Metastatic Hormone-Sensitive Prostate Cancer: Current Status and Future Directions

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UCDAVIS HEALTH | COMPREHENSIVE CANCER CENTER

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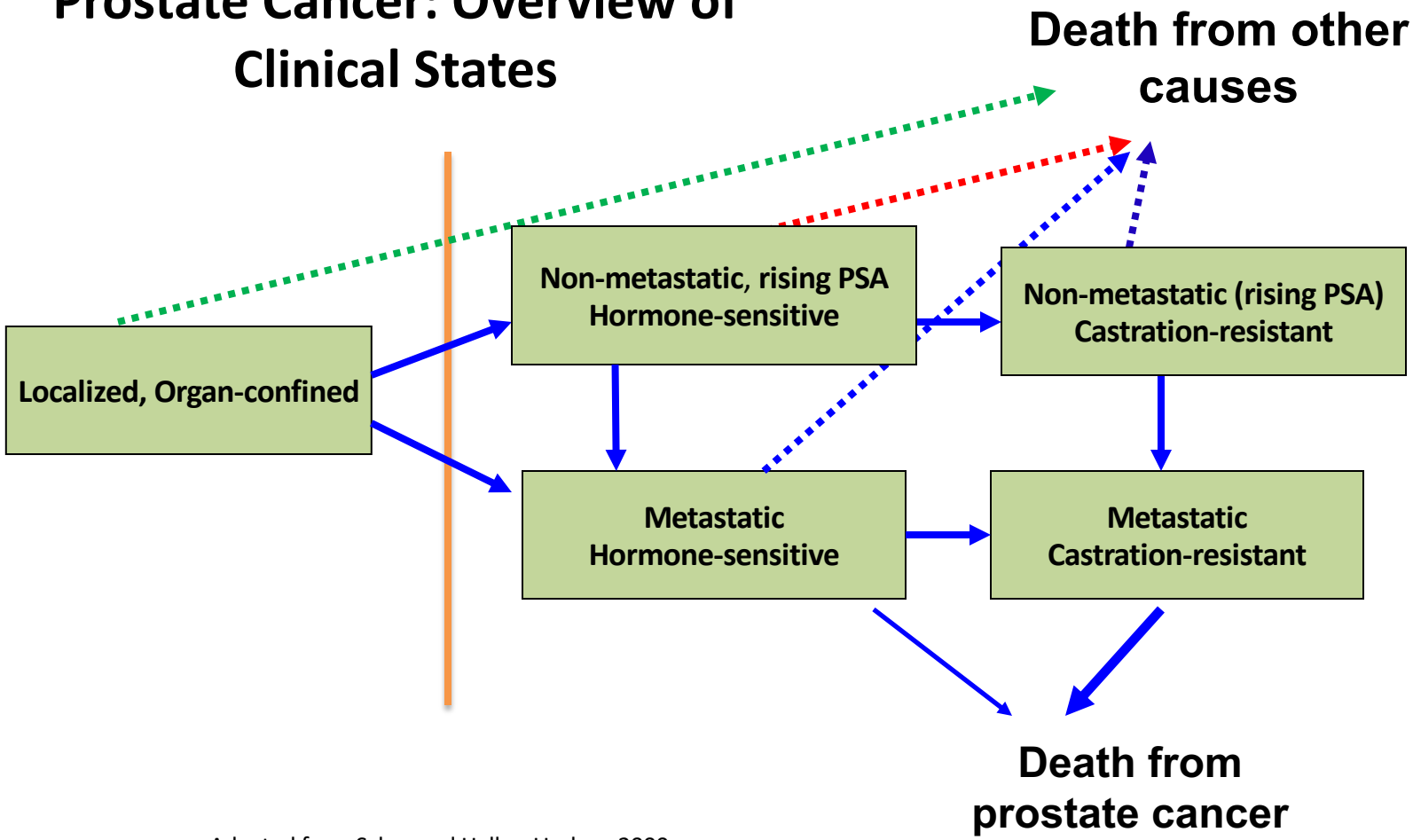
Prostate Cancer: Overview of Clinical States



Adapted from Scher and Heller, Urology 2000

Treatment Goals in Advanced Prostate Cancer

Biochemical (PSA-only) & metastatic disease: Asymptomatic

- Prolong life
- Prevent morbidity: skeletal-related events, pain

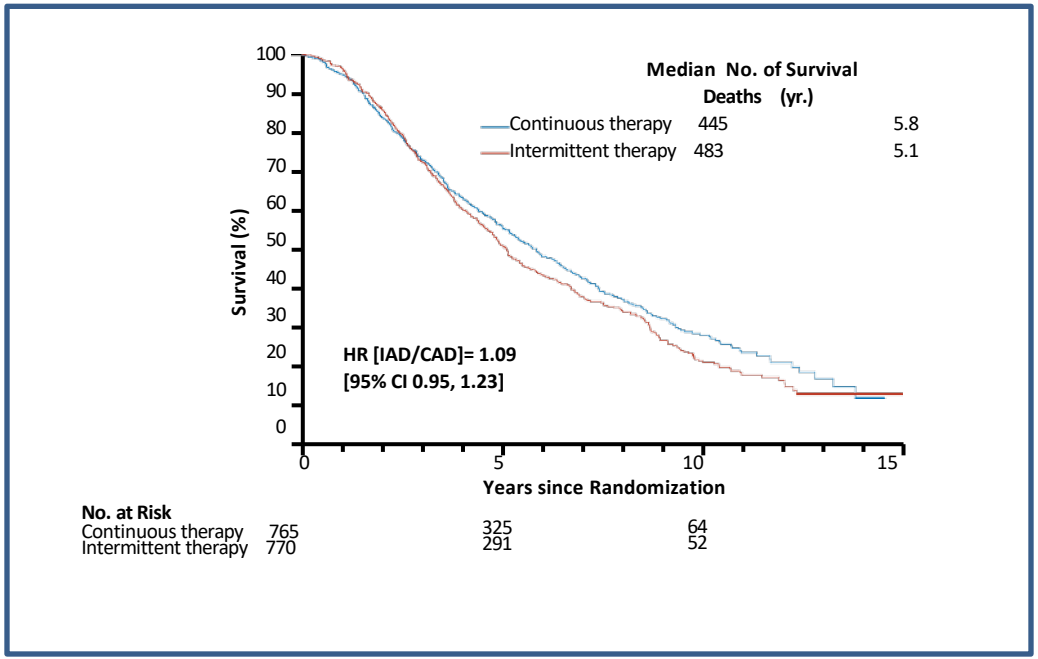
Metastatic disease: Symptomatic

- Palliate symptoms
- Enhance quality of life
- Prolong life

Advanced hormone-sensitive prostate cancer

- **Initial treatment is castration**
  - Bilateral orchiectomy
  - LHRH agonist (e.g., Goserelin or Leuprolide)
  - LHRH antagonist (e.g., Degarelix)
- **For men with metastatic disease, <u>treatment intensification</u> is standard-of-care**
  - ADT plus a 2nd or 3rd agent

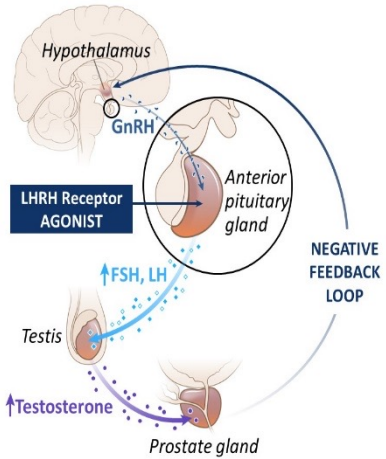
SWOG S9346: Intermittent vs. Continuous ADT



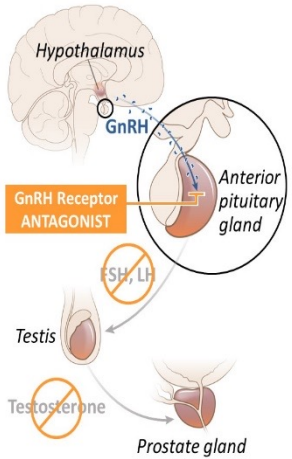
Intermittent therapy was “not non-inferior” to continuous ADT

Hussain M et al. *N Engl J Med* 2013;368:1314-25.

ADT: LHRH agonist vs antagonist

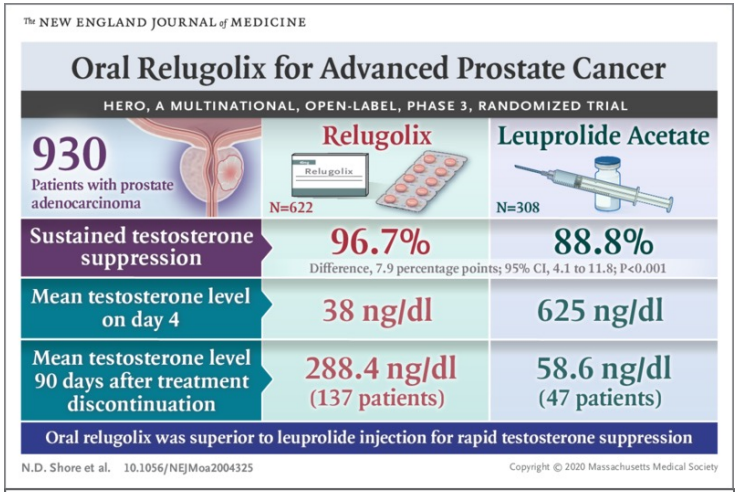


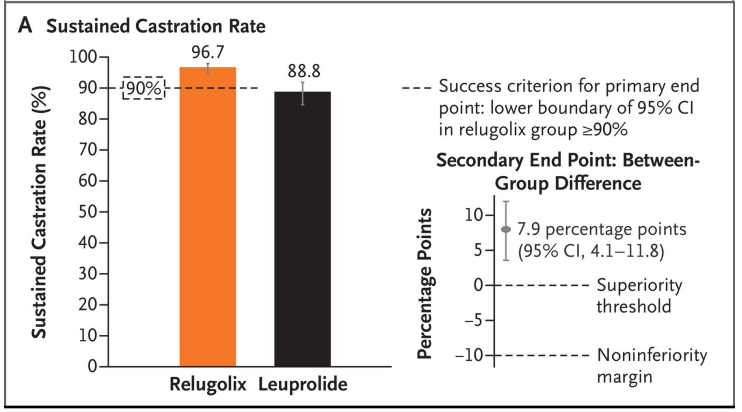
Leuprolide, Goserelin, Triptorelin



Degarelix, Relugolix

	Relugolix (N = 622)	Leuprolide (N = 308)
Hot flush	54.3%	51.6%
Fatigue	21.5%	18.5%
Constipation	12.2%	9.7%
Diarrhea*	12.2%	6.8%
Arthralgia	12.1%	9.1%
Hypertension	7.9%	11.7%



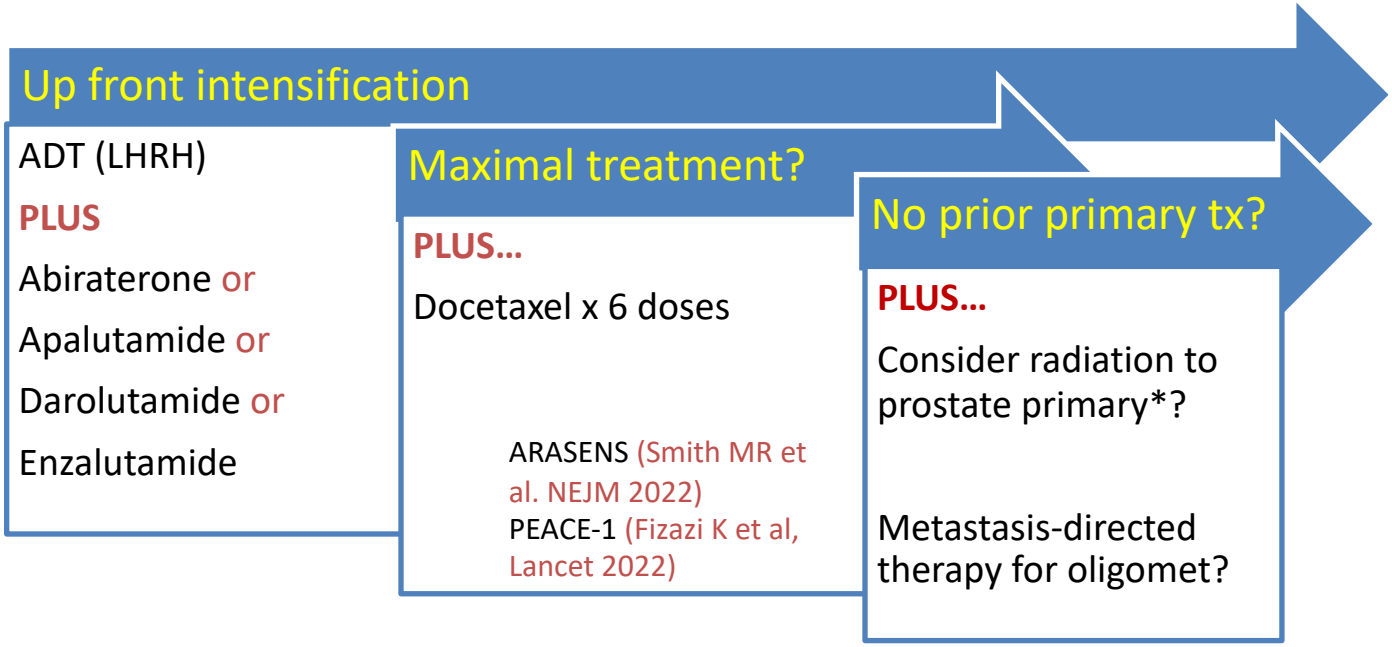


Shore, NEJM 2020

Emerging paradigms in mHSPC

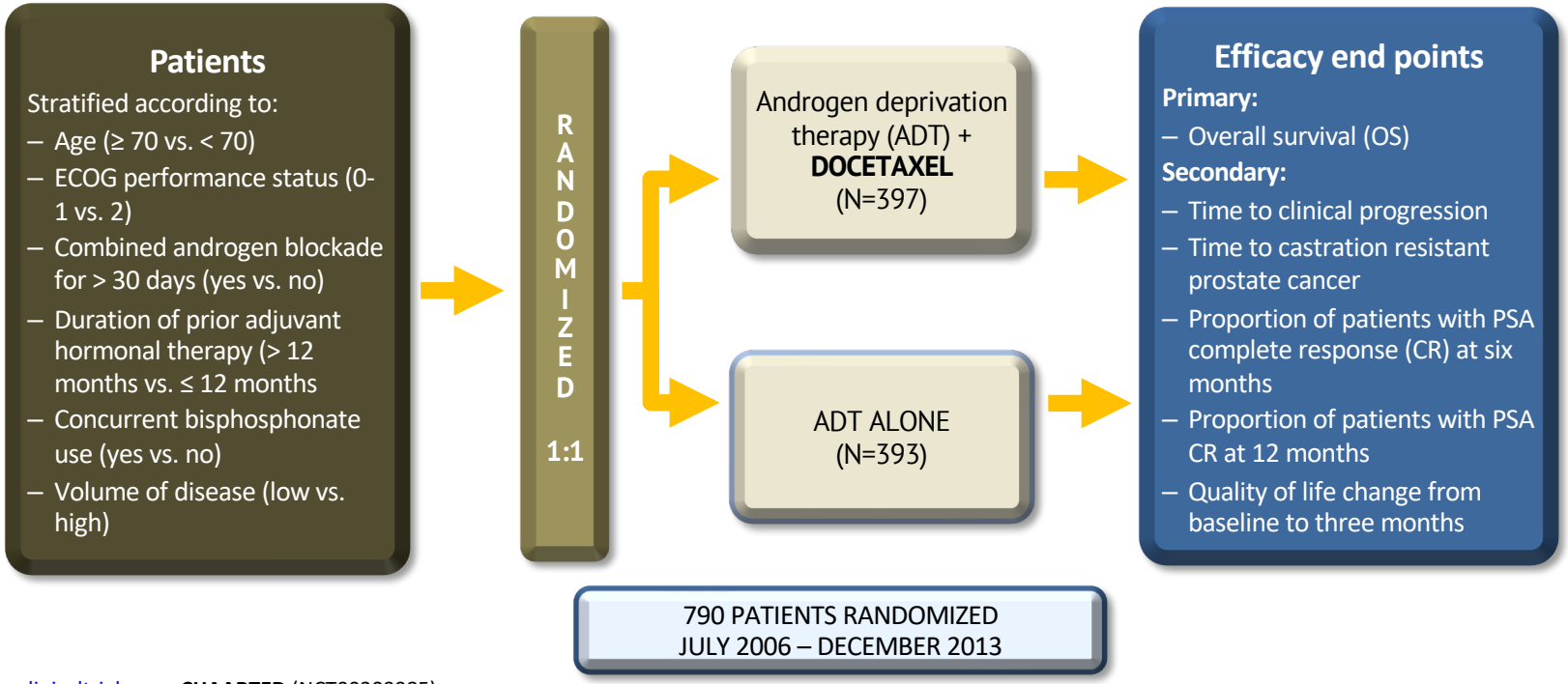
Phase III trials:

- STAMPEDE - Doce (James N, Lancet 2016)
- CHAARTED (Sweeney CJ, NEJM 2015)
- STAMPEDE - Abi (James N, NEJM 2017)
- LATITUDE (Fizazi K, NEJM 2017)
- ENZAMET (Davis I, NEJM 2019)
- ARCHES (Armstrong A, JCO 2019)
- TITAN (Chi KN, NEJM 2019)
- PEACE 1 (Fizazi K, Lancet 2022)
- ARASENS (Smith MR, NEJM 2022)



Slide courtesy of T. Dorff

CHAARTED: Androgen Deprivation Therapy With or Without Chemotherapy

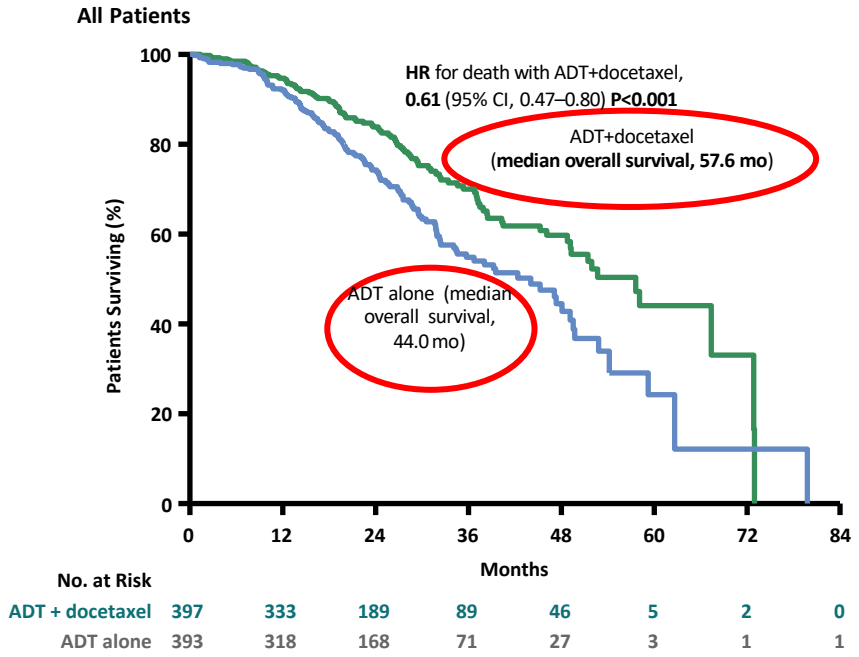


www.clinicaltrials.gov: **CHAARTED** (NCT00309985)

Sweeney C et al. *N Engl J Med* 2015; 373:737-46.

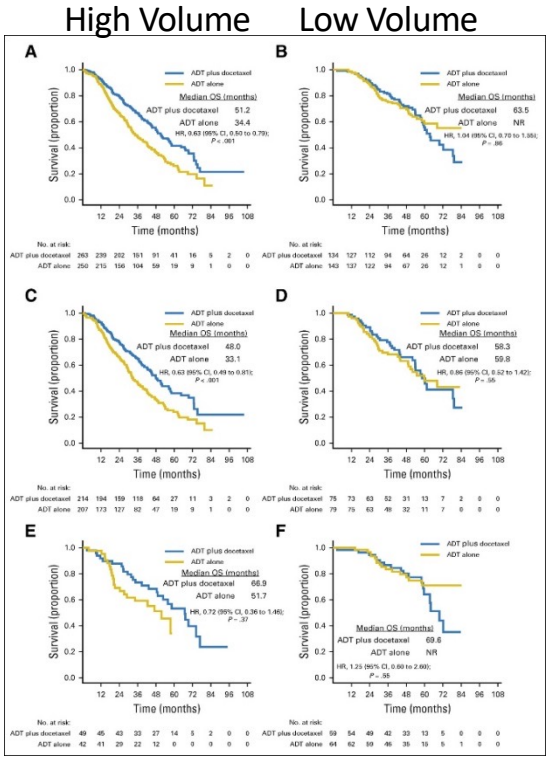
CHAARTED: Overall Survival (OS) Benefit

The median OS was 13.6 months longer with the addition of early docetaxel to ADT than with ADT alone

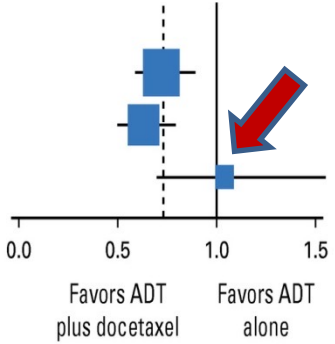


Sweeney C et al. *N Engl J Med* 2015; 373:737-46.

CHAARTED: Updated Analysis on OS Benefit by Disease Volume Status



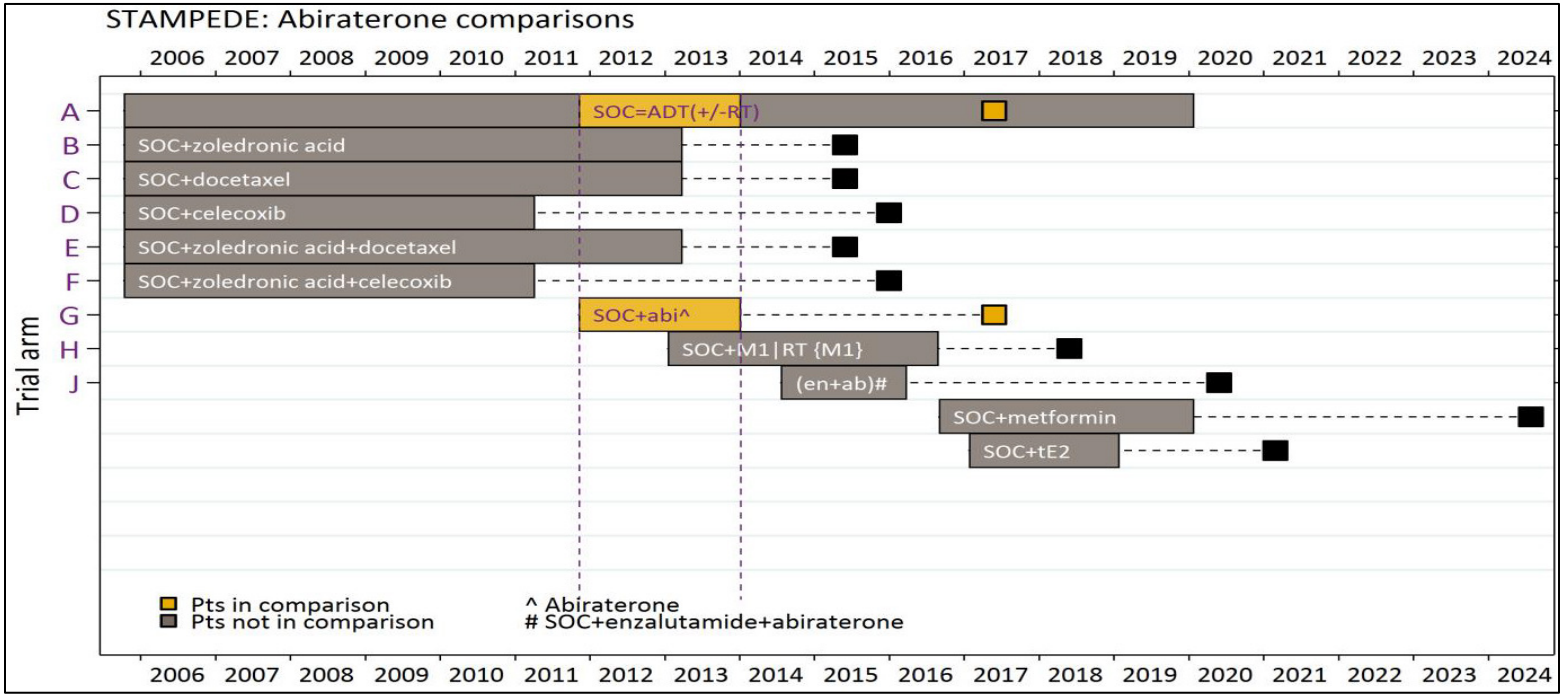
Group	No.	HR	95% CI
Overall	790	0.72	0.59 to 0.89
High-volume disease	513	0.63	0.50 to 0.79
Low-volume disease	277	1.04	0.70 to 1.55



www.clinicaltrials.gov: **CHAARTED** (NCT00309985)

Kyriakopoulos CE et al. *J Clin Oncol* 2018 36(11):1080-1087

STAMPEDE Trials in Advanced Prostate Cancer



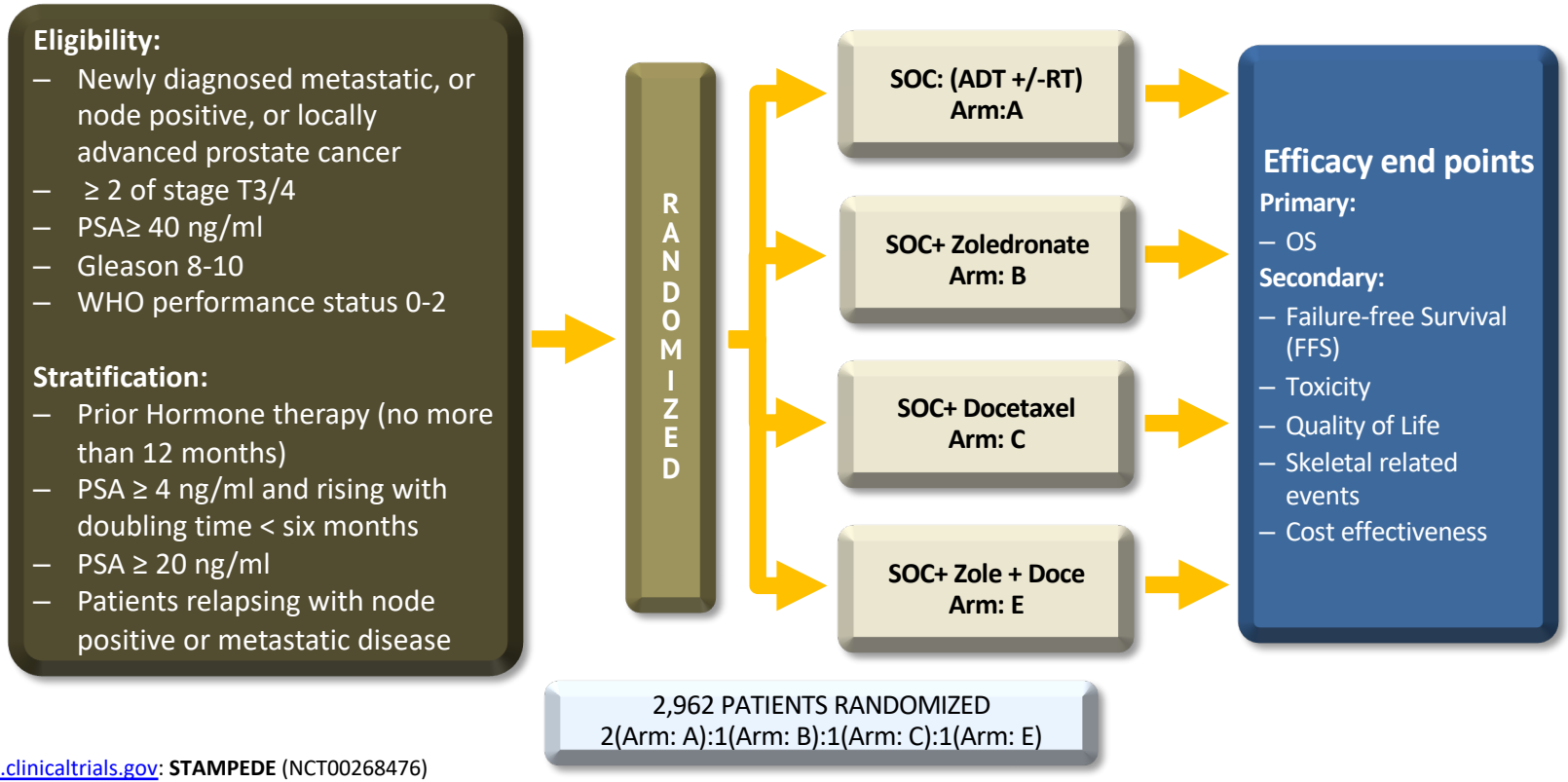
Systemic Therapy in Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy

A multi-stage multi-arm randomized controlled trial

www.clinicaltrials.gov: **STAMPEDE** (NCT00268476)

PI: Nicholas D. James

STAMPEDE Trial with Docetaxel and Zolendronic Acid

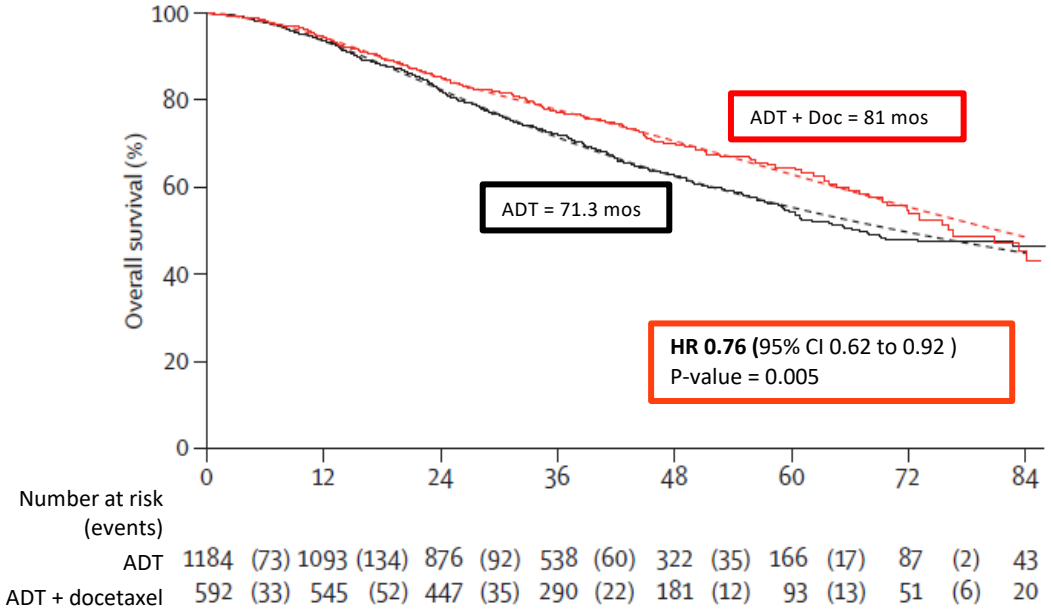


www.clinicaltrials.gov: **STAMPEDE** (NCT00268476)

James ND et al. *Lancet* 2016; 387:1163-77.

STAMPEDE Trial with Docetaxel and Zolendronic Acid

(Arms: A, B, C, and E)

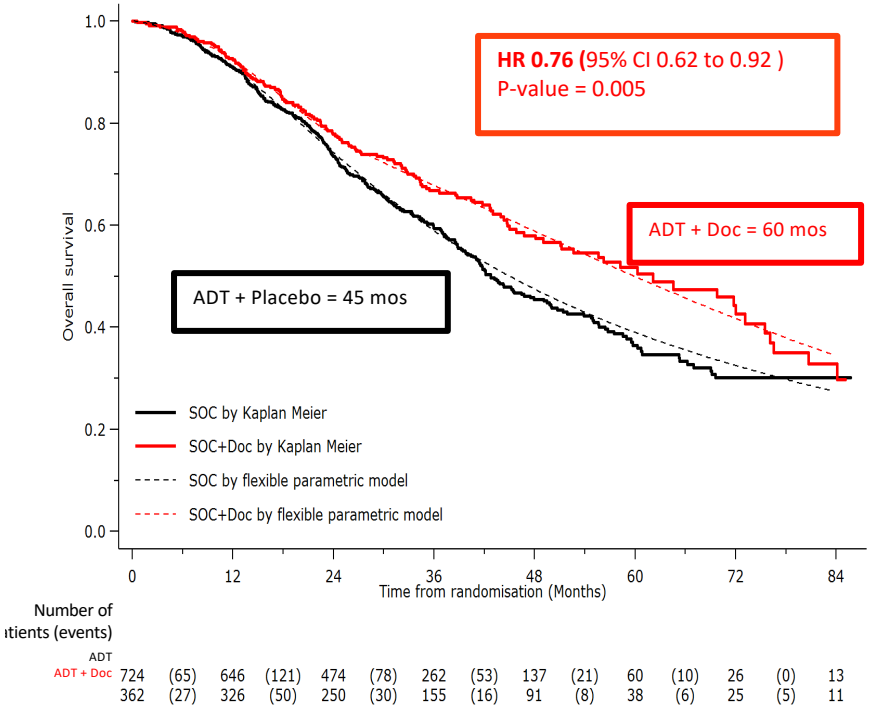


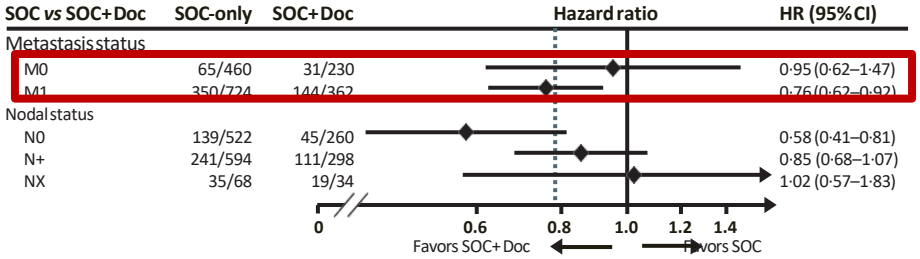
No effect on survival with zolendronic acid

James ND et al. Lancet 2016; 387:1163-77.

STAMPEDE Trial with Docetaxel: OS in M1 and M0 Subsets

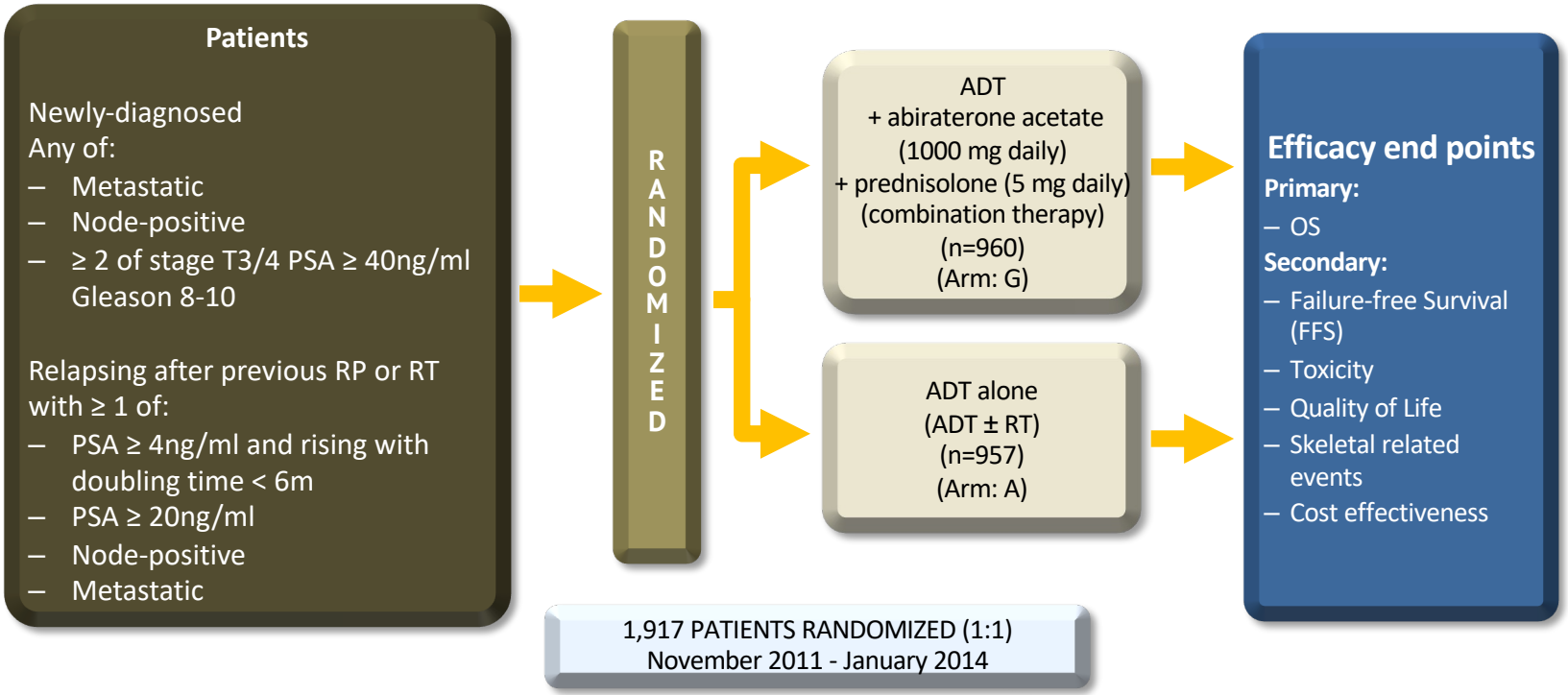
M1 disease (61%, n=1817)





James ND et al. Lancet 2016; 387:1163-77.

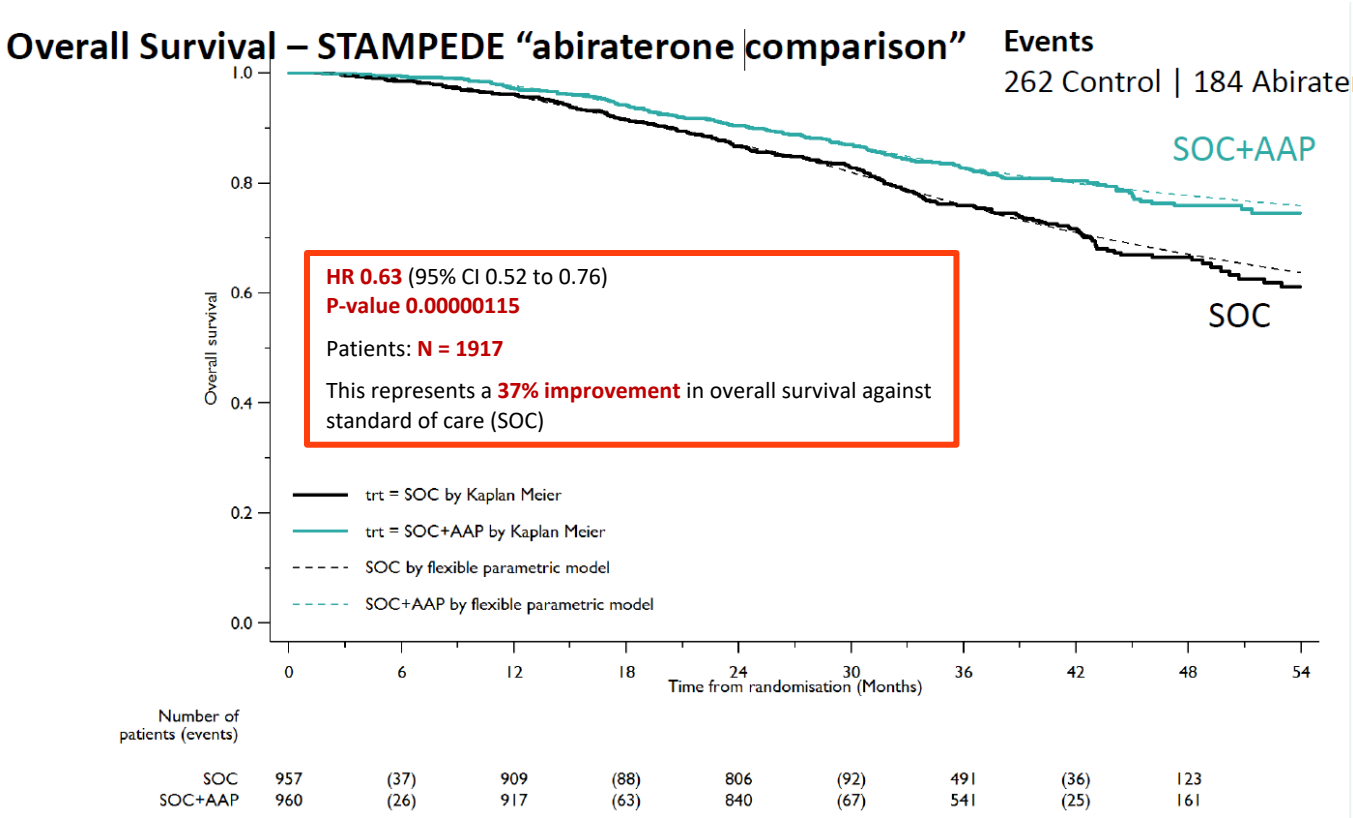
STAMPEDE Trial: Abiraterone and Prednisolone



www.clinicaltrials.gov: **STAMPEDE** (NCT00268476)

James ND et al. N Engl J Med 2017; 377:338-351

STAMPEDE: OS Benefit with Upfront Abiraterone

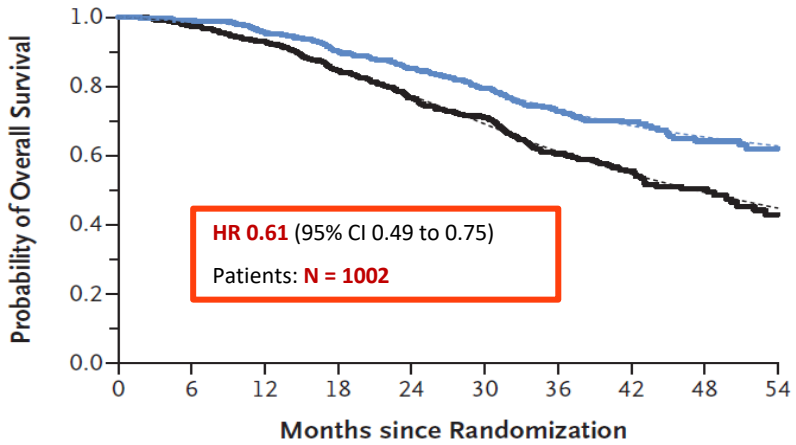


http://www.stampedetrial.org/87548/87552/ASCO_abiraterone_comparison_results

James ND et al. N Engl J Med 2017; 377:338-351

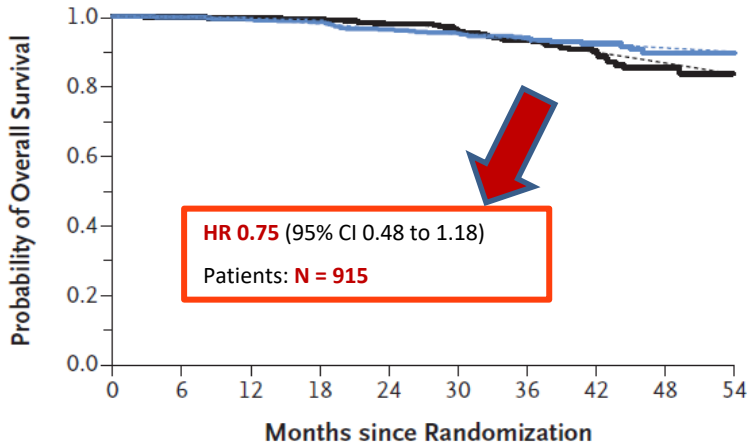
STAMPEDE Trial with Abiraterone: OS in M1 and M0 Subsets

C Overall Survival in Patients with Metastatic Disease



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

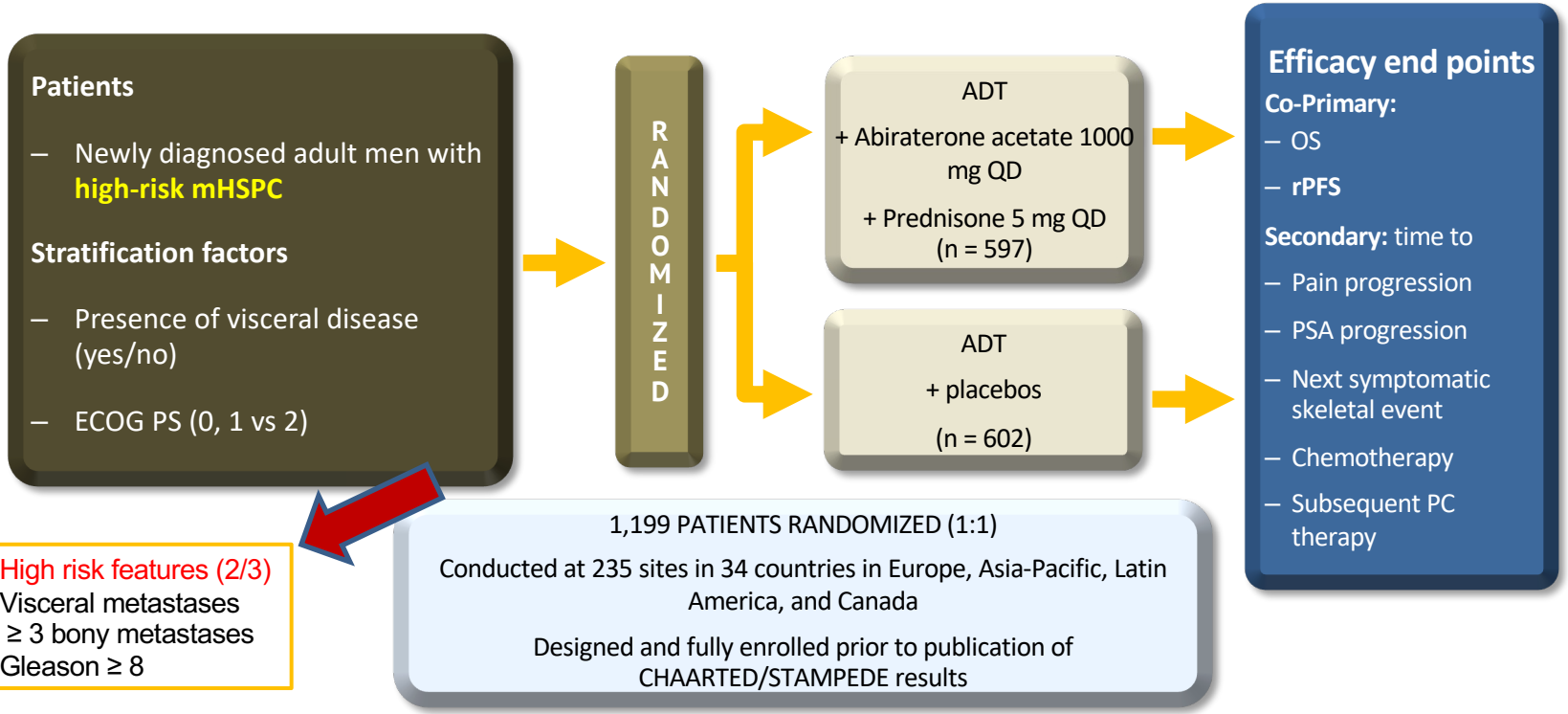
E Overall Survival in Patients with Nonmetastatic Disease



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

James ND et al. N Engl J Med 2017; 377:338-351

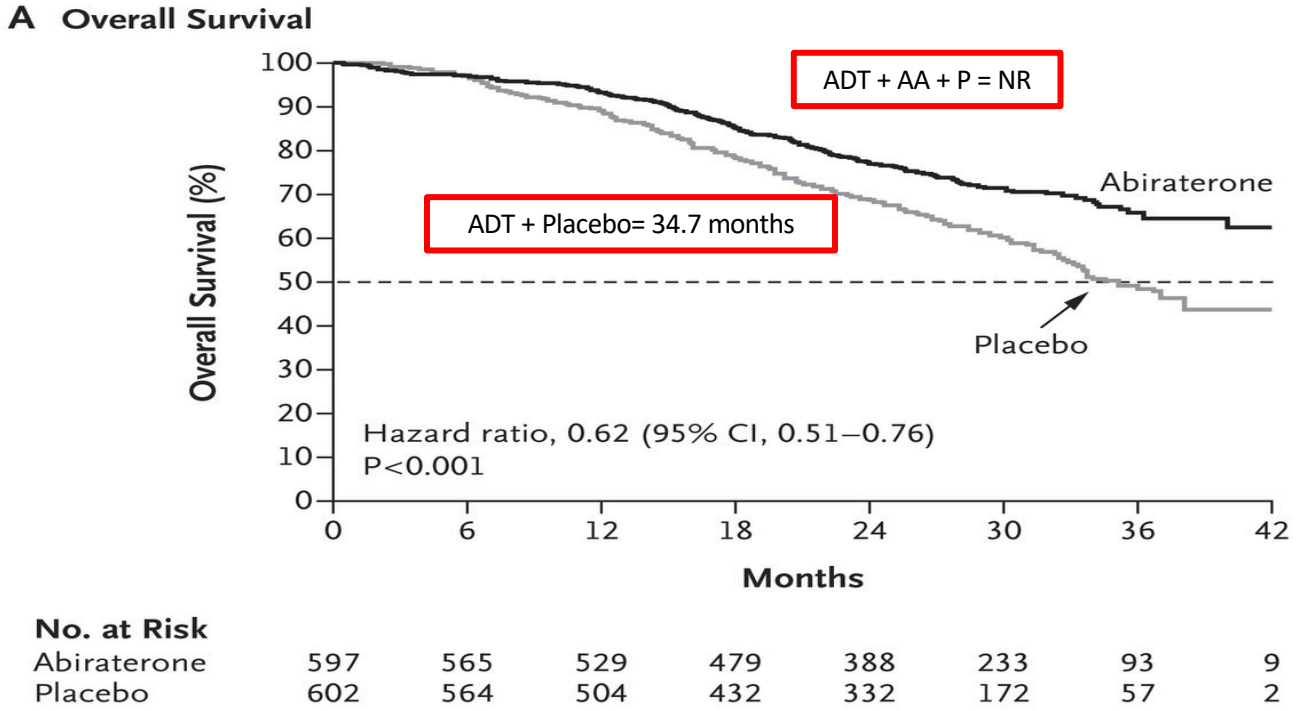
LATITUDE: Abiraterone and Prednisone



www.clinicaltrials.gov

Fizazi, K et al. *N Engl J Med* 2017; 377:352-360.

LATITUDE Trial: Survival Benefit



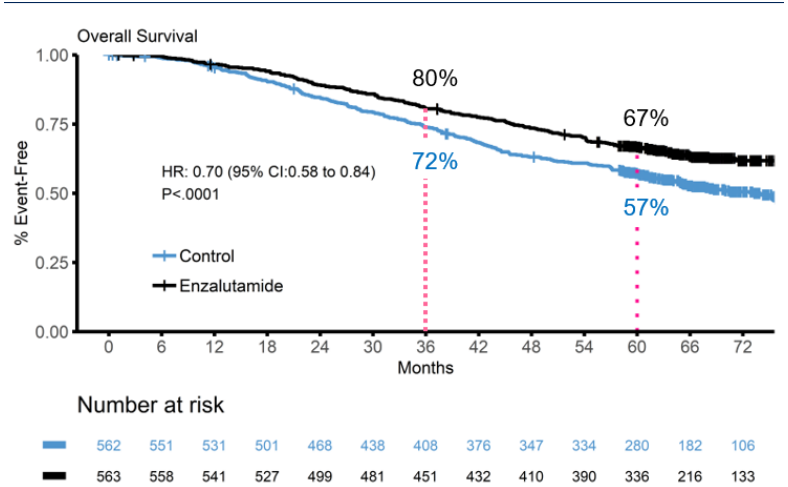
Fizazi, K et al. *N Engl J Med* 2017; 377:352-360.

ENZAMET study schema

- Prior to randomization testosterone suppression up to 12 weeks, and up to 2 cycles of docetaxel, were allowed.
- Intermittent testosterone suppression and cyproterone were not allowed
- NSAA: bicalutamide; nilutamide; flutamide
- *High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column)
- **Adult Co-morbidity Evaluation-27

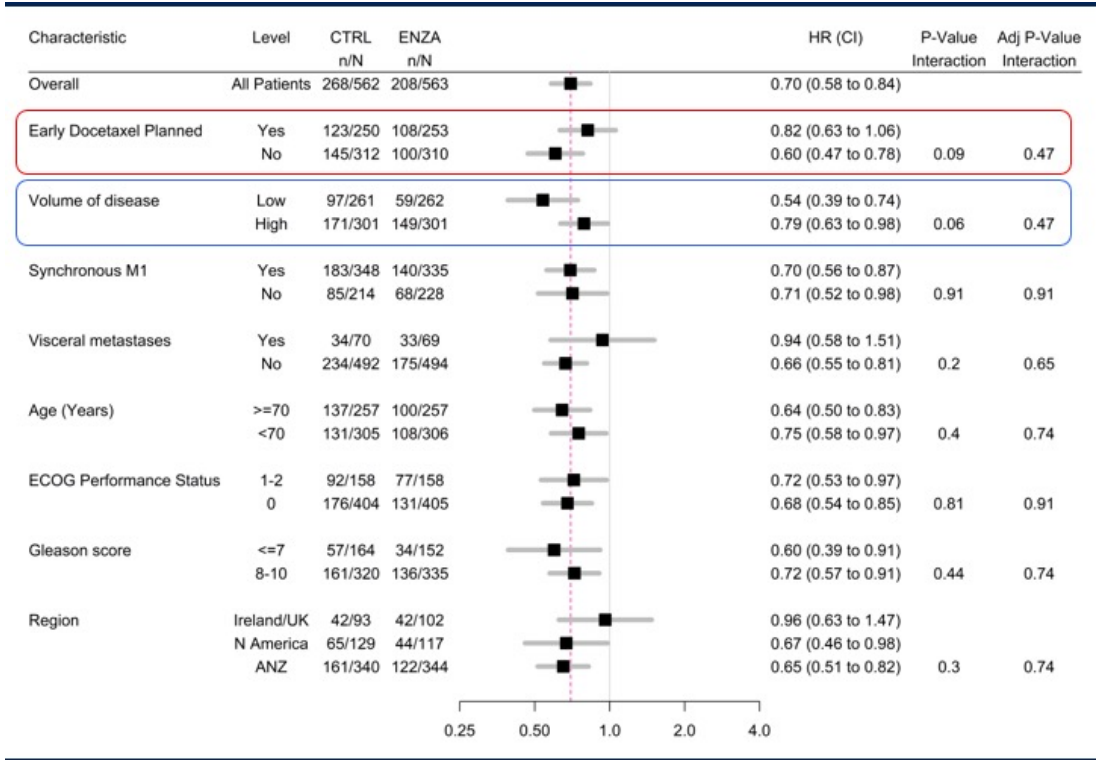
Davis, ASCO 2022

Updated OS results from ENZAMET (ASCO 22)



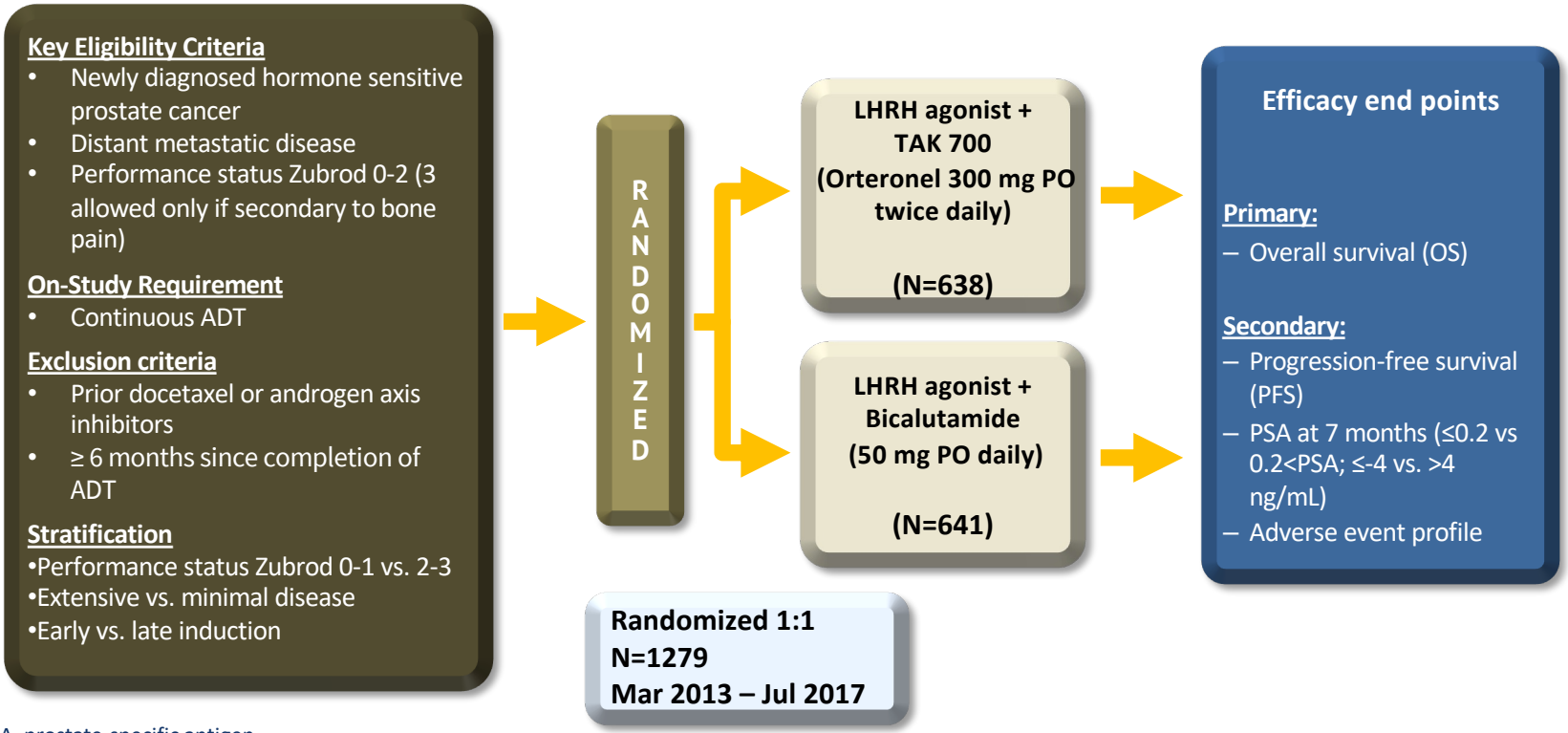
Median OS:

Control (NSAA): 73.2 mo (64.7 - NR)
Enzalutamide: NR (NR - NR)



Davis, ASCO 2022

SWOG S1216: A phase III randomized trial comparing androgen deprivation therapy (ADT) plus TAK-700 with ADT plus bicalutamide in patients (pts) with newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC)

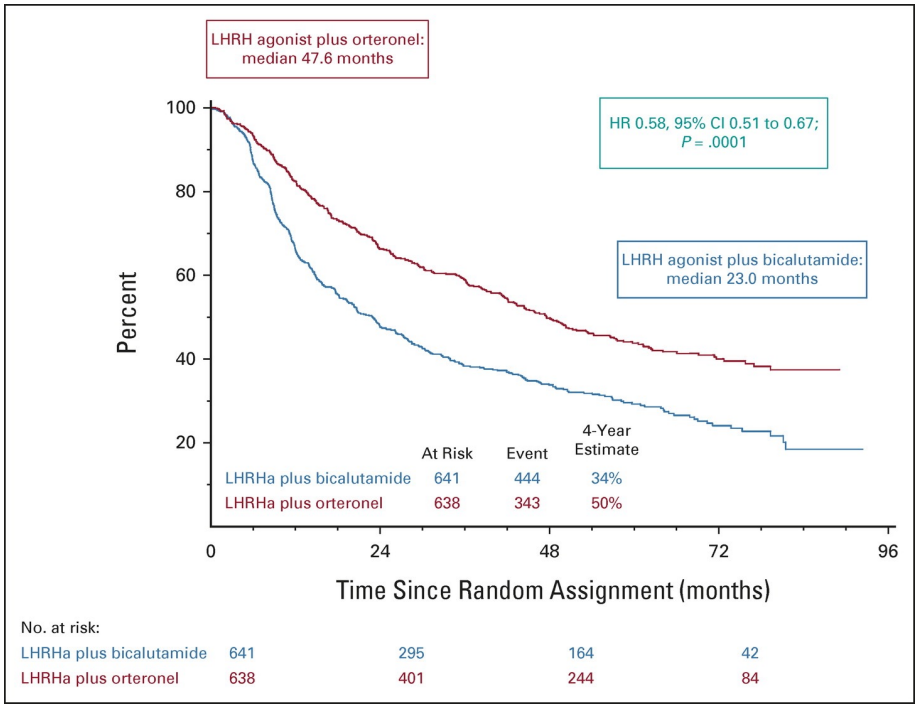


PSA, prostate-specific antigen.

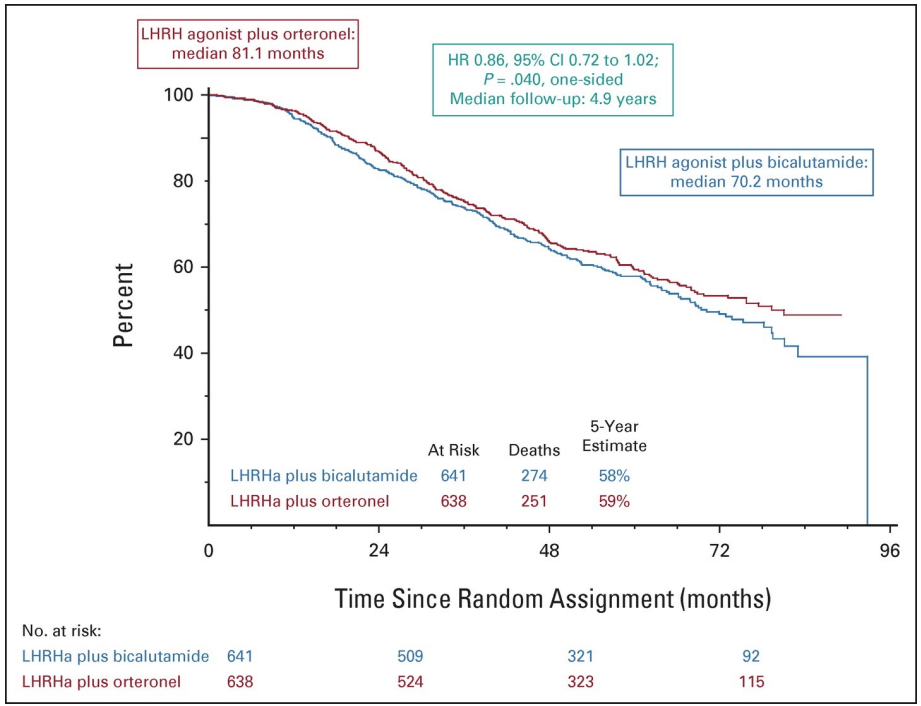
www.ClinicalTrials.gov (NCT01809691)

Agarwal, JCO 2022

SWOG S1216: ADT plus TAK-700 vs ADT plus bicalutamide in metastatic hormone-sensitive prostate cancer (mHSPC)



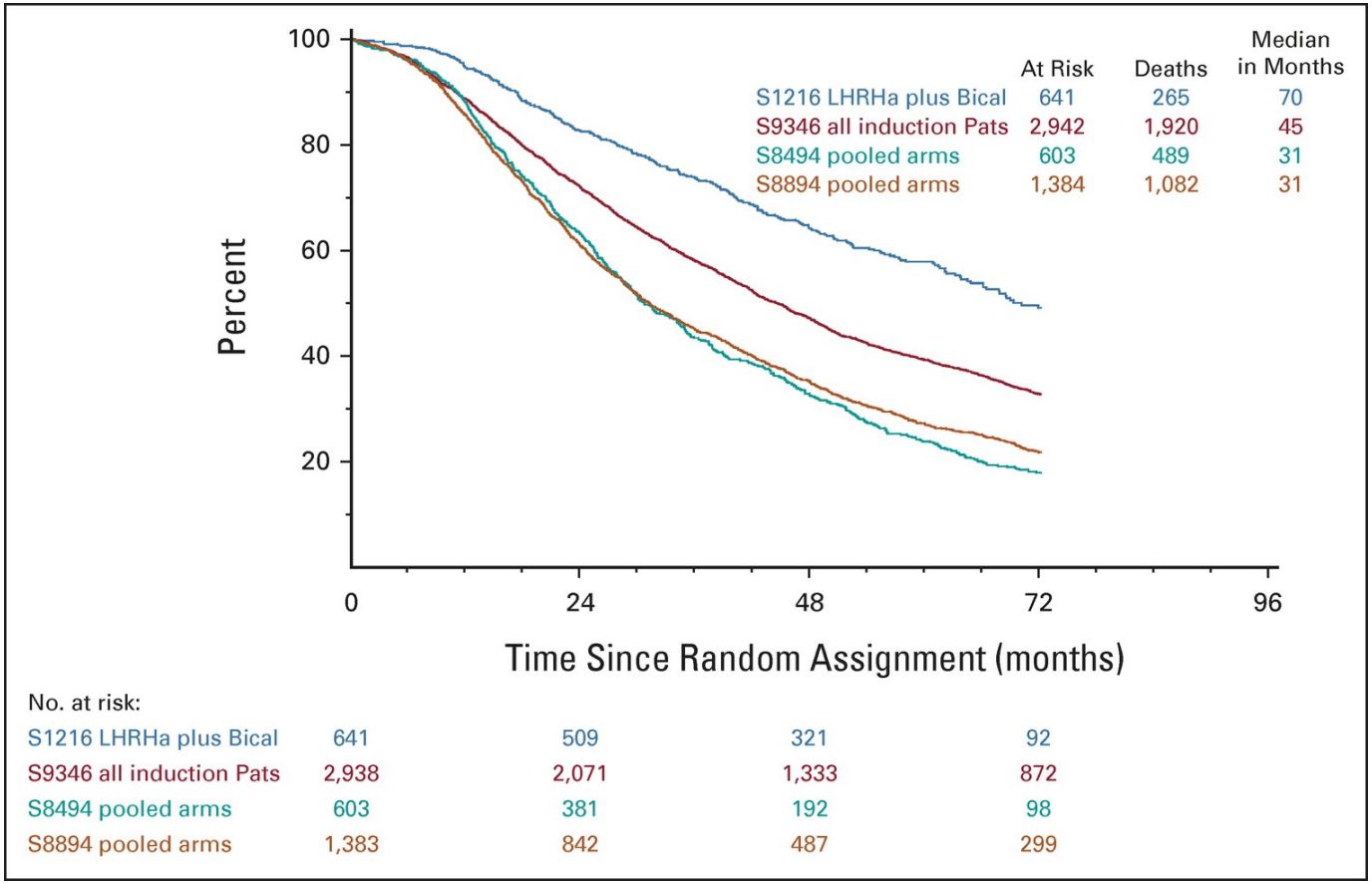
PFS



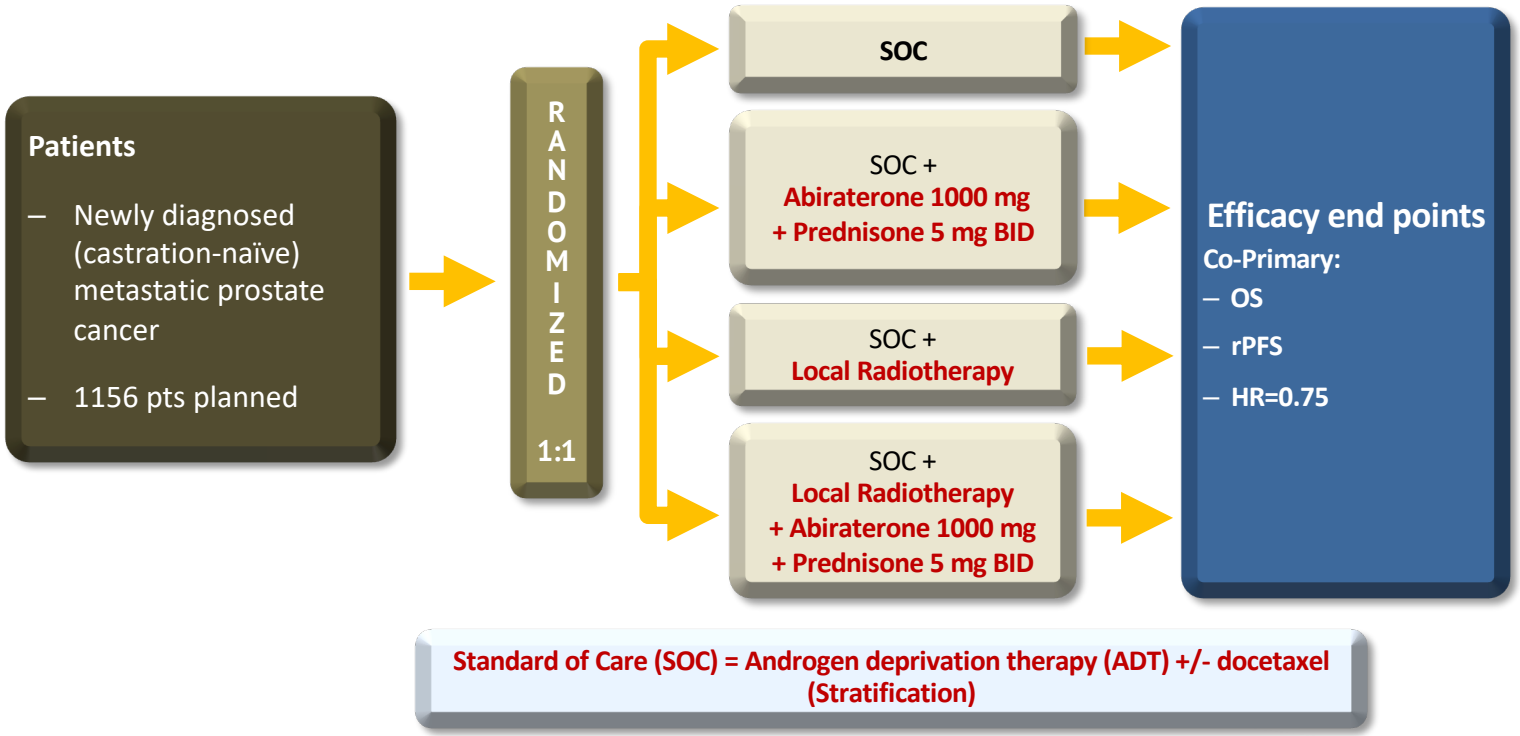
OS

Agarwal, JCO 2022

Control arm in S1216 outperformed historical OS benchmarks likely due to highly active next-line therapy



PEACE-1 Randomized Phase 3 Trial



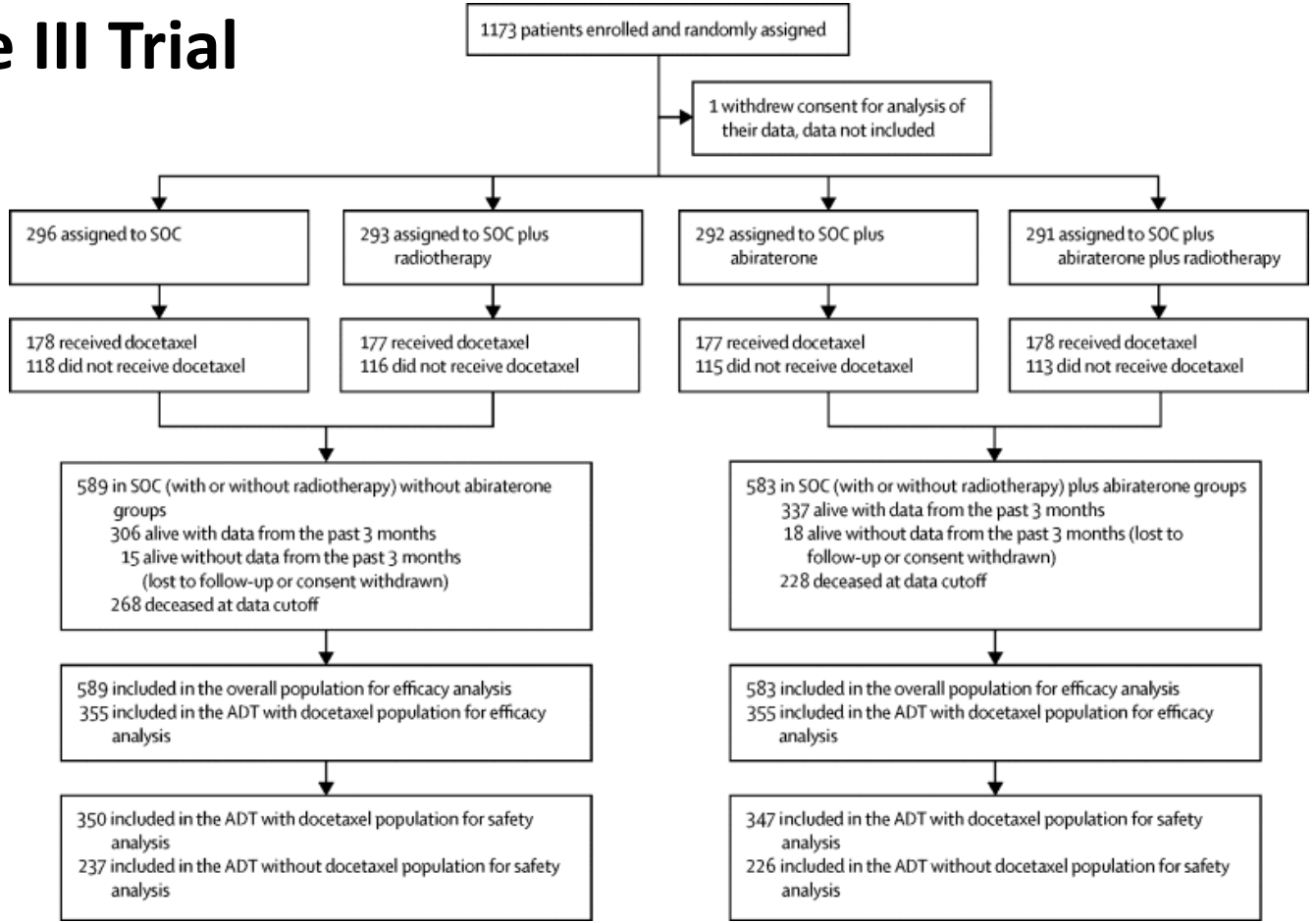
Fizazi, Lancet 2022

PEACE 1 Phase III Trial

Randomization
(2X2 Factorial: RT, Abi, RT+ Abi, SOC)

Docetaxel use

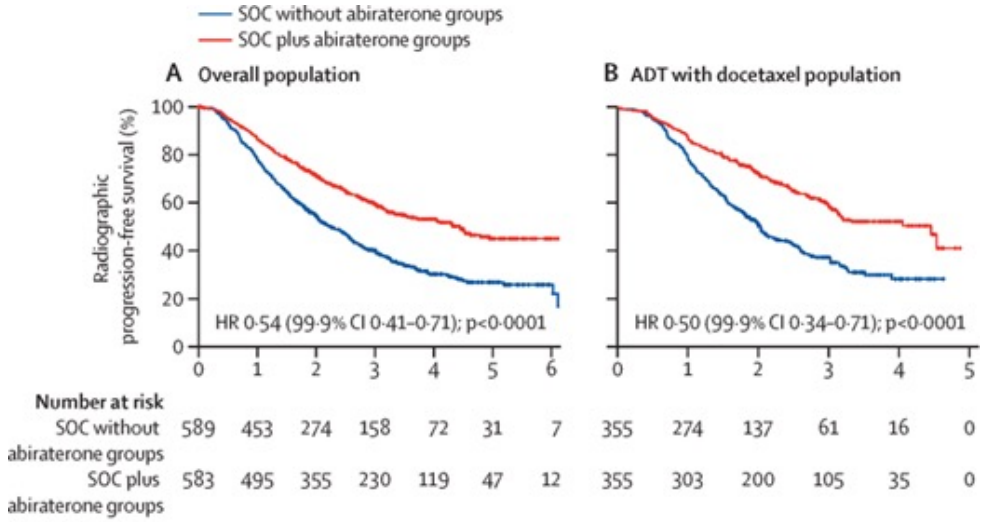
No Abi vs. Abi



Fizazi, Lancet 2022

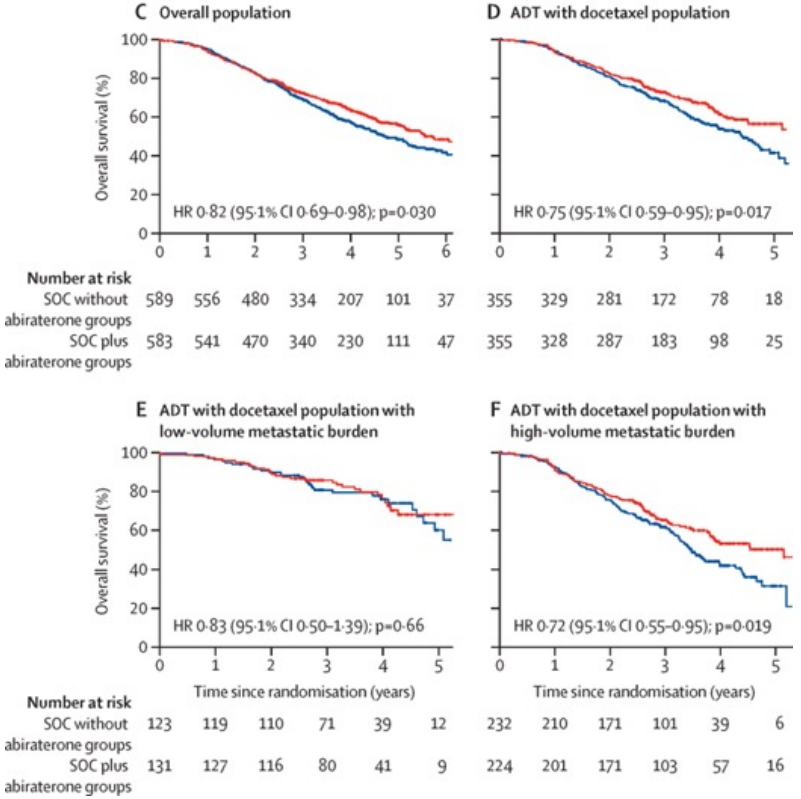
PEACE 1 Phase III Trial

Radiographic PFS



"Combining androgen deprivation therapy, docetaxel, and abiraterone in de novo metastatic castration-sensitive prostate cancer improved overall survival and radiographic progression-free survival with a modest increase in toxicity, mostly hypertension."

Overall Survival

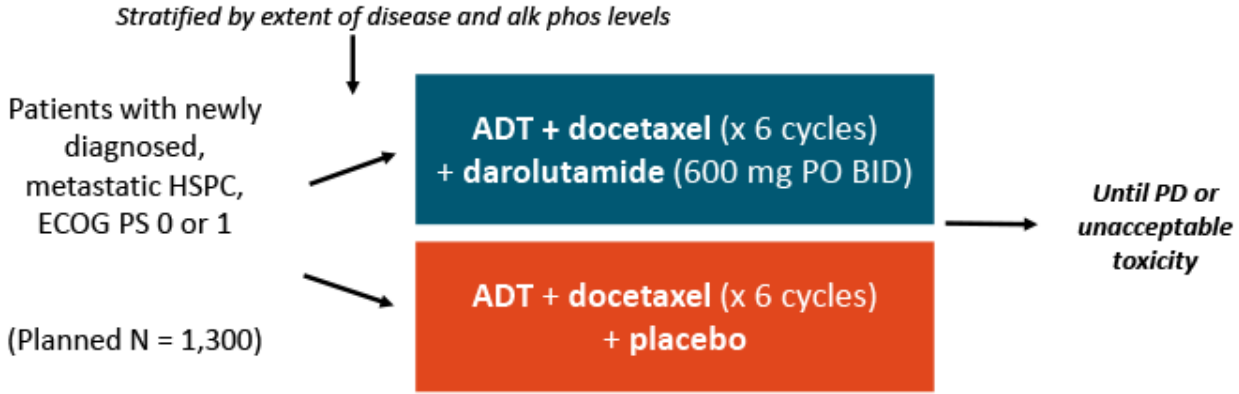


Low vs high volume disease

Fizazi, Lancet 2022

ARASENS Phase 3 Trial: Darolutamide in mHSPC

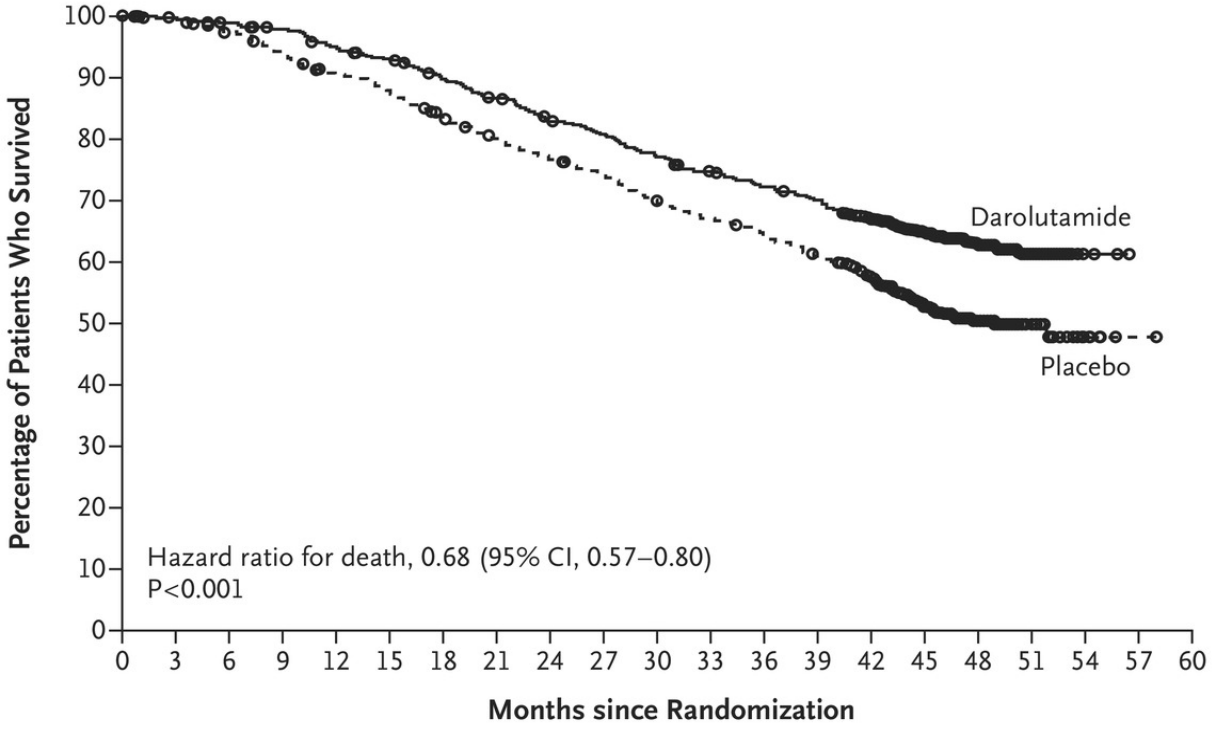
- Randomized, double-blind, placebo controlled, international trial > 300 sites in 23 countries



- Primary endpoint: OS
- Secondary endpoints: Time to CRPC, time to initiation of subsequent anticancer therapy, SSE-free survival, time to first SSE, time to first opioid use, time to pain progression, and time to worsening of physical symptoms
- Anticipated primary completion date: June 2021

NCT02799602.

ARASENS Phase III: ADT + Docetaxel +/- Darolutamide



	Median Survival (95% CI) *mo*
Darolutamide	NE
Placebo	48.9 (44.4–NE)

No. at Risk

Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

Smith, NEJM 2021

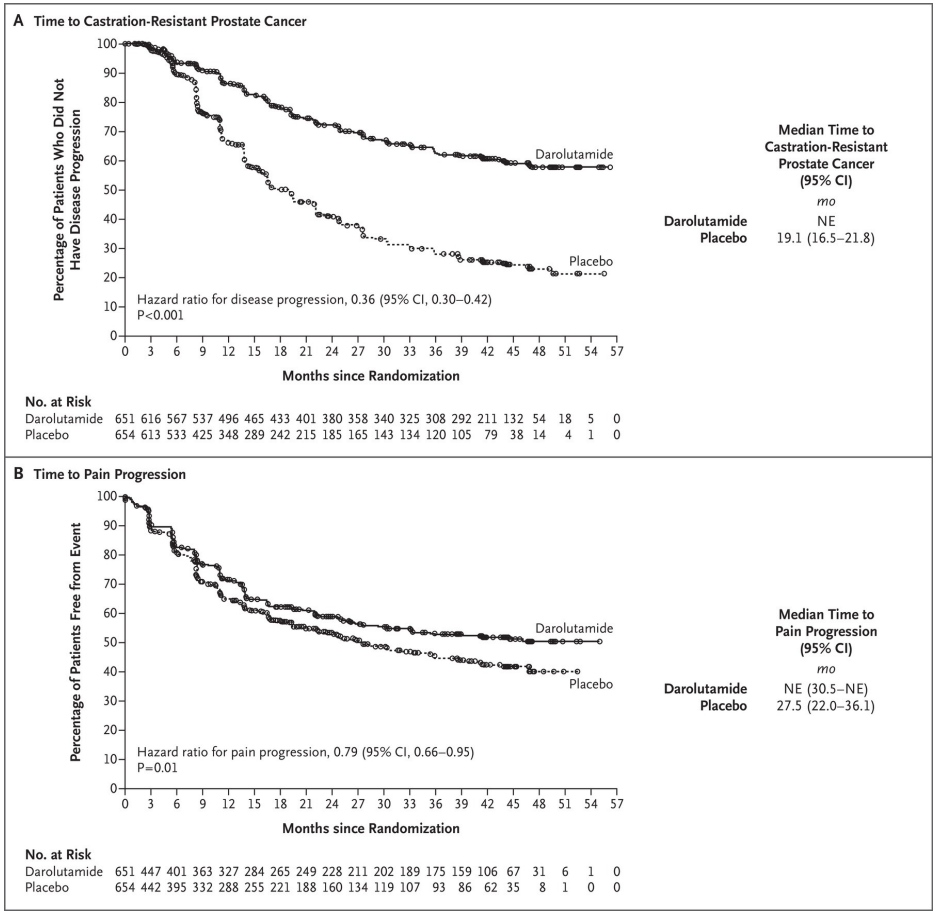


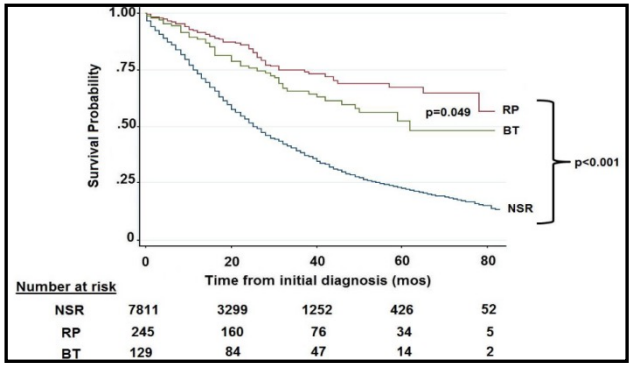
Table 3. Adverse Events.*

Event	Darolutamide–ADT–Docetaxel (N=652)†	Placebo–ADT–Docetaxel (N=650)†
	number of patients (percent)	
Any adverse event	649 (99.5)	643 (98.9)
Worst grade		
Grade 1	28 (4.3)	35 (5.4)
Grade 2	162 (24.8)	169 (26.0)
Grade 3	248 (38.0)	232 (35.7)
Grade 4	183 (28.1)	181 (27.8)
Grade 5	27 (4.1)	26 (4.0)
Serious adverse event	292 (44.8)	275 (42.3)
Adverse event leading to permanent discontinuation of trial agent		
Darolutamide or placebo	88 (13.5)	69 (10.6)
Docetaxel	52 (8.0)	67 (10.3)
Selected grade 3 or 4 adverse events‡		
Neutropenia§	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased ALT level	18 (2.8)	11 (1.7)
Increased AST level	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)

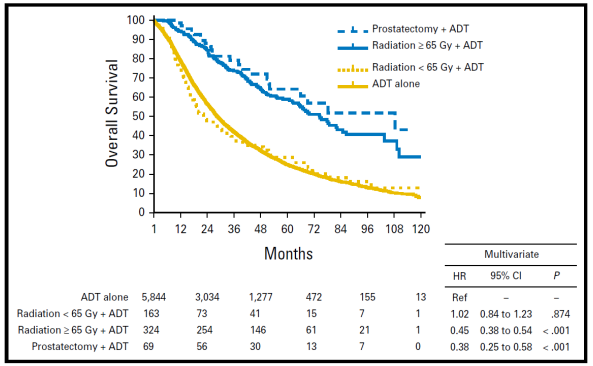
* ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† Three patients who underwent randomization never received the assigned trial treatment; all three patients were in the placebo group. One patient who was assigned to the placebo group but received darolutamide was included in the darolutamide group of the safety analysis set.
‡ In the column of data for patients who received darolutamide, ADT, and docetaxel, listed are all grade 3 or 4 events that occurred in at least 2% of the patients.
§ The neutropenia category includes the preferred terms of leukopenia, neutropenia, decreased neutrophil count, and decreased white-cell count.

Smith, NEJM 2021

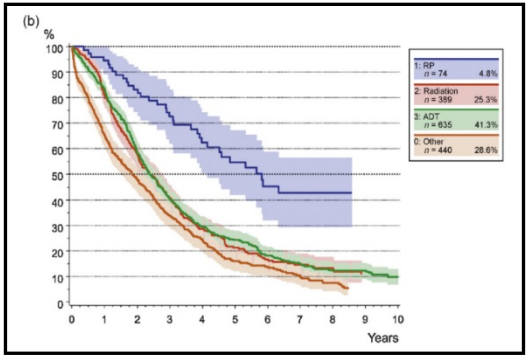
Control of Primary Prostate Linked to Longer Survival in Men with Metastatic Prostate Cancer



SEER - Culp et al Eur. Urol, 2014 Jun;65 (6):1058

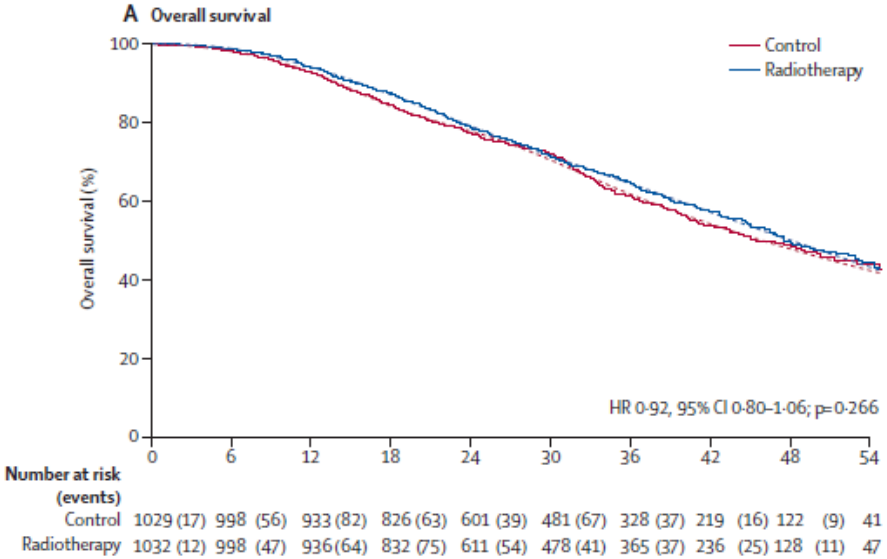


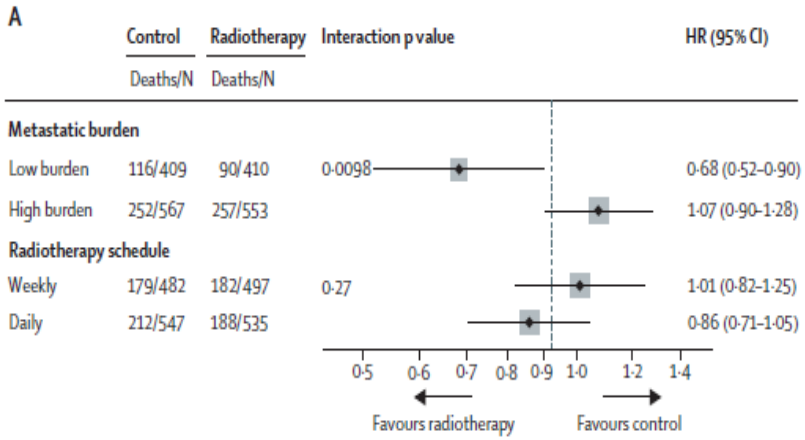
National Cancer Database - Rusthoven et al JCO, 2016 Aug 34; 2835-42



Munich Cancer Registry - Engel et al Eur Urol, 2014 Sep;66(3):602

STAMPEDE: Radiation to the prostate primary



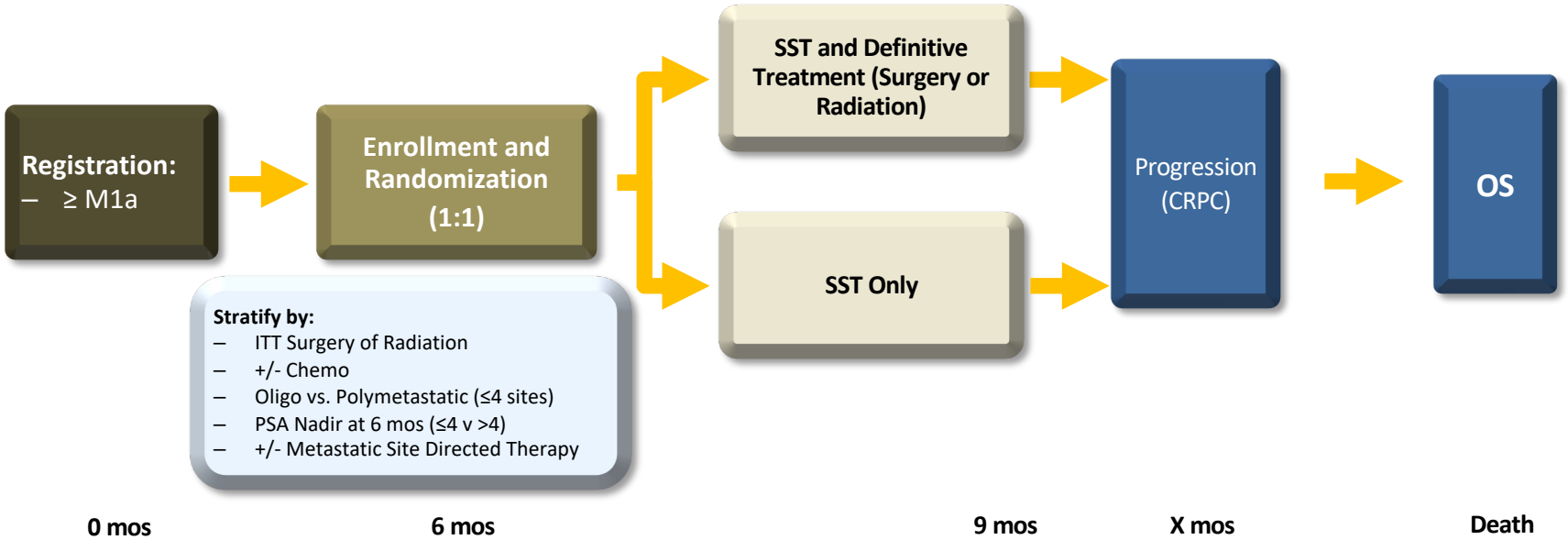


"Radiotherapy to the prostate did not improve overall survival for unselected patients with newly diagnosed metastatic prostate cancer."

However, OS benefit was seen in the low-volume subset

Parker, Lancet 2018

SWOG 1802 – Randomized Phase III Trial of Standard Systemic Therapy (SST) vs. SST Plus Definitive Treatment of the Primary Tumor in mHSPC



PI: Brian Chapin, MD

Conclusions

- Intensified ADT is standard of care for mHSPC
  - Low volume M1 disease: ADT plus abiraterone, enzalutamide, or apalutamide
  - High volume M1 disease: ADT plus docetaxel, abiraterone, enzalutamide, apalutamide, docetaxel + abi, or docetaxel + darolutamide
- No data for adding abiraterone or docetaxel many months later for a patient already on ADT or adding abiraterone after previously completing six cycles of docetaxel
- Role of Radium 223 or ADCs (Lu-177 PSMA) in HSPC remains to be defined
- No recommendation on sequencing until biomarkers or prospective data are available
- Accrual to clinical trials remains a high priority