GU cancer: metastatic CRPC

Early clinical trial unit

SITEP

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Dr Christophe Massard

ESMO Symposium on Signalling Pathways in Cancer
Targeting the PI3K/AKT/mTor pathway in cancer
Sitges-Barcelona, 28 February - 1 March 2014

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Institut de cancérologie
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Disclosure

- Participation to advisory boards, speaker or investigator for:

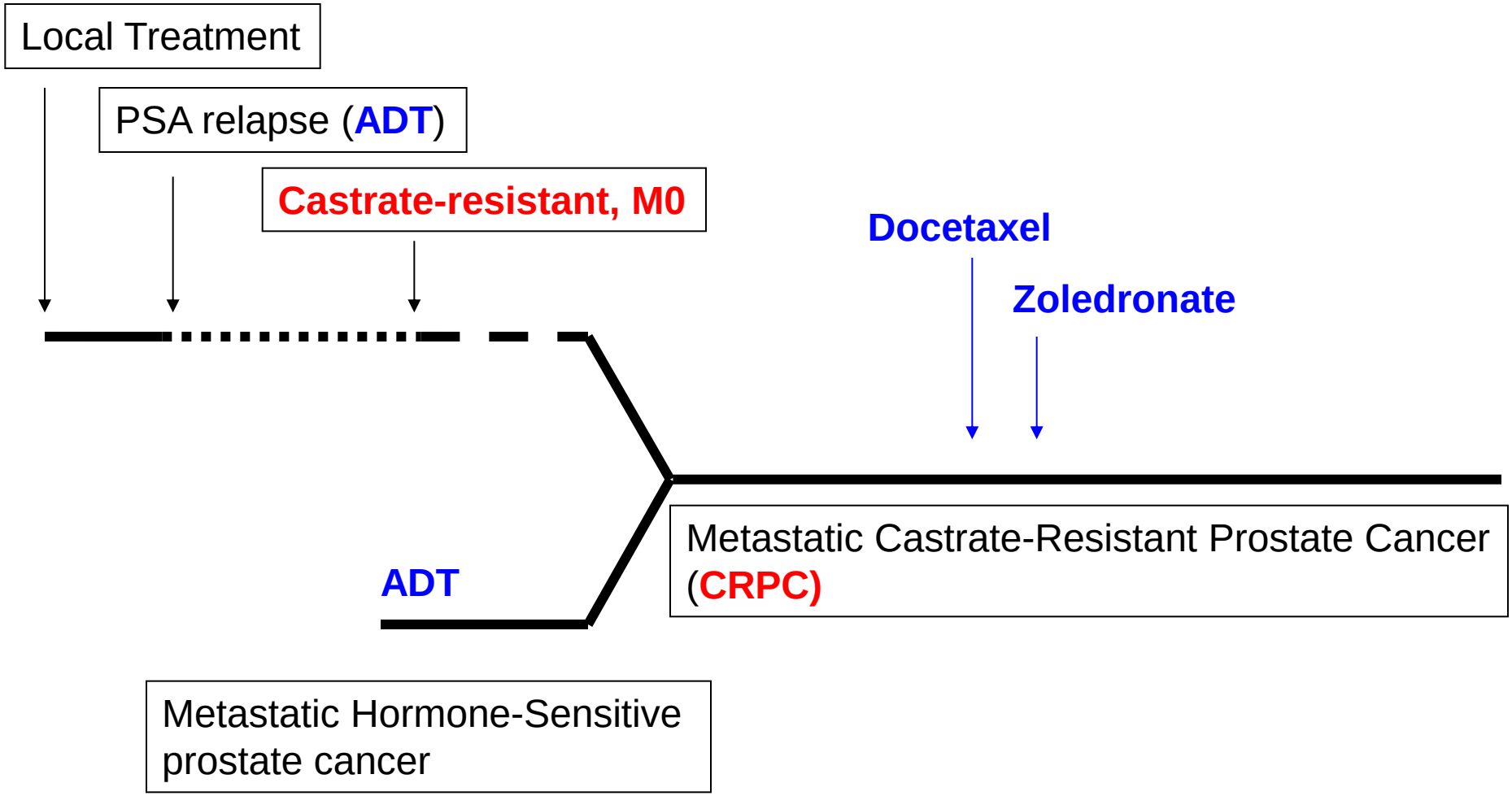
  Amgen, Astellas, Astra Zeneca, Bayer, Celgene, Genentech, Ipsen, Jansen, Lilly, Novartis, Pfizer, Roche, Sanofi-Aventis

Lost in translation…

- CRPC in 2014
- Molecular alterations and CRPC
- Clinical trials and PI3K/AKT/mTOR inhibitors in CRPC

- **CRPC in 2014**
  - **A new paradigm for our patients!**
- Molecular alterations and CRPC
- Clinical trials and PI3K/AKT/mTOR inhibitors in CRPC

Advanced prostate cancer: Natural history (in the 2000s)



Old Paradigm

- “Prostate cancer is chemo-resistant.”
- “Prostate cancer is hormone-sensitive for about 2 years, and when progression occurs while on hormones, this defines hormone-refractory prostate cancer (HRPC).”
- “When hormone-refractory status is reached, survival is about 1 year.”
- “bone mets are not an issue.”

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… Good news from the last 5 years!

A new paradigm in CRPC

- “Prostate cancer is chemo-resistant.”

- “Prostate cancer is hormone-sensitive for about 2 years… when progression occurs while on hormones, this defines hormone-refractory prostate cancer (HRPC).”

- “When hormone-refractory status is reached, survival is about 1 year.”

- “bone mets are not an issue.”

Castration-resistant prostate cancer: a new paradigm

- "Castration-resistant prostate cancer" (CRPC) was proposed by the PCWG2 as an alternative term to describe patients for whom hormone therapy has failed and who have progressive disease despite castration levels of androgen

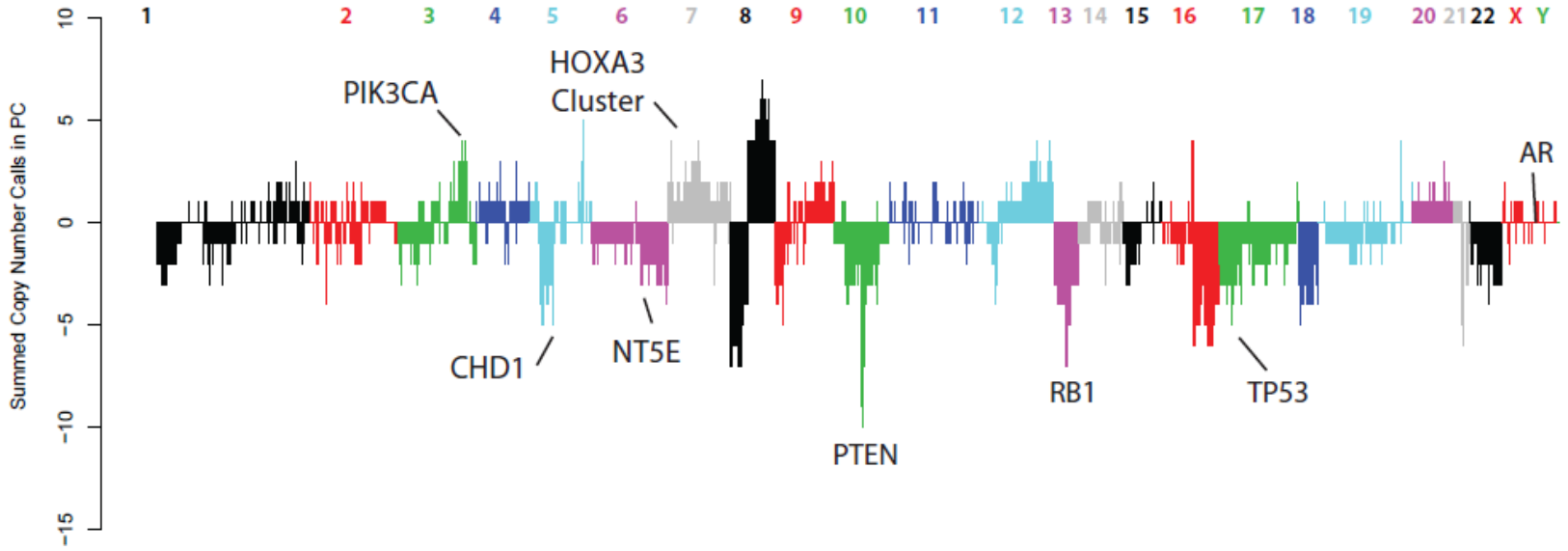
- Despite castration levels of androgen, the androgen receptor (AR) signalling pathway remains active
  - Several pathways are thought to be involved in disease pathogenesis
  - Potential targets

PCWG2 = Prostate Cancer Clinical Trials Working Group 2.

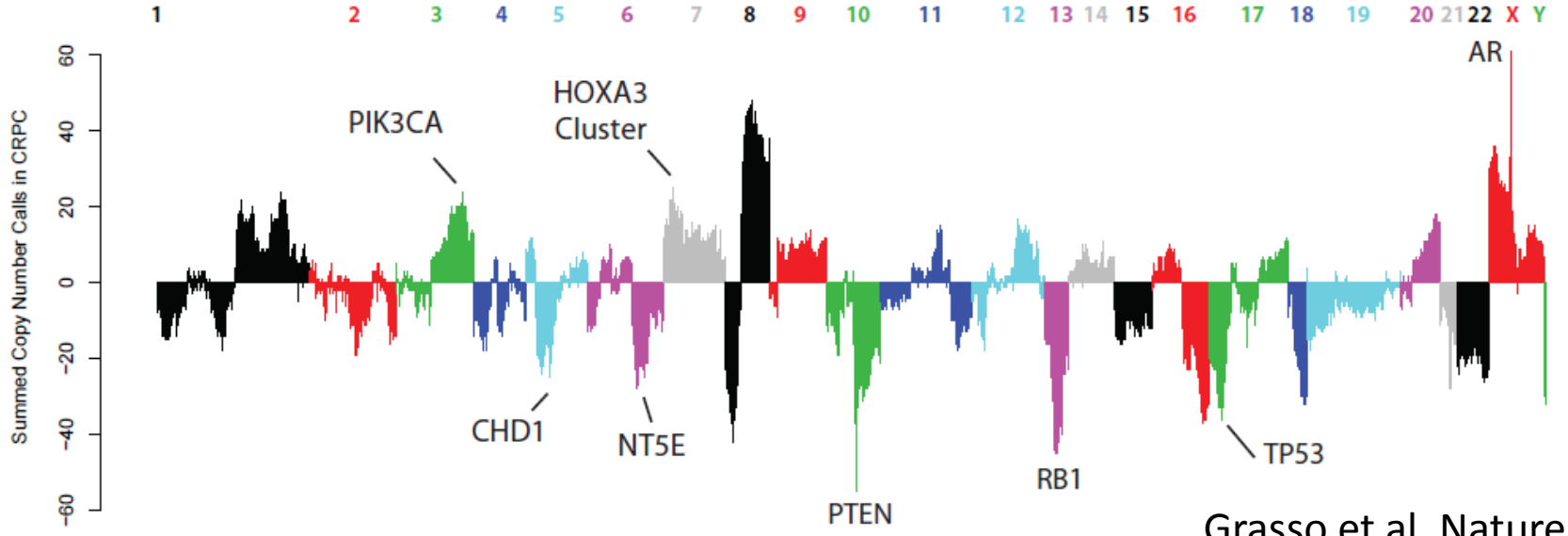
Bonkhoff H, et al. Prostate. 2010;70:100-12.
Fizazi K, et al. Eur J Cancer. 2009;45 Suppl 1:379.
Locke JA, et al. Cancer Res. 2008;68:6407.

Androgen Receptor is a key driver in mCRPC

Localized PC

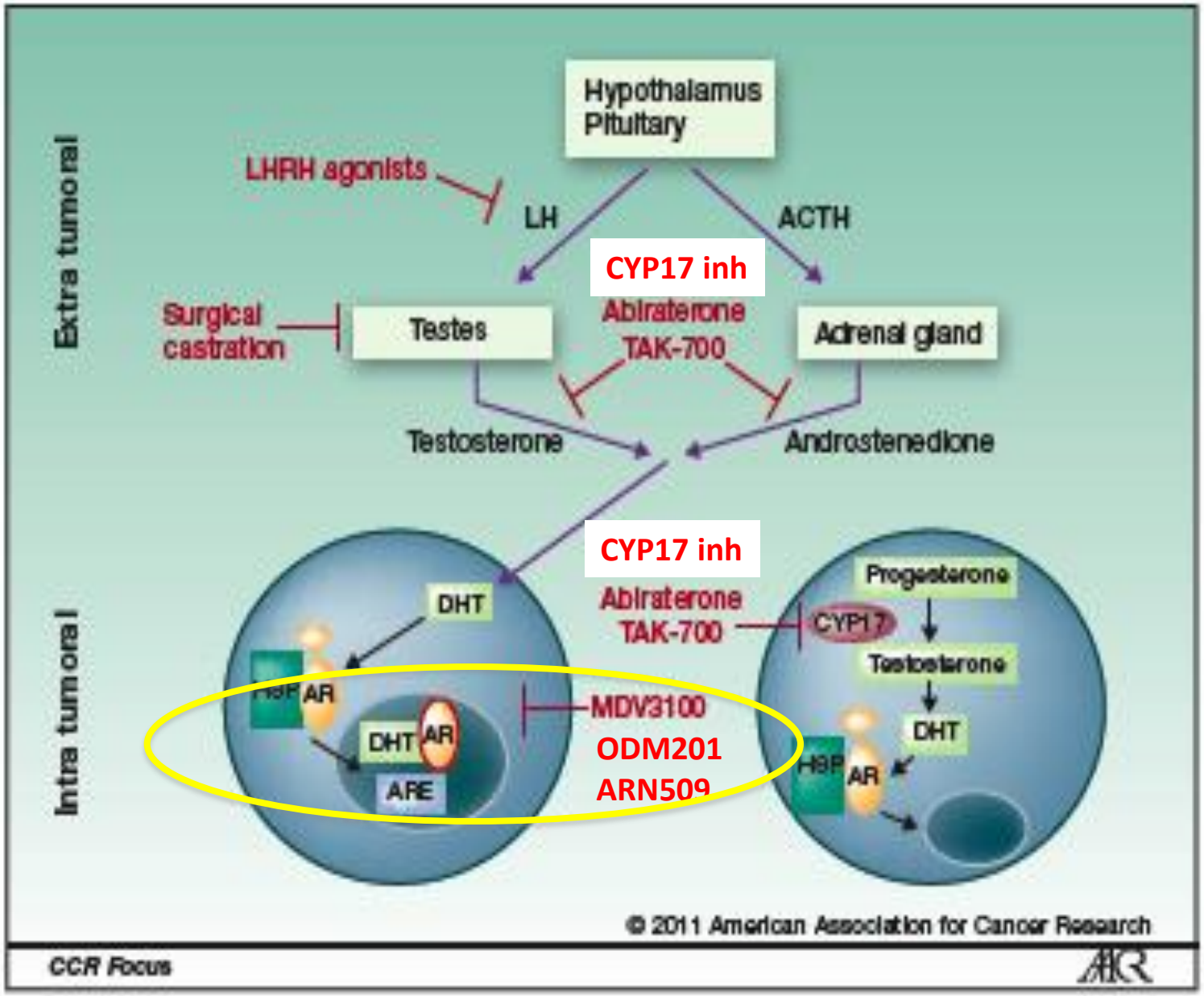


CRPC

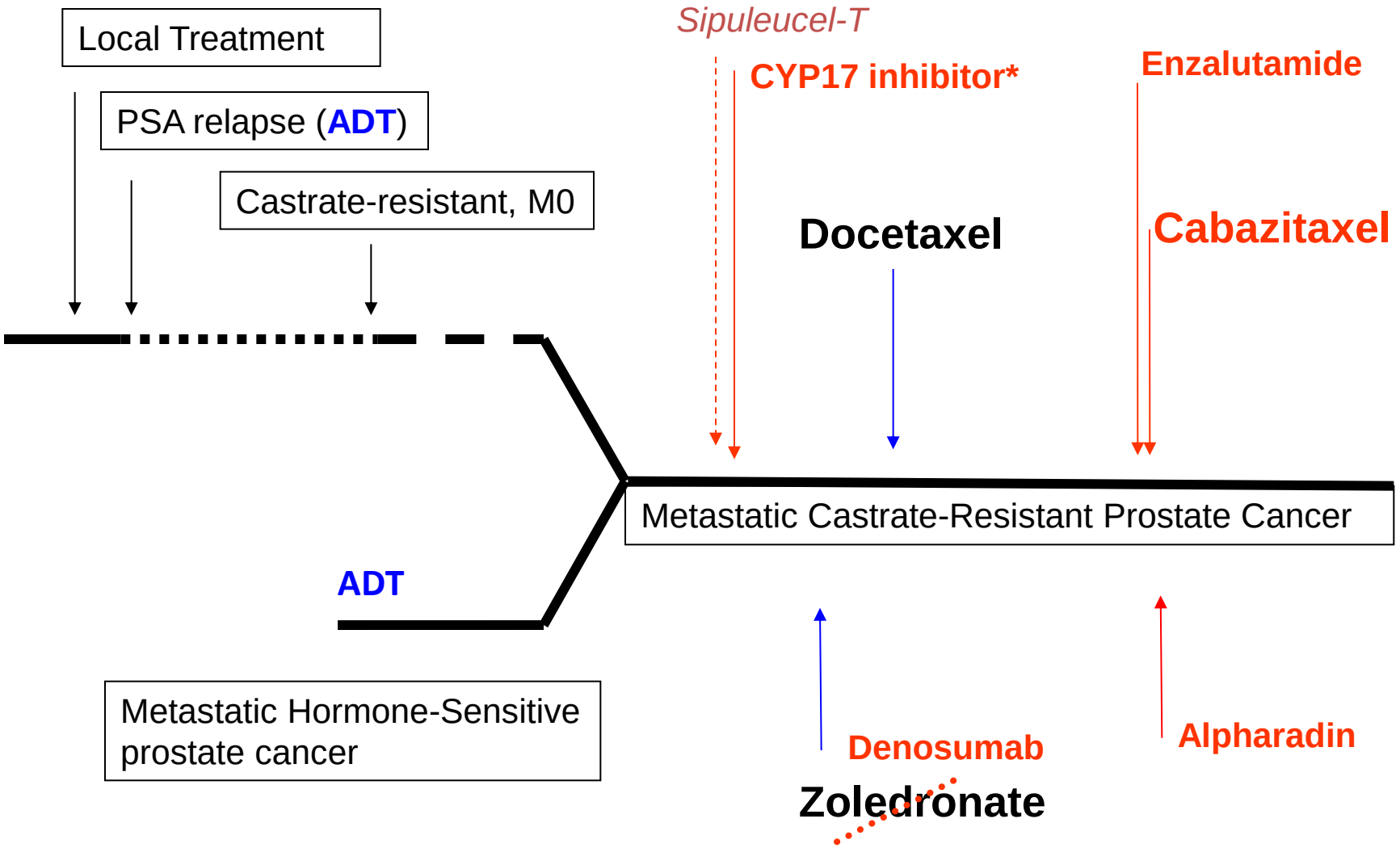


Grasso et al, Nature 2011

Androgen Receptor is a key driver in mCRPC



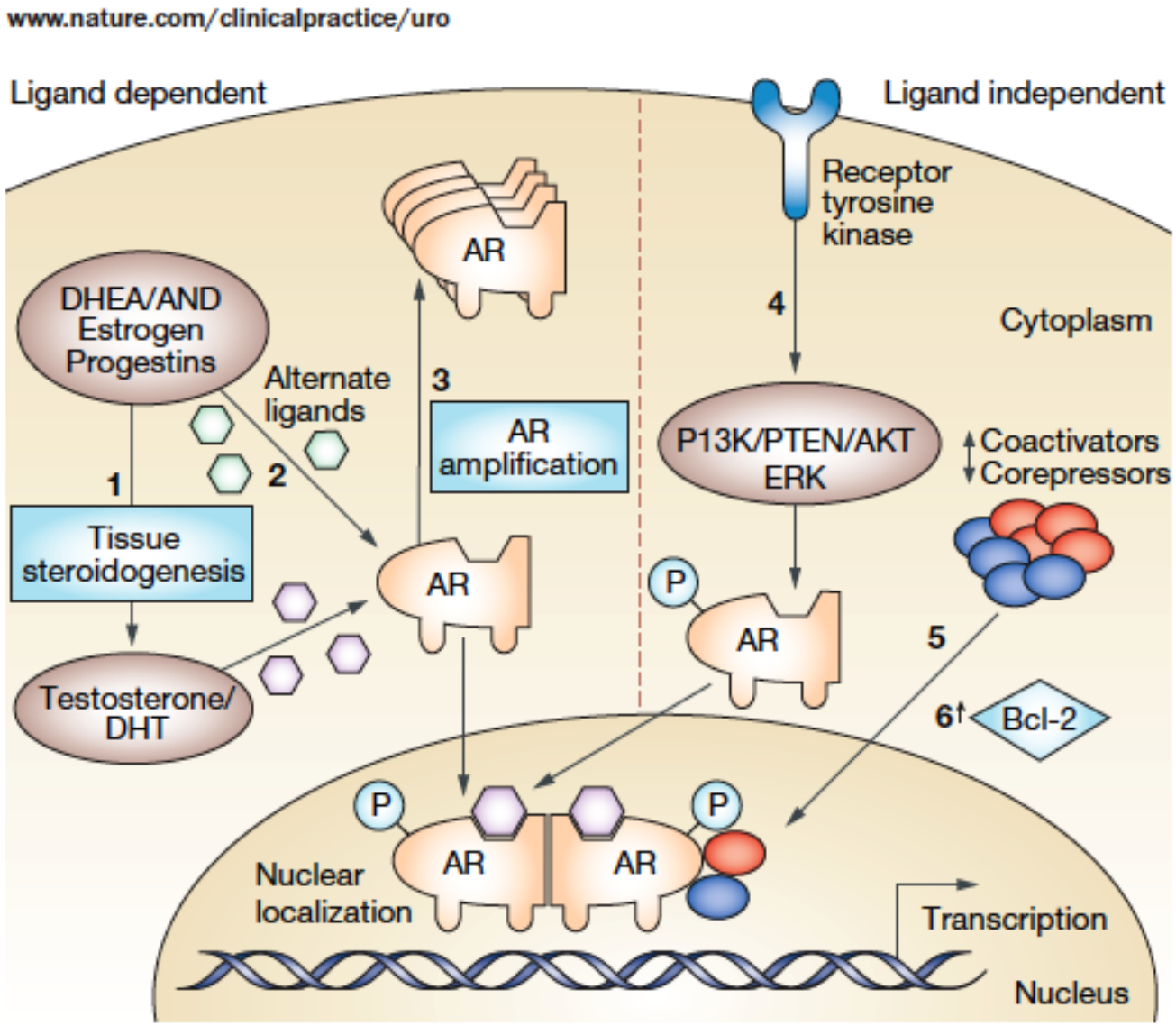
Evolution? …



Pr Fizazi, Dr Albiges

- CRPC in 2014
- **Molecular alterations and CRPC**
  - **AR pathway and PI3K/AKT/mTOR**
- Clinical trials and PI3K/AKT/mTOR inhibitors in CRPC

Androgen Receptor is a key driver in mCRPC



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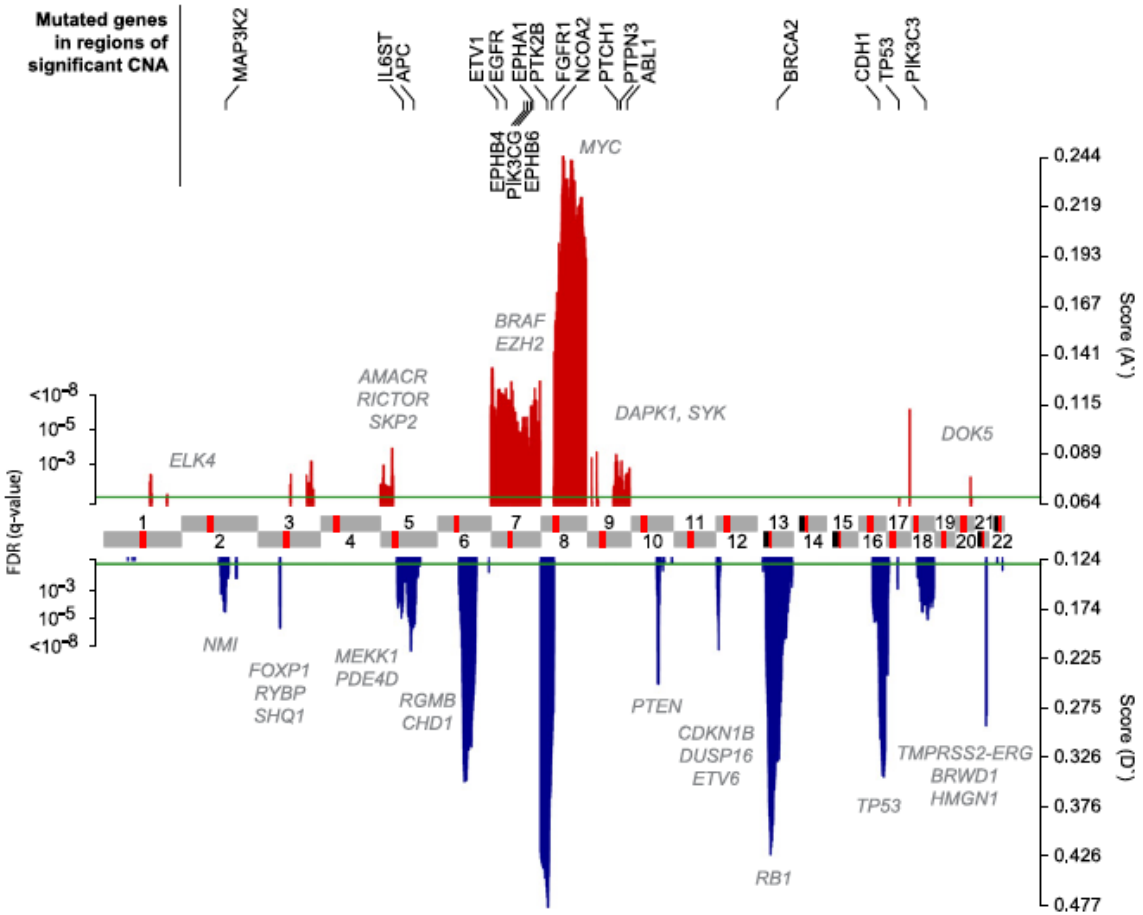
Cancer Cell
Article

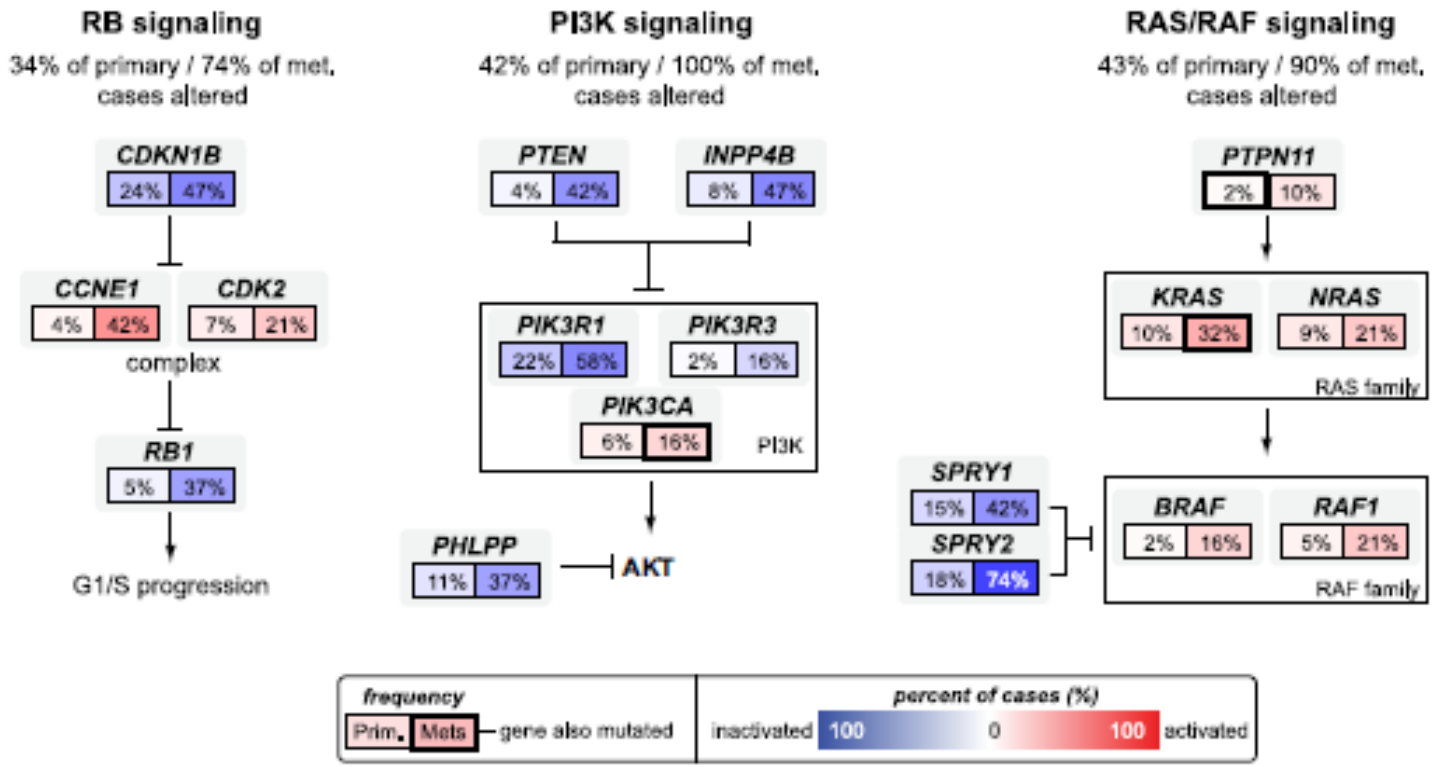
Integrative Genomic Profiling of Human Prostate Cancer

Barry S. Taylor,[1,8] Nikolaus Schultz,[1,8] Haley Hieronymus,[2,8] Anuradha Gopalan,[3] Yonghong Xiao,[3] Brett S. Carver,[4] Vivek K. Arora,[2] Poorvi Kaushik,[1] Ethan Cerami,[1] Boris Reva,[1] Yevgeniy Antipin,[1] Nicholas Mitsiades,[5] Thomas Landers,[2] Igor Dolgalev,[2] John E. Major,[6] Manda Wilson,[6] Nicholas D. Socci,[6] Alex E. Lash,[6] Adriana Heguy,[2] James A. Eastham,[4] Howard I. Scher,[5] Victor E. Reuter,[3] Peter T. Scardino,[4] Chris Sander,[1] Charles L. Sawyers,[2,7,*] and William L. Gerald[2,3,9]



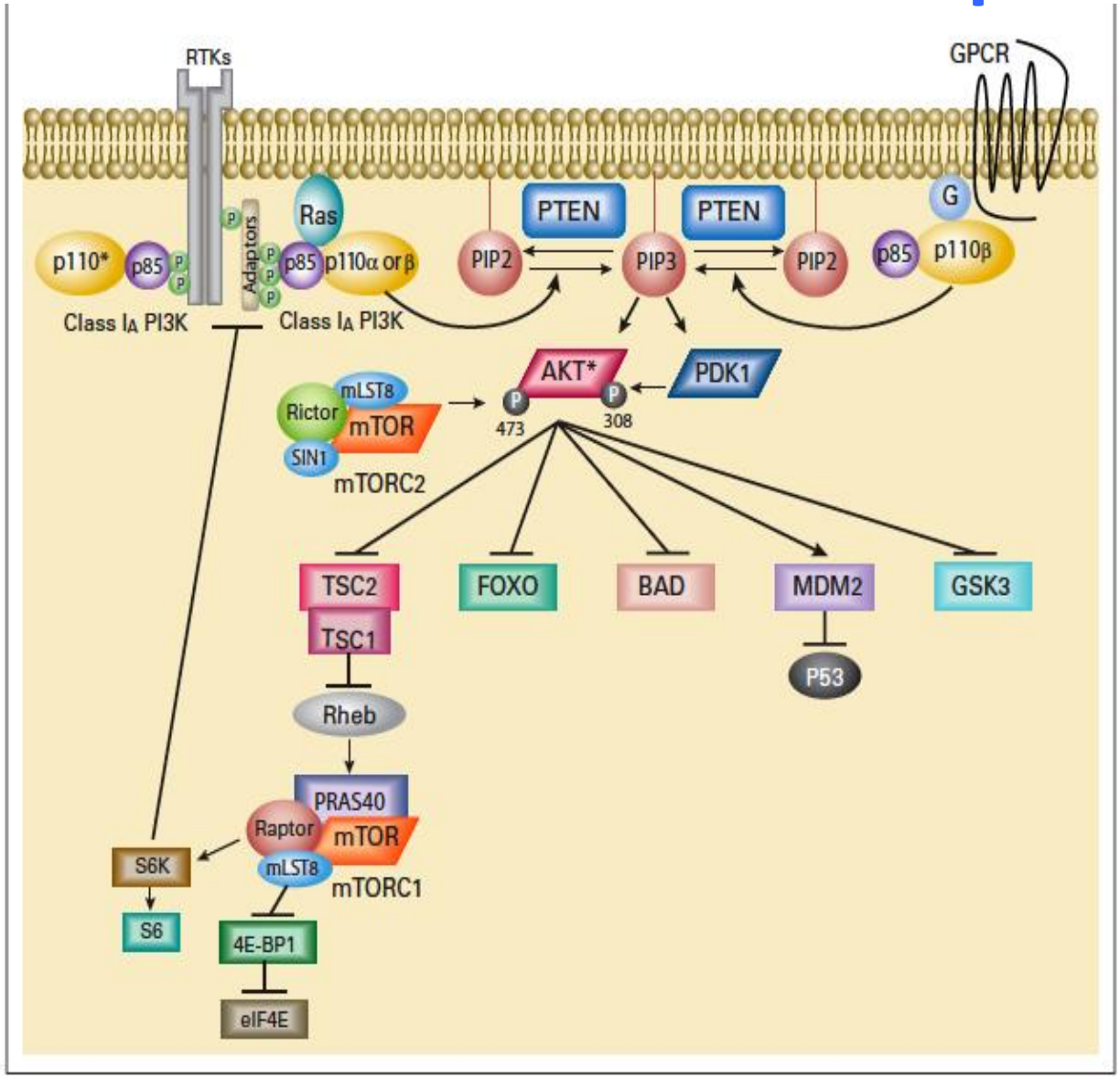
Taylor et al, Cancer Cell 2010

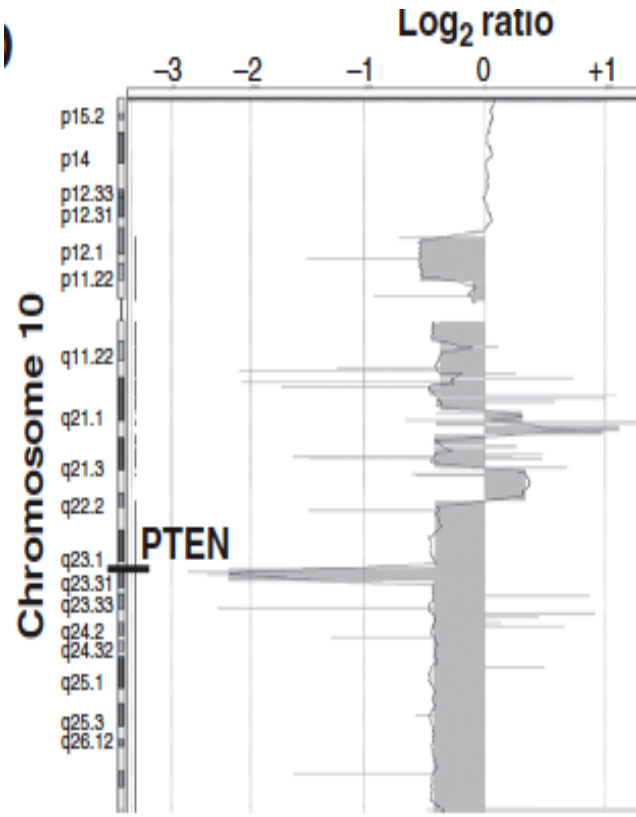
Genes and pathways dysregulation in prostate cancer



Taylor et al, Cancer Cell 2010

PI3K-AKT-mTOR and prostate cancer

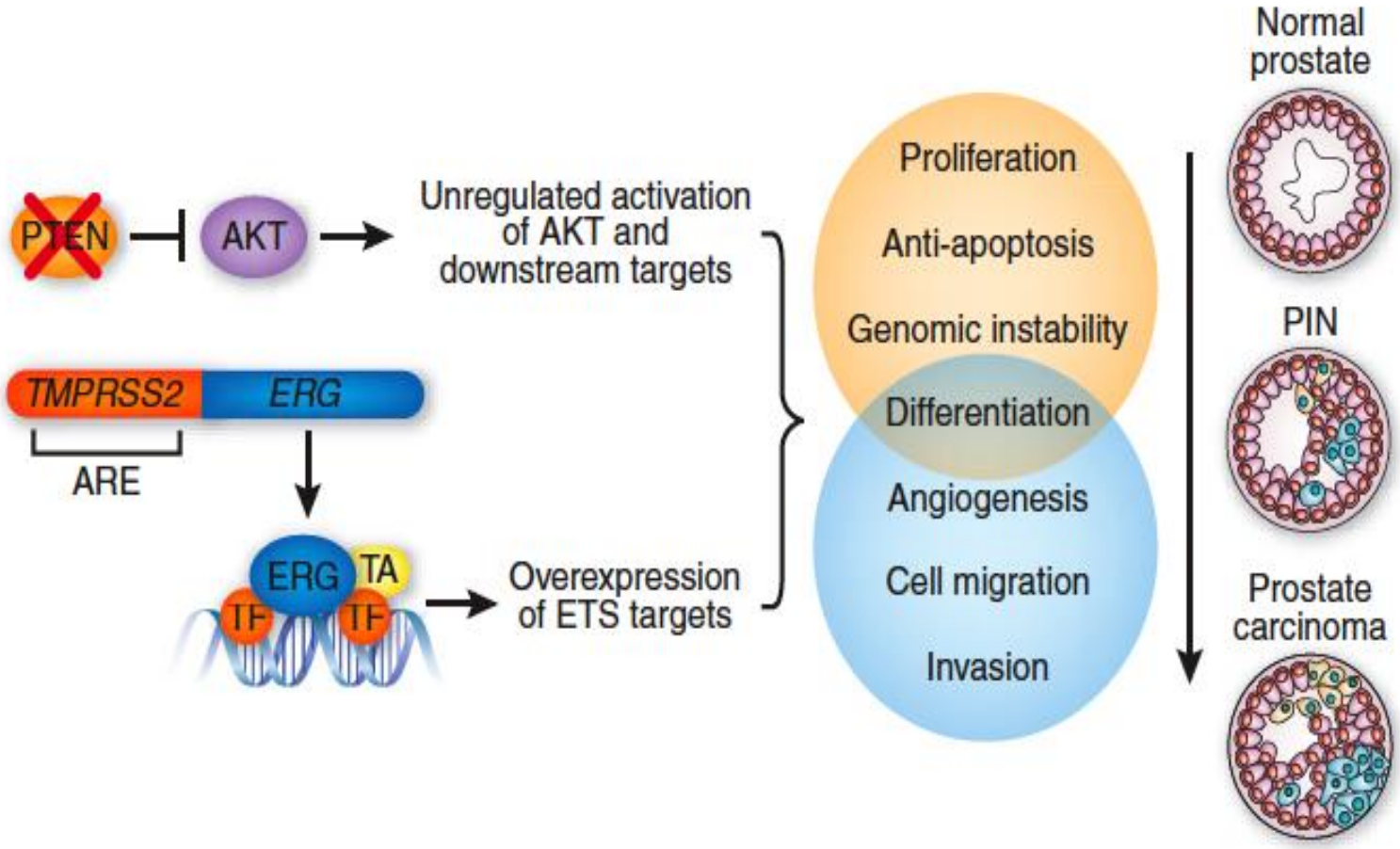




20-40% PTEN loss

Courtney et al, JCO 2010

TMPRSS2-ERG and PTEN loss



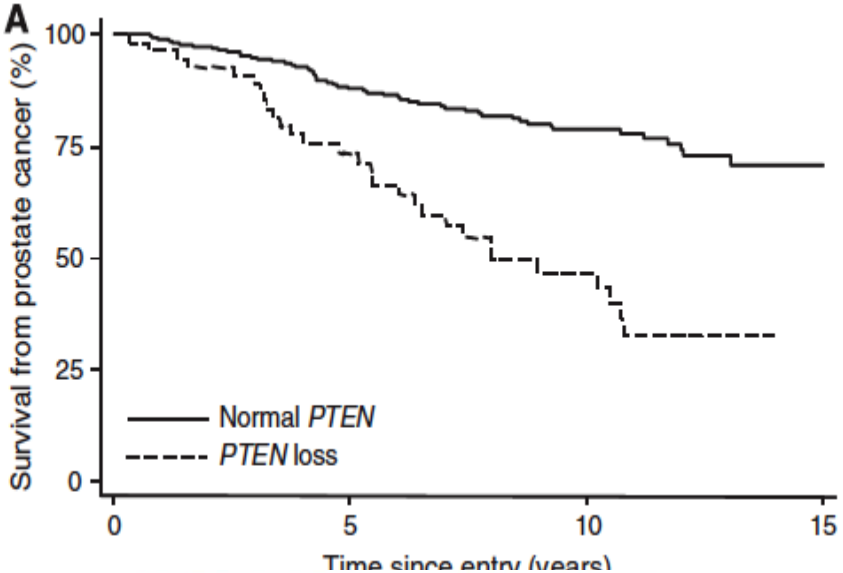
Squire, Nat Genetics 2009; Kings et al, 2009; Carver et al, 2009

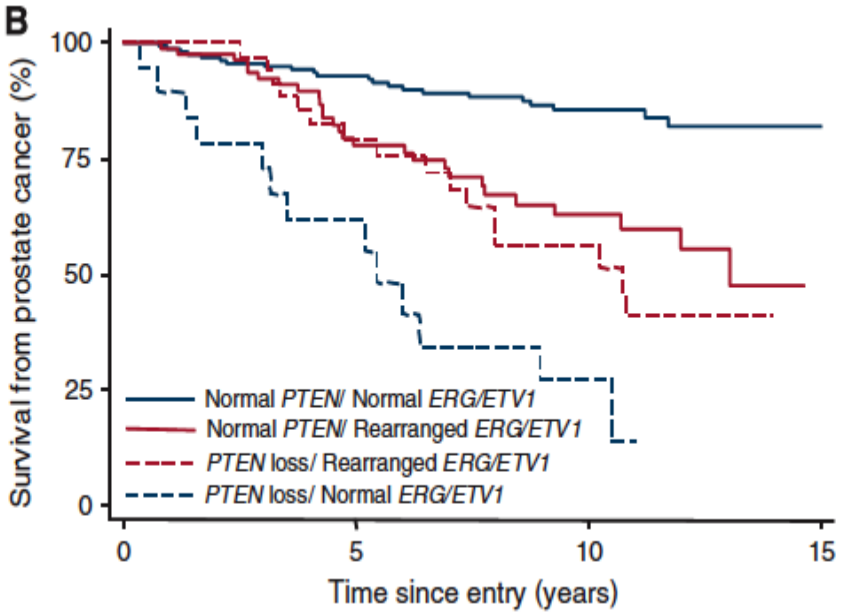
British Journal of Cancer (2010), 1 – 7

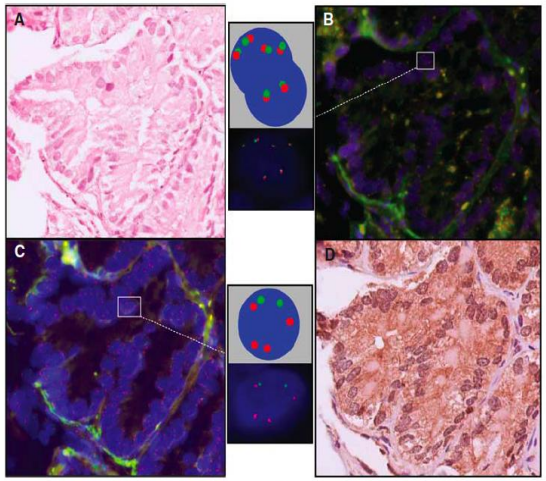
www.bjcancer.com

Full Paper

Molecular characterisation of *ERG*, *ETV1* and *PTEN* gene loci identifies patients at low and high risk of death from prostate cancer



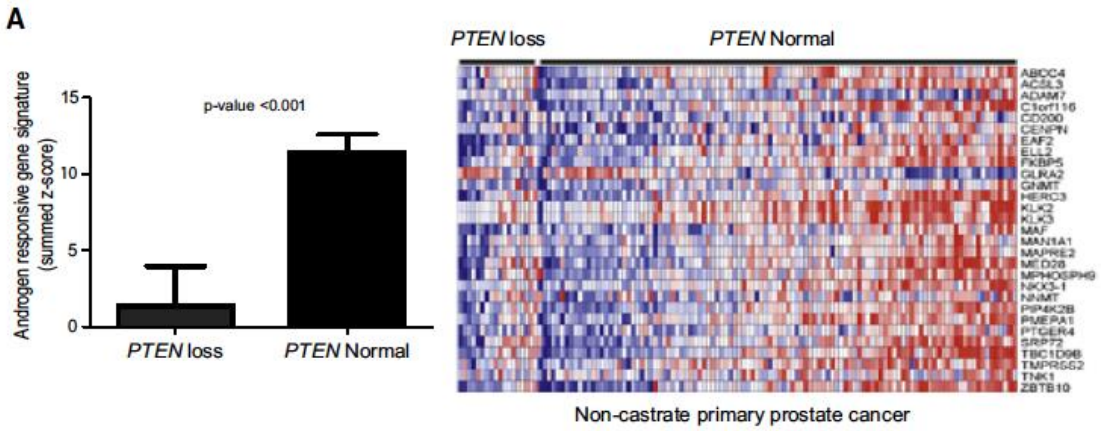


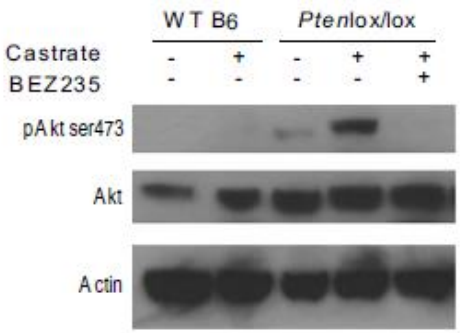


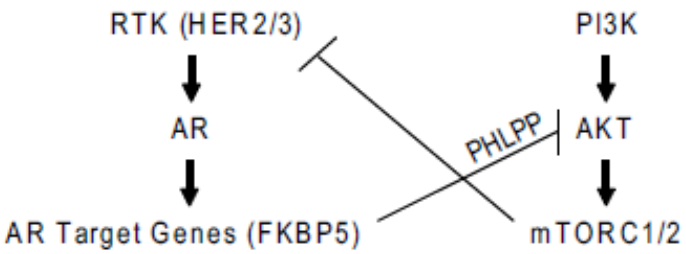
PTEN loss and ERG/ETV1 gene rearrangements and prognosis of prostate cancer patients

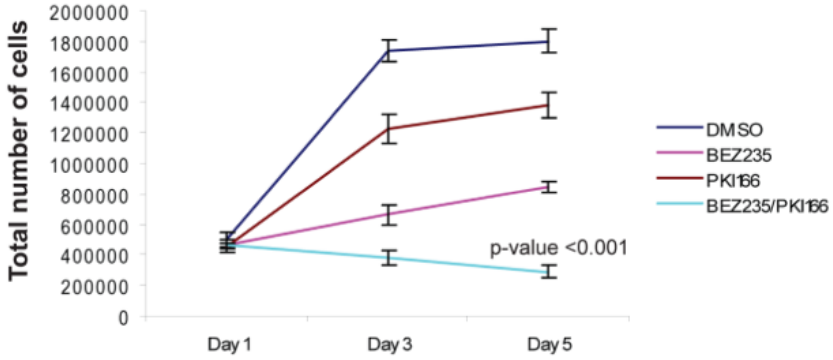
Reid et al, BJC 2010

PI3K/AKT/mTOR and AR pathways









Inhibition of the PI3K pathway restores, in part, androgen responsive signaling in *PTEN* loss prostate cancers

Carver et al, Cancer cell 2011

- CRPC in 2014
- Molecular alterations and CRPC
- **Clinical trials and PI3K/AKT/mTOR inhibitors in CRPC**
  - **From phase I/II to molecular medicine**

PTEN/Akt Pathway Cooperates with Androgen Receptor Signaling

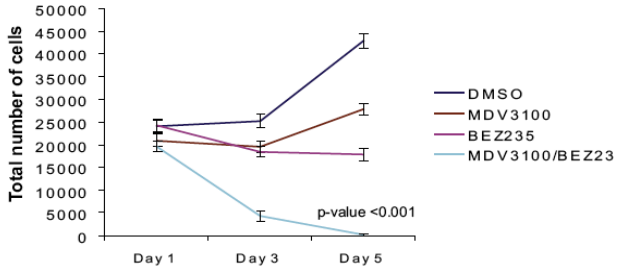
Reciprocal feedback between AR and PI3K/AKT

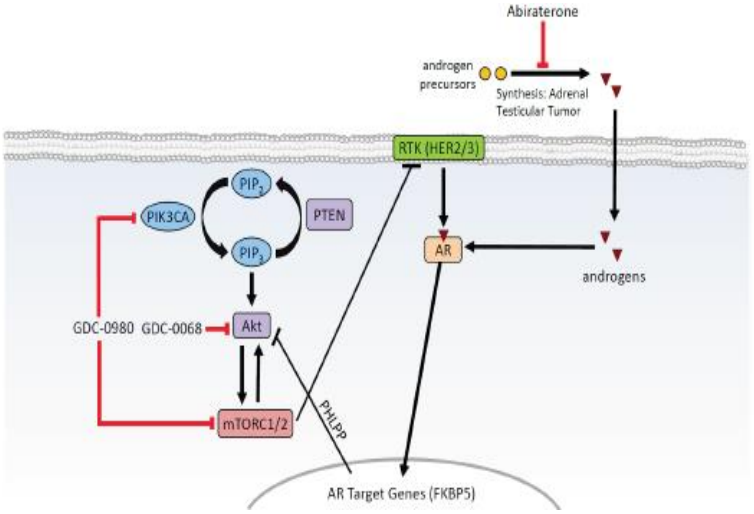
Reciprocal Feedback Regulation of PI3K and Androgen Receptor Signaling in PTEN-Deficient Prostate Cancer

Cancer Cell 19, 575–586, May 17, 2011

A

Charles Sawyers Group:

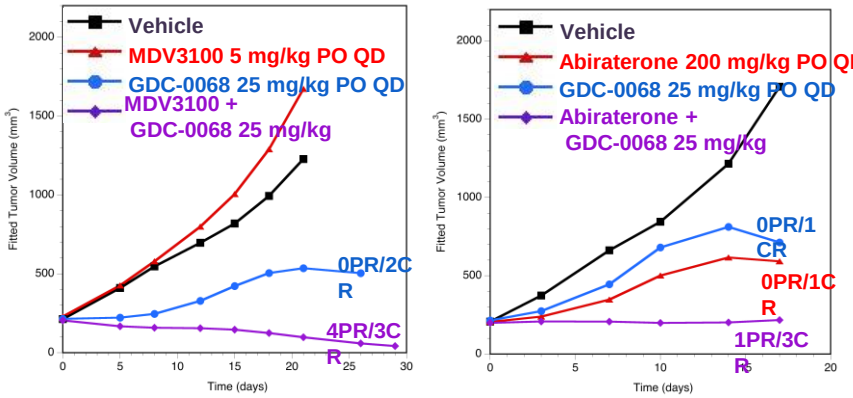




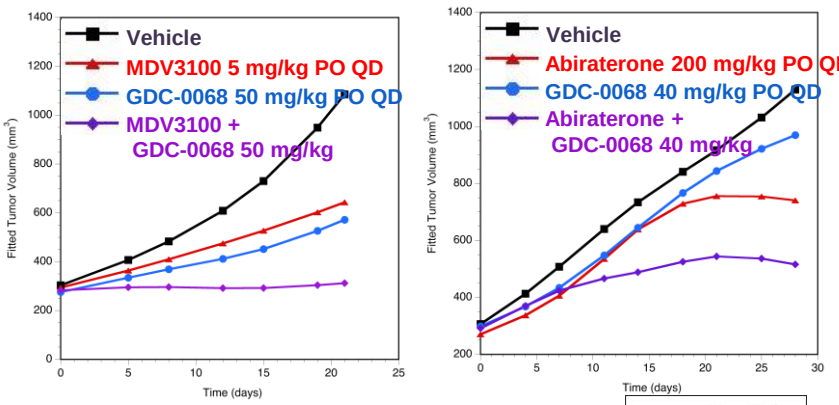
Note: ~60% of CRPC exhibit PTEN low/loss

Combination effects between GDC-0068 and anti-androgen across prostate mouse models

LnCaPx1.2: PTEN null, AR+



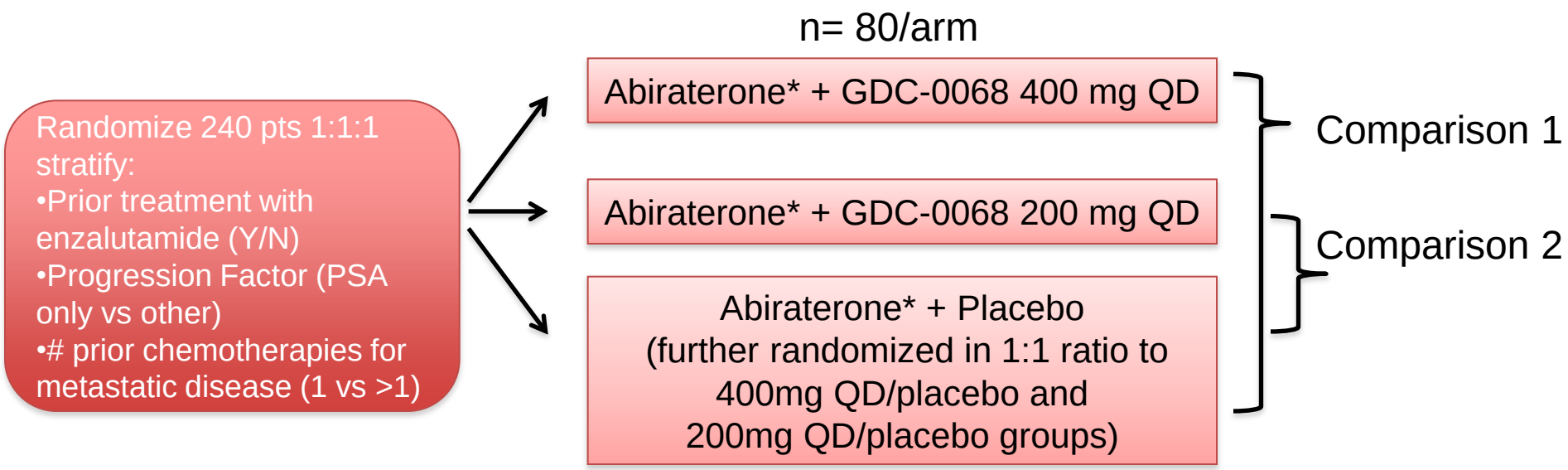
LuCaP35V: PTEN low, AR+



Courtesy Premal Patel

gRED Genentech Research & Early Development

Randomized, double-blind, placebo-controlled Ph II study (GDC-0068 + Abiraterone)



***Abiraterone (1000mg) and prednisone/prednisolone (5mg BID)**
Assignment to the 200 mg/placebo or 400mg/placebo group is known, treatment is blinded

1˚ endpoint
- radiographic PFS in all patients and in PTEN loss

2˚ endpoints (in all patients and in PTEN loss):
- Overall Survival
- Clinical Activity: PSA response rate, Tumor response rate and duration
- CTC enumeration
- Pain symptoms (modified Brief Pain Inventory –Short Form, mBFI-sf)

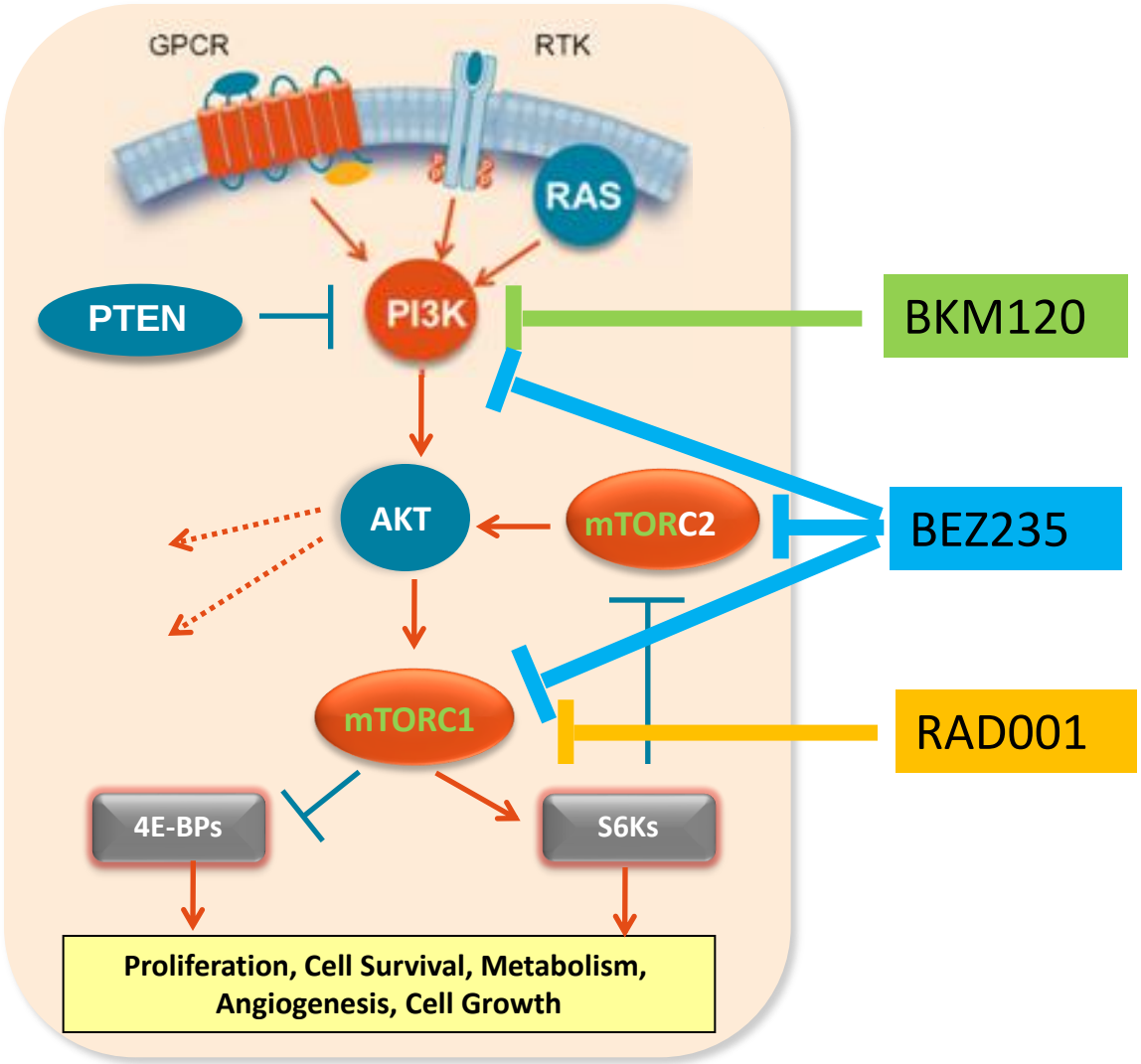
2˚ endpoints (in all patients):
- Safety
- PK

Courtesy Premal Patel

PI3K Pathway Inhibition Novartis compounds

- BEZ235
  - PI3K (pan-class I)
  - mTOR (mTORC1 & mTORC2)
- BKM120
  - PI3K (pan-class I)
- RAD001 (Afinitor)
  - mTOR (mTORC1 only)

mTORC1 = mTOR complex 1
mTORC2 = mTOR complex 2

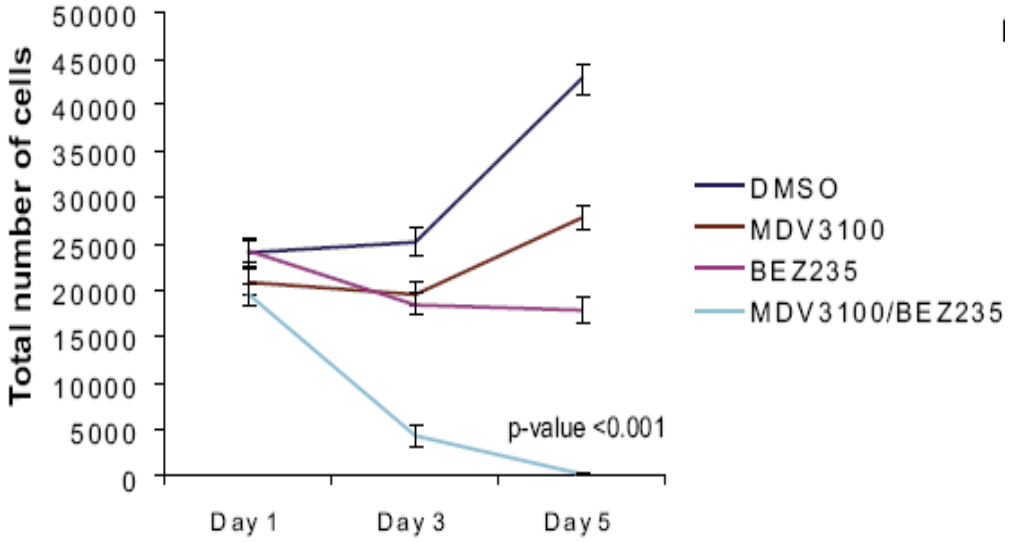


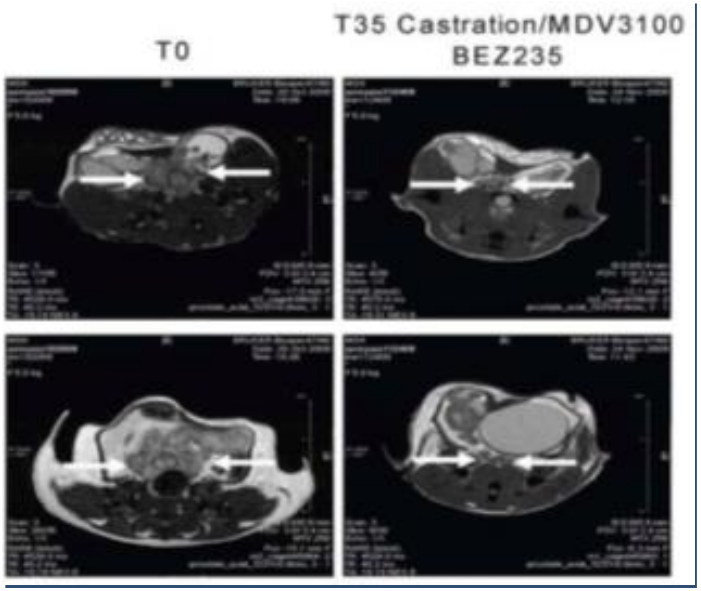
Courtesy C Massacesi and L Trandafir

PI3Ki patwhay in Prostate Cancer

Rationale to study BEZ235 and BKM120 in prostate cancer

- Frequent PI3K pathway alterations (mainly PTEN loss in ~70–80% of CRPC)
- Interaction and reciprocal feedback regulation between AR and PI3K signaling pathway with potential involvement in treatment resistance[1,2]





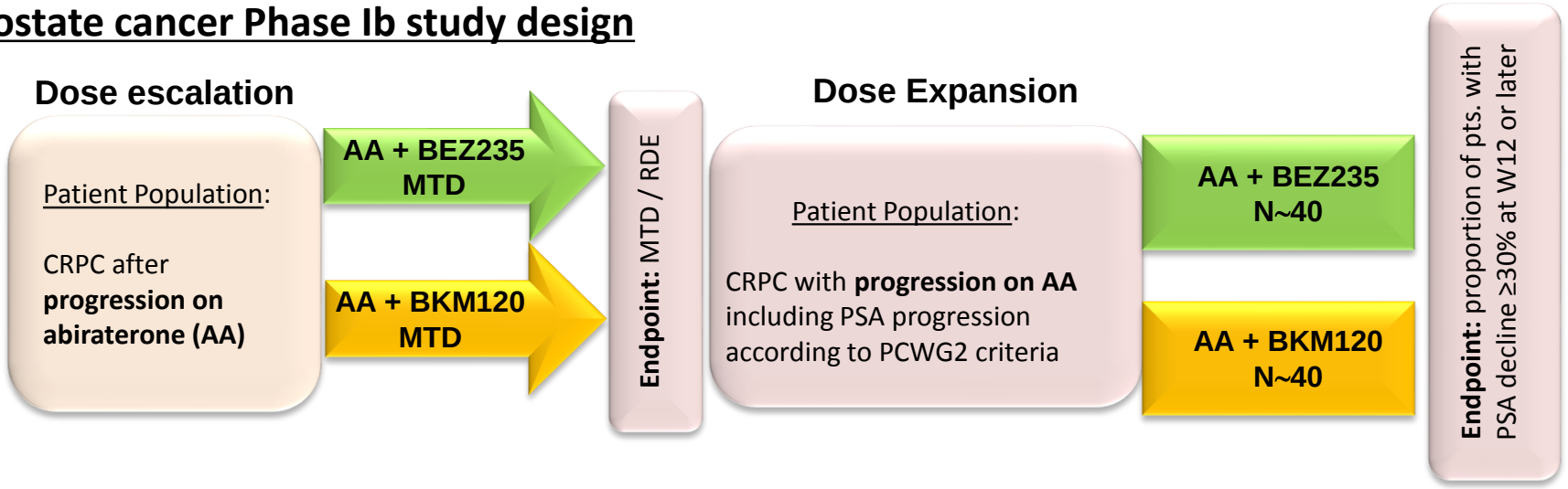
Combination of MDV3100 + BEZ235 causes near-complete tumor regressions in *PTEN*-deficient mouse model and in human prostate cancer xenografts[1]

1 Mulholland et al 2006; 2 Carver et al, 2011

Courtesy C Massacesi and L Trandafir

BEZ235D2101 Phase Ib in CRPC patients after Abiraterone failure

Prostate cancer Phase Ib study design



Courtesy C Massacesi and L Trandafir

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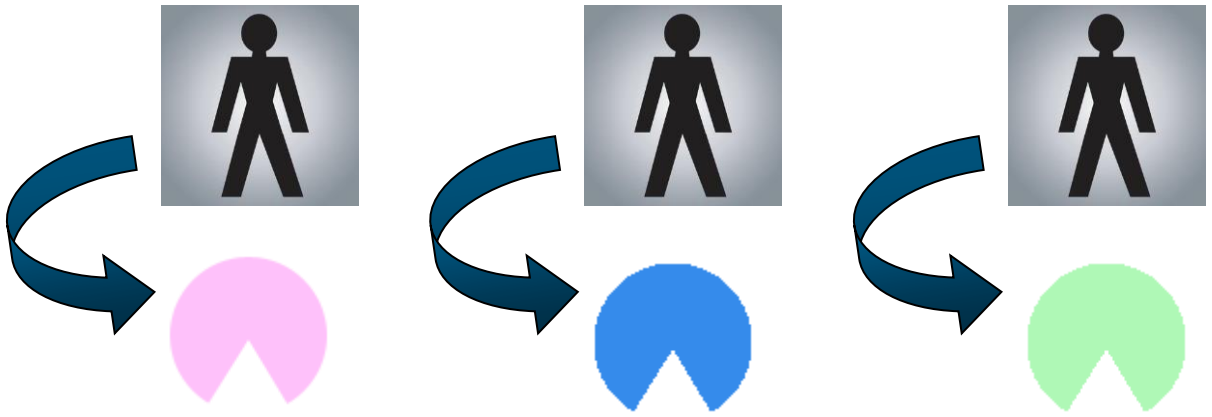
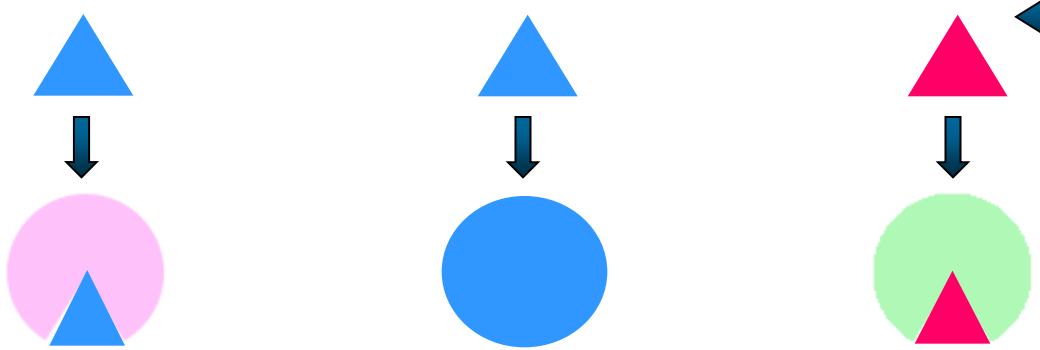
Choosing among available options??

One size does not fit all !

Selecting the right therapy?





Wrong match | **The right drug for the tumor type** | **Wrong match**

Modified from D Weaver, On-Q-ity

Time for personalized treatment in CRPC?

« The right treatment for the right patient »

- Can we predict the following:
  1- Who benefits from chemotherapy?
  2- Who may respond to subsequent endocrine manipulations (CYP17 inh, MDV 3100)?
  3- Are taxanes and CYP17 inh cross-resistant?
  4- Which patient benefit from Alpharadin?
  5-What is a prostate cancer?

Time for personalized treatment in CRPC?

« The right treatment for the right patient »

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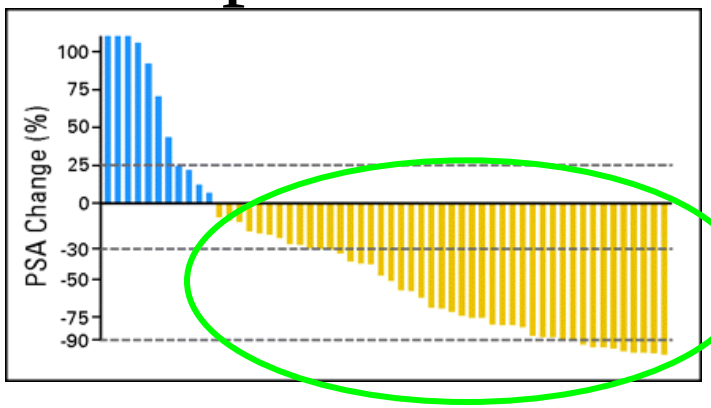
  5-What is a prostate cancer?

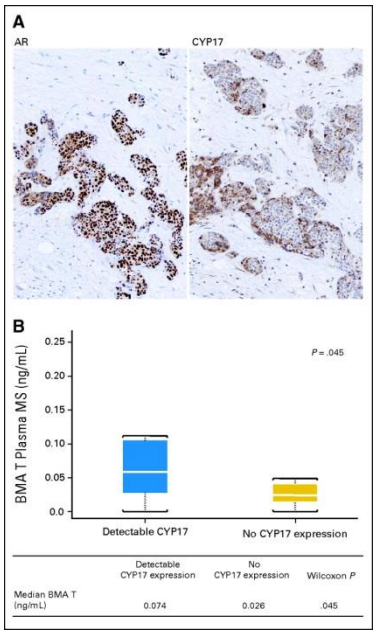
An elegant but complex way to identify patients who benefit from CYP17 inh



Who are the responders?
(defined as pts on drug for>4 months)

↓

Bone marrow biopsy:
- Intense AR nuclear expression and
- CYP 17 expression



Yes:
« Responders »: **82%**
(12/13)

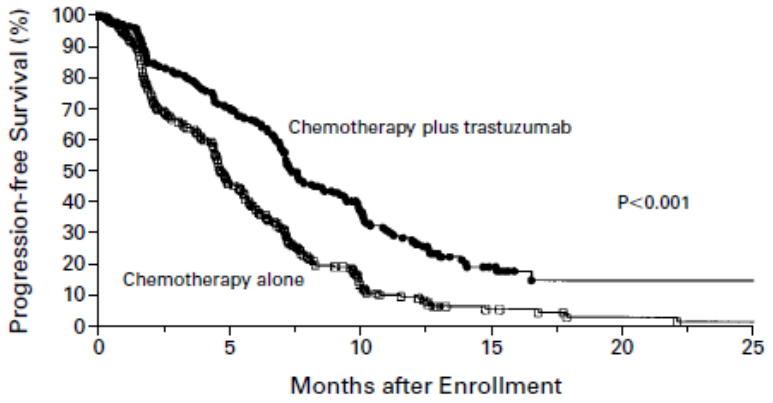
p<0.001

No:
« Responders »: **18%**
(2/12)

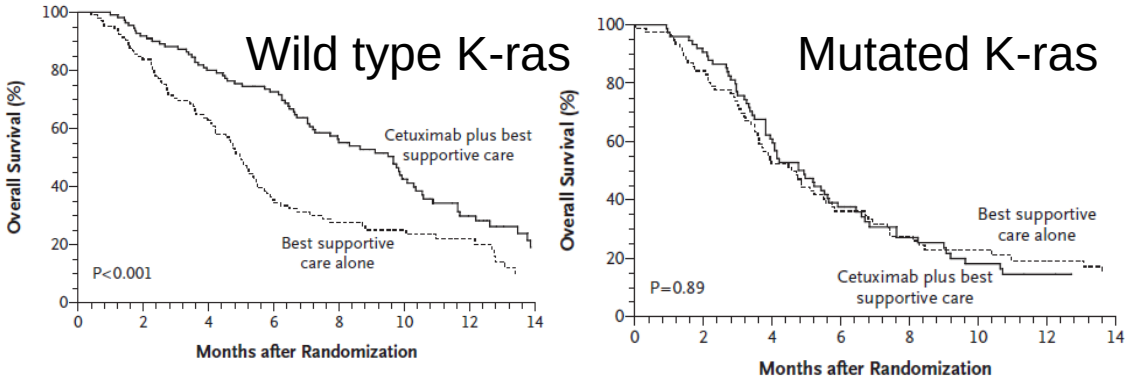
Efstathiou E, J Clin Oncol 2011; 30: 637-643

Success stories of Personalized Medicine

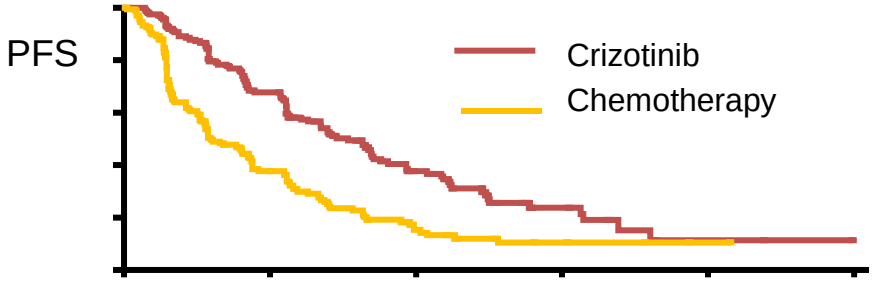
Breast cancer:
Trastuzumab in **HER2 +** tumors
(Slamon,
N Engl J Med 2001, 344: 783-92)



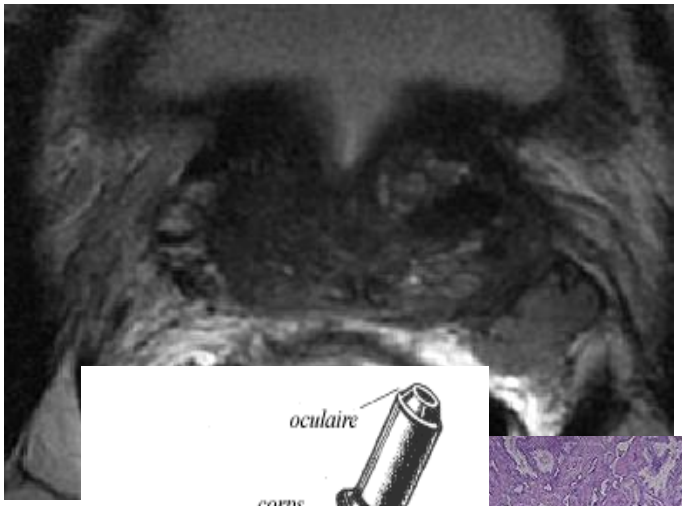
Colo-rectal cancer:
Cetuximab in **K-ras wt** tumors
(Karapetis CS,
N Engl J Med 2008; 359: 1757-65)

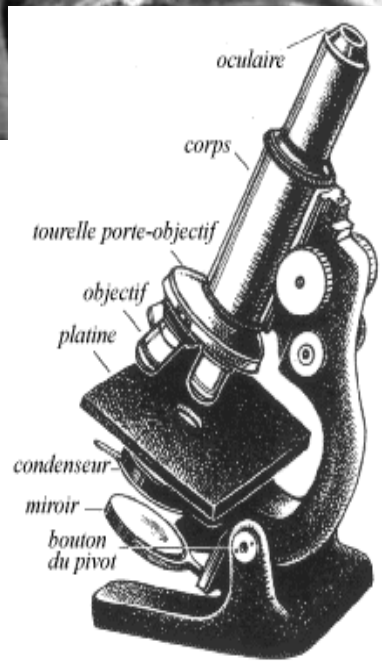


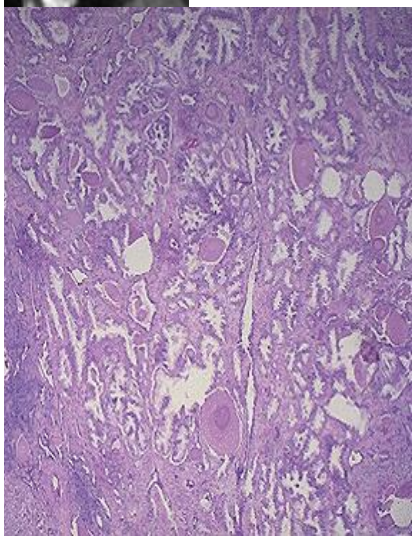
Non-small cell lung cancer:
Crizotinib in **Alk+** tumors
(Shaw AT,
ESMO 2012, Abstr 2862)



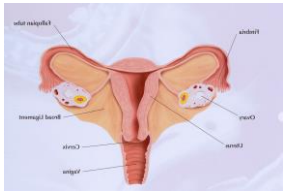
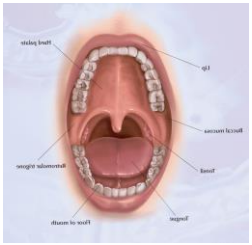
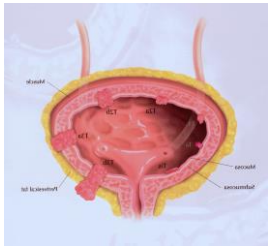
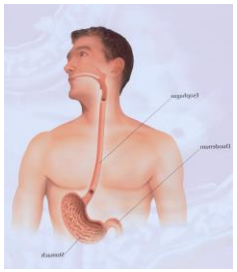
What is Prostate Cancer ? An Old view





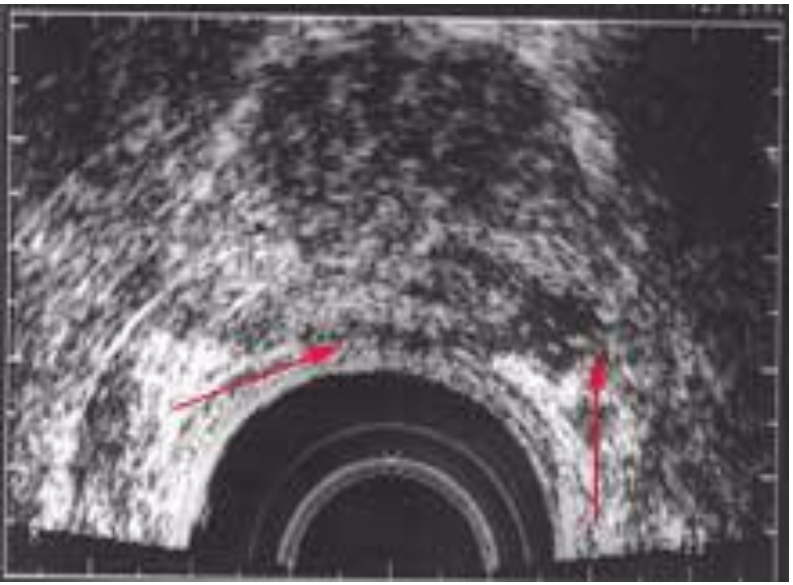


The same treatment for everybody?
For different disease?

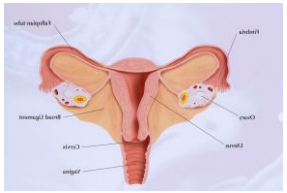
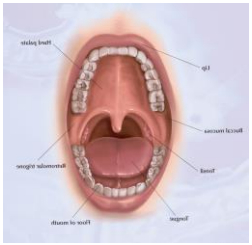
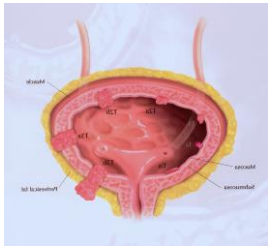
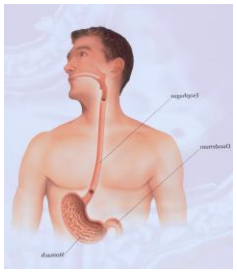
Pathology-based therapy

cytotoxic



IGF-1R activation
Bcl2 expression
P53
Pim Kinase

Molecular classification and Target-oriented therapy

Pathology-based therapy

cytotoxic

Courtesy to Dr Besse

ERG transl

PTEN loss

AR amplification mutation

BRACness

MYC amplification

?

IGF-1R activation
Bcl2 expression
P53
Pim Kinase

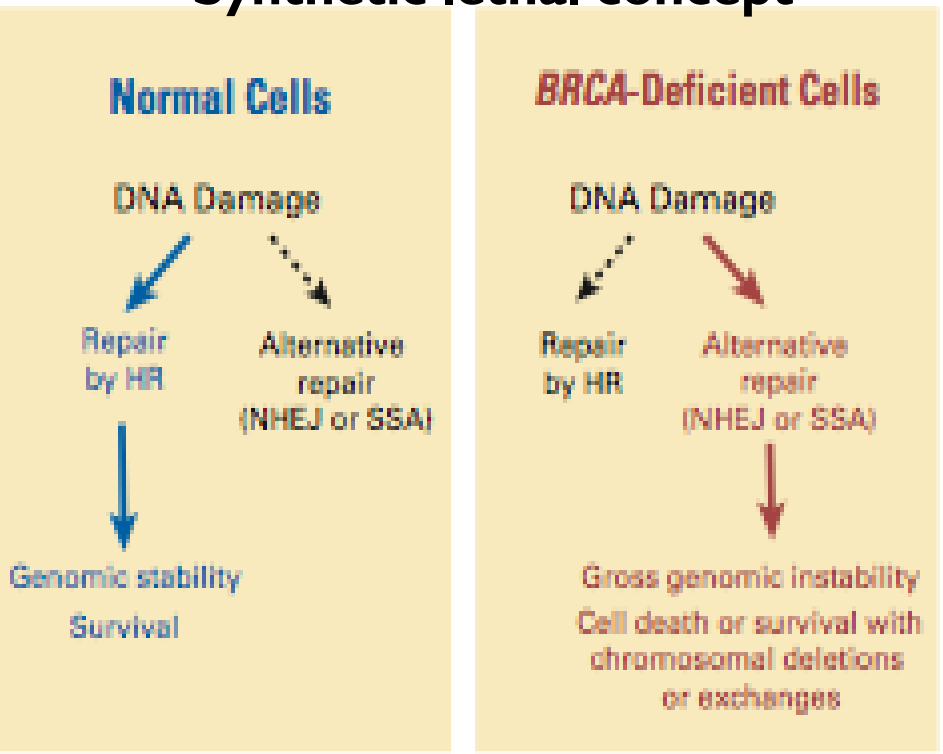
Molecular classification and Target-oriented therapy

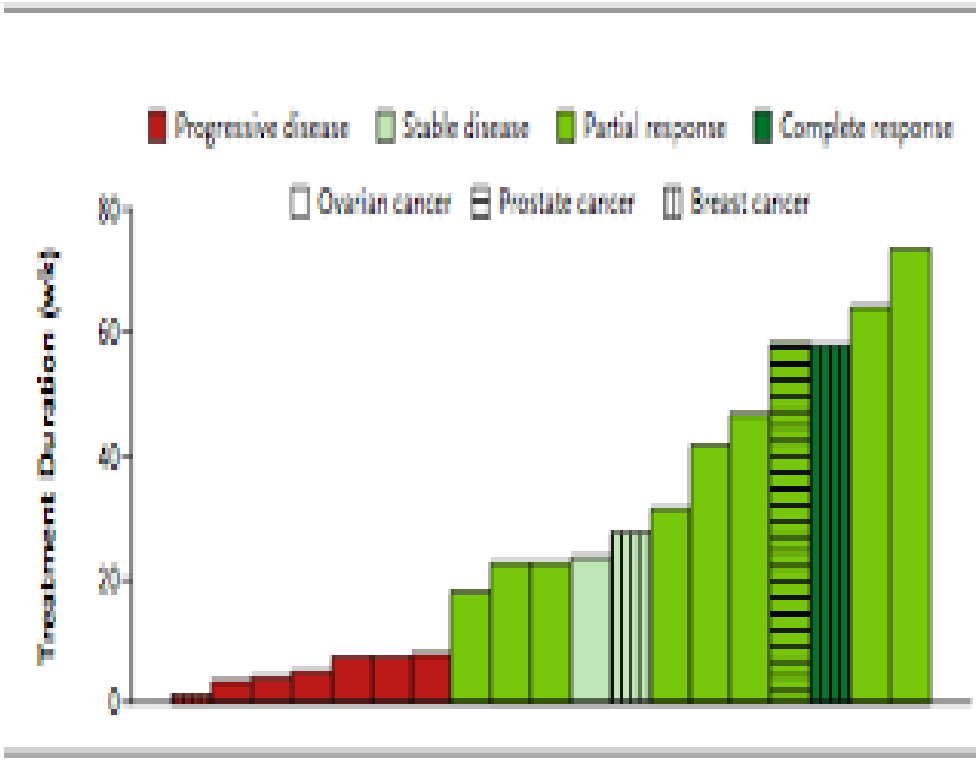
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2009 VOL. 361 NO. 2

Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers

Synthetic lethal concept





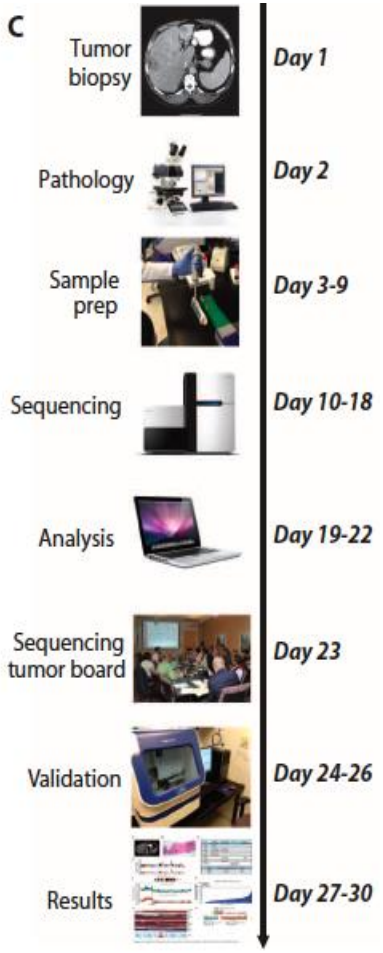
Ashworth A, JCO 2008; Fong et al, NEJM 2009

Science Translational Medicine
AAAS

Personalized Oncology Through Integrative High-Throughput Sequencing: A Pilot Study

Sameek Roychowdhury, *et al.*

Sci Transl Med **3**, 111ra121 (2011);
DOI: 10.1126/scitranslmed.3003161

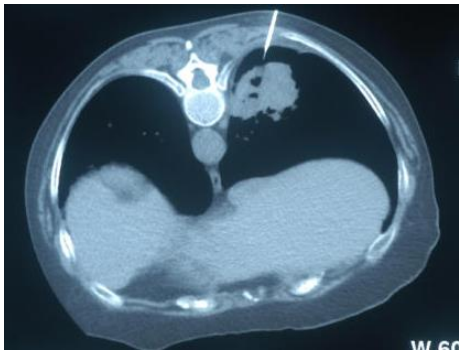


No	Diagnosis	Age (years)	Previous therapies	Sequence results	Potential pathways for therapeutic intervention	Examples of approved or investigational agents
1	Metastatic castrate-resistant prostate cancer	67	Leuprolide + bicalutamide	PTEN deletion	PI3K inhibitors	BEZ235, GDC-0941, XL147
			Diethylstilbestrol	AR amplification	Androgen signaling	Abiraterone, MDV3100
			NY-ESO vaccine study	TMPRSS2-ERG rearrangement	PARP inhibitors	Olaparib, BSI-201, ABT-888
			Azacytidine + valproic acid study	CPNE4-NEK11 rearrangement	(NIMA kinases?)	??
				TP53 mutation		
2	Metastatic prostate cancer	61	Hormone naïve (newly diagnosed)	PTEN deletion	PI3K inhibitors	BEZ235, GDC-0941, XL147
				TMPRSS2-ERG rearrangement	PARP inhibitors (UMich trial)	Olaparib, BSI-201, ABT-888
				PLK1 outlier expression	Polo kinase inhibitors	BI2536, GSK461364A, ON-01910
				TP53 mutation		
3	Metastatic colorectal cancer	46	FOLFOX + cetuximab	NRAS mutation	BRAF and MEK inhibitors	PLX4032, GSK2118436, AZD6244
			Irinotecan + cetuximab phase 1: TAK-901	CDK8 amplification	PI3K inhibitors	BEZ235, GDC-0941, XL147
					CDK inhibitors	Flavopiridol, PD0332991
4	Metastatic melanoma	48	Multiple surgical resections	HRAS mutation	BRAF and MEK inhibitors	PLX4032, GSK2118436, AZD6244
				CDKN2C rearrangement	PI3K inhibitors	BEZ235, GDC-0941, XL147
					CDK inhibitors	Flavopiridol, PD0332991

MOSCATO/WINTHER-PETRUS (prostate cancer)

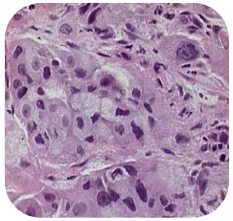
Patient with metastatic cancer

Tumor biopsy with or without normal tissue



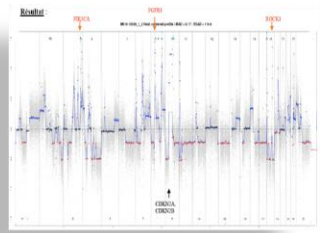
MOLECULAR PORTRAIT

Histological control

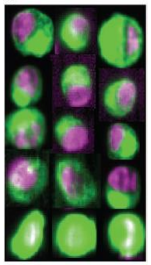


% tumor cells

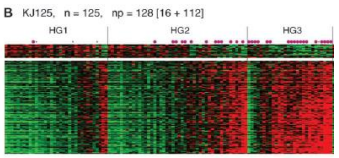
CGH



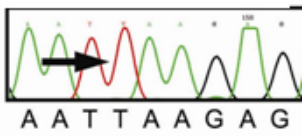
CTC



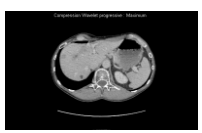
Transcriptome



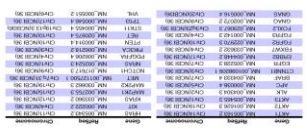
mutations



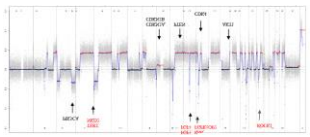
Molecular classification and Target-oriented therapy



TUMOR BIOSPY



SEQCan



CGHarray Agilent

Early clinical trial unit

SITEP

www.igr.fr

MOSCATO M15

62 years old patient

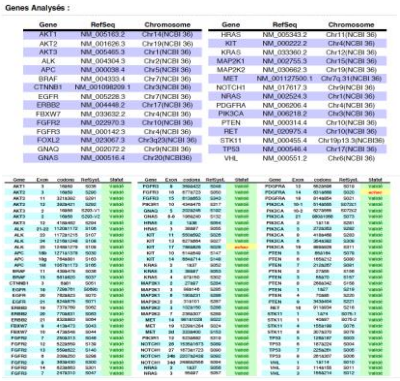
Castration resistant prostate cancer

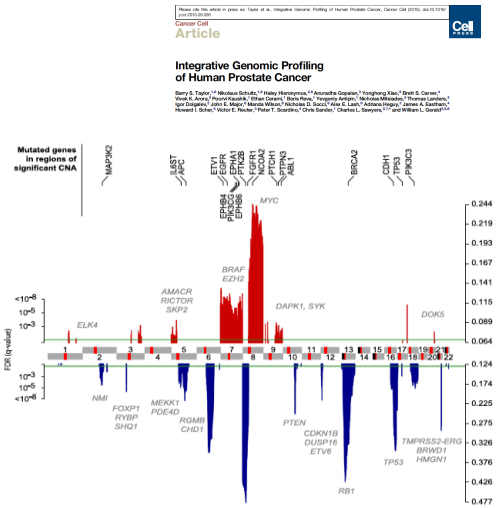
Bone and lymph nodes mets

Previous Rx: agoniste LHRH, docetaxel, Inhibitor of androgen biosynthesis

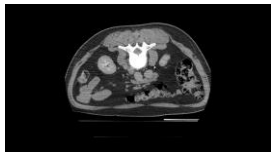
01/2012: LN and bone progression

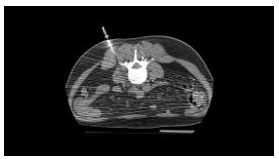
Mutation TP53



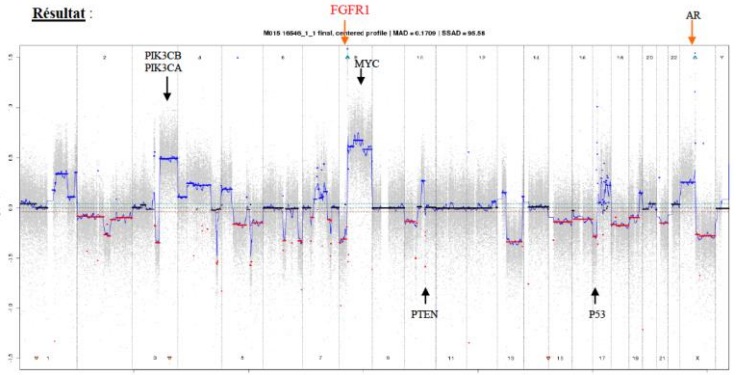


Prostate cancer biology





Amp FGFR1, MYC, AR and PTEN loss



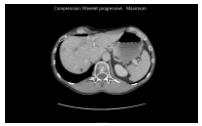
>50%

4 trials at IGR, SITEP

CRPC pts with bone and lymhp nodes mets previsouly treated with docetaxel chemotherapy
Amp FGFR1, MYC, AR and PTEN loss
Proposition: PTEN loss oriented P1 trial … and then?

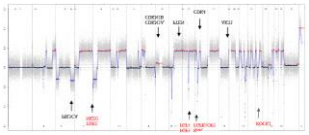
Early clinical trial unit

SITEP www.igr.fr



TUMOR BIOSPY

SEQCan



CGHarray Agilent

MOSCATO M15

62 years old patient

Castration

Bone and ly

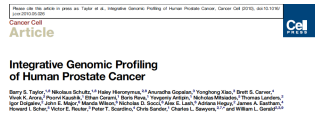
Previous Rx

docetaxel,

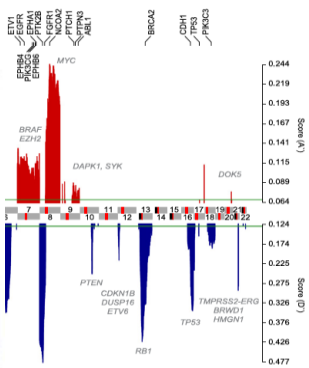
biosynthesi

01/2012: LI

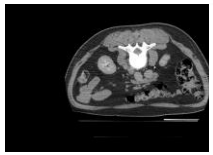
Mutation TP53



Integrative Genomic Profiling of Human Prostate Cancer



cancer biology



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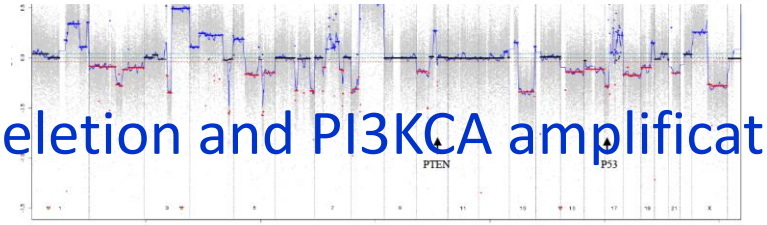

PTEN deletion and PI3KCA amplification

4 trials at IGR, SITEP

CRPC pts with bone and lymhp nodes mets previsouly treated with docetaxel chemotherapy
Amp FGFR1, MYC, AR and PTEN loss
Proposition: PTEN loss oriented P1 trial … and then?

Take-Home Messages

- Prostate cancer is as chemosensitive as other major epithelial cancers
- Prostate cancer is usually still androgen-driven at the castration-resistant stage
- Its unique capacity to generate bone mets should be used to better tailor therapy
- The long delay before symptomatic progression makes CaP an ideal candidate for vaccine approaches
- Inhibition of PI3K/AKT/mTOR is very promising
- **Need to move toward personalized « molecular » oncology in CRPC**

Aknowledgements

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✓Bastien Job

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✓ **And Industrial partnerships**

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Thank you…

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Thank you…and discussion