

Integration of Treatment Options for Metastatic Castrate Resistant Prostate Cancer (mCRPC)- 2013

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Castrate Resistant Prostate Cancer

- Prior to the last 5-10 years it was common to hear the terms “hormone refractory prostate cancer” or “androgen independent prostate cancer” for disease that progressed after orchiectomy or while on LHRH agonist therapy
- We now know that androgen receptor signaling remains the primary driver of cell growth in this setting in 95% or more of cases
- “Castrate Sensitive” and “Castrate Resistant” are now the more accurate terms, as what we are describing is only disease which regresses with elimination of gonadal androgen, or progresses in the face of elimination of these same testicular androgens

Improving Survival in mCRPC

- Prior to 2004, no agent had demonstrated the ability to improve survival in patients with mCRPC.
- Estramustine was available since 1980 and Mitoxantrone/Prednisone was approved in 1996 on the basis of better pain palliation vs. prednisone alone, with no survival benefit
- Starting in 2004 we have 5 agents FDA approved, and another in expedited review, that have shown survival benefit in phase III clinical trials

Agents that Improve Survival

FDA Approvals

Docetaxel(**D**) q 3 weeks with prednisone(**P**)- in 2004

Sipuleucel-T(**Sip-T**)-2010

Cabazitaxel(**C**) with prednsione-2010

Abiraterone acetate(**AA**) with prednisone-2011

Enzalutamide(**E**)-2012

Radium 223(**Ra-223**)-2013?

Docetaxel(D) and Prednisone(P)

- **D** 75 mg/m² q 3 w with **P** 5 mg bid was tested vs. **D** q w 5/6 weeks with **P** bid vs. Mitoxantrone(**M**) q 3 weeks with **P** bid. The trial was a mix of patients with and without symptoms(i.e. pain) in this TAX-327 trial
- Only the 3 week regimen of **D/P** showed a survival benefit vs **M/P**
- **D/P** in the q 3 week regimen was approved by the FDA in 2004 and became the standard of care for metastatic CRPC

Sipuleucel-T(Sip-T)

- **Sip-T** was tested vs. Control in patients without cancer related pain requiring narcotics, with overall survival as primary endpoint. About 15% of the patients enrolled had prior treatment with docetaxel
- There was no difference in time to progression, and at progression control patients could choose to receive 3 infusions of autologous cellular immunotherapy product prepared from cells frozen at their initial leukaphereses
- **Sip-T** was approved by the FDA in 2010 on the basis of survival benefit vs. control in this trial (IMPACT), and a previous trial (9901) showing identical results
- The FDA label is for asymptomatic or minimally symptomatic patients, and that definition means only that the patient is not taking any narcotics for cancer related pain. Pre or post docetaxel is not specified in the label

Kantoff, PW, et al, NEJM 2010;363:411-422

Cabazitaxel(C) and Prednisone(P)

- In the TROPIC trial, **C/P** was tested vs **M/P** in patients with mCRPC treated prior with at least one chemotherapy regimen containing docetaxel
- The primary endpoint of overall survival was met
- The FDA approved **C/P** for treatment of mCRPC progressing after prior treatment with **D/P** in 2010. There is no mention of symptoms in the FDA label.

Abiraterone Acetate with Prednisone

- In the Cougar-301 trial, abiraterone acetate (**AA**) with **P**, both oral daily, was tested vs. placebo and **P** in patients with mCRPC progressing after prior docetaxel
- This was a mixture of asymptomatic and symptomatic patients
- The primary endpoint of overall survival was met and **AA** with **P** was approved in 2011 for patients progressing after prior treatment with docetaxel

AA with P

- A second phase III trial, Cougar -302 tested **AA** and **P** vs. placebo and **P** in patients with mCRPC who had not received prior chemotherapy.
- Patients could not be taking narcotics for cancer related pain, i.e. were asymptomatic or minimally symptomatic
- The primary endpoint of time to radiographic progression was met and there was a very strong trend toward improvement in overall survival
- The FDA expanded the label of **AA** at the end of 2012 to include all patients with mCRPC without any mention of symptoms or prior chemotherapy

Enzalutamide (E)

- **E** oral daily was tested in the AFFIRM trial vs. placebo in patients with mCRPC with disease progression after prior treatment with **D**
- This trial contained a mixture of asymptomatic and symptomatic patients
- The primary endpoint of overall survival was met, and the FDA approved **E** for the treatment of mCRPC in patients who have previously received **D**

Radium-223, or alphasaradin (Ra-223)

- **Ra-223** was tested in the ALSYMPCA trial vs. placebo in patients with mCRPC with bone dominant metastatic disease (no visceral metastases), and cancer related pain requiring narcotic analgesics
- Patients either had prior **D**, or were ineligible for, or refused prior **D**
- Trial results have demonstrated pain improvement, but also overall survival benefit.
- Currently, **Ra-223** is being evaluated under an expedited review by the FDA with anticipated decision prior to year end 2013

The Sequencing Dilemma

- Because of the 6 year gap between the approval of **D/P** and the newer agents, an artificial construct of “pre or post **D**” was created
 - This construct is almost totally related to the regulatory approval process, and has little to do with what might be the best medical reasons for sequence choices
- The other sequencing factor has been “asymptomatic/minimally symptomatic” vs. “symptomatic”
 - There are treatments such as **Sip-T**, which are more appropriate for earlier clinical states in which patients do not have symptoms from their prostate cancer. However, the absence of symptoms is not a contraindication for other treatments, e.g. chemotherapy

The Sequencing Dilemma

- Is there a best choice for sequence of therapy for the 5 approved agents with survival benefit in mCRPC?
- If there is a best sequence, how will **Ra-223** fit into the sequencing if FDA approved?
- How do clinical trials of new or existing agents fit in?

Assumptions for this Discussion

- Since we have little or no data on combination therapy, these new agents should be used in sequence individually.
- All patients are willing and medically eligible to receive all of these treatments
- Treatment sequence is suggested on the best medical choice, not the FDA label
- I do not believe that symptoms by themselves should dictate a certain therapy (e.g. chemotherapy only for patients with pain)
- All patients with bone metastases receive either zoledronic acid or denosumab. My personal preference is denosumab based on superiority vs. zoledronic acid in a large phase III trial
- I believe in the efficacy of all of these therapies, based on review of the clinical trial data, as well as extensive personal experience

Caveats and Opinions

- **We have no data managing patients with severe comorbidities such as end stage renal failure (dialysis), severe cardiomyopathy, Child-Pugh class C liver failure**
- **In real life some patients will refuse certain treatments, especially the dreaded word “chemotherapy”**
- **In my opinion, a physician who cares for a patient with CRPC, should be willing and able to use all the agents.**
- **When a phase III trial has demonstrated survival benefit, I do not understand unwillingness by a physician to use that treatment based on their perceptions of lack of “cost benefit” or “not believing the results”. Phase III data is Level 1 Evidence. A decision not to use a treatment needs to be made in discussion with an informed patient and family.**
- **Lack of experience is not a good reason for not using a new therapy with proven survival benefit**
- **None of my recommendations are based on “medical economics”. If cost is an issue, the patient should have the last word whenever possible**

Concepts I Believe About Cancer, Including mCRPC

- **Any treatment works better against a smaller rather than larger tumor burden, so treat early rather than later**
- **Waiting for symptoms to occur is a very bad idea, and in my opinion, is likely to adversely impact survival**
- **I never “assume the conclusion”**
- **Patients with mCRPC need to be monitored frequently and carefully**
 - **I see most patients every 3-6 weeks unless I am convinced that they are stable, then q 3 months**

Sequence-Choice Number 1

- Sip-T, for most but not all patients
- Patients with cancer related pain that requires narcotics are not candidates for immediate Sip-T
- Patients with a life expectancy of less than 12 months are not good candidates for ever receiving Sip-T

Rationale for Initial Sip-T

- **Sip-T appears to take at least 6 months to achieve clinical benefit**
 - Survival and time to pain progression curves separate at 6 months in IMPACT trial
- **Patients with the lowest disease burden are more likely to benefit from Sip-T**
 - Patients with lowest PSA at entry in IMPACT trial had the most survival benefit vs. control (HR=0.51), and median overall survival difference of 13 months
- **Delaying this therapy in a patient who is currently asymptomatic/minimally symptomatic may result in loss of opportunity due to the development of cancer related pain**

Rationale for Initial Sip-T, cont.

- Treatment can be completed in as little as 4 weeks
- Treatment continues to activate the patient's immune system after therapy is completed, presumably for the duration of their life
- Any treatment given after Sip-T is given with concurrently active Sip-T in the "background"
- The use of Sip-T does not preclude the use of any other treatment later
- There are no absolute contraindications-age, comorbidities, performance status, expected survival, even the presence of pain. These are all matters in which to use clinical judgment.

Using Sip-T later

- Patients with a single dominant bone lesion causing pain
 - I would consider local **RT** to that site followed by **Sip-T**
- Patients with multiple areas of pain-use another regimen first (**D/P, AA/P, E**)
 - With resolution of pain and stabilization of disease, **Sip-T** could be the next therapy

Later Sip-T in Asymptomatic Patients

- Patients with rapidly proliferating disease, i.e. PSA-DT of 2 months or less, or with rapid appearance of new lesions or growth of soft tissue lesions
- My choice would be to treat with **D/P** first, and if disease responds well and is stable after 6-10 cycles, taper **P** rapidly and then use **Sip-T**

A patient case example

- **Dx 2009, PSA 87.5, 12/12 cores+, G1 9**
- **ADT and RT started, RT done 3/2010**
- **PSA nadir 0.08 7/2010**
- **10/2010 PSA 2.15 on ADT**
- **1/2011 PSA 13.15 on ADT, now has bone mets on NaFl PET, but no pain**
- **PSA doubling time 3 weeks**
- **2/2011 start D/P q 3 weeks**

A patient case example, cont.

- **6 cycles D/P, PSA nadir 0.03 7/2011**
- **P tapered, PSA stable**
- **9/2011 start and complete Provenge**
- **Continue leuprolide and denosumab**
- **12/2012 PSA 0.01**
- **1/2012 PSA less than 0.01**
- **Since then PSA remains undetectable (14 mos.)**
- **NaFI PET 3/2013 improved, but still one lesion with increased activity. Others sclerotic without activity.**

2. Target Androgen Receptor(AR)

- We now know that **AR** pathway continues to be the main driver of growth in mCRPC cells and we have two new agents to target the pathway
- So far, we can target this pathway by decreasing the ligands that activate **AR** when they bind, and by using an agent that binds **AR** and prevents normal ligand binding, **AR** activation, nuclear translocation, and DNA binding of the activated **AR** complex

Target AR

- **I would choose AR targeting before cytotoxic therapy in most patients because**
 - **Based on the Cougar trials, I think the AA responses are more frequent, deeper, and more durable in the prechemotherapy setting. My guess is that the same will be true with E once the PREVAIL trial is done.**
 - **Most patients prefer to delay chemotherapy**
 - **AA and E are well tolerated and less toxic than chemotherapy**

Targeting AR

- **AA**-diminishes **AR** ligand (androgens) synthesis in all tissues (testes, adrenals, and tumor tissue)
- **AA** blocks the 17-hydroxylase and 17-20 lyase enzymatic activity of CYP-17, and thus blocks androgen synthesis directly at the cellular level in any tissue

Targeting AR

- **E** is a selective **AR** antagonist, which binds **AR** with greater affinity than older “antiandrogens” such as bicalutamide, flutamide, nilutamide.
- **E** has yet to show any agonist activity
- **E** blocks translocation of activated **AR** to the nucleus and also blocks binding of activated **AR** to DNA

Sequencing AR Therapy

- **Combining AA and E-no data on efficacy or safety as yet, and cost would be high**
- **AA before E or vice versa-no data**
- **Hypothetical reasons for a sequence**
 - **Resistance to AA likely to be induction of enzymes that by pass CYP-17 and produce androgens by these “back door” pathways**
 - **Resistance to E likely to be mutations or new splice variants of AR that are constitutively active, or pathways that bypass AR entirely**

Sequencing AR Therapy

- Pending data from clinical trials, I use **AA** prior to **E**, and have seen good clinical activity of **E** after **AA**
- We need a trial of **AA** plus **E** vs. **AA** followed by **E** vs. **E** followed by **AA**, but the only trial I have heard about will look at **AA** plus **E** vs **AA** followed by **E**

After AR Targeting

- **Docetaxel/prednisone is the obvious choice**
 - **D/P has been equivalent to, or superior to every other docetaxel combination tested**
 - **Elderly men tolerate this treatment quite well**
 - **I usually treat 8-10 cycles, depending on when the PSA nadir occurs**
 - **After a “chemo vacation”, responders usually respond to another course of D/P**
 - **Chemotherapy is not just for symptomatic patients-waiting for pain compromises survival**

After Docetaxel/Prednisone

- Cabazitaxel/Prednisone(**C/P**)
- **C/P** has unequivocal activity post docetaxel, even in patients whose cancer is progressing while actually receiving **D/P**
- Toxicity is similar to, or less than **D/P** in my experience
- I always use peg-filgastrim on day 2

What about Alpharadin?

- **Alpharadin is Ra-223, an alpha particle emitter (2 protons, 2 neutrons)**
 - There is minimal bone marrow toxicity for alpha as opposed to beta emitters
 - The large alpha particle requires no shielding
- **It is primarily taken up by bone**
 - Ra is in the same column as Ca in the periodic table
 - Therefore, the target is the organ, not the cancer cell

Alpharadin Data

- In the ALSYMPCA trial Ra-223 showed a survival benefit and pain improvement vs. placebo
- Treatment was administered intravenously monthly for 6 months
- Patients had bone only or bone dominant disease and bone pain
- All had prior D/P unless unfit or had refused D/P

Where is Ra-223's place in mCRPC?

- **Bone only or bone dominant disease**
 - No visceral metastases
 - No bulky lymph node disease
 - Since there is survival benefit, patients without pain may be appropriate for therapy
- **Initially RA-223 will probably fit in best as salvage therapy after the other 5 agents**
- **Later, clinical trial data may lead to use earlier, either as a single agent or perhaps in combination with any of the other agents**

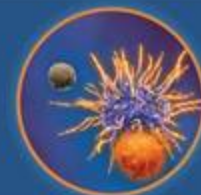
Clinical trials???

- In my opinion, it is always appropriate to sequence clinical trials into the therapy of eligible patients with prostate cancer
- These could be trials of new agents in late stage mCRPC, or trials of combinations of, or sequencing of existing agents

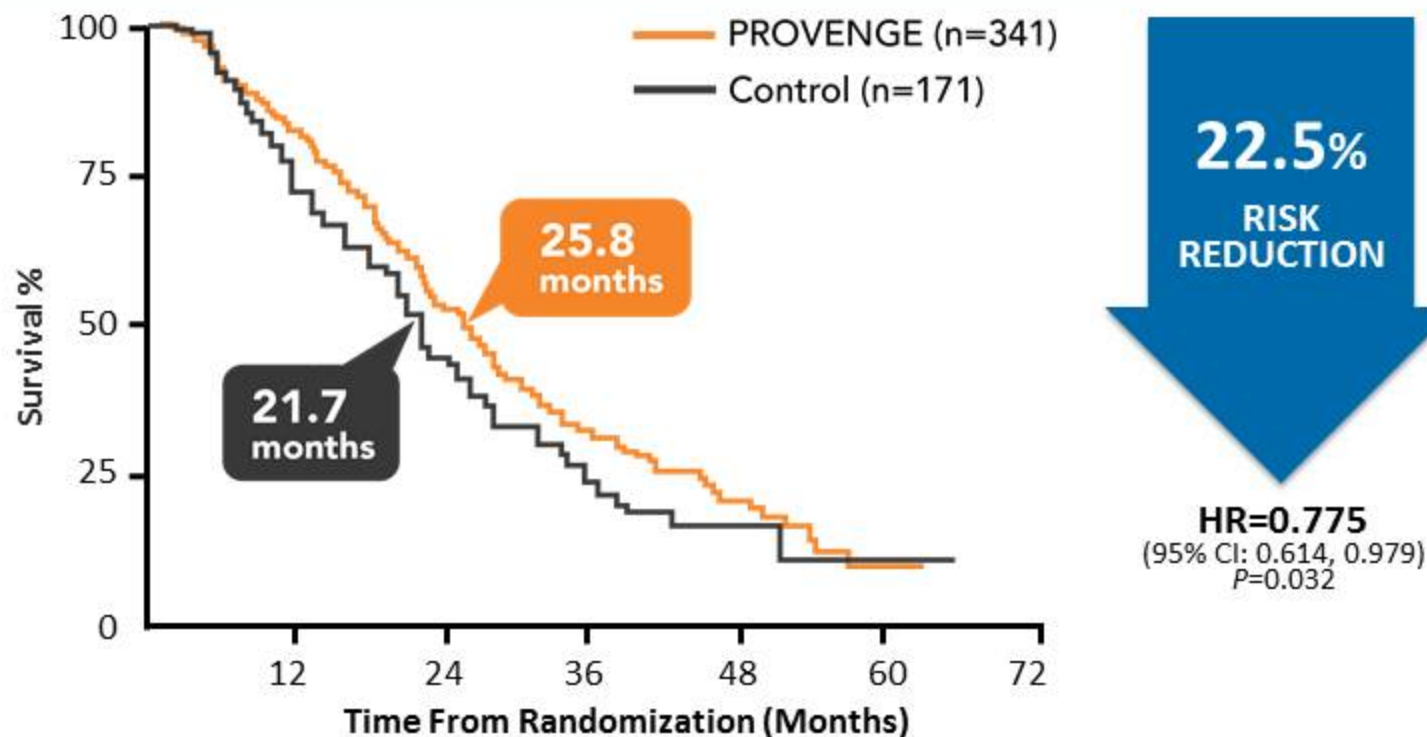
Summary

- We have 5, and soon 6, agents that improve survival in mCRPC-**USE THEM ALL !!!**
- For the typical patient my sequence of choice would be:
 - **Sip-T, AA/P, E, D/P, C/P, Ra-223**
- Exception, rapid disease proliferation
 - **D/P, Sip-T, AA/P, E, D/P, C/P, Ra-223**

PROVENGE (sipuleucel-T) Extends Median OS Beyond 2 Years



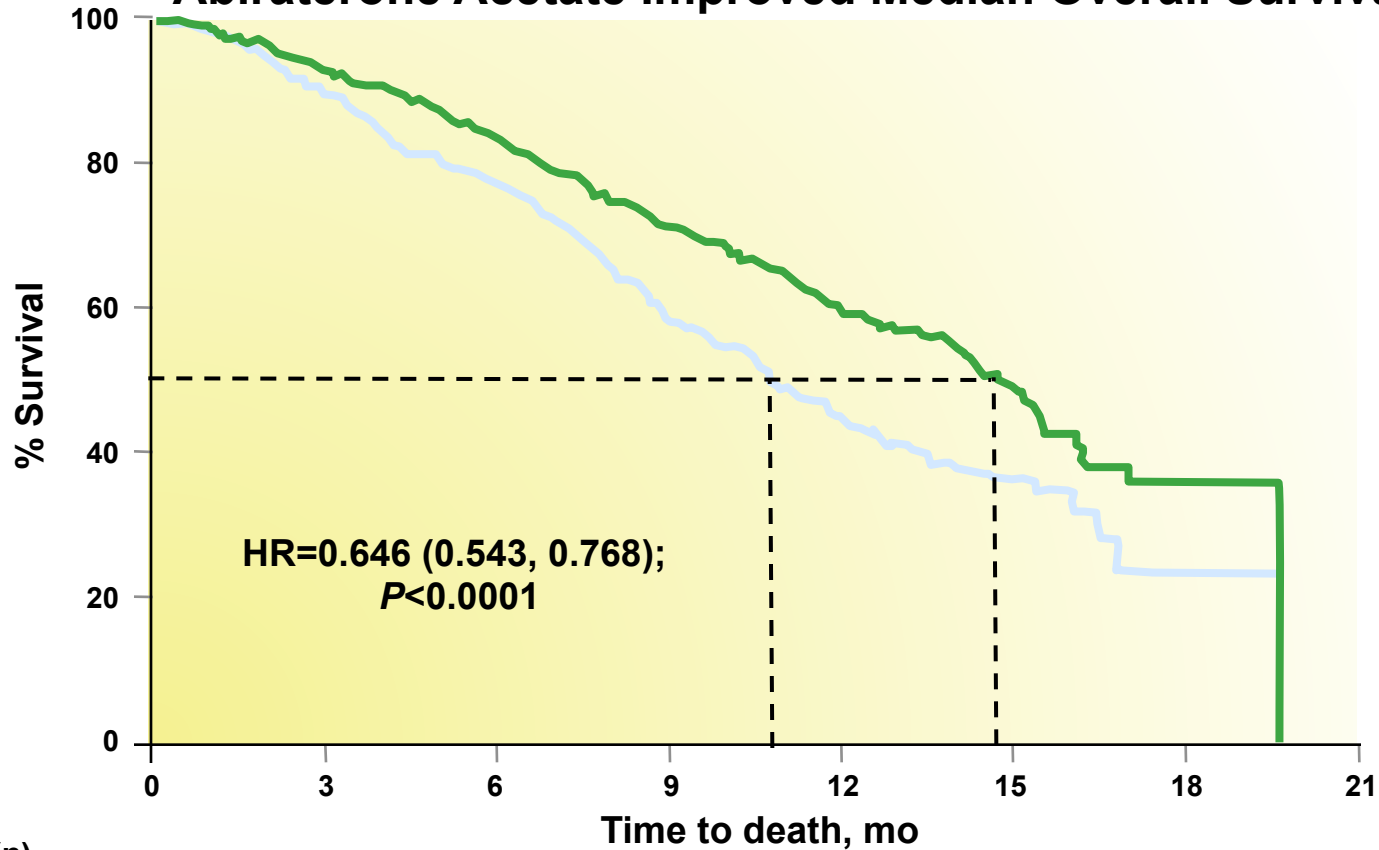
Overall Survival Benefit of PROVENGE



64% of patients in the control group crossed over to receive an investigational autologous immunotherapy made from cryopreserved cells

Cougar 301-Overall survival

Abiraterone Acetate Improved Median Overall Survival

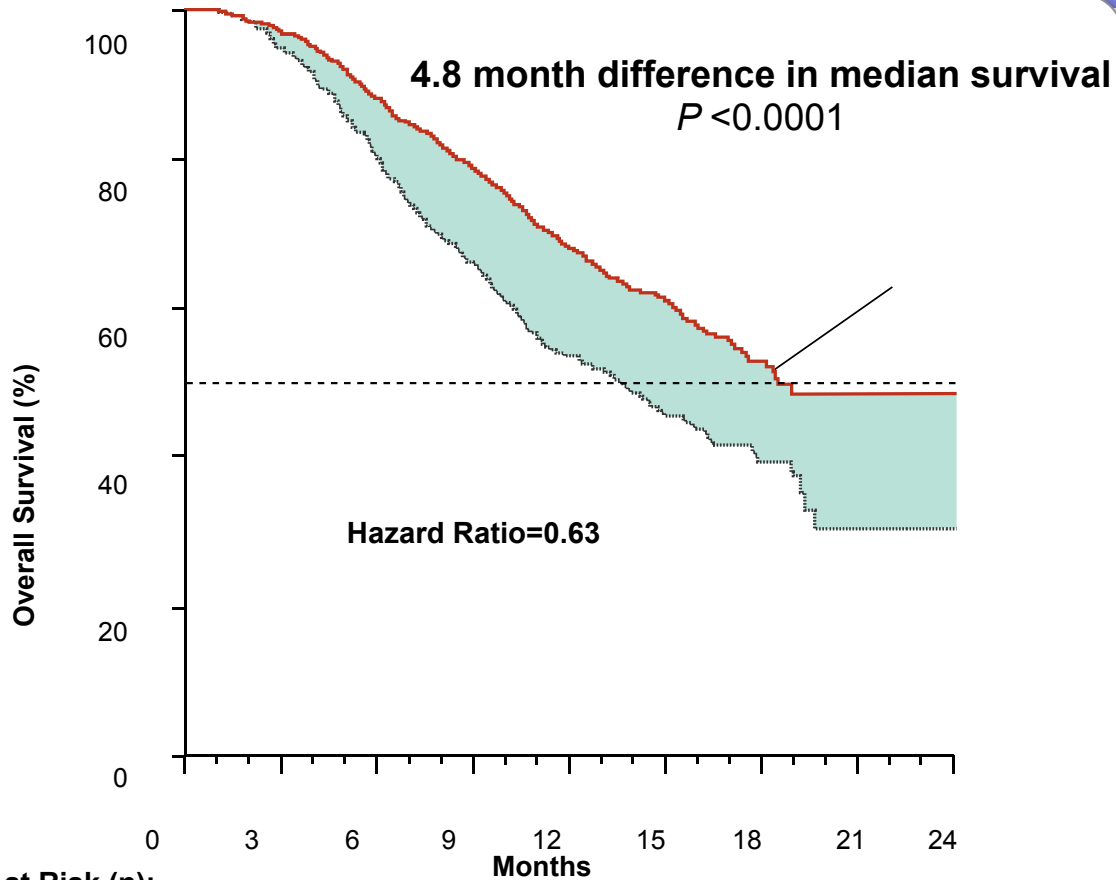


HR=0.646 (0.543, 0.768);
 $P < 0.0001$

Survivors (n)

| | | | | | | | | |
|---------------------|-----|-----|-----|-----|-----|----|---|---|
| Abiraterone acetate | 797 | 736 | 657 | 520 | 282 | 68 | 2 | 0 |
| Placebo | 398 | 355 | 306 | 210 | 105 | 30 | 3 | 0 |

AFFIRM Trial-Overall Survival



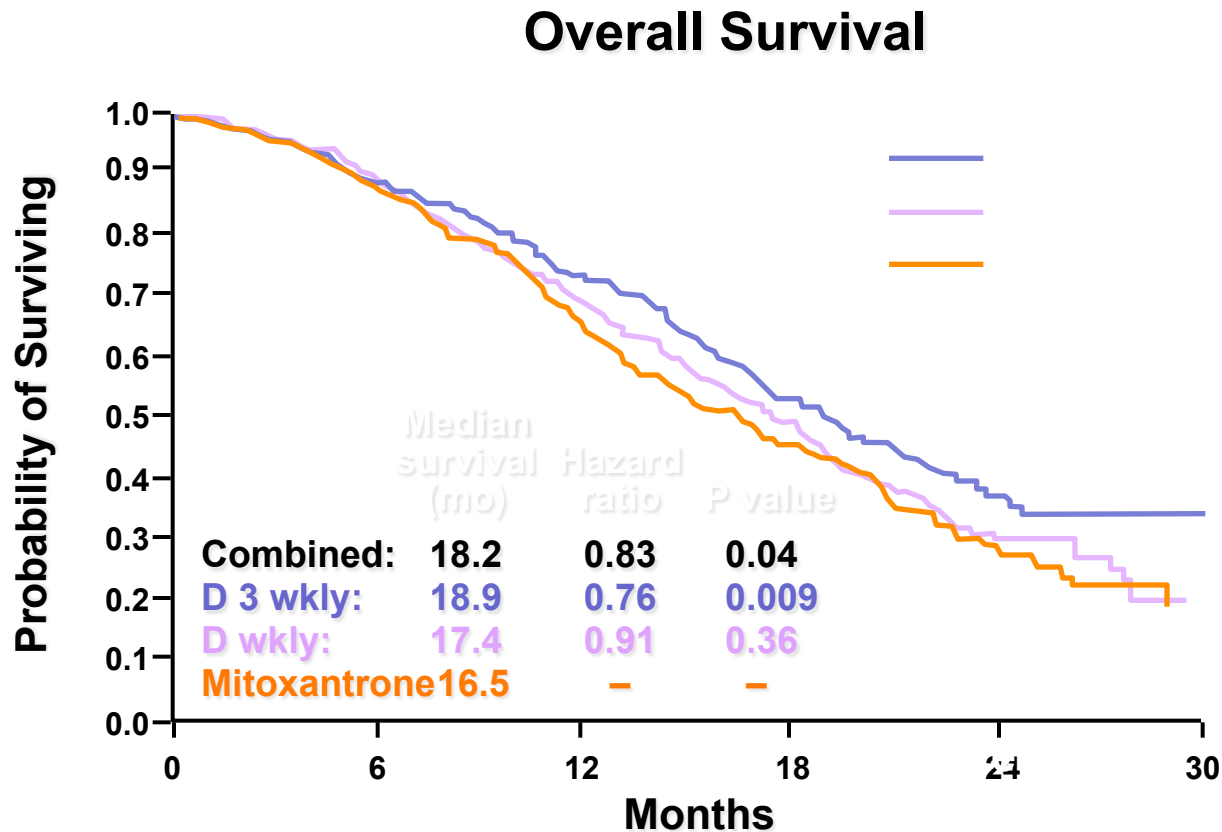
Enzalutamide demonstrated a statistically significant improvement in overall survival vs placebo

Patients at Risk (n):

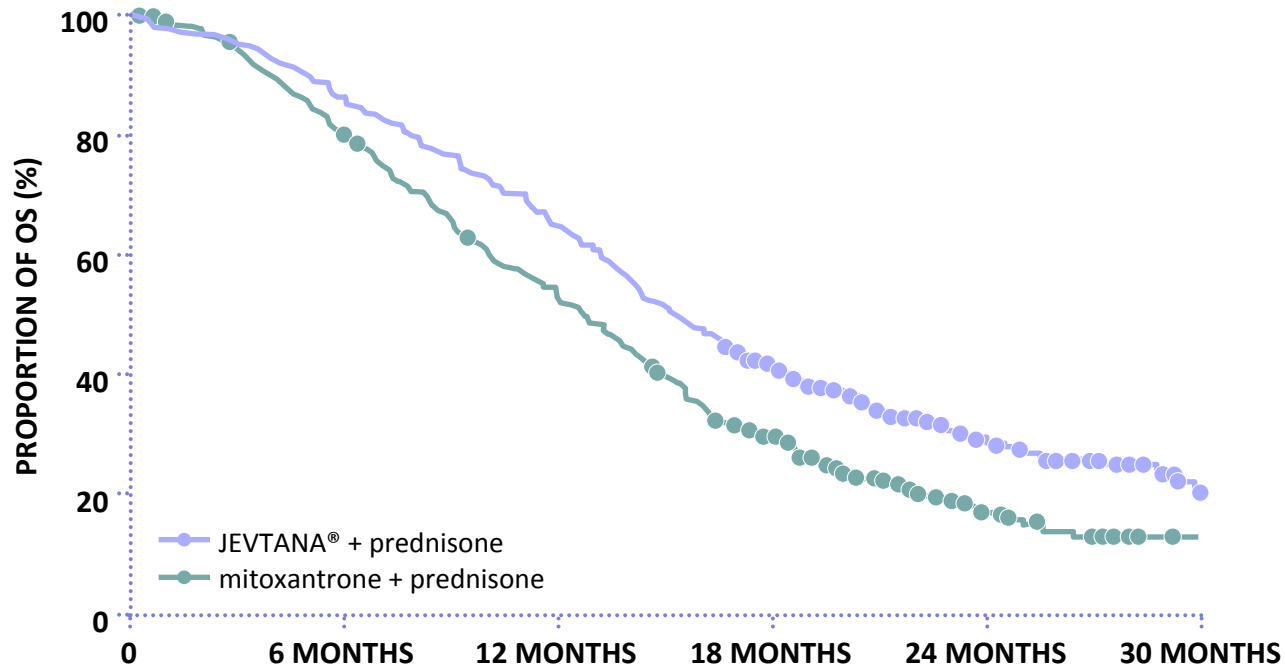
| Time (Months) | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 |
|---------------------|-----|-----|-----|-----|-----|-----|----|----|----|
| Placebo | 800 | 775 | 701 | 627 | 400 | 211 | 72 | 3 | 0 |
| Enzalutamide | 399 | 376 | 317 | 263 | 167 | 81 | 33 | 3 | 0 |

CI = confidence interval.
HR = hazard ratio.

TAX 327-Overall Survival



TROPIC Trial-Overall survival



- Median OS with cabazitaxel was 15.1 months compared to 12.7 months with mitoxantrone
- 30% reduced risk of death (HR=0.70) with cabazitaxel compared to mitoxantrone

deBono JS, et al, [Lancet](#) 2010;376(9747):1147-54.