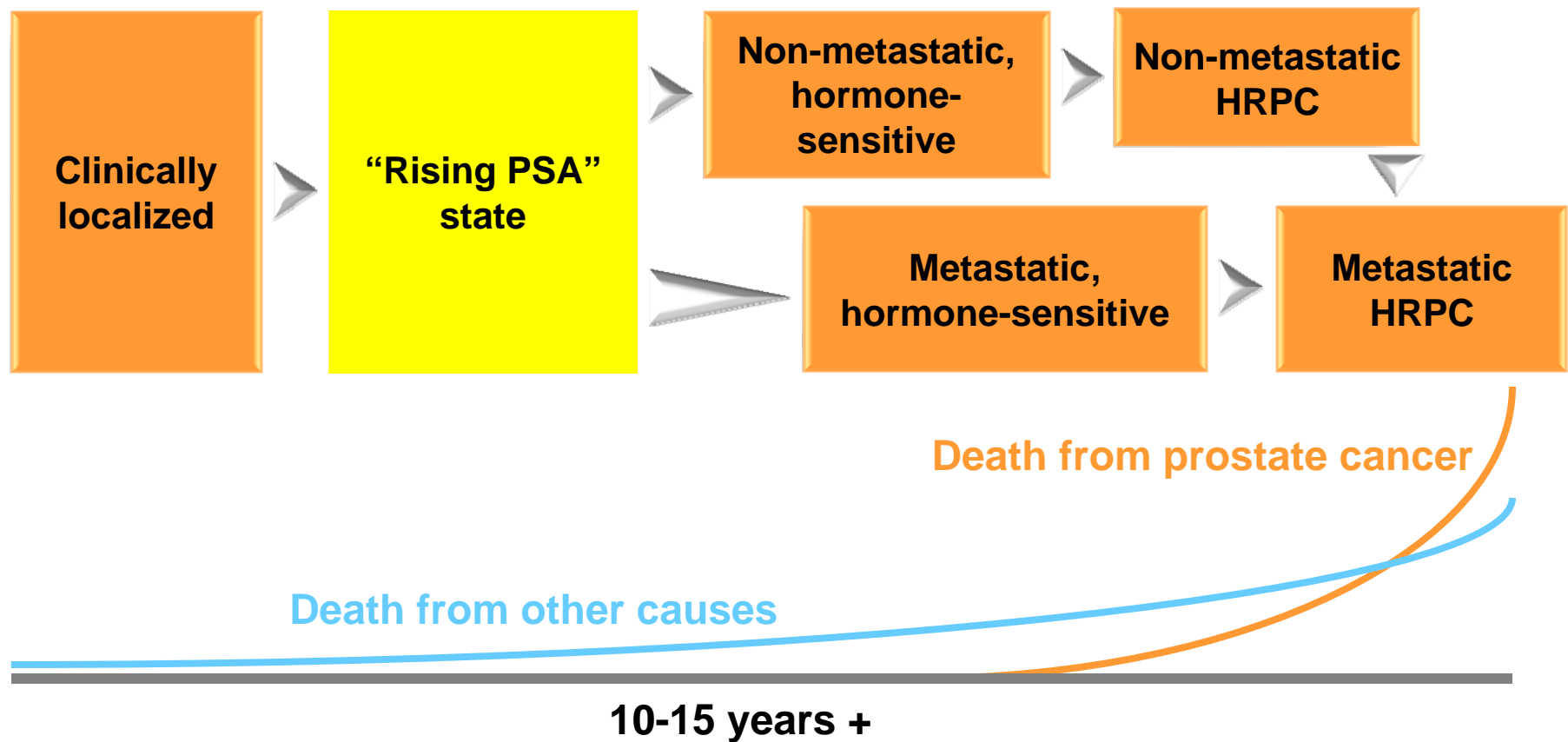


*HRPC=CRPC=AIPC

Clinical States of Prostate Cancer



Clinical States of Prostate Cancer

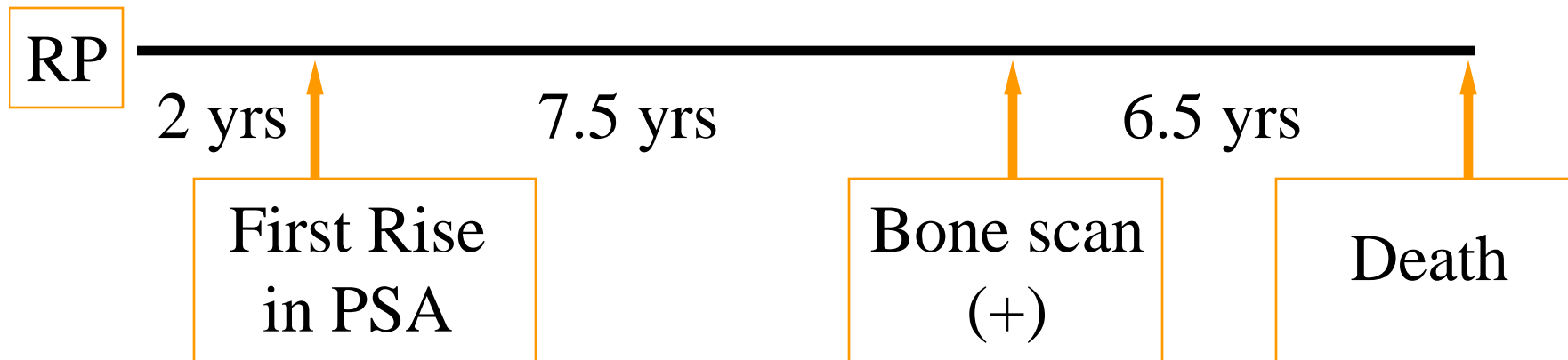


Failure of Local Therapy

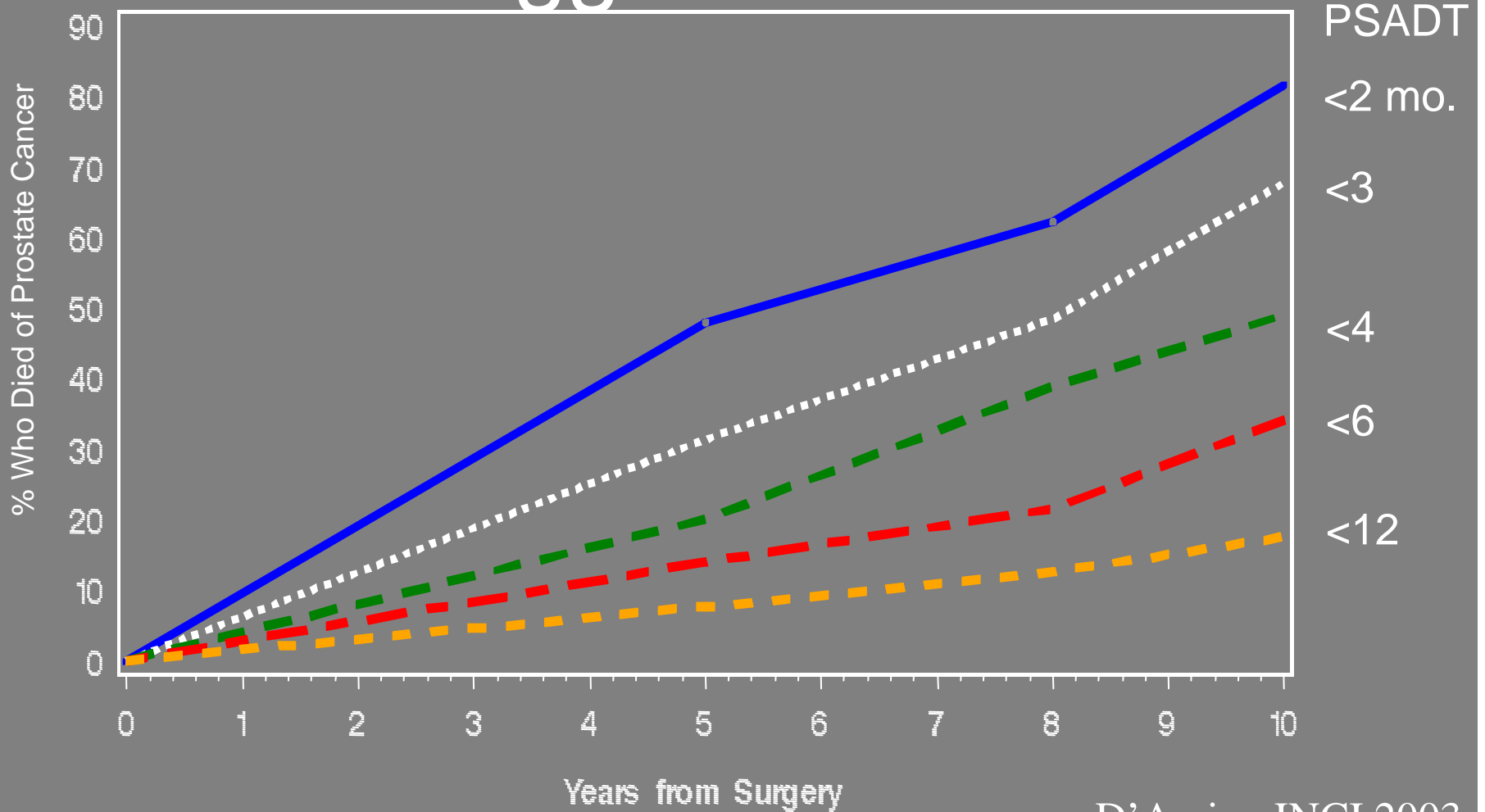
- Most men treated for localized prostate cancer are cured
- About 1/3 recur, initially as a rising PSA alone (“biochemical failure”)
- Little is known about optimal management of rising PSA patients

Natural History of Rising PSA

- Patrick Walsh (@ Johns Hopkins)
- ~15% relapsed after surgery
- No hormones until (+) bone scan



Rapid PSA Doubling Time (PSADT) = More Aggressive Cancer



Investigational Therapies for Rising PSA

- Lifestyle or diet
 - Pomegranate juice
- Novel targeted therapies
 - Rosiglitazone (Avandia)
 - Celecoxib (Celebrex)
 - Thalidomide/Revlimid
 - Statins
- Vaccines?

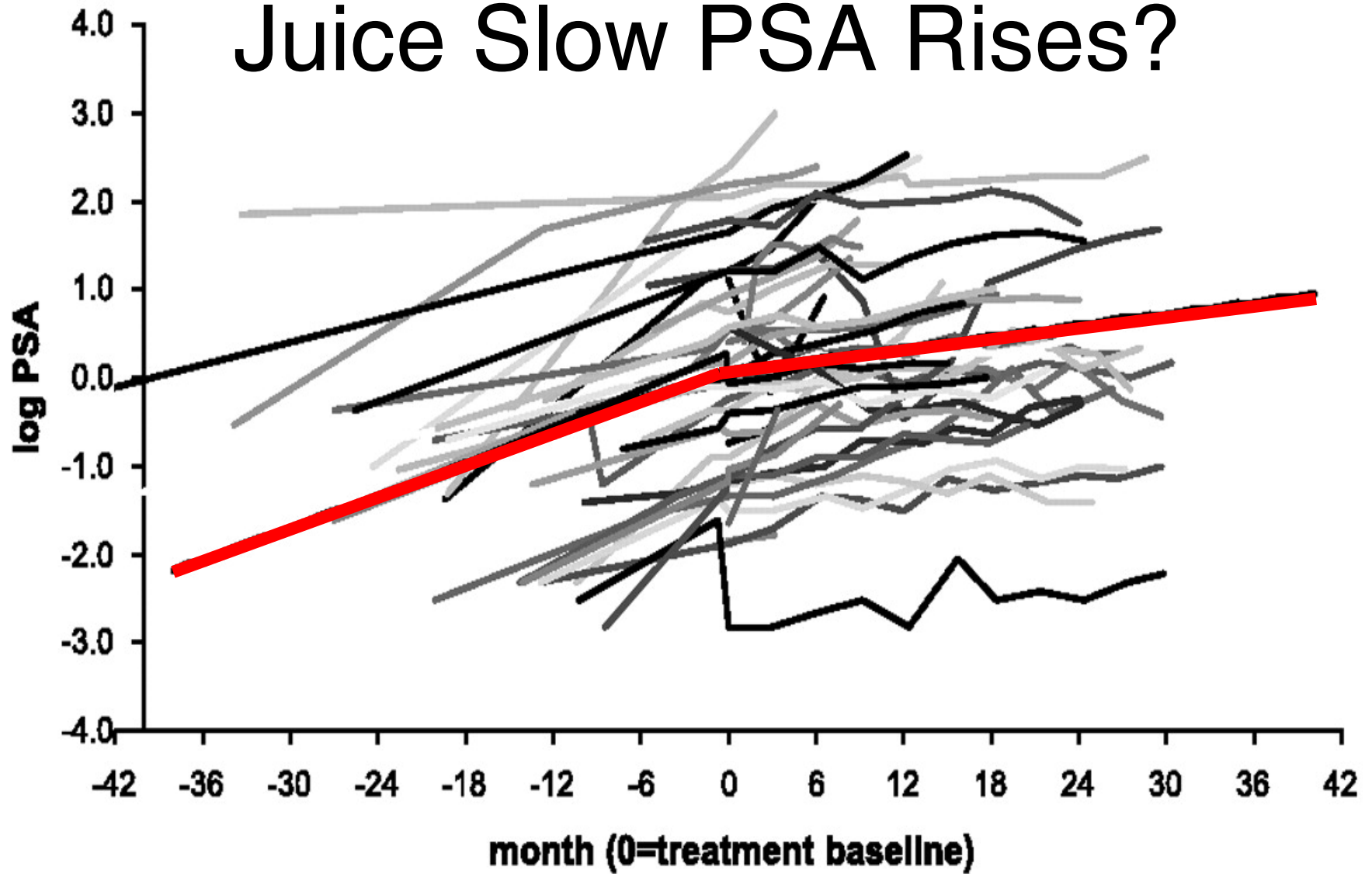
Pomegranate Juice?



- 46 patients with rising PSA, no mets (UCLA)
- 8 oz daily pomegranate juice
- PSADT
 - Pre-juice: median 11.5 mo
 - Post-juice: median 28.7 mo
 - $p < 0.001$
- 83% showed some improvement of PSADT

Pantuck CCR 2006; updated AUA 2009

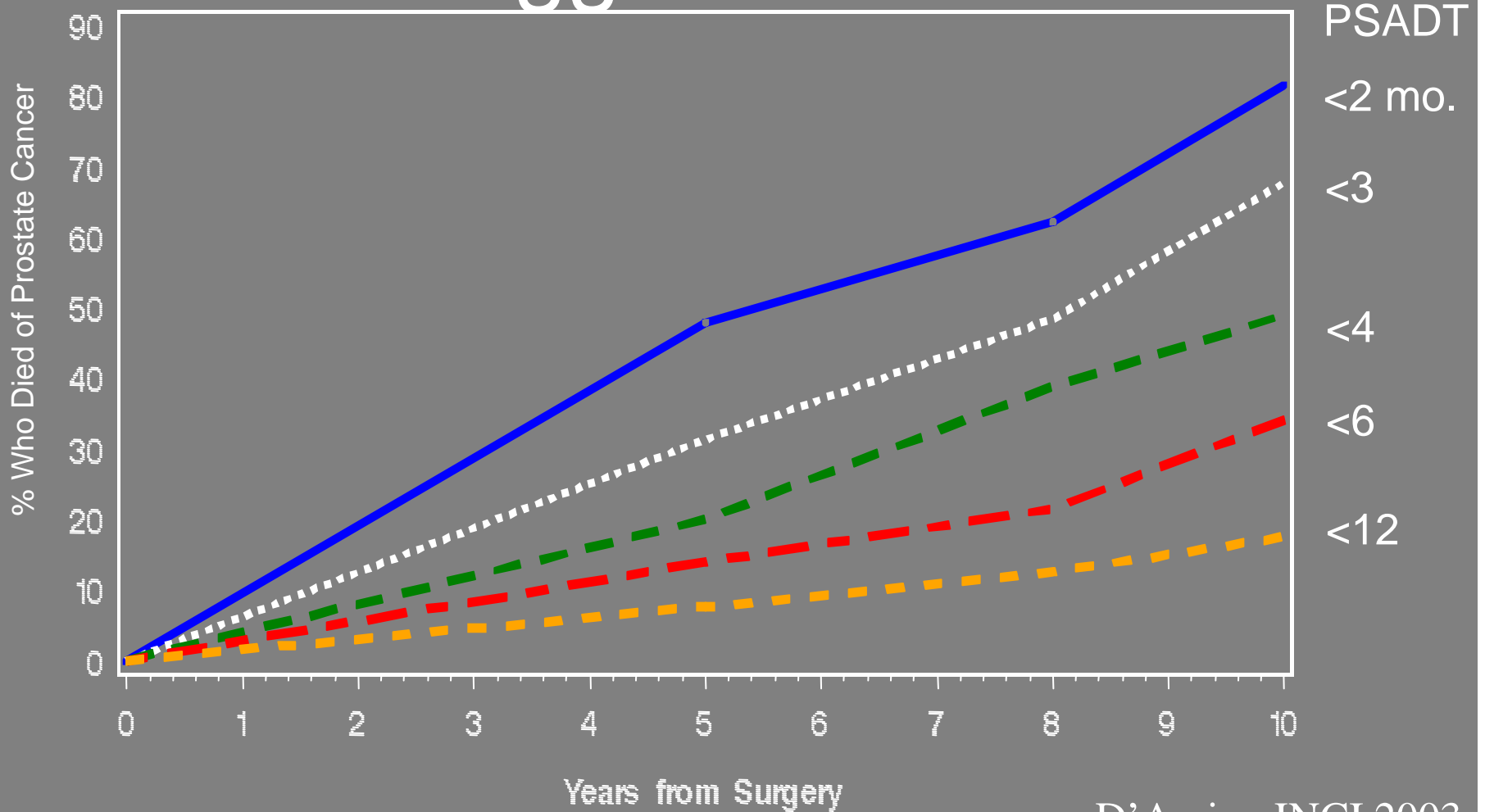
Does Pomegranate Juice Slow PSA Rises?





A larger
clinical trial
is underway,
so it's too
soon to say

Rapid PSA Doubling Time (PSADT) = More Aggressive Cancer



Chemohormonal Therapy in Rapid PSADT patients (≤ 8 mo)



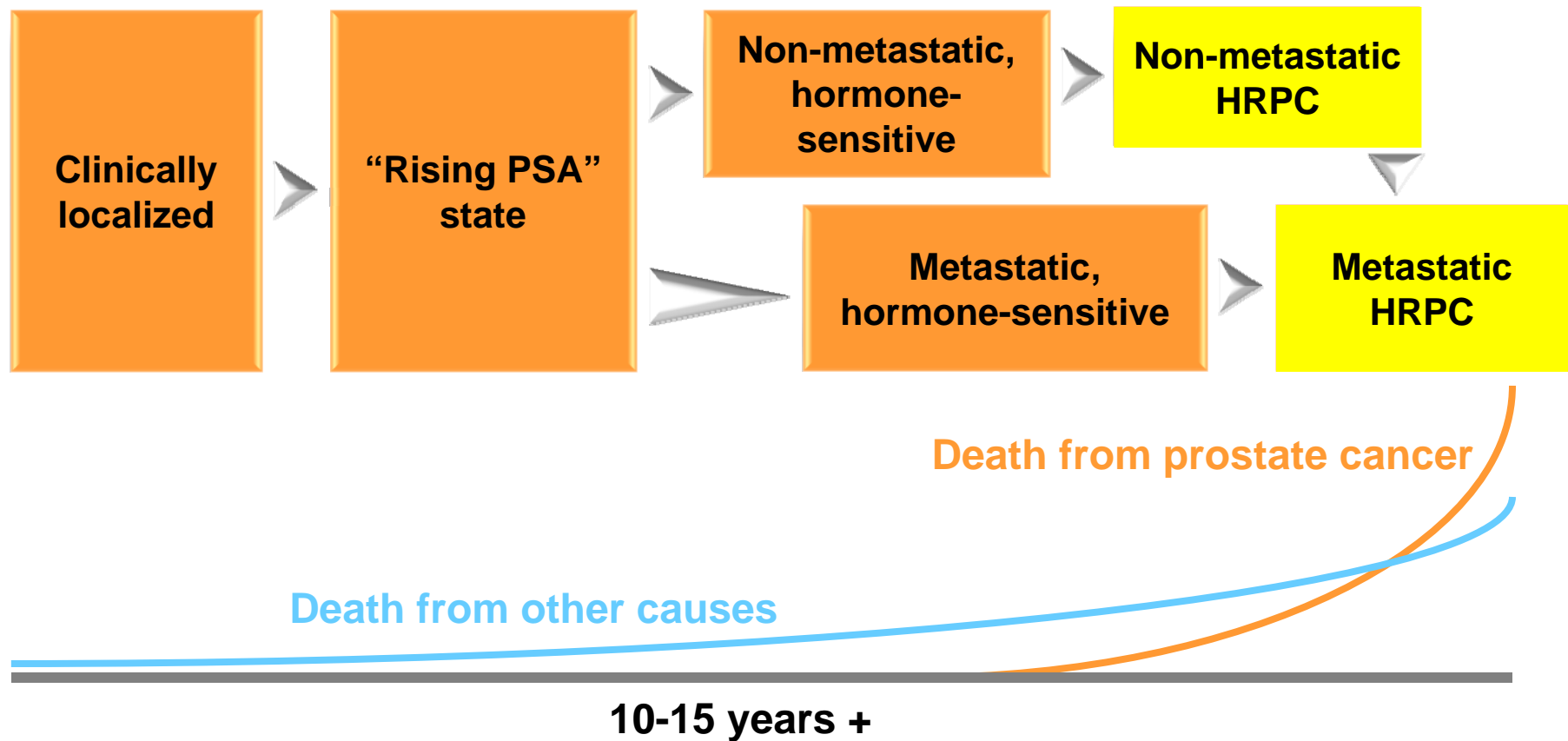
n = 40

PI: Dr. Taplin

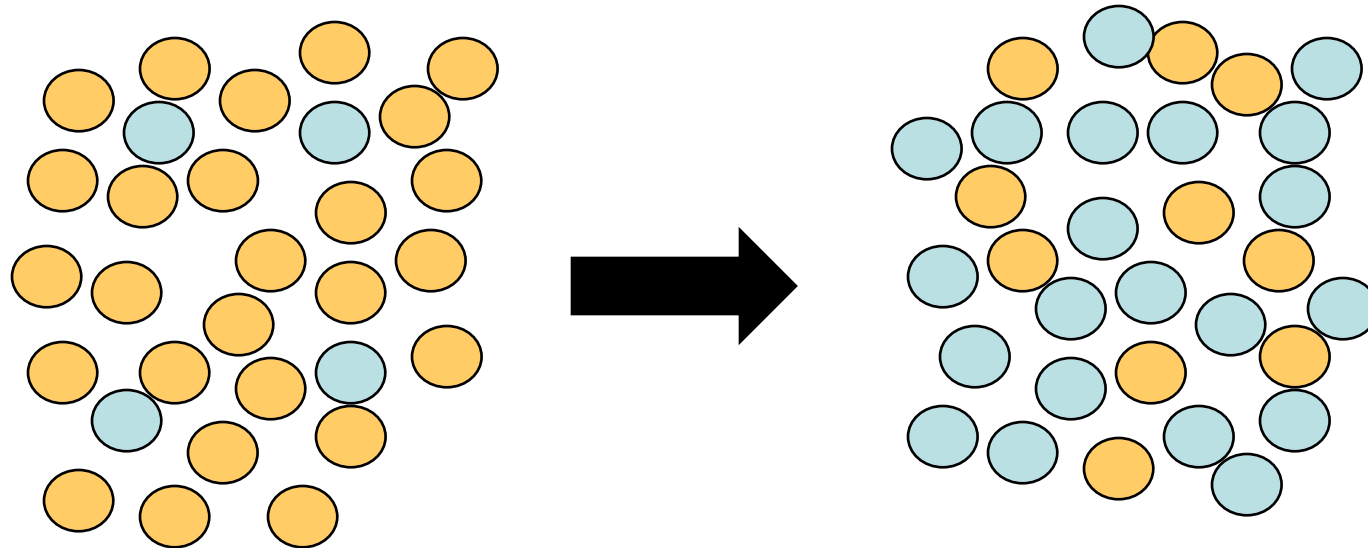
Conclusions: Rising PSA State

- Biochemical failure is heterogeneous
- All patients should not be treated alike
- PSADT should guide therapeutic decisions
 - Observation or diet in slow PSADT patients
 - Hormones alone once PSA ~ 10 ng/ml?
 - Chemohormonal therapy in rapid PSADT patients?

Clinical States of Prostate Cancer

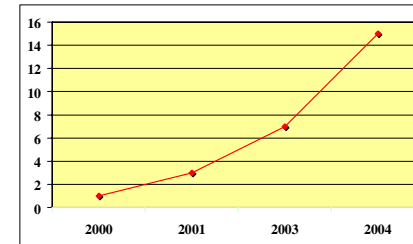
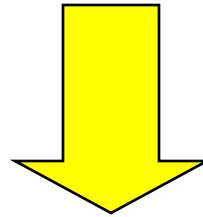


Hormone-Refractory Prostate Cancer (HRPC)*

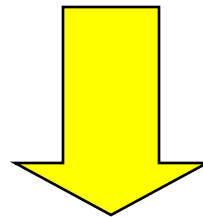


*HRPC=CRPC=AIPC

Initial Hormonal Therapy



Secondary Hormonal Therapy



Chemotherapy



Secondary Hormonal Therapy for HRPc

Therapy	Number of trials	PSA response rate (range)
Casodex	2	20-24%
Nilandron	3	29-50%
Nizoral (Ketoconazole)	4	31-63%
Estrogens	5	21-86%

Testosterone

- Testicles: 90%
- Adrenal glands: 10%
- Prostate cancer cells ?



Can we block testosterone better?

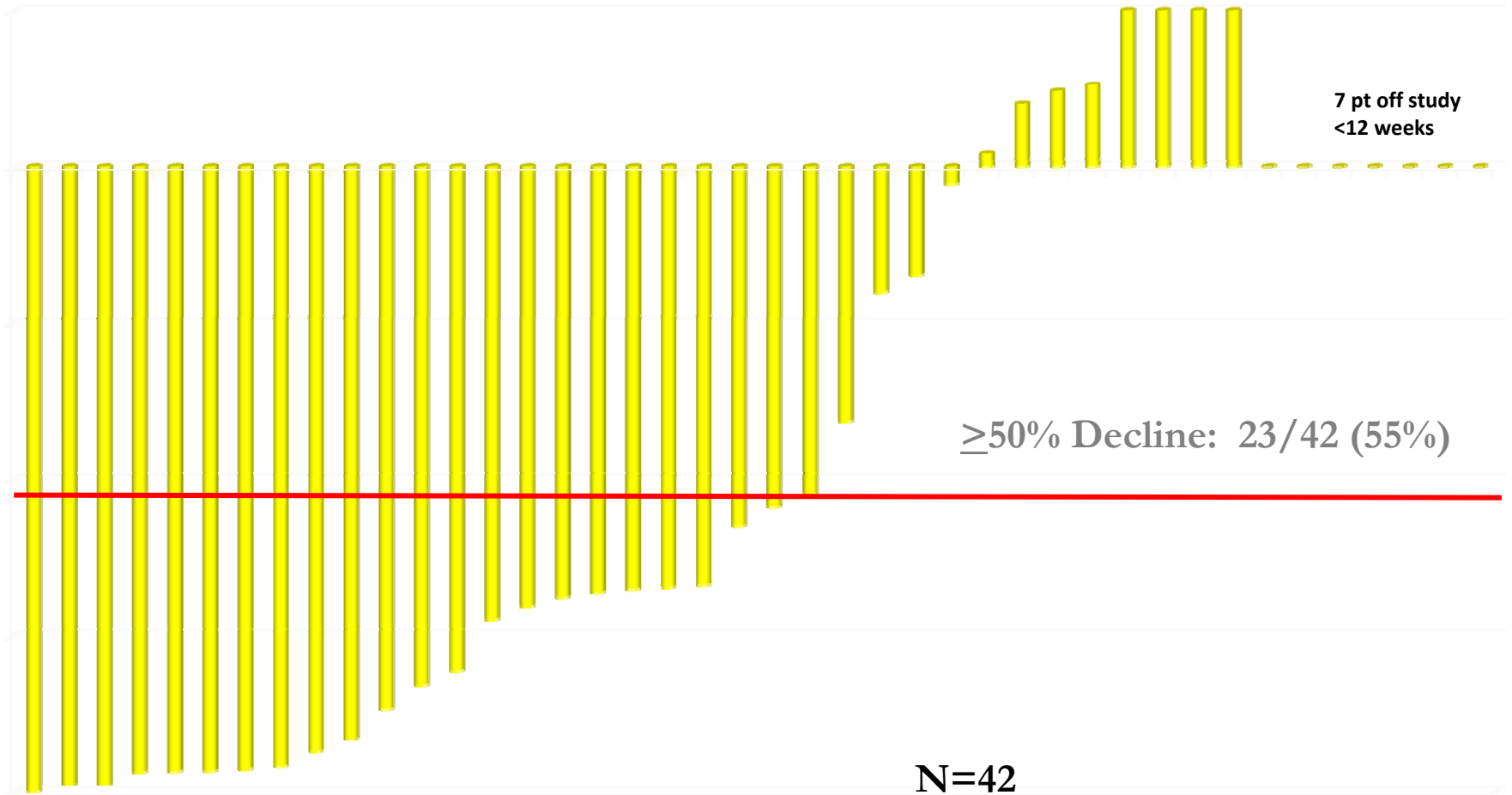
- MDV 3100: a better antiandrogen?
- Abiraterone: a better adrenal blocker?

MDV 3100: A Novel Antiandrogen

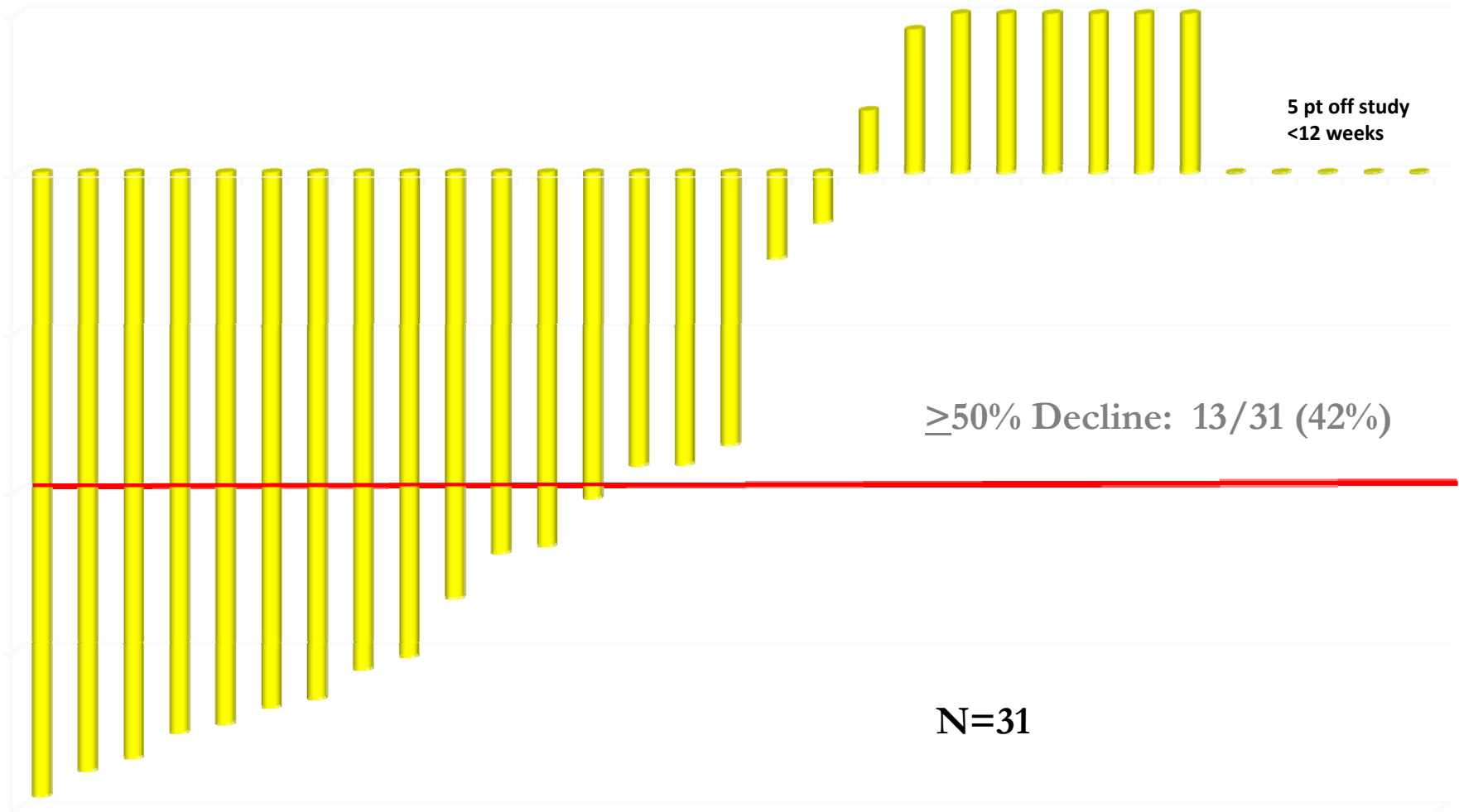
- Blocks androgen receptor (AR) from moving into the nucleus and activating growth genes
- Phase I/II trial HRPC pre and post chemotherapy
- 7 dose levels tested (24 men each)
- Responses at all dose levels
- Well tolerated so far

PI: Dr. Taplin

% PSA Change from Baseline at 12 wks In Men Who Have Not Received Chemotherapy



% PSA Change from Baseline at 12 wks In Men Who Have Already Received Chemotherapy



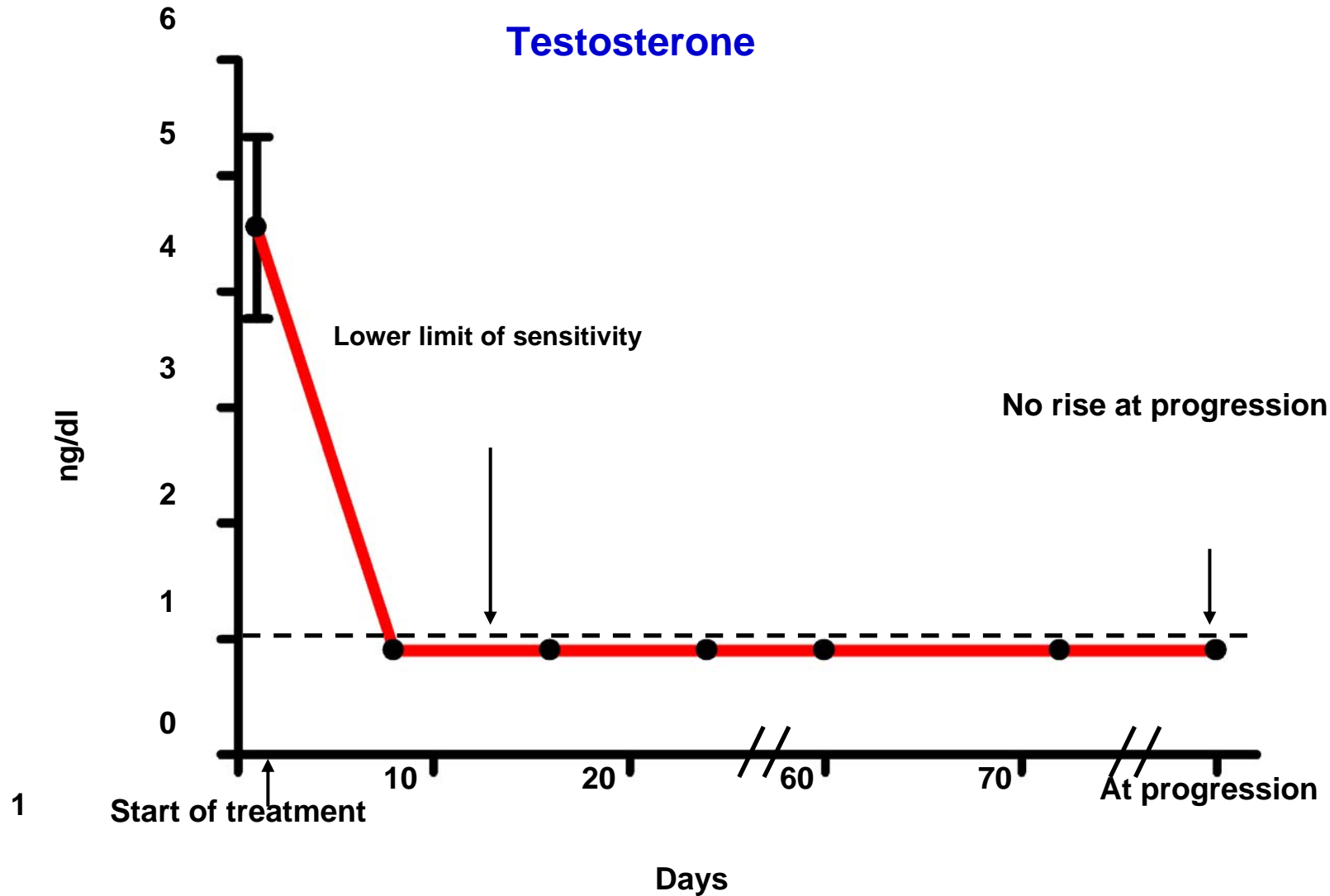
Conclusions

- MDV3100 is a safe, novel antiandrogen pill
- Has substantial antitumor activity both before and after chemotherapy has been used
 - Early studies show that most men have drops in PSA with treatment

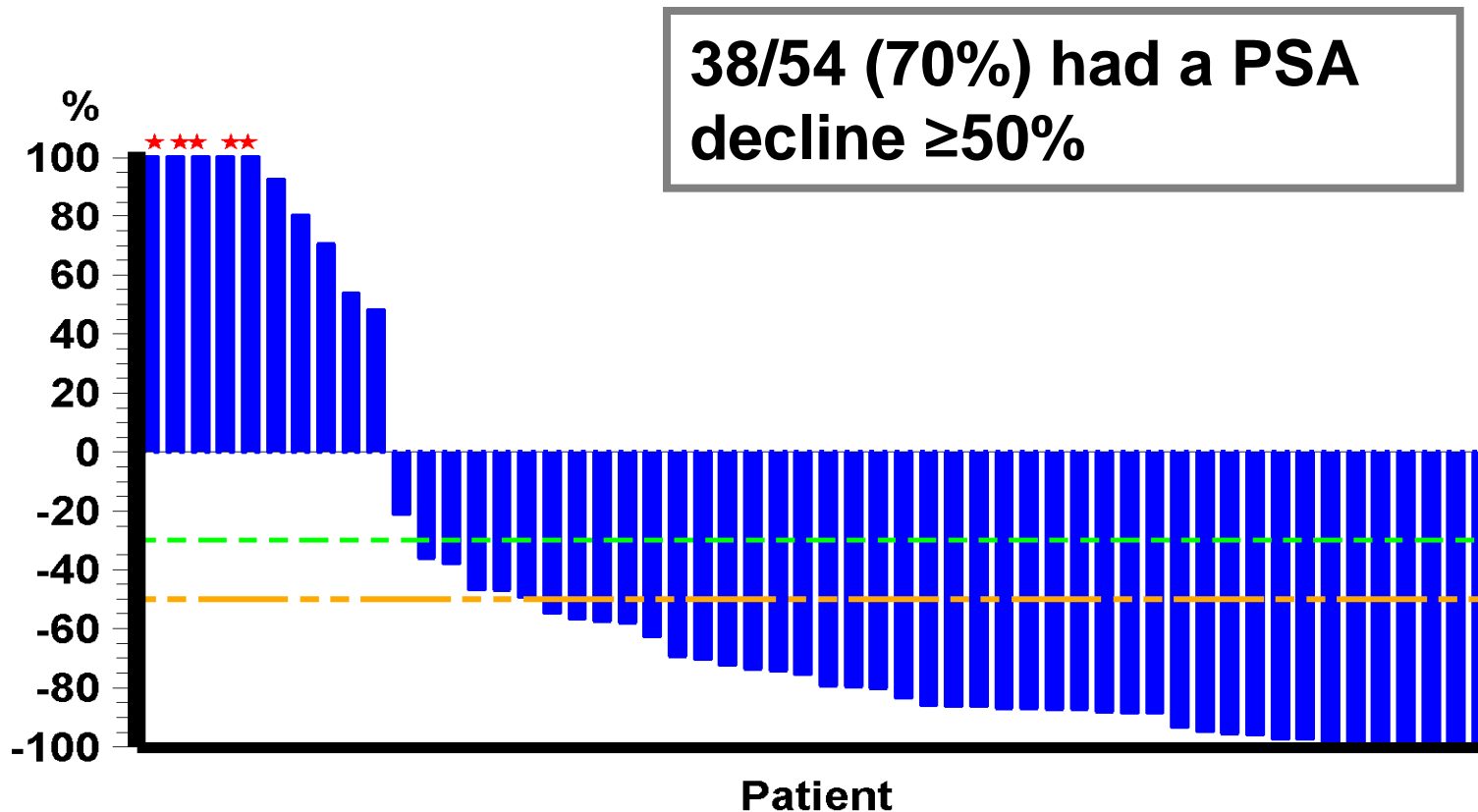
Abiraterone (“Abi”)

- Blocks testosterone production from the adrenal gland
- Phase I/II trials completed
- PSA responses in the majority of patients
- Responses seen even after ketoconazole and chemotherapy

Abiraterone suppresses testosterone

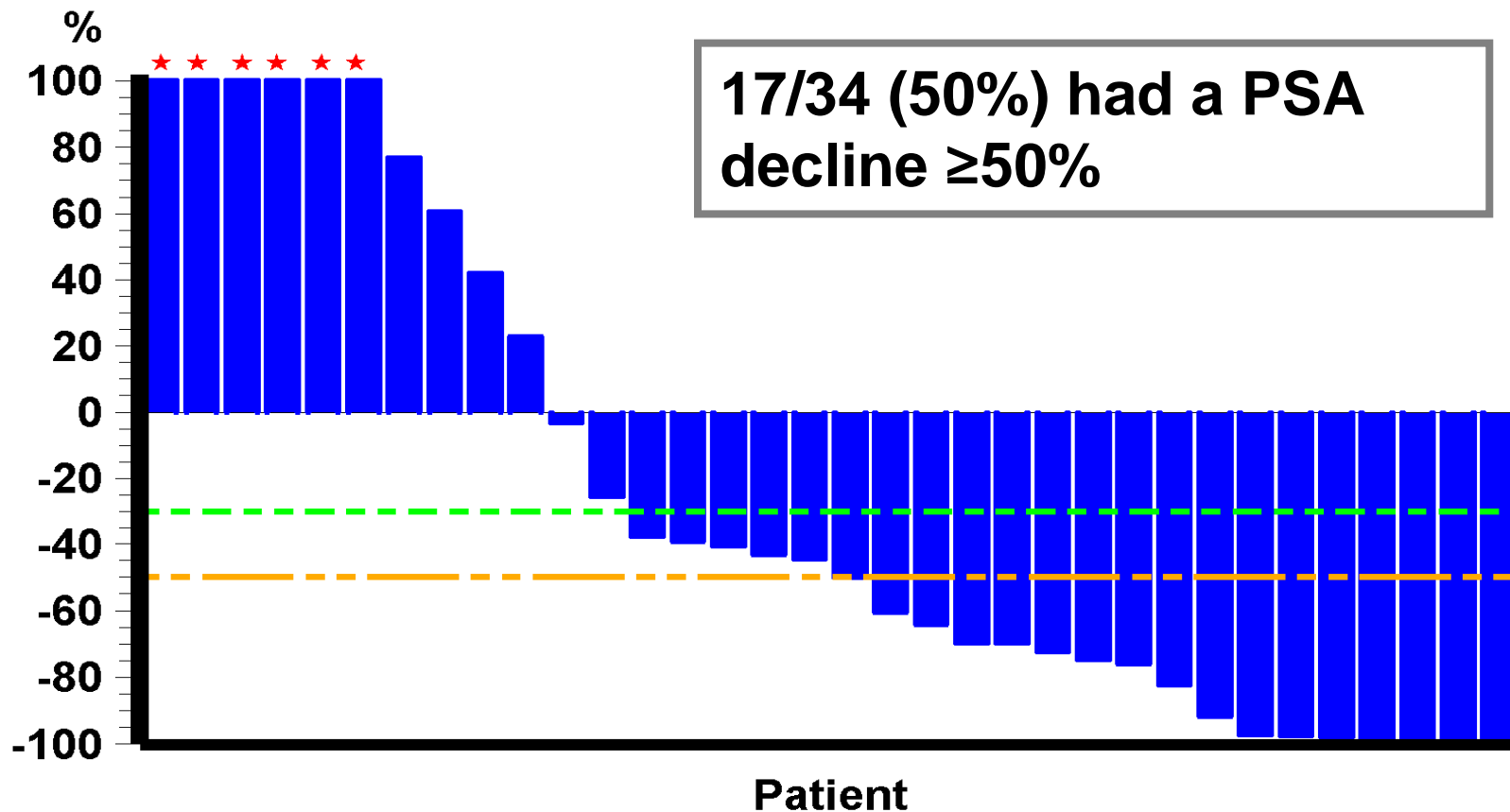


Pre-Chemotherapy (n=54): Maximal PSA Decreases



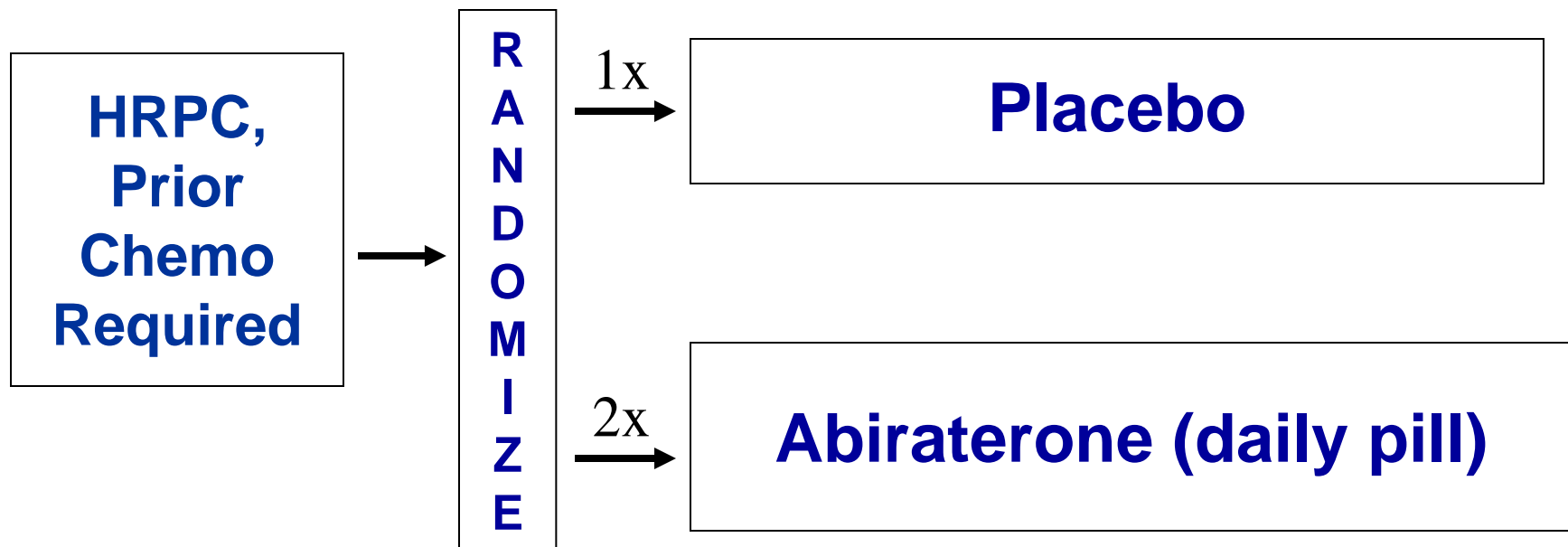
*---Patient PSA Value Clipped

Post-Chemotherapy (n=34) Maximal PSA Decreases



*---Patient PSA Value Clipped

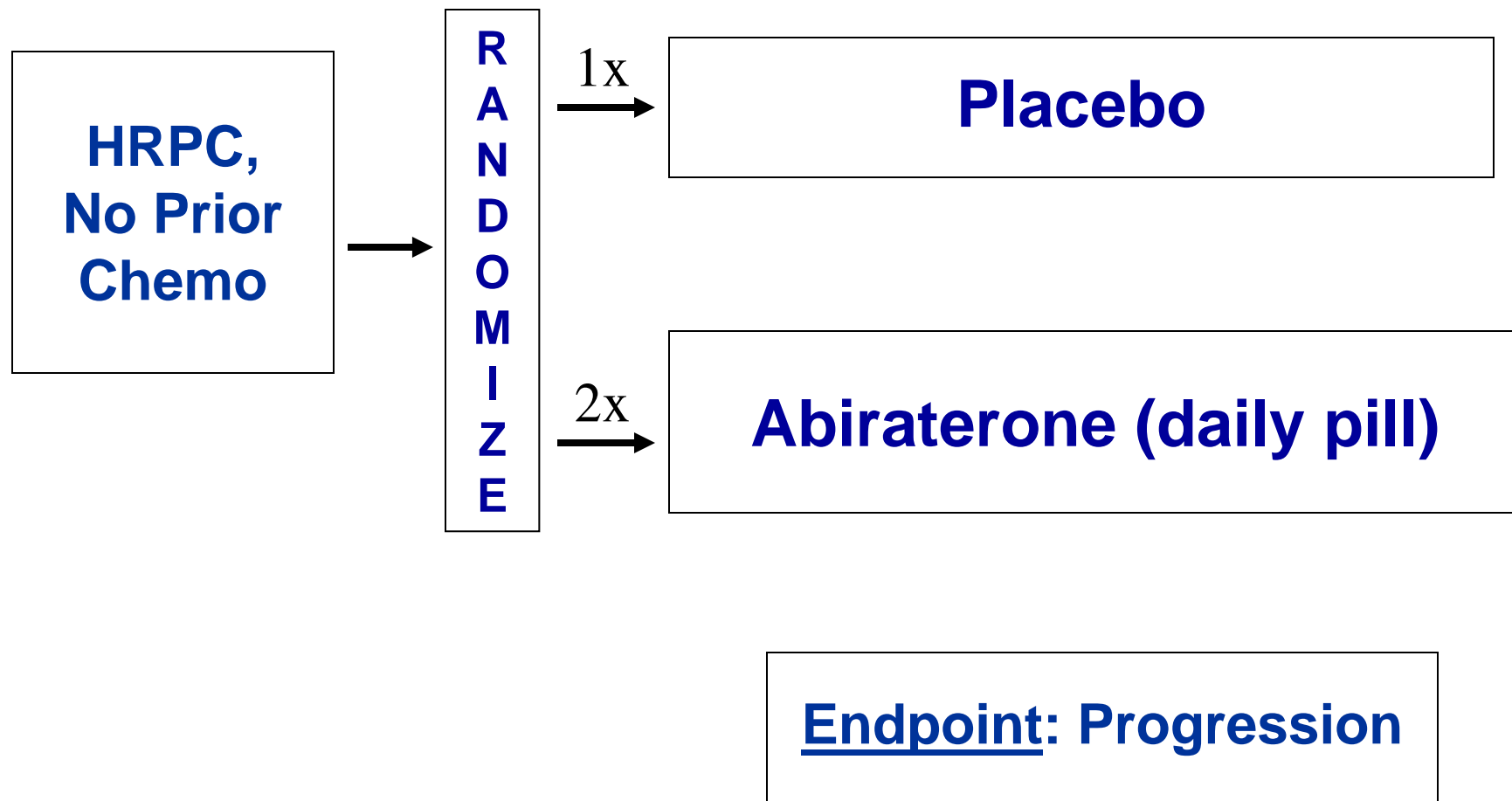
Phase III Study: Abiraterone vs Placebo (completed)



n = 1158

Endpoint: Survival

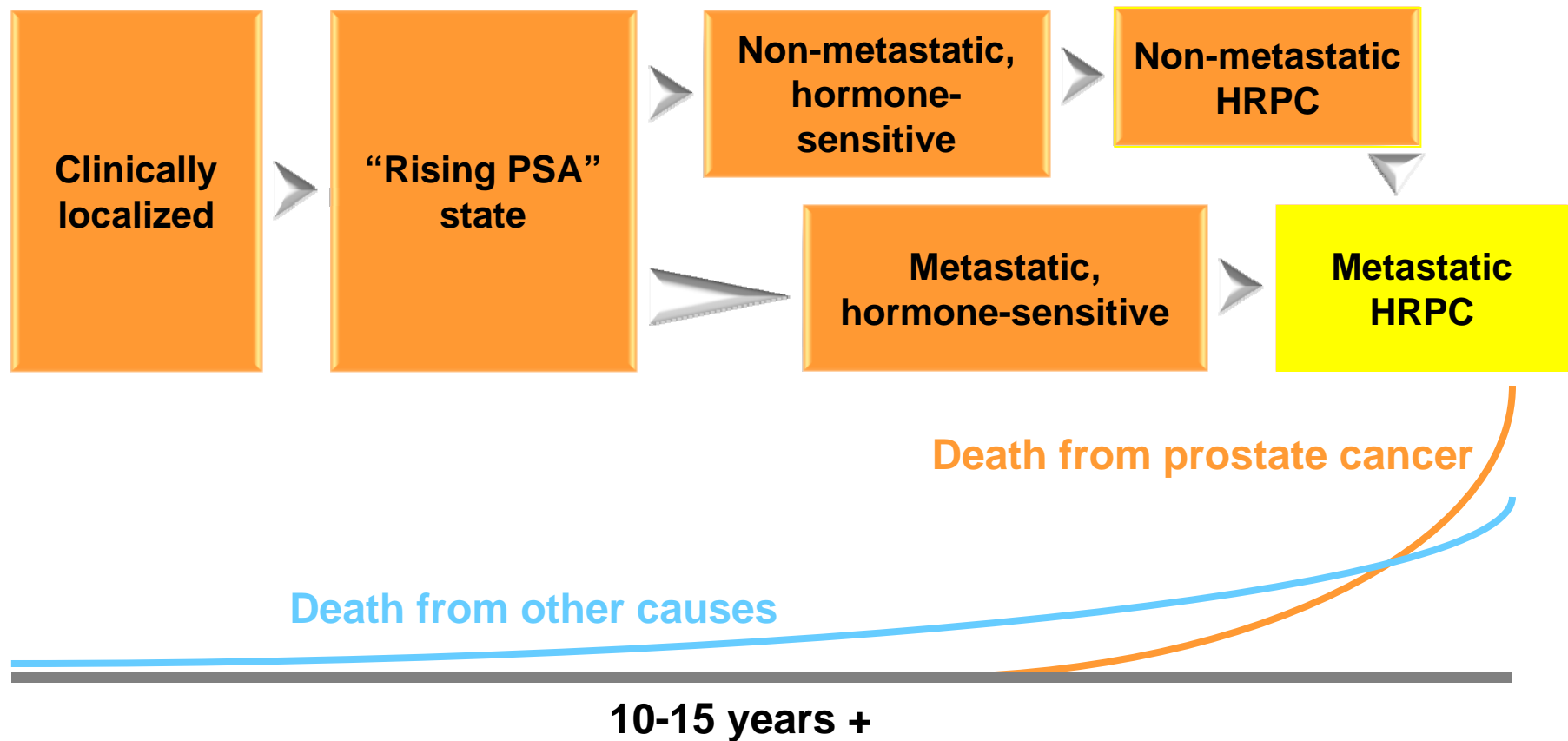
Phase III Study: Abiraterone vs Placebo Now Opening Pre-Chemo



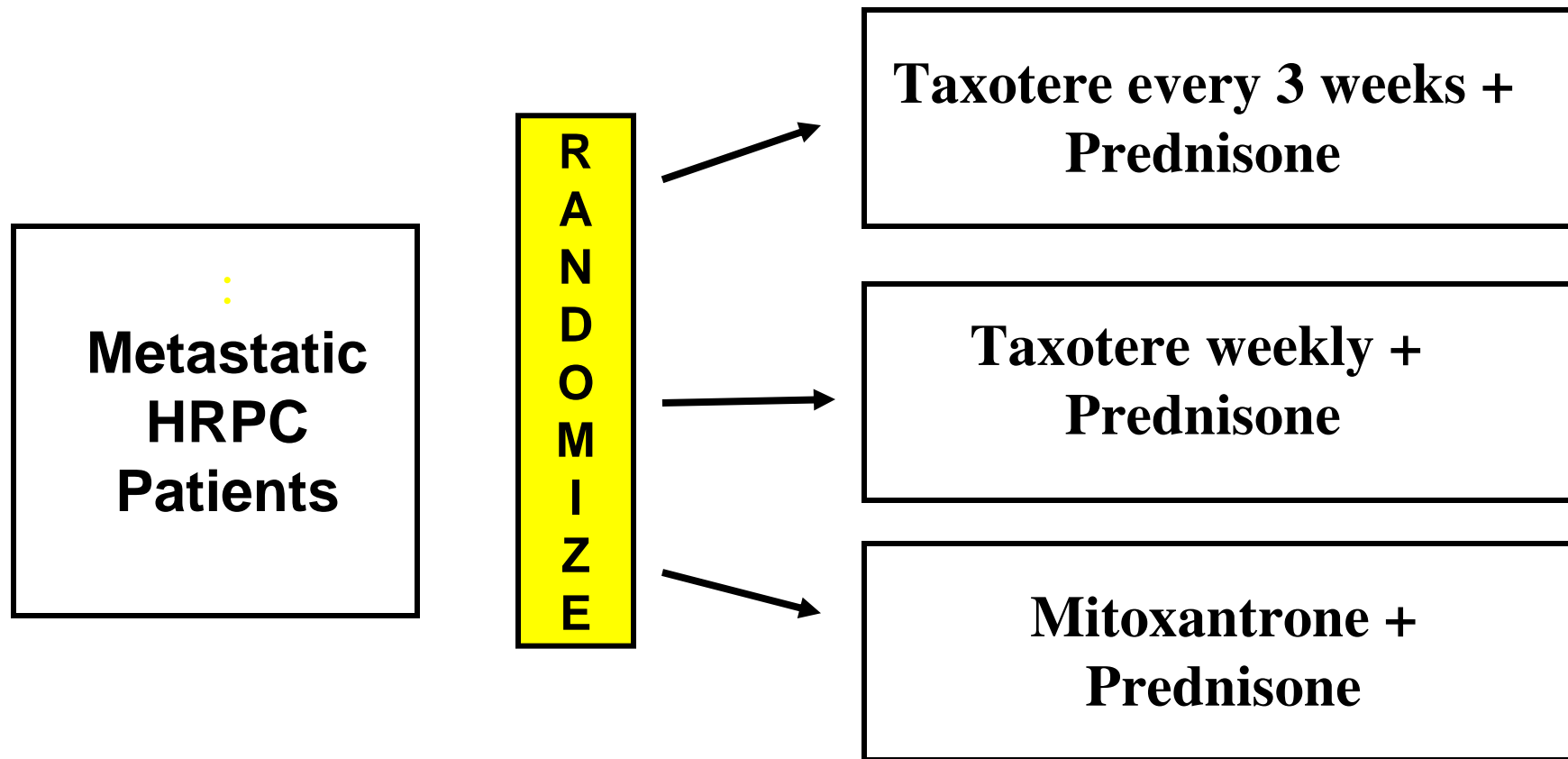
Secondary Hormone Therapy

- “Starve the cactus!”
- Even after first line hormones (Lupron, Zoladex, Eligard, etc), secondary hormone pills can help to control prostate cancer
- New drugs such as MDV3100 and abiraterone are very promising

Clinical States of Prostate Cancer



Taxotere Chemotherapy for HRPC

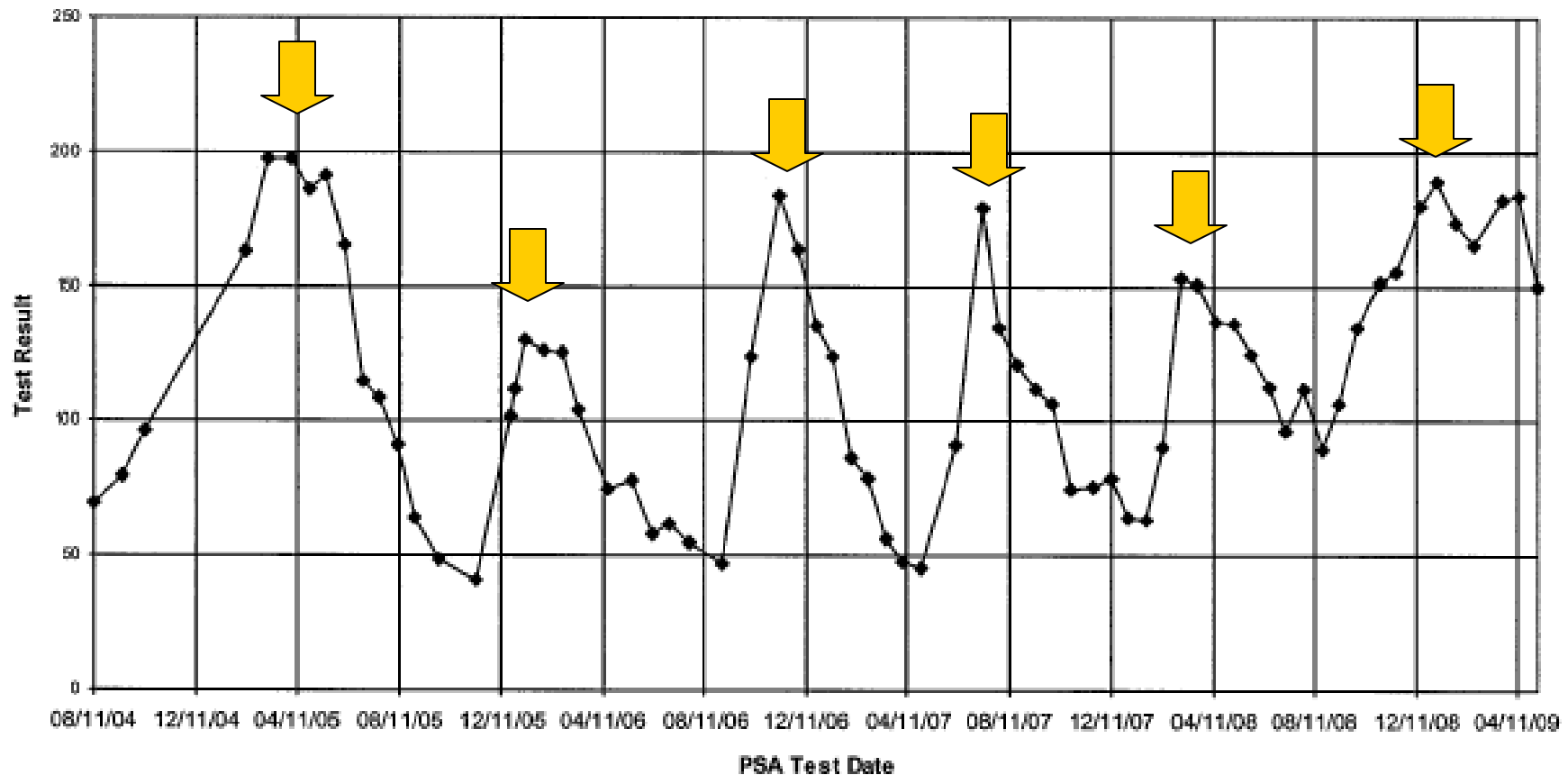


Treatment duration in all 3 arms = 30 weeks

Taxotere Prolongs Survival >20%

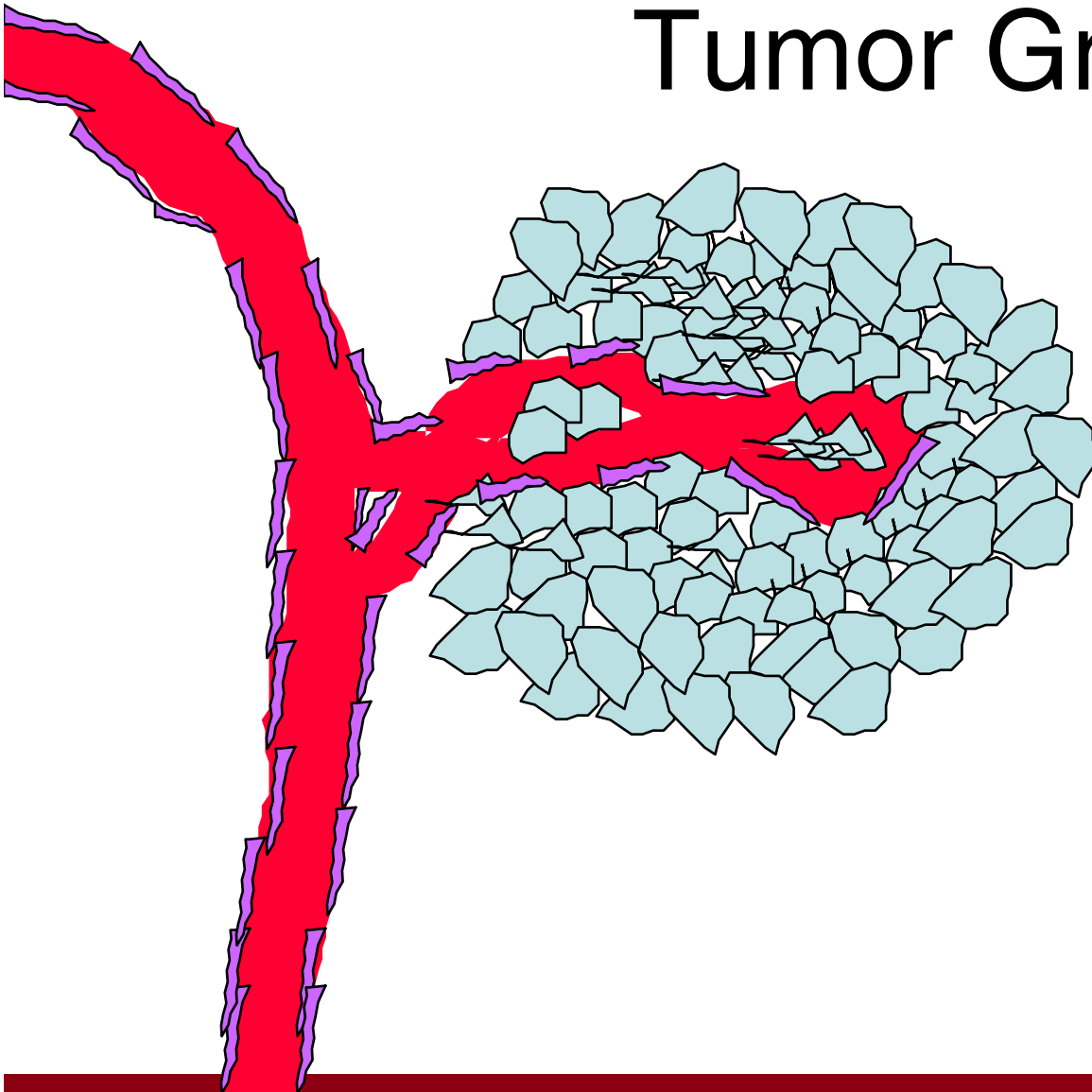
	Taxotere	Mitoxantrone	P-value
Survival	19.2 mo	16.3 mo	0.004
% PSA Response	45	32	0.0005
% Less Pain	35	22	0.01

A 75 year old Attorney Receiving Intermittent Taxotere Chemotherapy



5 years

Angiogenesis is Necessary for Tumor Growth

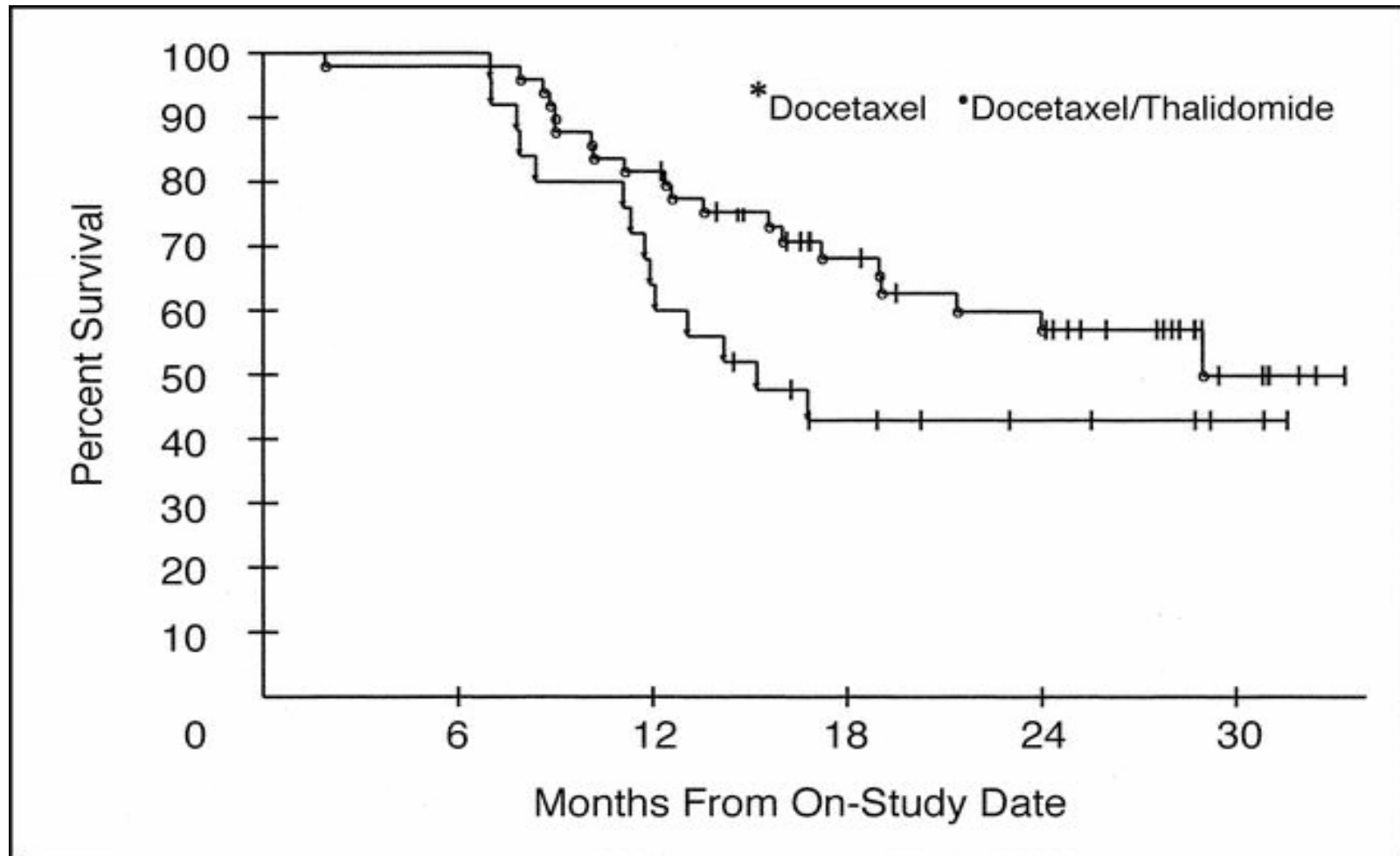


ANGIOGENESIS
INHIBITORS

Thalidomide

Avastin

Survival: Taxotere +/- Thalidomide

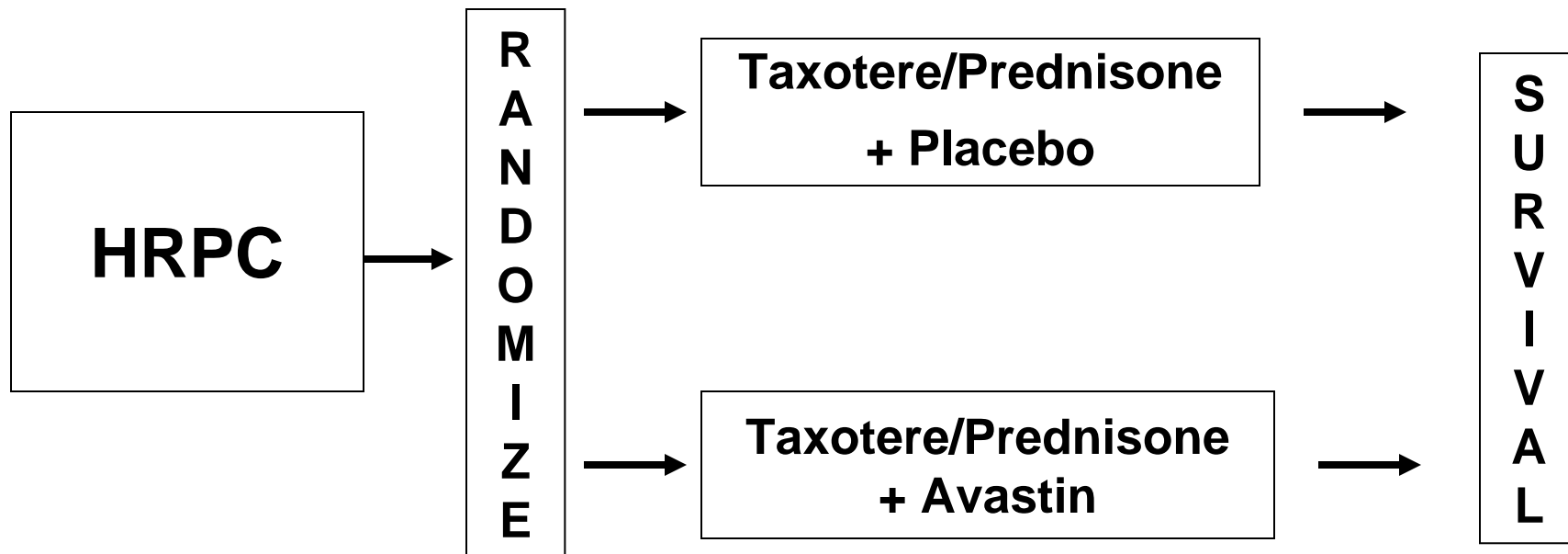


Dahut JCO 2004

Taxotere + Avastin in HRPC

- PSA response: 77%
- Measurable response: 44%
- Median time to progression: 10.3 mo

Completed Phase III Trial of Taxotere +/- Avastin in HRPC



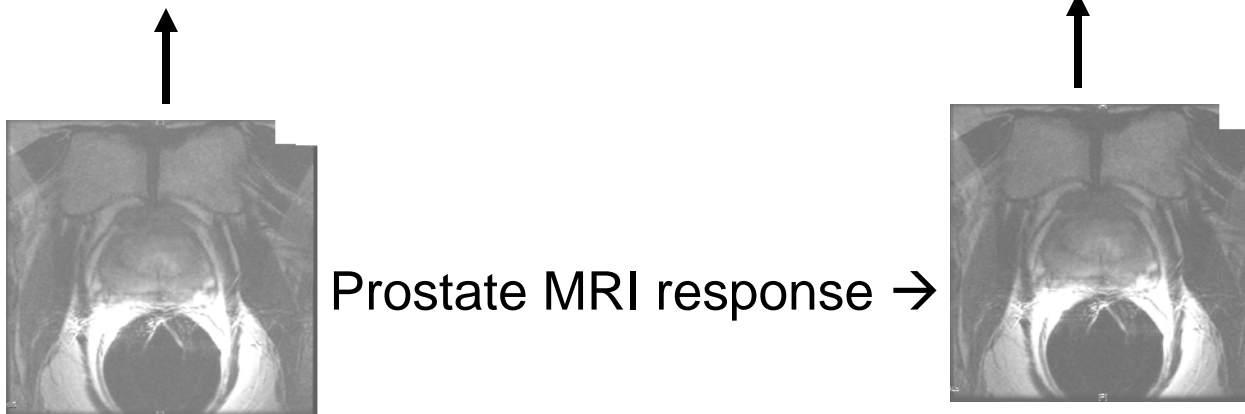
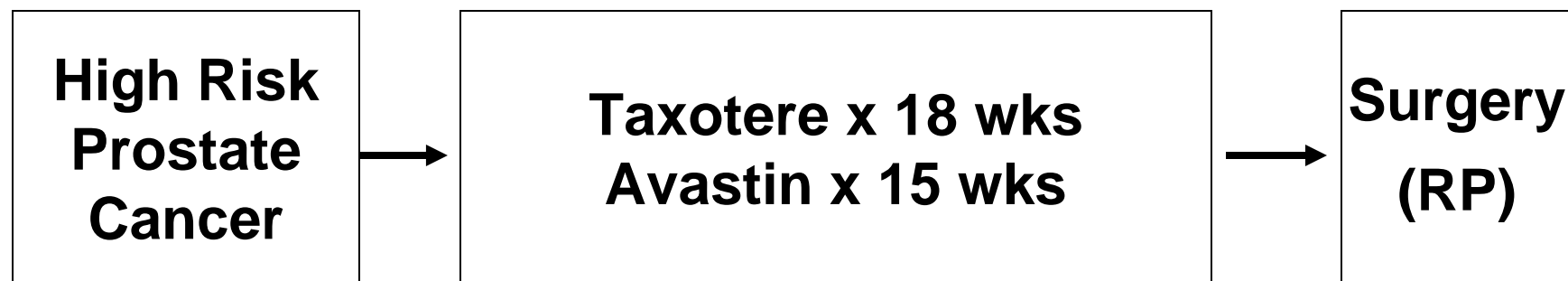
n = 1020

If Taxotere + Avastin is Better for HRPC, Then...

Ongoing trials discussed earlier:

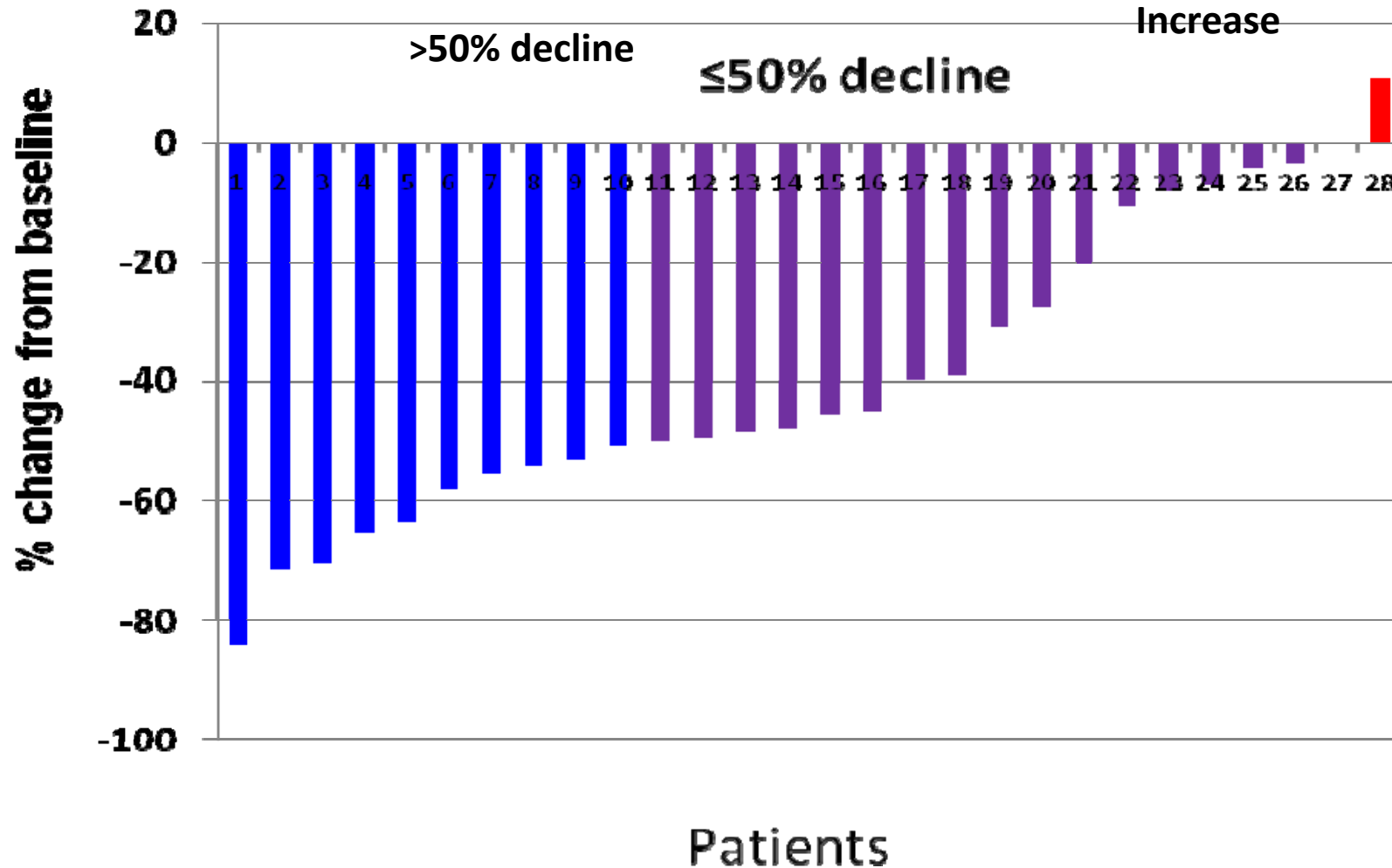
- Preoperative in high risk patients
- Rising PSA, with rapid PSADT

Preoperative Taxotere + Bevacizumab in High Risk Cancer



n = 42
PI: Oh

erMRI Response

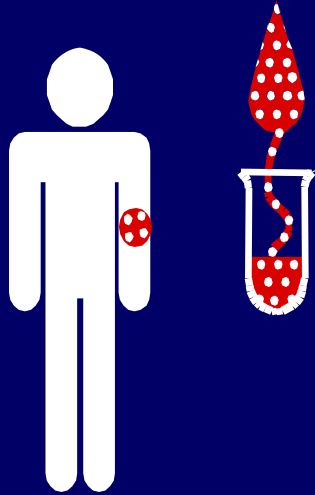


Therapeutic Options After Taxotere

- Traditional options
 - Chemotherapy (Novantrone, carboplatin)
 - Radiopharmaceutical (Quadramet, radium)
- Active areas of clinical investigation
 - Chemotherapy (Ixempra)
 - Vaccines (Provenge)
 - Targeted therapy (Sutent)

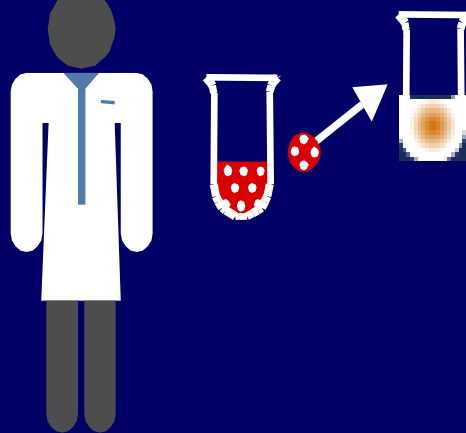
Sipuleucel-T: Patient-Specific Therapy

Day 1
Leukapheresis



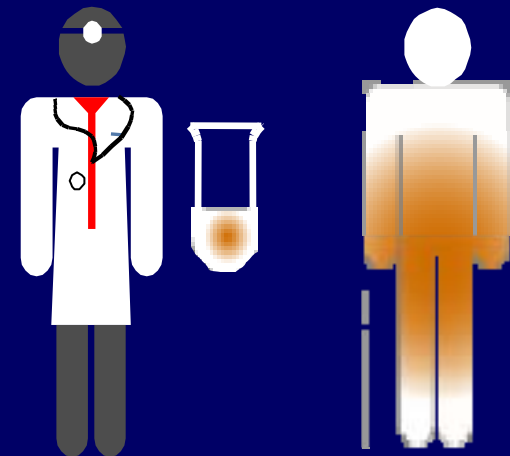
Apheresis Center

Day 2-3
sipuleucel-T is
manufactured



Dendreon

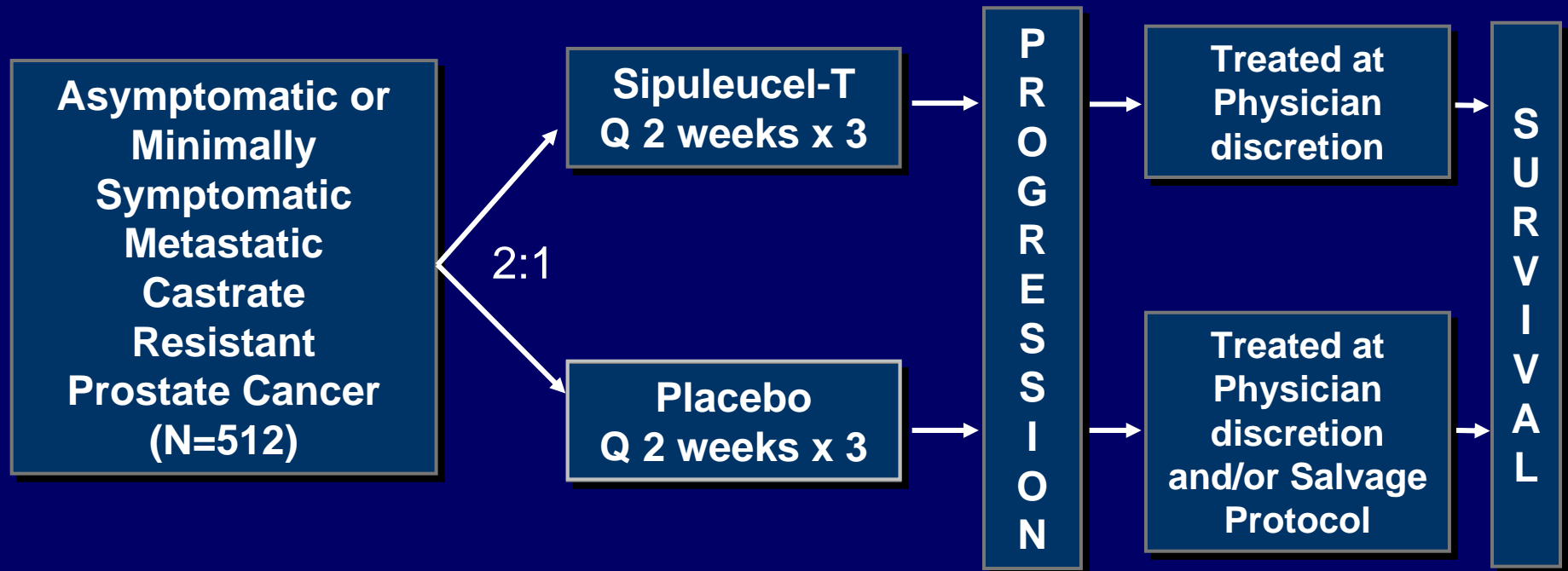
Day 3-4
Patient is infused



Doctor's Office

COMPLETE COURSE OF THERAPY:
Weeks 0, 2, 4

Randomized Phase 3 IMPACT Trial (IMMunotherapy Prostate AdenoCarcinoma Treatment)



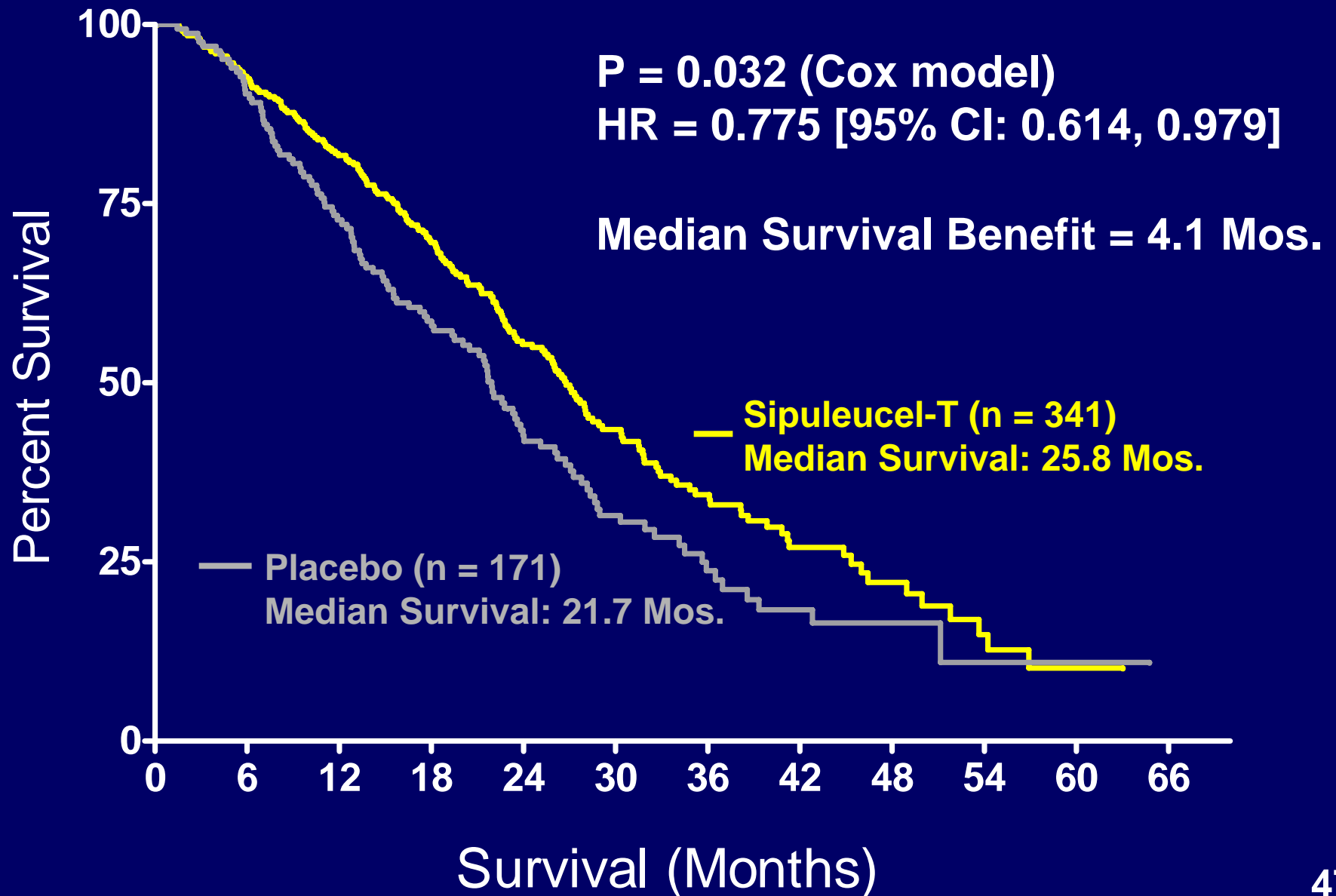
Primary endpoint:

Overall Survival

Secondary endpoint:

Time to Objective Disease Progression

IMPACT Overall Survival: Primary Endpoint Intent-to-Treat Population



Side Effects

- Most common
 - Chills (54%)
 - Fever (29%)
 - Headache (16%)
- Severe
 - No significant differences compared with placebo

So What's The Story With Provenge?

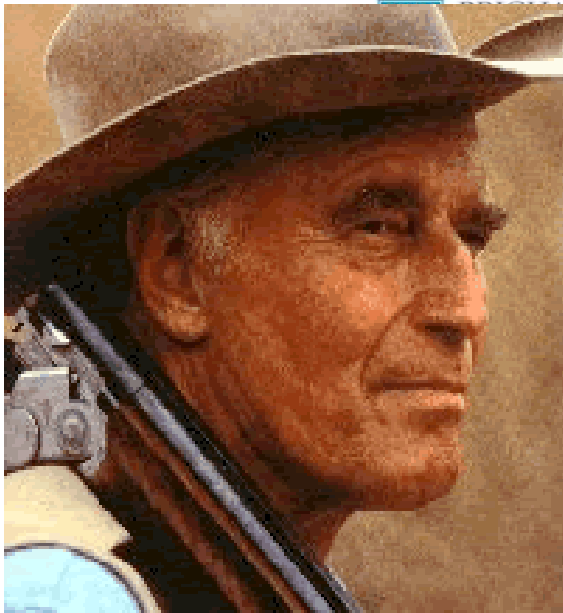
- Looks promising for FDA approval
- 2 studies which confirm improvements in survival
- Treatment is done in 1 month
 - You feel no different
- Not clear how it works
- Will be an important additional treatment for metastatic HRPC

Conclusions

- Many novel strategies to improve outcome with prostate cancer
 - Early use of chemotherapy in combination with surgery and radiation
 - New chemo combinations
 - Immunotherapy/vaccines
 - More effective hormones
 - New targeted therapies



M A
N'S H



EDICAL

