Best fellowship project 1

ESMO Translational Fellowship 2014-2016

Title of the project:
Novel biological profiles of sensitivity and/or resistance to Abiraterone and/or Enzalutamide in patients with castration-resistant prostate cancer (CRPC)

Fellow: Vincenza Conteduca, MD, PhD

Home Institute:
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), Meldola, Italy

Chief Urological and Gynecological Unit:
Dr Ugo De Giorgi

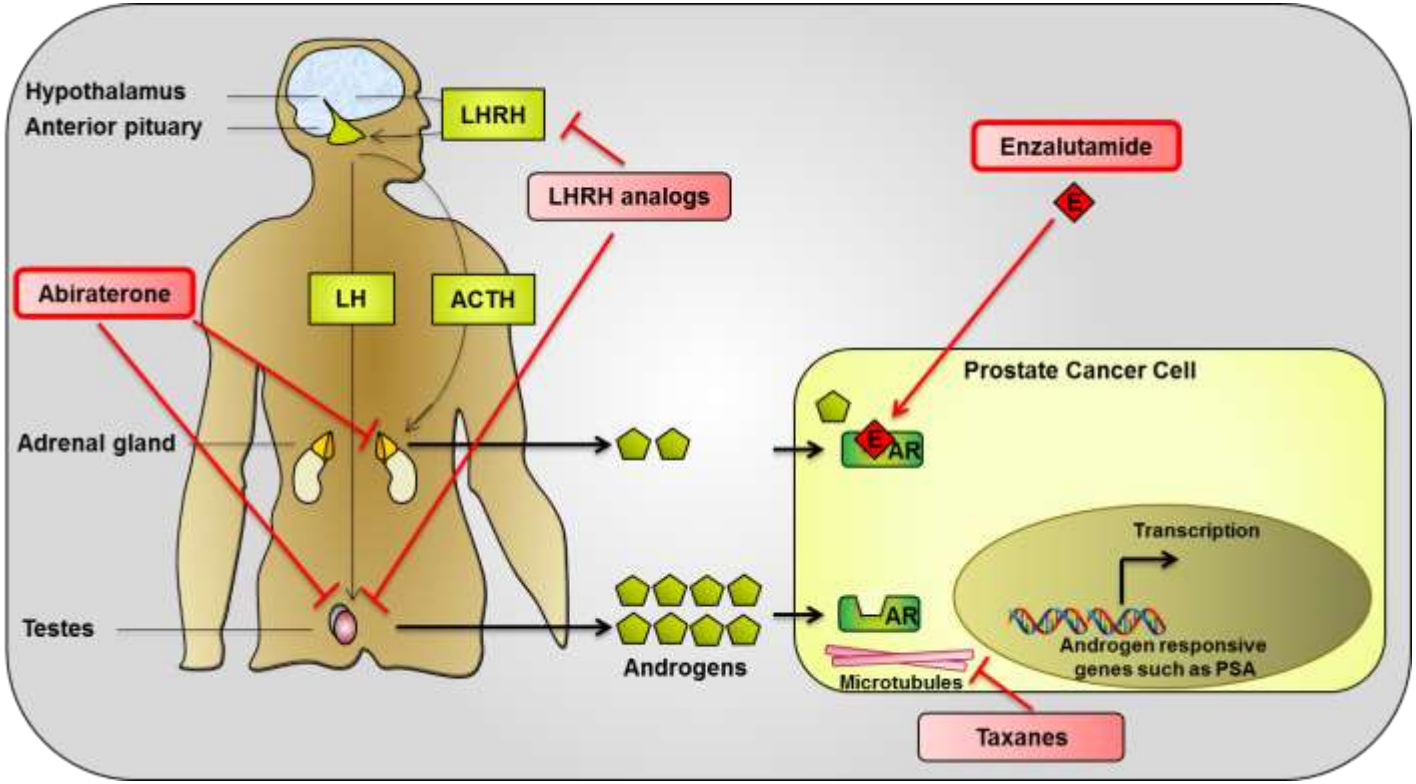
Host Institute:
The Institute of Cancer Research, Sutton, UK

Mentor: Dr Gerhardt Attard

DISCLOSURE

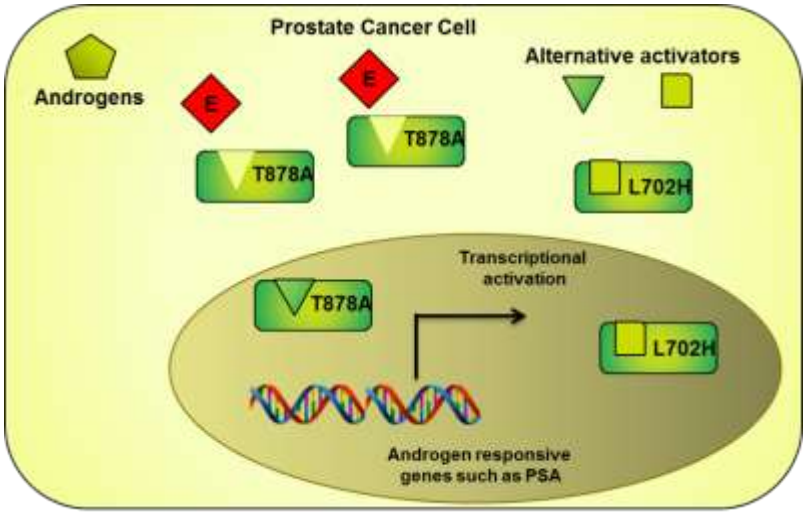
I have nothing to declare

Androgen signalling and Anti-androgen therapies in Prostate Cancer

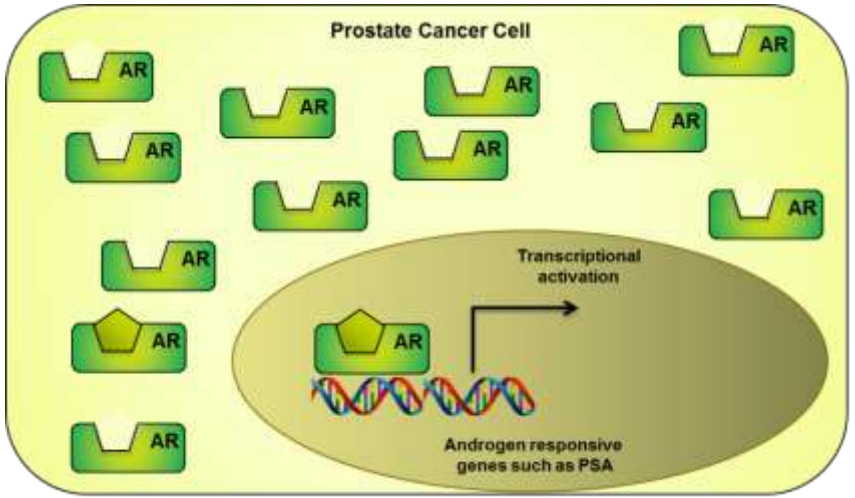


Mechanisms of resistance to Anti-androgen therapies in Prostate Cancer

Point Somatic Mutations of Androgen Receptor (5-30%)



Amplification of Androgen Receptor (10-50%)



Liquid biopsy / ctDNA studies to monitor treatment resistance in CRPC patients

Manuscripts from ESMO fellowship:

1) Plasma AR and abiraterone-resistant prostate cancer, *Romanel A, Gasi Tandefelt D,* ***Conteduca V*** *et.al,* Science Translational Medicine, 2015

2) Androgen receptor gene status in plasma DNA associates with worse outcome on enzalutamide or abiraterone for castration-resistant prostate cancer: a multi-institution correlative biomarker study, ***Conteduca V*** et.al, Annals of Oncology, 2017

- **Conteduca V**, et al. Long-term clinical impact of PSA surge in castration-resistant prostate cancer patients treated with abiraterone, Prostate 2017
- Salvi S, Casadio V, **Conteduca V**, et al. Circulating AR copy number and outcome to enzalutamide in docetaxel-treated metastatic castration-resistant prostate cancer. Oncotarget. 2016
- **Conteduca V**, et al. Persistent Neutrophil to Lymphocyte Ratio >3 during Treatment with Enzalutamide and Clinical Outcome in Patients with Castration-Resistant Prostate Cancer. PLoSOne. 2016
- **Conteduca V**, et al. Association Between Early PSA Increase and Clinical Outcome in Patients Treated with Enzalutamide for Metastatic Castration Resistant Prostate Cancer. Mol Diagn Ther 2016
- Salvi S, Casadio V, **Conteduca V**, et al. CYP17A1 polymorphisms and clinical outcome of castration-resistant prostate cancer patients treated with abiraterone. Int J Biol Markers. 2016
- **Conteduca V**, et al. Impact of visceral metastases on outcome to abiraterone after docetaxel in castration-resistant prostate cancer patients. Future Oncol 2015
- Salvi S, Casadio V, **Conteduca V**, et al. Circulating cell-free AR and CYP17A1 copy number variations may associate with outcome of metastatic castration-resistant prostate cancer patients treated with abiraterone. Br J Cancer 2015
- **Conteduca V**, et al. Chromogranin A is a potential prognostic marker in prostate cancer patients treated with enzalutamide. Prostate 2014

ctDNA studies to monitor treatment resistance in CRPC patients

Aim: To identify genomic aberrations that associate and/or emerge with resistance to abiraterone or enzalutamide

Strategy: Sequentially collected plasma samples

Study 1) **Targeted NGS** allowing;

- Quantitation of circulating tumour DNA fraction
- Identification of aberrations in *AR, PTEN, TP53, SPOP, FOXA1 and CYP17A1*

Study 2) **Droplet Digital PCR** allowing;

- Detection and validation of *AR* aberrations

Hypothesis: *AR* aberrations found in liquid biopsies associate with resistance to abiraterone and enzalutamide

Study 1)

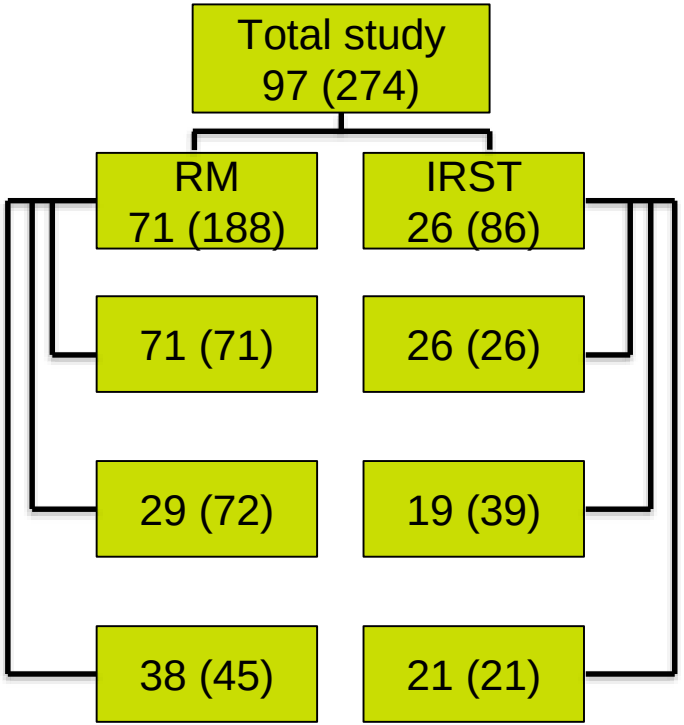
Plasma AR and abiraterone-resistant prostate cancer,

Romanel A, Gasi Tandefelt D, **Conteduca V** et.al,

Science Translational Medicine, 2015

Study Design

- Patients receiving abiraterone between 2011-2014
- Mostly post-chemotherapy patients
- Royal Marsden hospital (RM), London, UK
- Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola, Italy



Targeted NGS

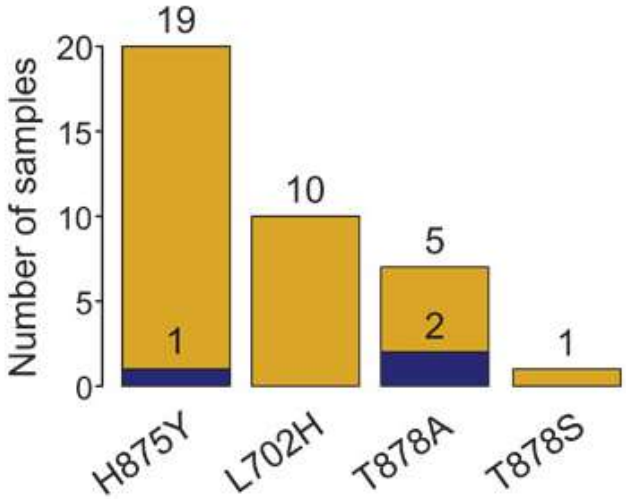
- Targeted NGS panel covering 39,000bp (median coverage = 1434X)
- Input of 6-10ng DNA
- Ion Ampliseq NGS

Chromosome and gene targets	Bases covered	Amplicons (n)	Amplicon bp length
8p23 including NKX3.1	10017	87	73-140
10q23 including PTEN	8060	37	64-133
CYP17A1	2315	21	82-134
FOXA1	1526	14	87-129
TP53	2036	19	93-128
SPOP	1682	16	72-127
21q22 including TMPRSS2-ERG	12005	107	75-137
AR	3478	30	78-137

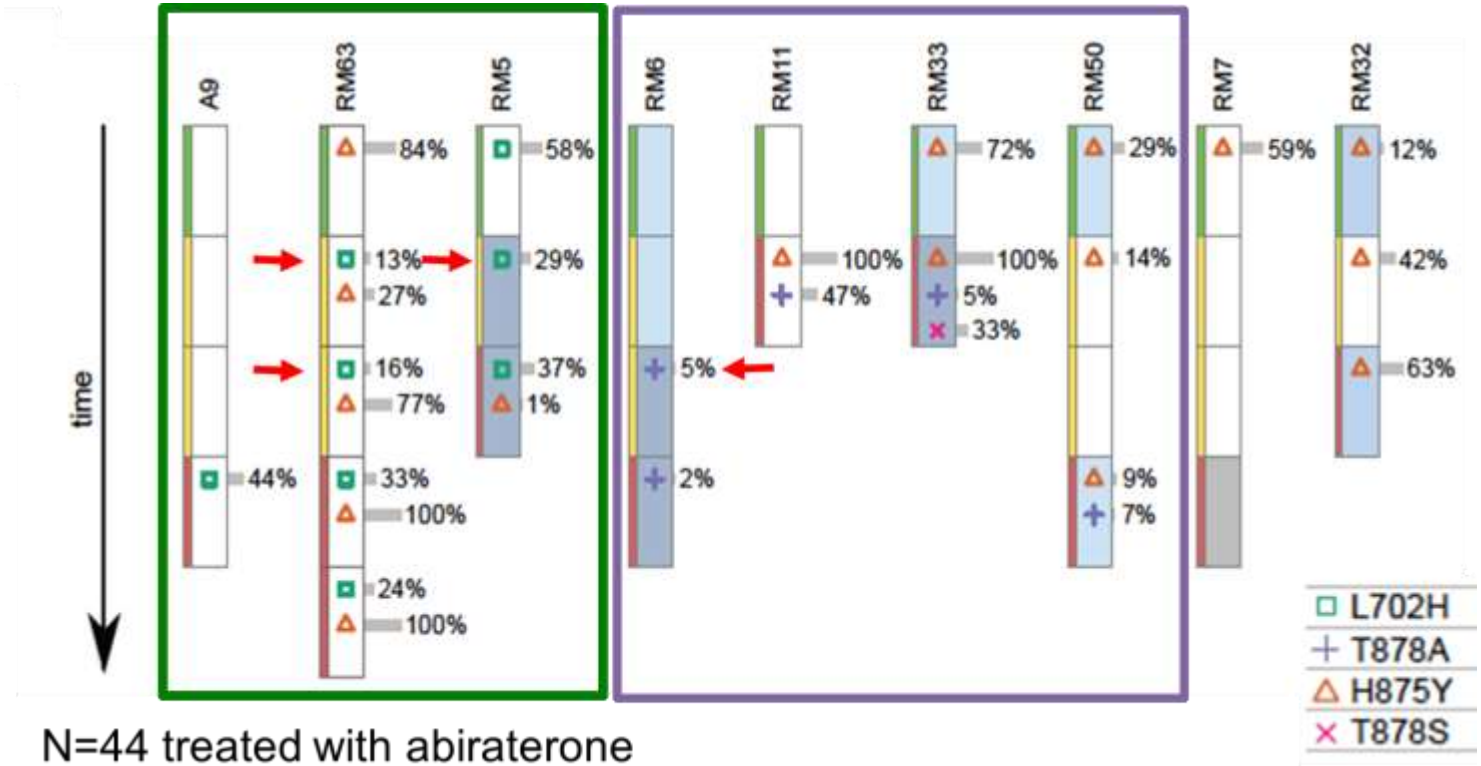
AR aberrations : Mutual exclusivity between *AR* gained and mutated alleles

	n = 217	Mut *n* (%)	WT *n* (%)
81	*AR* gain	3 (4%)	78 (96%)
136	*AR* CN neutral	23 (17%)	113 (83%)

P value = 0.004
OR, 0.190

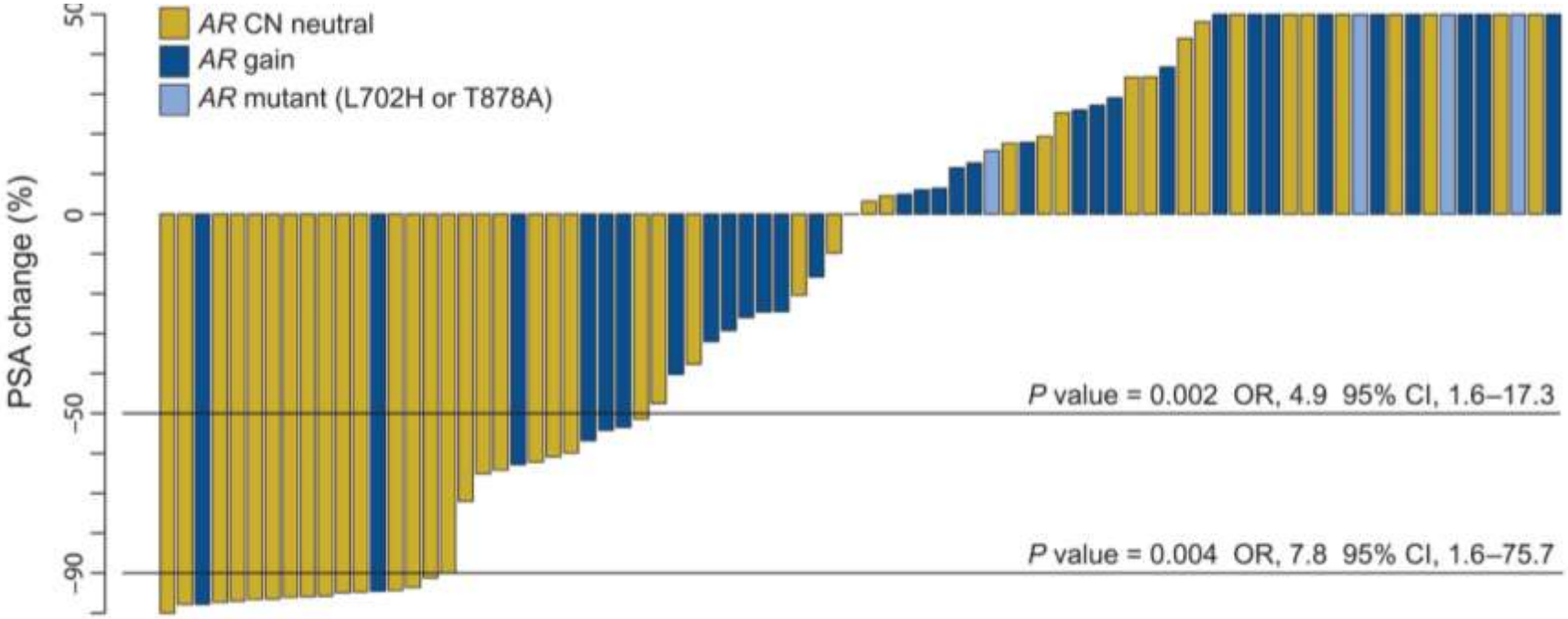


Emergence and persistence of *AR* L702H and T878A mutations with abiraterone treatment

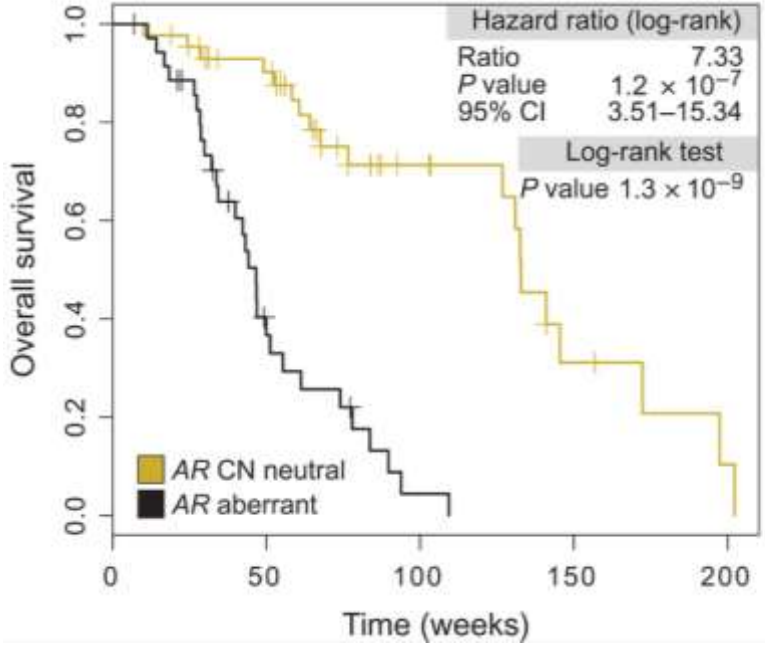


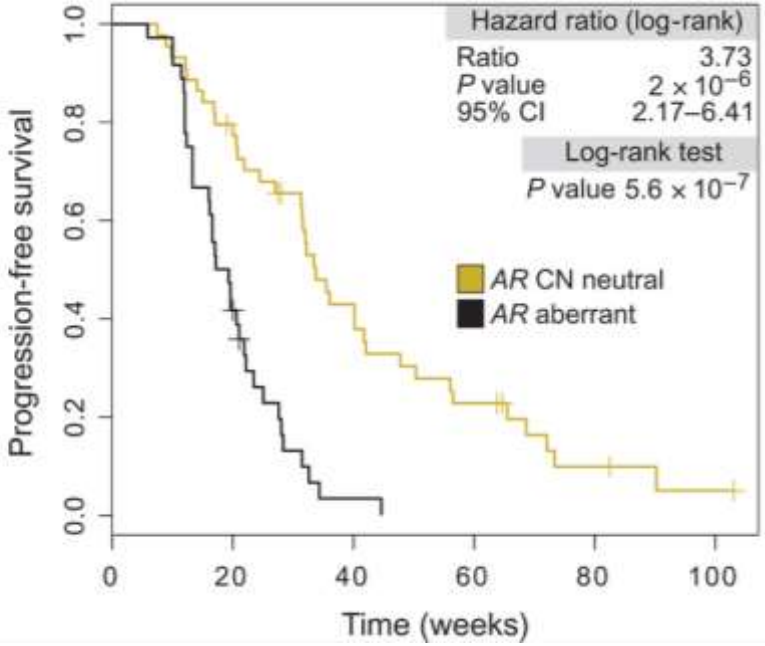
N=44 treated with abiraterone

Association of *AR* gene status with PSA response



Association of *AR* status with overall survival and progression-free survival

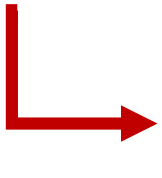




Study 2)

Androgen receptor gene status in plasma DNA associates with worse outcome on enzalutamide or abiraterone for castration-resistant prostate cancer: a multi-institution correlative biomarker study,

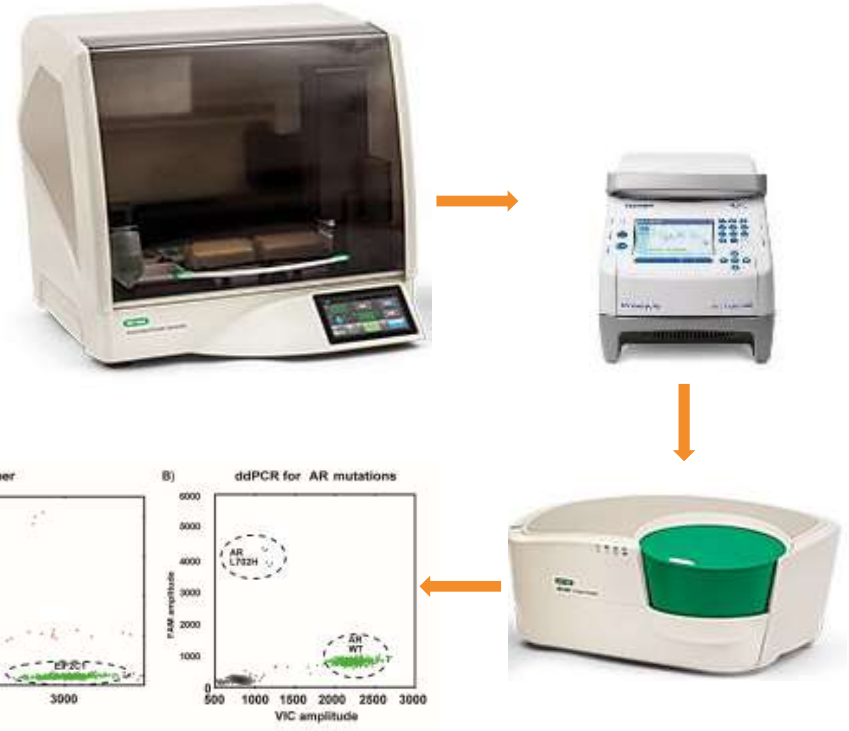
Conteduca V et al, Annals of Oncology, 2017



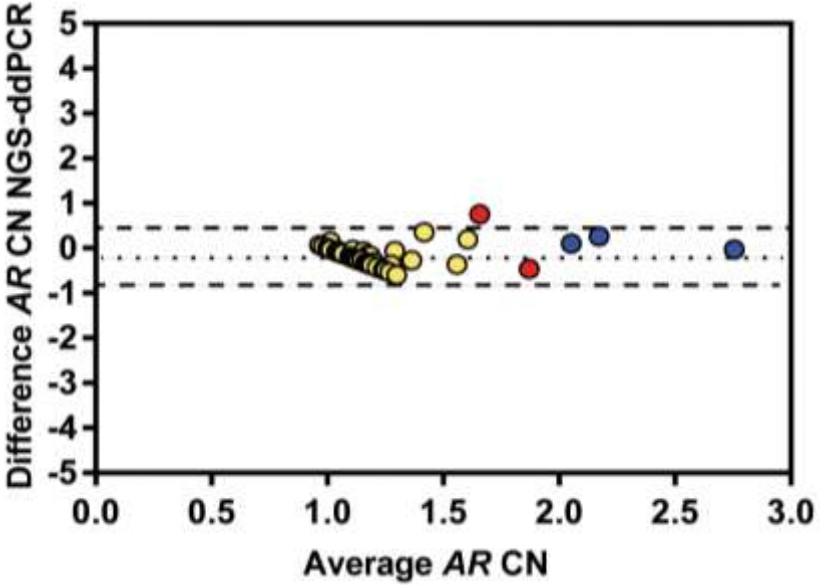
Conquer Cancer Foundation Merit Award 2017

Droplet Digital PCR for determining *AR* status in plasma

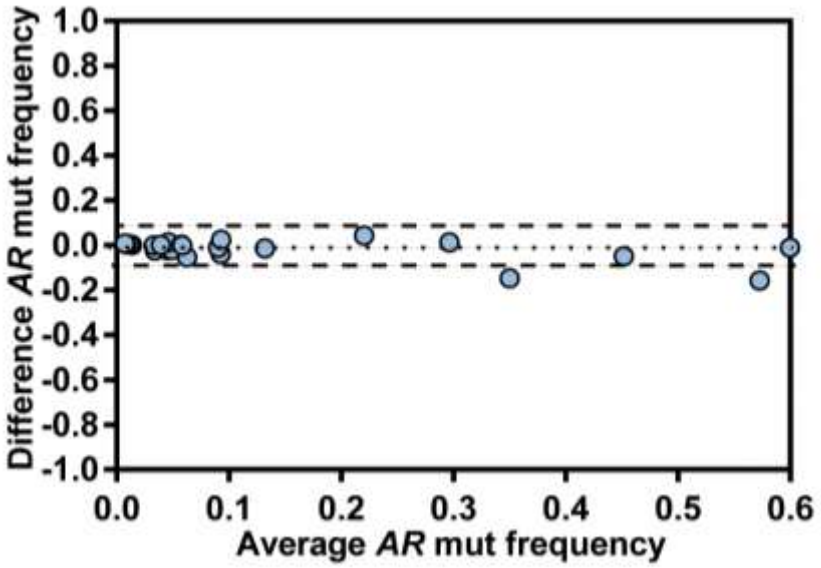
- A PCR reaction divided into 20000 droplets by mixing the PCR solution with oil
- The fluorescence intensity is measured for each droplet
- Allows absolute quantification of DNA copies
- Suitable for low DNA input 1-3ng
- Multiplexing assay with 4 reference genes



Method comparison of Targeted NGS and ddPCR for determining *AR* status



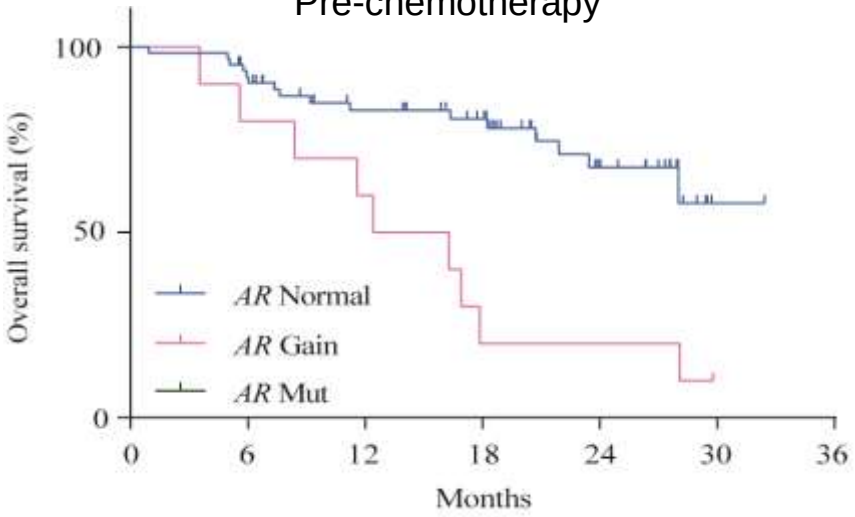
Bias **-0.20**
SD of bias **0.81**



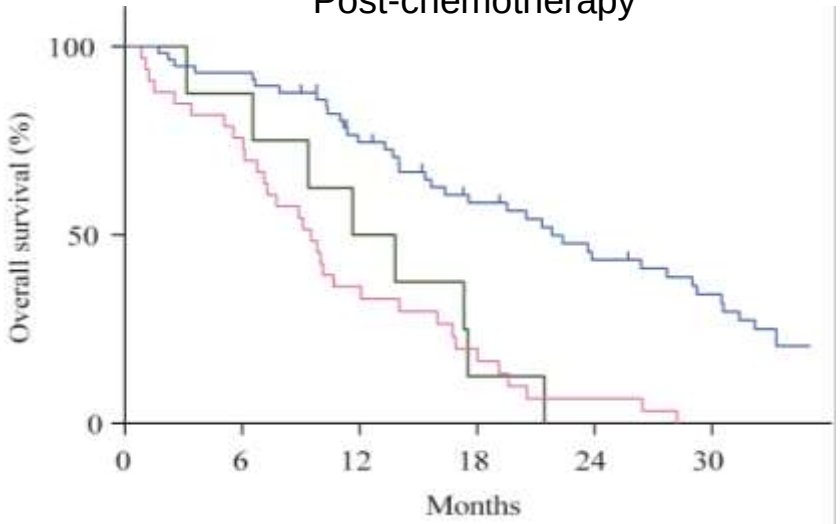
Bias **-0.018**
SD of bias **0.046**

Association of *AR* status with overall survival in patient treated with abiraterone or enzalutamide

Pre-chemotherapy

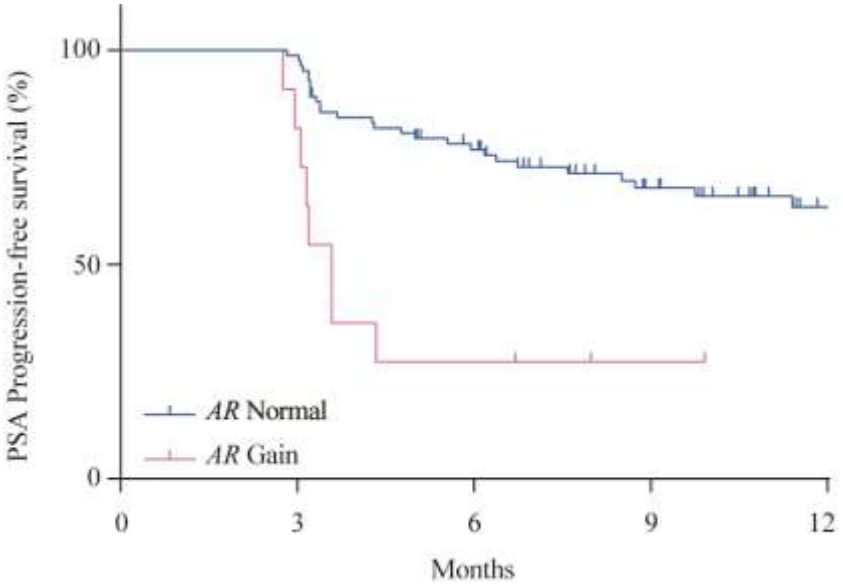


Post-chemotherapy

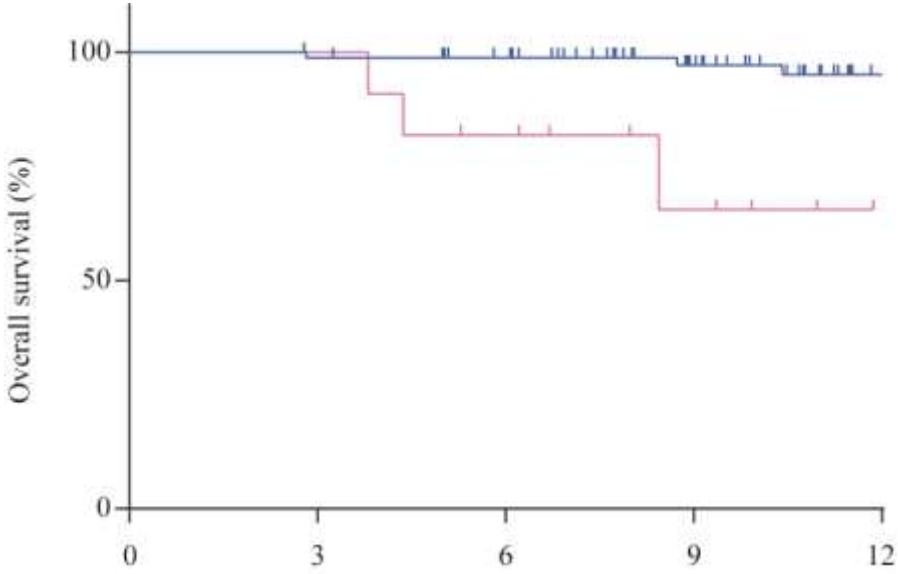


***AR* gain (yes vs no): HR 4.26 (2.76-6.55), p<0.001**
***AR* mutant (yes vs no): HR 3.80 (1.77-8.15), p=0.001**

Confirmation of data in the second cohort (PREMIERE trial)



HR: 4.33 (1.94-9.68)
p-value: <0.001



HR: 11.08 (2.16-56.95)
p-value: 0.004

CONCLUSIONS

- Higher incidence of AR L702H/T878A in 15-20% of patients progressing on abiraterone – opportunity for early treatment change
- AR copy number gain/mutations associate with resistance to abiraterone or enzalutamide (irrespective of chemotherapy status)

FUTURE DIRECTIONS

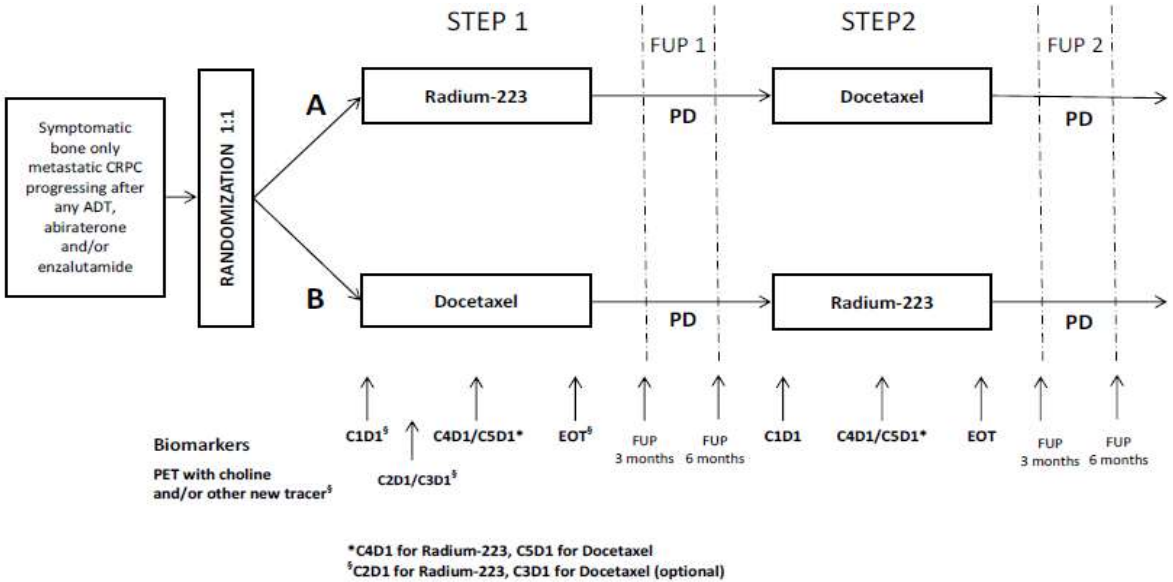
- Patient randomisation/treatment decision based on plasma DNA profile
- Evaluation of circulating *AR* aberrations in patients treated with other therapies for CRPC
- Identification of additional mechanisms of resistance to systemic treatments

17th joint ECCO-AACR-EORTC-ESMO Workshop 'Methods in Clinical Cancer Research'

Randomized, multicentre phase II trial of the sequencing of Radium-223 and Docetaxel plus prednisone in symptomatic bone-only mCRPC

Approval in 2017 – Trial ongoing

Protocol Code: IRST185.04
IRST-Identifier Code: L2P1304
Eudract number: 2016-004452-29
Date and Version No: 22/02/2017 – Version 1.0
Short title/Acronym: RAPSON
Chief Investigator: Dr. Vincenza Conteduca



Acknowledgements

ICR The Institute of Cancer Research

Gert Attard &
Treatment Resistance Group
Daniel Wetterskog, Anna Wingate, Karolina Nowakowska, Anjui Wu, Anu Jayaram, Paolo Cremaschi, Emily Grist, Delila Gasi-Tandefelt, Lesley Carr

IRST, Meldola Italy

Ugo De Giorgi &
Uro-ginecological Group
Samanta Salvi, Valentina Casadio, Giorgia Gurioli, Cristian Lolli, Giuseppe Schepisi, Alberto Farolfi, Filippo Martignano, Luca Burgio, Cecilia Menna,, Lorena Rossi, Delia Delisi, Sara Testoni, Valentina Galla', Giorgia Ravaglia, Dino Amadori,

Other collaborations:

- PREMIERE study, Spain
Enrique Gonzalez-Billalabeitia
Enrique Grande, Maria Piedad Fernandez-Perez, et al.

- University of Trento, Italy
Francesca Demichelis
Alessandro Romanel, Nicola Casiraghi, et al.

- Weill Cornell University, New York
Himisha Beltran, et al.

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