METASTATIC PROSTATE CANCER MANAGEMENT

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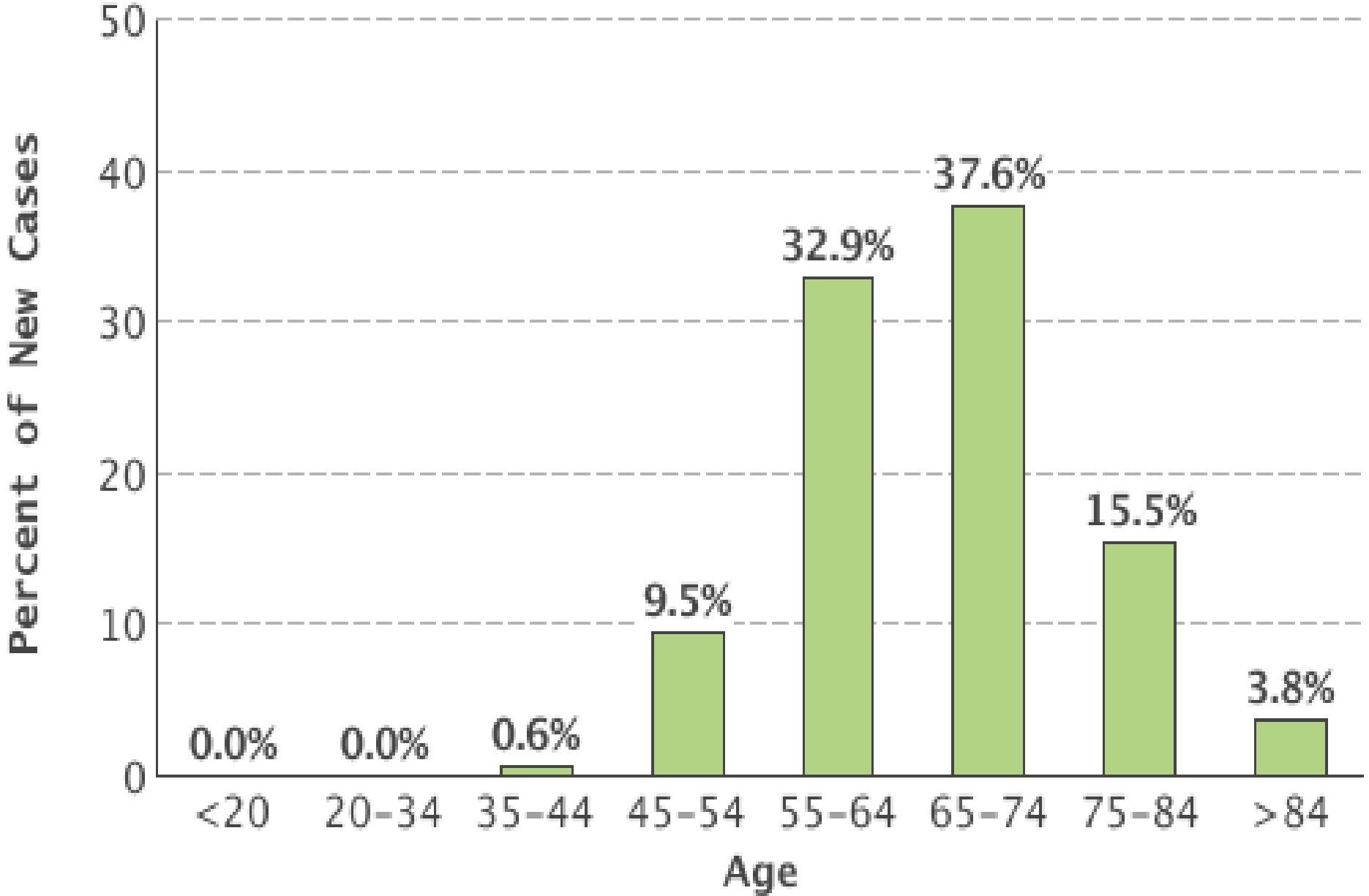
Prostate Cancer- Statistics

- Most common cancer in men after a skin cancer (**29%** of all male malignancies)
- **~161K** cases with ~ **27K** deaths in 2017 (NIH Data)
- **~ 11.6%** (one in nine) men will be diagnosed with prostate cancer (based on 2010-2014)
- **60 %** of the cases are diagnosed in men with age > **65.**
- Rare in age less than **40**

New Cases Prostate Cancer by Age



Prostate Cancer- Risk Factor

- Risk Factors
  - Increasing Age (the most important factor)
    - The average age of diagnosis is **66**
  - Race (**blacks> whites > Asians**)
    - African American are **70%** more likely to develop prostate cancer compare to white males.
  - Family history (2-fold increase risk if 1st degree)
  - Diet: Higher fat and low Selenium/Vegetable
  - Supplemental Testosterone use
  - Genetic: **BRCA1 and BRAC2** Mutation
- No known modifiable risk factors

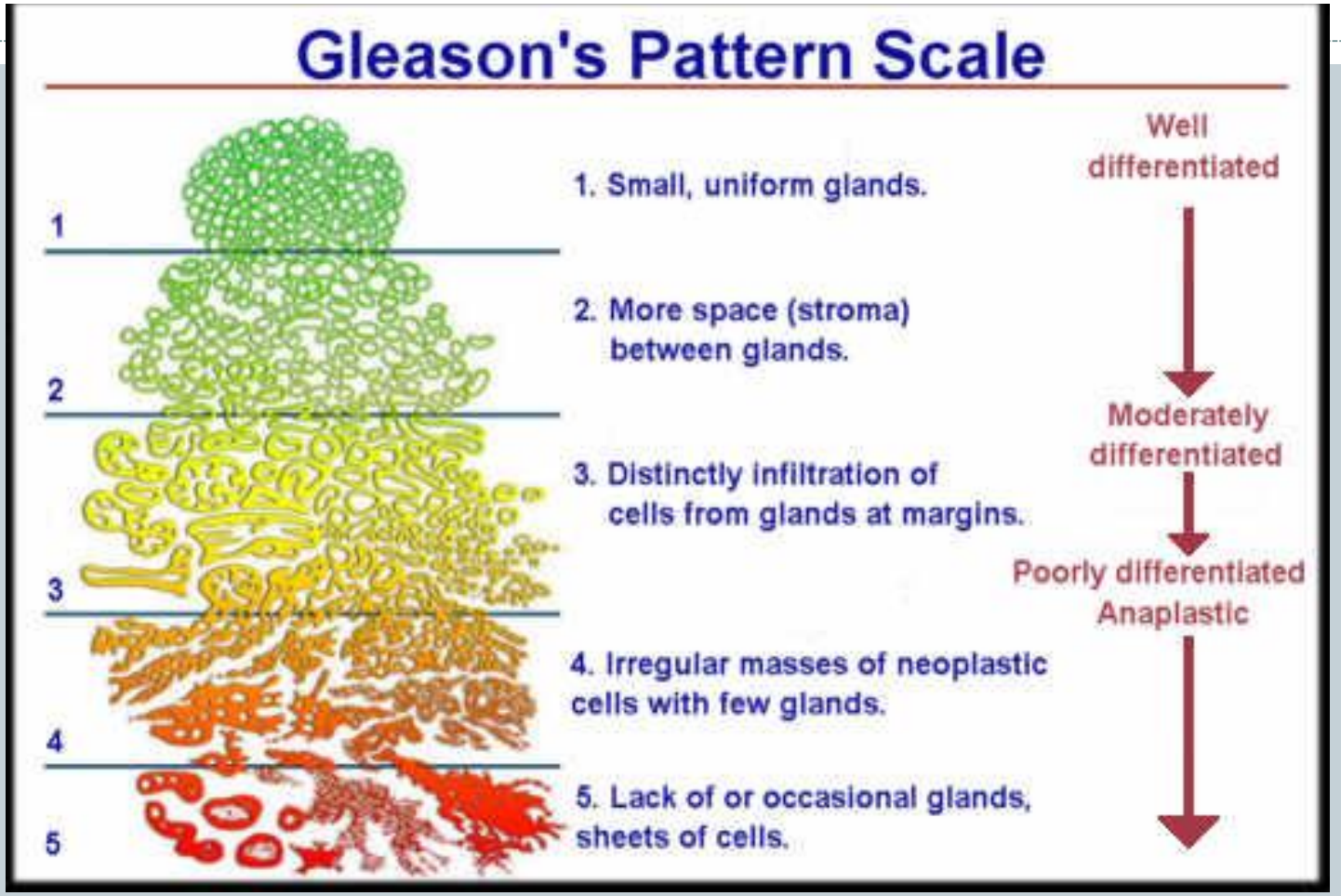
Prostate Cancer – Diagnosis

- Mostly done with PSA rising
- Hyperplasia Symptoms
- Metastatic Disease (Bone Pain)
- DRE (Nodularity, Asymmetry)
- Trans-rectal biopsy
- If biopsy is positive, only additional studies (CT, bone scan, etc.) if symptoms suggest

Prostate Cancer – Staging

- Risk of death dependent on **Stage**
- Based on **TNM** staging
  - T- stand to the extent of the main tumor
    - T1 (no Clinical Appearance)
    - T2 (Prostate only)
    - T3 (Through Prostate Capsule but not fixed)
    - T4 (invade adjacent tissue and fixed)
  - N - Stand for the spread of cancer to nearby/Regional lymph nodes (N1-3)
  - M- Stand for distant organ spread

Gleason Score
1960s, Revised 2005



Two tissue samples scored (1-5). Added, max score = 10

Gleason 7 or higher – consideration for genetic testing

Prostate Cancer – Staging

- Risk, T, Gleason Score and PSA at diagnosis, life expectancy
- Stage I-III break down (stage I: Low; Stage II intermediate; Stage III high risk)

Risk	T	Gleason	PSA
Low	1-2a	2-6	<10
Intermed	2b-2c	7	10-20
High	3a	8-10	>20

Stage IV: Metastatic Disease

Prostate Cancer – Treatment Overview

- Depends on stage and risk factor for the local disease
- For local disease (stage I-III)
  - Surgery
  - Radiation Therapy
  - Watchful Waiting
  - Androgen Deprivation Therapy
- For Distant Metastatic disease (stage IV disease)
  - Androgen Deprivation Therapy
    - Older agents vs. newer agents
  - Chemotherapy

Management of Metastatic Prostate Cancer

Trend In Metastatic Prostate Cancer

- Weiner Ab et al; looked at the incidence of Metastatic prostate cancer from **2004 to 2013** (**)
- The data collected in **1089** health care facility here in U.S
- The incidence of metastatic prostate cancer increased from **2007-2013**
  - In all patient population it Increase in **72%** In **2013** compare to **2004**
  - In People age **55-69** increased **92%**
- While the incidence of low risk prostate cancer has decreased by **37%** during this time

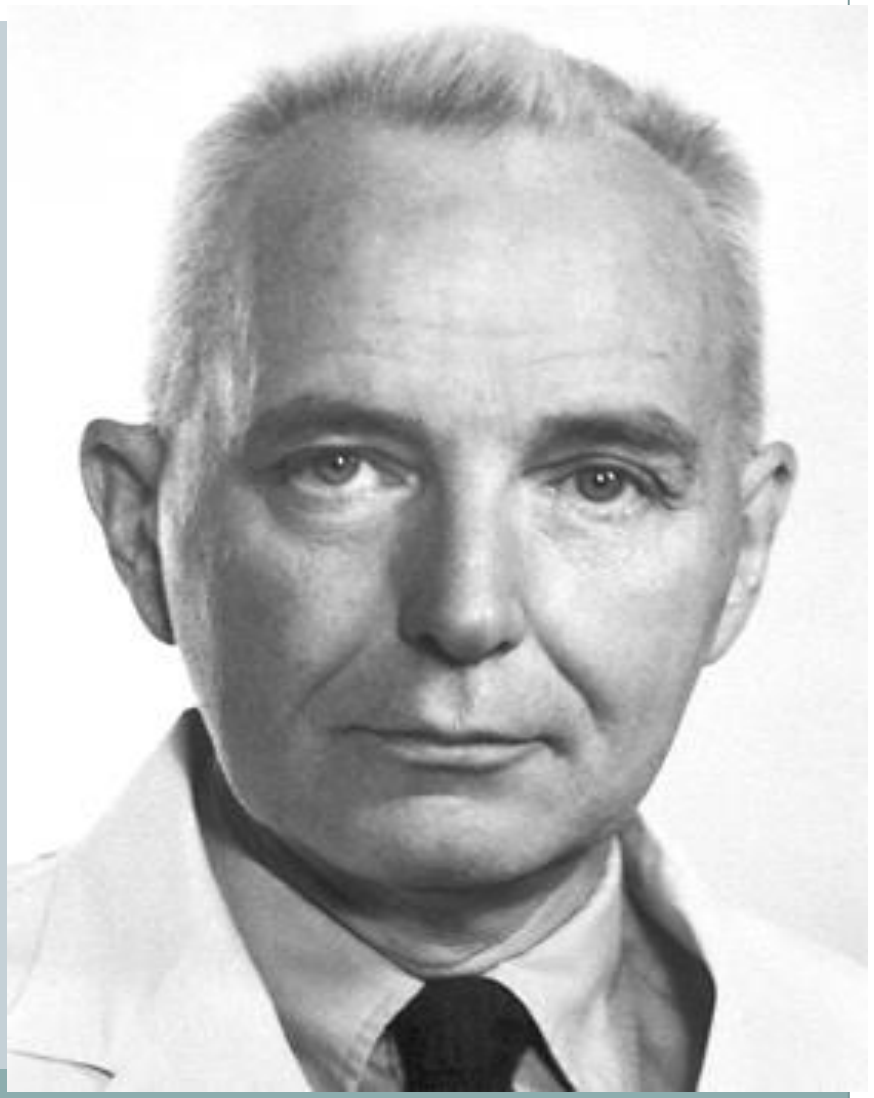
- (**)Prostate Cancer and prostatic disease volume 19 Issue: Page 393=397

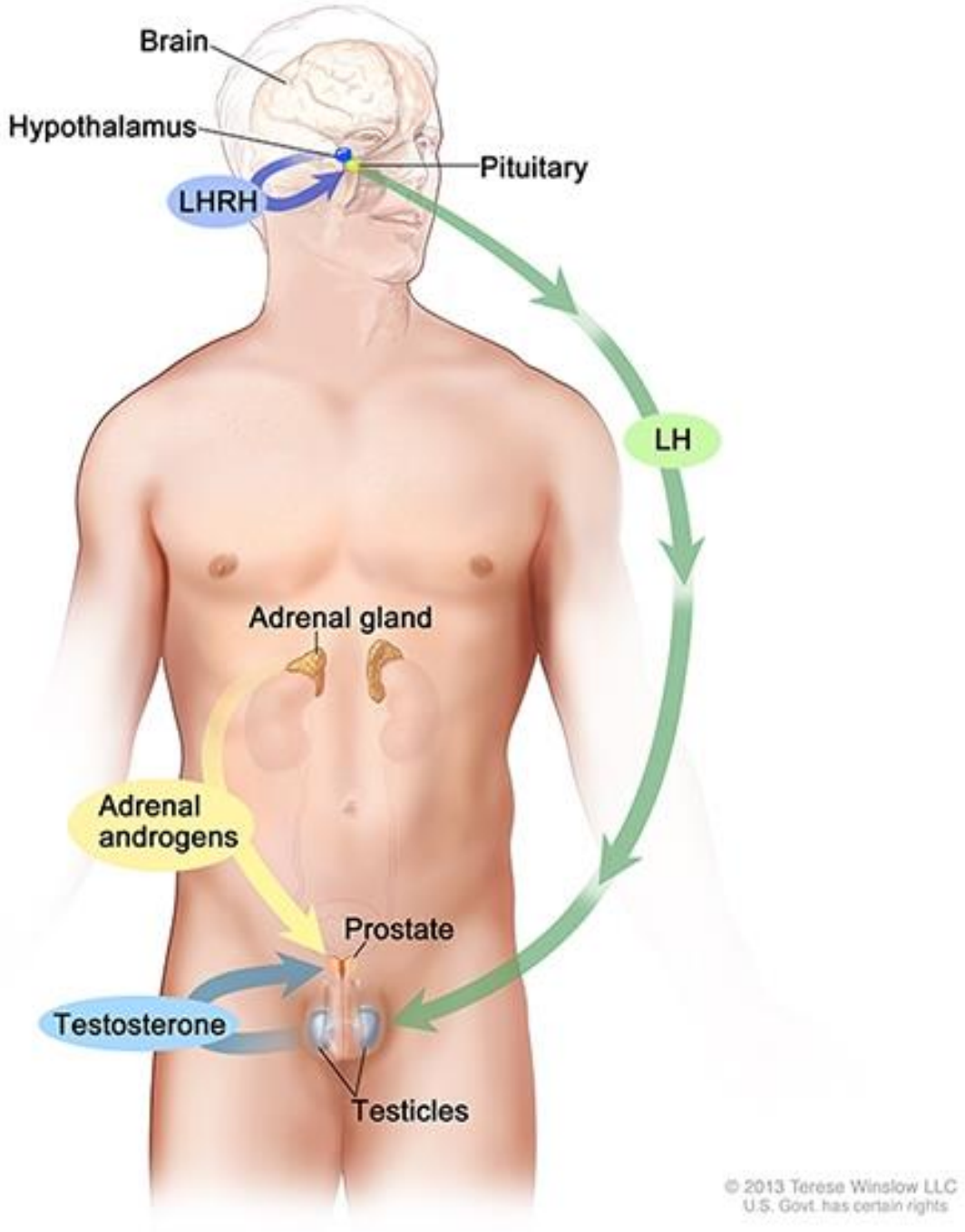
Historical Treatment of Prostate Cancer

Androgen deprivation therapy (ADT) is a back bone of the metastatic cancer treatment since the 1940s

- Orchiectomy showed regression of prostate cancer

  Charles Huggins and Clarence V. Hodges (castration and estrogen)





Androgen Deprivation Therapy (ADT)

- Traditional Anti-Androgen Agents
  - GnRH Agonist: Disrupt pituitary-testes axis = decrease T level
    - Lupron (SC injection)
  - Androgen Receptor Blocker: Block androgen receptor on cancer cells (Oral Agents)
    - Bicalutamide (Casodex), Flutamide and Nilutamide
- Second Generation Anti Androgen treatment
  - Androgen Synthesis Blocker:
    - Zytiga (Abiraterone)
      - It is given with steroid
  - Androgen Receptor Antagonist:
    - Xtandi (Enzalutamide)
      - No steroid is needed

Historic Survival Rate for Metastatic Disease

- The Survival data of prostate cancer with ADT alone
  - The Median overall survival for metastatic prostate cancer treated with **ADT is 30-33 mo**. (Tagen et. al J Urol 2012;188:1164-1169)
  - No significant improvement of overall survival in metastatic prostate cancer from **1988-2009** (Cancer 2014;120:818-823)
    - Patient presented with metastatic prostate cancer in California over 20 years, this incudes close 20,000 patients

Can We Do Better?

- The two studies looked this
  - They both looked the role of **Chemotherapy** upfront in addition to the **ADT**
- CHAARETED Clinical Trial
  - U.S Clinical Trial
  - Completed **2015**
- STAMPEDE Clinical Trial
  - U.K Clinical Trial
  - Multi-Phase Clinical Trial

CHAARTED Clinical Trial

- Compared ADT vs. ADT + Docetaxel (Add 6 cycle)
- Including Criteria
  - Metastatic hormone sensitive disease
  - No prior treatment
  - Exclude local disease with high risk features
- Primary goal
  - Overall Survival.
- Secondary goal
  - Rate PSA Increase
  - Time to Castration Resistance
  - Time to clinical Progression

Table 1. Baseline Characteristics of the Patients.*

Characteristic	ADT plus Docetaxel (N=397)	ADT Alone (N=393)
Age — yr		
Median	64	63
Range	36–88	39–91
Race — no. (%)†		
White	344 (86.6)	330 (84.0)
Black	39 (9.8)	37 (9.4)
Other	4 (1.0)	6 (1.5)
Unknown	10 (2.5)	20 (5.1)
ECOG performance status — no. (%)‡		
0	277 (69.8)	272 (69.2)
1	114 (28.7)	115 (29.3)
2	6 (1.5)	6 (1.5)
Volume of metastases — no. (%)§		
Low	134 (33.8)	143 (36.4)
High	263 (66.2)	250 (63.6)
Visceral metastases — no. (%)	57 (14.4)	66 (16.8)
Gleason score — no. (%)¶		
4–6	21 (5.3)	21 (5.3)
7	96 (24.2)	83 (21.1)
8–10	241 (60.7)	243 (61.8)
Unknown	39 (9.8)	46 (11.7)
PSA level at start of ADT — ng/ml		
Median	50.9	52.1
Range	0.2–8540.1	0.1–8056.0
Prior treatment for prostate cancer — no. (%)		
No local therapy	289 (72.8)	286 (72.8)
Primary radiation	27 (6.8)	33 (8.4)
Prostatectomy	81 (20.4)	73 (18.6)
Missing data	0	1 (0.3)
Adjuvant ADT — no. (%)	18 (4.5)	16 (4.1)
Time from start of ADT to randomization — mo‖		
Median	1.2	1.3
Range	0.03–3.9	0.03–3.9
No ADT before randomization — no. (%)	51 (12.8)	52 (13.2)

* There were no significant differences in characteristics between the two groups when analyzed with the use of the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables, with the categories for "unknown" or "missing data" excluded. ADT denotes androgen-deprivation therapy, and PSA prostate-specific antigen.

† Race was self-reported.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. One patient assigned to ADT alone did not have an on-study form submitted, so the ECOG performance-status score was unknown, but the stratification by the site placed the patient into the stratum of a performance-status score of 2 at randomization.

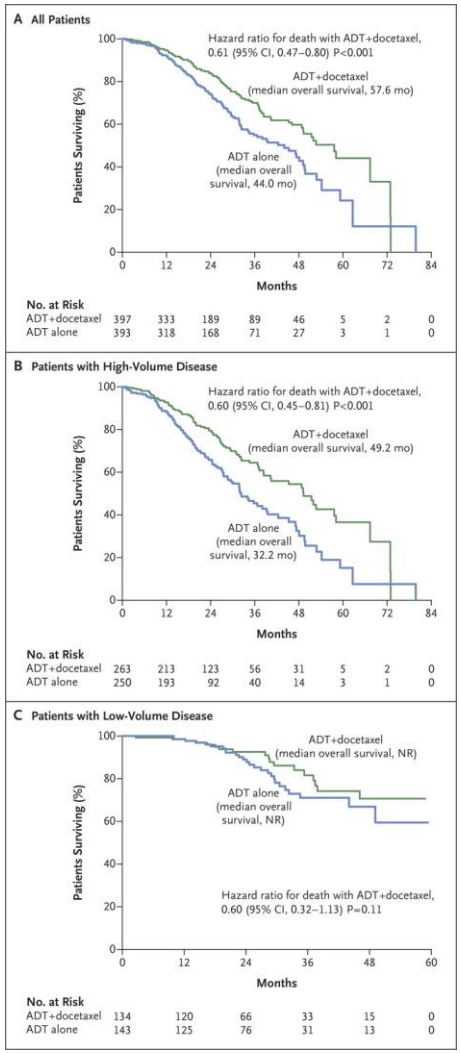
§ A high volume of metastases was defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis. One patient assigned to ADT alone did not have an on-study form submitted, so the volume of metastases was unknown, but the stratification by the site placed the patient into the high-volume stratum at randomization.

¶ Gleason scores range from 2 to 10, with higher scores indicating a more aggressive form of prostate cancer and a worse prognosis.

‖ Time from start of ADT to randomization is among patients who started ADT before randomization.

Result of CHAARTED Study

- Median Overall Survival
  - ADT + Docetaxel **57 mo**.
  - ADT only **44 mo**.
- For Patient with high volume disease
  - ADT + Docetaxel **49.2 mo**.
  - ADT only **32.3 mo.**
- Patient with low volume disease
  - Median survival not reached


A All Patients
Hazard ratio for death with ADT+docetaxel, 0.61 (95% CI, 0.47–0.80) P<0.001
ADT+docetaxel (median overall survival, 57.6 mo)
ADT alone (median overall survival, 44.0 mo)
Patients Surviving (%)
100
80
60
40
20
0
0 12 24 36 48 60 72 84
Months
No. at Risk
ADT+docetaxel 397 333 189 89 46 5 2 0
ADT alone 393 318 168 71 27 3 1 0
B Patients with High-Volume Disease
Hazard ratio for death with ADT+docetaxel, 0.60 (95% CI, 0.45–0.81) P<0.001
ADT+docetaxel (median overall survival, 49.2 mo)
ADT alone (median overall survival, 32.2 mo)
Patients Surviving (%)
100
80
60
40
20
0
0 12 24 36 48 60 72 84
Months
No. at Risk
ADT+docetaxel 263 213 123 56 31 5 2 0
ADT alone 250 193 92 40 14 3 1 0
C Patients with Low-Volume Disease
ADT+docetaxel (median overall survival, NR)
ADT alone (median overall survival, NR)
Hazard ratio for death with ADT+docetaxel, 0.60 (95% CI, 0.32–1.13) P=0.11
Patients Surviving (%)
100
80
60
40
20
0
0 12 24 36 48 60
Months
No. at Risk
ADT+docetaxel 134 120 66 33 15 0
ADT alone 143 125 76 31 13 0

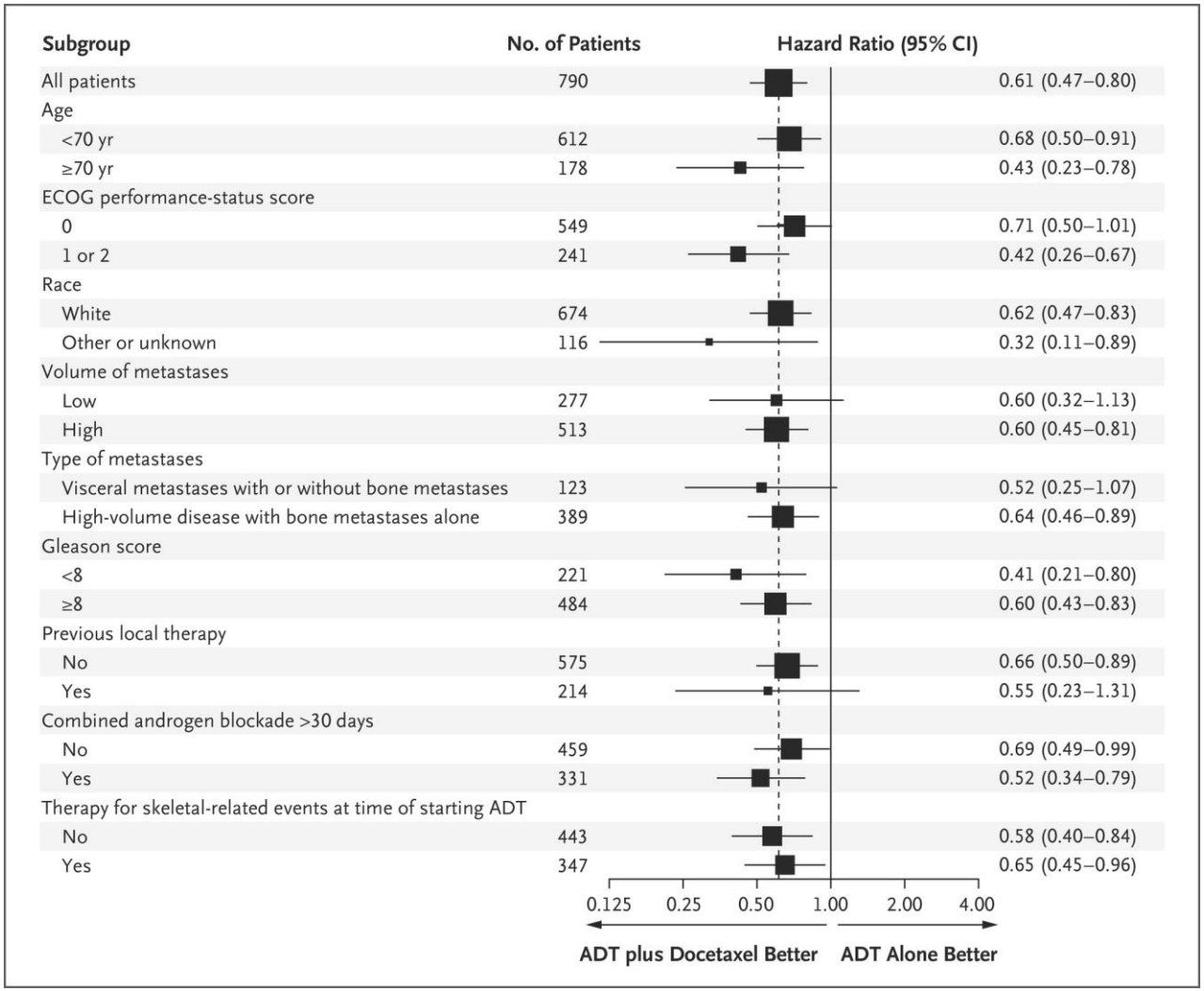

Subgroup
No. of Patients
Hazard Ratio (95% CI)
All patients 790 0.61 (0.47–0.80)
Age
<70 yr 612 0.68 (0.50–0.91)
≥70 yr 178 0.43 (0.23–0.78)
ECOG performance-status score
0 549 0.71 (0.50–1.01)
1 or 2 241 0.42 (0.26–0.67)
Race
White 674 0.62 (0.47–0.83)
Other or unknown 116 0.32 (0.11–0.89)
Volume of metastases
Low 277 0.60 (0.32–1.13)
High 513 0.60 (0.45–0.81)
Type of metastases
Visceral metastases with or without bone metastases 123 0.52 (0.25–1.07)
High-volume disease with bone metastases alone 389 0.64 (0.46–0.89)
Gleason score
<8 221 0.41 (0.21–0.80)
≥8 484 0.60 (0.43–0.83)
Previous local therapy
No 575 0.66 (0.50–0.89)
Yes 214 0.55 (0.23–1.31)
Combined androgen blockade >30 days
No 459 0.69 (0.49–0.99)
Yes 331 0.52 (0.34–0.79)
Therapy for skeletal-related events at time of starting ADT
No 443 0.58 (0.40–0.84)
Yes 347 0.65 (0.45–0.96)
0.125
0.25
0.50
1.00
2.00
4.00
ADT plus Docetaxel Better
ADT Alone Better

Table 2. Secondary End Points.

End Point	ADT plus Docetaxel (N=397)	ADT Alone (N=393)	P Value	Hazard Ratio (95% CI)
PSA level <0.2 ng/ml at 6 mo — no. (%)	127 (32.0)	77 (19.6)	<0.001	
PSA level <0.2 ng/ml at 12 mo — no. (%)	110 (27.7)	66 (16.8)	<0.001	
Time to castration-resistant prostate cancer — mo*				
Median	20.2	11.7	<0.001	0.61 (0.51–0.72)
95% CI	17.2–23.6	10.8–14.7		
Time to clinical progression — mo†				
Median	33.0	19.8	<0.001	0.61 (0.50–0.75)
95% CI	27.3–41.2	17.9–22.8		

* The time to castration-resistant prostate cancer was the time until documented clinical or serologic progression with a testosterone level of less than 50 ng per deciliter (or source documentation of medical castration or surgical castration).

† Clinical progression was defined by increasing symptoms of bone metastases; progression according to the Response Evaluation Criteria in Solid Tumors, version 1.0; or clinical deterioration due to cancer according to the investigator's opinion.

Table 3. Adverse Events of Grade 3 or Higher among the 390 Patients Who Received the Docetaxel-Containing Regimen and Had Follow-up Data Available.*

Event	Grade 3	Grade 4	Grade 5
	no. of patients (%)		
Allergic reaction	7 (1.8)	1 (0.3)	0
Fatigue	16 (4.1)	0	0
Diarrhea	4 (1.0)	0	0
Stomatitis	2 (0.5)	0	0
Neuropathy, motor	2 (0.5)	0	0
Neuropathy, sensory	2 (0.5)	0	0
Thromboembolism	1 (0.3)	2 (0.5)	0
Sudden death	0	0	1 (0.3)
Anemia	4 (1.0)	1 (0.3)	0
Thrombocytopenia	0	1 (0.3)	0
Neutropenia	12 (3.1)	35 (9.0)	0
Febrile neutropenia	15 (3.8)	9 (2.3)	0
Infection with neutropenia	5 (1.3)	4 (1.0)	0
Any event	65 (16.7)	49 (12.6)	1 (0.3)

* Patients were classified according to the worst grade reported across all body systems. Patients assigned to ADT plus docetaxel were monitored every 3 weeks during the time docetaxel was administered and then every 3 months, whereas patients assigned to the ADT-alone group were seen every 3 months after randomization. Toxic effects in the group that received ADT plus docetaxel were captured at this frequency to ascertain the adverse-event profile of chemotherapy. The adverse-event profile of ADT was assumed to be common to the two groups. The potential risk of ascertainment bias for adverse events and early progression in the ADT-plus-docetaxel group was recognized, but such bias, if it existed, would have favored the ADT-alone group.

Conclusion of the CHAARTED Trial

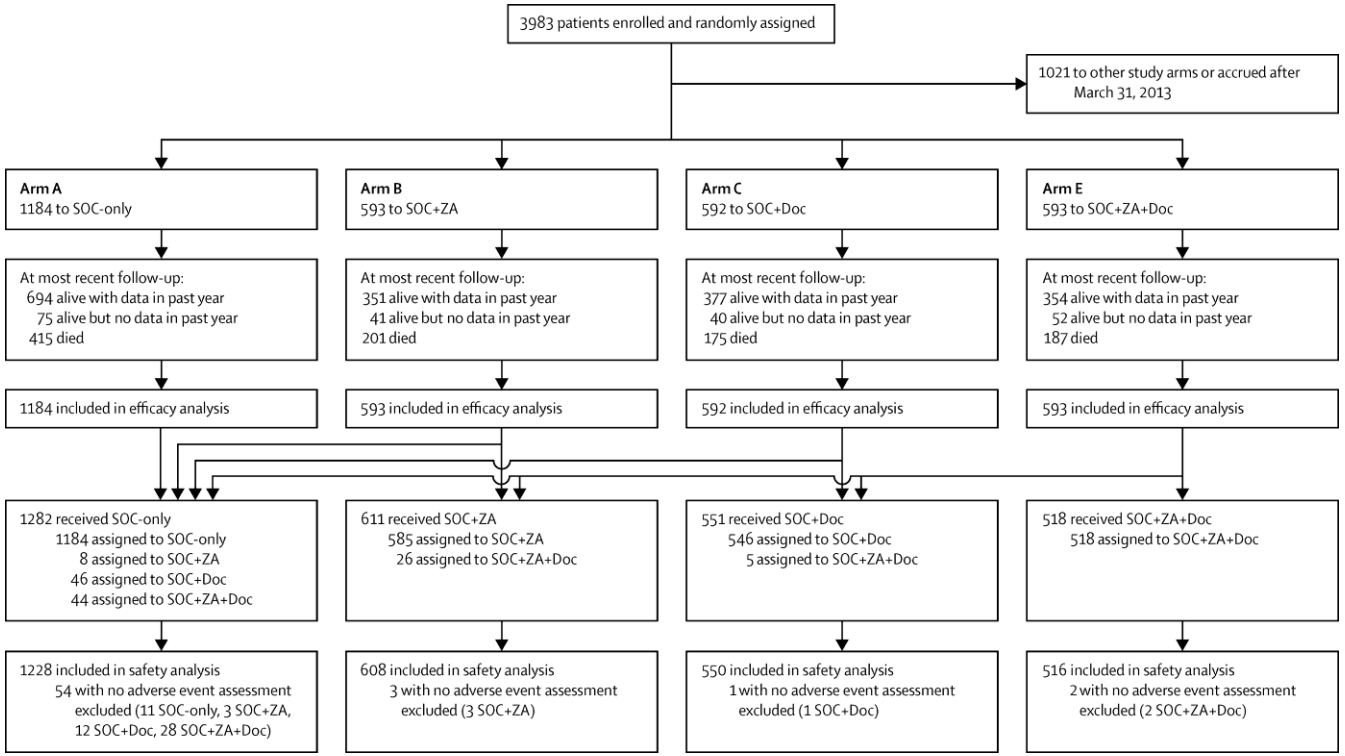
- Addition of Six cycles of Docetaxel to ADT a the beginning to a metastatic prostate cancer resulted
  - In significantly longer overall survival
  - Increase the rate PSA increase interval
  - Increase time to castration resistance prostate cancer than that with ADT alone.

STAMPEDE Clinical Trial

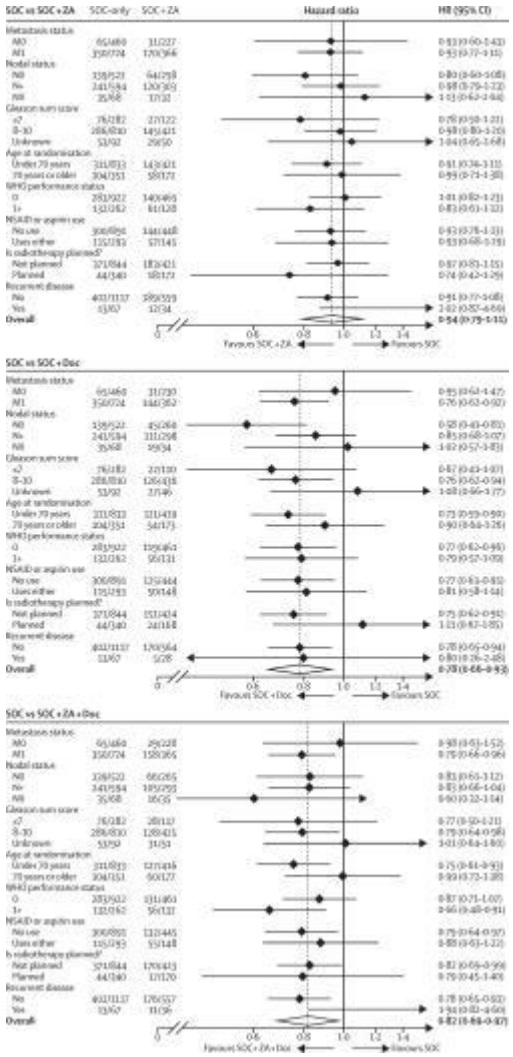
- European Multi-Stage Clinical Trial
- The study had four Arms
- ~ 2,962 men were evaluated
  - ADT (1184 Pt.)
  - ADT + Zometa (593 pt.)
  - ADT + 6 cycles of Docetaxel (592 pt.)
  - ADT + Zometa + 6 cycles of Docetaxel (593 Pt.)
- The average age is 65

STAMPEDE Clinical Trial

- All are hormone-naive prostate cancer
  - 61% Metastatic disease (61%)
  - **39% in High Risk Category (31%)**
- Patient were enrolled in the study from **Oct 5,2005** to **March, 2013**
- Patients were followed for a median of **42** months.
- Primary end point of the study
  - Overall survival
- Data was published August 2015



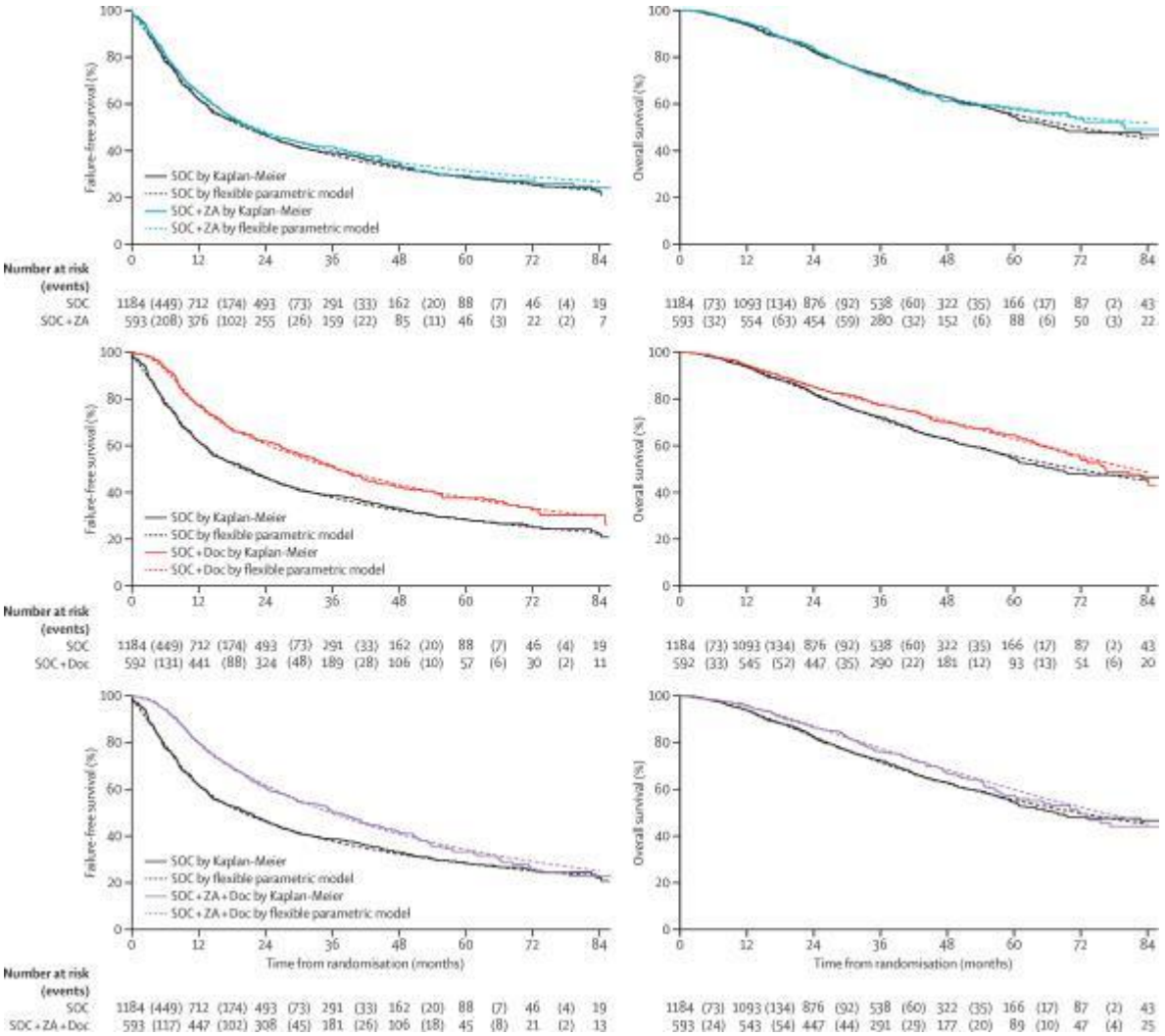
The Lancet 2016 387, 1163-1177DOI: (10.1016/S0140-6736(15)01037-5)



The Lancet 2016 387, 1163-1177DOI: (10.1016/S0140-6736(15)01037-5)

STAMPEDE Clinical Trial

- Primary Goal result of median OS
  - SOC 71 Mo.
  - SOC + Docetaxel 81 Mo.
  - SOC + Docetaxel + Zometa 76 Mo.
- Sub-set analysis of patient with only metastatic disease
- Median OS
  - SOC 45 mo.
  - SOC + DOC 60 mo.



The Lancet 2016 387, 1163-1177DOI: (10.1016/S0140-6736(15)01037-5)

Conclusion of the STAMPEDE Trial

- "Docetaxel should be considered for routine practice in suitable men with newly diagnosed metastatic disease. It should be considered for selected men with high-risk, non-metastatic disease in view of substantial prolongation of failure-free survival."
  - Nicholas D. James, MD, PhD, of the University of Warwick and Queen Elizabeth Hospital Birmingham, United Kingdom – Lead Investigator

STAMPEDE and CHAARTED clinical Trial have changed the management of hormone sensitive chemotherapy

How About the Role of Second Generation ADT Agents?

Most Recent Data

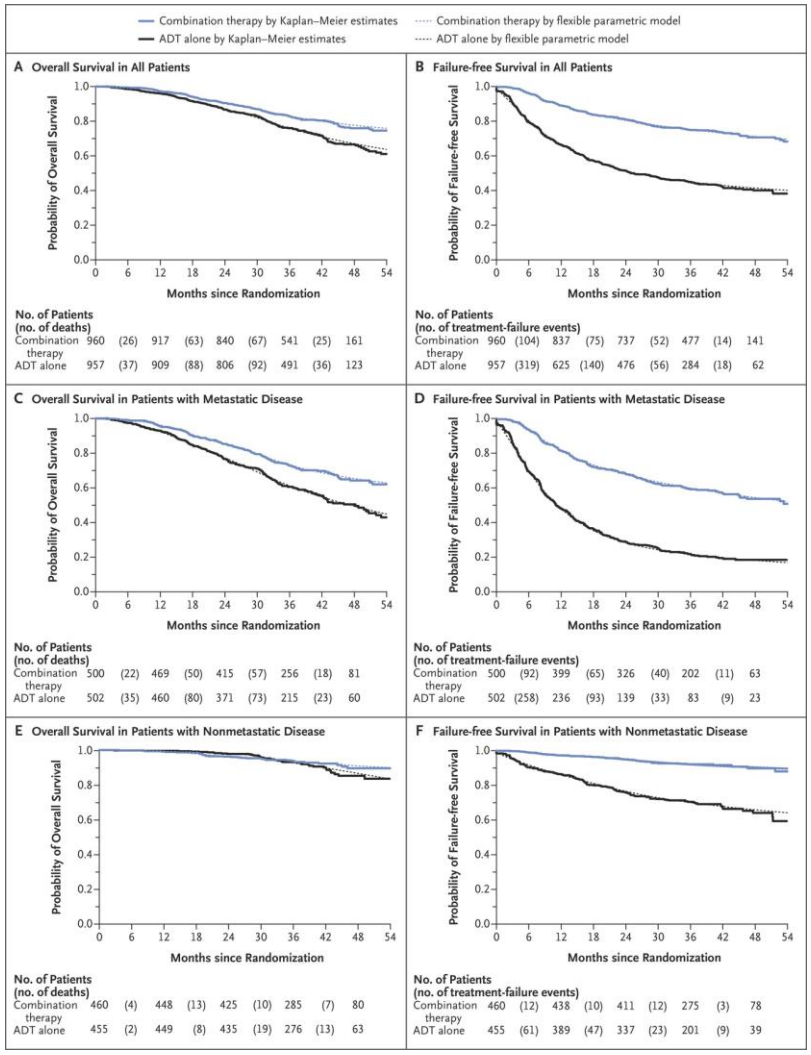
- Two studies looked role of traditional ADT combined with Abiraterone (new agent)
- LATITUDE
  - Looked only metastatic disease
- STAMPEDE II
  - Includes certain high risk non metastatic disease

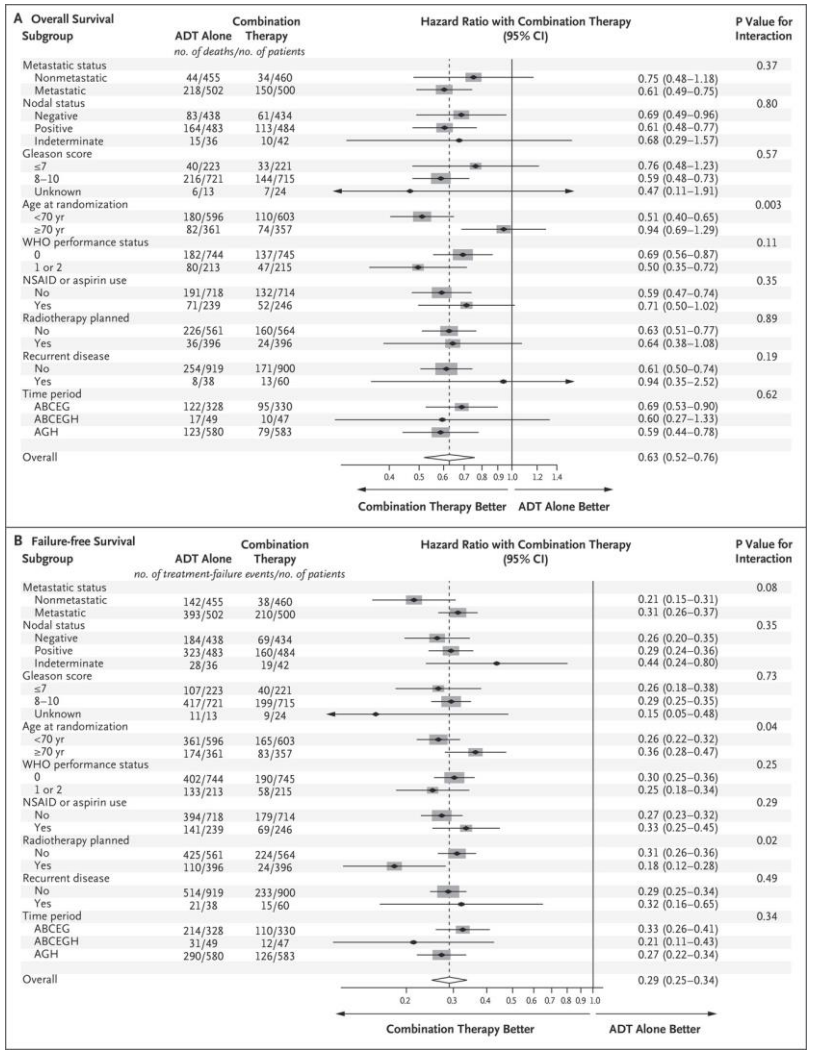
STAMPEDE Clinical Trial II

- Compare the ADT vs. Abiraterone (Zytiga) + ADT
- Patient included in study
  - 95 % of the patients were newly diagnosed
  - Metastatic disease (52%)
  - Locally advance disease
    - 20 % node positive disease
    - 28 % node negative disease
- 1917 Patients were enrolled in the clinical trial from November 2011 to January 2014
- Patient were followed for 40 mo.
- Median age was 67

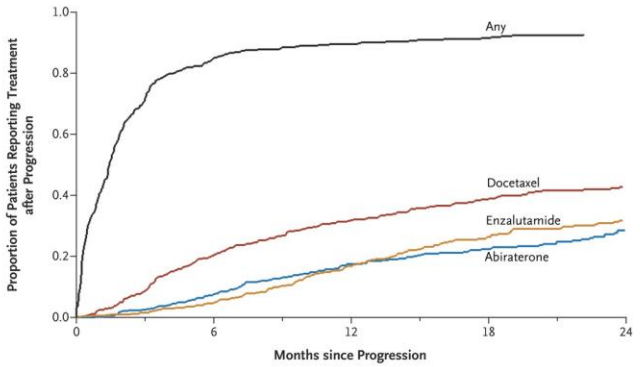
STAMPEDE Clinical Trial II Result

- 3 yr. overall survival
  - 83% for the Abiraterone
  - 76% in the standard treatment group.
  - 184 death on the combination while 262 death in ADT only
- 3 year failure free survival
  - 75% in combination group
  - 45 % in ADT alone
- 3 year skeletal event free rate
  - 88% in combine group
  - 78% ADT alone group
- Abiraterone lower treatment failure by 71%


Combination therapy by Kaplan–Meier estimates
ADT alone by Kaplan–Meier estimates
Combination therapy by flexible parametric model
ADT alone by flexible parametric model
A Overall Survival in All Patients
Probability of Overall Survival
Months since Randomization
No. of Patients (no. of deaths)
Combination therapy 960 (26) 917 (63) 840 (67) 541 (25) 161
ADT alone 957 (37) 909 (88) 806 (92) 491 (36) 123
B Failure-free Survival in All Patients
Probability of Failure-free Survival
Months since Randomization
No. of Patients (no. of treatment-failure events)
Combination therapy 960 (104) 837 (75) 737 (52) 477 (14) 141
ADT alone 957 (319) 625 (140) 476 (56) 284 (18) 62
C Overall Survival in Patients with Metastatic Disease
Probability of Overall Survival
Months since Randomization
No. of Patients (no. of deaths)
Combination therapy 500 (22) 469 (50) 415 (57) 256 (18) 81
ADT alone 502 (35) 460 (80) 371 (73) 215 (23) 60
D Failure-free Survival in Patients with Metastatic Disease
Probability of Failure-free Survival
Months since Randomization
No. of Patients (no. of treatment-failure events)
Combination therapy 500 (92) 399 (65) 326 (40) 202 (11) 63
ADT alone 502 (258) 236 (93) 139 (33) 83 (9) 23
E Overall Survival in Patients with Nonmetastatic Disease
Probability of Overall Survival
Months since Randomization
No. of Patients (no. of deaths)
Combination therapy 460 (4) 448 (13) 425 (10) 285 (7) 80
ADT alone 455 (2) 449 (8) 435 (19) 276 (13) 63
F Failure-free Survival in Patients with Nonmetastatic Disease
Probability of Failure-free Survival
Months since Randomization
No. of Patients (no. of treatment-failure events)
Combination therapy 460 (12) 438 (10) 411 (12) 275 (3) 78
ADT alone 455 (61) 389 (47) 337 (23) 201 (9) 39

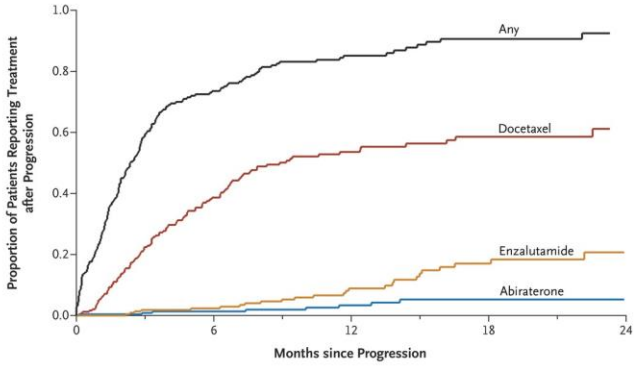

A Overall Survival
Subgroup
ADT Alone
Combination Therapy
no. of deaths/no. of patients
Hazard Ratio with Combination Therapy (95% CI)
P Value for Interaction
Metastatic status 0.37
Nonmetastatic 44/455 34/460 0.75 (0.48–1.18)
Metastatic 218/502 150/500 0.61 (0.49–0.75)
Nodal status 0.80
Negative 83/438 61/434 0.69 (0.49–0.96)
Positive 164/483 113/484 0.61 (0.48–0.77)
Indeterminate 15/36 10/42 0.68 (0.29–1.57)
Gleason score 0.57
≤7 40/223 33/221 0.76 (0.48–1.23)
8–10 216/721 144/715 0.59 (0.48–0.73)
Unknown 6/13 7/24 0.47 (0.11–1.91)
Age at randomization 0.003
<70 yr 180/596 110/603 0.51 (0.40–0.65)
≥70 yr 82/361 74/357 0.94 (0.69–1.29)
WHO performance status 0.11
0 182/744 137/745 0.69 (0.56–0.87)
1 or 2 80/213 47/215 0.50 (0.35–0.72)
NSAID or aspirin use 0.35
No 191/718 132/714 0.59 (0.47–0.74)
Yes 71/239 52/246 0.71 (0.50–1.02)
Radiotherapy planned 0.89
No 226/561 160/564 0.63 (0.51–0.77)
Yes 36/396 24/396 0.64 (0.38–1.08)
Recurrent disease 0.19
No 254/919 171/900 0.61 (0.50–0.74)
Yes 8/38 13/60 0.94 (0.35–2.52)
Time period 0.62
ABCEG 122/328 95/330 0.69 (0.53–0.90)
ABCEGH 17/49 10/47 0.60 (0.27–1.33)
AGH 123/580 79/583 0.59 (0.44–0.78)
Overall 0.63 (0.52–0.76)
0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.2 1.4
Combination Therapy Better
ADT Alone Better
B Failure-free Survival
Subgroup
ADT Alone
Combination Therapy
no. of treatment-failure events/no. of patients
Hazard Ratio with Combination Therapy (95% CI)
P Value for Interaction
Metastatic status 0.08
Nonmetastatic 142/455 38/460 0.21 (0.15–0.31)
Metastatic 393/502 210/500 0.31 (0.26–0.37)
Nodal status 0.35
Negative 184/438 69/434 0.26 (0.20–0.35)
Positive 323/483 160/484 0.29 (0.24–0.36)
Indeterminate 28/36 19/42 0.44 (0.24–0.80)
Gleason score 0.73
≤7 107/223 40/221 0.26 (0.18–0.38)
8–10 417/721 199/715 0.29 (0.25–0.35)
Unknown 11/13 9/24 0.15 (0.05–0.48)
Age at randomization 0.04
<70 yr 361/596 165/603 0.26 (0.22–0.32)
≥70 yr 174/361 83/357 0.36 (0.28–0.47)
WHO performance status 0.25
0 402/744 190/745 0.30 (0.25–0.36)
1 or 2 133/213 58/215 0.25 (0.18–0.34)
NSAID or aspirin use 0.29
No 394/718 179/714 0.27 (0.23–0.32)
Yes 141/239 69/246 0.33 (0.25–0.45)
Radiotherapy planned 0.02
No 425/561 224/564 0.31 (0.26–0.36)
Yes 110/396 24/396 0.18 (0.12–0.28)
Recurrent disease 0.49
No 514/919 233/900 0.29 (0.25–0.34)
Yes 21/38 15/60 0.32 (0.16–0.65)
Time period 0.34
ABCEG 214/328 110/330 0.33 (0.26–0.41)
ABCEGH 31/49 12/47 0.21 (0.11–0.43)
AGH 290/580 126/583 0.27 (0.22–0.34)
Overall 0.29 (0.25–0.34)
0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Combination Therapy Better
ADT Alone Better

A ADT Alone



No. of Patients (no. of patients reporting treatment after progression)									
Any	535	(441)	70	(20)	38	(7)	28	(4)	23
Docetaxel	535	(102)	374	(51)	271	(25)	197	(12)	145
Abiraterone	535	(38)	434	(43)	331	(18)	247	(16)	162
Enzalutamide	535	(24)	448	(52)	331	(35)	229	(15)	165

B Combination Therapy



No. of Patients (no. of patients reporting treatment after progression)									
Any	248	(168)	51	(21)	21	(6)	9	(1)	2
Docetaxel	248	(83)	110	(25)	58	(5)	32	(1)	13
Abiraterone	248	(3)	179	(3)	122	(2)	71	(0)	32
Enzalutamide	248	(5)	179	(10)	116	(8)	62	(2)	25

Table 2. Worst Adverse-Event Grade Reported during Entire Time in the Trial.*

Variable	ADT Alone	Combination Therapy
Safety population		
No. of patients	960	948
Patients with an adverse event — no. (%)		
Any grade	950 (99)	943 (99)
Grade 3–5	315 (33)	443 (47)
Grade 5 only†	3 (<1)	9 (1)
Grade 3–5 adverse events — no. (%)		
Endocrine disorders‡	133 (14)	129 (14)
Cardiovascular disorders	41 (4)	92 (10)
Hypertension	13 (1)	44 (5)
Myocardial infarction	9 (1)	10 (1)
Cardiac dysrhythmia	2 (<1)	14 (1)
Musculoskeletal disorders	46 (5)	68 (7)
Gastrointestinal disorders	40 (4)	49 (5)
Hepatic disorders	12 (1)	70 (7)
Increased ALT level	4 (<1)	53 (6)
Increased AST level	2 (<1)	10 (1)
General disorders	29 (3)	45 (5)
Fatigue	15 (2)	21 (2)
Edema	0	5 (1)
Respiratory disorders	23 (2)	44 (5)
Dyspnea	7 (1)	18 (2)
Laboratory abnormalities	21 (2)	34 (4)
Hypokalemia	3 (<1)	12 (1)
Intention-to-treat population		
Total no. of patients	957	960
No. of patients in safety analysis	953	955
Patients with an adverse event — no. (%)		
Any grade	943 (99)	950 (99)
Grade 3–5	312 (33)	446 (47)
Grade 5 only†	3 (<1)	9 (1)

* ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† In the ADT-alone group, there were two events of myocardial infarction and one event of bronchopneumonia. In the combination group, there were two events of pneumonia (one including sepsis), two events of stroke, and one event each of dyspnea, lower respiratory tract infection, liver failure, pulmonary hemorrhage, and chest infection.
‡ Endocrine disorders included hot flashes and impotence.

Conclusion STAMPEDE II

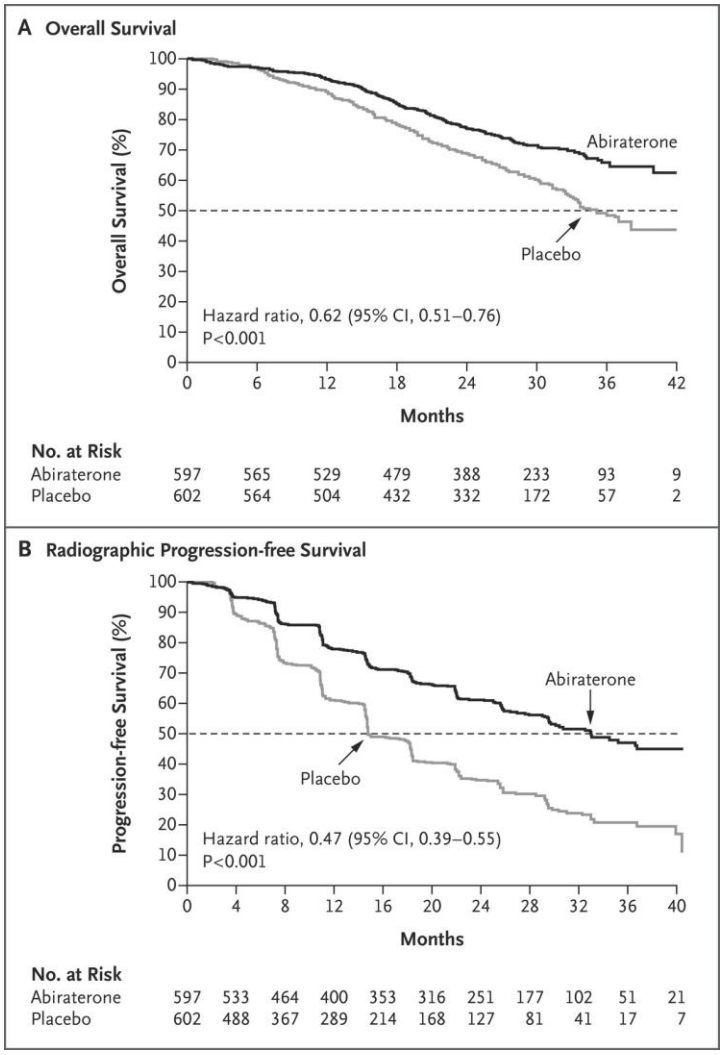
- Among men with locally advanced or metastatic prostate cancer, ADT plus Abiraterone and prednisolone was associated with significantly higher rates of overall and failure-free survival than ADT alone.

LATITUDE Study

- Multinational (**34** countries) Phase 3 Clinical Trial double blind study
- Compare Androgen-Deprivation therapy vs. Androgen-Deprivation Androgen + Abiraterone
- Inclusion criteria
  - Metastatic Castration Sensitive prostate cancer
- The primary end point of the study
  - Overall survival
  - Radiographic progression free survival

LATITUDE Study

- 1199 Patient were enrolled in the clinical trial
- Patient were followed **30.4** mo.
- Median overall survival
  - Not reached vs. **34.7** mo.
- Median Radiographic event free survival
  - **33.0** mo. vs. **14.8** mo.
- Study also significant improvement on secondary points
  - PSA Progression
  - Symptomatic skeletal event
  - Pain progression


A Overall Survival
Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Abiraterone
Placebo
Hazard ratio, 0.62 (95% CI, 0.51–0.76)
P<0.001
0
6
12
18
24
30
36
42
Months
No. at Risk
Abiraterone 597 565 529 479 388 233 93 9
Placebo 602 564 504 432 332 172 57 2
B Radiographic Progression-free Survival
Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Abiraterone
Placebo
Hazard ratio, 0.47 (95% CI, 0.39–0.55)
P<0.001
0
4
8
12
16
20
24
28
32
36
40
Months
No. at Risk
Abiraterone 597 533 464 400 353 316 251 177 102 51 21
Placebo 602 488 367 289 214 168 127 81 41 17 7

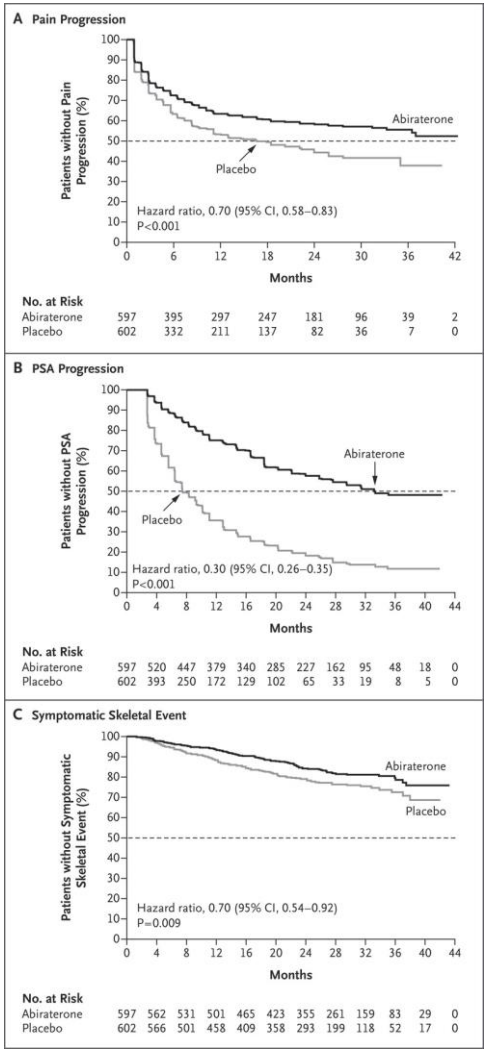

A Pain Progression
Patients without Pain Progression (%)
Abiraterone
Placebo
Hazard ratio, 0.70 (95% CI, 0.58–0.83)
P<0.001
Months
No. at Risk
Abiraterone 597 395 297 247 181 96 39 2
Placebo 602 332 211 137 82 36 7 0
B PSA Progression
Patients without PSA Progression (%)
Abiraterone
Placebo
Hazard ratio, 0.30 (95% CI, 0.26–0.35)
P<0.001
Months
No. at Risk
Abiraterone 597 520 447 379 340 285 227 162 95 48 18 0
Placebo 602 393 250 172 129 102 65 33 19 8 5 0
C Symptomatic Skeletal Event
Patients without Symptomatic Skeletal Event (%)
Abiraterone
Placebo
Hazard ratio, 0.70 (95% CI, 0.54–0.92)
P=0.009
Months
No. at Risk
Abiraterone 597 562 531 501 465 423 355 261 159 83 29 0
Placebo 602 566 501 458 409 358 293 199 118 52 17 0

Table 1. Prespecified Secondary and Exploratory Efficacy End Points.*

End Point	Abiraterone Group (N=597)	Placebo Group (N=602)	Hazard Ratio (95% CI)	P Value†
Secondary end points				
Median time to pain progression (mo)	NR	16.6	0.70 (0.58–0.83)	<0.001
Median time to PSA progression (mo)	33.2	7.4	0.30 (0.26–0.35)	<0.001
Median time to next symptomatic skeletal event (mo)	NR	NR	0.70 (0.54–0.92)	0.009
Median time to chemotherapy (mo)	NR	38.9	0.44 (0.35–0.56)	<0.001
Median time to subsequent prostate cancer therapy (mo)	NR	21.6	0.42 (0.35–0.50)	<0.001
Exploratory end point				
Patients with a PSA response (%)‡	91	67	1.36 (1.28–1.45)	<0.001

* CI denotes confidence interval, PSA prostate-specific antigen, and NR not reached.
† P values for secondary end points were calculated by means of a stratified log-rank test and those for the exploratory end point by means of a chi-square test.
‡ A PSA response was defined as a decrease of at least 50% from the baseline value. The comparison for this exploratory end point was calculated as an odds ratio.

Table 2. Adverse Events.*

Adverse Event	Abiraterone Group (N=597)			Placebo Group (N=602)		
	number of patients (percent)					
Any adverse event	558 (93)			557 (93)		
Grade 3 or 4 adverse event	374 (63)			287 (48)		
Any serious adverse event	165 (28)			146 (24)		
Any adverse event leading to treatment discontinuation	73 (12)			61 (10)		
Adverse event leading to death	28 (5)			24 (4)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Graded adverse events†						
Hypertension	219 (37)	121 (20)	0	133 (22)	59 (10)	1 (<1)
Hypokalemia	122 (20)	57 (10)	5 (1)	22 (4)	7 (1)	1 (<1)
ALT increased	98 (16)	31 (5)	2 (<1)	77 (13)	8 (1)	0
Hyperglycemia	75 (13)	26 (4)	1 (<1)	68 (11)	18 (3)	0
AST increased	87 (15)	25 (4)	1 (<1)	68 (11)	9 (1)	0
Bone pain	74 (12)	20 (3)	0	88 (15)	17 (3)	0
Cardiac disorder						
Any	74 (12)	15 (3)	5 (1)	47 (8)	6 (1)	0
Atrial fibrillation	8 (1)	2 (<1)	0	2 (<1)	1 (<1)	0
Anemia	54 (9)	12 (2)	3 (1)	85 (14)	26 (4)	1 (<1)
Back pain	110 (18)	14 (2)	0	123 (20)	19 (3)	0
Fatigue	77 (13)	10 (2)	0	86 (14)	14 (2)	0
Spinal-cord compression	14 (2)	12 (2)	0	12 (2)	7 (1)	3 (<1)

* Listed are the most common adverse events and events of special interest. The latter were selected on the basis of the safety profile of phase 2 and phase 3 studies of abiraterone. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† Listed in descending order are events that were reported in at least 2% of the patients in either group. Among other events of special interest, grade 3 peripheral edema was reported in 0.3% of the patients in the abiraterone group and in 0.5% of those in the placebo group; grade 3 or 4 fluid retention or congestive heart failure was not reported in either group. Grade 3 hot flush was reported in one patient in the placebo group, and grade 1 irritability was reported in three patients in the abiraterone group.

Conclusion LATITUDE Study

- Among men with metastatic prostate cancer, ADT plus Abiraterone is associated with significantly higher rates of overall and failure-free survival than ADT alone.

Future Clinical Trials

- Clinical Trial
  - ADT + Docetaxel vs. ADT + Abiraterone vs. vs. ADT + Abiraterone + Docetaxel
- Immune Therapy
  - Anti-PDL 1 ?
  - Anti CTLA-4 ?

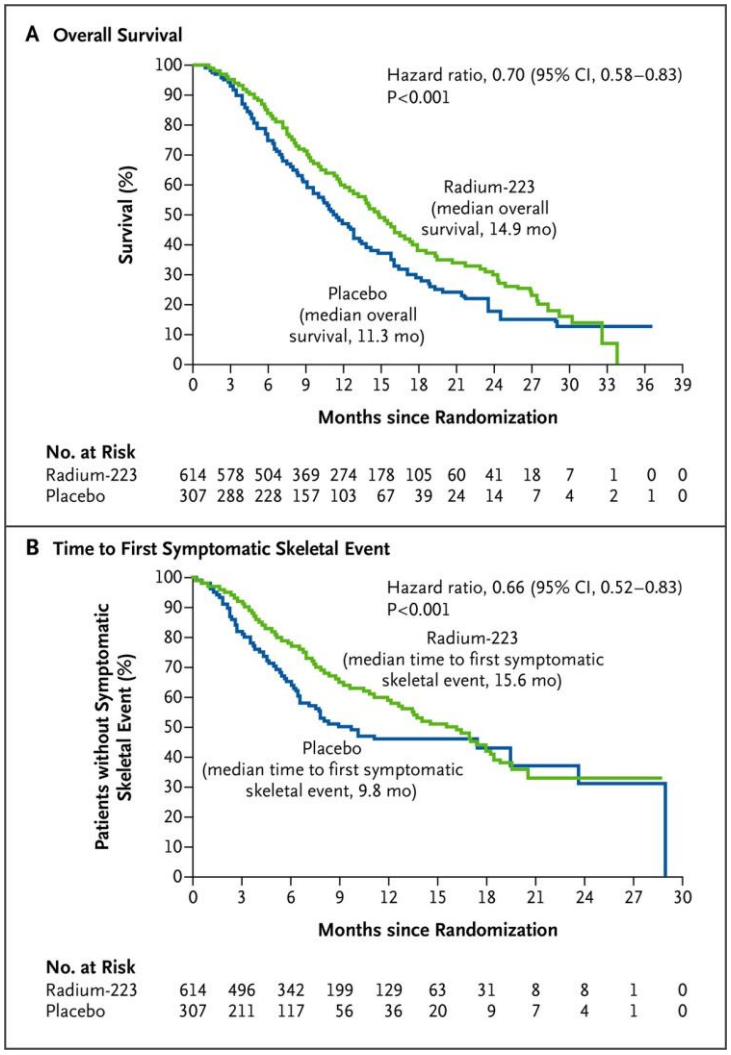
Palliative Agent in Metastatic Prostate Cancer

Symptom Management in Prostate Cancer

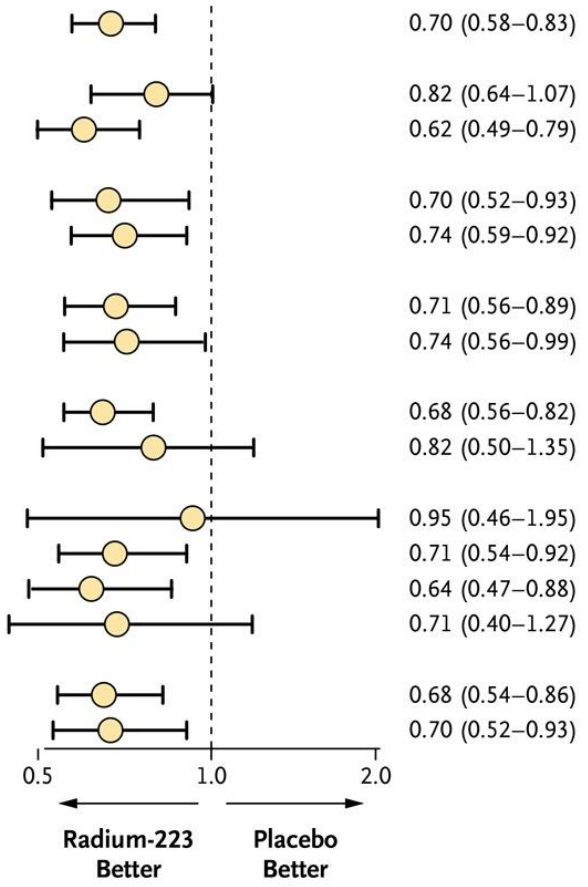
- Symptom Management in Metastatic Prostate Cancer disease improves QOL (morbidity and mortality)
- Prevention of bone event is one of the most important aspect of prostate cancer management.
- We have different agents for prevention of bone related events
  - Bisphosphonate
    - can be given in any stage of the disease so long as patient has bone disease
    - prevent osteoporosis
  - RANKL Mab (Denosumab)
  - Radium-223:
    - It can only be given in castration resistance disease
    - it is the only bone agent that has survival data

ALSYMPCA Clinical Trial

- Randomized double placebo clinical trial
- Compare Radium-223 with standard of care
  - In patient symptomatic bone disease
  - Castrate resistance prostate cancer patient
- Radium-223 an alpha emitter than selectively target bone metastases with alpha particle
- Primary end point of the study
  - Overall Survival
- Secondary end point
  - First Symptomatic Skeletal Event
  - Biochemical End Point


A Overall Survival
Hazard ratio, 0.70 (95% CI, 0.58–0.83)
P<0.001
Radium-223
(median overall
survival, 14.9 mo)
Placebo
(median overall
survival, 11.3 mo)
Survival (%)
Months since Randomization
No. at Risk
Radium-223 614 578 504 369 274 178 105 60 41 18 7 1 0 0
Placebo 307 288 228 157 103 67 39 24 14 7 4 2 1 0
B Time to First Symptomatic Skeletal Event
Hazard ratio, 0.66 (95% CI, 0.52–0.83)
P<0.001
Radium-223
(median time to first symptomatic
skeletal event, 15.6 mo)
Placebo
(median time to first symptomatic
skeletal event, 9.8 mo)
Patients without Symptomatic
Skeletal Event (%)
Months since Randomization
No. at Risk
Radium-223 614 496 342 199 129 63 31 8 8 1 0
Placebo 307 211 117 56 36 20 9 7 4 1 0

Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)



Thank You & Questions?