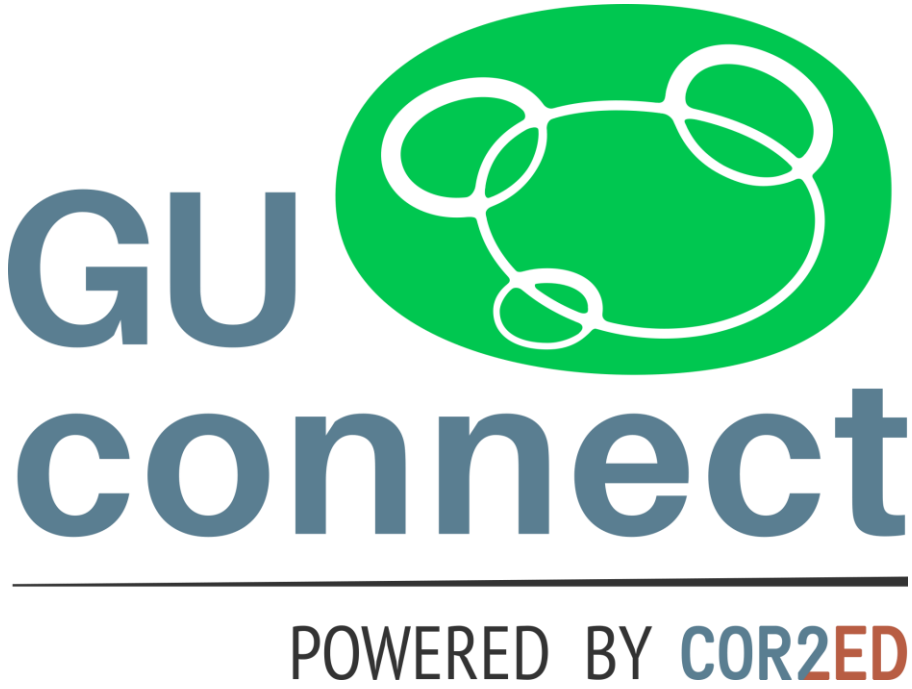
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# UPDATE ON RECENT CUTTING-EDGE TRIALS: TREATMENTS NOW AVAILABLE FOR NEWLY DIAGNOSED mHSPC PATIENTS

**Dr. Neal Shore,** Carolina Urologic Research Centre, USA
**Assoc. Prof. Neeraj Agarwal,** Huntsman Cancer Institute, USA
**Prof. Steven Joniau,** University Of Leuven, Belgium

# INTRODUCTION:
# ADVANCED TREATMENT FOR PATIENTS WITH ANDROGEN SENSITIVE METASTATIC PROSTATE CANCER...

# WHAT IS NEW?

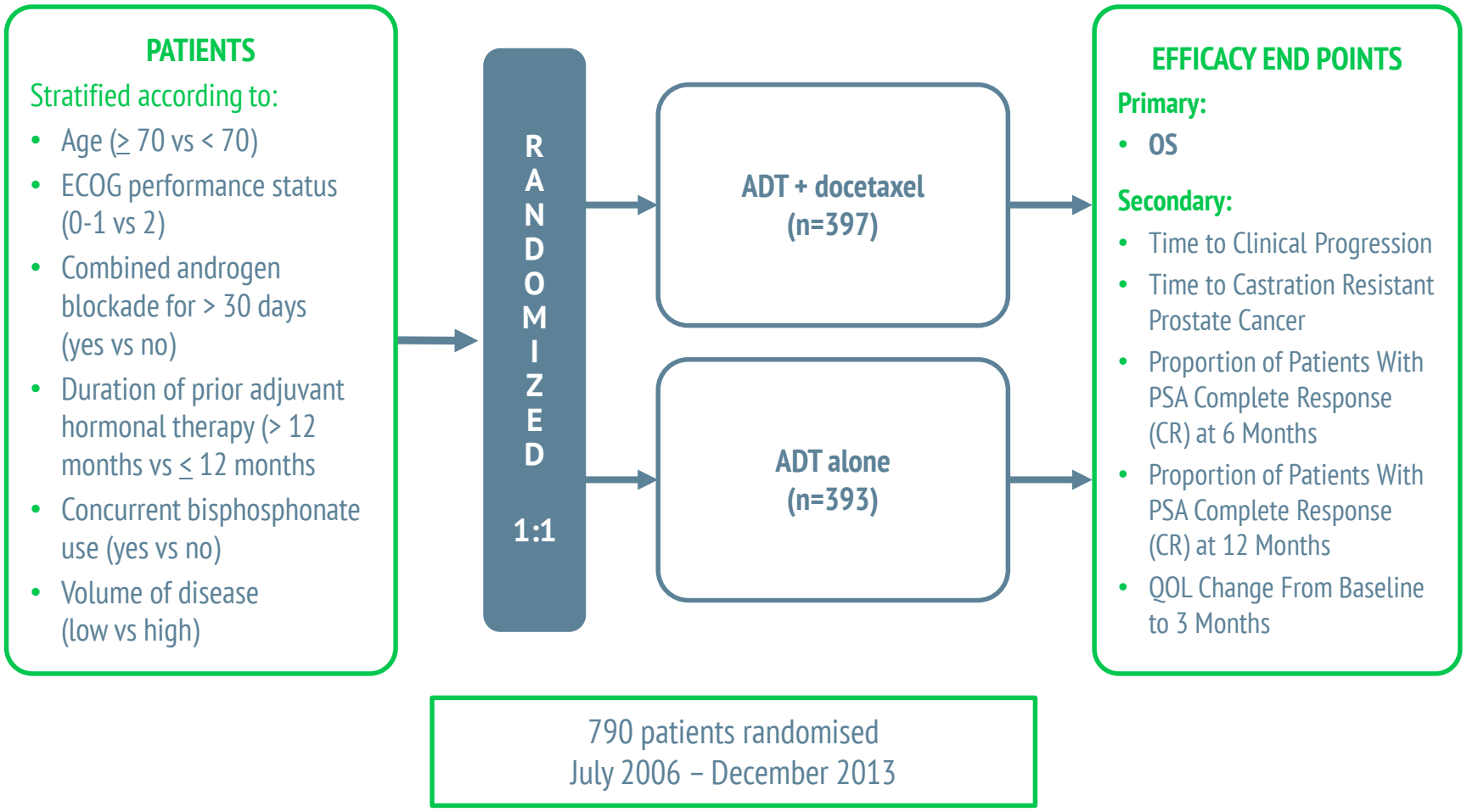
# BACKGROUND

- Prostate cancer accounts for around one fifth of all male cancers
- Most men with prostate cancer are given hormone therapy and this is often effective for a short time
- In most cases over time progression occurs
- Three trials have reported on this relevant topic with STAMPEDE and LATITUDE as the most recent:
  - **CHAARTED**[1]: Androgen ablation therapy with or without chemotherapy in treating patients with metastatic prostate cancer
  - **STAMPEDE**[2]: Systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy: a multi-stage multi-arm randomised controlled trial
  - **LATITUDE**[3]: A phase 3, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naïve prostate cancer patients

1. Sweeney, Christopher J et al. N Engl J Med 2015; 373:737-746
2. James, Nicholas D et al. N Engl J Med 2017; 377:338-351
3. Fizazi, Karim et al. N Engl J Med 2017; 377:352-360

# CHAARTED: ANDROGEN ABLATION THERAPY WITH OR WITHOUT CHEMOTHERAPY IN TREATING PATIENTS WITH METASTATIC PROSTATE CANCER

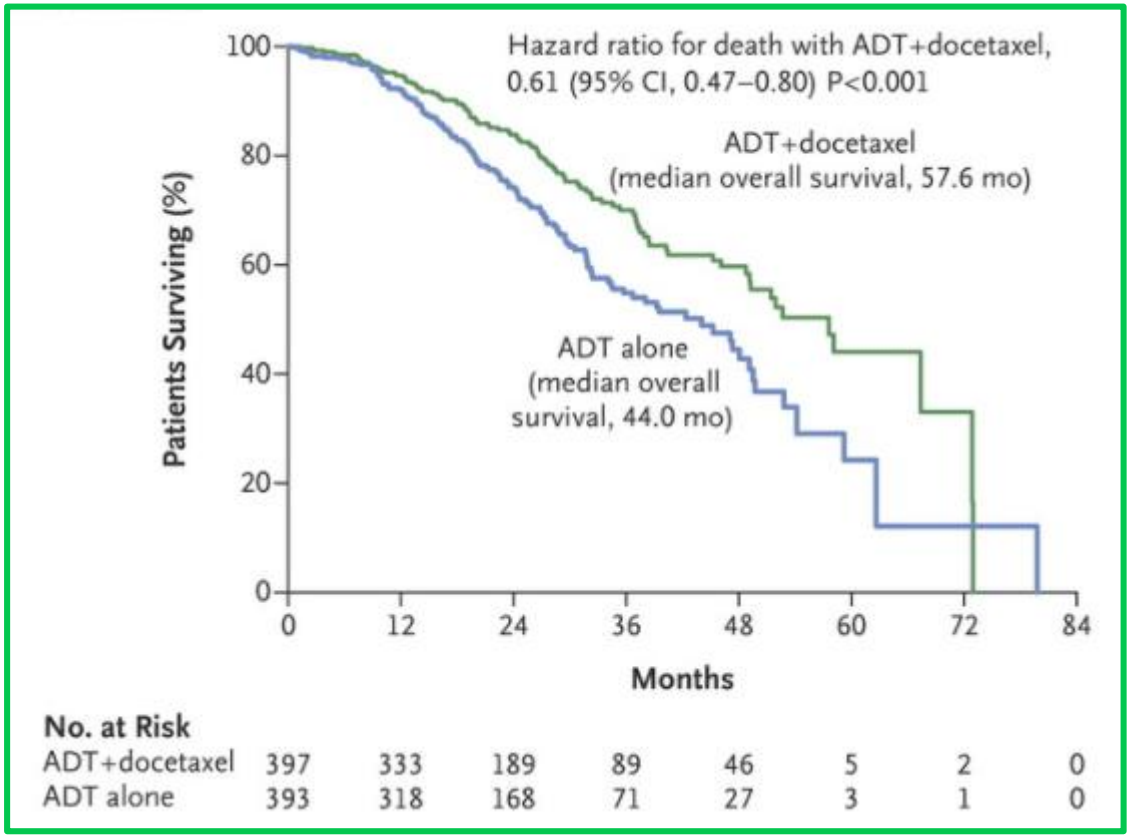
# OVERALL STUDY DESIGN OF CHAARTED



# CHAARTED: OVERALL SURVIVAL BENEFIT

## OVERALL SURVIVAL (OS)

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



# CONCLUSIONS CHAARTED

- The combination of standard ADT and six cycles of docetaxel resulted in significantly longer OS than that with standard ADT alone in men with mHSPC
  - **Median OS 13.6 months longer**
  - Longer time to development of castration resistance
  - Higher rate of decrease in PSA levels to less than 0.2 ng/ml at 12 months

- **Clinical benefit was more pronounced among patients with a higher burden of disease**
  - Median OS 17.0 months longer in the combination group than in ADT-alone

- **CHAARTED established the benefit of ADT in combination** and set the scene for STAMPEDE AND LATITUDE

Sweeney, Christopher J et al. N Engl J Med 2015; 373:737-746

# STAMPEDE: SYSTEMIC THERAPY IN ADVANCING OR METASTATIC PROSTATE CANCER: EVALUATION OF DRUG EFFICACY: A MULTI-STAGE MULTI-ARM RANDOMISED CONTROLLED TRIAL

# OVERALL STUDY DESIGN OF STAMPEDE

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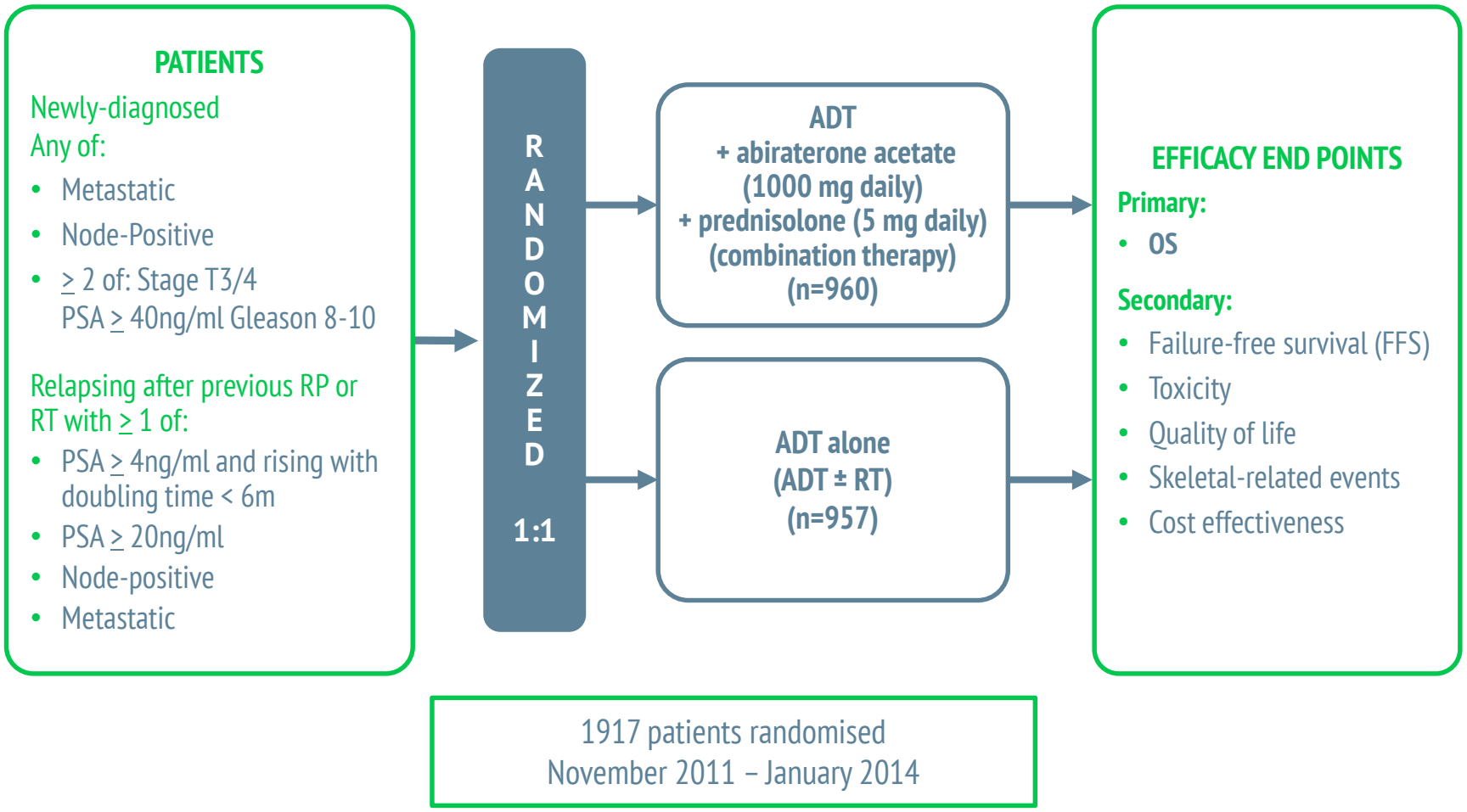


James, Nicholas D et al. N Engl J Med 2017; 377:338-351

# STAMPEDE: 37% RISK REDUCTION OF DEATH

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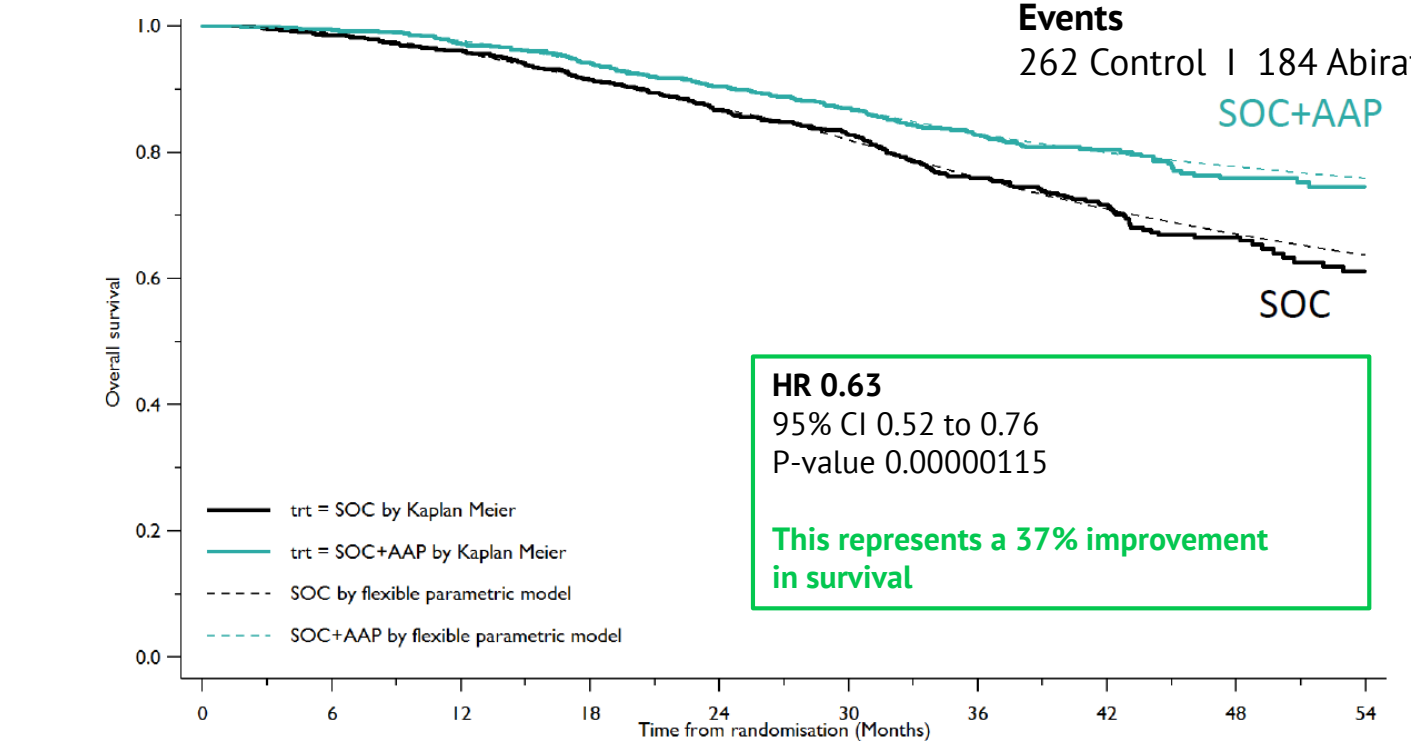
## OVERALL SURVIVAL – STAMPEDE "ABIRTERONE COMPARISON"




Number of patients (events)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SOC | 957 | (37) | 909 | (88) | 806 | (92) | 491 | (36) | 123 |
| SOC+AAP | 960 | (26) | 917 | (63) | 840 | (67) | 541 | (25) | 161 |

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

# CONCLUSIONS STAMPEDE

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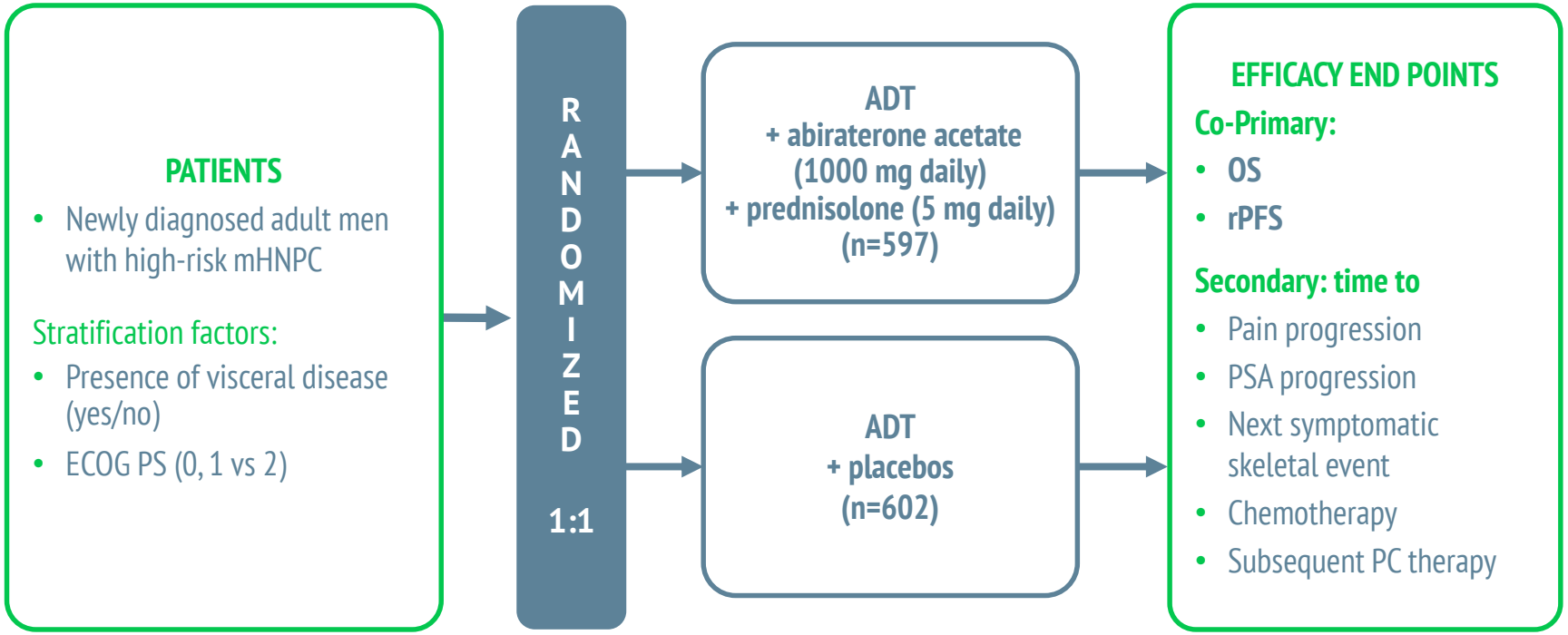
- In hormone naïve prostate cancer abiraterone acetate + prednisolone improves
  - **OS by 37%**
  - Failure free survival by 71%
  - Symptomatic skeletal events by 55%
- Treatment was **well tolerated**
- **Abiraterone acetate + prednisolone should be part of the standard of care** for men starting long-term androgen deprivation therapy

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

# LATITUDE: A PHASE 3, DOUBLE-BLIND, RANDOMIZED TRIAL OF ANDROGEN DEPRIVATION THERAPY WITH ABIRATERONE ACETATE PLUS PREDNISONE OR PLACEBOS IN NEWLY DIAGNOSED HIGH-RISK METASTATIC HORMONE-NAÏVE PROSTATE CANCER PATIENTS

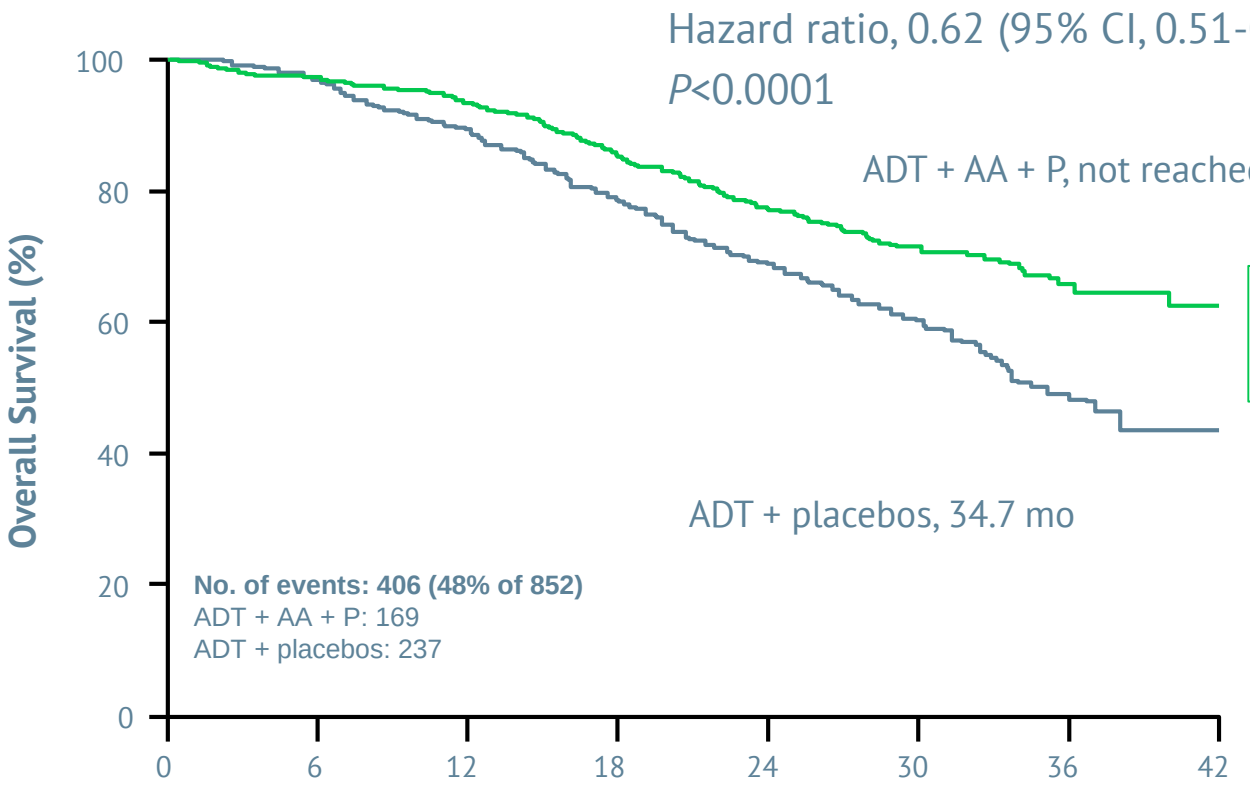
# OVERALL STUDY DESIGN OF LATITUDE




Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results

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

# LATITUDE: 38% RISK REDUCTION OF DEATH




**OS rate at 3 years:**
**ADT + AA + P: 66%**
**ADT + placebos: 49%**

Median follow-up: 30.4 months

| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ADT + AA + P | 597 | 565 | 529 | 479 | 388 | 233 | 93 | 9 |
| ADT + placebos | 602 | 564 | 504 | 432 | 332 | 172 | 57 | 2 |

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

# CONCLUSIONS LATITUDE

- In the phase 3 LATITUDE, addition of AA + P to ADT led to:
  - Significantly improved OS with a **38% reduction in the risk of death**
  - Significantly **prolonged rPFS** (53% reduction) and all secondary end points

- The overall **safety profile of ADT + AA + P was consistent with prior studies** in patients with metastatic castration-sensitive prostate cancer

# IN SUMMARY

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- **STAMPEDE and LATITIUDE continue to build the body of evidence seen with CHAARTED** in favour of combination therapy in men with mHSPC
- The Survival Benefit and HRs in both **STAMPEDE and LATITUDE are remarkably consistent**
- Whilst the patient populations in the two trials are broadly similar, there are some differences to be noted and this raises the question around **where to 'stop' when considering combination therapy;**
  - LATITUDE: eligible patients must have had documented distant metastatic disease
  - STAMPEDE: M0-patients were permitted to be enrolled in this trial
- A clinical **challenge exists in considering 2 different treatment options** – chemohormonal vs ADT/novel oral hormonal agent
- **Various factors must be considered** when selecting the right treatment for the right patient such as OS, toxicities, access, specific sub-populations and co-morbidities
- These trials may not only change the way in which mHSPC is treated, but will **also impact on the treatment of CRPC**

1. Sweeney, Christopher J et al. N Engl J Med 2015; 373:737-746
2. James, Nicholas D et al. N Engl J Med 2017; 377:338-351
3. Fizazi, Karim et al. N Engl J Med 2017; 377:352-360

# REVIEW PERSPECTIVES

# NORTH AMERICA

# WHAT TO OFFER THE PATIENTS

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## NO DIRECT COMPARISON OF THESE TWO APPROACHES

**Challenges:**

- Docetaxel + P and AA + P are two valid approaches but have **not been compared** with one another
- **No consensus** among oncologists regarding which one to use
- **No biomarkers available to predict response** to these approaches, and help treatment selection

# PROS AND CONS

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## DOCETAXEL + P VERSUS AA + P

| Docetaxel + P | AA + P |
|---|---|
| Limited duration of therapy (18 weeks) | Much longer duration of therapy (often in years) |
| Lower cost ($32,000 for a six-dose cycle) | Very expensive ($8,000 to $9,000 per month or ~$200,000 over two years) |
| More affordable to patients: no copay for most men (i.e. >65 years, who are on Medicare) | Less affordable to patients: high co-pay for most, often hundreds of dollars per month |
| Higher toxicities (myelo-suppression, neuropathy etc.) | Lower toxicities (hypertension, hypokalemia, oedema) |
| Requires frequent visits to doctor's office for infusion, and monitoring | Less frequent visits, no infusions |

# WHAT IS THE RIGHT CHOICE?

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## DOCETAXEL + P VERSUS AA + P

Until biomarkers are available to select patients, the following factors may help:

- **Patient's choice:**
  - Inconvenience and taking time out from work for hospital appointments for repeated infusions for docetaxel versus outpatient oral therapy with AA
  - Type of insurance coverage available leading to affordability of AA
  - Concerns about being on prednisone for years
- **Doctor's preference:**
  - Anecdotal experiences of individual oncologist with each of these approaches
- **Co-morbidities:**
  - Pre-existing neuropathy precluding the use of docetaxel
  - Pre-existing grade 2-3 hypertension
  - Severe osteoporosis precluding the use of AA + P

# FUTURE DIRECTIONS

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## IS THE COMBINATION OF DOCETAXEL + AA + P THE ANSWER?

- This question will be answered by **PEACE-1** (see next slide)
- If yes, it will be accompanied by additional concerns of cost and toxicities
- Multiple **other novel androgen axis inhibitors** being tested with their own advantages and disadvantages compared to docetaxel and AA (see next slide)
- Most important issue is the **development of predictive biomarkers of response** to improve efficacy and reduce cost and toxicities for a given patient

# ONGOING TRIALS OF NOVEL ANDROGEN AXIS INHIBITORS

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## ONGOING PHASE III CLINICAL TRIALS EVALUATING ADT + ANDROGEN AXIS INHIBITION IN mHSPC

| Trial Name | Arms | # Pts. | 1° endpoint | NCT # | Anticipated Read-out |
|---|---|---|---|---|---|
| ENZA-MET | ADT +/- doce + enza vs. NSAA | 1100 | OS | NCT02446405 | 2020 |
| ARCHES | ADT +/- doce + enza vs. placebo | 1100 | rPFS | NCT02677896 | 2023 |
| TITAN | ADT +/- doce + apa vs. placebo | 1000 | OS | NCT02489318 | 2021 |
| ARASENS | ADT + doce + ODM-201 vs. placebo | 1300 | OS | NCT02799602 | 2022 |
| S1216 | ADT + TAK-700 vs. bicalutamide | 1304 | OS | NCT01809691 | 2022 |
| PEACE-1 | ADT +/- doce, +/- RT, +/- abi | 916 | OS, rPFS | NCT01957436 | 2020 |

ADT, androgen-deprivation therapy; doce, docetaxel; enza, enzalutamide; NSAA, non-steroidal androgen antagonist; OS, overall survival; rPFS, radiographic progression-free survival; apa, apalutamide; abi, abiraterone acetate; RT, radiotherapy;

*Values reflect failure-free survival instead of PFS.

Reference: PMID: 28816716. Hahn A. Agarwal N.

# REVIEW PERSPECTIVES

# EUROPE

# CHAARTED: OVERALL SURVIVAL BENEFIT

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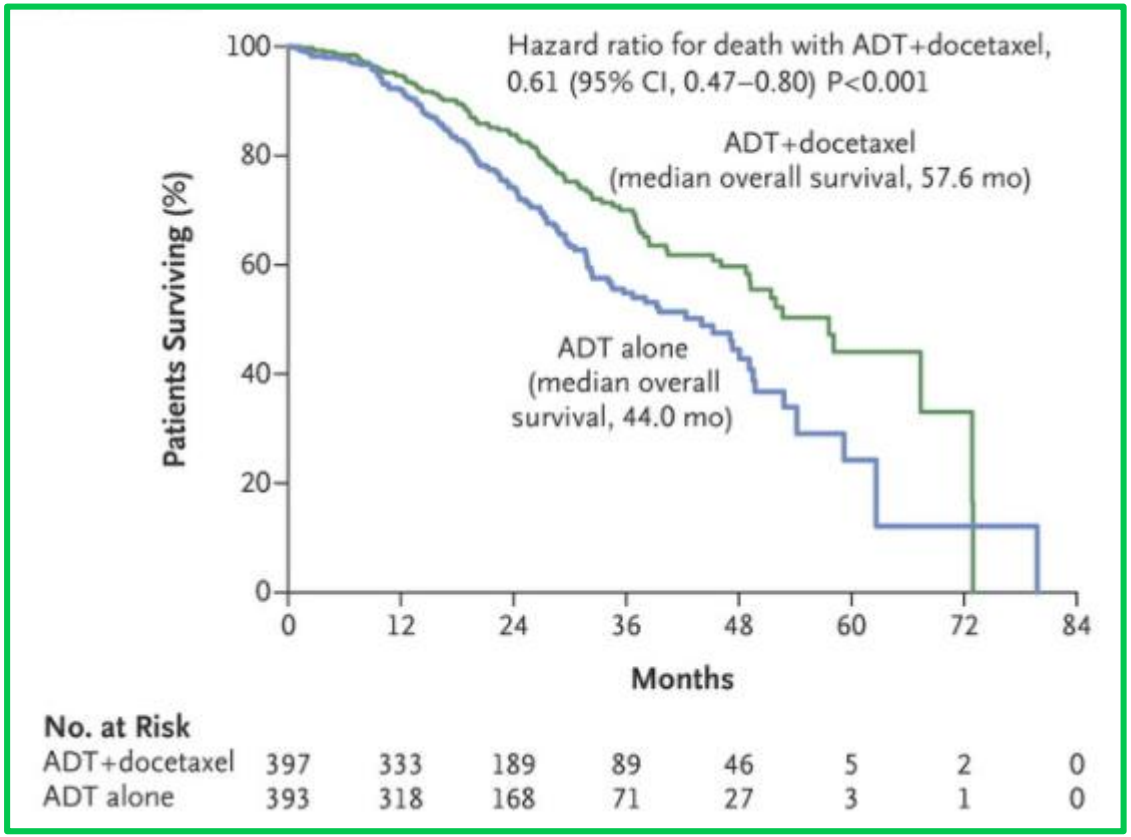

# STAMPEDE: OVERALL SURVIVAL BENEFIT

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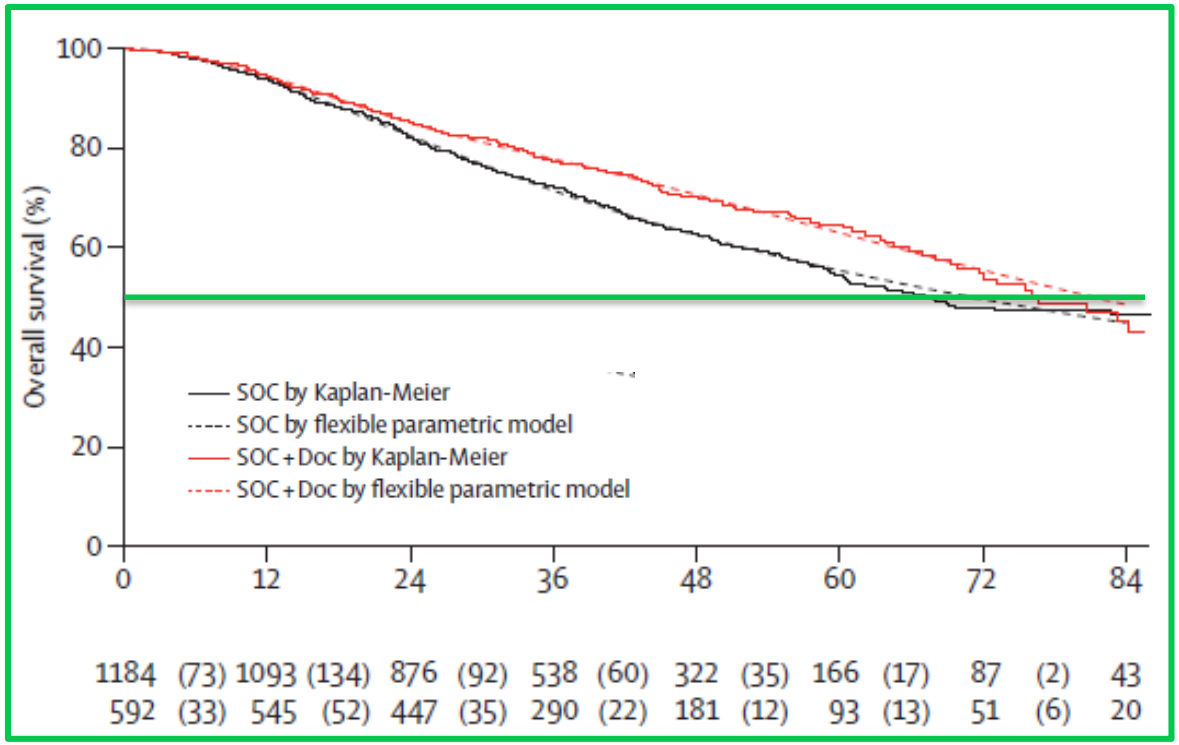
## OVERALL SURVIVAL (OS)

- The median OS was 10 months longer with the addition to ADT of early docetaxel than with ADT alone




James Nicholas D, et al. Lancet 2016; 387:1163-77

# EAU GUIDELINES ON PROSTATE CANCER

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## GUIDELINES FOR THE FIRST-LINE TREATMENT OF METASTATIC PROSTATE CANCER

| Recommendations | LE | GR |
|---|---|---|
| Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy. | 1a | A |
| Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with chemotherapy. | 1b | A |
| Do not prescribe abiraterone acetate or enzalutamide outside of a clinical trial. | 3 | A |
| Use castration combined with any local treatment (radiotherapy/surgery) in an investigational setting only. | 3 | A |

# SOME MEN WITH OLIGO-METASTATIC PROSTATE CANCER MAY BENEFIT FROM RP/RT

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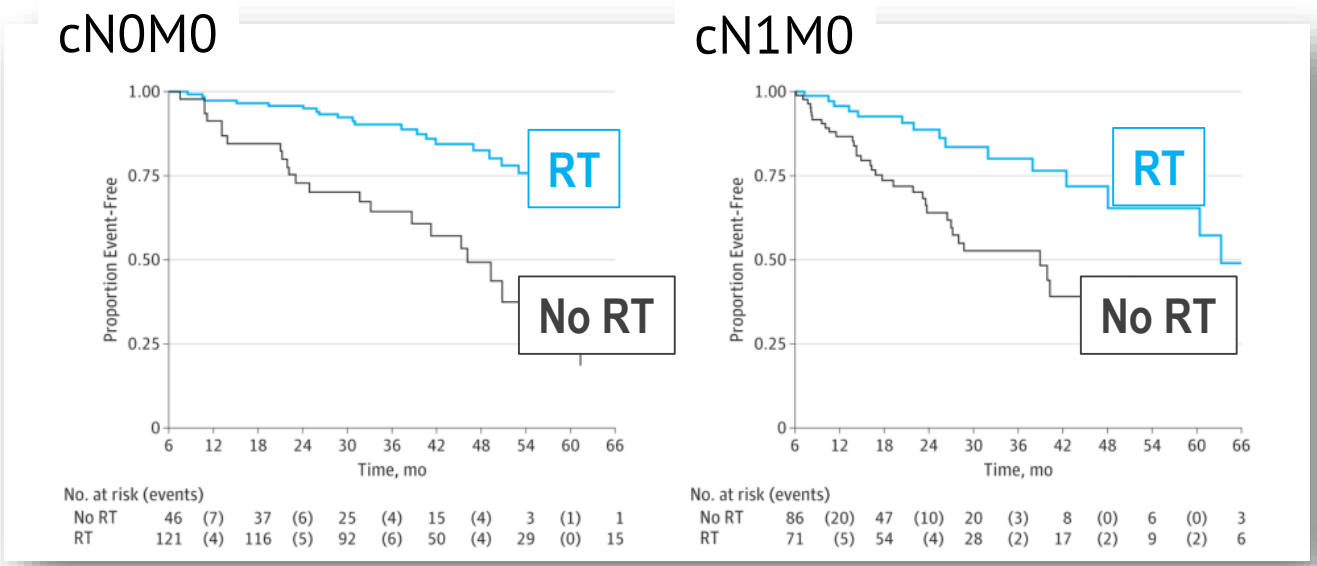
## DATA FROM THE CONTROL ARM OF STAMPEDE

- **PFS** improved when adding RT to ADT in patients with cN1 PCa




James Nicholas D, et al. JAMA Oncol. 2015 Nov 25:1-10

# SOME MEN WITH OLIGO-METASTATIC PROSTATE CANCER MAY BENEFIT FROM RP/RT

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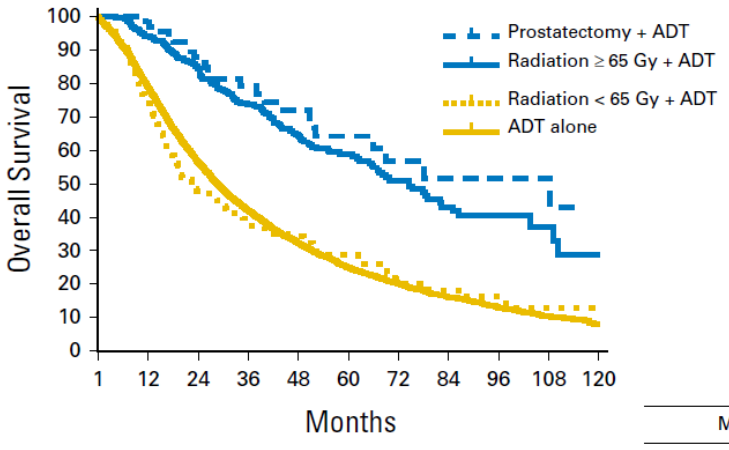
## DATA FROM THE NATIONAL CANCER REGISTRY

- **OS** improved when adding RP of RT (≥ 65 Gy) to ADT in patients with M1 PCa




| | | | | | | | Multivariate | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | HR | 95% CI | *P* |
| ADT alone | 5,844 | 3,034 | 1,277 | 472 | 155 | 13 | Ref | – | – |
| Radiation < 65 Gy + ADT | 163 | 73 | 41 | 15 | 7 | 1 | 1.02 | 0.84 to 1.23 | .874 |
| Radiation ≥ 65 Gy + ADT | 324 | 254 | 146 | 61 | 21 | 1 | 0.45 | 0.38 to 0.54 | < .001 |
| Prostatectomy + ADT | 69 | 56 | 30 | 13 | 7 | 0 | 0.38 | 0.25 to 0.58 | < .001 |

Rusthoven C, et al. J Clin Oncol 2016 34(24):2835-42

# EAU GUIDELINES ON PROSTATE CANCER

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## GUIDELINES FOR THE FIRST-LINE TREATMENT OF METASTATIC PROSTATE CANCER

| Recommendations | LE | GR |
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| Do not prescribe abiraterone acetate or enzalutamide outside of a clinical trial. | 3 | A |
| Use castration combined with any local treatment (radiotherapy/surgery) in an investigational setting only. | 3 | A |

# ONGOING PROSPECTIVE TRIALS OF PROSTATE-TARGETED THERAPY IN SYNCHRONOUS (OLIGO)METASTATIC PROSTATE CANCER

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| Study (ClinicalTrials.gov ID) | Phase | Design | Primary outcome measure | Estimated completion |
|---|---|---|---|---|
| TRoMbone: Testing Radical prostatectomy in men with prostate cancer and oligoMetastases to the bone: a randomised controlled feasibility trial (ISRCTN15704862) | II | Randomised, open-label, parallel assignment | Feasibility to randomise (measured at 6 m) | Completed April 2017 |
| HORRAD: A randomised study about the effect on survival of HT versus HT plus local external RT in patients with primary diagnosed metastasised PCa (ISRCTN06890529) | III | Randomised active-controlled parallel-group trial | Survival | Completed accrual |
| Safety and early efficacy of RP for newly diagnosed very high risk locally advanced and OMPCa (NCT02971358) | I/II | Open-label, single group assignment | The rate of perioperative complications within 90 days from surgery (Clavien-Dindo) | November 2016 |
| Combining ipilimumab, degarelix, and RP in men with newly diagnosed metastatic castration sensitive PCa or ipilimumab and degarelix in men with biochemically recurrent castration sensitive PCa after RP (NCT02020070) | II | Non-randomised, open-label, parallel assignment | Undetectable PSA (time frame at 12 and 20 m) from the start of treatment | December 2017 |
| BST or BST plus definitive treatment (RT or surgery) of the primary tumour in mPCa (NCT01751438) | II | Randomised, open-label, parallel-assignment | PFS | March 2018 |
| Cytoreductive prostatectomy in patients with newly diagnosed metastatic PCa (NCT02458716) | I | Open-label, single group assignment | Rate of major peri-operative complications (Clavien-Dindo ≥III) within 90 days of surgery | August 2018 |
| ADT or ADT plus definitive treatment (RT or surgery) in OMPCa (NCT02742675) | II | Randomised, open-label, parallel assignment | PFS | March 2019 |
| LoMP: Local treatment with RP for newly-diagnosed mPCa (NCT02138721) | II | Non-randomised, open-label, parallel assignment | Castration-refractory PCa PFS; Time to first disease-related event (time frame for either: up to 10 y) | May 2019 |
| g-RAMPP: Impact of RP as primary treatment in patients with PCa with limited bone metastases (NCT02454543) | III | Randomised, open-label, parallel assignment | Cancer-specific survival (time frame: 5 y) | April 2020 |
| PEACE1: A phase III of ADT +/- docetaxel +/- local RT +/- abiraterone acetate in metastatic hormone-naïve PCa (NCT01957436) | III | Randomised, open-label, parallel assignment | Survival (time frame 5.5. y)<br>OS and PFS | October 2023 |

ADT, androgen deprivation therapy; BST, best systemic therapy; HT, hormonal therapy' ISRCTN, International Standard Randomised Controlled Trial Number; LN, lymph node; mPCa, metastatic prostate cancer; OMPCa, oligometastatic prostate cancer; OS, overall survival; PCa, prostate cancer; PFS, progression-free survival; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy

# CONCLUSIONS

# CONCLUSIONS

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- Treatment of patients with mHSPC requires a **multidisciplinary approach** between Medical Oncologists and Urologists
- The results from the 3 trials indicate that **treatment has moved beyond monotherapy ADT** for high volume mPC patients
- When deciding on whether to combine ADT with abiraterone or docetaxel, a number of **selection factors** are to be considered
- **Further trials** continue to investigate how to combine or sequence therapy, whilst others studies focus on the benefit in sub-populations (low volume metastatic and high risk localized disease)
- Implications on **resistance patterns and therapeutic selection** when CRPC ensues must also be considered
- A review of the treatment landscape in different regions indicates that **accessibility and cost** also impact upon treatment decisions

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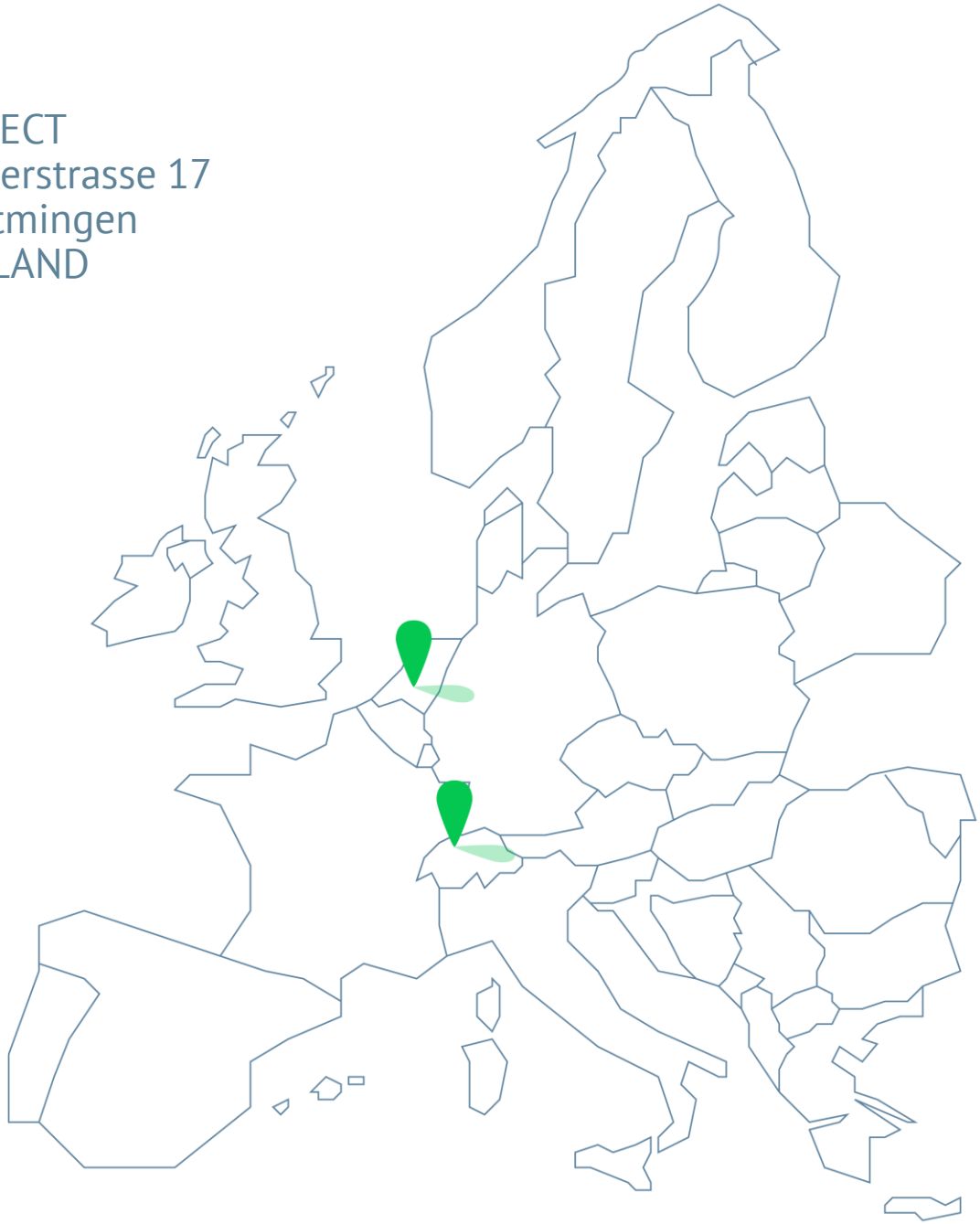

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