# Translating the evidence into clinical practice in Metastatic Prostate Cancer Management

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# Disclosures

| Type of affiliation/ financial interest | Name of commercial company |
|---|---|
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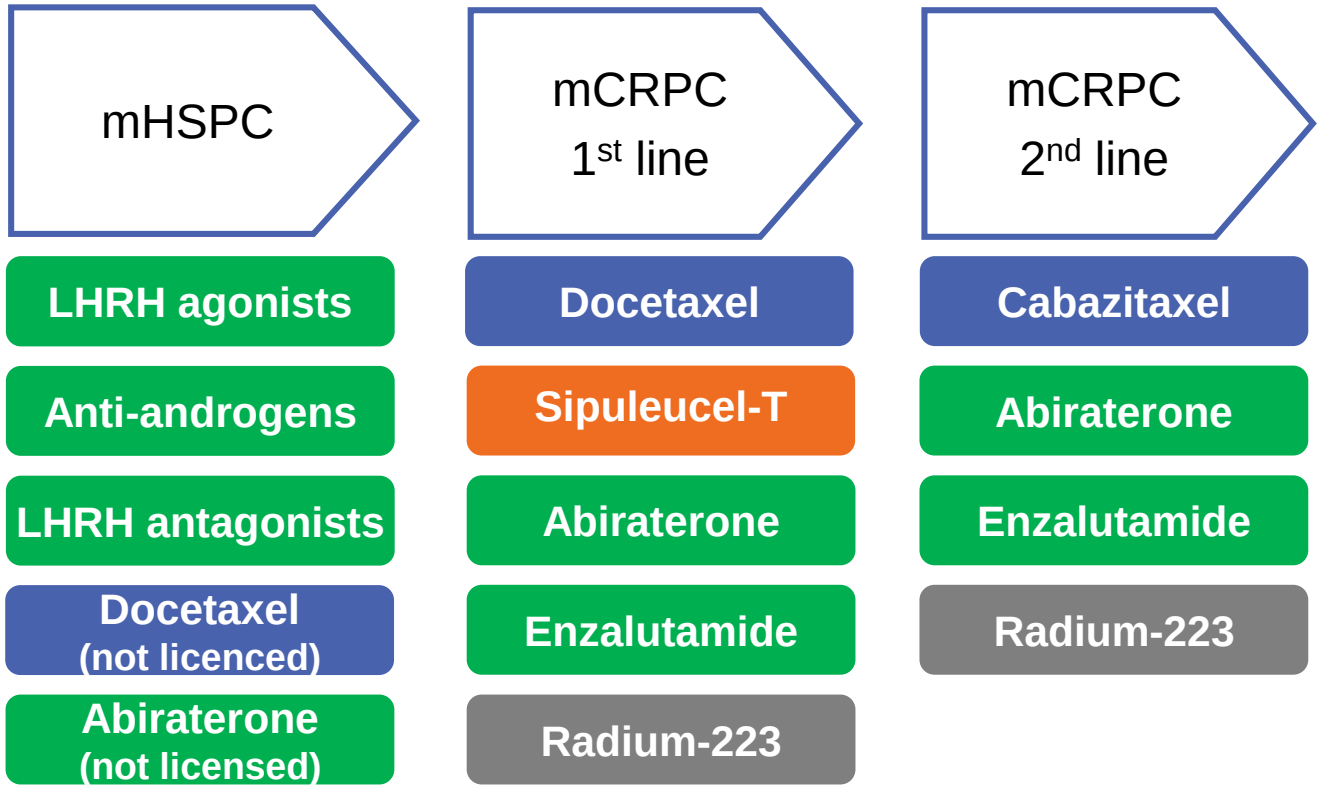
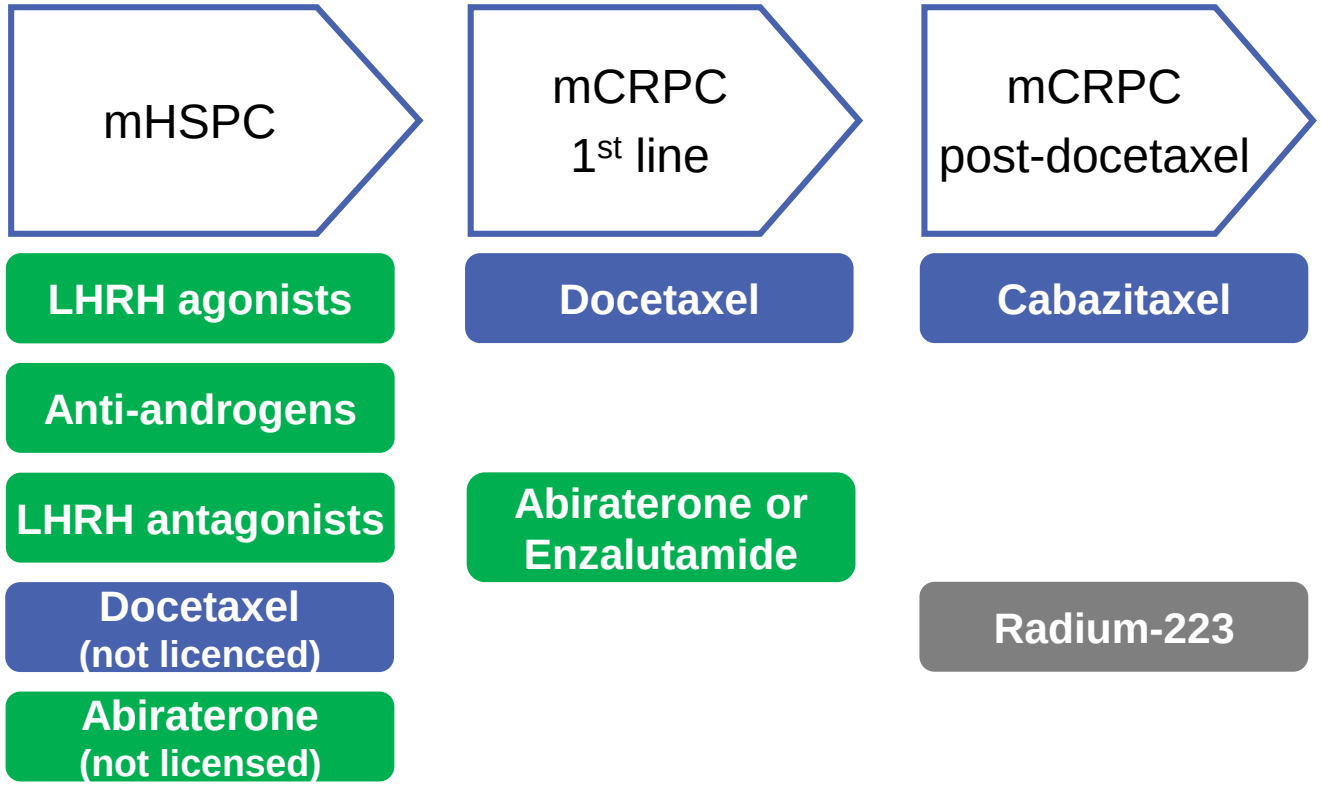
Honorarium from Sanofi Genzyme for this meeting

# Management of metastatic PCa
# Current options available

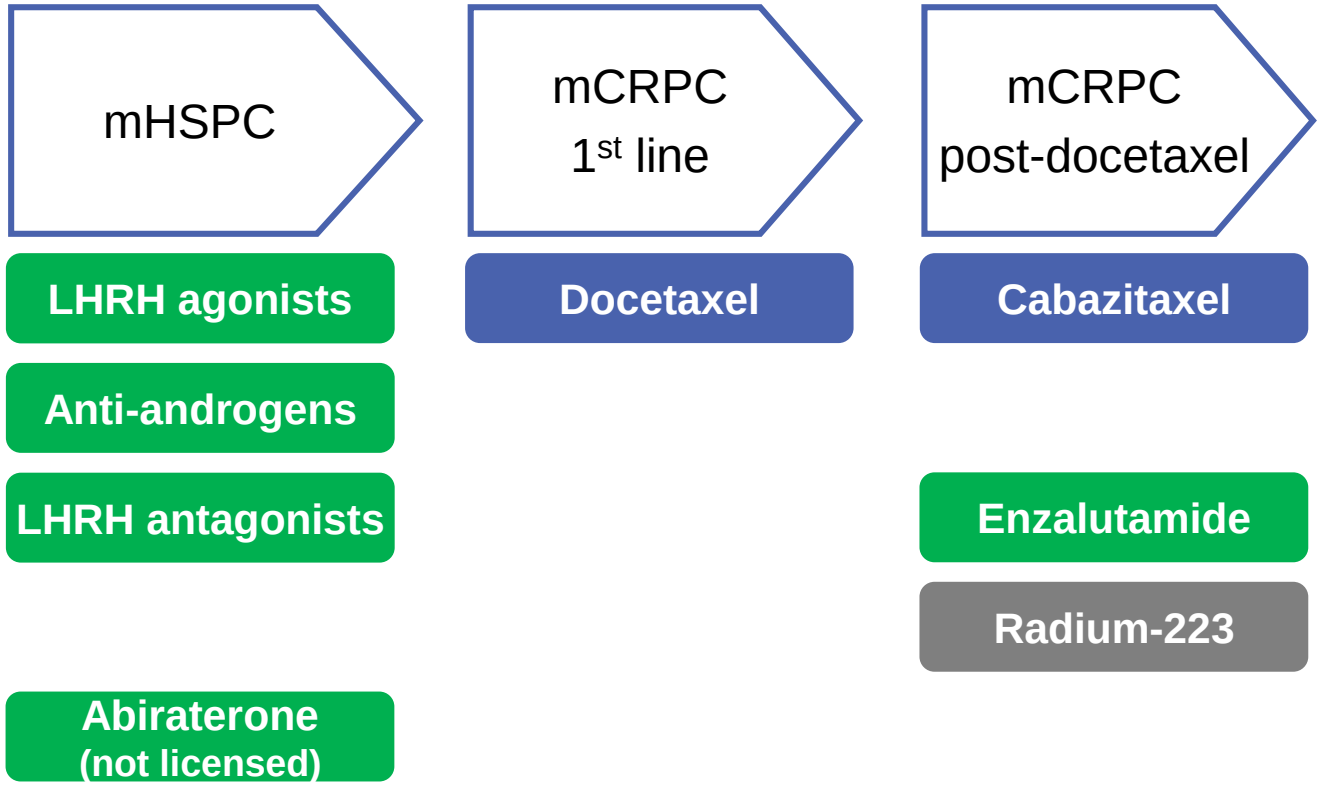



*LHRH: luteinising hormone-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer*

# Management of metastatic PCa
# Current options available



# Management of metastatic PCa
# Current options available



# Phase III trials in metastatic PCa

| Study | Agents | N | Indication | HR (95% CI) | ΔOS (mo) |
|---|---|---|---|---|---|
| CHAARTED[1] | DOC vs ADT | 790 | Metastatic hormone –sensitive PCa (mHSPC) | 0.61 (0.47-0.80) | **+13.6** |
| STAMPEDE[2] | DOC/P vs ADT | 1,086 | mHSPC | 0.73 (0.59-0.89) | **+22.0** |
| LATITUDE[3] | ABI/P vs ADT | 1,199 | High-risk mHSPC | 0.62 (0.51-0.76) | Not reached |
| STAMPEDE[4] | ABI/P vs ADT | 1,002 | mHSPC | 0.61 (0.49-0.75) | Not reached |
| TAX-327[5] | DOC/P vs mito/P | 1,006 | mCRPC, symptomatic or not | 0.76 (0.62-0.94) | +2.9 |
| IMPACT[6] | Sipuleucel-T vs pbo | 512 | mCRPC (pre-DOC)<br>Mild/no symptoms , no visceral mets | 0.78 (0.61-0.98) | +4.1 |
| TROPIC[7] | CABA/P vs mito/P | 755 | mCRPC (post-DOC) | 0.70 (0.59-0.83) | +2.4 |
| COU-AA-302[8] | ABI/P vs P | 1,088 | mCRPC (pre-DOC)<br>Mild/no symptoms , no visceral mets | 0.81 (0.70-0.93) | +4.4 |
| COU-AA-301[9] | ABI/P vs P | 1,195 | mCRPC (post-DOC) | 0.74 (0.64-0.86) | +4.6 |
| PREVAIL[10] | ENZA vs pbo | 1,717 | mCRPC (pre-DOC)<br>Mild/no symptoms, 11% visceral mets | 0.71 (0.60-0.84) | +4.0 |
| AFFIRM[11] | ENZA vs pbo (or | 1,199 | mCRPC (post-DOC) | 0.63 (0.53- | +4.8 |

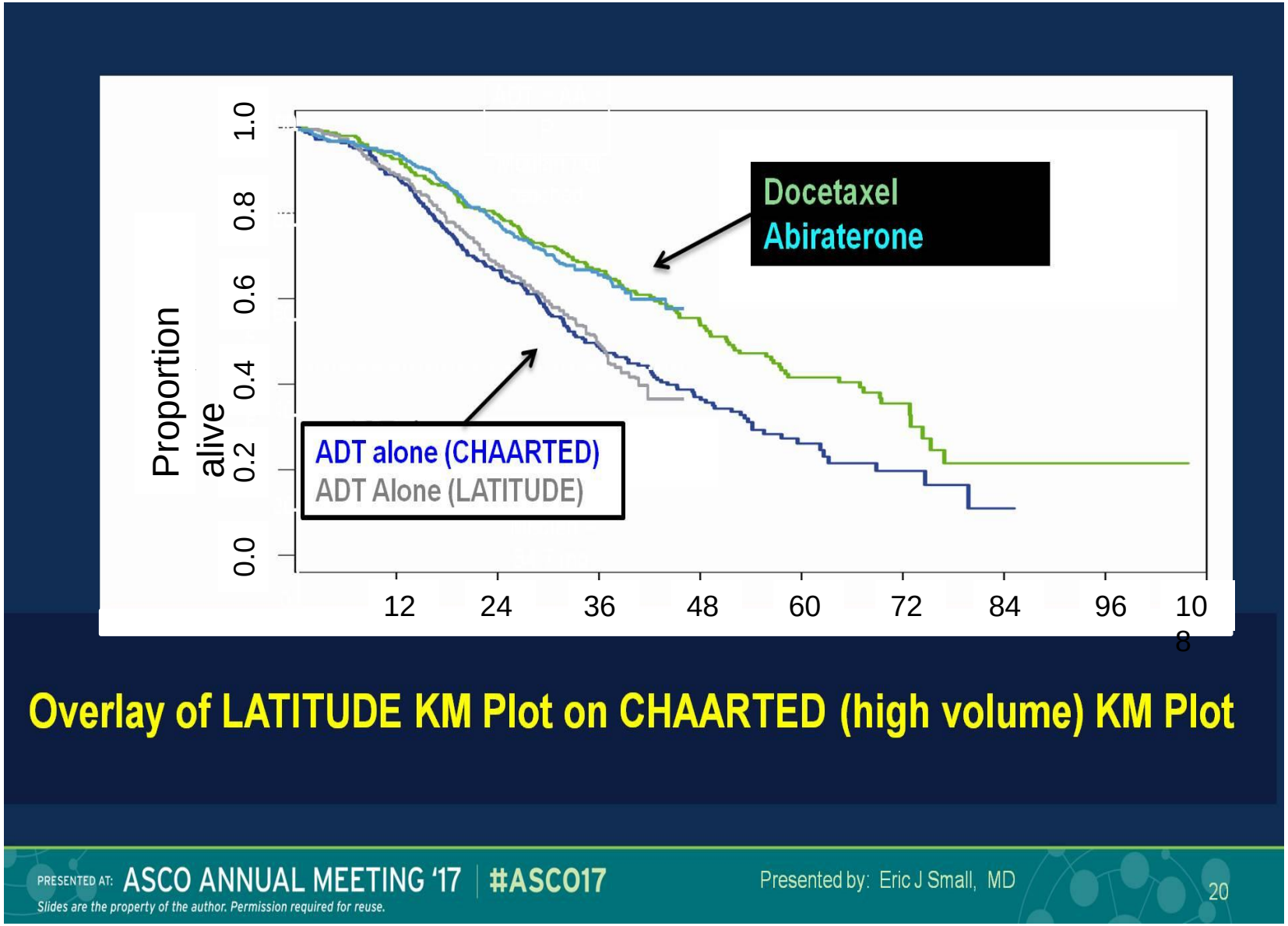
# In mHSPC, for a patient who is fit to receive docetaxel chemotherapy

If there was approval and funding available to treat an eligible mHSPC individual with

**ADT + docetaxel**

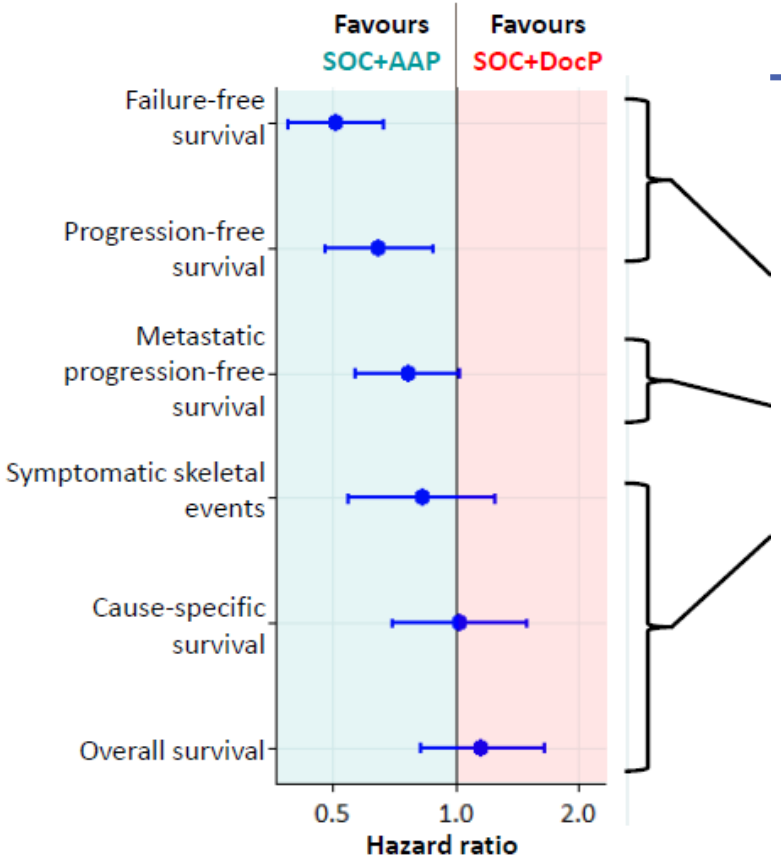
**ADT + abiraterone**

What would you choose?




Presented By Eric Small at 2017 ASCO Annual Meeting

# STAMPEDE – Abiraterone+ADT & Docetaxel+ADT comparison in M0/M1 patients




## Summary

Head-to-head data in 566 pts (Nov-2011 to Mar-2013)

Strong evidence favouring AAP

Weak evidence favouring AAP

No good evidence of a difference

➔ Proportionately different time spent in each disease state

Toxicity profiles quite different and well known

*AAP: abiraterone acetate plus prednisolone*

Presented By Matt Sydes at 2017 ESMO Meeting (LBA 31)

# Changing paradigm of mHSPC treatment will result in two new scenarios

- Progression post upfront docetaxel

- Progression post upfront abiraterone

# Progression post-upfront docetaxel

- No reliable evidence available
- New area of disease based on recent changes with upfront docetaxel being incorporated
- Pragmatic decision making
  - Based on time to progression
  - Trajectory of disease
  - Patient fitness
- Overall prognosis is unfortunately not good

# Progression post-upfront docetaxel

- Pragmatic decision making
  - Based on time to progression
  - Trajectory of disease
  - Patient fitness
- My treatment strategy:
  - If progression <6 months post-upfront docetaxel → cabazitaxel
  - If progression >1 year → same aspects as mCRPC treatment strategy
  - If progression between 6-12 months → cabazitaxel preferred and individual case based strategy

# Progression post-upfront abiraterone

- No robust data available

- It is likely treatment paradigm will involve earlier use of docetaxel for mCRPC and subsequent post-docetaxel therapies
  - Potentially earlier use of DOC-cabazitaxel
  - Further ART would probably not be meaningfully beneficial
  - Radium-223 would probably have the same role as now

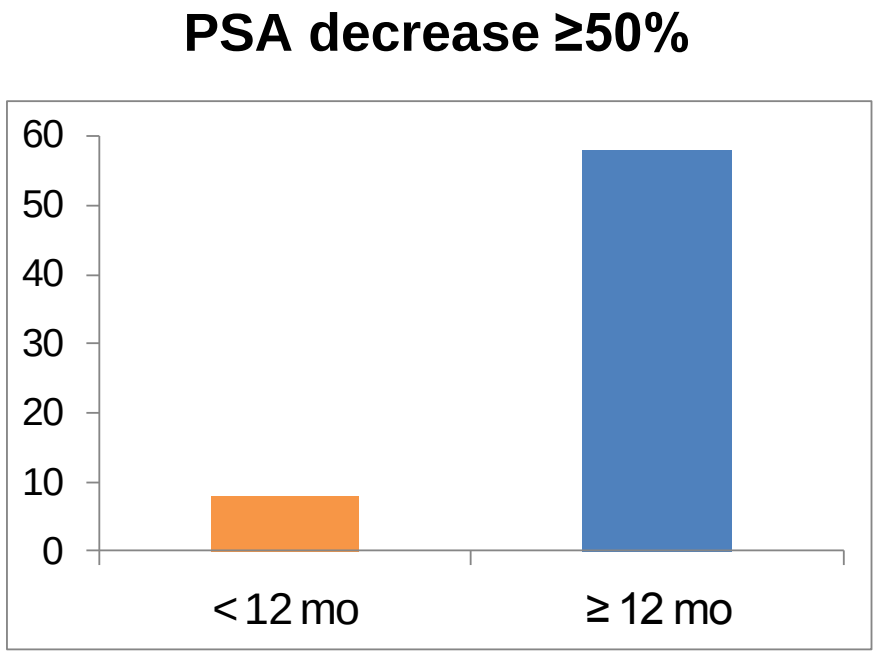
*ART: androgen receptor targeted agents*

# The ‘real’ issues

- Primary ART resistant mCRPC
  - How to identify?
  - Why to identify?
  - What to do in such cases?
- Monitoring treatment
  - How frequently?
  - Which modality?
- Switching treatment
  - When to switch?
  - What will the next treatment be?

# Primary resistance to ART

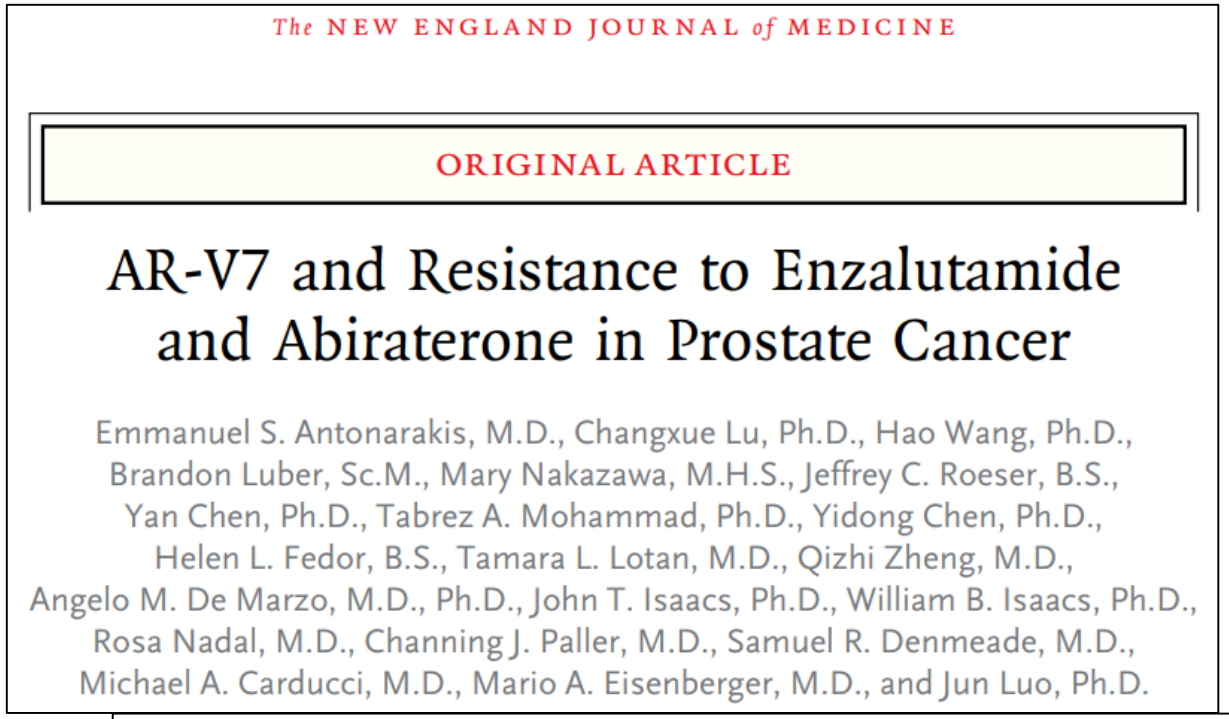
# Primary resistance to ART
# Who to identify?




Retrospective cohort of 173 patients, including 57 treated with enzalutamide in AFFIRM phase III trial[1]

- Short response (<1 year) to first ADT may predict poor response to subsequent ART[1]
- Perhaps the only reliable clinical parameter
- The other factor to consider is the 'aggressiveness' of the cancer

Loriot Y et al. Eur J Cancer 2015;51:1946-52

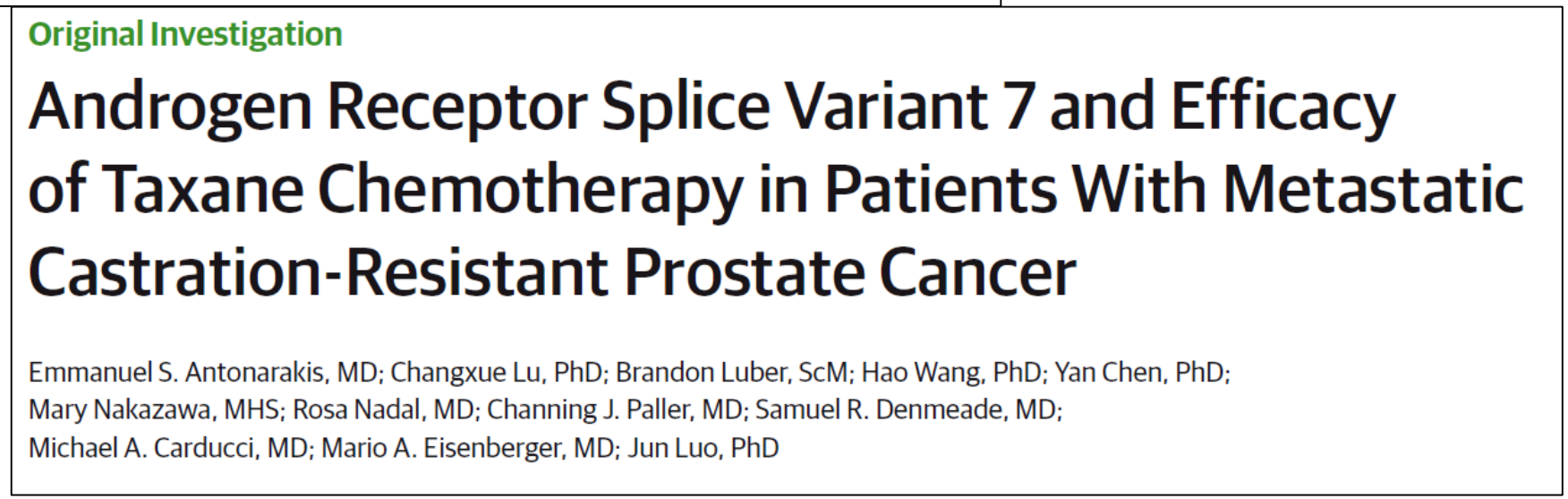


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.



Original Investigation

# Androgen Receptor Splice Variant 7 and Efficacy of Taxane Chemotherapy in Patients With Metastatic Castration-Resistant Prostate Cancer

Emmanuel S. Antonarakis, MD; Changxue Lu, PhD; Brandon Luber, ScM; Hao Wang, PhD; Yan Chen, PhD; Mary Nakazawa, MHS; Rosa Nadal, MD; Channing J. Paller, MD; Samuel R. Denmeade, MD; Michael A. Carducci, MD; Mario A. Eisenberger, MD; Jun Luo, PhD

Antonarakis ES et al. N Engl J Med 2014;371:1028-38; Antonarakis ES et al. JAMA Oncol 2015;1:582-91

# Primary resistance to ART
# Who to identify?

- Not all patients will benefit with ART
- Likelihood of increased primary resistance if more lines of previous therapy
- Despite this factor……most clinicians will use ART as their preferred modality in **ALL** cases of mCRPC
- Whilst ART is the optimum therapy for **MAJORITY** of mCRPC cases it is not the optimum therapy for **ALL** cases
- The challenge for the uro-oncologist is to use clinical factors to decide which patients are likely to have primary resistance to ART and offer chemotherapy as the preferred option for these cases

# Primary resistance to ART
# What to do in such cases?

- Discuss with the patient the proposed sequencing
  - Docetaxel chemotherapy first
- Explain the concept of chemotherapy continuum
  - If disease progression after 3 cycles of docetaxel then switch to cabazitaxel
- Address the concern factors associated with chemotherapy
- If ART given then ensure frequent and relevant monitoring
  - Patient should not loose the opportunity of availing the next treatment

# Monitoring treatment

# Monitoring treatment

**mCRPC patient on abiraterone or enzalutamide**

Is it important to do radiological monitoring for a patient who is symptomatically doing well and PSA is controlled on ART

# Monitoring treatment

- **Aim of monitoring**
  - Ensure appropriate switching if not benefitting from current treatment
  - Prevent significant decline in performance status before offering subsequent treatment

**If the patient is eligible for a subsequent treatment option, then monitoring should be done methodically and as per schedule**

- **Frequency and modality**
  - Clinical: every cycle
  - Biochemical: PSA every 4 weeks
  - Radiological: every 3 months if other parameters stable otherwise earlier

Prostate Cancer and Prostatic Diseases (2017) 20, 221–227
www.nature.com/pcan

ORIGINAL ARTICLE

# Radiographic progression with nonrising PSA in metastatic castration-resistant prostate cancer: *post hoc* analysis of PREVAIL

AH Bryce[1], JJ Alumkal[2], A Armstrong[3], CS Higano[4], P Iversen[5], CN Sternberg[6], D Rathkopf[7], Y Loriot[8], J de Bono[9], B Tombal[10], S Abhyankar[11,15], P Lin[12], A Krivoshik[13], D Phung[14] and TM Beer[2]

**BACKGROUND:** Advanced prostate cancer is a phenotypically diverse disease that evolves through multiple clinical courses. PSA level is the most widely used parameter for disease monitoring, but it has well-recognized limitations. Unlike in clinical trials, in practice, clinicians may rely on PSA monitoring alone to determine disease status on therapy. This approach has not been adequately tested.

**METHODS:** Chemotherapy-naive asymptomatic or mildly symptomatic men ($n = 872$) with metastatic castration-resistant prostate cancer (mCRPC) who were treated with the androgen receptor inhibitor enzalutamide in the PREVAIL study were analyzed *post hoc* for rising versus nonrising PSA (empirically defined as $> 1.05$ vs $\leqslant 1.05$ times the PSA level from 3 months earlier) at the time of radiographic progression. Clinical characteristics and disease outcomes were compared between the rising and nonrising PSA groups.

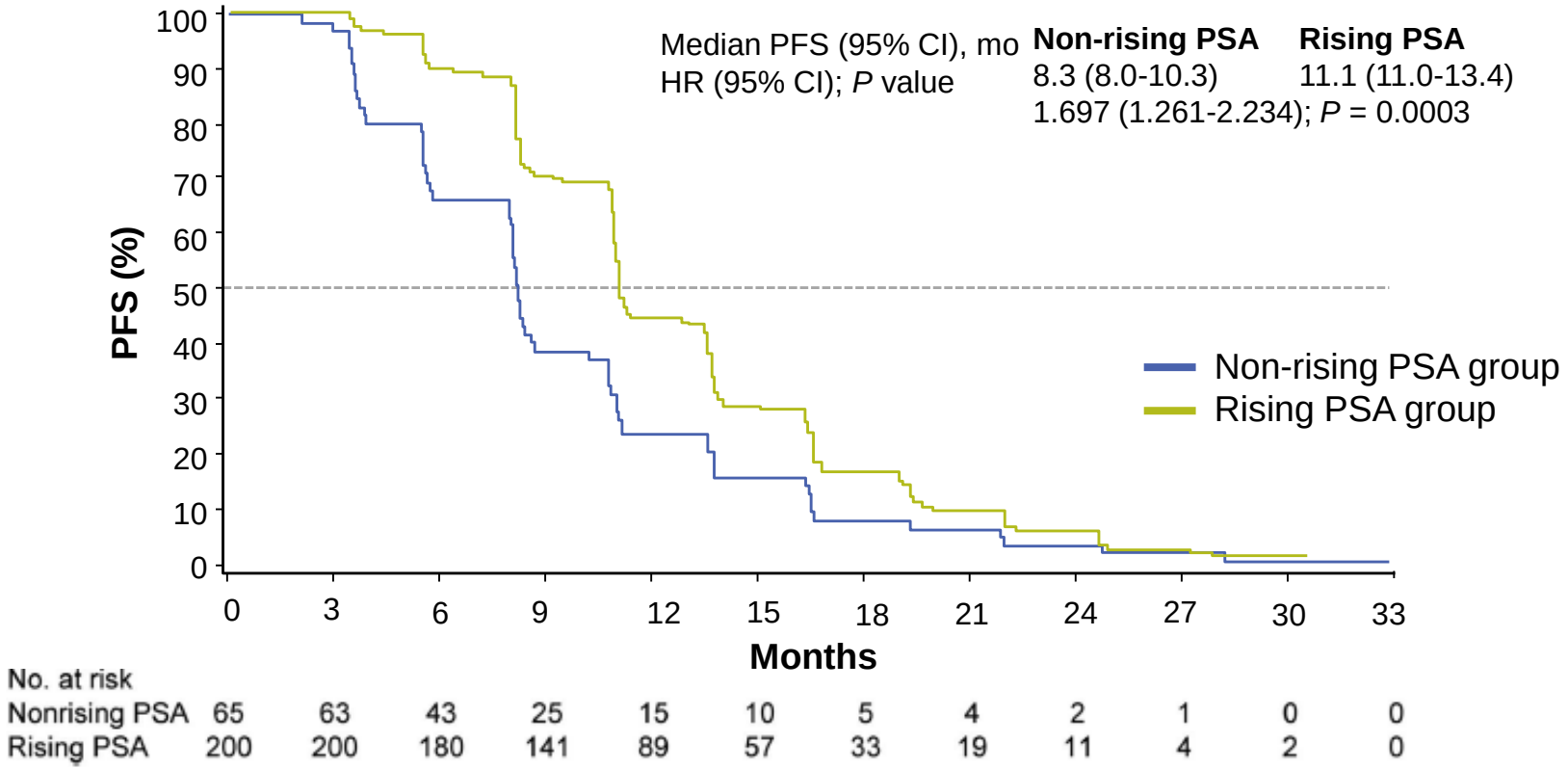
**RESULTS:** Of 265 PREVAIL patients with radiographic progression and evaluable PSA levels on the enzalutamide arm, nearly one-quarter had a nonrising PSA. Median progression-free survival in this cohort was 8.3 months versus 11.1 months in the rising PSA cohort (hazard ratio 1.68; 95% confidence interval 1.26–2.23); overall survival was similar between the two groups, although less than half of patients in either group were still at risk at 24 months. Baseline clinical characteristics of the two groups were similar.

**CONCLUSIONS:** Non-rising PSA at radiographic progression is a common phenomenon in mCRPC patients treated with enzalutamide. As restaging in advanced prostate cancer patients is often guided by increases in PSA levels, our results demonstrate that disease progression on enzalutamide can occur without rising PSA levels. Therefore, a disease monitoring strategy that includes imaging not entirely reliant on serial serum PSA measurement may more accurately identify disease progression.

*Prostate Cancer and Prostatic Diseases* (2017) **20,** 221–227; doi:10.1038/pcan.2016.71; published online 24 January 2017

ut of 4 patients with radiographic progression have a non-rising PS

# PREVAIL post-hoc analysis




Patients with radiographic progression and non-rising PSA have a worse prognosis

Bryce AH et al. Prostate Cancer Prostatic Dis 2017;20:221-7

European Journal of Cancer 61 (2016) 44–51

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

# Early PSA response is an independent prognostic factor in patients with metastatic castration-resistant prostate cancer treated with next-generation androgen pathway inhibitors

Alina Fuerea, Giulia Bacian
Christophe Massard, Maric
Yohann Loriot*

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

*Editorial by XXX on pp. x–y of this issue*

# Prostate-specific Antigen Decline After 4 Weeks of Treatment with Abiraterone Acetate and Overall Survival in Patients with Metastatic Castration-resistant Prostate Cancer

*Pasquale Rescigno, David Lorente, Diletta Bianchini, Roberta Ferraldeschi, Michael P. Kolinsky, Spyridon Sideris, Zafeiris Zafeiriou, Semini Sumanasuriya, Alan D. Smith, Niven Mehra, Anuradha Jayaram, Raquel Perez-Lopez, Joaquin Mateo, Chris Parker, David P. Dearnaley, Nina Tunariu, Alison Reid, Gerhardt Attard, Johann S. de Bono **

# Switching treatment

# When to switch treatment?

- Generally accepted view is that 2 out of the following 3 factors should be met
  - PSA progression
  - Radiological progression
  - Symptomatic progression

- However, unequivocal radiological progression which is clinically meaningful on its own warrants change in therapy

# No longer clinically benefitting

Progression versus

the decision to discontinue therapy

# Switching treatment scenarios in mCRPC

- Progression on ART (abiraterone/enzalutamide)
- Progression on docetaxel

# Cross-resistance between ART agents

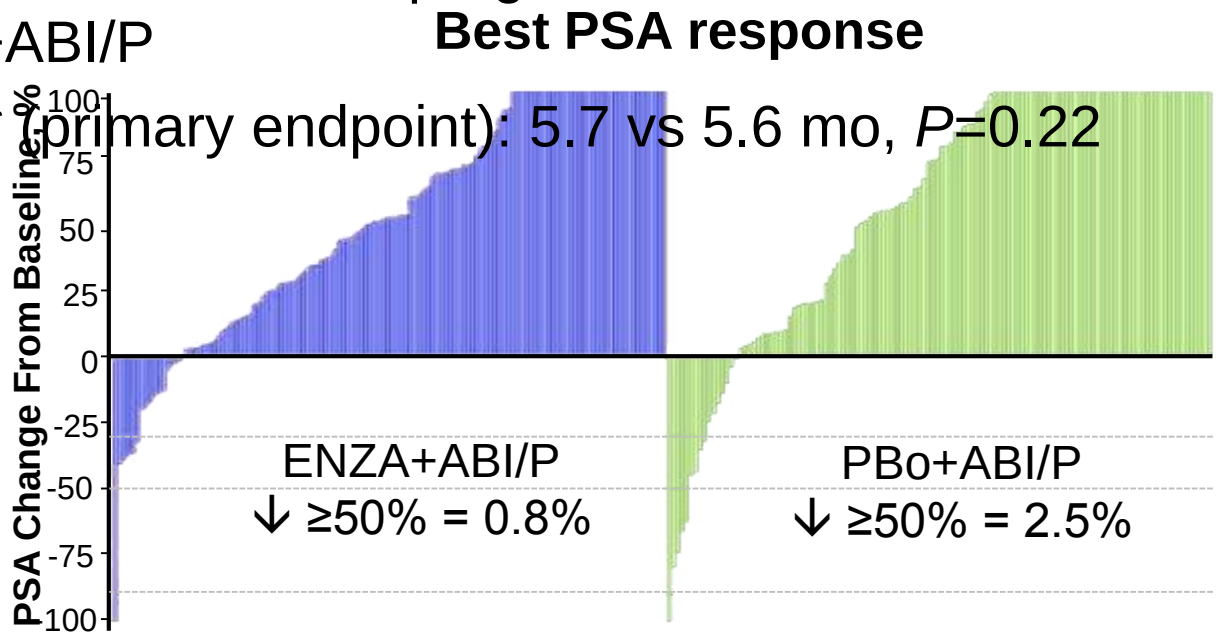
- Poor response to ENZA if progression on ABI
- Poor response to ABI if progression on ENZA

- NICE (UK) does not permit use of sequential ART if there is progression on first ART

https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/prostate-cancer

# Cross-resistance between ART agents

- PLATO - Prospective, phase IV, double-blind, pbo-controlled study
  in 251 chemonaive mCRPC with PSA response to ENZA > 3 months
- Randomized at PSA progression to ENZA+ABI/P vs Pbo+ABI/P
- PFS* (primary endpoint): 5.7 vs 5.6 mo, *P*=0.22

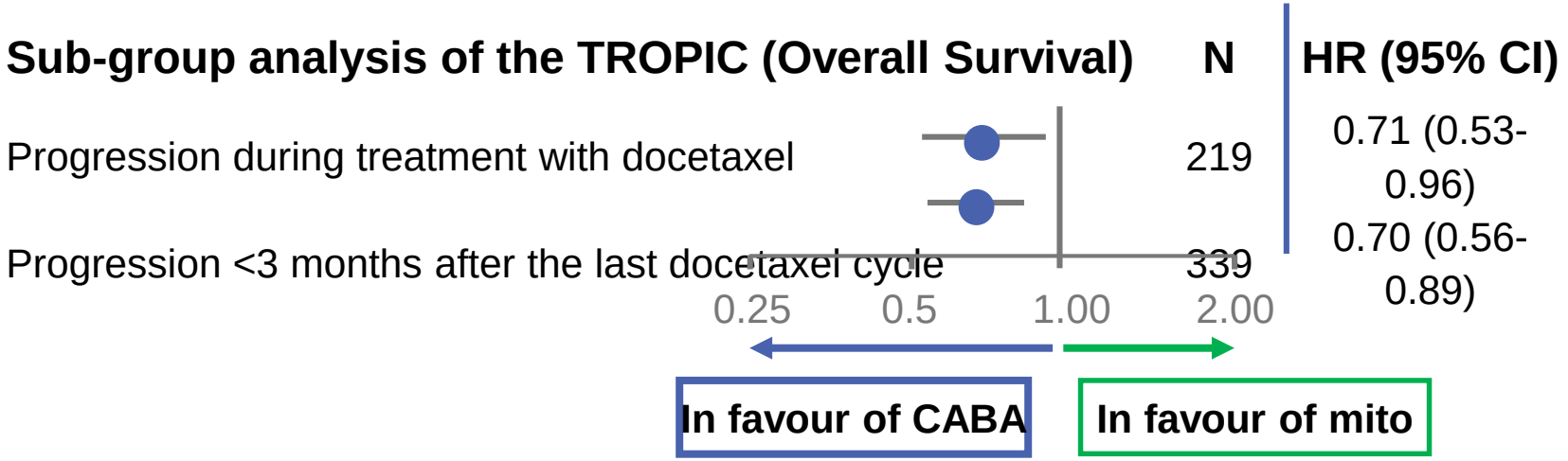



**PFS: radiological progression or unequivocal clinical progression*

Attard G et al. J Clin Oncol 2017.35.(suppl).(abstract 5004 (podium presentation) - NCT01995513

# Cabazitaxel is effective in patients progressing during or rapidly after last docetaxel cycle

## TROPIC trial[1-2]

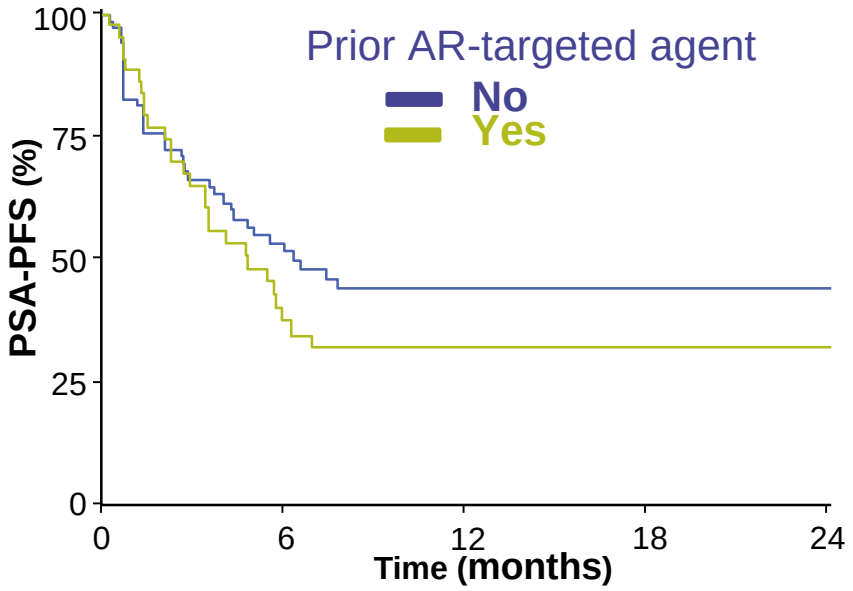



## Cabazitaxel also acts in cases of primary resistance to docetaxel[3]

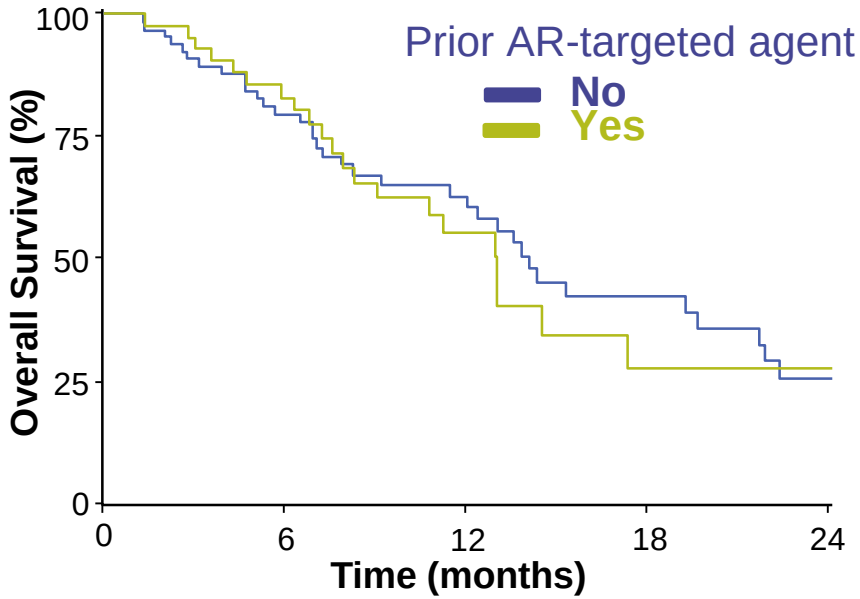
1. De Bono J et al. Lancet 2010;376:1147-54; 2. Oudard S et al. Future Oncol 2011;7:497-506;
3. Di Lorenzo G et al. Eur Urol 2014;65:502-7

# Cabazitaxel remains active in patients progressing with an AR-targeted agent

## Progression-free survival



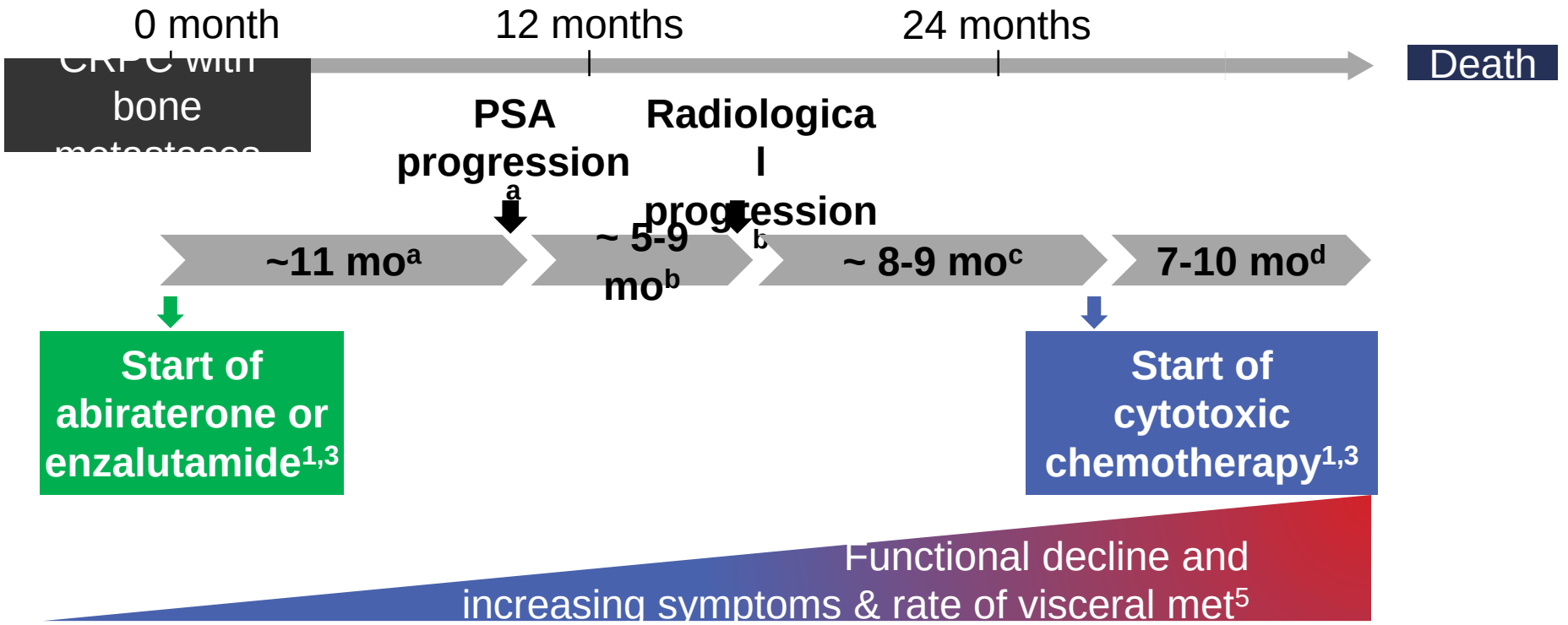

## Overall survival




Prospective, randomized phase 2 study of cabazitaxel ± budesonide

Van Soest R et al. Eur J Cancer 2015;51:2562-9

# A closer look at time to events in the COU-AA-302 and PREVAIL studies

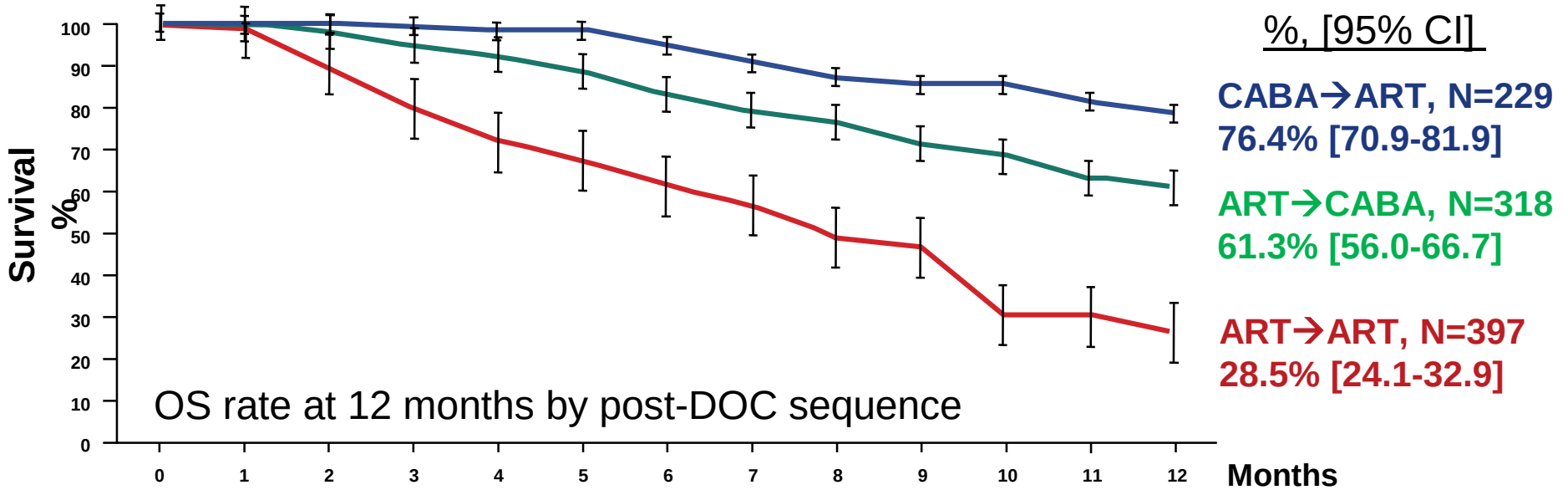



| | Median time to … (months) | | | |
|---|---|---|---|---|
| | a: PSA progression | b: Radiological PFS | c: Start of cytotoxic chemotherapy | d: Death |
| COU-AA-302 | 11.1[1] | 16.5[1] | 25.2[1] | 34.7[2] |
| PREVAIL | 11.2[3] | 20.0[4] | 28.0[3] | 35.3[4] |

# Is there an optimal treatment sequence in mCRPC?

# Systematic review of 13 published retrospective studies in mCRPC (N=1016)

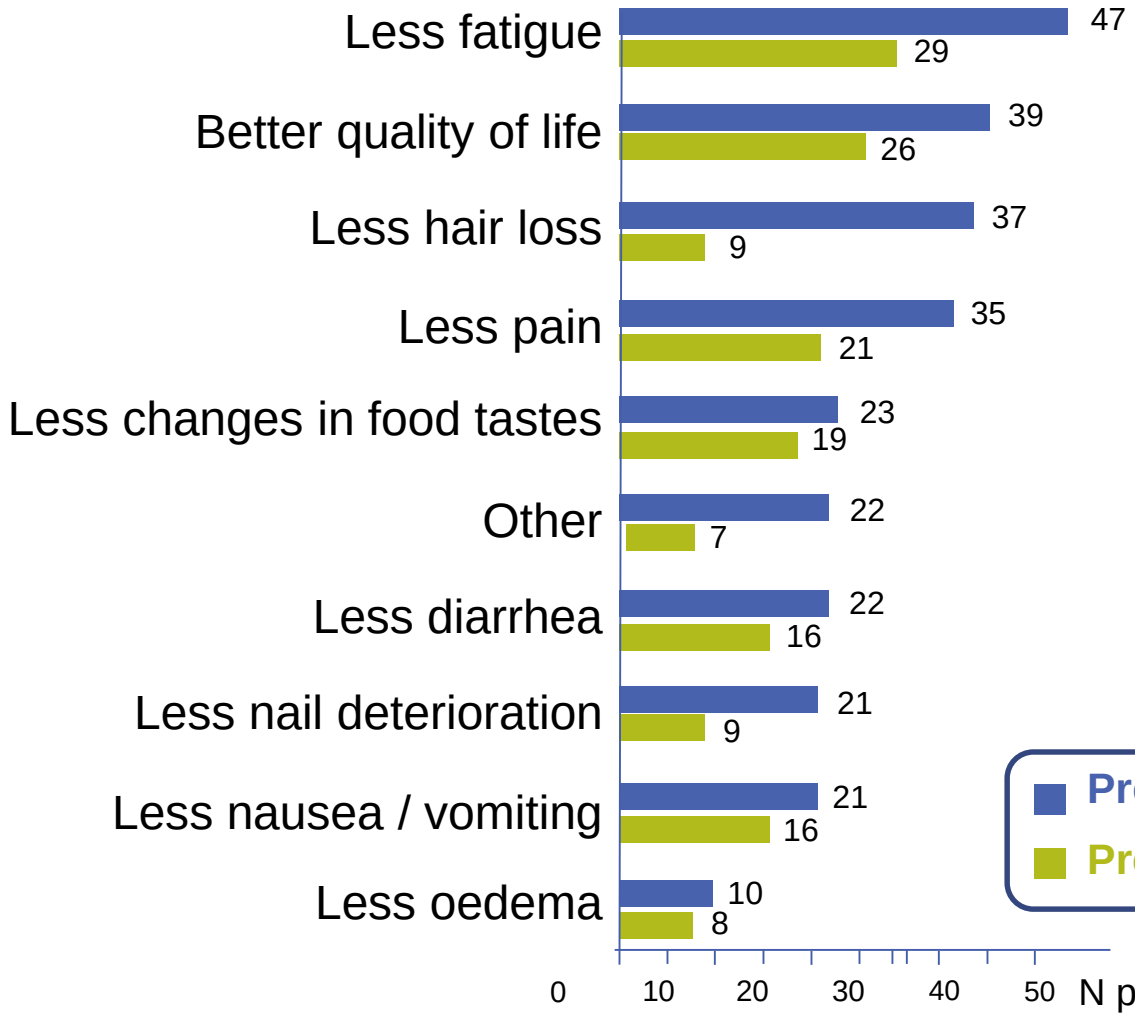
**2 taxanes (DOC, CABA) and 1 ART seem to give better OS than 1 taxane (DOC) and 2 ART in sequence**




**…..despite this majority of mCRPC cases get maximum of 1 chemotherapy**

Maines F et al. Crit Rev Hematol Oncol 2015;96:498-506

# CABA-DOC phase III trial
# Patient preference




- 195 chemonaive mCRPC pts
- Randomized to :
  - DOC (4 cycles) → CABA (4 cycles)
  - or CABA (4 cycles) → DOC (4 cycles)
- Primary endpoint: patient preference ***"Which treatment did you prefer? "***
  - 27% preferred DOC
  - 43% preferred CABA
  - 30% had no preference

Fizazi K et al. Ann Oncol 2017;28:276 (abstract 802P and poster presentation)

# The ‘concern factor’ with chemotherapy patient acceptance

- **Important to establish the goals for long term**
- Remember it is **NOT** ***‘one OR the other’***
  it is ***‘one AFTER the other’***
- It appears that earlier use of chemotherapy will be potentially advantageous
  - Also likely to be better tolerated
  - Two basic questions to consider
    1. **Is the patient likely to die from his mCRPC?**
    2. **Is the patient fit and willing to have chemotherapy?**

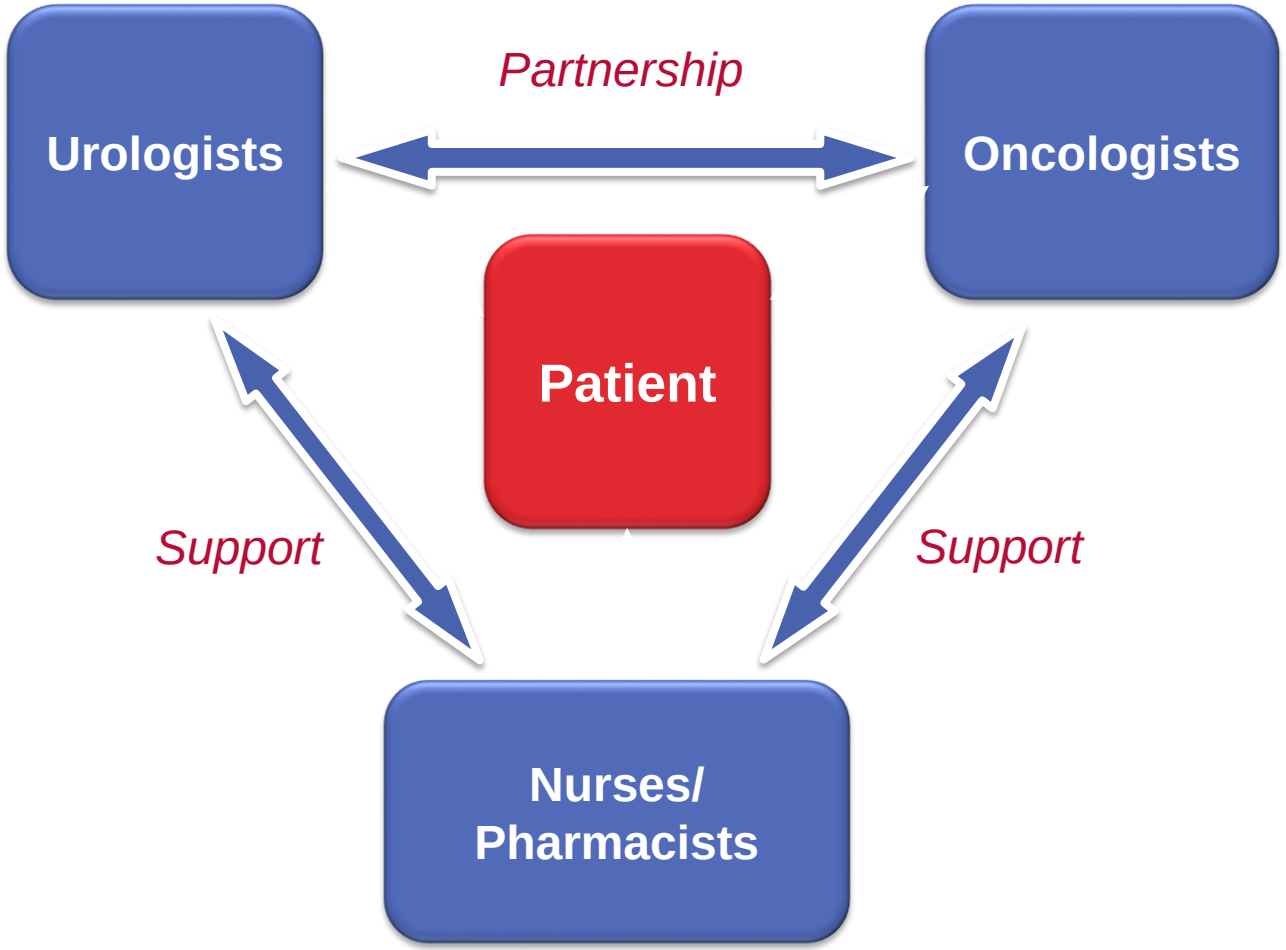
**My View:**
**If the answer to both these questions is ‘YES’ then preferable**

**to use chemotherapy earlier rather than as a last resort**

# The challenge for the uro-oncologist in mCRPC

- **To identify mCRPC patients with poor response to enzalutamide or abiraterone**
  *... and to offer them first-line chemotherapy*
- **To identify disease progression on first-line treatment**
  **at an early time point**
  *… and to offer subsequent therapy before performance status deteriorates*
- **To pro-actively manage adverse events of new treatment options**
  *… to optimize treatment outcomes (quality of life, survival)*
- **Multidisciplinary care a key to success!!**

# Patient management
# A patient-centered partnership



# My personal view and hope…

‘All Eligible Patients should avail the benefits of all proven and effective treatments to …

**MAXIMISE SURVIVAL WITH PRESERVED/IMPROVED QOL’**

# Thank you