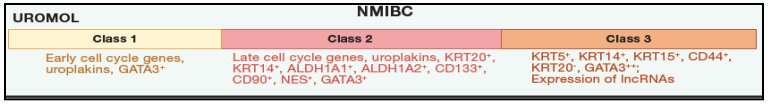
I SIMPOSIO NACIONAL de ONCOLOGÍA de PRECISIÓN

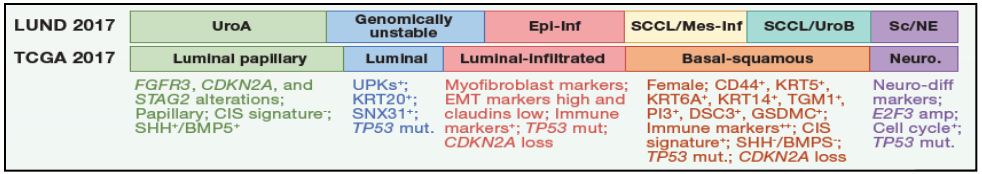
Vigo, del **28** de **febrero** al **1** de **marzo** de **2019**

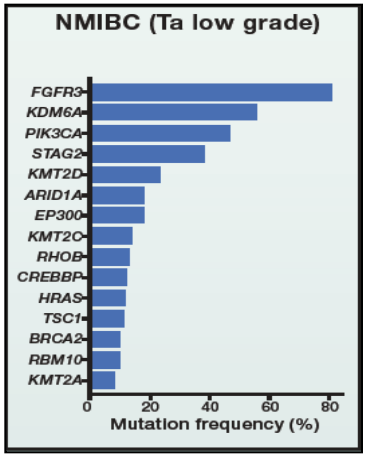
Tumores genitourinarios: riñón, vejiga y próstata

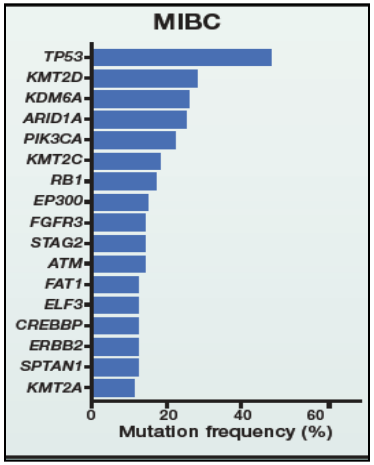
Dr. Enrique González Billalabeitia
Servicio de Hematología y Oncología Médica
Hospital G.U. Morales Meseguer
Murcia

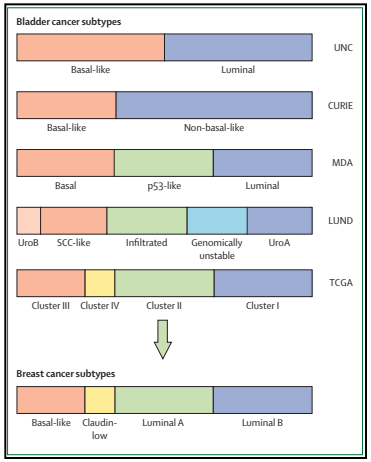
Bladder Cancer: Molecular Classification



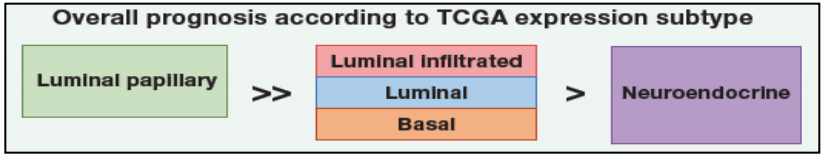








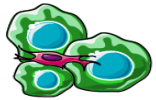
Hurst C. Cancer Cell 2018

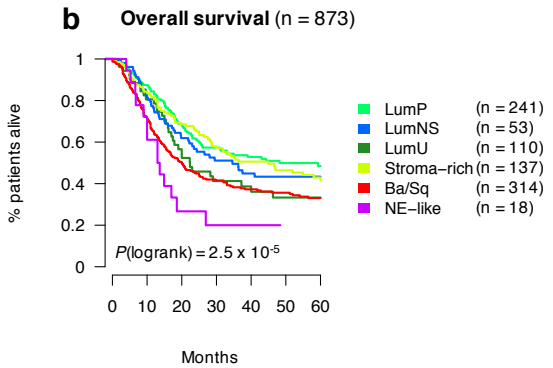


UNC= University of North California, CURIE= Institute Marie Curie,
MDA = MD Anderson Cancer Center, LUND = University of Lund

The Consensus Molecular Classification of Muscle-invasive Bladder Cancer

1750 MIBC transcriptomic profiles from 6 published classification cohorts identifies **6 molecular classes**

	24%	8%	15%	15%	35%	3%
	Luminal Papillary	Luminal Non-Specified	Luminal Unstable	Stroma-rich	Basal/Squamous	Neuroendocrine-like
						
Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 ++ CDKN2A -	PPAR-γ ++	PPAR-γ ++ E2F3 +, ERBB2 + Genomic instability		EGFR +	TP53 --, RB1 --, Cell cycle +
Mutations	*FGFR3* (40%), *KDM6A* (38%), *STAG2* (22%)	*ELF3* (35%)	*TP53* (76%), *ERCC2* (22%) TMB +, APOBEC +		*TP53* (61%), *RB1* (25%)	*TP53* (94%) *RB1* (39%)
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology	Micropapillary variants			Squamous differentiation	Neuroendocrine differentiation
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

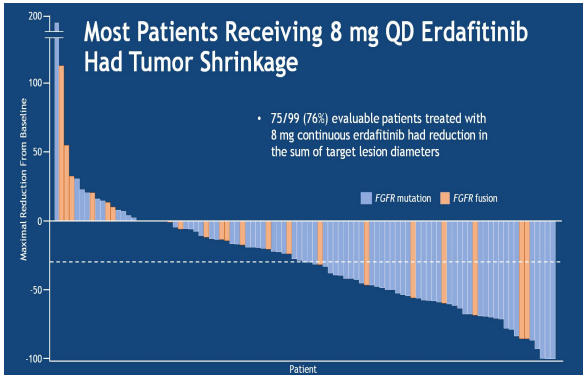


The Bladder Cancer Molecular Taxonomy Group
https://www.biorxiv.org/content/early/2018/12/10/488460

CAN GENETICS HELP US TO IMPROVE TREATMENT STRATEGIES IN MIBC?

Preliminary results suggest activity of FGFR inhibitors in metastatic Urothelial Carcinoma with FGFR3 alterations

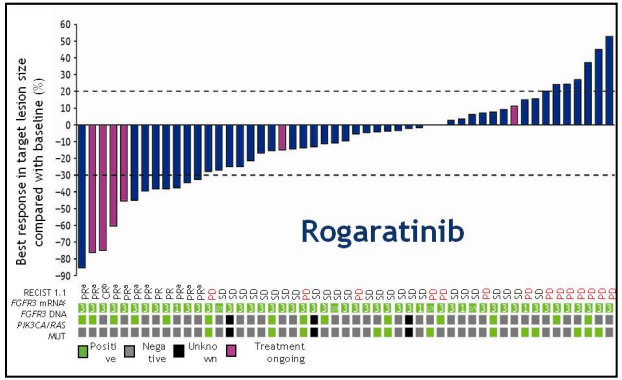
Erdafitinib (JNJ-42756493)



ORR: 40% (40/99)

Siefker-Radtke et al J Clin Oncol 2018 (abstr 4503)

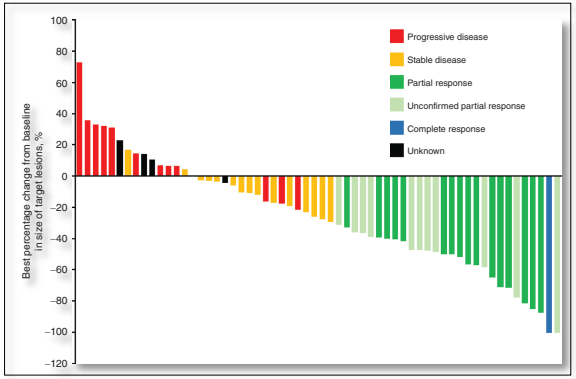
Rogaratinib



ORR: 24% (12/51)

Joerger M, et al. J Clin Oncol 2018(abstr4513).

BGJ398



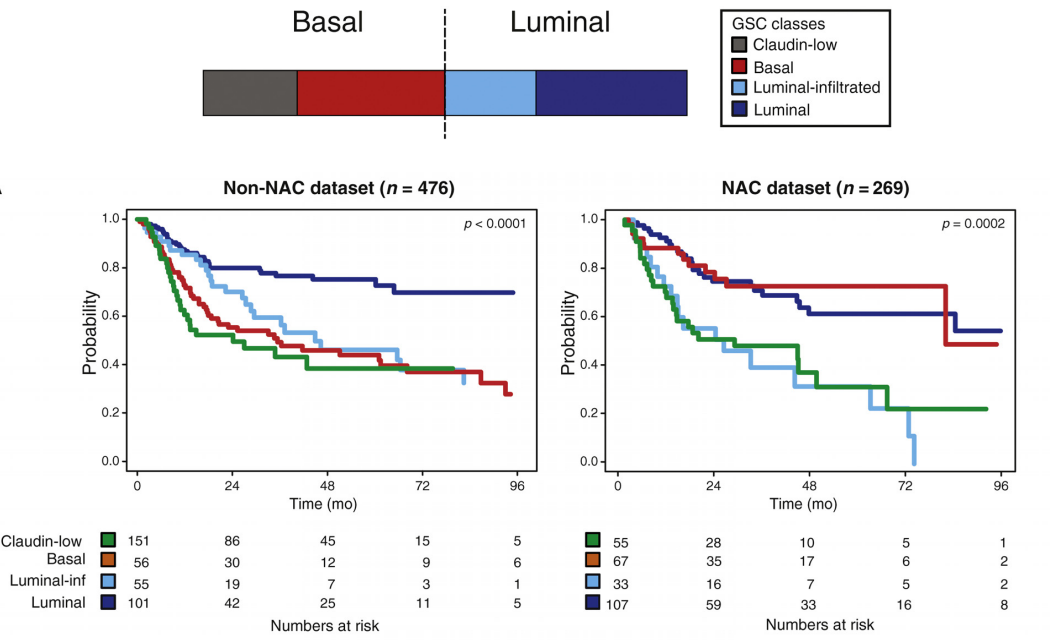
ORR: 25.4%

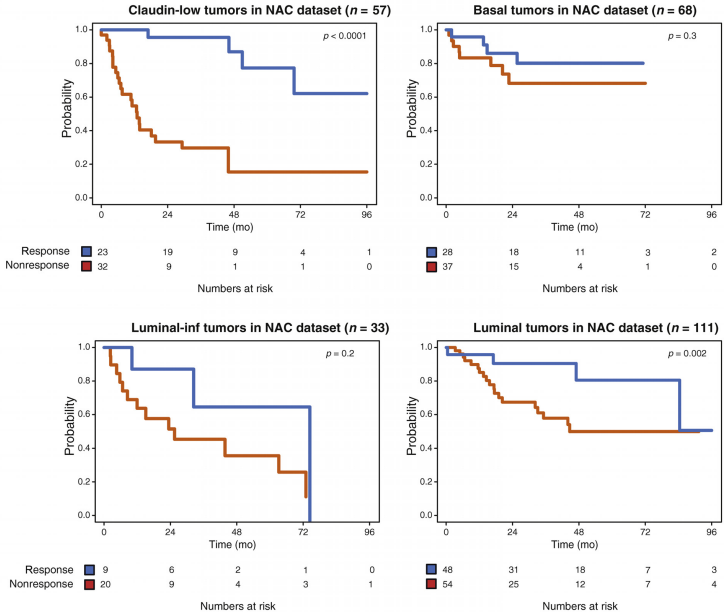
Pal S, et al. Cancer Discov 2018;36

Precision Medicine in Neoadjuvant CT

Biomarker	N	Translational relevance	Reference
ERCC2 mutation	50	Association with pathologic response	*Van Allen EM et al, Cancer Discov 2014*
ERCC2 mutation	48+54	Association with improved OS in 2 independent cohorts of cisplatin-treated MIBC patients	*Liu D et al. JAMA Oncol 2016* *Plimack ER et al, Eur Urol 2015* *Plimack ER et al, ASCO 2014*
ATM/RB1/FANCC mutations	34	Association with improved pT<2 response and OS	*Plimack ER et al, Eur Urol 2015*
ATM/RB1/FANCC mutations	25	Association with improved pT<2 response	*Anari F et al, Eur Urol Oncol 2018*
ERBB2 mutations	71	Association with pT0 response	*Groenendijk FH et al, Eur Urol 2015*
DNA damage response (DDR) gene alterations	46	Association with pT<2 response and RFS with dose-dense GC	*Iyer G et al, J Clin Oncol 2018*
Single-sample genomic subtyping classifier	343	Basal tumors benefited the most from neoadjuvant chemotherapy administration	*Seiler R et al, Eur Urol 2017*

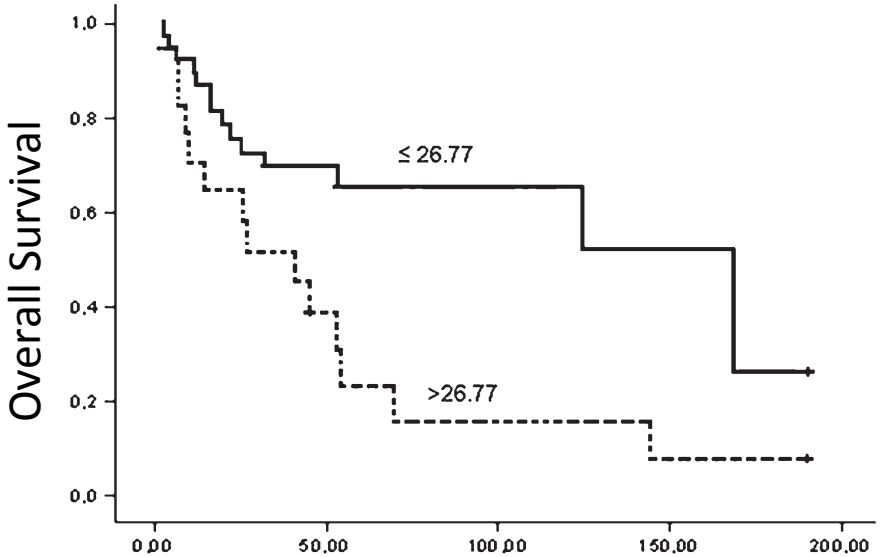
Genomic Subtyping Classifier (GSC) to predict consensus subtypes with highest clinical impact in the context of NAC.





Seiler R. Eur Urol 2017

BRCA1 mRNA levels associate better outcome



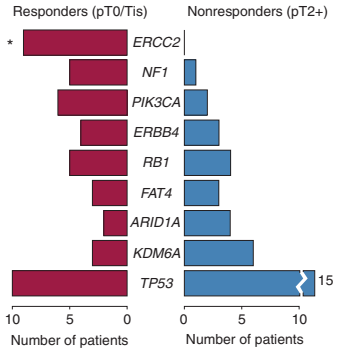
	N	Median	95% CI	5-yr survival (95% CI)	p
≤26.77	39	168	54.9-281.1	64.1 (48.2-80)	0.002
>26.77	18	34	14.5-53.5	12.1 (0-27.8)	

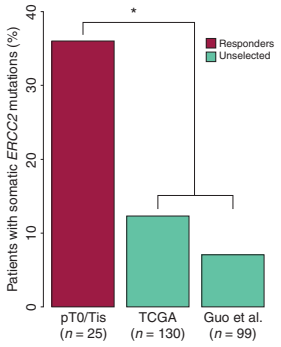
Font A. Ann Oncol 2011

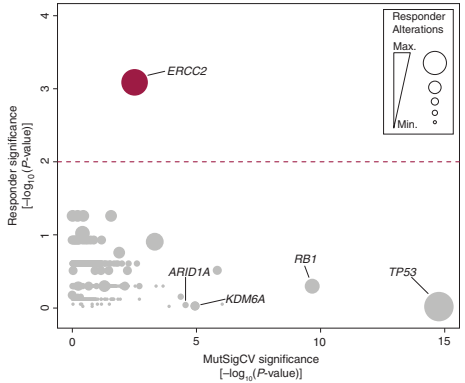
RESEARCH ARTICLE

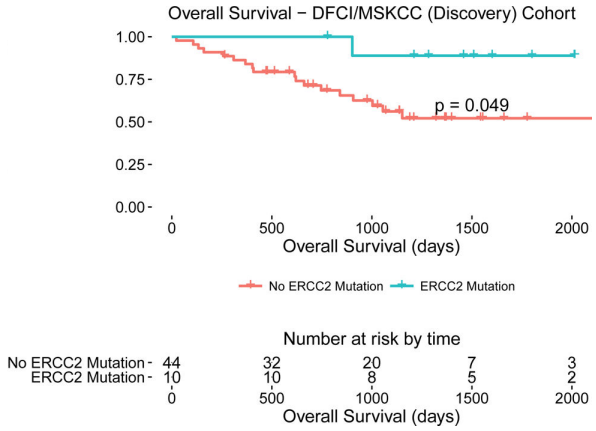
Somatic *ERCC2* Mutations Correlate with Cisplatin Sensitivity in Muscle-Invasive Urothelial Carcinoma

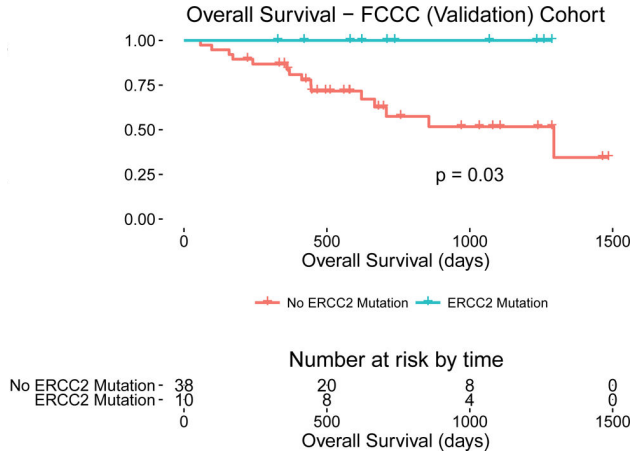
Eliezer M. Van Allen[1,2], Kent W. Mouw[3,4], Philip Kim[5], Gopa Iyer[6,7], Nikhil Wagle[1,2], Hikmat Al-Ahmadie[6,8], Cong Zhu[2], Irina Ostrovnaya[9], Gregory V. Kryukov[2], Kevin W. O'Connor[3], John Sfakianos[5], Ilana Garcia-Grossman[7], Jaegil Kim[2], Elizabeth A. Guancial[10], Richard Bambury[7], Samira Bahl[2], Namrata Gupta[2], Deborah Farlow[2], Angela Qu[1], Sabina Signoretti[11], Justine A. Barletta[11], Victor Reuter[6,8], Jesse Boehm[2], Michael Lawrence[2], Gad Getz[2,12], Philip Kantoff[1], Bernard H. Bochner[5,6], Toni K. Choueiri[1], Dean F. Bajorin[6,7], David B. Solit[6,7,13], Stacey Gabriel[1], Alan D'Andrea[3,4], Levi A. Garraway[1,2], and Jonathan E. Rosenberg[6,7]











Cancer Discovery 2014

Liu D. JAMA Oncol. 2016

European Association of Urology

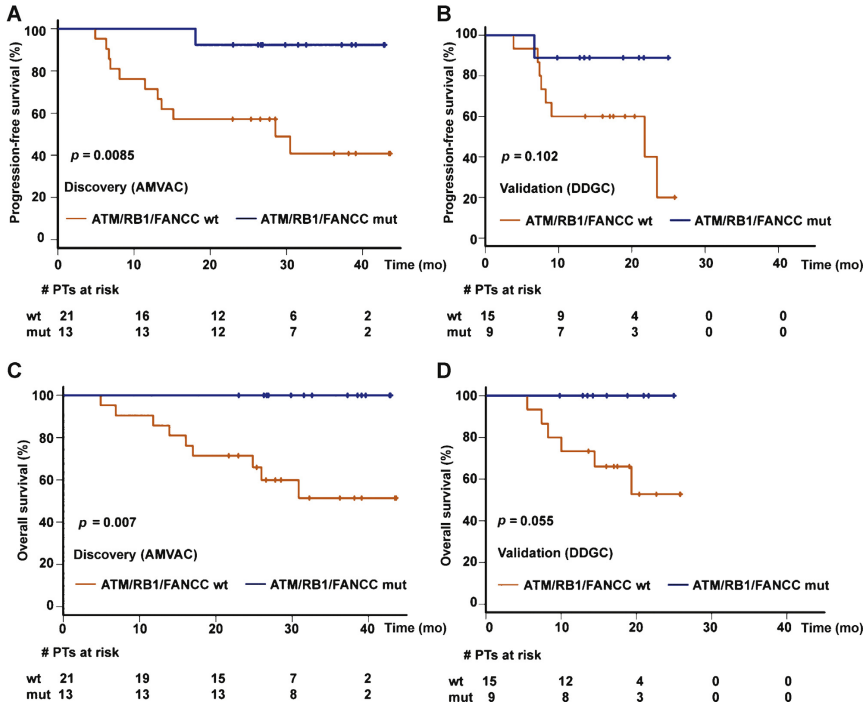
VOLUME 36 · NUMBER 19 · JULY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Platinum Priority – Bladder Cancer

Editorial by Cyrill A. Rentsch, Frank Stenner, Christian Ruiz and Lukas Bubendorf on pp. 968–969 of this issue

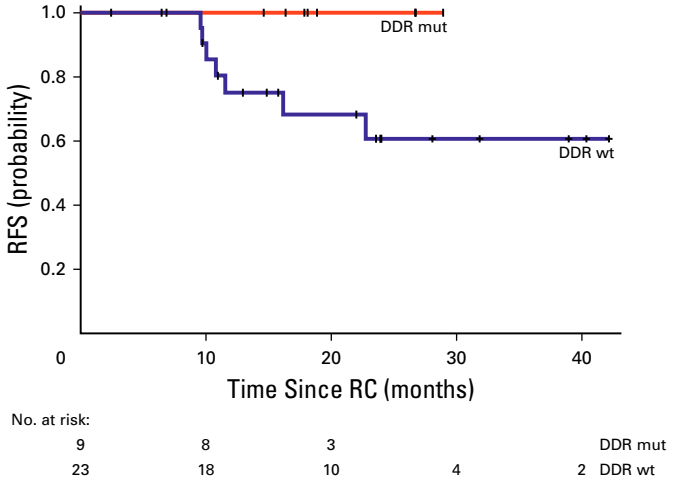
Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based Chemotherapy in Muscle-invasive Bladder Cancer



Plimack ER. Eur Urol 2015

Multicenter Prospective Phase II Trial of Neoadjuvant Dose-Dense Gemcitabine Plus Cisplatin in Patients With Muscle-Invasive Bladder Cancer

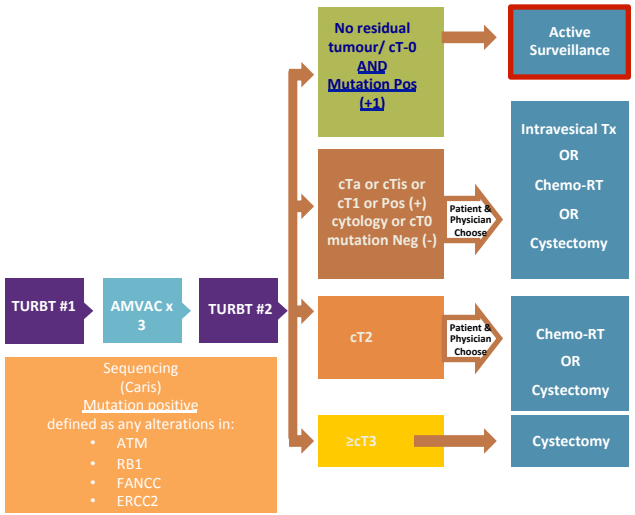
Gopa Iyer, Arjun V. Balar, Matthew I. Milowsky, Bernard H. Bochner, Guido Dalbagni, S. Machele Donat, Harry W. Herr, William C. Huang, Samir S. Taneja, Michael Woods, Irina Ostrovnaya, Hikmat Al-Ahmadie, Maria E. Arcila, Jamie C. Riches, Andreas Meier, Caitlin Bourque, Maha Shady, Helen Won, Tracy L. Rose, William Y. Kim, Brooke E. Kania, Mariel E. Boyd, Catharine K. Cipolla, Ashley M. Regazzi, Daniela Delbeau, Asia S. McCoy, Hebert Alberto Vargas, Michael F. Berger, David B. Solit, Jonathan E. Rosenberg, and Dean F. Bajorin



Iyer. J Clin Oncol 2016

Clinical trials with NAC including DDR in MIBC

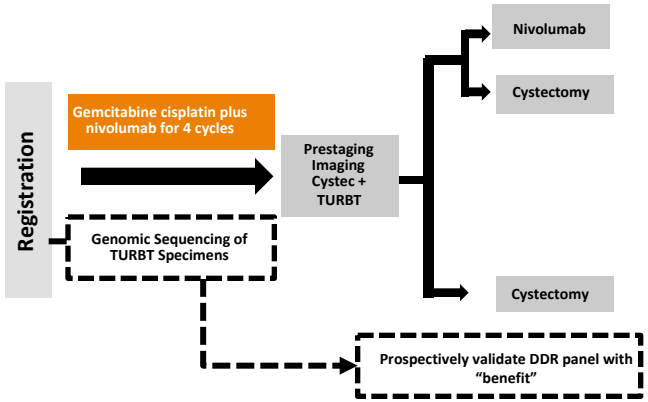
RETAIN BLADDER



Primary Endpoint: Metastasis-free survival (MFS) at 2 years. Non-inferiority design with a 14% margin between risk-adapted design (MFS=78%) and standard-of-care (MFS=64%). Sample size=70 with an 82% power. Type I error=0.045

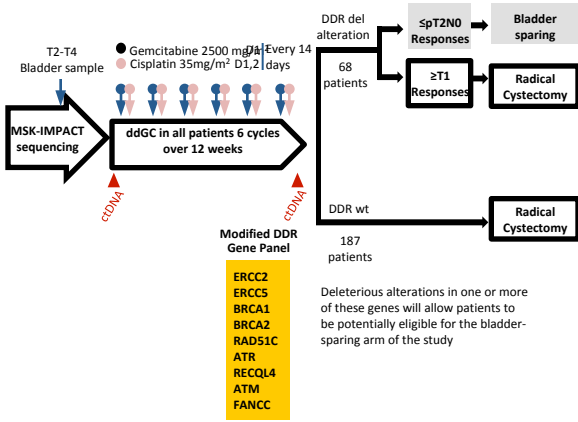
NCT02710734

HCRN 16-257



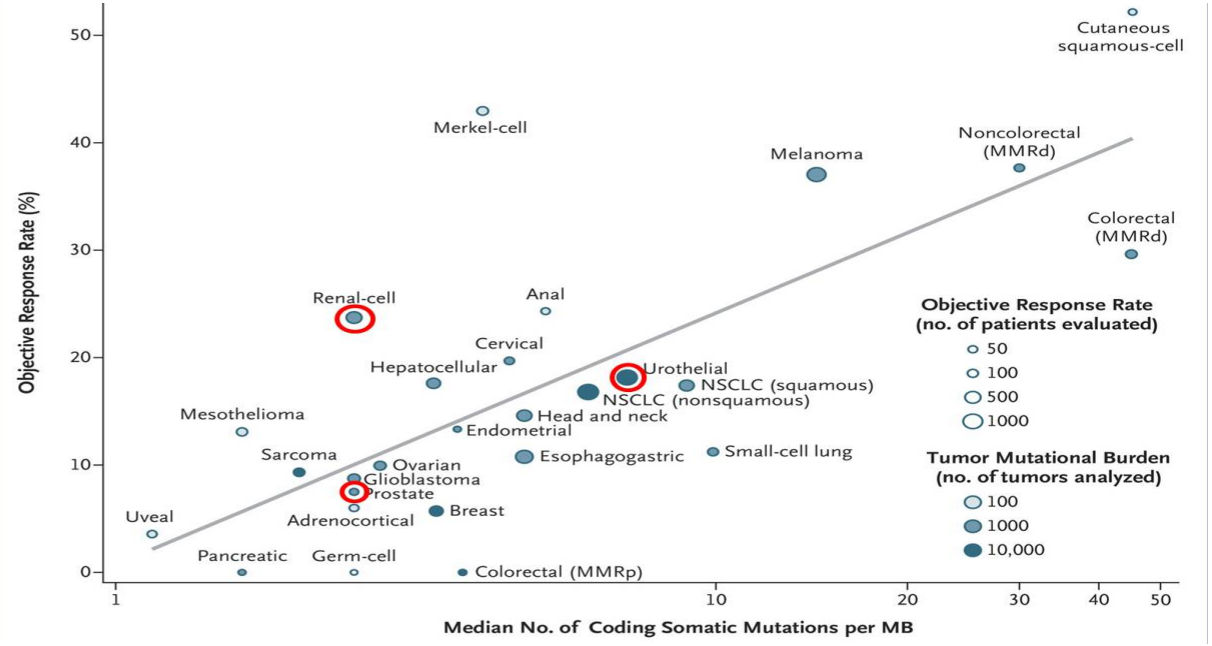
PI: Matt Galsky

AO31701



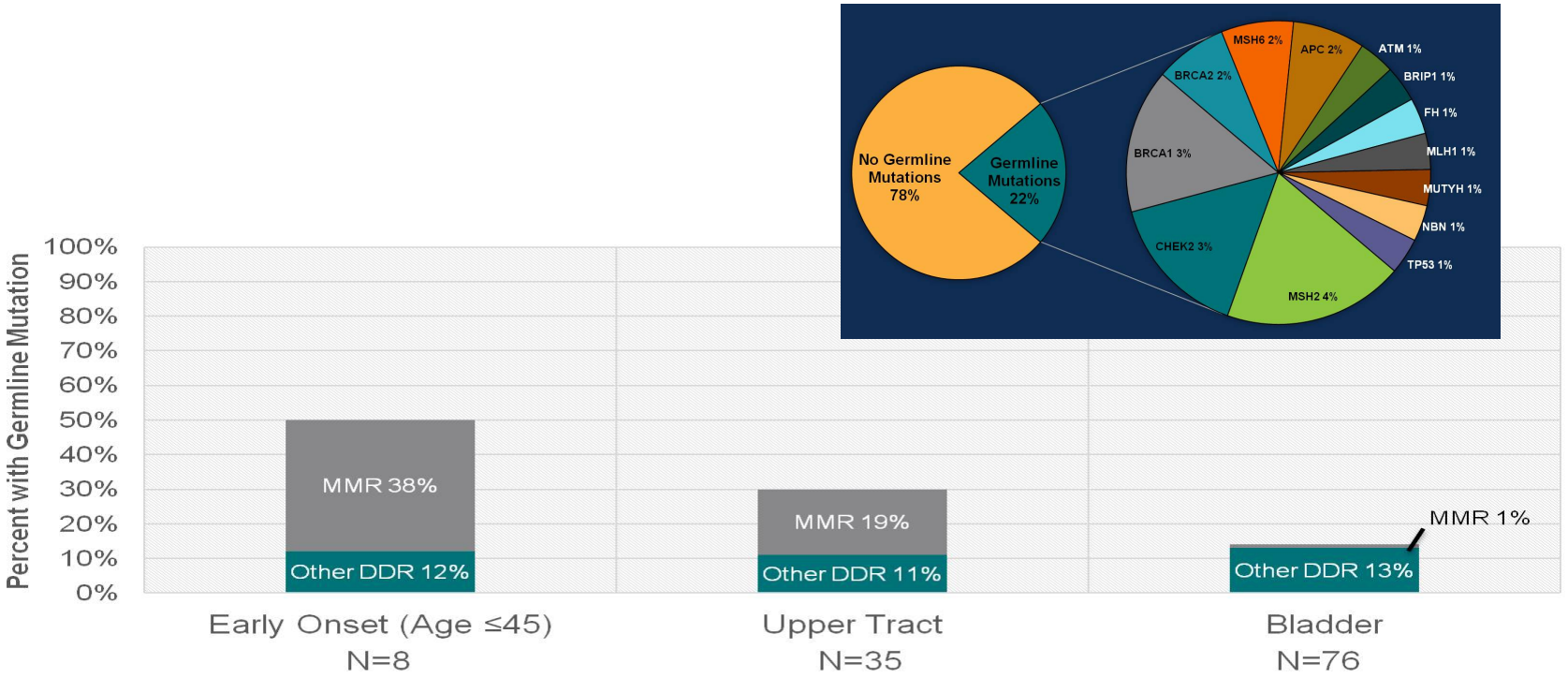
Deleterious alterations in one or more of these genes will allow patients to be potentially eligible for the bladder-sparing arm of the study

TMB and response to anti-PD1



Yarchoan et al. N Engl J Med 2017

MissMatch Repair defects are frequently observed in urothelial carcinoma



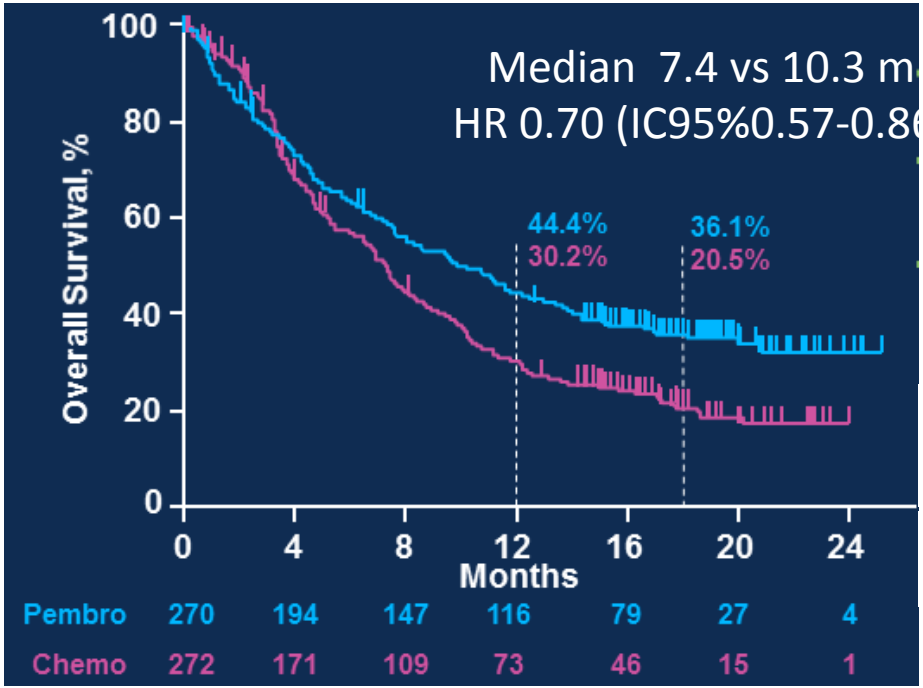
Carlo M. ASCO 2017

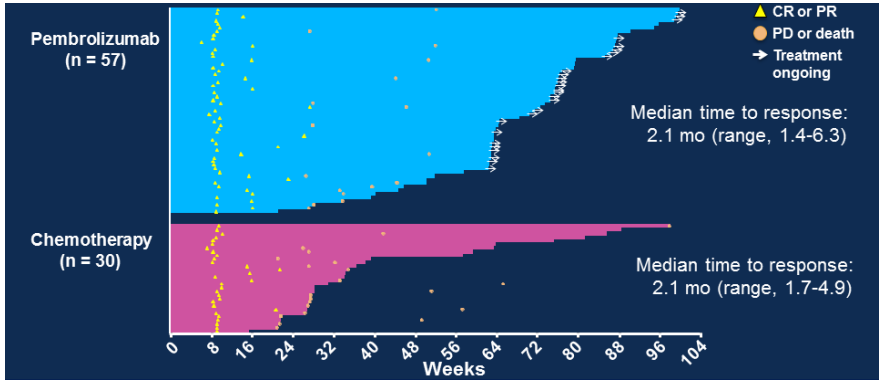
Efficacy in patients in progression to cisplatin

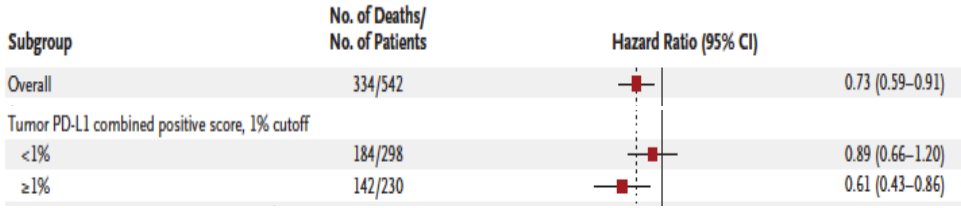
	Pembrolizumab[1]	Atezolizumab[2]	Nivolumab[3]	Avelumab[4]	Durvalumab[5]
Study design	Phase 3	Phase 3	Phase 2	Phase 1b	Phase 1/2
N	270	462	265	44	191
Dose	200 mg/3w	1200 mg/3w	3 mg/kg/2w	10 mg/kg/2w	10 mg/kg/2w
ORR	21.1%	13%	19.6%	18.2%	17.8%
Ongoing (%;Median FU)	72%/14.1m	63%/17.3m	77%/7m	75%/16.5m	81%/5.8m
PFS (median)	2.1	2.1*	2.0	2.7	1.5 m
OS (median)	10.3	8.6	8.7	13.6	18 m
Toxicity					
G3-5	13.5%	20%	18%	6.8%	7.5%
G5	1.5 % (0.5% IR)	1% IR	1%	0%	1.5%

[1] Belmunt J. N Engl J Med 2017; [2] Powles T. EAS 2017; [3] Sharma P. Lancet Oncol 2017; [4] Apolo A. J Clin Oncol 2017; [5] Powles T. JAMA Oncol 2017

KEYNOTE-045: Pembrolizumab associates long-lasting responses and improves Overall Survival in cisplatin treated patients





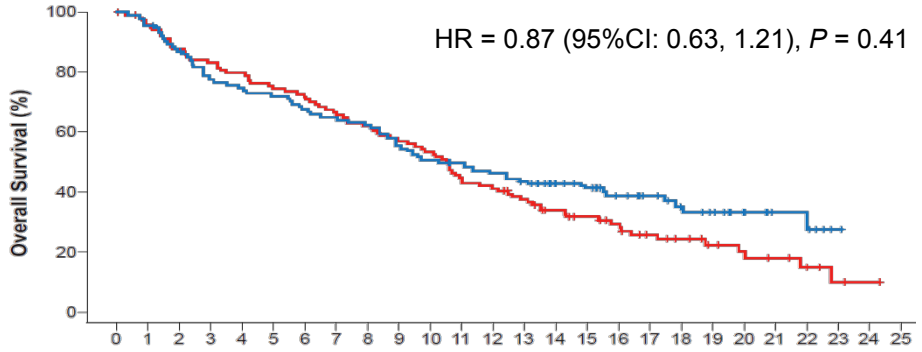


Belmunt J. N Engl J Med 2017

IMvigor211

Primary Endpoint (PDL1 2/3)

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)



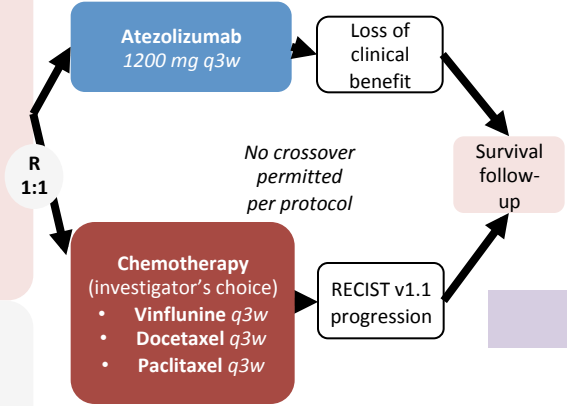
Key Eligibility Criteria[a]

- mUC with progression during or following platinum-based chemotherapy
  - ≤ 2 prior lines of therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Evaluable sample for PD-L1 testing
- TCC histology as primary component

(N = 931)

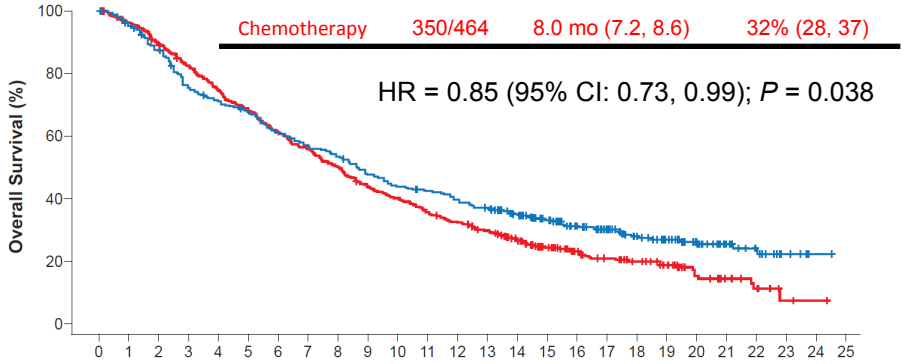
Stratification Factors

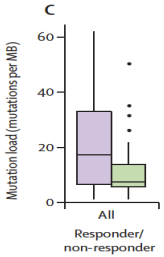
- No. of risk factors[b] (0 vs. 1/2/3)
- Liver metastases (yes vs. no)
- PD-L1 status (0/1 vs. 2/3)
- Chemotherapy (vinflunine vs. taxanes)

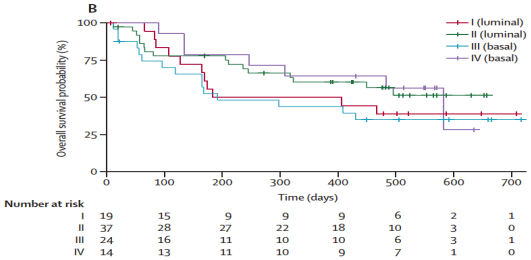


ITT

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	324/467	8.6 mo (7.8, 9.6)	39% (35, 44)
Chemotherapy	350/464	8.0 mo (7.2, 8.6)	32% (28, 37)







Efficacy in patients 1st line un-fit

	Pembrolizumab[1] (KEYNOTE-052)	Atezolizumab[2] (IMvigor210 1L)
Study design	Phase 2	Phase 2
N	370	119
Dose	200 mg/3w	1200 mg/3w
ORR	24% (5%CR)	23% (9% CR)
Ongoing (%;Median FU)	82%/6m	70%/17.2m
PFS (median)	2	2.7
OS (median)	NR	15.9
Toxicity • G3-4 • G5	 10% <0.01 (1 pt)	 16% <0.01 (1 pt)

Efficacy in patients 1st line un-fit

	Pembrolizumab[1] (KEYNOTE-052)	Atezolizumab[2] (IMvigor210 1L)
Study design	Phase 2	Pha
N	370	119
Dose	200 mg/3	1200 mg/3w
ORR	%CR)	23% (9% CR)
Ongoing (%;Median	82%/6m	70%/17.2m
	2	2.7
(median)	NR	15.9
Toxicity • G3-4 • G5	10% <0.01 (1 pt)	16% <0.01 (1 pt)

May,2018- FDA warning. Only for patients PDL1+ (~40%)

Phase 3 trials of CheckPoint Inhibitors plus chemotherapy

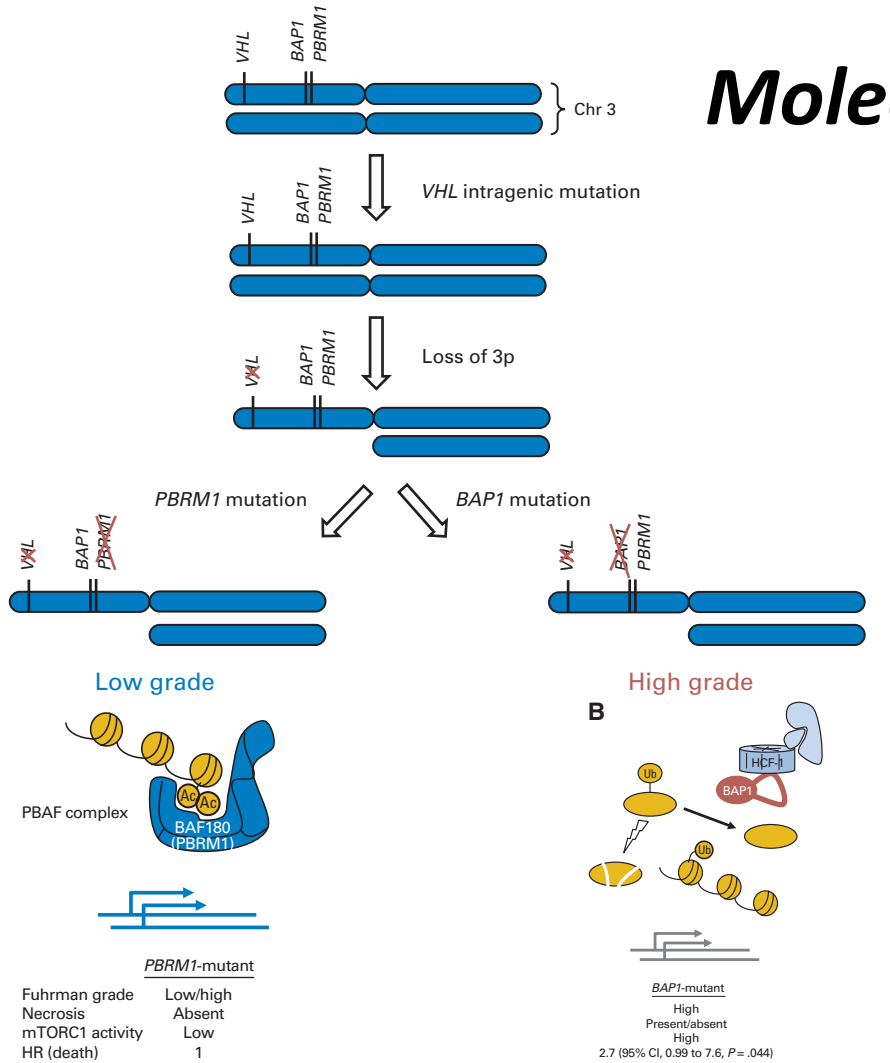
Trial	Population	Study Arms	Primary Endpoints/Expected
KEYNOTE-361	Advanced or Metastatic Urothelial Carcinoma (N= 990)	Pembro +- CT vs CT	PFS, OS (2019)
IMvigor-130	Advanced or Metastatic Urothelial Carcinoma (N = 1200)	Atezo +- CT vs CT	PFS, OS (2020)
DANUBE	Cisplatin Elegible or Inelegible (N=1340)	Avelumab +- Tremelimumab vs SOC	PFS, OS (2018)
CHECKMATE-901	Cisplatin Elegible or Inelegible (N=1097)	IPI + NIVO vs SOC	PFS, OS (2020)

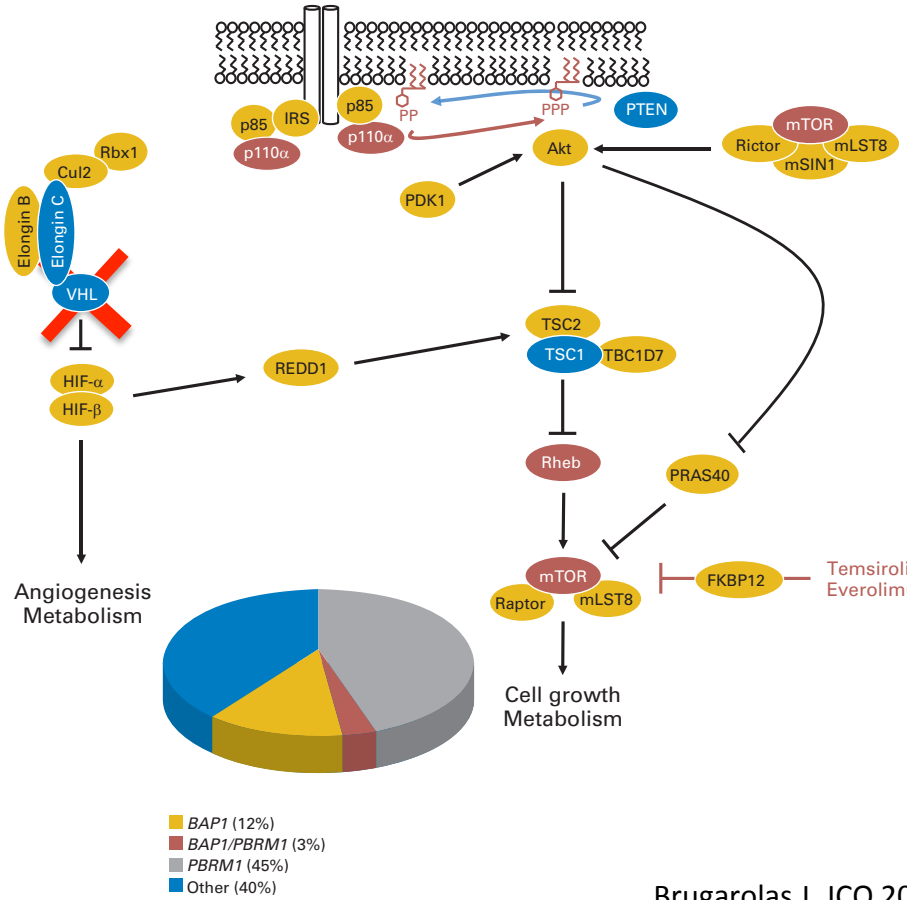
May 2018. FDA halts accrual of low PD-L1 patients due to relatively worse OS in single agent anti-PD1/PDL1 arms

Bladder Cancer: Personalized therapies

- Clinical criterias (ECOG, Renal function..) are the most important factors to date.
- PD-L1 positivity is required for the treatment of cisplatin-inelegible patients with front line CPI.
- Molecular subtypes and genomic aberrations (DDR, ERCC2) are included in the design of current clinical trials
- Future trials include CT and CPI, and BKs in this setting need to be validated.

Molecular Genetics of ccRCC





Brugarolas J. JCO 2014

Clear-Cell Renal Cell Cancer

Table 1. ccRCC-Mutated Genes

Genes	TCGA Cohort		Japanese Cohort*	
	Tumors With Mutation (%)	Passenger Probability (*q* value)	Tumors With Mutation (%)	Passenger Probability (*q* value)
VHL	52.3	< .0001	39.6†	< .0001
PBRM1	32.9	< .0001	26.4	< .0001
SETD2	11.5	< .0001	11.3	< .0001
BAP1	10.1	< .0001	7.5	< .0001
MTOR	6	< .0001	5.7	.0431
TCEB1	0.7	.0566	4.7‡	< .0001
PIK3CA	2.9	< .0001	4.7	.0268
KDM5C	6.7	< .0001	3.8	.12
TP53	2.2	< .0001	2.8	.0176
PTEN	4.3	< .0001	1.9	.116

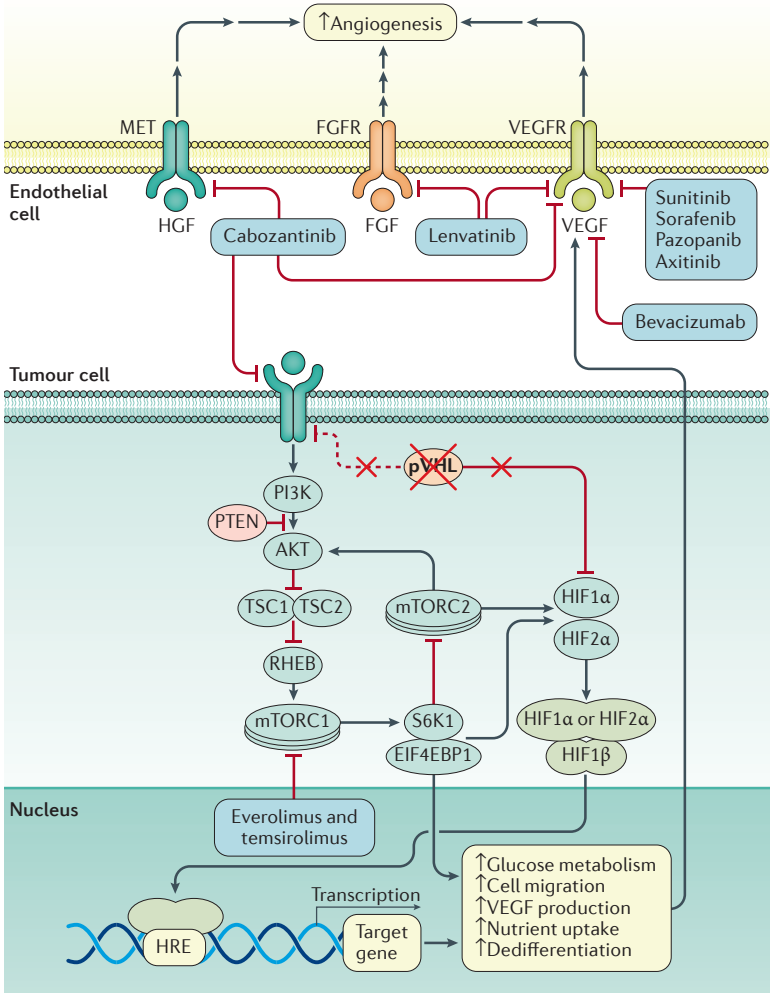
Abbreviations: ccRCC, clear-cell renal cell carcinoma; TCGA, The Cancer Genome Atlas.

*Mutations found by whole exome sequencing.

†Including complementary approaches overall *VHL* mutation rate, 66%.

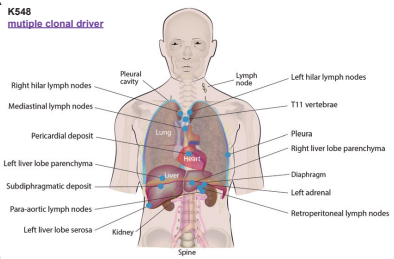
‡Possibly higher *TCEB1* mutation rates in preselected ccRCC population.

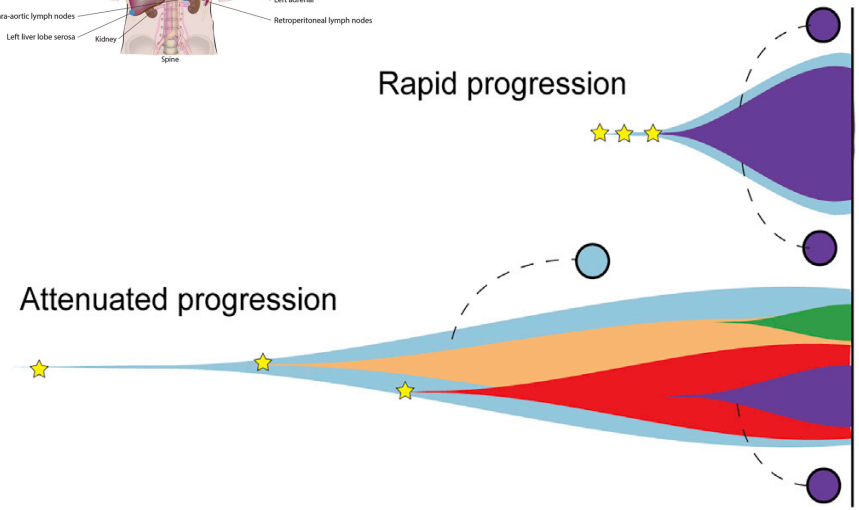
Data are obtained from Creighton et al (Table S4).[5] and Sato et al (Table S4).[6] For methodology, see Creighton et al[5] and Sato et al.[6]



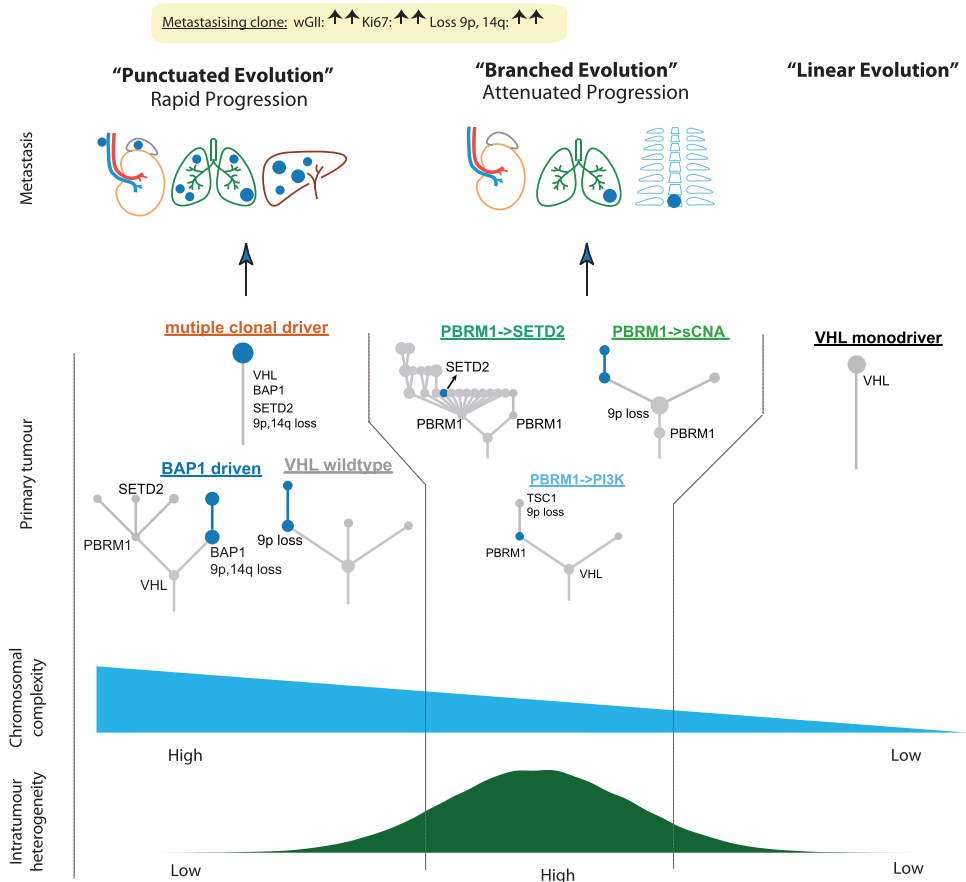
Hsieh JJ. Nat Rev Dis Prim 2017

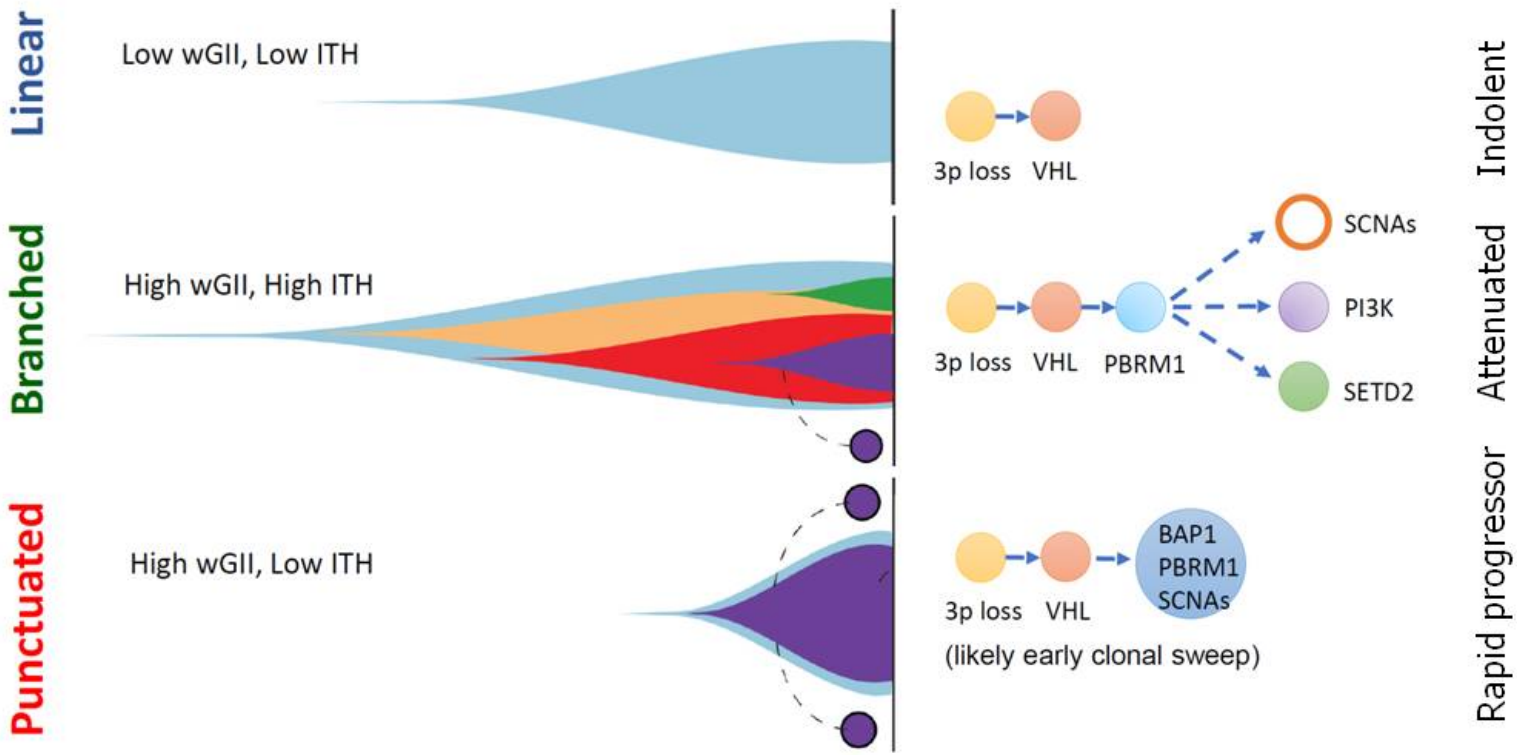
TRACERx Renal Cancer





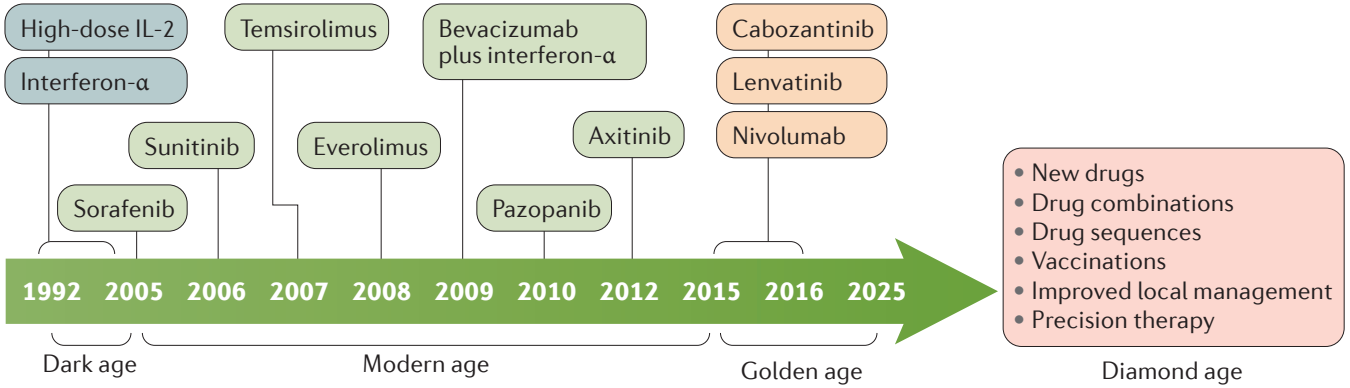
Turajlic S .. Swanton C. Cell 2018

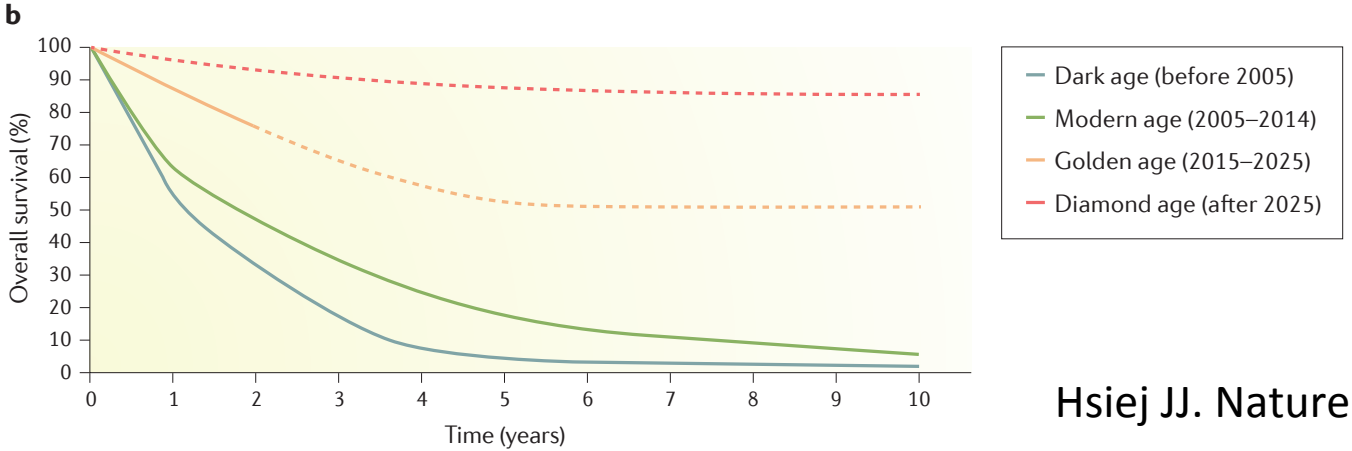




Adapted from Turajlic.Cell 2018; Brugarolas 2018

The ages of ccRCC





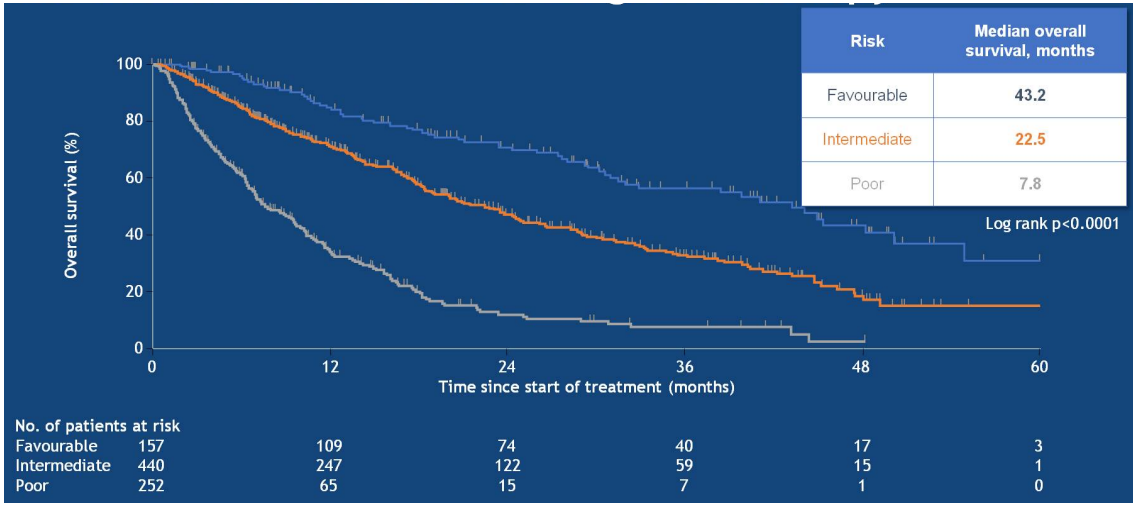
Hsiej JJ. Nature Primer 2017

International Metastatic RCC Database Consortium (IMDC) Criteria

IMDC risk factor in RCC	Value
Karnofsky PS	<80%
Time from initial diagnosis to treatment	<1 year
Hemoglobin	<LLN
Corrected calcium	>10 mg/dL
Platelet count	>ULN
Neutrophil count	>ULN

Number of risk factors[1]	Risk Group	Median overall survival at line of therapy, months		
		1L	2L	3L
0	Favourable	43.2	35.3	29.9
1–2	Intermediate	22.5	16.6	15.5
≥3	Poor	7.8	5.4	5.5

IMDC First line



Heng DYC. Lancet Oncol 2013; 14: 141-8

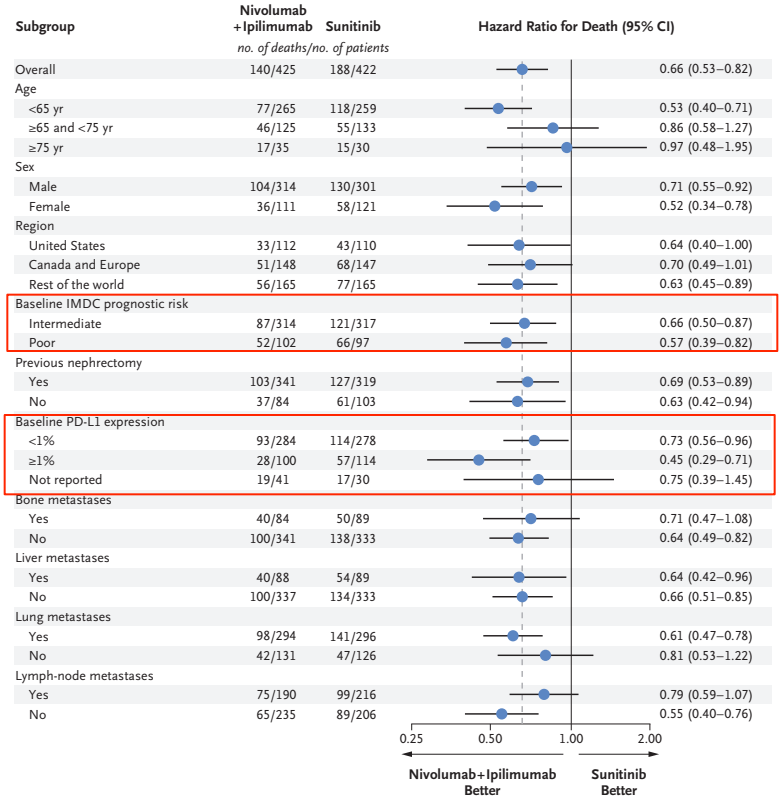
Front-Line Phase 3 trials

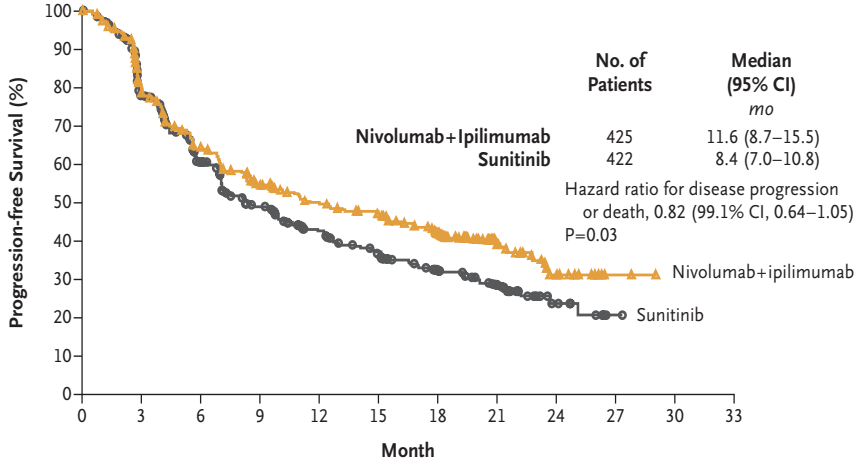
	JAVELIN Renal 101 Per IRC		KEYNOTE-426		CheckMate 214 (Intermediate- and Poor-Risk Patients)	
	Avelumab + Axitinib (N = 442)	Sunitinib (N = 444)	Pembrolizumab + Axitinib (N = 432)	Sunitinib (N = 429)	Nivolumab + Ipilimumab (N = 425)	Sunitinib (N = 422)
ORR (95% CI), %	**51 (46.6, 56.1)**	**26 (21.7, 30.0)**	**59.3**	**35.7**	**42 (36-47)**	**27 (22-31)**
CR	3	2	NR	NR	9	1
PR	48	24			32	25
SD	30	46			31	45
PD	12	19			29	17
Not evaluable	6	8			8	12
Patients with ongoing response, %	70	71	NR		72	63
Median PFS (95% CI), months, HR	**13.8 (11.1, NE)**	**8.4 (6.9, 11.1)**	**15.1**	**11.1**	**11.6 (8.7, 15.5)**	**8.4 (7.0, 10.8)**
	HR = 0.69 (95% CI: 0.563, 0.840) P = 0.0001		**HR = 0.69 [95% CI 0.57-0.84]; P = 0.0001**		**HR 0.82 (99.1% CI, 0.64 -1.05); P = 0.03**	
OS HR	NR		HR 0.53		HR 0.63	
12 mo OS rate, %	**86.3**	83.0	**89.9**	78.3	**80.0**	60.0
All TRAEs, %	95	96	NR		93	97
Grade 3/4 TRAEs, %	**55**	**55**	**62.9 (Gr. 3-5)**	**58.1 (Gr. 3-5)**	**46**	**63**
TRAEs leading to discontinuation of all study drugs, %	4	8	6.3	10.1	22	12
TRAEs leading to death, n	3	1			8	4

Gulley JL. ASCO GU 2019

Check-Mate 214

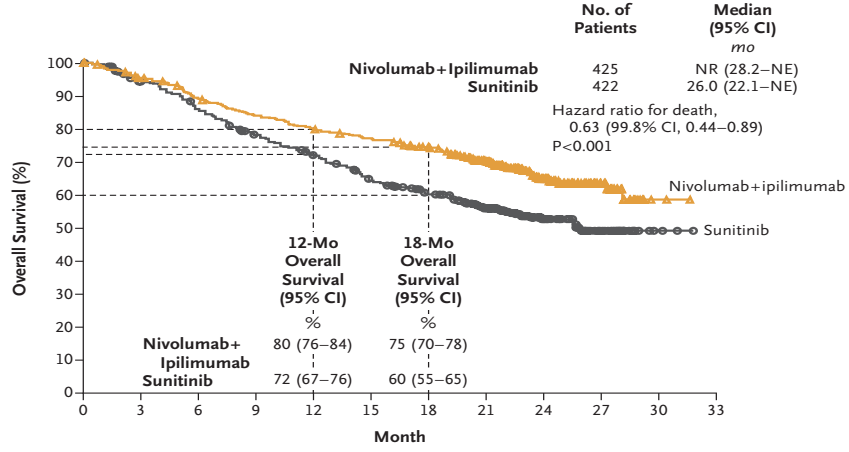
(Intermediate-Poor Prognosis mRCC)





No. at Risk

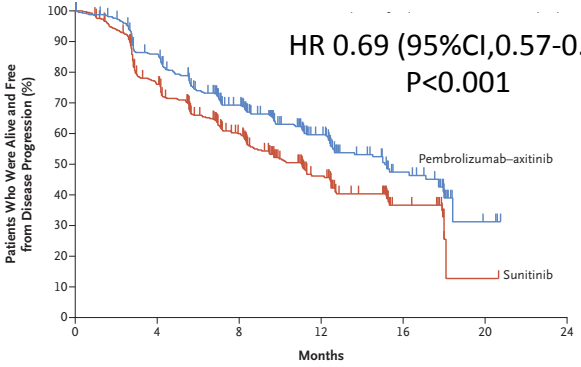
Nivolumab+ipilimumab	425	304	233	187	163	149	118	46	17	3	0
Sunitinib	422	282	191	139	107	86	57	33	11	1	0

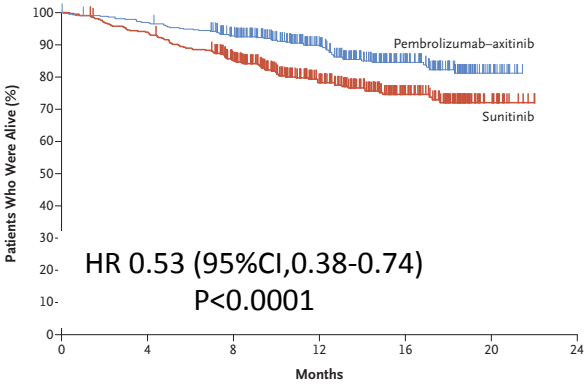


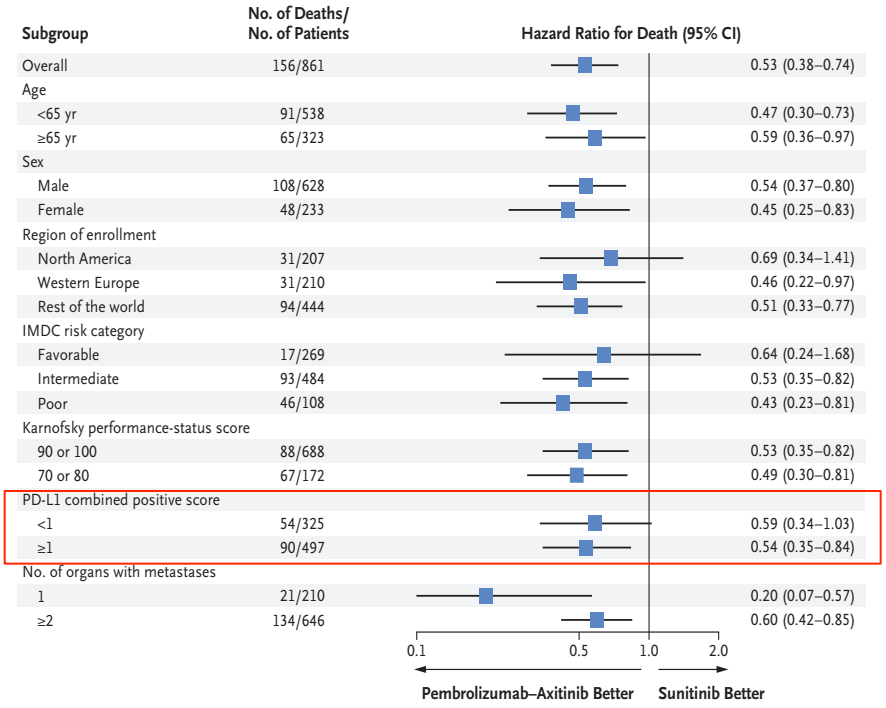
No. at Risk

Nivolumab+ipilimumab	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

KeyNote 426 : Pembrolizumab-Axitinib vs Sunitinib

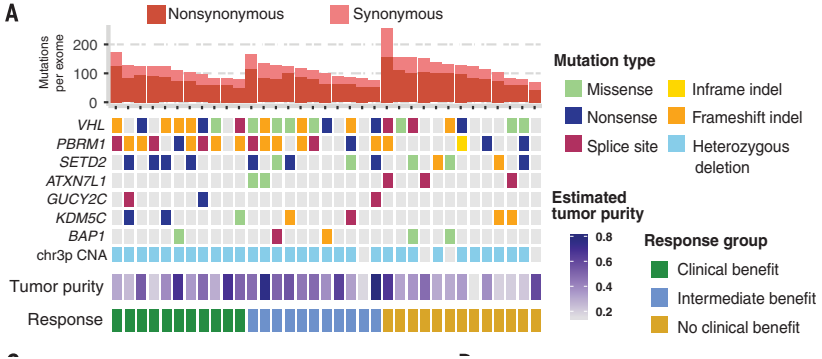


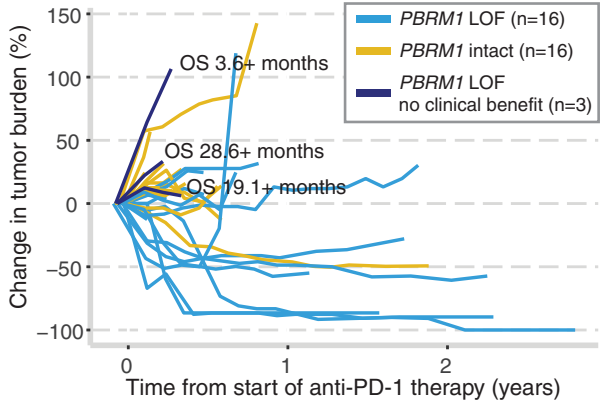


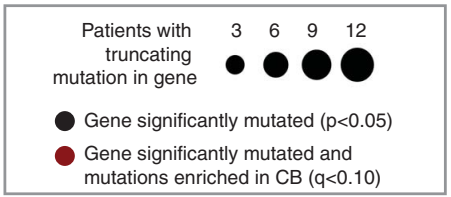


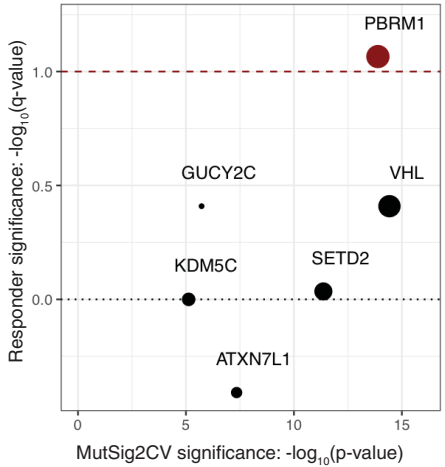
Rini B. N Engl J Med 2019

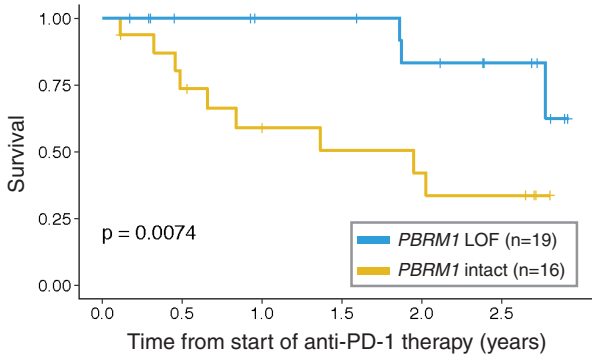
PBMR1 associates with greater benefit from Anti-PD1 therapy





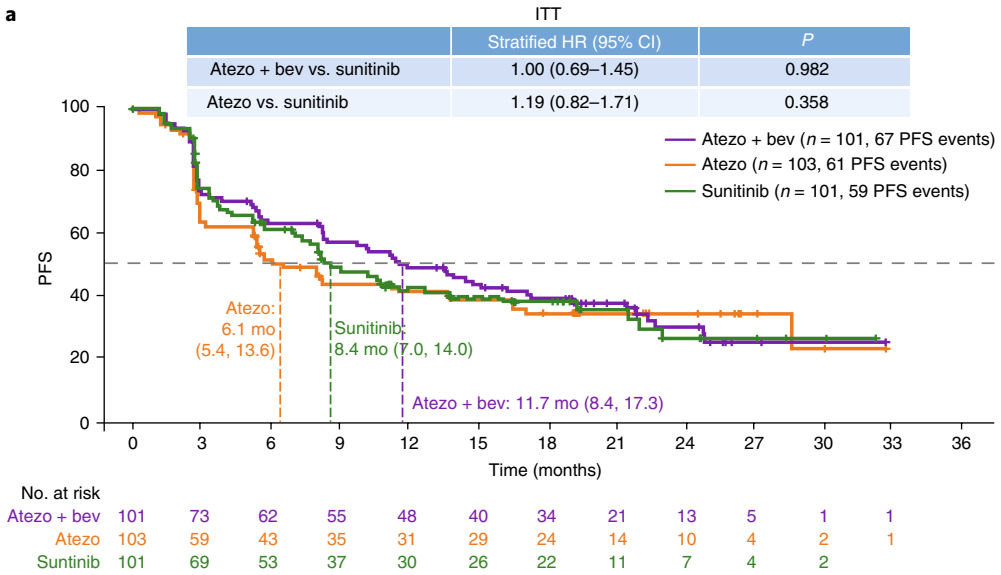




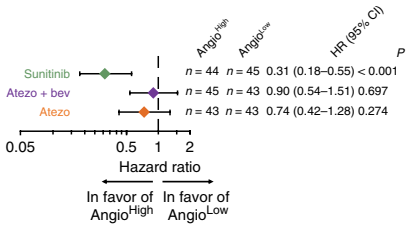


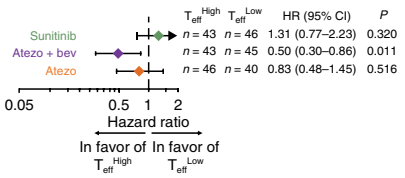
Miao D. Science 2018

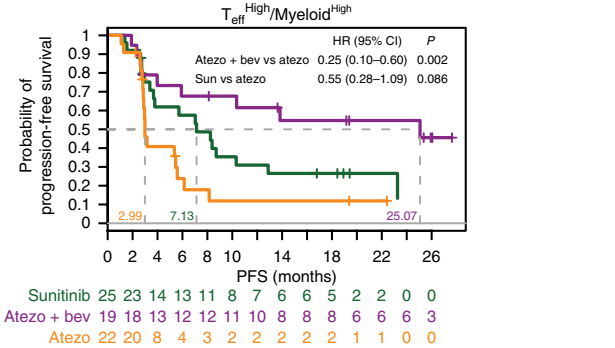
Immotion 150: Randomized Phase 2



Gene Expression Signatures







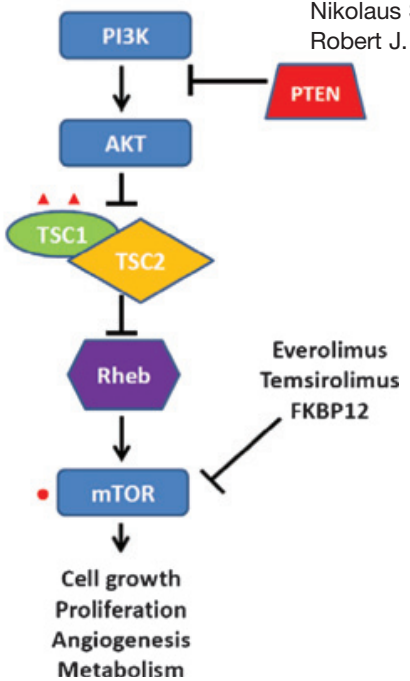
McDermott. Nat Med 2018

Predictive Biomarkers and Personalized Medicine
See related article by Chism and Rathmell, p. 1721

Clinical Cancer Research

Tumor Genetic Analyses of Patients with Metastatic Renal Cell Carcinoma and Extended Benefit from mTOR Inhibitor Therapy

Martin H. Voss[1,8], A. Ari Hakimi[2,6], Can G. Pham[6], A. Rose Brannon[3], Ying-Bei Chen[3], Luis F. Cunha[6], Oguz Akin[4], Han Liu[6], Shugaku Takeda[6], Sasinya N. Scott[3], Nicholas D. Socci[5], Agnes Viale[7], Nikolaus Schultz[5], Chris Sander[5], Victor E. Reuter[3], Paul Russo[2], Emily H. Cheng[3,6], Robert J. Motzer[1,8], Michael F. Berger[3,6], and James J. Hsieh[1,6,8]



2

		R1	R2	R3	M1	
PI3K/Akt/mTOR pathway alterations	**Somatic mutations**					**Complete functional loss of TSC1**
	TSC1 frameshift (c.1738delAT)	X	X	X	X	
	CNA					
	Heterozygous loss of Chr 9	X	X	X	X	
Other pertinent genomic alterations	**Somatic mutations**					
	VHL missense (H115N)	X	X	X	X	
	TP53 missense (R273H)	X	X	X	X	
	CNA					

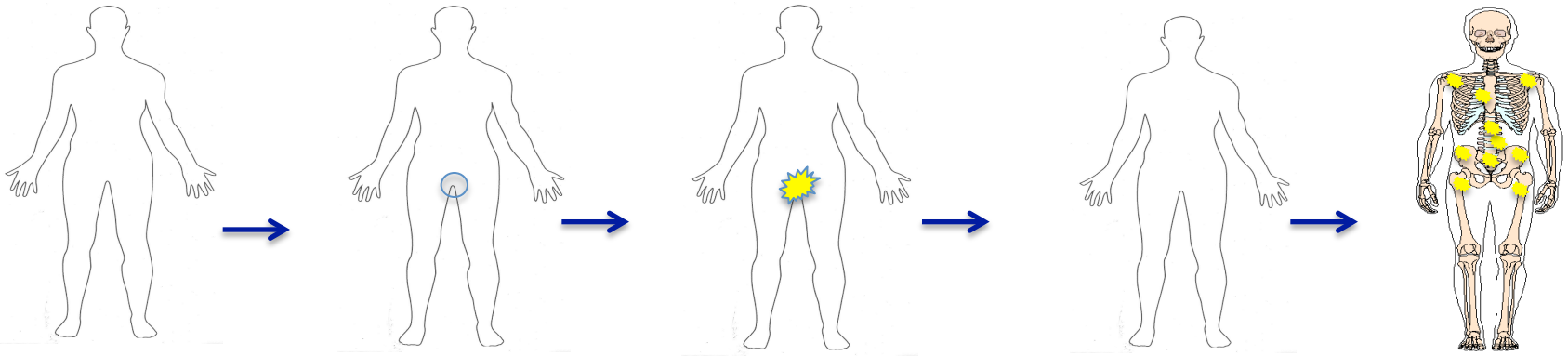
	Sex	Age	Histologic RCC subtype	MSKCC risk score[a,b]	Number of prior regimens	Treatment duration on prior VEGF-targeted agent (months; agent)	Number of metastatic sites	Rapalog	Treatment duration on rapalog (months)
1	F	58	Clear	Int	1	14 (sunitinib)	≥3	Temsirolimus	27
2	F	73	Clear	Int	1	3 (sunitinib)[c]	1	Temsirolimus	34
3	M	66	Clear	Int	2	5 (sunitinib)	≥3	Everolimus	20
4	F	60	Clear	Fav	3	11 (sunitinib)	>3	Temsirolimus	28
5	F	50	Unclassified	Fav	1	2 (sunitinib)	≥3	Temsirolimus	45+

Voss MH. Clin Cancer Res 2014

Clear-Cell Renal Cell Carcinoma: Precision Medicine

- Current treatments are guided by clinical factors and drug coverage by the health systems
- Currently proposed BK need to be prospectively validated in combination treatments

Genetic evolution in Prostate Cancer



Inflammation
Oxidative Stress
Telomere shortening

Senescence

Myc

TMPRSS2-ERG

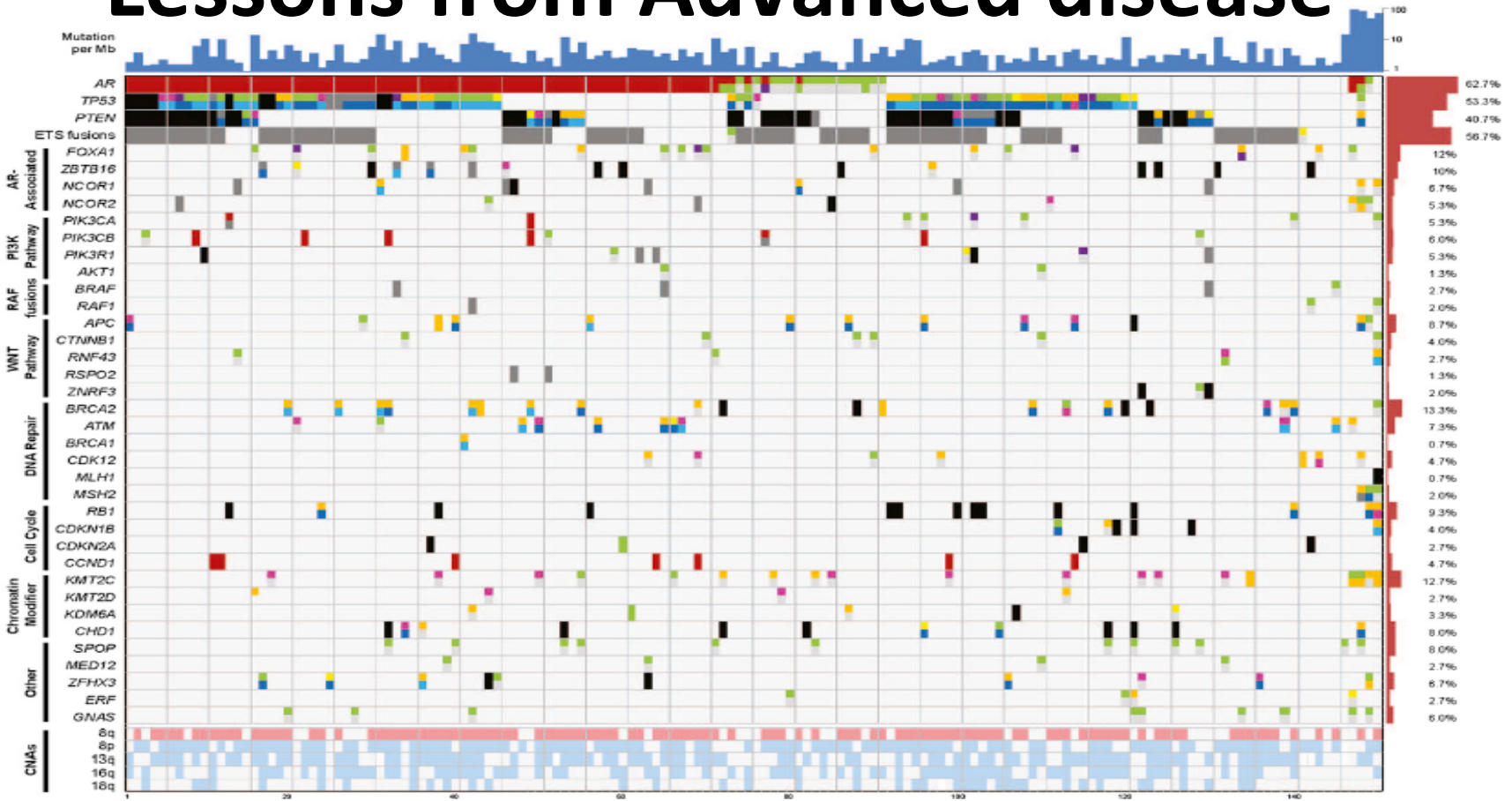
PTEN inactivation

ERK/MAPK activation
P53 inactivation
Rb inactivation

EZH2,
P53, Rb inactivation

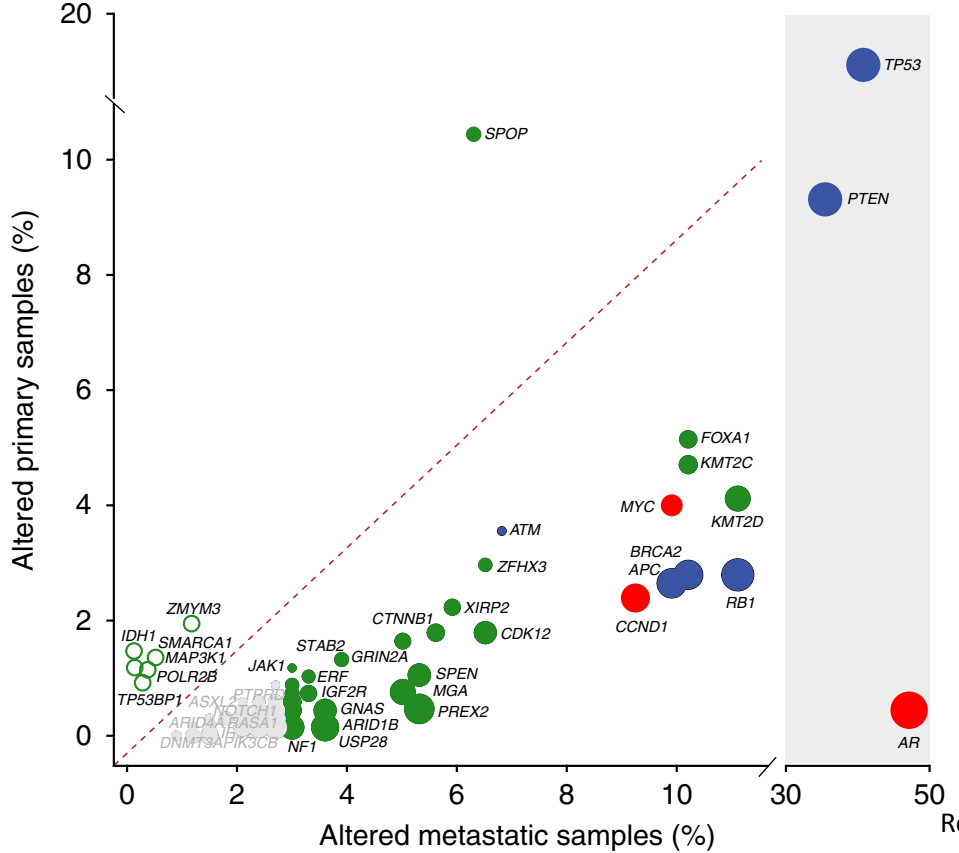
No disease	Pre-invasive disease (PIN)	Invasive disease	Rising PSA No visible metastasis	Metastatic Disease
Prevention of the disease	Prevention of invasion	Local treatment (RP or RT) or observation (only selected pts)	"Prevention" of evident metastatic disease	Systemic treatment (ADT, HT, CT)

Lessons from Advanced disease



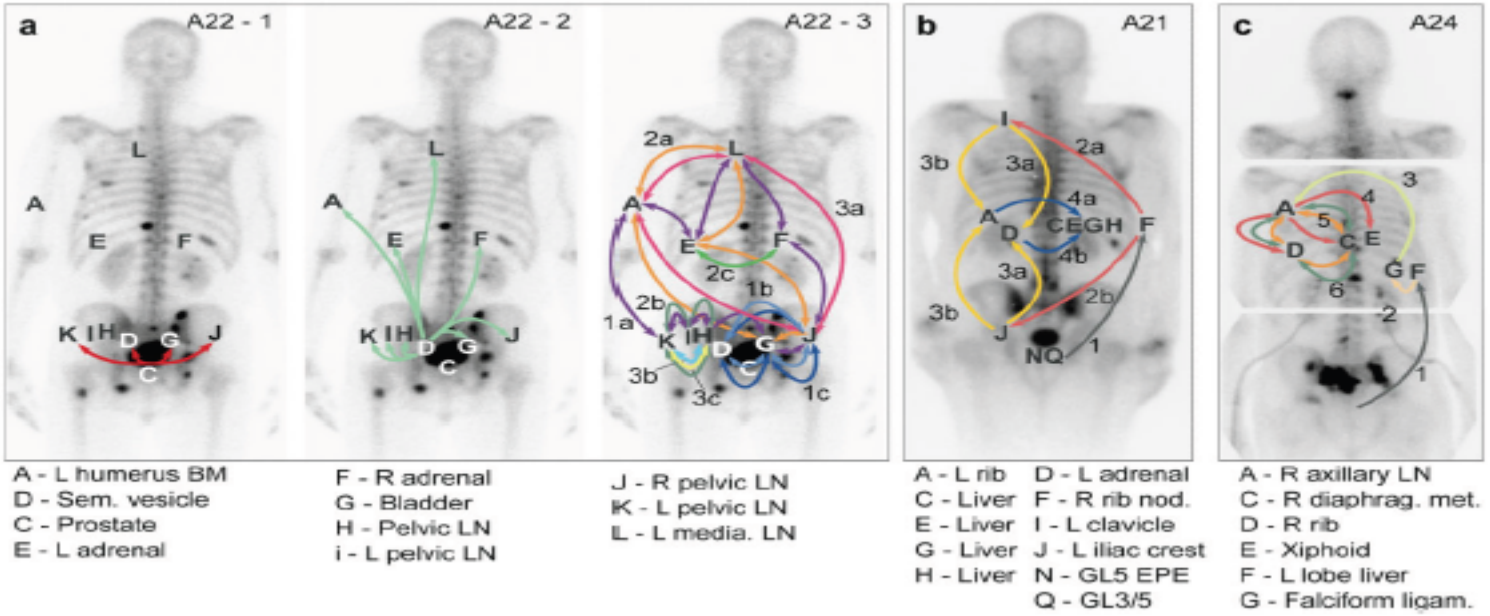
Robinson, D. *et al*. *Cell* **161,** 1215–1228 (2015).

Key molecular events in mCRPC compared to primary PCa



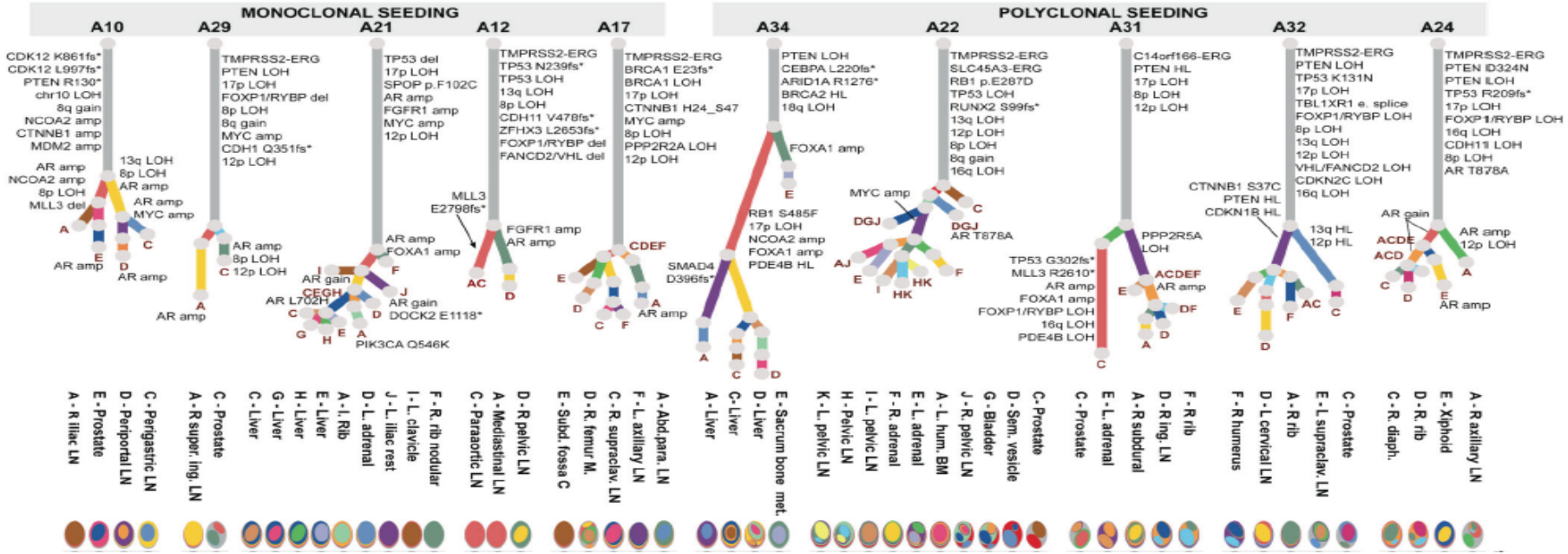
Robinson, D. *et al*. *Cell* **161,** 1215–1228 (2015).

Metastasis pattern of spread

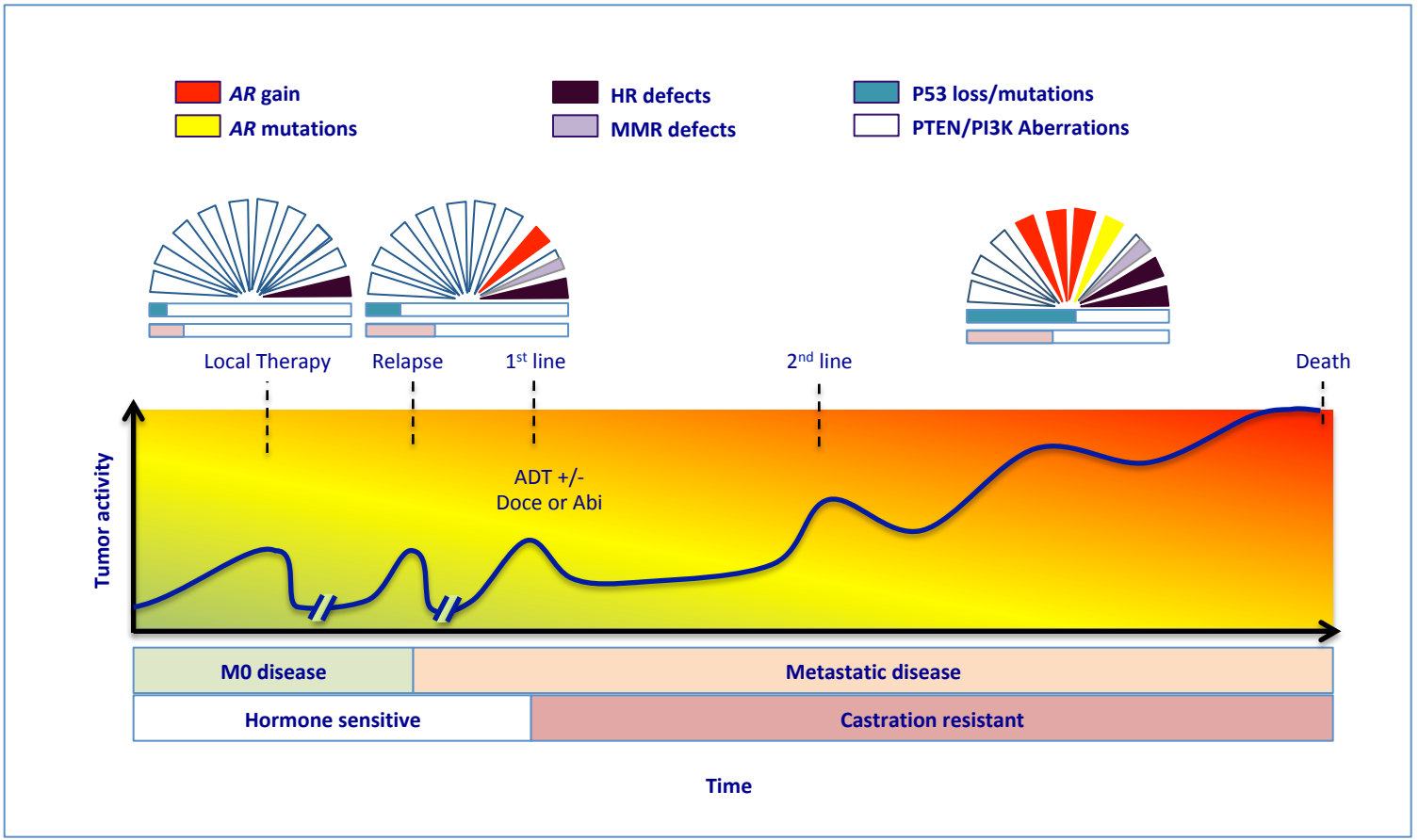


Gundem, G. *et al. Nature* **520,** 353–357 (2015).

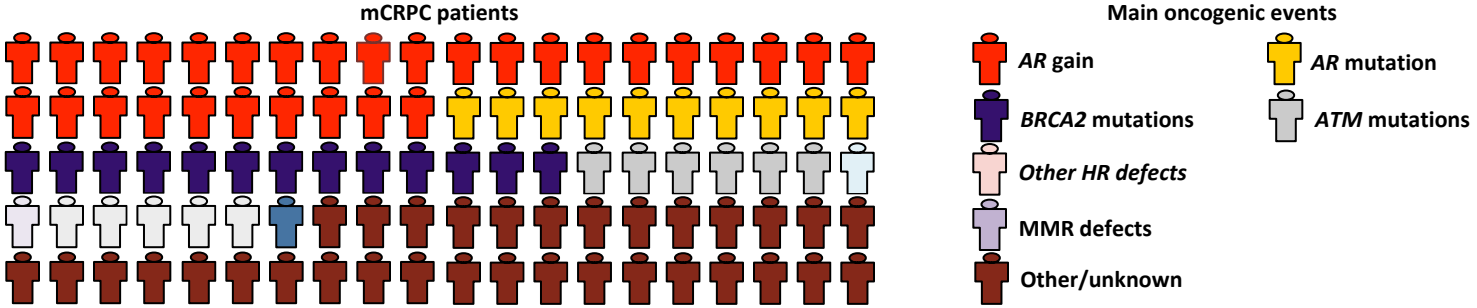
The evolutionary history of lethal metastatic prostate cancer.



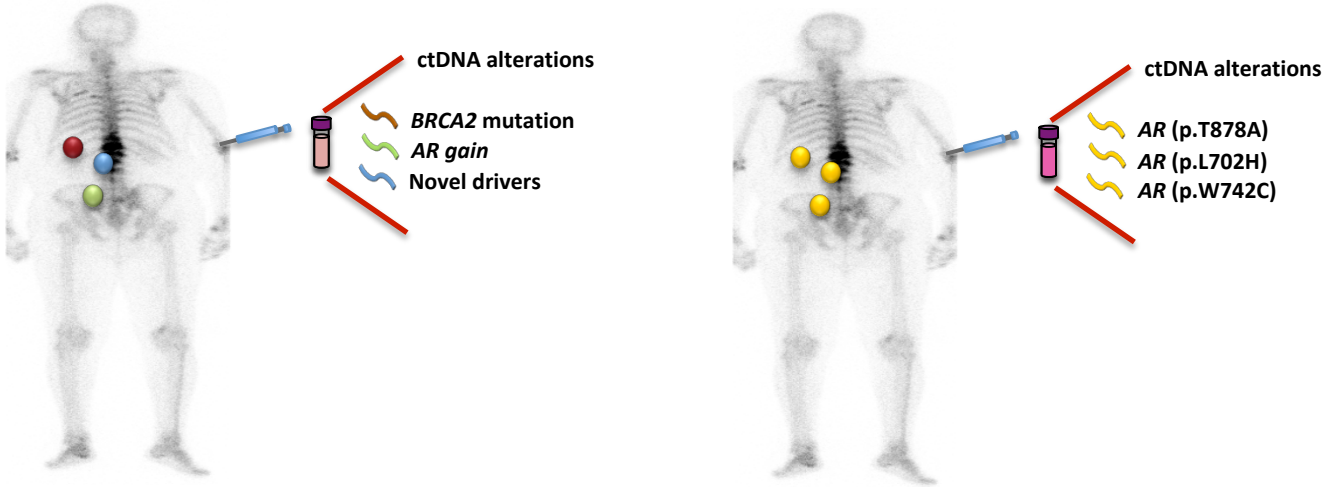
Gundem, G. *et al. Nature* **520,** 353–357 (2015).


AR gain
AR mutations
HR defects
MMR defects
P53 loss/mutations
PTEN/PI3K Aberrations
Local Therapy
Relapse
1st line
2nd line
Death
ADT +/-
Doce or Abi
Tumor activity
M0 disease
Metastatic disease
Hormone sensitive
Castration resistant
Time

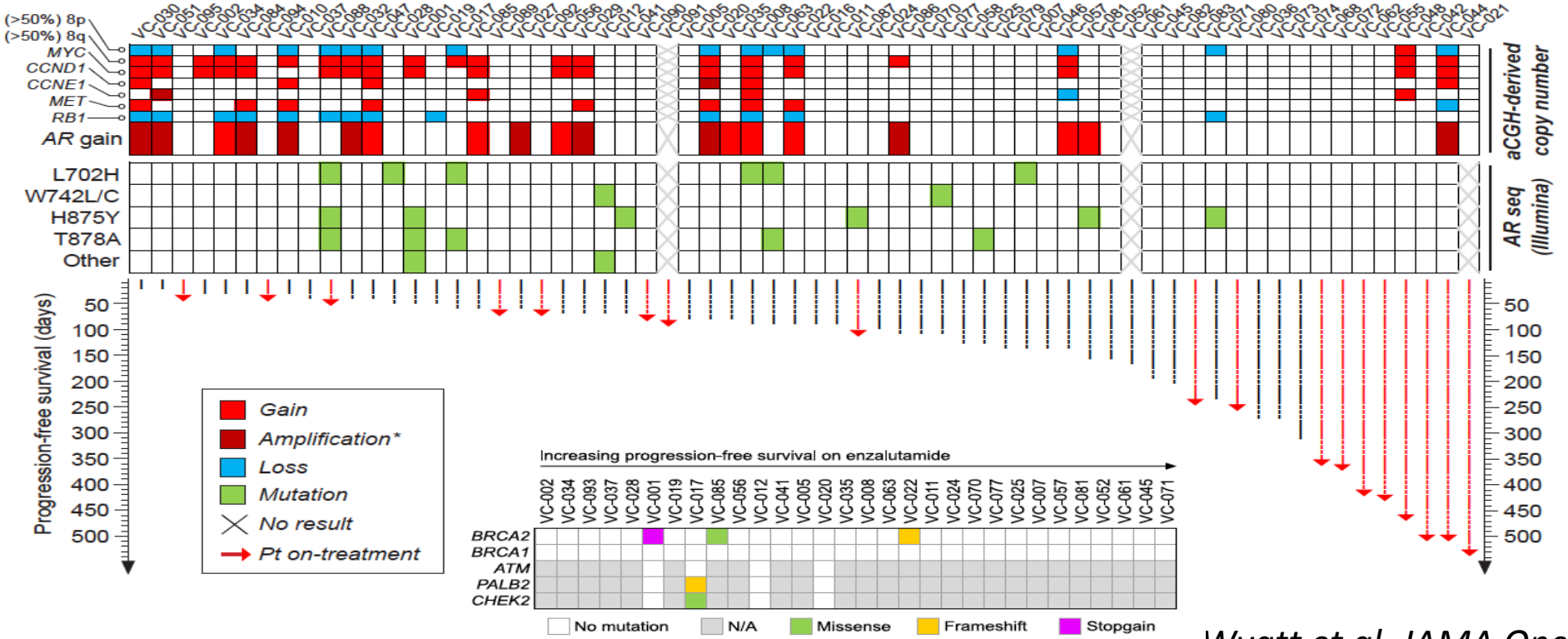
A


mCRPC patients
Main oncogenic events
AR gain
AR mutation
BRCA2 mutations
ATM mutations
Other HR defects
MMR defects
Other/unknown

B

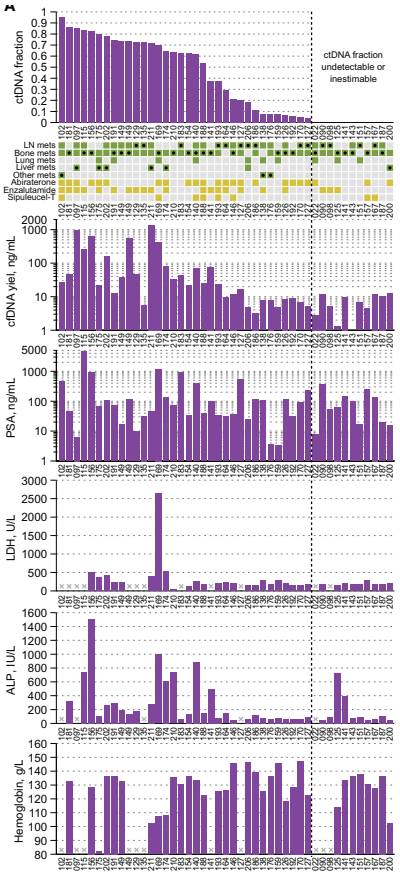

ctDNA alterations
BRCA2 mutation
AR gain
Novel drivers
ctDNA alterations
AR (p.T878A)
AR (p.L702H)
AR (p.W742C)

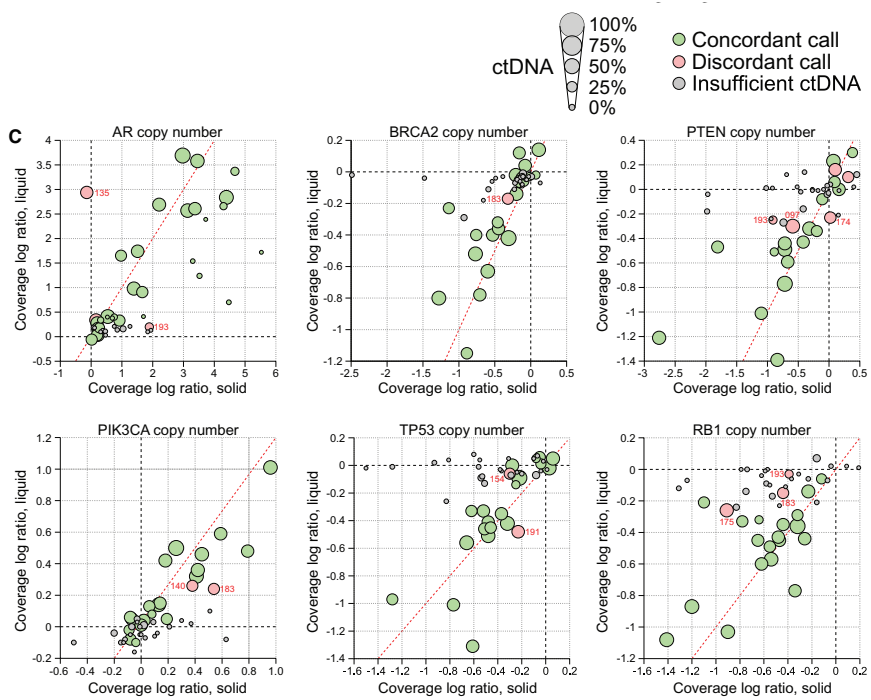
Plasma DNA study is clinically relevant



Wyatt et al, JAMA Onc 2

Concordance of Circulating Tumor DNA and Matched Metastatic Tissue Biopsy in Prostate Cancer





Wyatt, A. W. et al. J Natl Cancer Inst 110, 1–9 (2017)

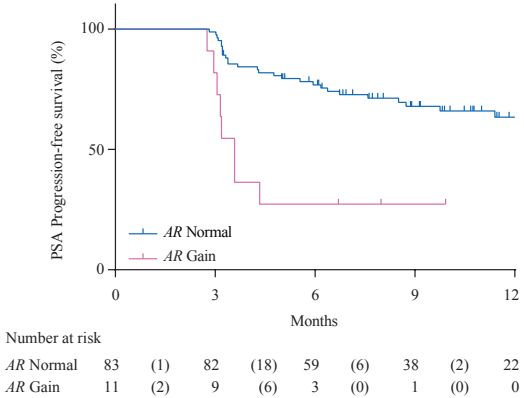
Multiple Genomic markers Correlate with TTP

Genomic Alteration	Median TTP Positive vs Negative* (months)	Univariate		Multivariate***	
		HR	P-value	HR	P-value
BRCA2/ATM truncating mutation	**1.8 vs 8.0**	**6.14 (3.35-11.26)**	**<0.001**	**5.34 (2.84-10.03)**	**<0.001**
TP53 inactivation**	**3.3 vs 10.2**	**2.78 (1.92-4.03)**	**<0.001**	**2.21 (1.38-3.55)**	**0.001**
PI3K pathway	**3.3 vs 10.4**	**2.73 (1.91-3.90)**	**<0.001**	**1.95 (1.31-2.90)**	**<0.001**
AR amplification	**5.0 vs 9.3**	**2.05 (1.43-2.93)**	**<0.001**	1.29 (0.85-2.09)	0.271
RB1 inactivation**	**3.6 vs 8.2**	**2.03 (1.36-3.04)**	**<0.001**	1.45 (0.95-2.21)	0.08
SPOP mutation	7.3 vs 7.4	1.00 (0.51-1.97)	1.00		
AR mutation	6.2 vs 7.4	1.02 (0.53-1.95)	0.95		

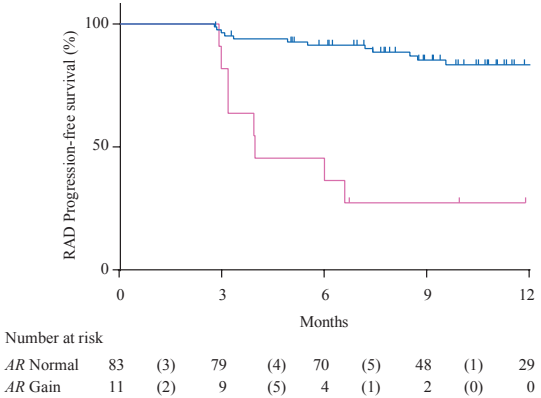
Includes patients without ctDNA. ** Mutation, deletion or rearrangement. *** includes trial arm, presence of quantifable ctDNA and clinical prognostic factors (LDH, ALP, Visceral Mets, ECOG PS).

Adapted from Kim Chi at 2017 ASCO Annual Meeting

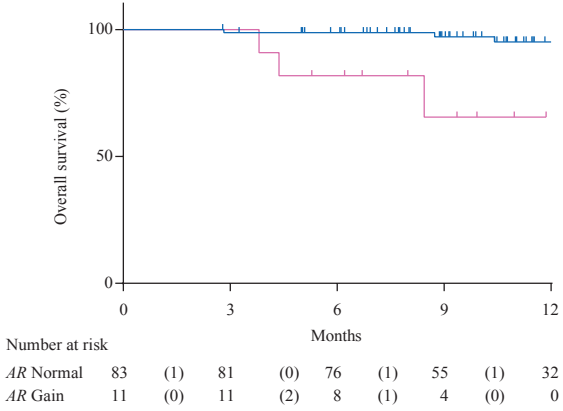
Plasma AR status is associated with worse outcome



Median sPFS: 3.60 versus 15.5 months
HR, 4.33; 95% CI 1.94-9.68; P < 0.001



Median rPFS: 3.90 months versus not reached
HR, 8.06; 95% CI, 3.26-19.93; P < 0.001

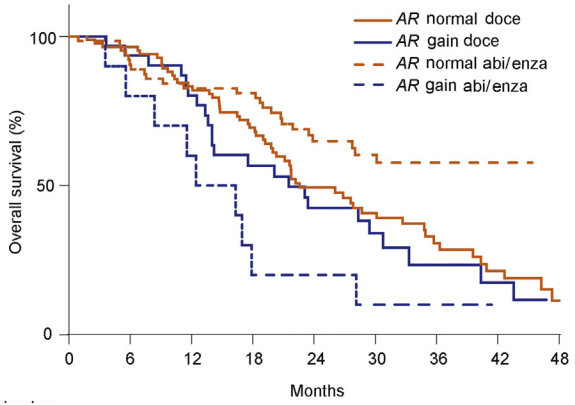


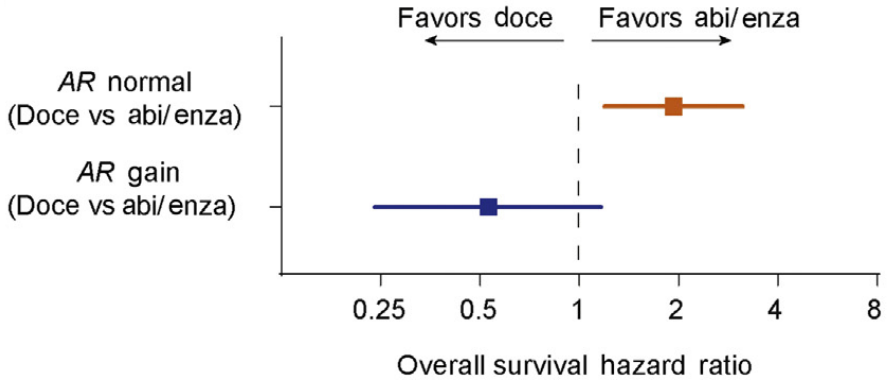
Median OS: medians not reached
HR, 11.08; 95% CI, 2.16-56.95; P = 0.004

Conteduca V & Grande E. Annals of Oncology 2017

Plasma Androgen Receptor and Docetaxel for Metastatic Castration-resistant Prostate Cancer

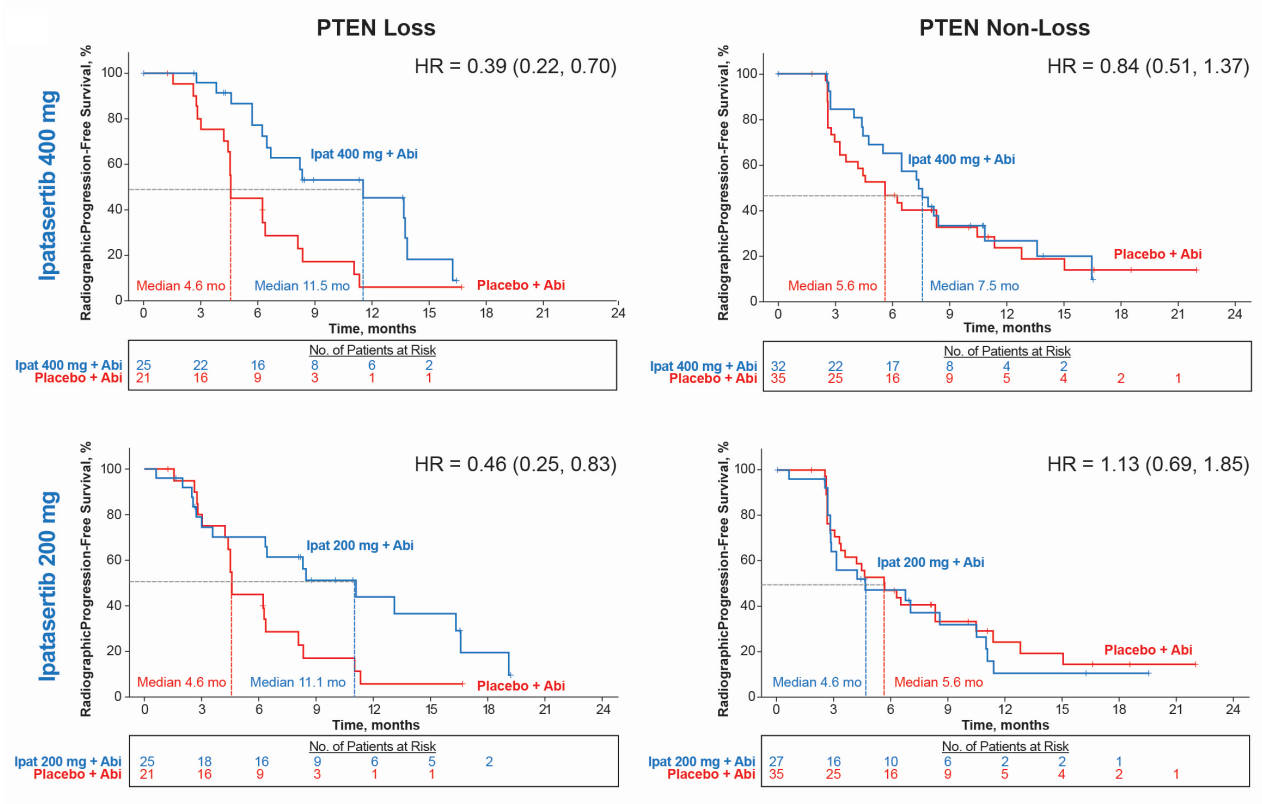
Vincenza Conteduca [a,b,†,], Anuradha Jayaram [b,c,d,†], Nuria Romero-Laorden [e,f,†], Daniel Wetterskog [b,d], Samanta Salvi [a], Giorgia Gurioli [a], Emanuela Scarpi [a], Elena Castro [e,g], Mercedes Marin-Aguilera [h], Cristian Lolli [a], Giuseppe Schepisi [a], Antonio Maugeri [a], Anna Wingate [b,d], Alberto Farolfi [a], Valentina Casadio [a], Ana Medina [i], Javier Puente [j], Mª José Méndez Vidal [k], Rafael Morales-Barrera [l], Jose C. Villa-Guzmán [m], Susana Hernando [n], Alejo Rodriguez-Vida [o], Aránzazu González-del-Alba [p], Begoña Mellado [h], Enrique Gonzalez-Billalabeitia [q,r], David Olmos [e,s,‡], Gerhardt Attard [b,c,d,‡,*], Ugo De Giorgi [a,‡]*





Conteduca V. Eur Urol 2019

PTEN-loss tumors might benefit from the addition of AKT inhibitors to Abiraterone in mCRCP

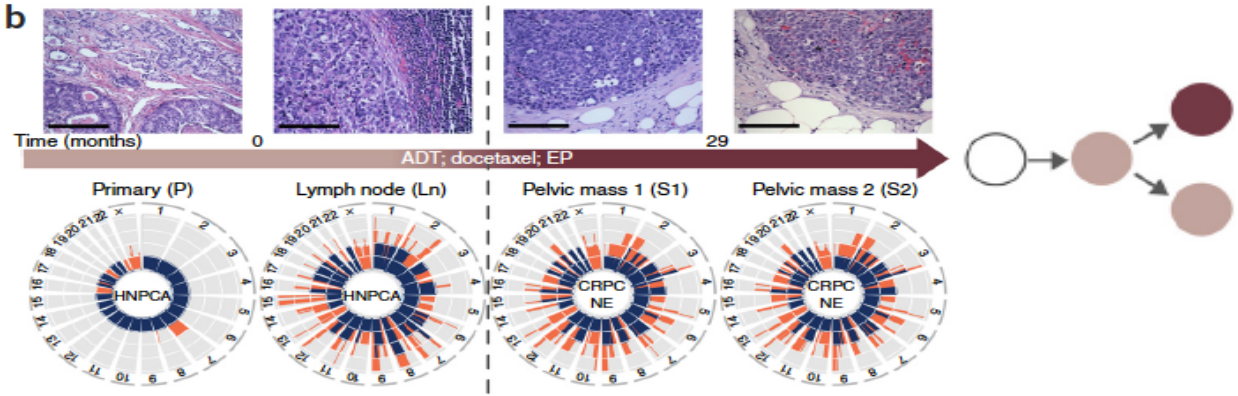


De Bono J. Clin Cancer Res 2018

Neuroendocrine PCa is derived from divergent differentiation

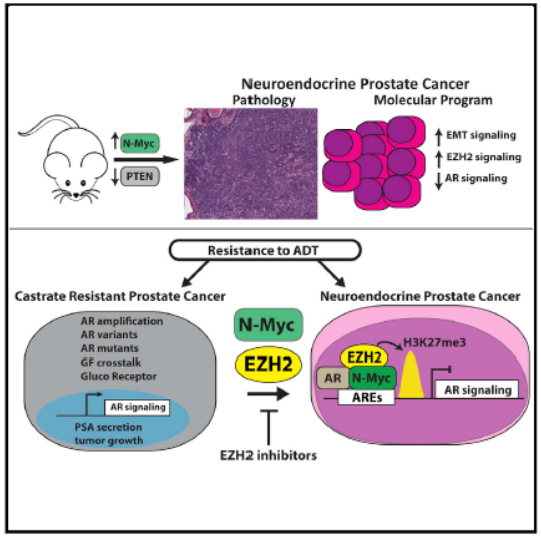
Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer

Himisha Beltran[1–3,13], Davide Prandi[4,13], Juan Miguel Mosquera[1,5], Matteo Benelli[4], Loredana Puca[1], Joanna Cyrta[1], Clarisse Marotz[1], Eugenia Giannopoulou[6], Balabhadrapatruni V S K Chakravarthi[7], Sooryanarayana Varambally[7], Scott A Tomlins[8], David M Nanus[2,3], Scott T Tagawa[2,3], Eliezer M Van Allen[9,10], Olivier Elemento[1,6], Andrea Sboner[1,5,11], Levi A Garraway[9,10,12,14], Mark A Rubin[1,3,5,14] & Francesca Demichelis[1,4,11,14]



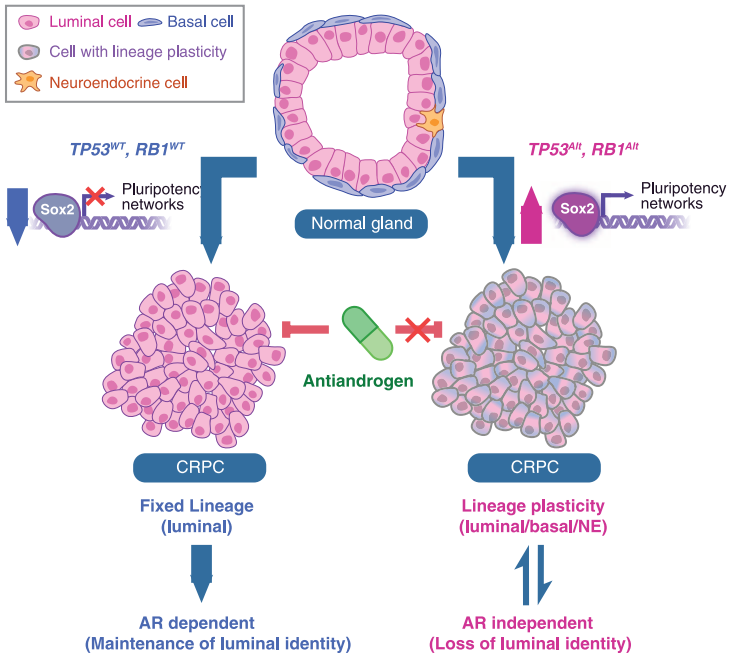
N-Myc Induces an EZH2-Mediated Transcriptional Program Driving Neuroendocrine Prostate Cancer

Etienne Dardenne,[1,11] Himisha Beltran,[2,3,4,11] Matteo Benelli,[5] Kaitlyn Gayvert,[6,7] Adeline Berger,[1] Loredana Puca,[4] Joanna Cyrta,[1,4] Andrea Sboner,[1,4,6,7] Zohal Noorzad,[1] Theresa MacDonald,[1] Cynthia Cheung,[1] Ka Shing Yuen,[1] Dong Gao,[8] Yu Chen,[3,8,9] Martin Eilers,[10] Juan-Miguel Mosquera,[1,4] Brian D. Robinson,[1,4] Olivier Elemento,[2,4,6] Mark A. Rubin,[1,2,4,6] Francesca Demichelis,[4,5] and David S. Rickman[1,2,4,12,*]
[1]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY 10065, USA

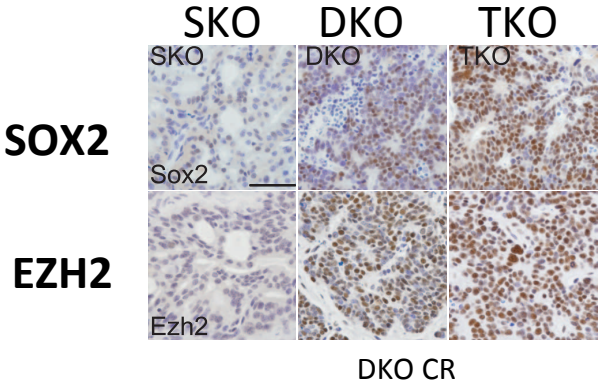


Beltran H. Nat Med 2016
Dardene E & Beltran H. Cancer Cell 2016

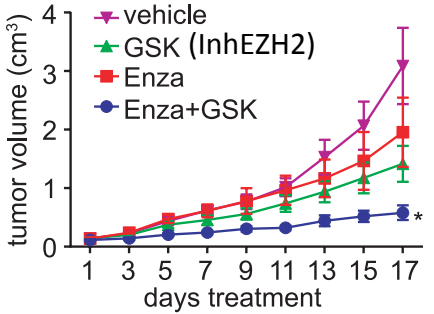
Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance



Mu, P. et al. Science 355, 84–88 (2017)

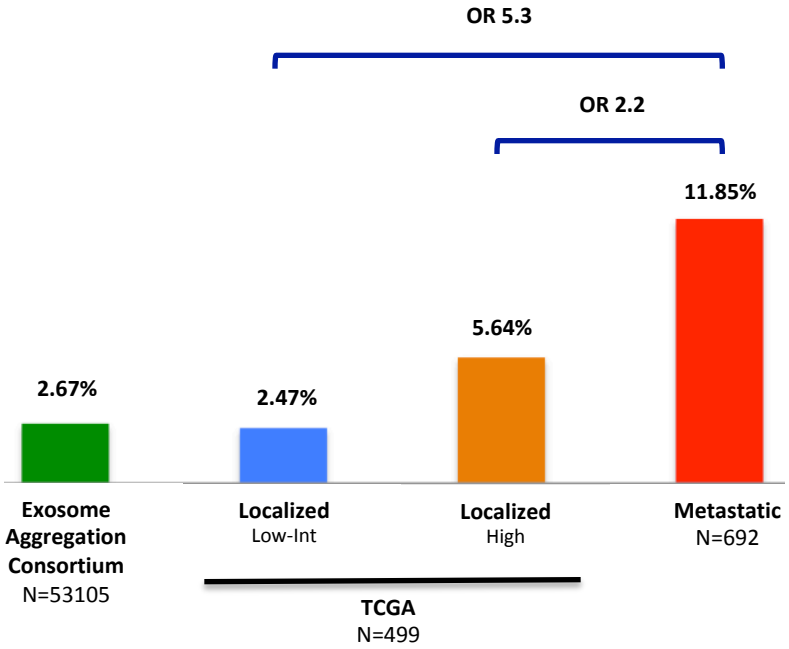


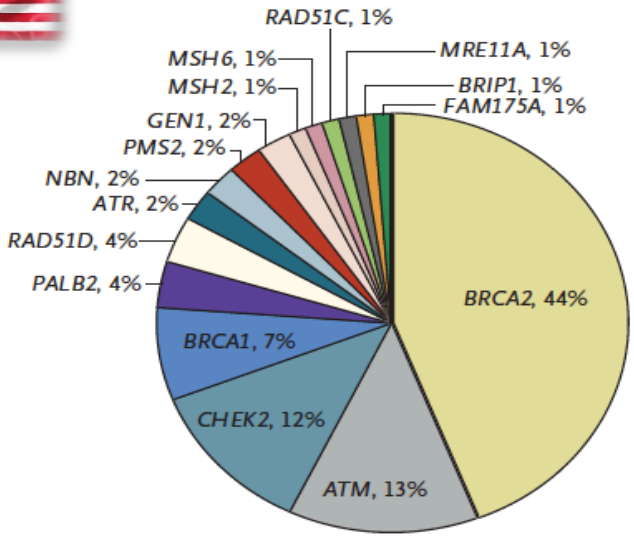
DKO CR



Ku, S.-Y. et al. Science 355, 78–83 (2017)

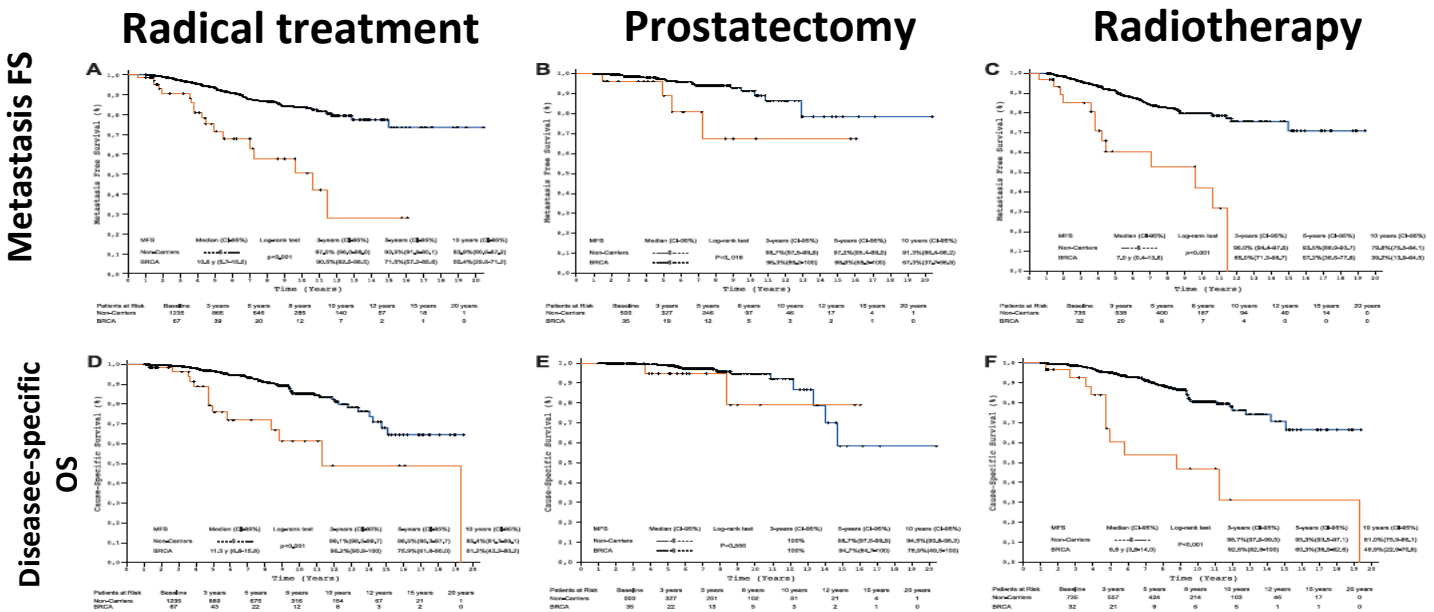
mPCa is associated with increased presence of germ-line mutations





Pritchard CC and Mateo J. N Engl J Med 2016

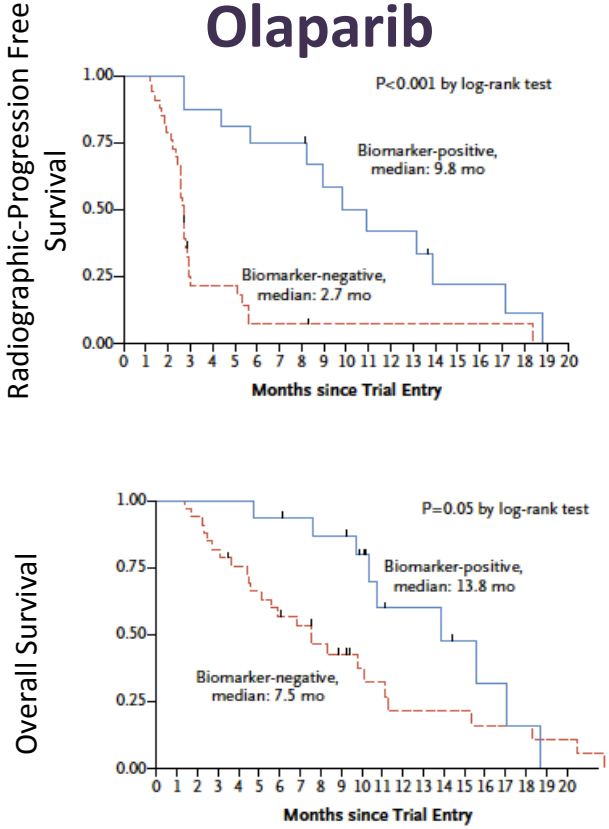
Effect of BRCA Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localised Prostate Cancer.



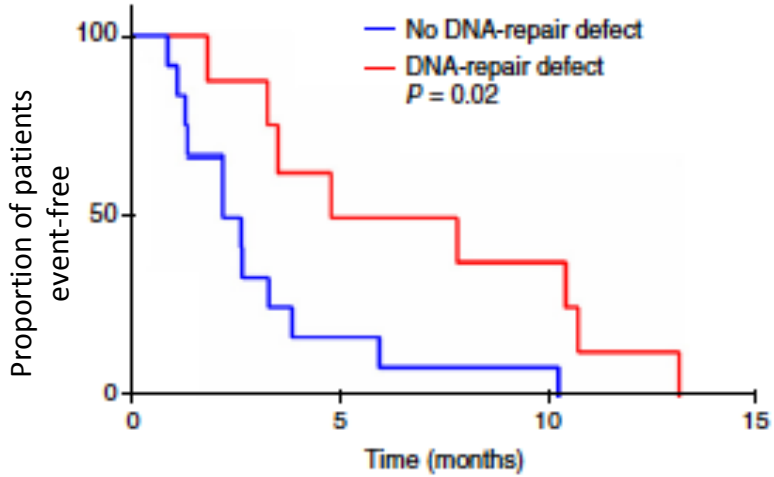
Castro, E. *et al.* David Olmos & Rosalind Eeles. *Eur Urol* **68,** 186–193 (2015)

HR-defects predict response to PARP inhibitors and platinum therapy

Olaparib

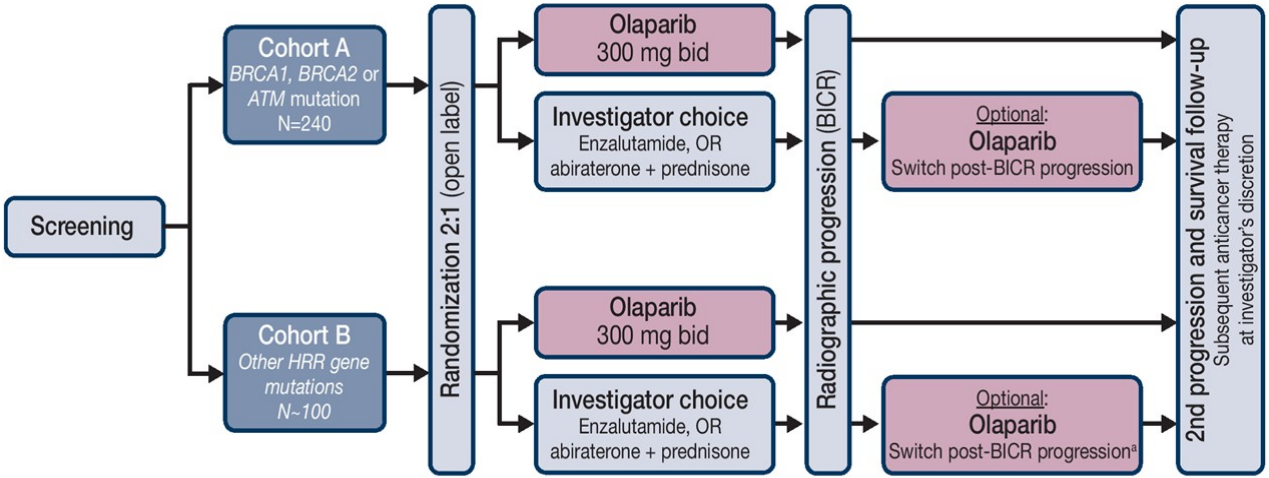


Platinum



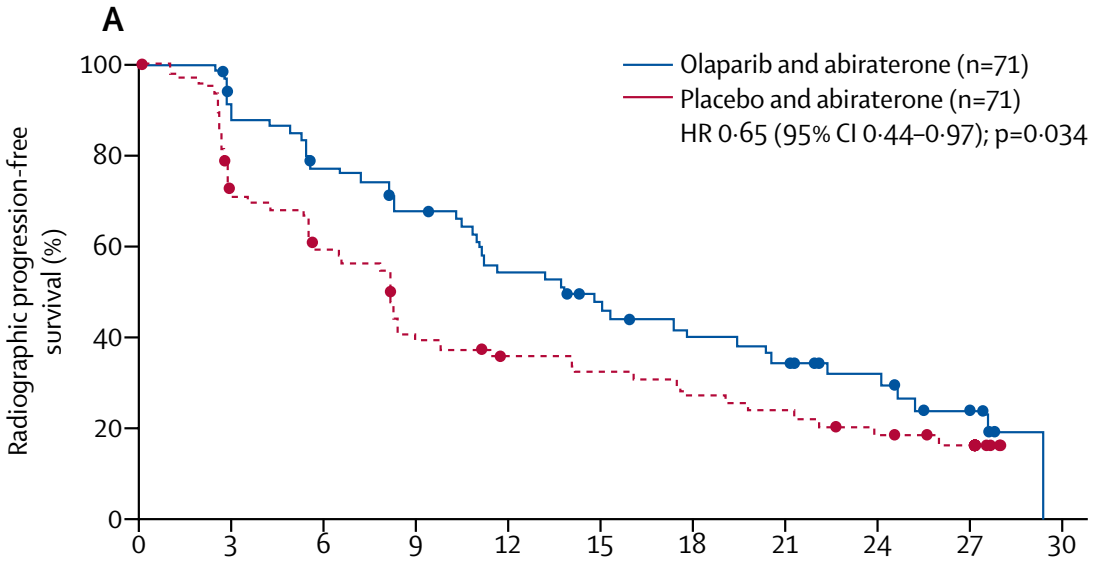
Mateo J. N Engl J Med 2015
Kumar A. Nat Med 2016
Cheng HH. Eur Urol 2016

Estudio Fase 3 de Olaparib en CaPRCm en progresión a Abi/Enza Estudio PROFOUND



NCT02987543

PARP inhibition increases activity of antiandrogen therapy in unselected patients

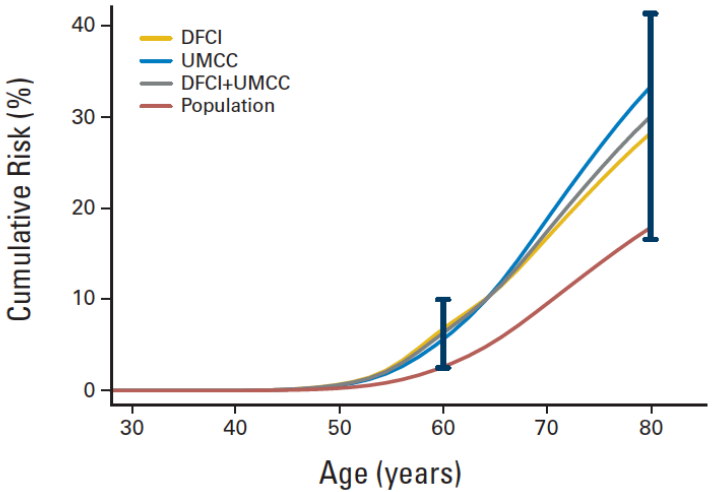


Number at risk (number censored)											
Olaparib and abiraterone	71 (0)	58 (5)	50 (6)	42 (8)	33 (9)	26 (12)	21 (13)	18 (13)	13 (17)	8 (19)	0 (25)
Placebo and abiraterone	71 (0)	48 (3)	39 (4)	25 (5)	21 (7)	19 (7)	16 (7)	14 (7)	10 (8)	7 (10)	0 (17)

Clarke. Lancet Oncol 2018

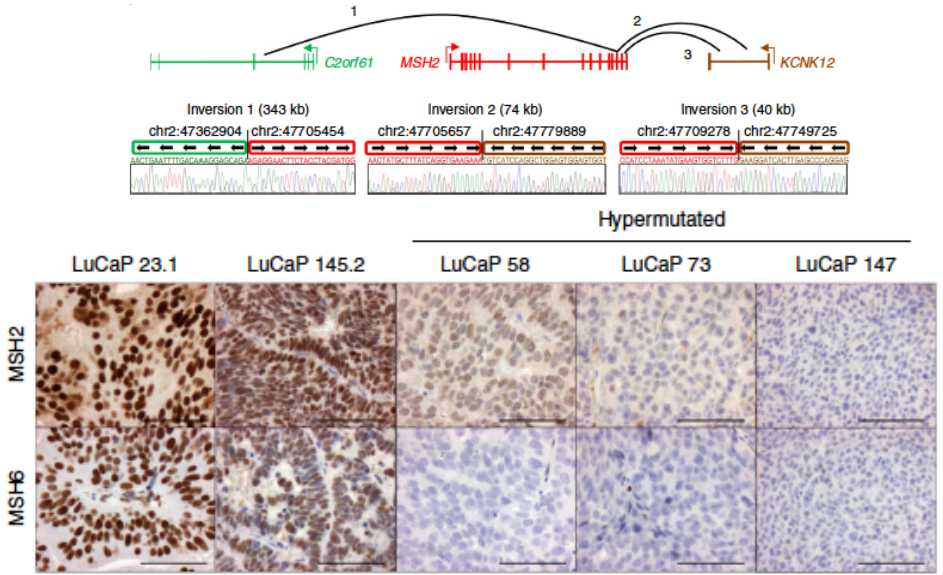
PCa can be hypermutated and associated with MSI-high

Lynch syndrome increases the risk of prostate cancer



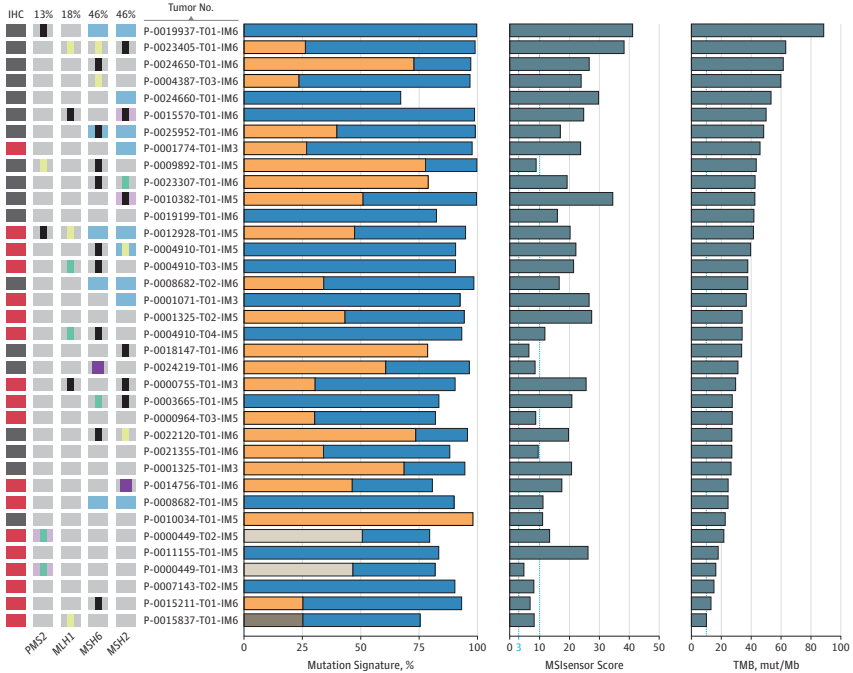
Raymond VM. J Clin Oncol 2013

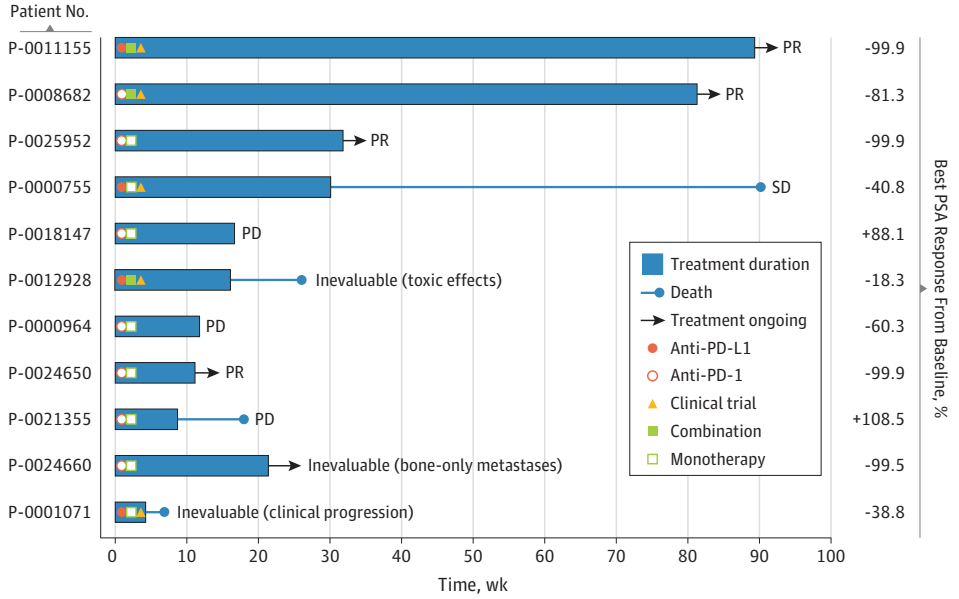
Advanced PCa can be associated with complex MSH2 and MSH6 mutations



Pritchard CC. Nat Comm 2014

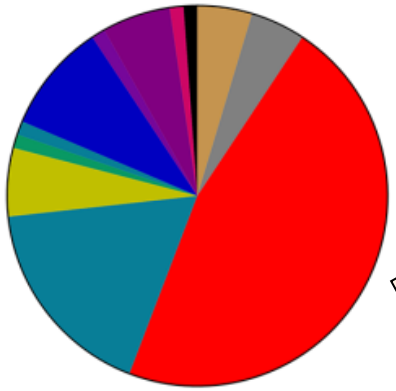
MSI is observed in 3% of Prostate Cancers in large cohorts





Abida. JAMA Oncol 2018

Agnostic treatment in MSI-High tumors: Anti-PD1 treatment- Prembolizumab



FDA APPROVED

Ampulla of
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C
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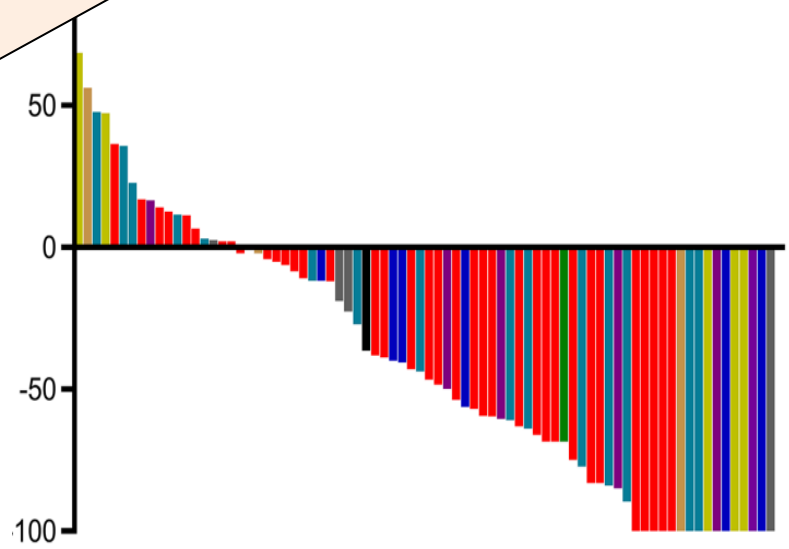
troesophageal
Neuroendocrine
Osteosarcoma
Pancreas
Prostate
Small Intestine
Thyroid
Unknown Primary



Le DT. Science 2017

Prostate Cancer: Precision Medicine

- Current treatments in mCRPC are guided by clinical factors, toxicity profile and drug coverage by the health systems
- Molecularly guided clinical trials are needed
- Currently proposed BK need to be prospectively validated in clinical trials

Acknowledgments

PREMIERE team:

Enrique Grande
María Piedad Fernández Pérez
Albert Font
Sergio Vázquez Estévez
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María José Méndez-Vidal
Miguel Angel Climent
Ignacio Duran
Enrique Gallardo
Angel Rodríguez
Carmen Santander
M Isabel Sáez
Javier Puente
Teresa Alonso
Julián Tudela
Alberto Martínez
Daniel Castellano
Enrique González Billalabeitia

Morales Meseseguer Lab:

Francisco Ayala de la Peña
Helena García Martínez
María Piedad Fernández Pérez
Julián Tudela
Alberto Martínez
Enrique González Billalabeitia

Attard`s Lab:

Gerhardt Attard
Daniel Wetterskog
Anuradha Jayaram
Anna Wingate
Paolo Cremaschi
Anjui
Karolina Nowakoska
Anjui Wu

IRST team (Meldola)

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Jun Luo