

Molecular Tumor Board
MTB Case Series

Dr. Niven Mehra
13 November 2019

Disclosures Niven Mehra

- Belangenverstrengeling voor deze lezing: geen
- Voor nascholing mogelijk relevante relaties met bedrijven: geen
- Onderzoeksgeld (instituut): Astellas, Janssen, Pfizer, Roche, Sanofi Genzyme
- Honorarium or travel grants : Roche, MSD, BMS, Bayer, Sanofi Genzyme, Astellas, Janssen, Roche

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De belangen van een MTB

- Persoonsgericht behandeladvies (klinisch onderzoek/off-label)
- Continue educatie
- Kostenefficiëntie binnen de zorg
- Wetenschappelijke output

Willemsen, A et al. NTVO 2019;16:264-70

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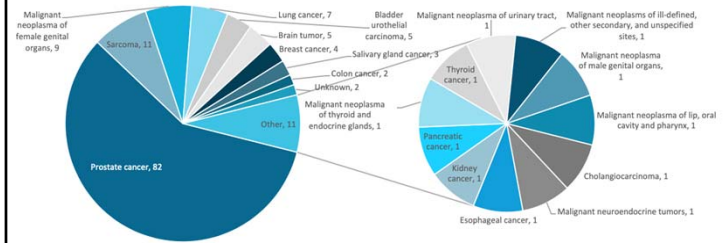
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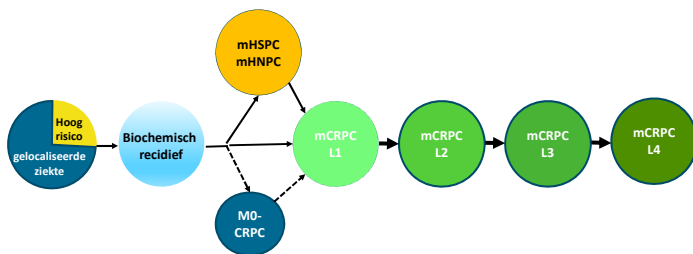
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MTB Radboudumc 2018



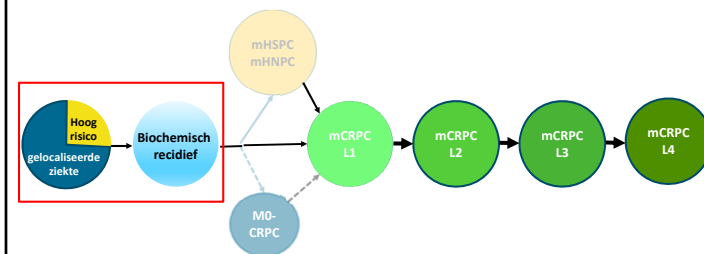
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Personalized medicine for patients with metastatic prostate cancer

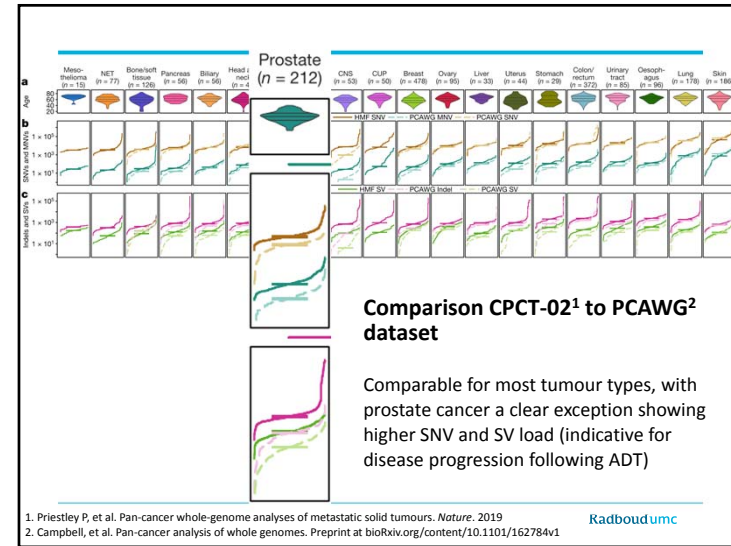
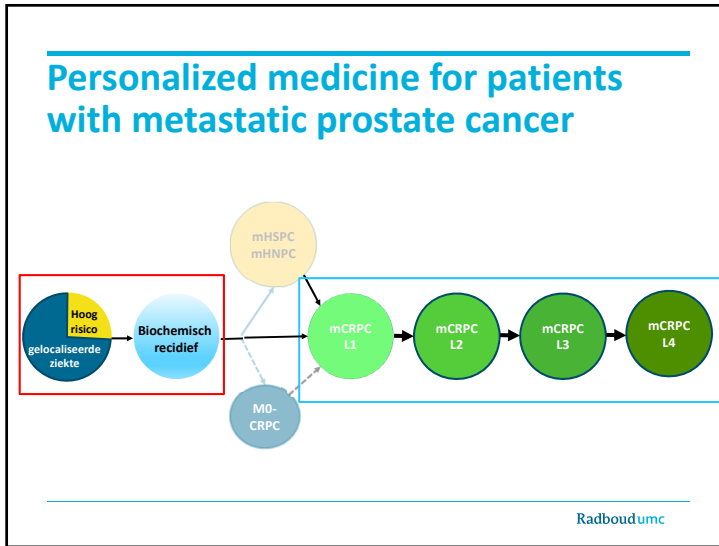


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Personalized medicine for patients with metastatic prostate cancer



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1. Priestley P, et al. Pan-cancer whole-genome analyses of metastatic solid tumours. *Nature*. 2019
 2. Campbell, et al. Pan-cancer analysis of whole genomes. Preprint at bioRxiv.org/content/10.1101/162784v1

Cell
Resource

Integrative Clinical Genomics of Advanced Prostate Cancer

Graphical Abstract

Authors
 Dan Robinson, Eliezer M. Van Allen, ..., Charles L. Sawyers, Arul M. Chinnaiyan

Correspondence
 sawyersc@mskcc.org (C.L.S.), arul@umich.edu (A.M.C.)

In Brief
 A multi-institutional integrative clinical sequencing analysis reveals that the majority of affected individuals with metastatic castration-resistant prostate cancer harbor clinically actionable molecular alterations, highlighting the need for genetic counseling to inform precision medicine in affected individuals with advanced prostate cancer.

Characteristics

High TMB/ MSI 4-7% **MMR** A

CDK12/ tandem duplicator 7% **HR/DDRd** B

BRCA2/ BRCAness 7% **HR** D

ATM 7% **DDRd**

DDRd (other) 10-15% **DDRd**

PTEN / PIK3CA 50% **PI3K**

CDKN2A/ CCND1 5% **Cell cycle**

MAP3K1 1% **MEK**

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Personalized medicine for patients with metastatic prostate cancer

Characteristics	n	Pathway	Cluster	Personalized medicine	Trials
High TMB/ MSI	4-7%	MMR	A	Checkpoint Immunotherapy, CD3-PSMA bite, DC vaccination	DRUP, INSPIRE, KEYLYNK-010, MK-921, MK-642
CDK12/ tandem duplicator	7%	HR/DDRd	B	Checkpoint immunotherapy, PARP inhibition	DRUP, INSPIRE, olaparib SOC, KEYLYNK-010, MK-921, MK-642
BRCA2/ BRCAness	7%	HR	D	PARP inhibition, checkpoint immunotherapy	DRUP, Olaparib SOC, INSPIRE, KEYLYNK-010, MK-921, MK-642
ATM	7%	DDRd		PARP inhibition	DRUP, Olaparib SOC, INSPIRE, KEYLYNK-010, MK-921, MK-642
DDRd (other)	10-15%	DDRd		PARP inhibition	DRUP, talazoparib
PTEN / PIK3CA	50%	PI3K		Ipatasertib / alpelisib	tbd
CDKN2A/ CCND1	5%	Cell cycle		Palbociclib	DRUP
MAP3K1	1%	MEK		Trametinib	DRUP

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Integrative Clinical Genomics of Advanced Prostate Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 20, 2015 VOL. 373 NO. 58

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carrera, S. Sardua, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nova Rodriguez, D. Robinson, A. Orsini, M. Taramelli, G. Bortolin, M. Pavia, P. Rubin, A. Gilman, J. Figueroa, C. Trudgill, G. Sesti, S. Jain, C. Rajh, A. Pribitkin, S. Hussain, B. Jones, T. Elliott, U. McGowan, D. Bismahon, J. Goodall, Z. Zelenko, C.T. Williams, R. Parakevicius, R. Bissani, B. Ellis, C. Forster, D. Roda, W. Yuan, Y. Ak, M. Cole, R. Brough, H. Pemberton, R. A'Hern, A. Swan, L.P. Kuntz, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.T. Fong, A.M. Chinnayyan, G. Hall and S.S. Bono

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carrera, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Longiro, M. Hussain, A. Chinnayyan, J. Vinton, J. Filipenko, L. Caraway, M.E. Taplin, S. Abdubayyan, G.C. Han, M. Brigstad, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.J. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robinson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

ESMO LBA12 PR

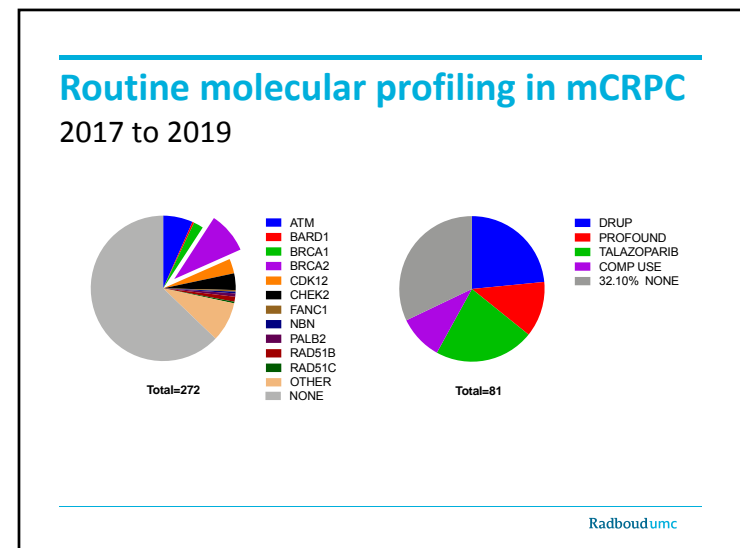
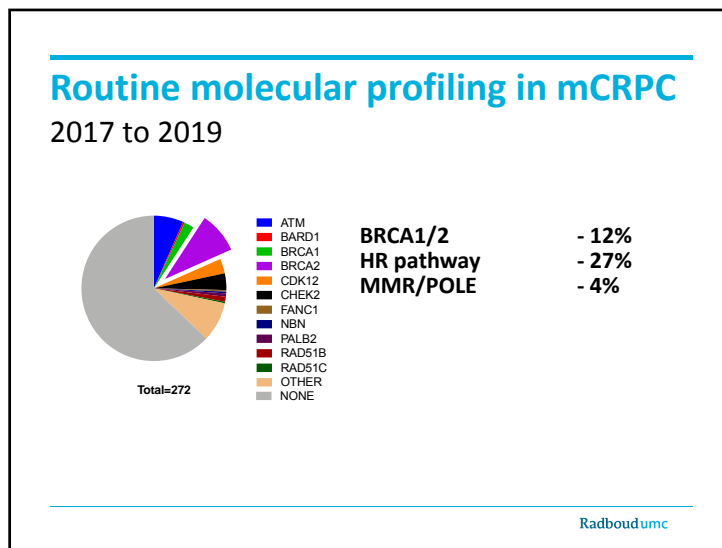
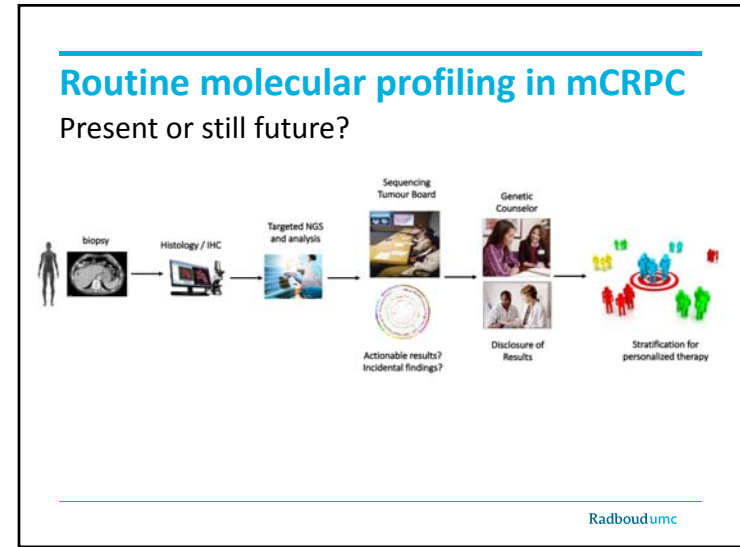
PROFOUND: PHASE III STUDY OF OLAPARIB VERSUS ENZALUTAMIDE OR ABIRATERONE FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER WITH HOMOLOGOUS RECOMBINATION REPAIR GENE ALTERATIONS

Maha Hussain,¹ Joaquin Mateo,² Karim Fizazi,³ Fred Saad,⁴ Neal Shore,⁵ Shahnawaz Sandhu,⁶ Kim N. Chi,⁷ Oliver Sartor,⁸ Neeraj Aggarwal,⁹ David Citron,¹⁰ Antonio Tilly-Vulliamy,¹¹ Przemyslaw Twardowski,¹² Niven Mehra,¹³ Carsten Goessi,¹⁴ Jiayu Kang,¹⁵ Joseph Burgetts,¹⁶ Wenting Wu,¹⁷ Alexander Koltman,¹⁸ Carrie A Adelman,¹⁹ Johann de Bono¹⁸

1. Dana-Farber Cancer Institute, Boston, MA; 2. University of Navarra, Madrid, Spain; 3. Institut Gustave Roussy, Paris, France; 4. Memorial Sloan-Kettering Cancer Center, New York, NY; 5. Dana-Farber Cancer Institute, Boston, MA; 6. University of Michigan, Ann Arbor, MI; 7. Dana-Farber Cancer Institute, Boston, MA; 8. Dana-Farber Cancer Institute, Boston, MA; 9. Dana-Farber Cancer Institute, Boston, MA; 10. Dana-Farber Cancer Institute, Boston, MA; 11. Dana-Farber Cancer Institute, Boston, MA; 12. Dana-Farber Cancer Institute, Boston, MA; 13. Dana-Farber Cancer Institute, Boston, MA; 14. Dana-Farber Cancer Institute, Boston, MA; 15. Dana-Farber Cancer Institute, Boston, MA; 16. Dana-Farber Cancer Institute, Boston, MA; 17. Dana-Farber Cancer Institute, Boston, MA; 18. AstraZeneca, Cambridge, UK; 19. The Centre for Cancer Research and Reproductive Sciences, London, UK.

This study was approved by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp, a subsidiary of Bristol-Myers Squibb (BMS) (USA/UK).

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Case 1 History

2015/6 diagnosis pT3bN0R1M0 prostate cancer, 49 years old
Gleason score 5+4, pathology review intraductal acinar adenocarcinoma

Prior therapy;

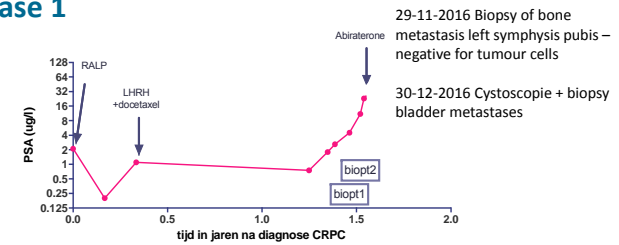
- 2015/6 Radical prostatectomy and extended lymph node resection
- 2016/1 LHRH
- 2016/2 Docetaxel 6# volgens CHAARTED schema
- 2016/10 Progressive disease with mediastinal lnn, metastasis os ischium, m.psoas

Referral to Radboudumc
Biopsy for molecular diagnostics

- 2016/12 Abiraterone-P

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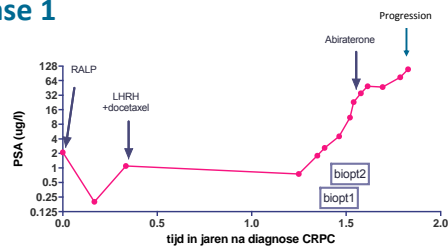
Case 1



- 2017/2 Radiotherapy 20Gy bladder for hematuria en retentio

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Case 1



- 2017/3 PD with new sclerotic bone metastases (pelvis/ clavicula/ costae/ L5), diffuse liver metastases, multiple lung metastases



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Case 1



CPCT-02 study

Whole genome sequencing: mutation **PIK3CB** and biallelic loss of **BRCA2**.
Mutational load 3.2 mutations/Mb

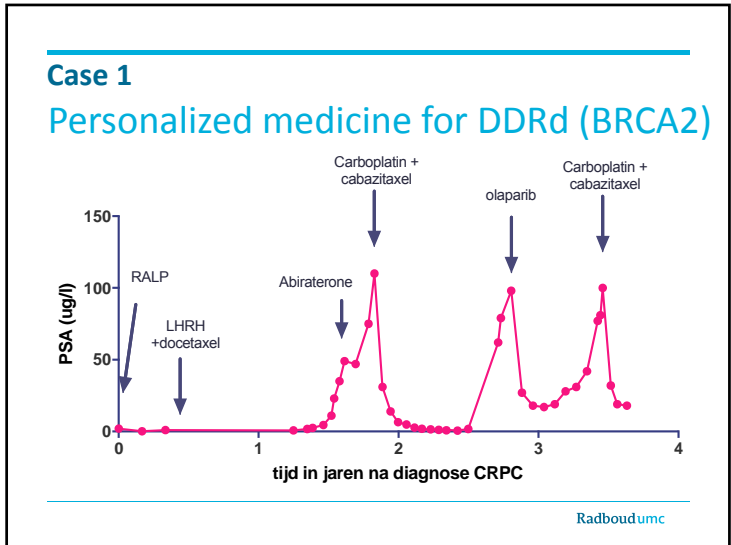
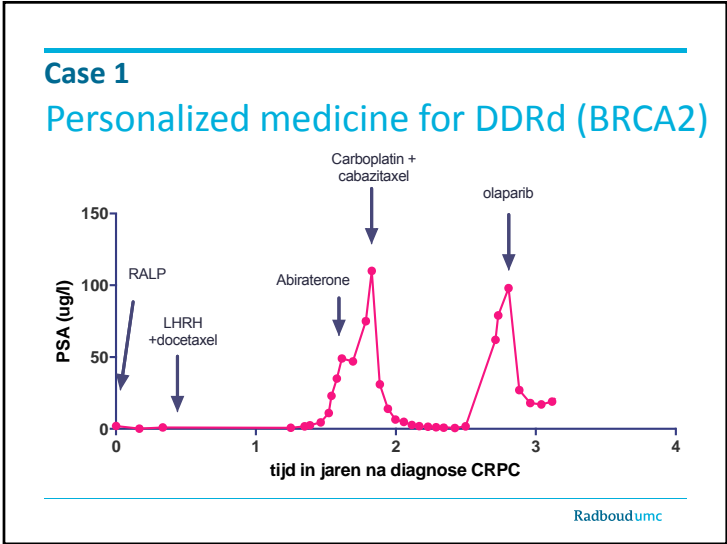
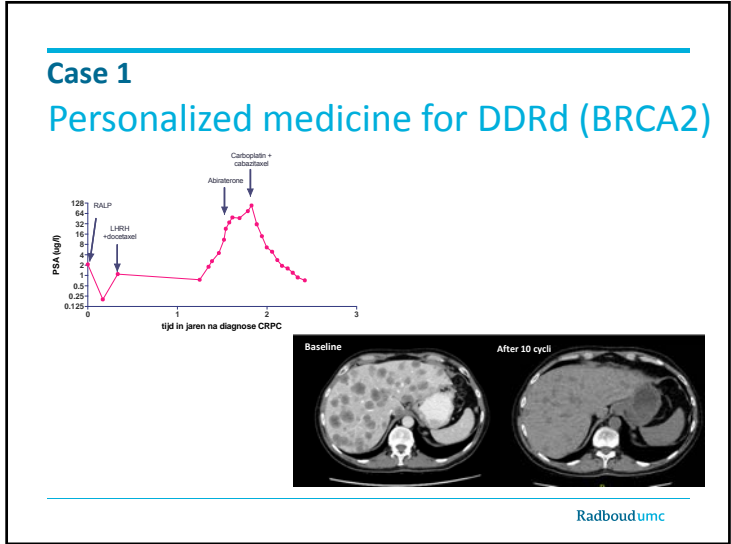
Pathology

MMR IHC **PSA** 30% focal positivity, 10-15% focal **PSMA** expression

MTB advise

PARP inhibitor or platinum-based chemotherapy

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Case 2 History

2012/6 diagnose pTxN1M1a prostaat carcinoom, iPSA 209, 51 jaar
 Gleason score 5+4, PA adenocarcinoom. BRCA1/2 dragerschap uitgesloten

Prior therapy;

- 2012/6 LHRH
- 2013/12 +bicalutamide
- 2014/12 Abiraterone-P
- 2016/2 Apalutamide (ARN-509)
- 2017/2 Fase 2 onderzoek DC vaccinatie
- 2018/6 Enzalutamide (weigert docetaxel)

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Case 2



Profound (FMI) en Talazoparib (FMI)
 Geen kwalificerende mutaties in panel van 15 en 12 DDR genen, resp.

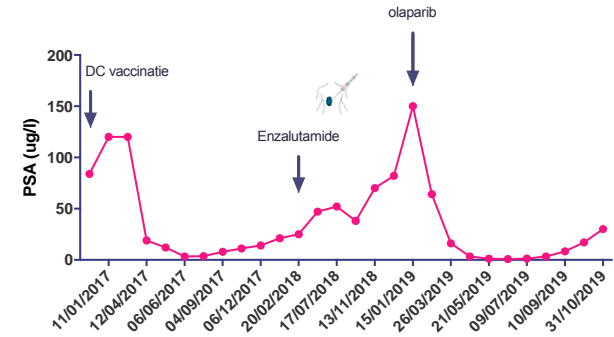
CPCT-02 study, dd 23-7-2018
 Whole genome sequencing: **BRCA2 p.Phe3077Ser** (VUS) en **BRCA2 p.Thr3085Ile** (VUS). **CN-LOH BRCA2**. **HR-deficientie score 0.94** (hoog).
 Mutational load 4.4 mutations/Mb.

MTB advies
 HRD signature. Beide BRCA2 varianten op zelfde allel. Mogelijk is er samenspraak tussen de aminozuren gezien locatie? PARP remmer in DRUP

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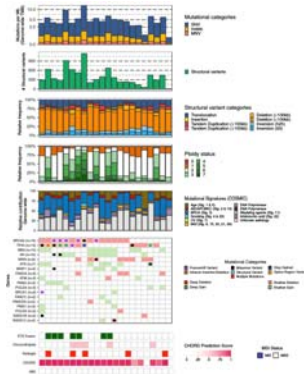
Case 2

Personalized medicine for BRCAness



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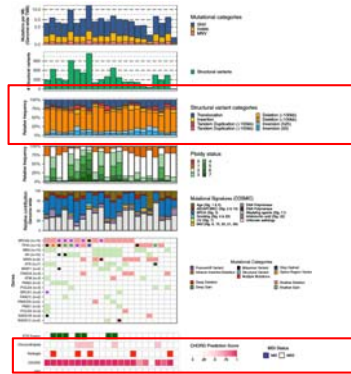
Distinct Hallmarks of BRCA Inactivation in mCRPC



1. LF. van Dessel, et al. The genomic landscape of metastatic castration-resistant prostate cancers reveals multiple distinct genotypes with potential clinical impact. *Not Commun.* 2019 (accepted).

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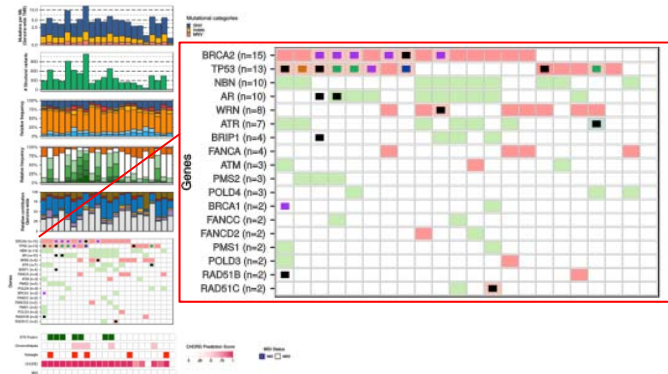
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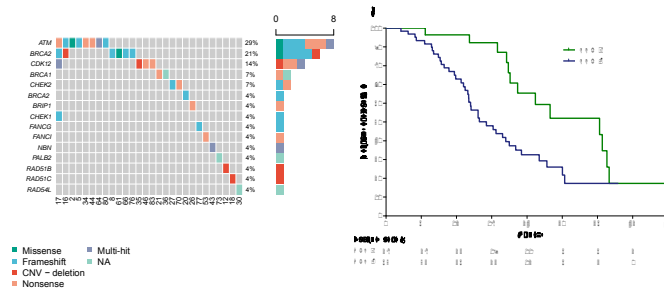
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Distinct Hallmarks of BRCA Inactivation in mCRPC



1. LF. van Dessel, et al. The genomic landscape of metastatic castration-resistant prostate cancers reveals multiple distinct genotypes with potential clinical impact. *Not Commun.* 2019 (accepted). Radboudumc

Impact of DNA damage repair defects on response to radium-223 and overall survival in mCRPC



1. M. van der Doelen, et al. The Impact of DDR Mutations on Response to Radium-223 and Overall Survival in metastatic Castration-Resistant Prostate Cancer. 2019 (submitted). Radboudumc

Conclusie en discussie

- Meerwaarde *routinematig* DNA diagnostiek in selecte tumortypen en bespreking binnen een MTB
- Routinematig DNA diagnostiek binnen MTB vergroot studie inclusie voor moleculair-geselecteerde klinische studies
- DNA diagnostiek met WES/WGS of targeted NGS binnen MTB creëert een infrastructuur waaruit wetenschappelijke vraagstellingen beantwoord kunnen worden
- Routinematig DNA diagnostiek voor bepaalde aberraties/ selecte tumortypes verbetert kwaliteit van leven (en is kostenefficiënt)

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Acknowledgements MTB

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Peter Slootbeek
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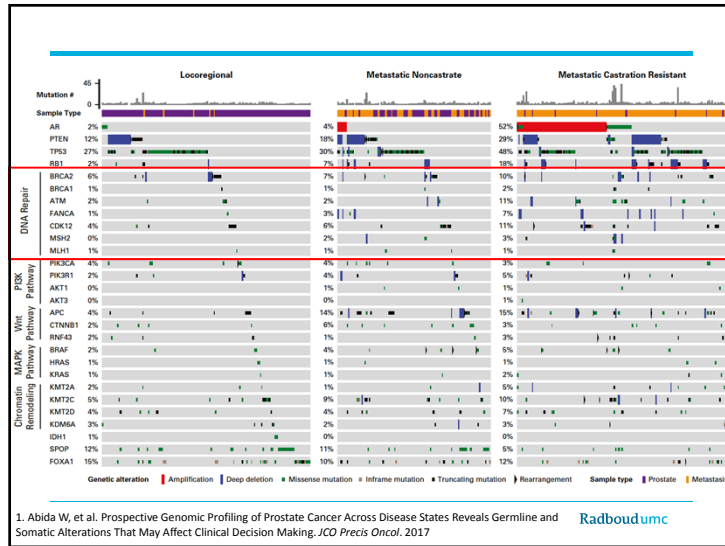
Pathology,
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Michiel Simons
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Lieneke Steeghs
Ingrid Vogelaar
Janneke Schuurs-
Hoeijmakers
Marjolijn Ligtenberg

Hartwig Foundation
Korneel Duijvesteyn
Edwin Cuppen

CPCT Radboudumc

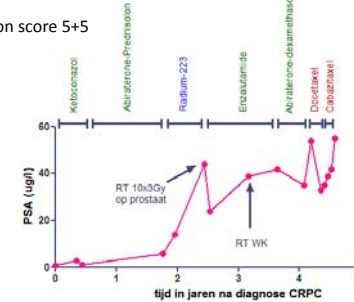


Case 2 History

2011 T4N1M1b prostate cancer, Gleason score 5+5

Prior treatments;

- 2011/11 LHRH
- 2012/11 - 2013/5 Ketoconazole
- 2013/5 – 2014/4 Abirateron + P
- 2014/4 – 2015/1 Radium-223
- 2015/1 – 2016/3 Enzalutamide
- 2016/4 – 2016/6 Abirateron + P
- 2016/6 – 2016/9 Docetaxel
- 2016/10 – 2016/12 Cabazitaxel
- Several times palliative radiotherapy



At presentation:

December 2016: radiological progressive disease with metastases in lymph nodes, bones, both adrenal glands, lungs and pancreas

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Case 2



Biopsy of subcutane soft tissue metastasis

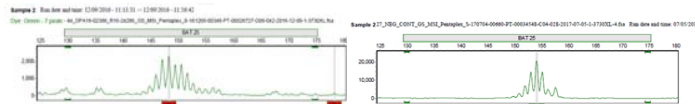
CPCT-02 study

Whole genome sequencing: high mutational burden with 2232 non-synonymous substitutions over the exome. Approximately 74 mutations/Mb (average 3-5 mutations/Mb). Mutation in **MSH6**.

Pathology

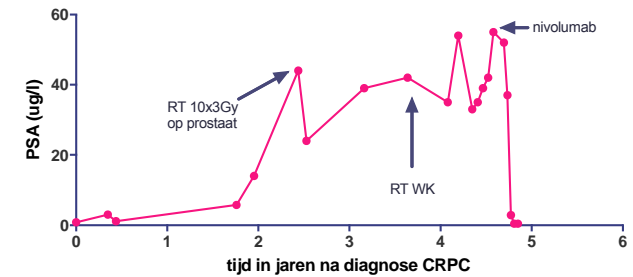
MMR IHC loss MSH2 and MSH6 protein expression.
PDL1 expression in 7% of tumor cells.

MSI instability (MSI-H) in markers BAT25 and NR24 (pentaplex).



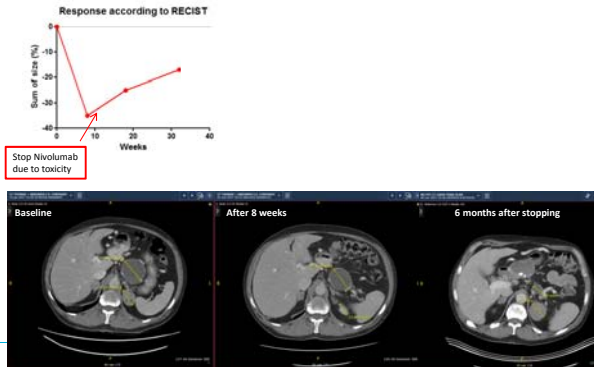
Case 1

Personalized medicine for MSI (MSH6)

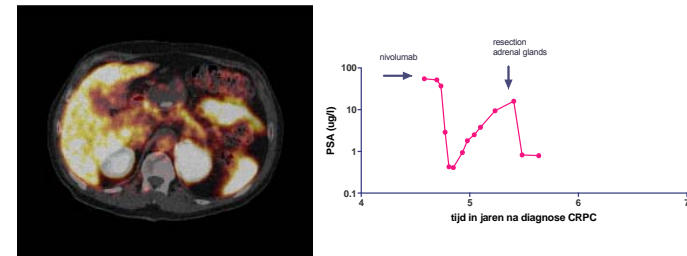


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Case 1 Personalized medicine for MSI (MSH6)

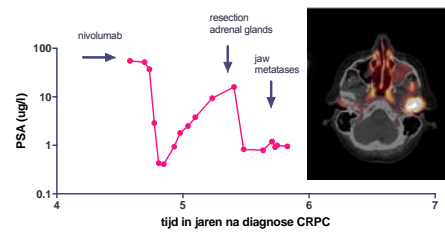


Case 1 Personalized medicine for MSI (MSH6)



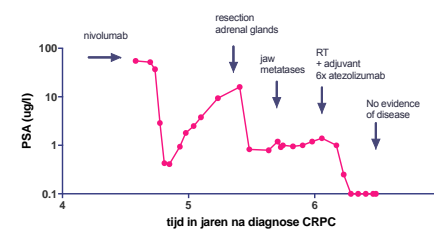
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Case 1 Personalized medicine for MSI (MSH6)



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Case 1 Personalized medicine for MSI (MSH6)



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