Advanced Prostate Cancer 2023: New Concepts

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Disclosure of Conflicts of Interest

Oliver Sartor, MD, has the following financial relationships to disclose:

Grant/Research Support - Advanced Accelerator Applications, Amgen, AstraZeneca, Bayer, Constellation, Endocyte, Invitae, Janssen, Lantheus, Merck, Progenics,Tenebio

Consultant: Advanced Accelerator Applications (AAA), Amgen, ArtBio, Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Inc., Clarity Pharmaceuticals, Clovi s, Constellation, Convergent, Dendreon, EMD Serono, Foundation Medicine, Fusion, Genzyme, Hengrui, Isotopen TechnologienMeunchen, Merck, Janssen, Morphimmune, Myovant, Myriad, Noria Therapeutics, Inc., NorthStar, Novartis, Noxopharm, Progenics, POINT Biopharma, Pfizer, Sanofi, Tenebio, Telix,Tessa, Theragnostics

Multi-modality skills to optimally manage prostate cancer

- Surgery
- Radiation Oncology
- Hormonal Therapy
- Chemotherapy

{ Old School }

- Genetics (Germline and Somatic)
- Molecular Imaging
- Artificial Intelligence
- Targeted Therapy
- Immunotherapy
- Molecularly Targeted Radiation

Genetics

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. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, R. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. [redacted] N. Schultz, P.W. Kantoff, D. Solit, M. Robson[redacted] Bono, and P.S. Nelson

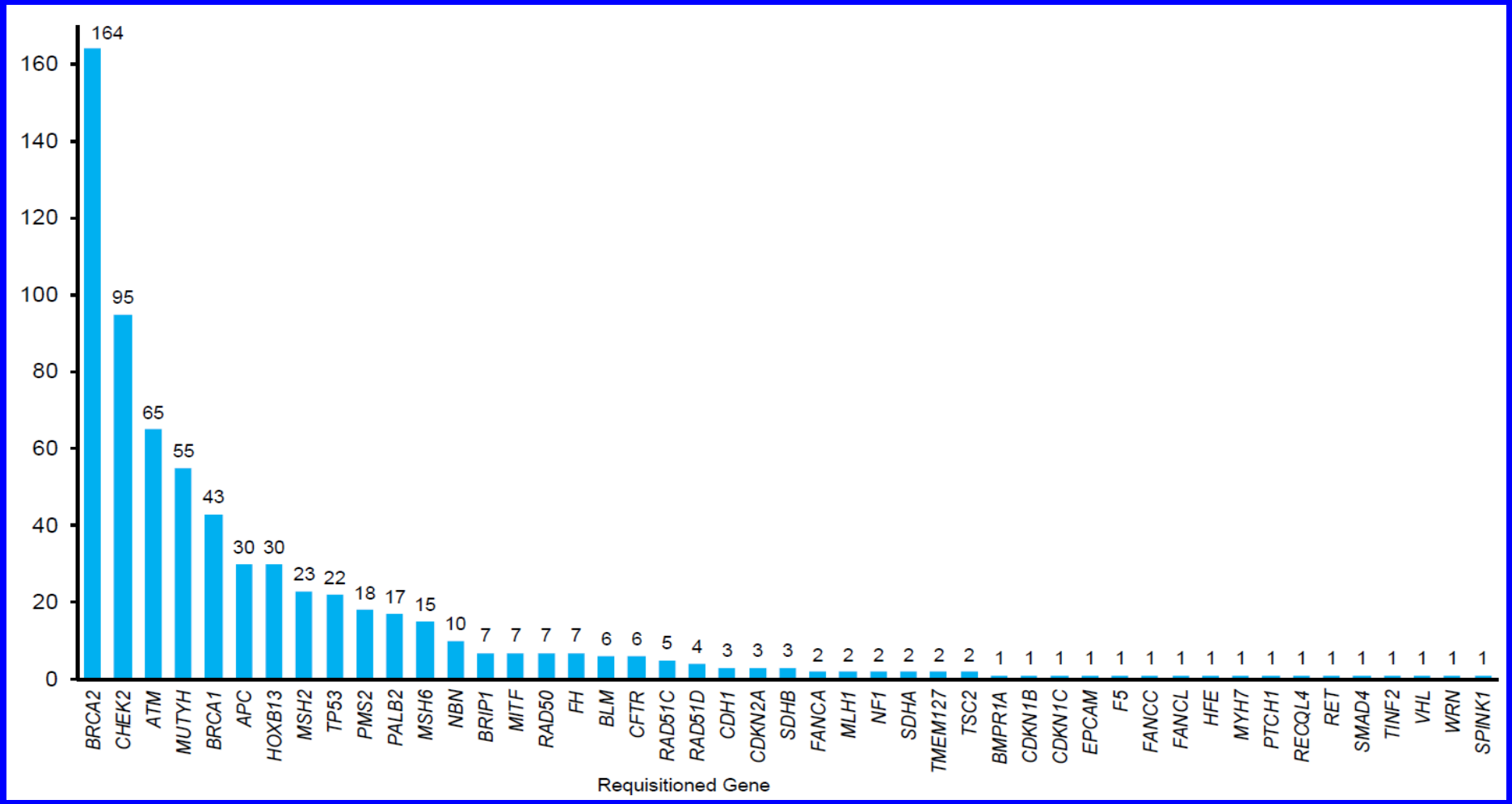
The Germline Proof

NEJM .ORG July 6, 2016

- 11.8% of men with metastatic prostate cancer
  - BRCA2 5.8%
  - CHEK2 1.9%
  - ATM 1.6%
  - BRCA1 0.9%
  - RAD51D and PALB2 0.4% each

Though BRCA2, CHEK2, ATM are common, note the number of rare pathogenic genetic alterations

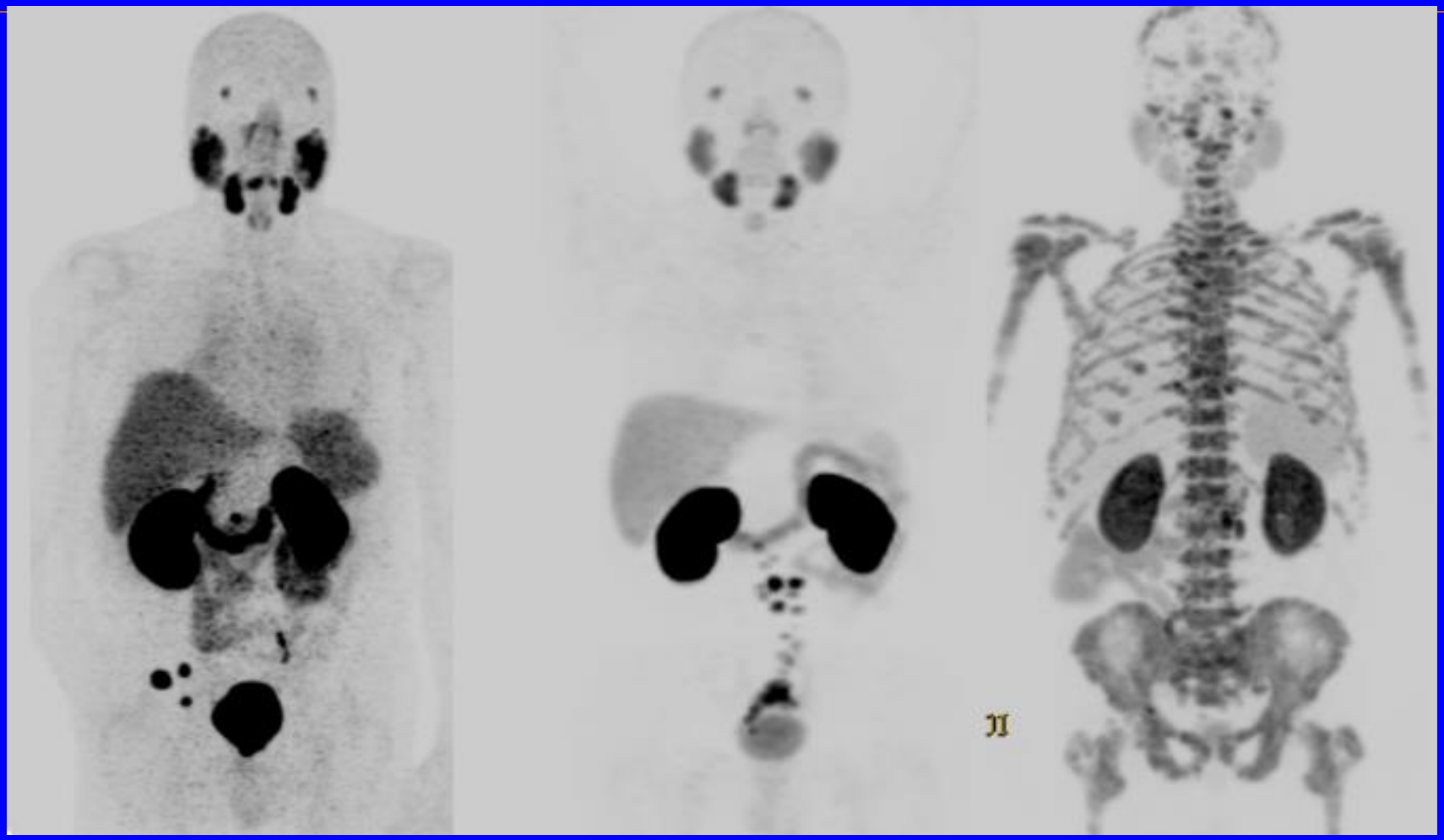
Nicolosi et al. JAMA Onc Feb 19, 2019



Molecular Imaging

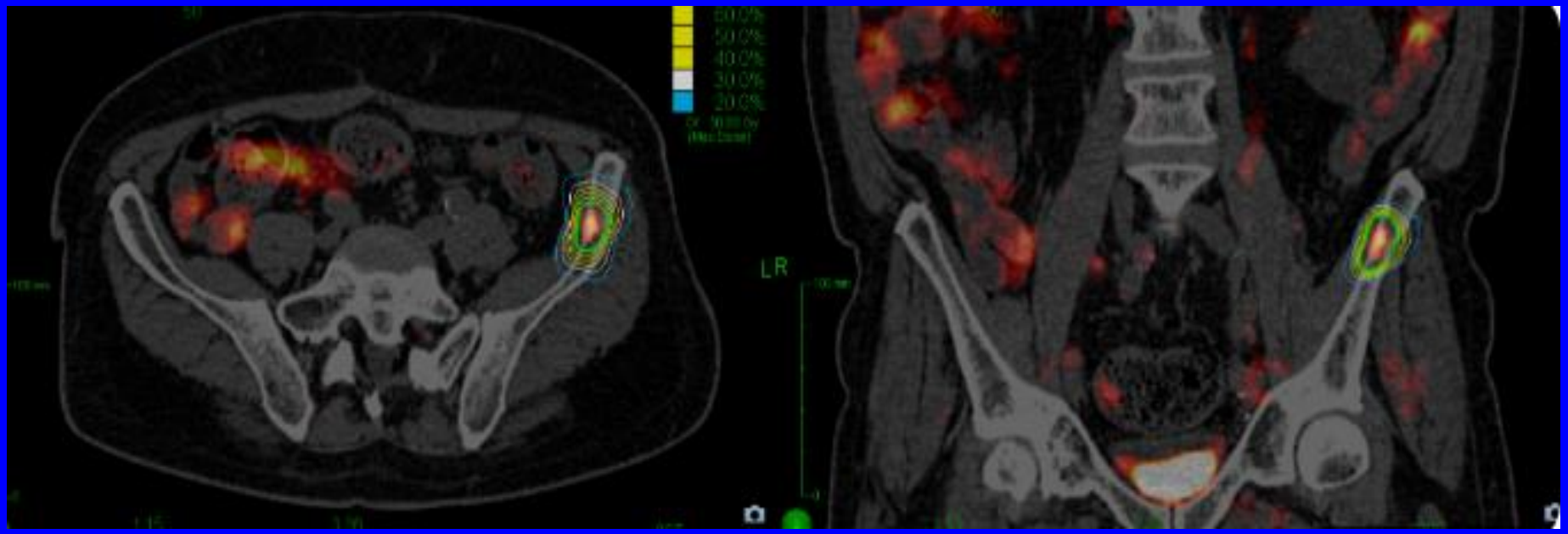
PSMA PET Imaging (^{18}F-DCFPyL)

Improved Sensitivity of Metastases



At least 10X better than CT

“Oligometastatic Disease”

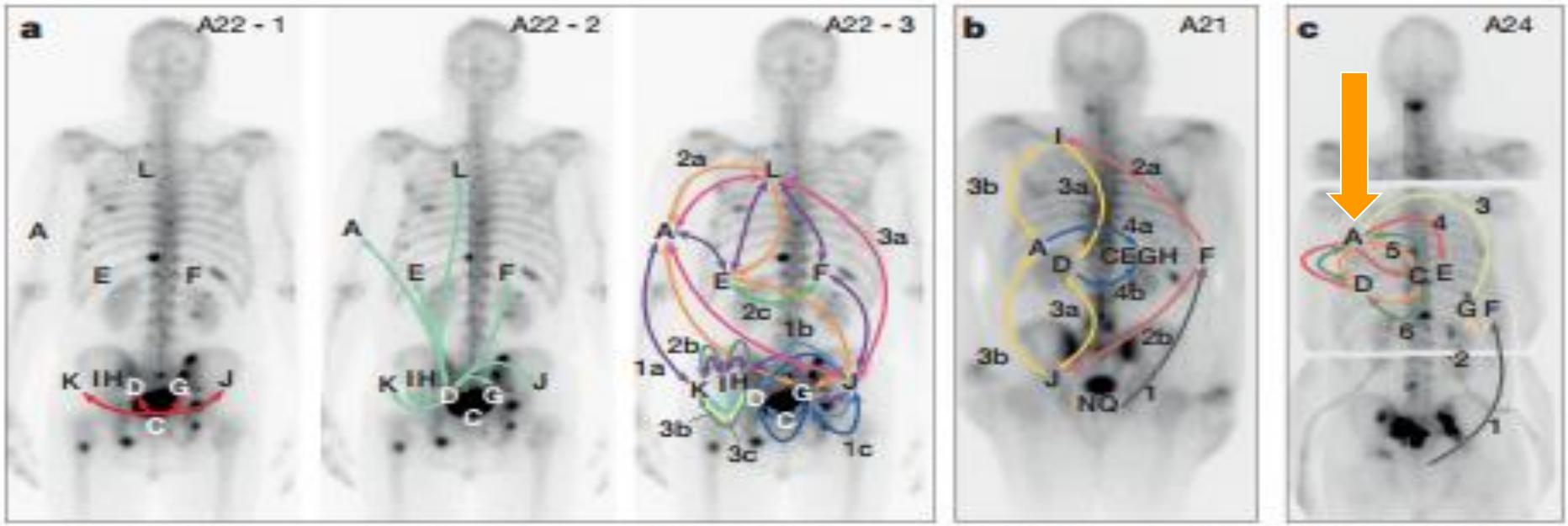


LETTER

doi:10.1038/nature14347

The evolutionary history of lethal metastatic prostate cancer

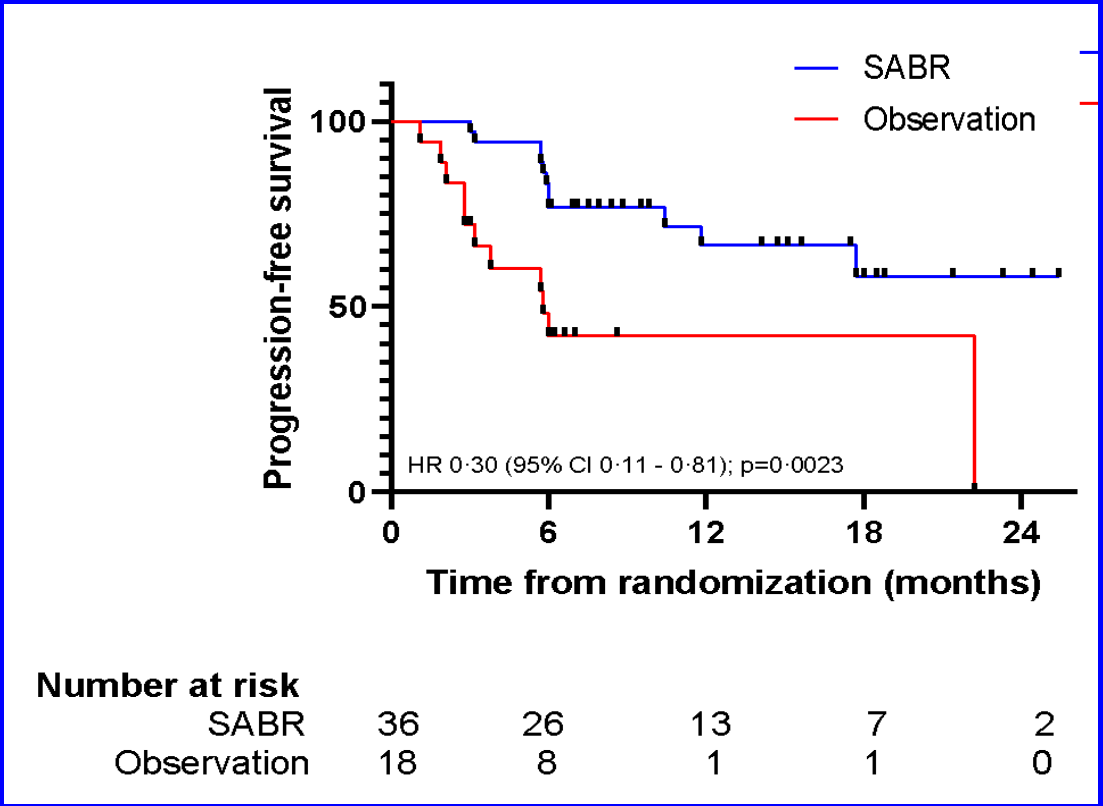
Gunes Gundem[1], Peter Van Loo[1,2,3], Barbara Kremeyer[1], Ludmil B. Alexandrov[1], Jose M. C. Tubio[1], Elli Papaemmanuil[1], Daniel S. Brewer[4,5], Heini M. L. Kallio[6], Gunilla Högnäs[6], Matti Annala[6], Kati Kivinummi[6], Victoria Goody[1], Calli Latimer[1], Sarah O'Meara[1], Kevin J. Dawson[1], William Isaacs[7], Michael R. Emmert-Buck[8]†, Matti Nykter[6], Christopher Foster[9], Zsofia Kote-Jarai[10], Douglas Easton[11], Hayley C. Whitaker[12], ICGC Prostate UK Group‡, David E. Neal[12,13]§, Colin S. Cooper[4,10]§, Rosalind A. Eeles[10,14]§, Tapio Visakorpi[6], Peter J. Campbell[1], Ultan McDermott[1]§*, David C. Wedge[1]* & G. Steven Bova[6]§*



If metastases begat metastases then eradication of early metastatic disease makes conceptual sense

Stereotactic body radiotherapy to oligo-metastatic disease a new standard of care

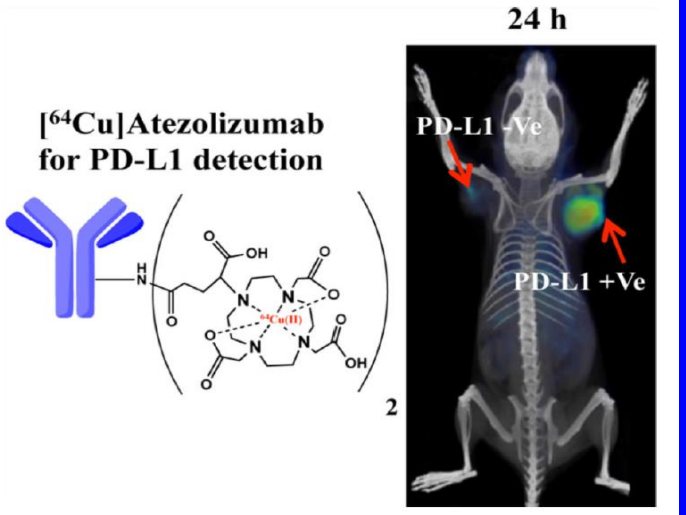
Targeted radiation significantly improved progression-free survival (PFS)



Hazard Ratio: 0.30
95% CI: 0.11 - 0.81
p-value: 0.0023

Phillips et al. JAMA Oncol 2020

Location of disease:
The beginning not the end of imaging



An effective immuno-PET imaging method to monitor CD8-dependent responses to immunotherapy

Richard Tavaré[a,b,1], Helena Escuin-Ordinas[c], Stephen Mok[b], Melissa N. McCracken[b], Kirstin A. Zettlitz[a,b], Felix B. Salazar[a,b], Owen N. Witte[b,d,e,f], Antoni Ribas[b,c,g,h,i], and Anna M. Wu[a,b,g,1]

Internalization of secreted antigen–targeted antibodies by the neonatal Fc receptor for precision imaging of the androgen receptor axis

Daniel L. J. Thorek,[1,2] Philip A. Watson,[3]* Sang-Gyu Lee,[2]* Anson T. Ku,[2] Stylianos Bournazos,[4] Katharina Braun,[5] Kwanghee Kim,[6] Kjell Sjöström,[7] Michael G. Doran,[2] Urpo Lamminmäki,[8] Elmer Santos,[2] Darren Veach,[2,9] Mesruh Turkekul,[10] Emily Casey,[11] Jason S. Lewis,[11,12] Diane S. Abou,[1] Marise R. H. van Voss,[1,13] Peter T. Scardino,[6,14] Sven-Erik Strand,[15] Mary L. Alpaugh,[16] Howard I. Scher,[17,18] Hans Lilja,[6,17,19,20,21†] Steven M. Larson,[2,9†] David Ulmert[6,11,22†]

Imaging of Prostate Cancer Using Gallium-68–Labeled Bombesin

Ida Sonni, MD*, Lucia Baratto, MD, Andrei Iagaru, MD

Molecular Imaging in Neuroendocrine Differentiation of Prostate Cancer

^{68}Ga-PSMA Versus ^{68}Ga-DOTA NOC PET-CT

Sharjeel Usmani, MBBS, MS, FEBNM, CBNC, Najeeb Ahmed, MRCP, FRCR,† Fahad Marafi, KBNM,* Rashid Rasheed, MBBS, MS,* Henney G. Amanguno, MD,* and Fareeda al kandari, KBNM**

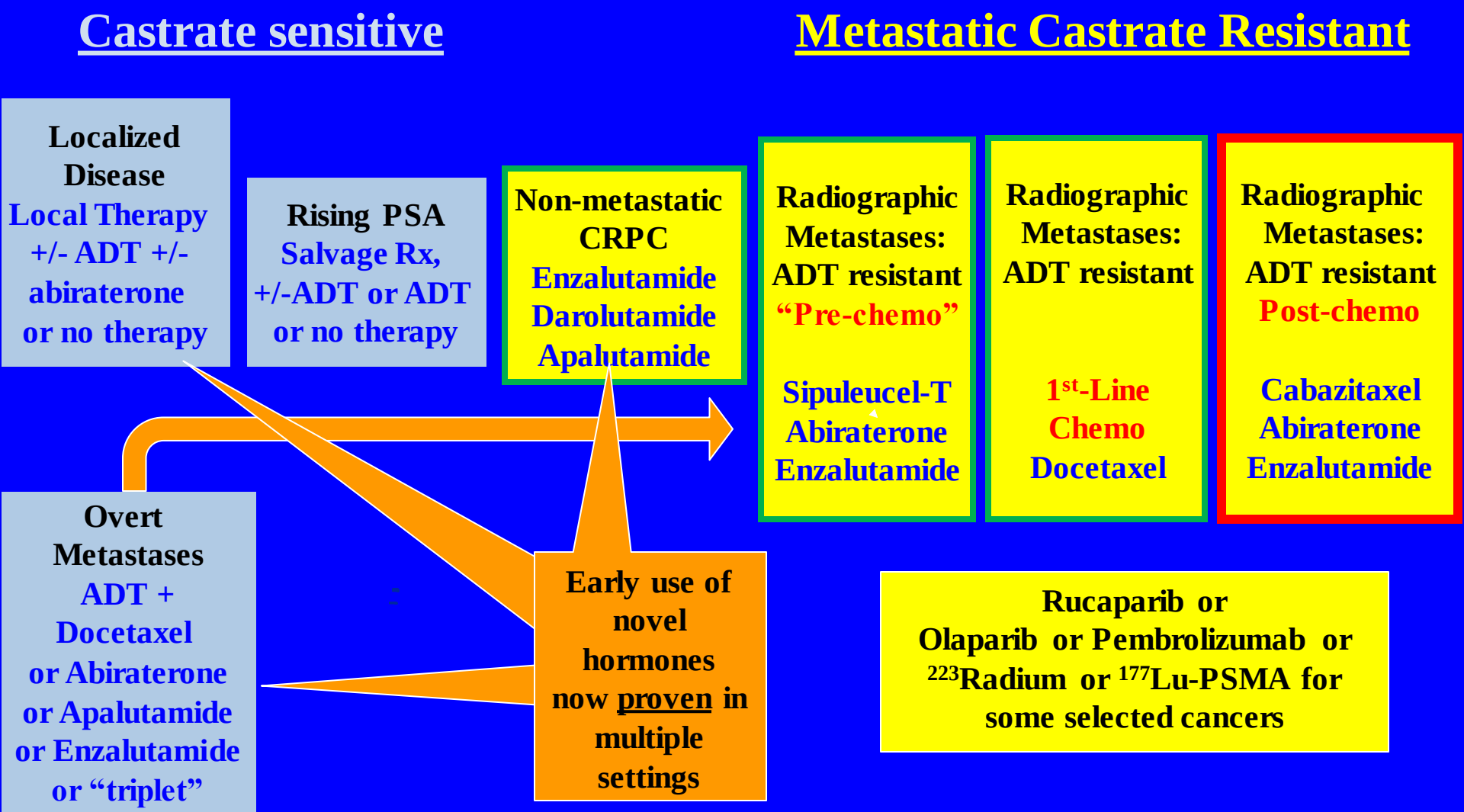
Pharmacokinetic Assessment of the Uptake of 16β-^{18}F-Fluoro-5α-Dihydrotestosterone (FDHT) in Prostate Tumors as Measured by PET

Bradley J. Beattie*[1], Peter M. Smith-Jones*[2], Yuliya S. Jhanwar[3], Heiko Schöder[2], C. Ross Schmidtlein[4], Michael J. Morris[5], Pat Zanzonico[4], Olivia Squire[2], Gustavo S.P. Meirelles[6], Ron Finn[2], Mohammad Namavari[7], Shangde Cai[2], Howard I. Scher[5], Steven M. Larson[2], and John L. Humm[4]

High Reproducibility of Tumor Hypoxia Evaluated by ^{18}F-Fluoromisonidazole PET for Head and Neck Cancer

Shozo Okamoto[1], Tohru Shiga[1], Koichi Yasuda[2], Yoichi M. Ito[3], Keiichi Magota[1], Katsuhiko Kasai[1], Yuji Kuge[4], Hiroki Shirato[2], and Nagara Tamaki[1]

Standard Therapies Today: New hormonal agents are moving earlier and earlier



Metastatic Hormone-Sensitive Prostate Cancer (HSPC) Landscape: Improvements in survival (1941-2021)

- ADT + docetaxel
  - CHAARTED (2015) and STAMPEDE (2015)
  - ADT + radiation to prostate in low volume metastatic disease
    - STAMPEDE (2018)
- ADT + abiraterone
  - LATITUDE (2019) and STAMPEDE (2020)
- ADT + enzalutamide
  - ENZAMET (2019) and ARCHES (2021)
- ADT + apalutamide
  - TITAN (2019)

Recent Updates for HSPC: New data on systemic treatments (2022-2023)

- PEACE-1 (M1)
  - ADT + docetaxel + abiraterone better than ADT + docetaxel
- ARASENS (M1)
  - ADT + docetaxel + darolutamide better than ADT + docetaxel
- STAMPEDE (M0)-High risk Non-Metastatic
  - ADT + radiation + abiraterone better than ADT + radiation

Do we accept PEACE-1 and ARASENS and use a triplet?

- No trials using ADT + “new hormone” +/- docetaxel so the contribution of docetaxel is unclear

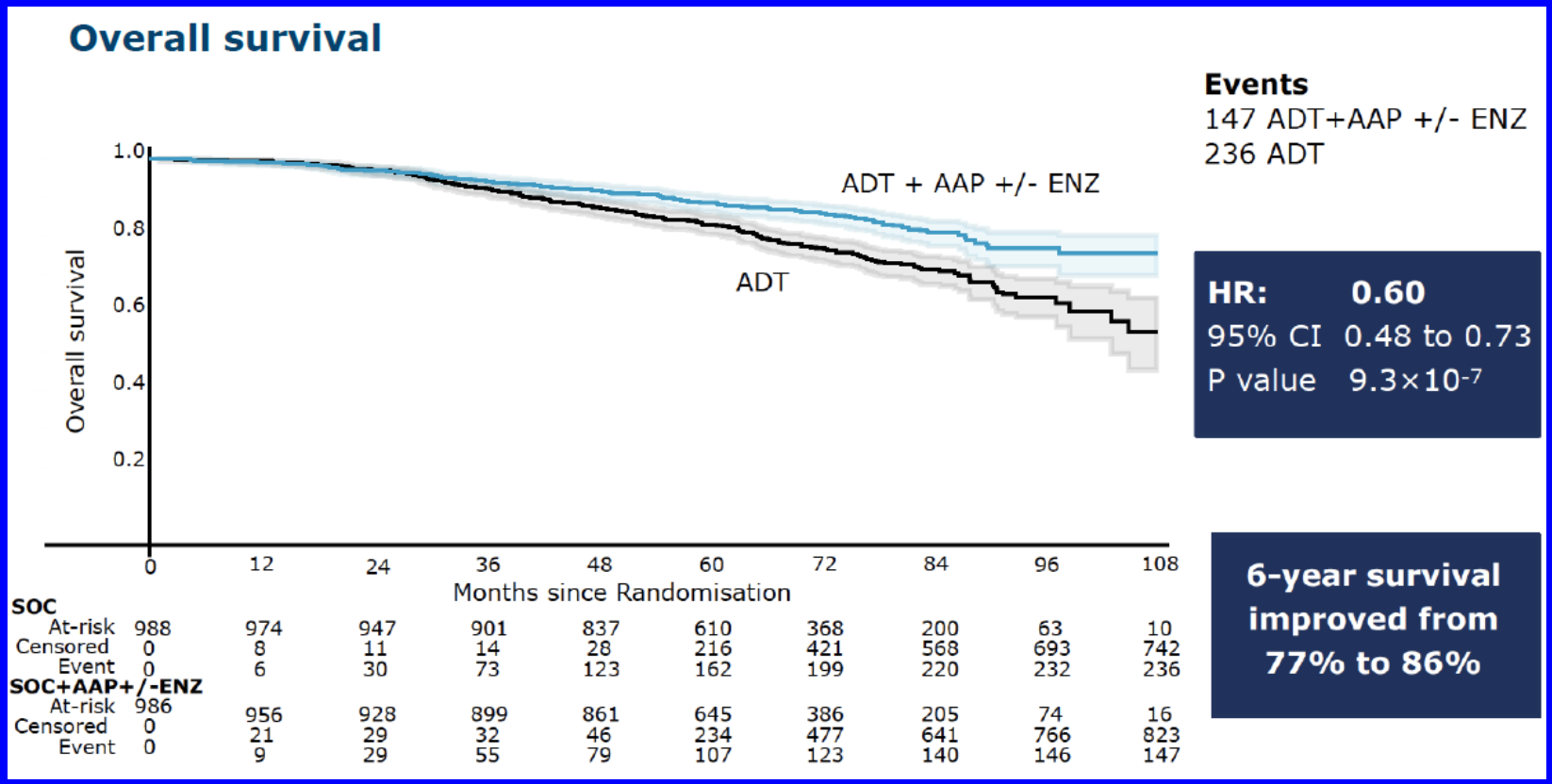
Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol

Gerhardt Attard, Laura Murphy, Noel W Clarke, William Cross, Robert J Jones, Christopher C Parker, Silke Gillessen, Adrian Cook, Chris Brawley, Claire L Amos, Nafisah Atako, Cheryl Pugh, Michelle Buckner, Simon Chowdhury, Zafar Malik, J Martin Russell, Clare Gilson, Hannah Rush, Jo Bowen, Anna Lydon, Ian Pedley, Joe M O'Sullivan, Alison Birtle, Joanna Gale, Narayanan Srihari, Carys Thomas, Jacob Tanguay, John Wagstaff, Prantik Das, Emma Gray, Mymoona Alzoueb, Omi Parikh, Angus Robinson, Isabel Syndikus, James Wylie, Anjali Zarkar, George Thalmann, Johann S de Bono, David P Dearnaley, Malcolm D Mason*, Duncan Gilbert, Ruth E Langley, Robin Millman, David Matheson, Matthew R Sydes†, Louise C Brown†, Mahesh K B Parmar†, Nicholas D James†, on behalf of the Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators‡*

Lancet 2022; 399: 447–60

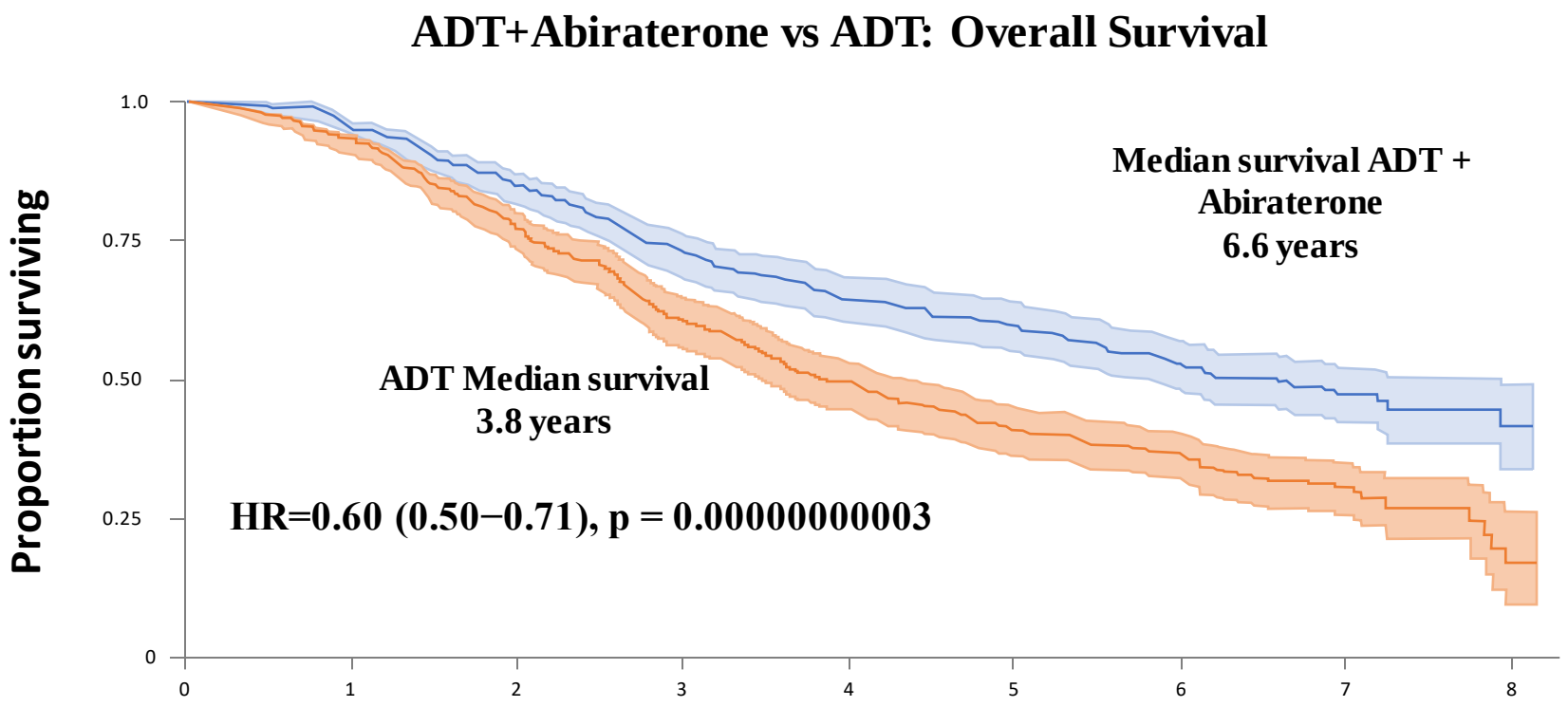
STAMPEDE: Overall Survival

Attard et al. ESMO 2021 LBA4



A Few Highlights To Consider on Hormone-Sensitive Disease

STAMPEDE randomized trial: Abiraterone plus prednisolone for hormone-naïve prostate cancer: Long-term results from metastatic (M1) patients



Nicholas James; oral presentation number 611O, ESMO 2020

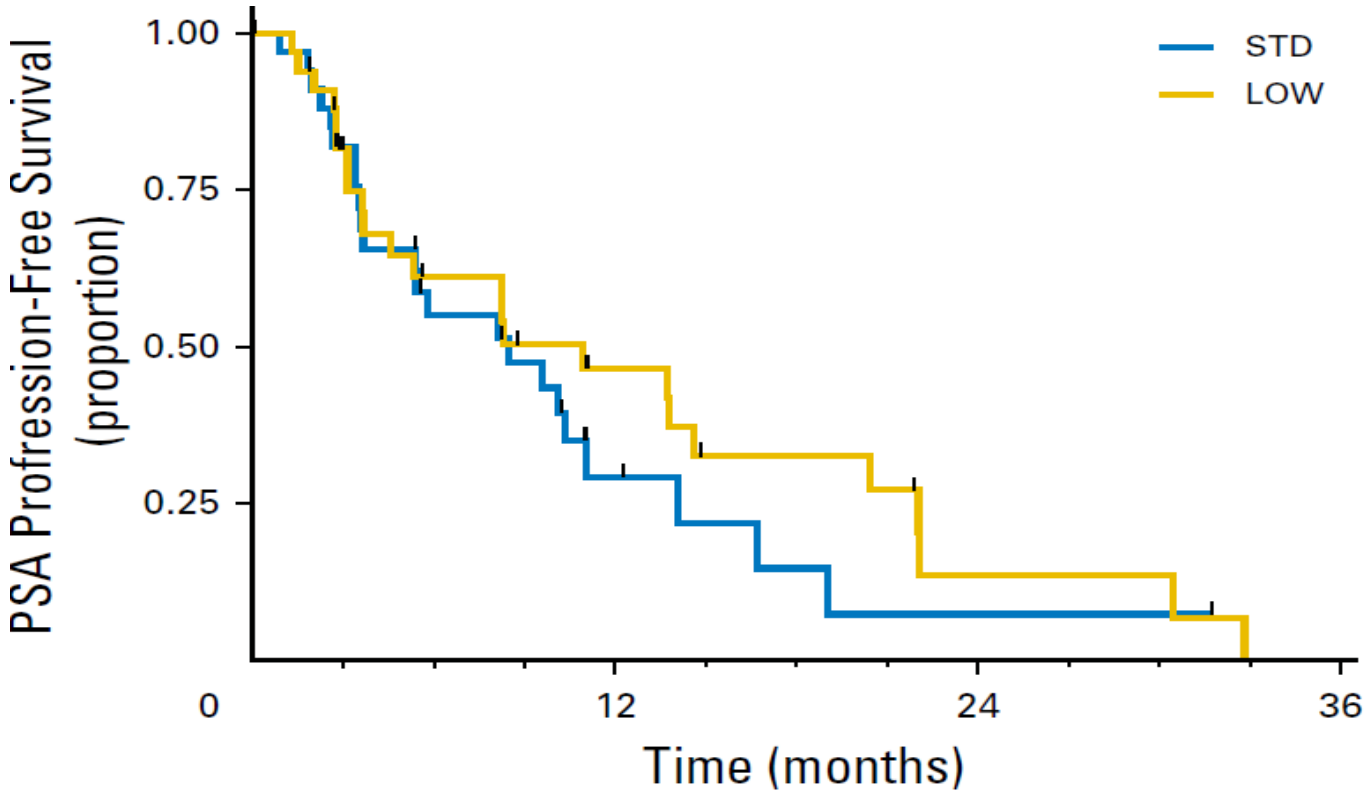
VOLUME 36 · NUMBER 14 · MAY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

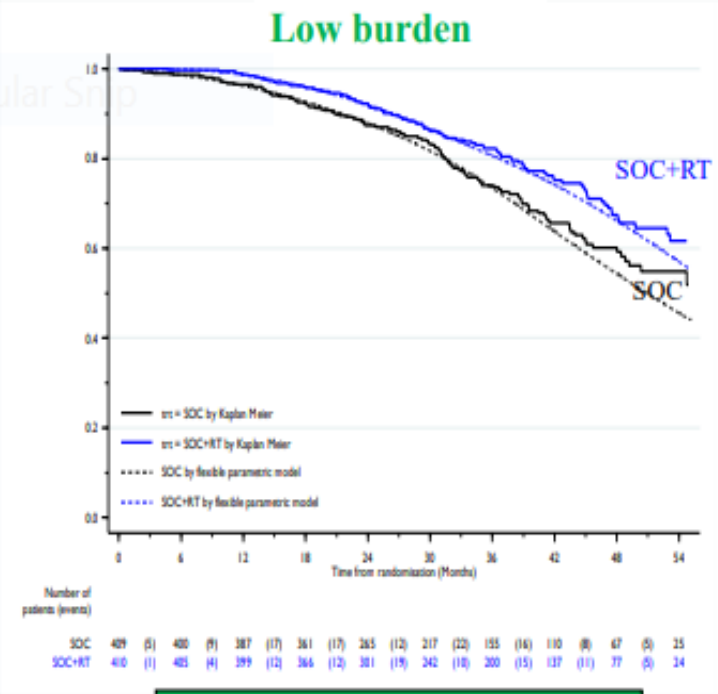
ORIGINAL REPORT

Prospective International Randomized Phase II Study of Low-Dose Abiraterone With Food Versus Standard Dose Abiraterone In Castration-Resistant Prostate Cancer

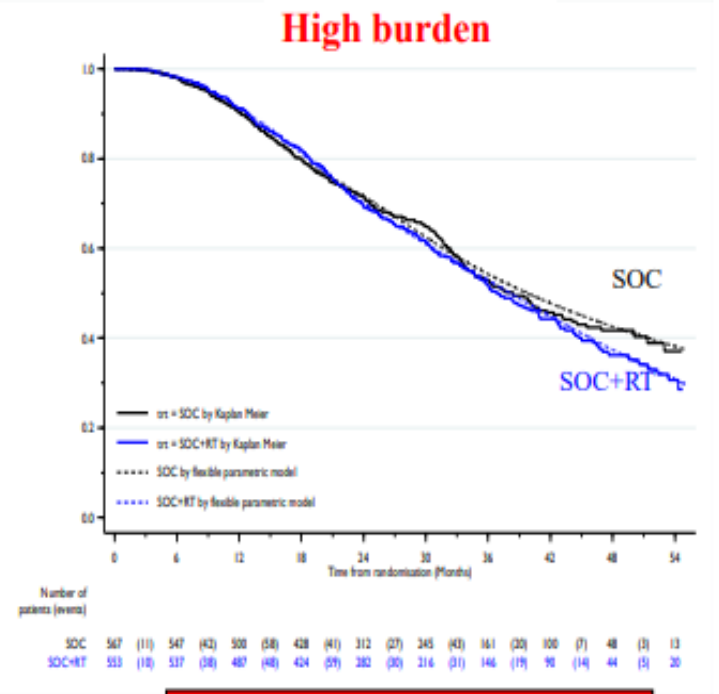
Russell Z. Szmulewitz, Cody J. Peer, Abiola Ibraheem, Elia Martinez, Mark F. Kozloff, Bradley Carthon, R. Donald Harvey, Paul Fishkin, Wei Peng Yong, Edmund Chiong, Chadi Nabhan, Theodore Karrison, William D. Figg, Walter M. Stadler, and Mark J. Ratain



Prostate radiotherapy in M1 (STAMPEDE): OS



HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%):
SOC = 73%
SOC+RT = 81%



HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%):
SOC = 54%
SOC+RT = 53%

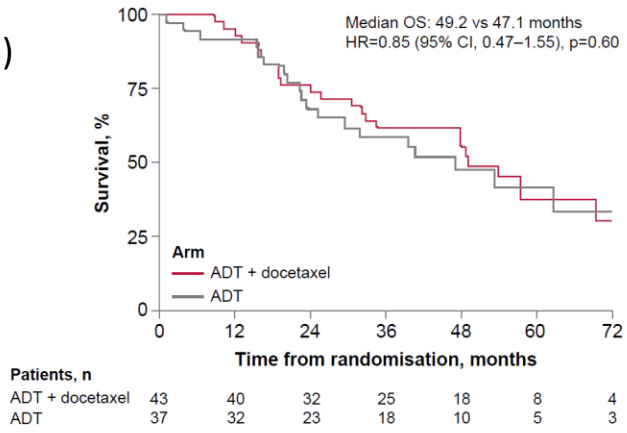
Parker C, ESMO 2018 and Lancet 2018

Hypothesis generation: transcriptomic profiling may improve patient selection for docetaxel

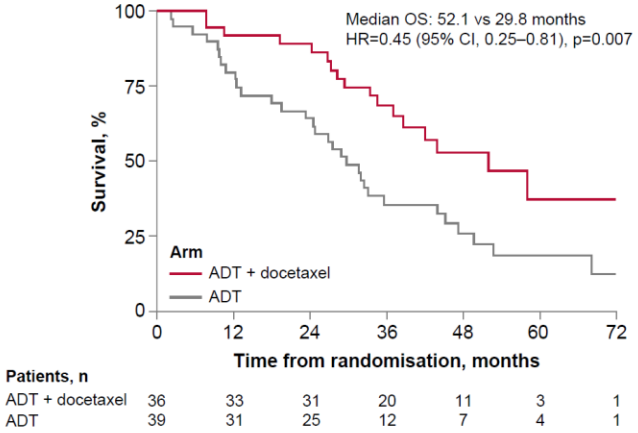
Correlative study of CHAARTED (N=160):

- PAM50 gene expression profiling:
- 52.1% basal (vs 33.2% localised)
- 46.1% luminal B (vs 32.7% localised)
- 1.8% luminal A (vs 34.1% localised)

PAM50 basal (50%)



PAM50 luminal B (48%)



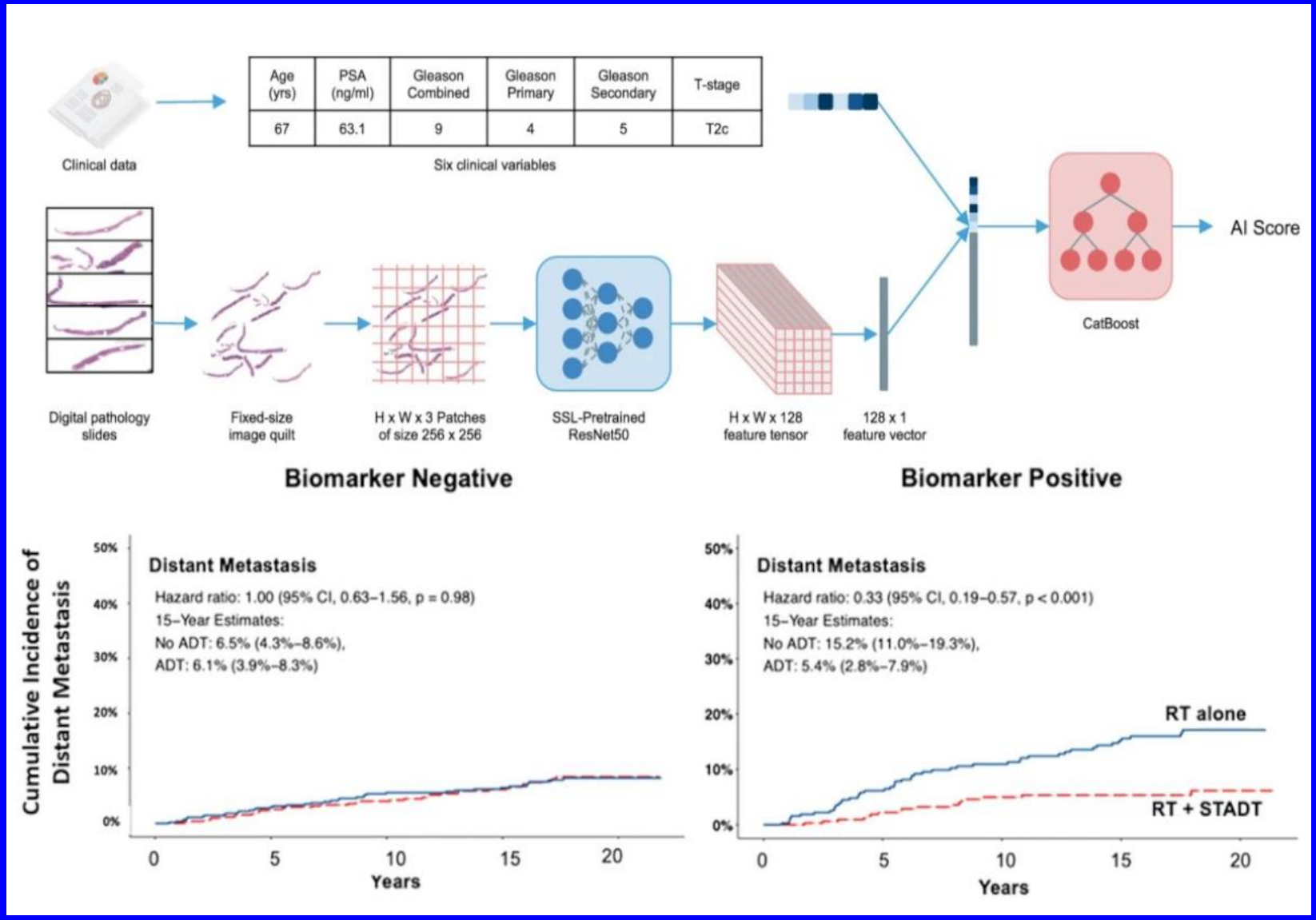
Docetaxel + ADT vs ADT appears to improve OS and time to mCRPC in luminal B subtype only

PAM50, Prediction Analysis

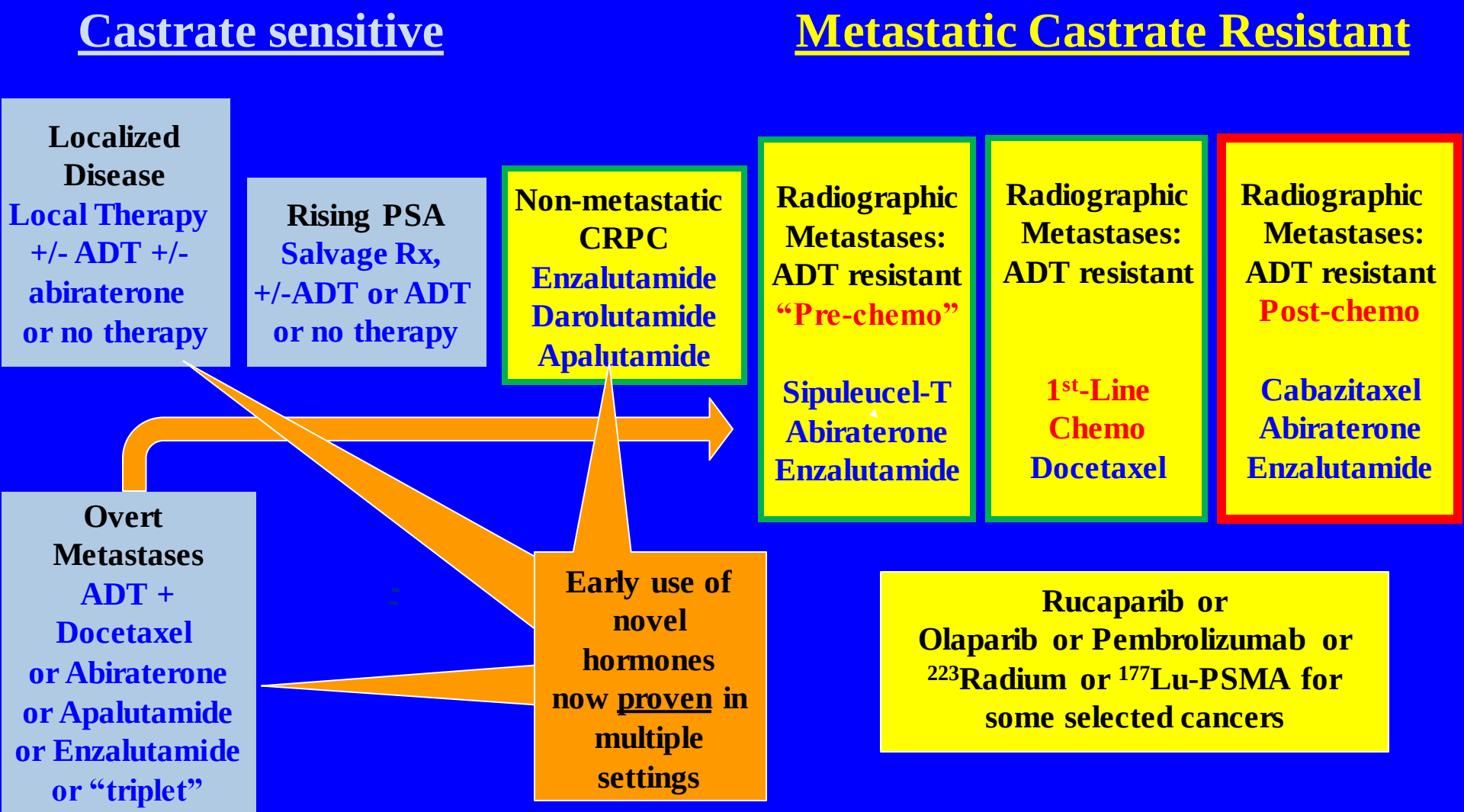
Hamid A …. Sweeney C. Annals of Oncology. 2021

Artificial Intelligence in Prostate Cancer (Artera AI)

Mohamad et al. ASTRO 2022



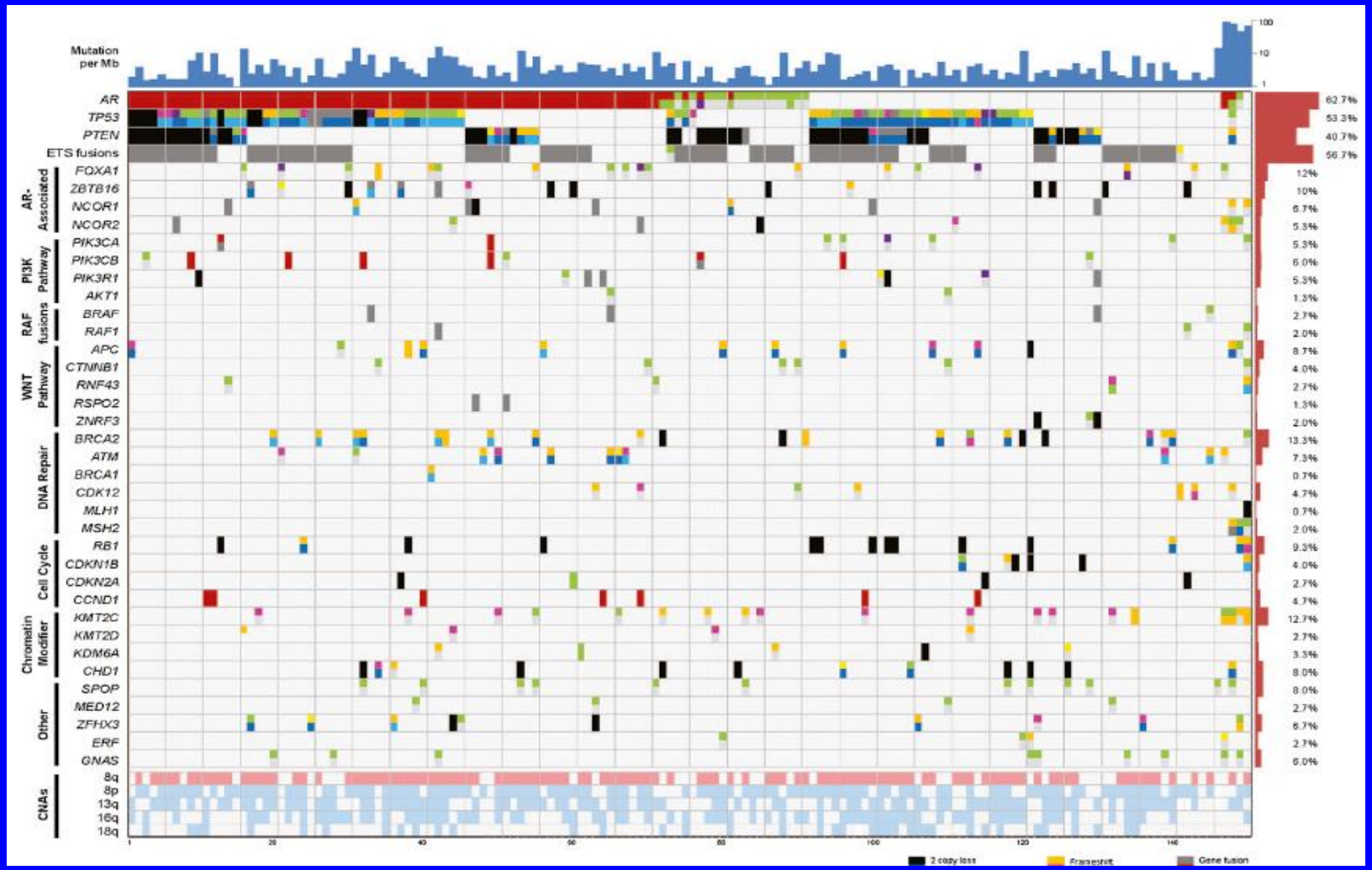
Standard Therapies Today: Moving to Castrate-Resistant Prostate Cancer



TRIAL	FRONT LINE mCRPC	HR	Survival (months)*
TAX 327	Docetaxel/prednisone vs mitoxantrone/prednisone	0.79	19.2 vs 16.3* (2.9 months)
IMPACT	Sipuleucel-T vs Control	0.78	25.8 vs 21.7 (4.1 months
COU-AA-302	Abiraterone/prednisone vs Placebo/prednisone	0.79	35.3 vs. 31.1* (4.2 months)
PREVAIL	Enzalutamide vs Placebo	0.71	35.3 vs. 31.3* (4.0 months)
	POST-DOCETAXEL mCRPC		
TROPIC	Cabazitaxel/prednisone vs mitoxantrone/prednisone	0.70	15.1 vs 12.7 (2.4 months)
COU-AA- 301	Abiraterone/prednisone vs Placebo/prednisone	0.74	15.8 vs 11.2* (4.6 months)
AFFIRM	Enzalutamide vs Placebo	0.63	18.4 vs 13.6 (4.8 months)
	BONE DOMINANT FRONT LINE and POST-DOCETAXEL mCRPC		
ALSYMPCA	Standard of care +/- radium-223	0.70	14.9 vs 11.3* (3.6 months)
	POST-ABI OR -ENZA OR POST-ABI OR -ENZA AND -DOCETAXEL (HRR SUBSET)		
PROfound	Olaparib vs abi/enza second line	0.69	19.1 vs 14.7** (4.4 months)
	Third Line (POST-ABI or -ENZA and POST-DOCETAXEL		
CARD	Cabazitaxel vs abi/enza second line	0.64	13.6 vs 11.0 (2.6 months)
VISION	Standard of care +/- PSMA-617 Lu-177***	0.62	15.3 vs 11.3 (4.0 months)

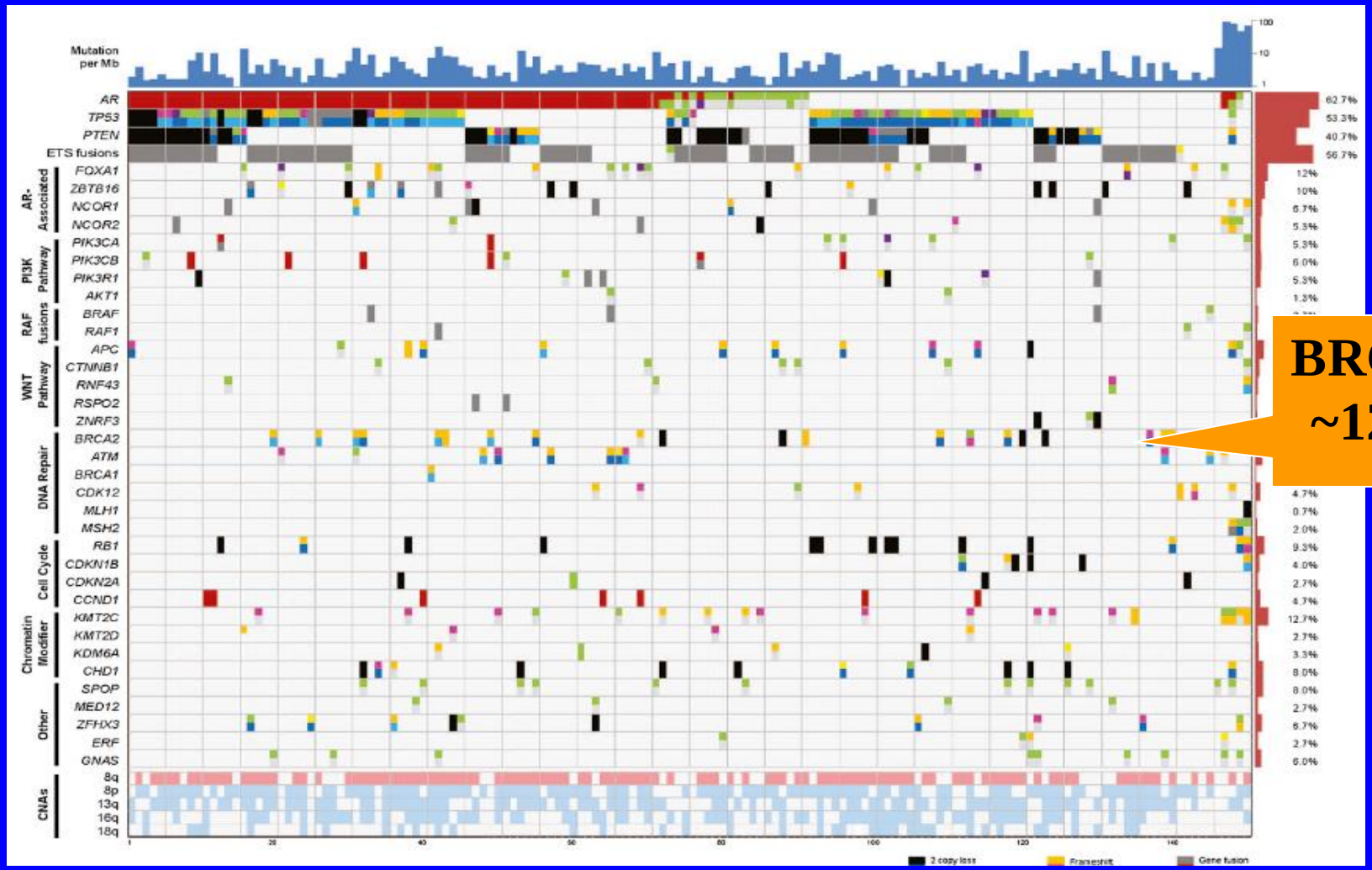
* Mature analysis **BRCA1/BRCA2 subset ***PSMA PET Positive subset

Challenges: Somatic Genetics show mCRPC is a heterogeneous group of diseases



Robinson et al. Cell 161:1215, 2015

Challenges: mCRPC is a heterogeneous group of diseases



Robinson et al. Cell 161:1215, 2015

Improved Survival: Phase III Olaparib Trial (PARP inhibition) in BRCA2 mutated Prostate Cancer

Sept 20, 2020

The NEW ENGLAND JOURNAL of MEDICINE

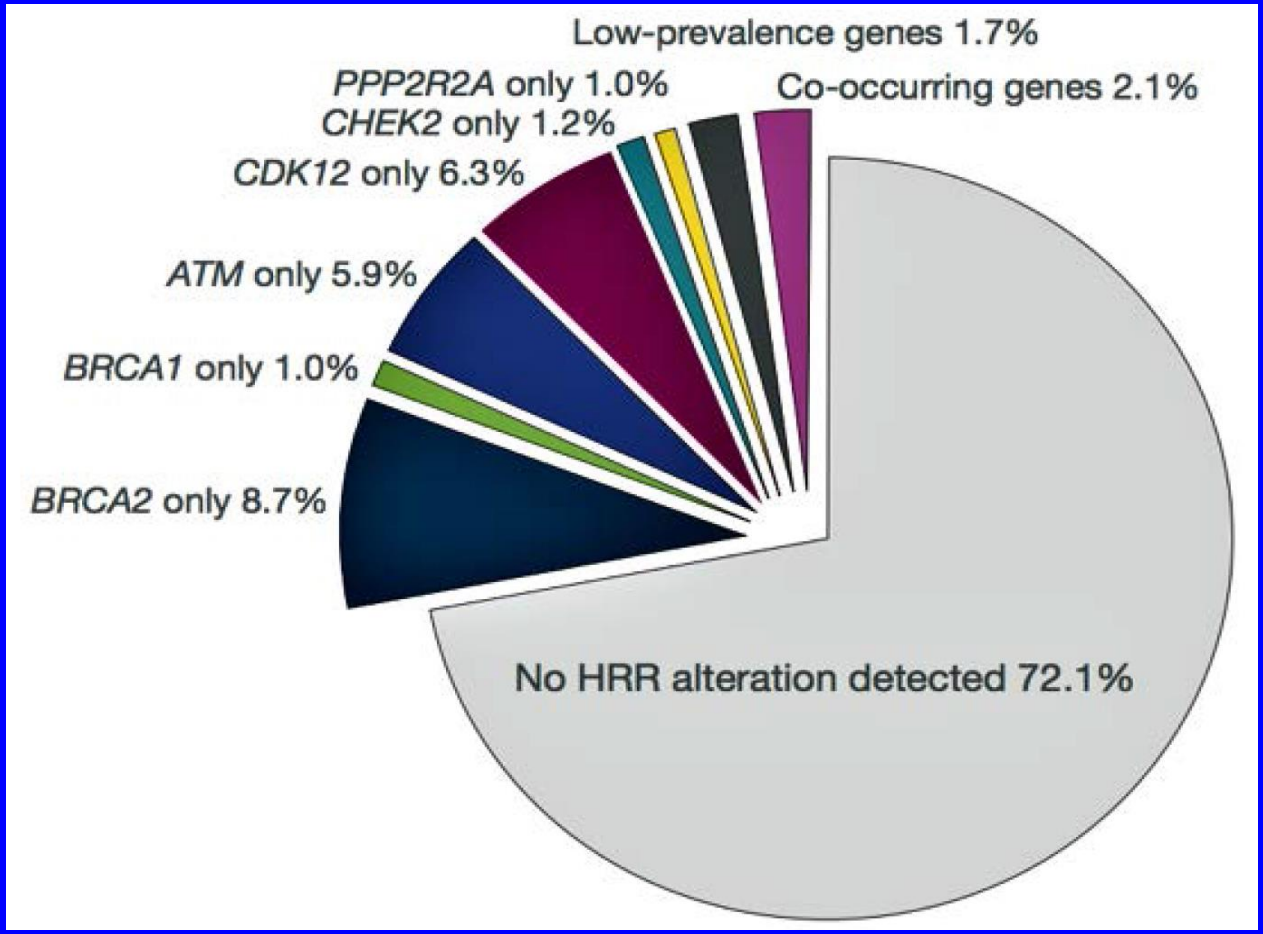
ORIGINAL ARTICLE

Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

M. Hussain, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, G. Roubaud, M. Özgüroğlu, J. Kang, J. Burgents, C. Gresty, C. Corcoran, C.A. Adelman, and J. de Bono, for the PROfound Trial Investigators*

PROfound data: 4047 pts tested, 28% had DNA repair defects 31% had Quality Issues with Genomic Assays

De Bono et al. ESMO 2019, #5118

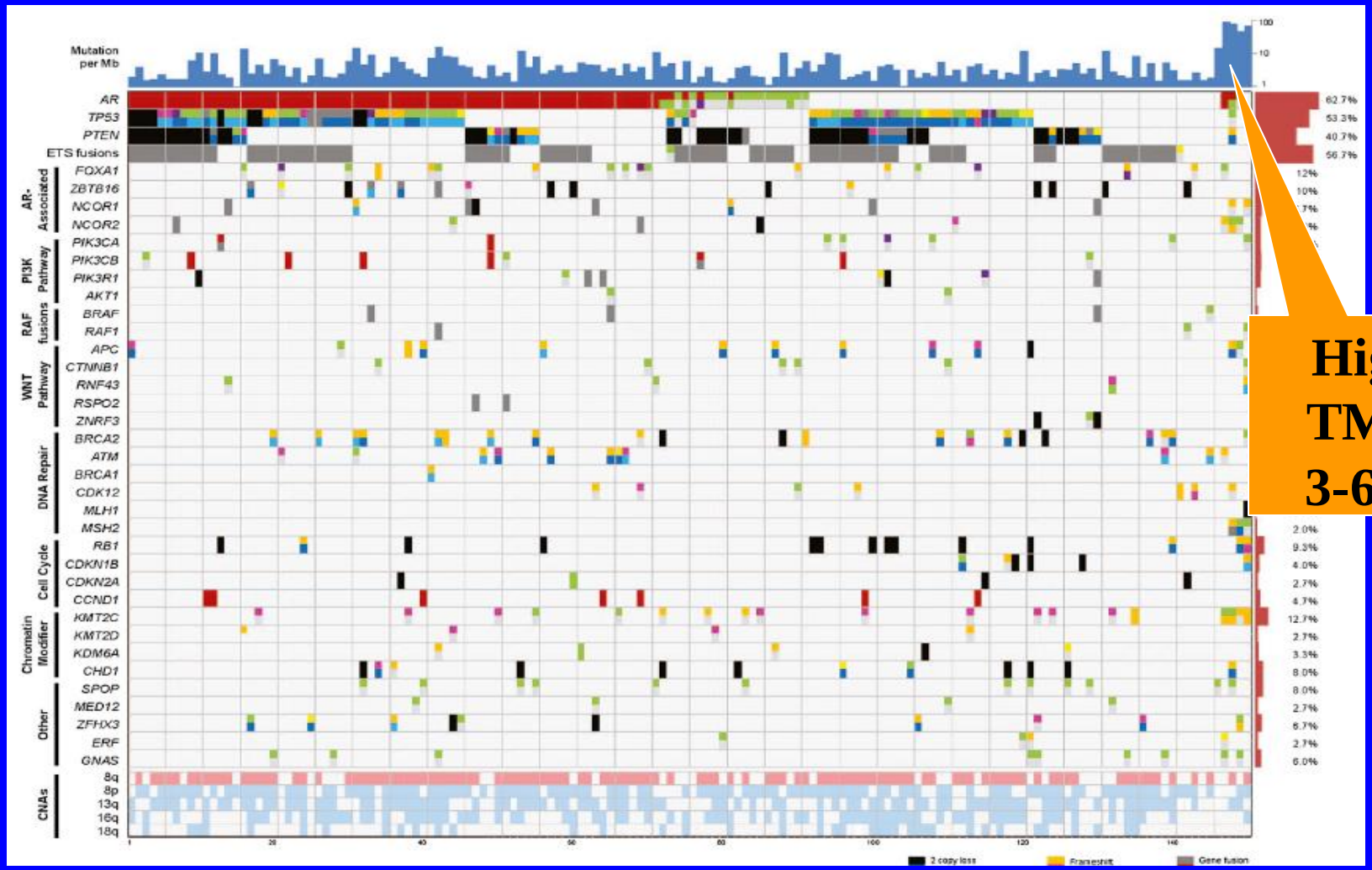


Assessment of circulating tumor DNA (ctDNA)

- ctDNA accessible in most everyone whereas tissue based assays can be problematic in prostate cancer

- FDA approval to identify eligible patients with specific mutations
  - Rucaparib for BRCA1/2 mutations (Aug 26, 2020)
  - Olaparib for BRCA1/2 or ATM mutations (Nov 9, 2020)

Challenges: mCRPC is a heterogeneous group of diseases

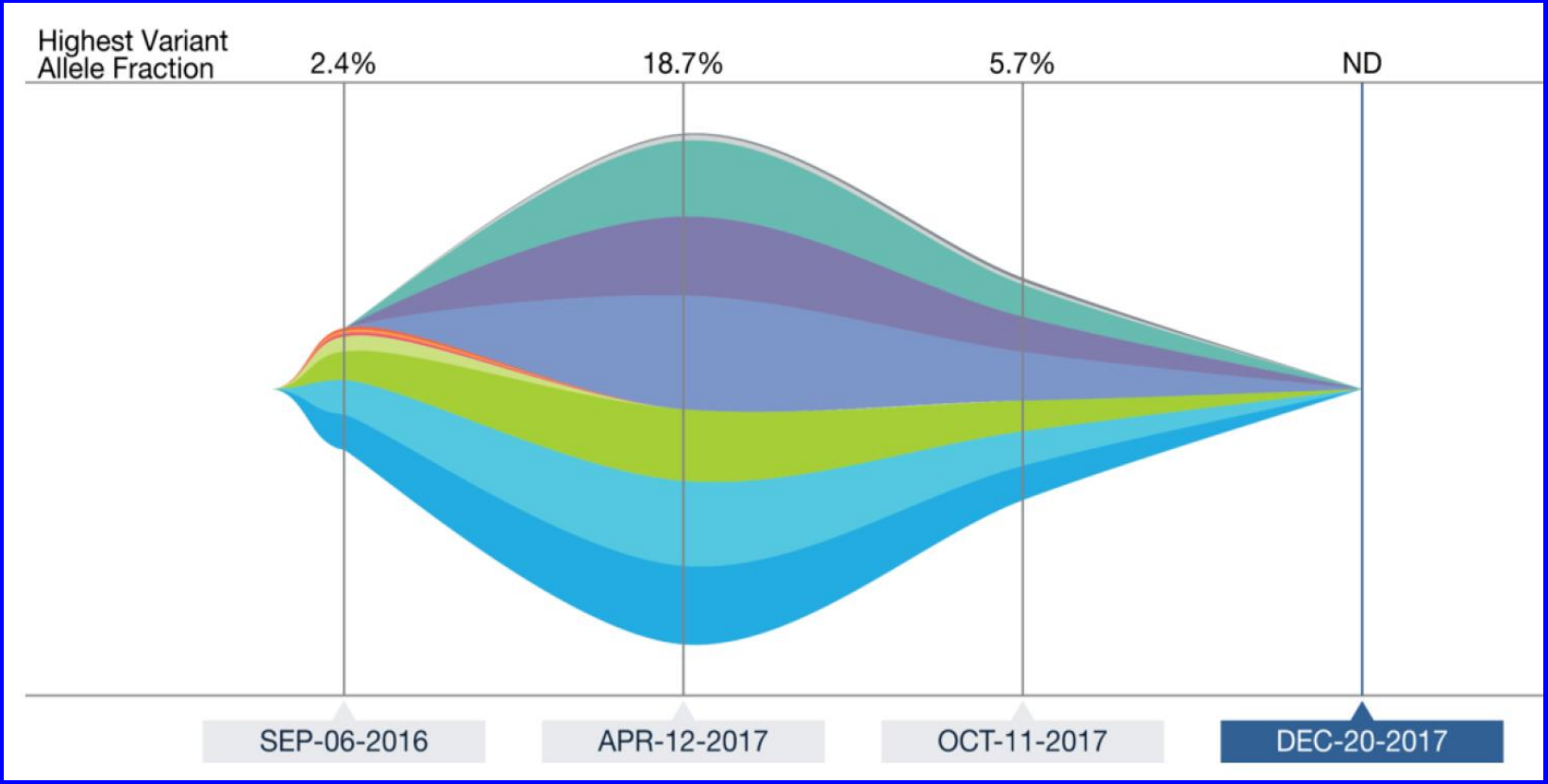


Robinson et al. Cell 161:1215, 2015

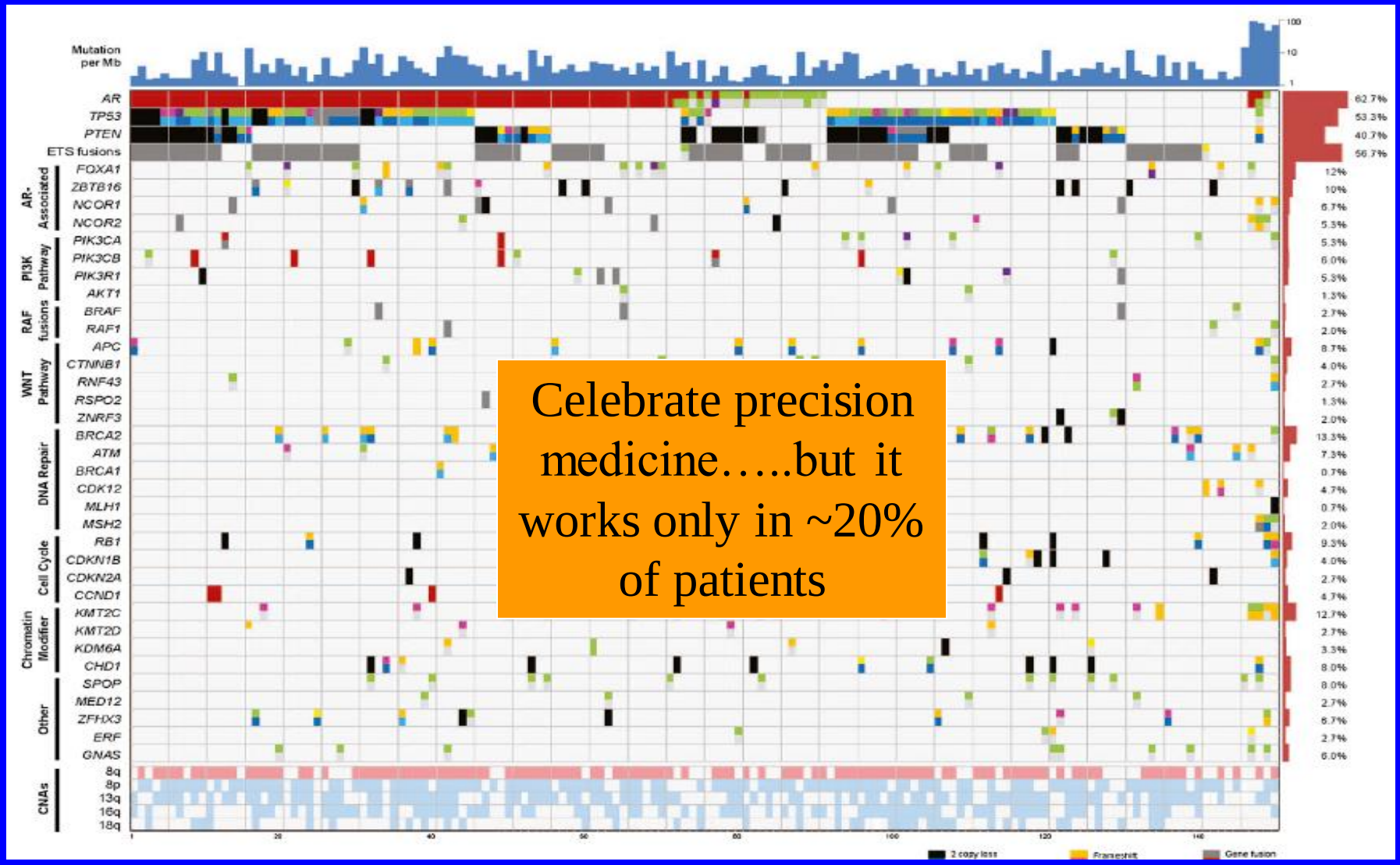
Immunotherapy (Pembrolizumab) FDA approved for tumors that are MSI high or high tumor mutational burden (>10 per Mb) or mismatch repair deficient

Do not miss these…..at times the response can be dramatic and long lived

cDNA changes after Pembrolizumab in a mCRPC patient with mismatch repair deficiency



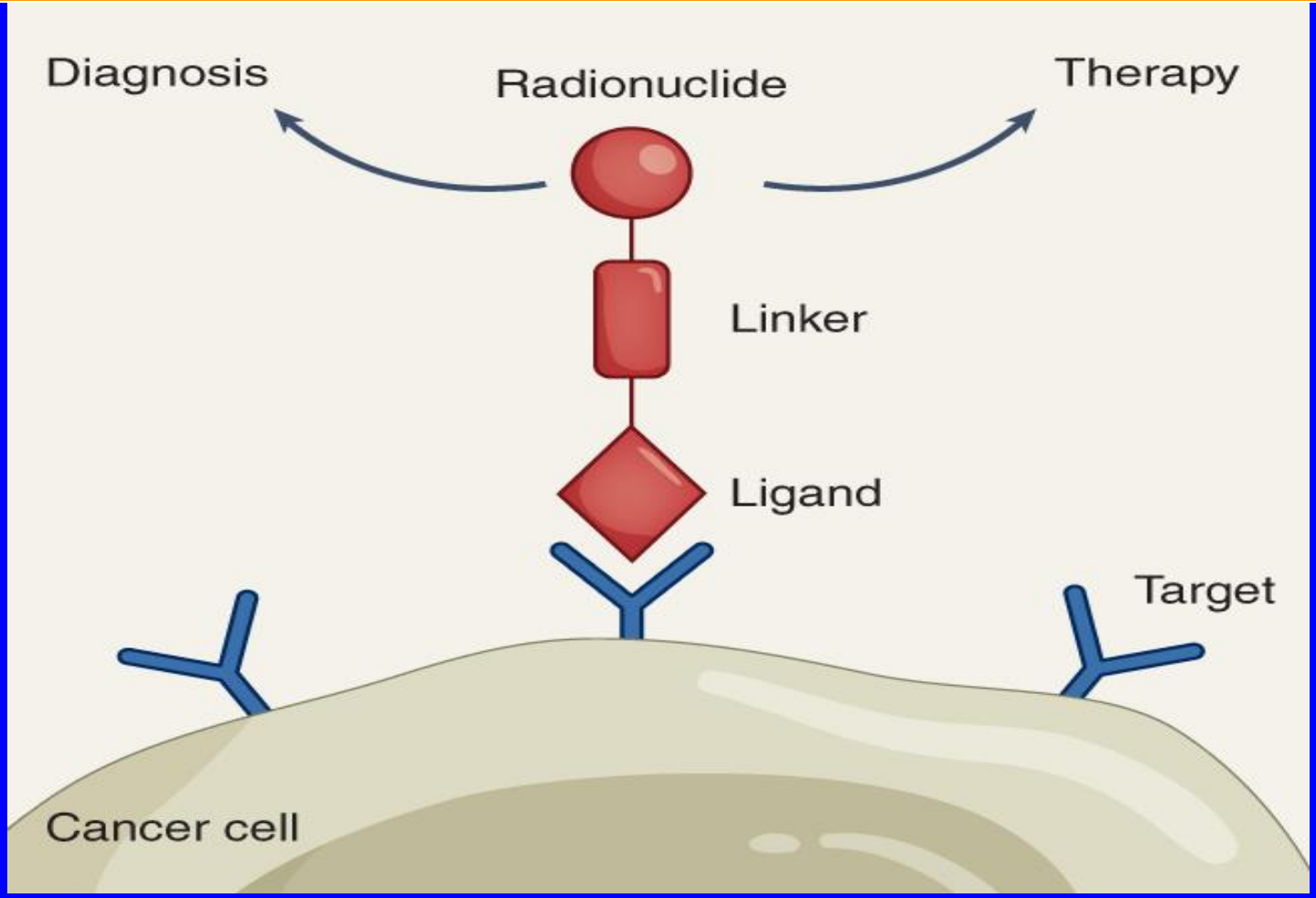
Challenges: CRPC is a heterogeneous disease with many molecular alterations



Celebrate precision medicine…..but it works only in ~20% of patients

Robinson et al. Cell 161:1215, 2015

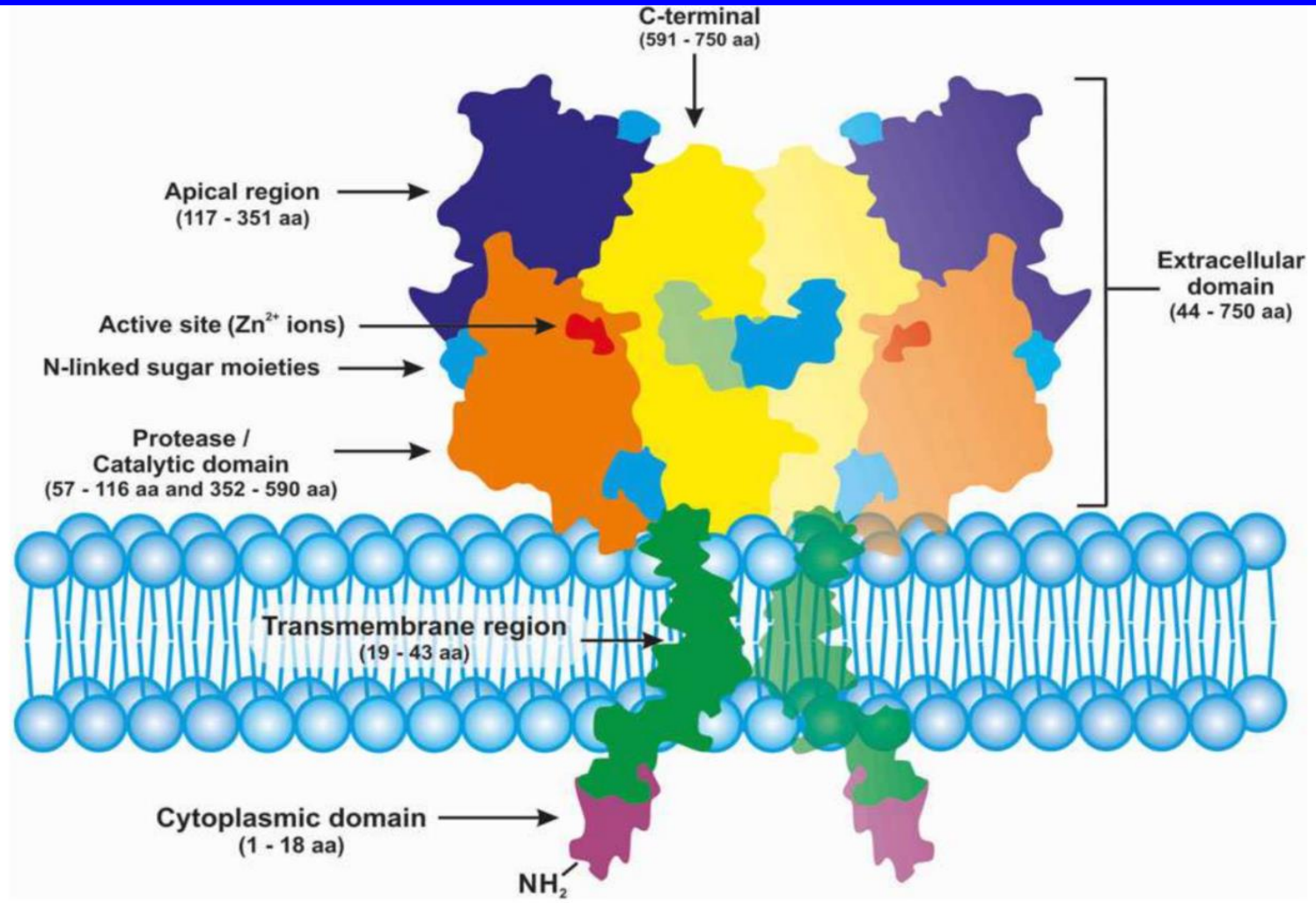
Theranostics:
See it…. Treat it…..Love it!



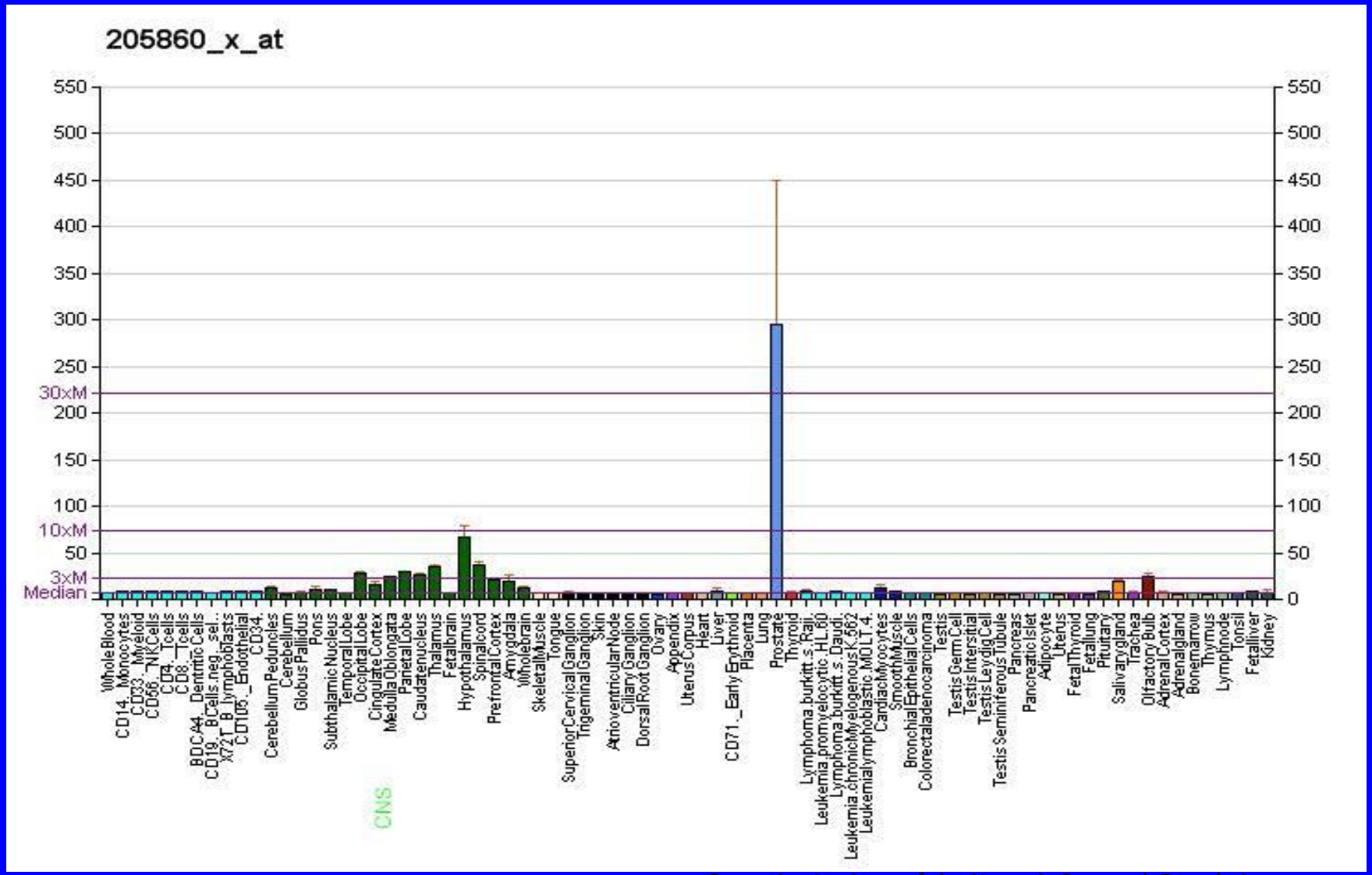
Cell surface target, a ligand, a linker, and an isotope

PSMA Targeted Therapies

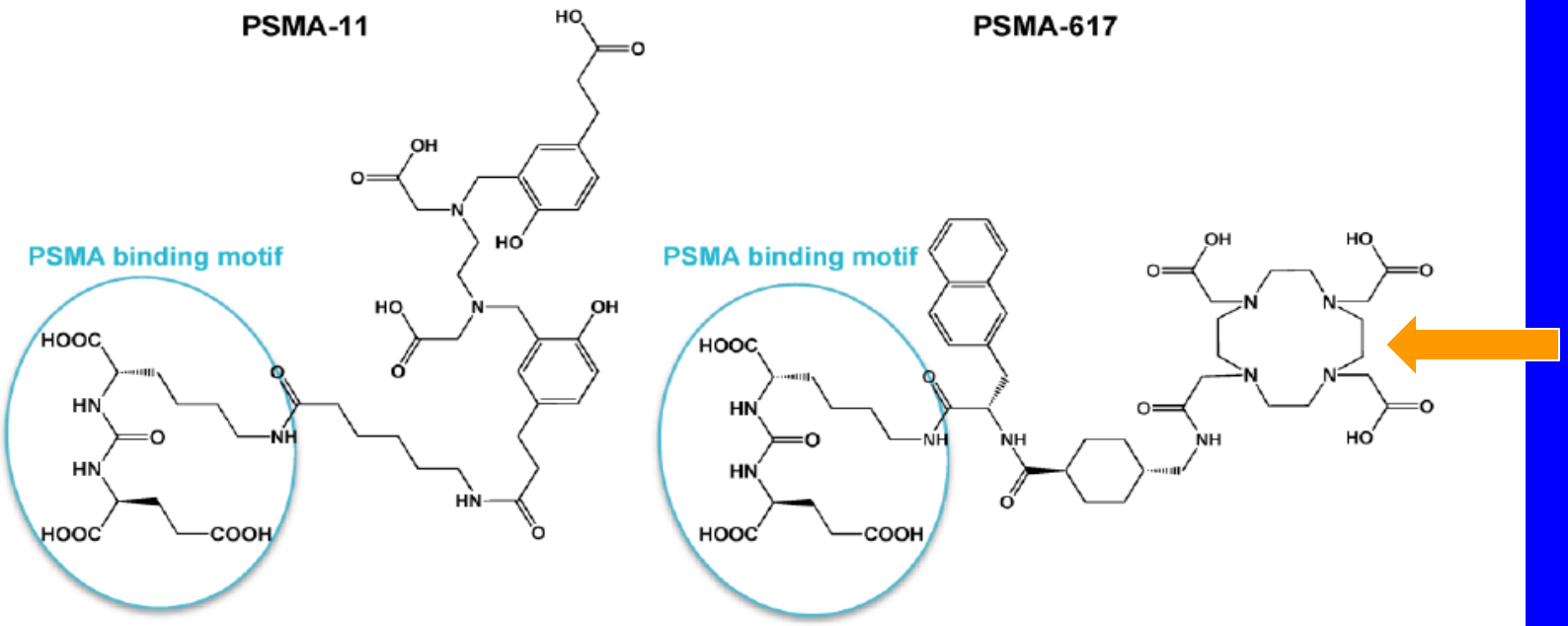
Image from O'Driscott C et al, Br J Pharm 2016



PSMA: Gene Expression High in the Prostate



PSMA binding molecules can be linked to diagnostic isotopes (^{68}Ga) or therapeutic isotopes (such as ^{177}Lu or ^{225}Ac)



Chatolic et al. Theragnostics 6:849, 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

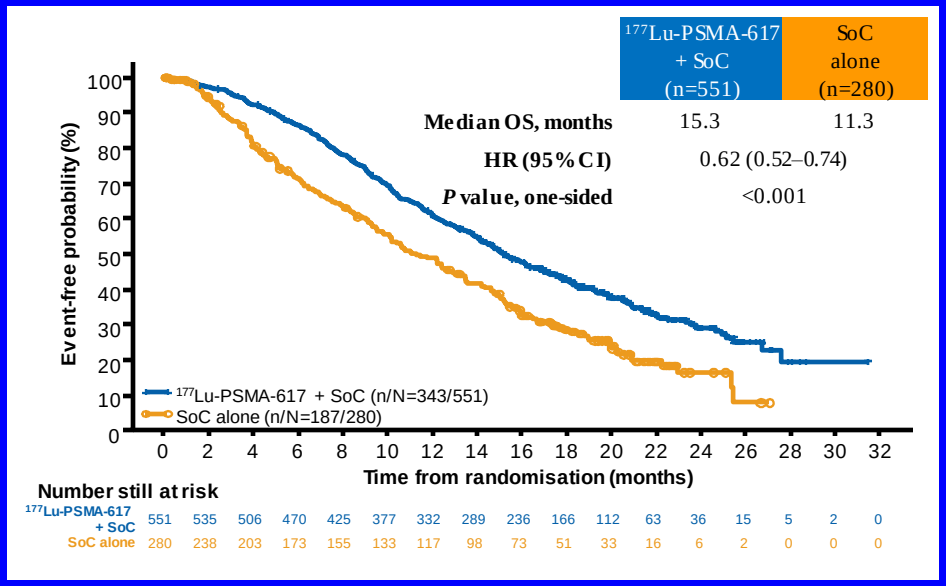
June 23, 2021

Active in those with PSMA PET positive metastatic disease

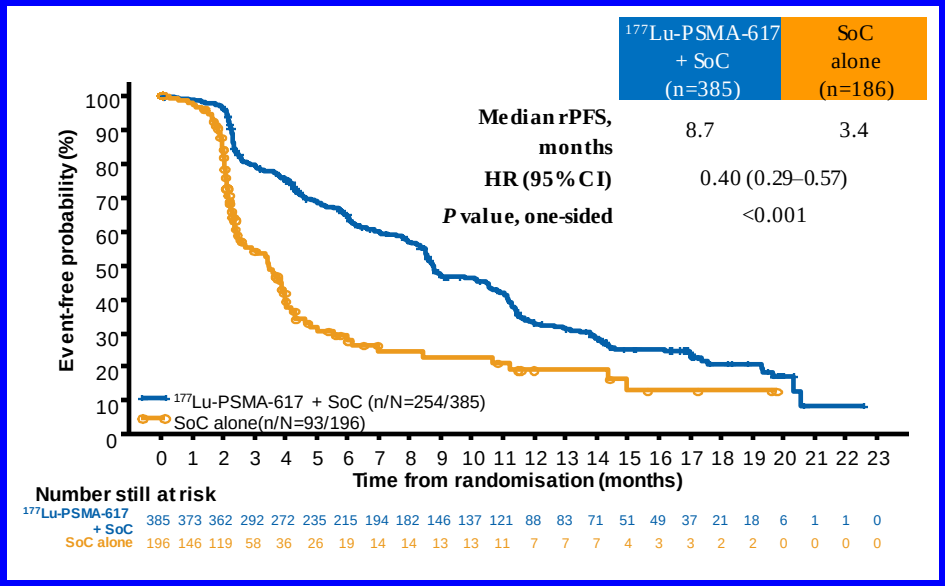
VISION: ^{177}Lu-PSMA-617 pivotal Phase III trial

VISION met both primary endpoints of OS and rPFS[1]

OS: 38% risk reduction for death[1]



rPFS: 60% risk reduction for progression/death[1]

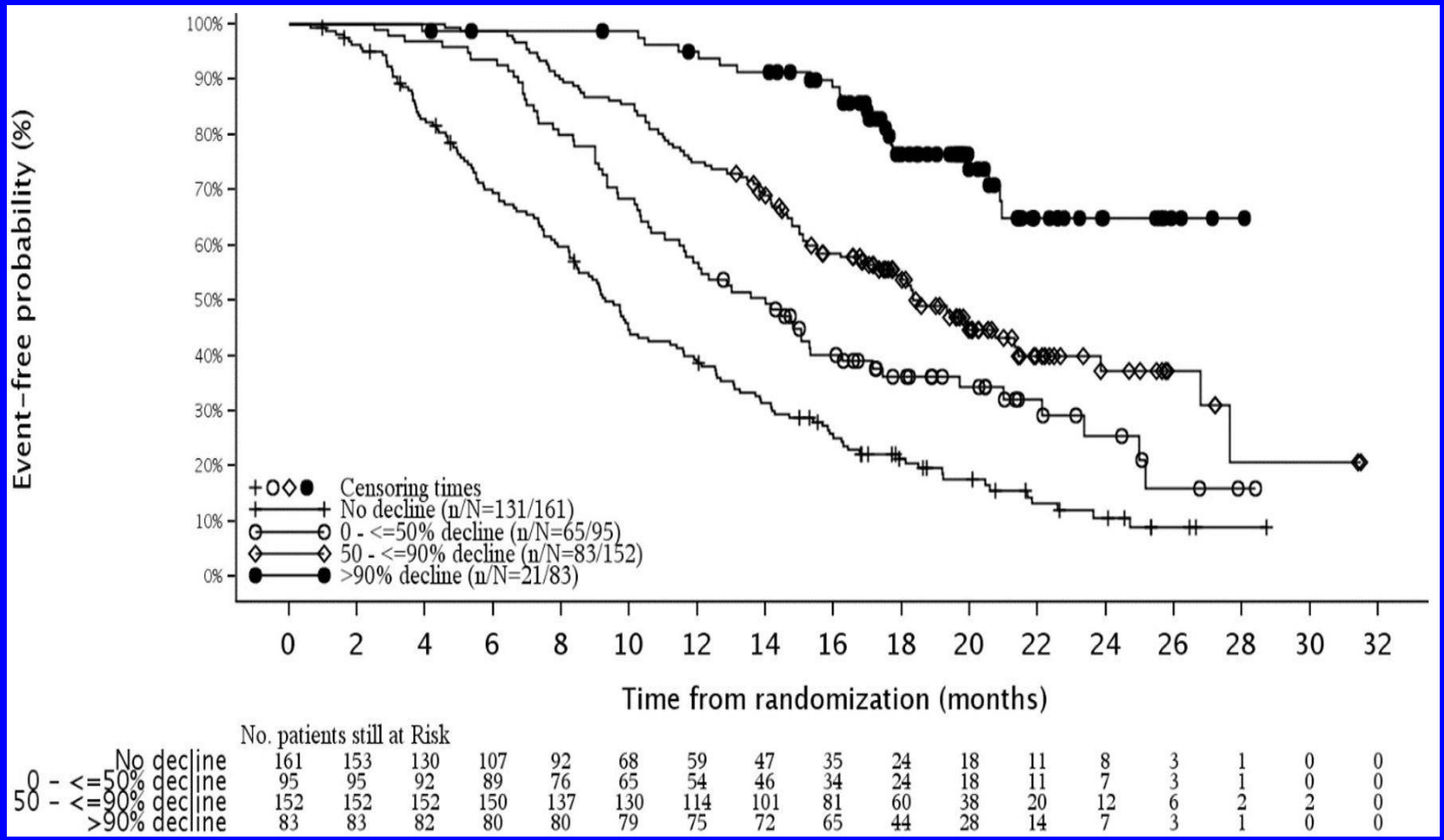


CI, confidence interval; HR, hazard ratio; OS, overall survival; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SoC, standard of care.

1. Sartor O, et al. N Engl J Med. 2021; doi: 10.1056/NEJMoa2107322. Online ahead of print.

PSA decline at <12 weeks and Overall Survival

Armstrong et al. Annals of Oncology (2022) 33 (suppl_7): S616-S652.

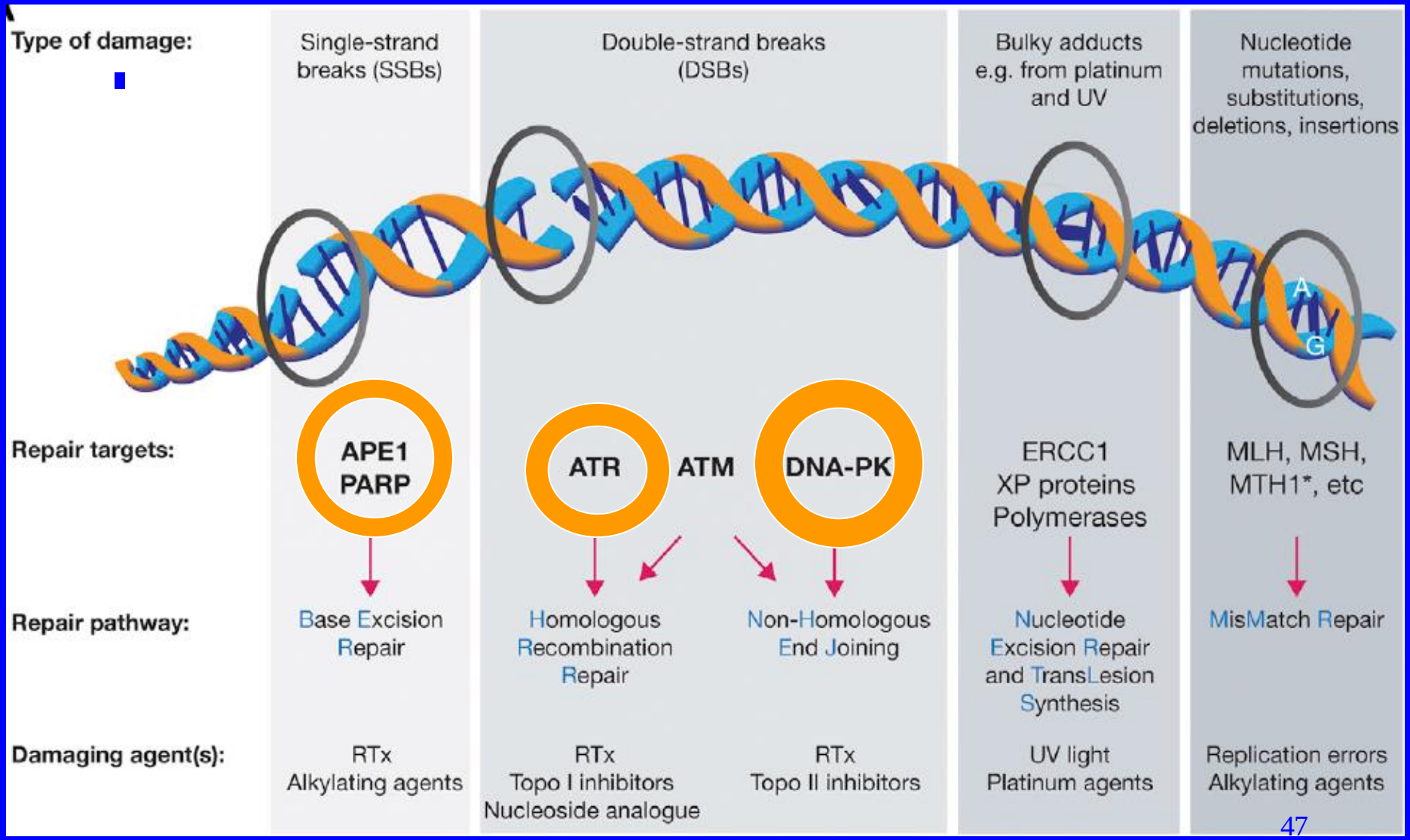


Synergistic opportunities with radiopharmaceuticals

Molecularly Targeted Isotopic Therapy

Small molecules, peptides, antibodies, minibodies, aptamers, and radionuclides

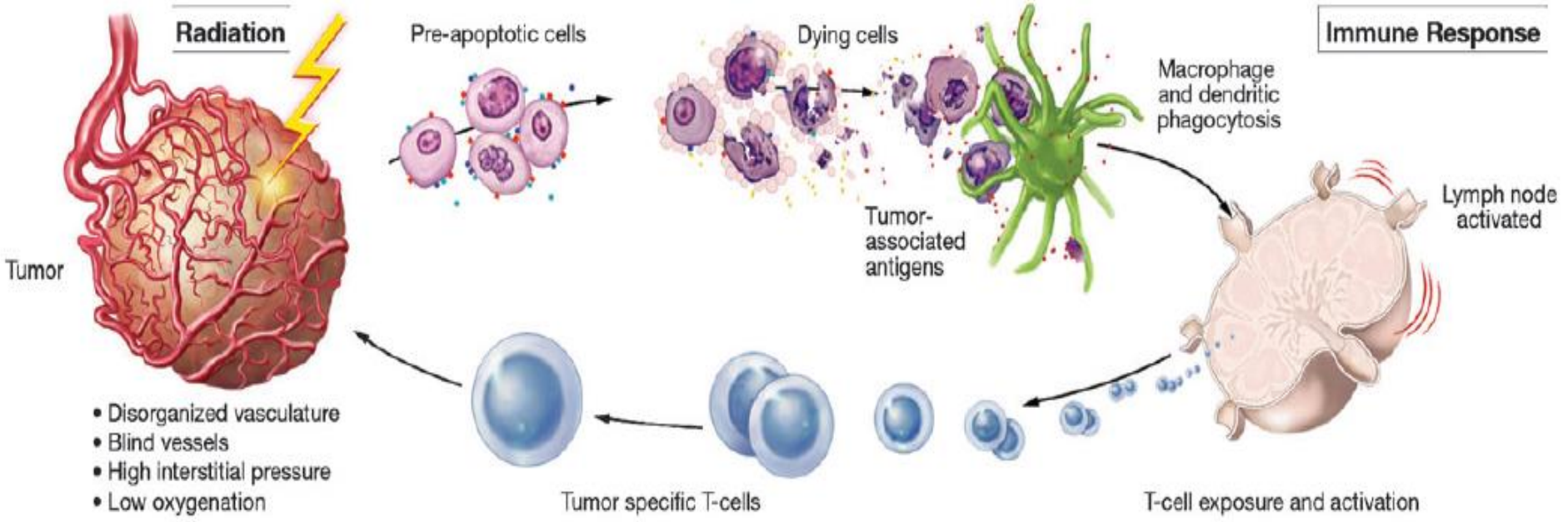
Targeting DNA damage repair pathways in combination with radionuclides



O'Connor, Molecular Cell 60, November 19, 2015

Antigen release from radiated tumor: Synergy with immunotherapies?

Kamrava et al., Molecular Biosystems: 5:1249–1372, 2009



Systemic/local immune enhancement

- Vaccine
- Checkpoint inhibitors
  - Anti-CTLA-4
  - Anti-PD-1
  - Anti-PD-L1
  - Anti-TIM3
- Co-stimulatory agonists
  - Anti-OX40
  - Anti-4-1BB
  - Anti-GITR
  - Anti-CD27
  - Anti-CD40
- Exogenous cytokines
  - IL-2
  - IL-7
  - IL-12
  - IL-15
  - IL-21
  - GM-CSF

New trials will bring PSMA Lu-177 in the pre-chemo mCRPC space

Novartis Pluvicto™ shows statistically significant and clinically meaningful radiographic progression-free survival benefit in patients with PSMA–positive metastatic castration-resistant prostate cancer

Dec 05, 2022

Ad hoc announcement pursuant to Art. 53 LR

- *Phase III PSMAfore trial with Pluvicto™ met the primary endpoint of radiographic progression-free survival (rPFS) in PSMA–positive mCRPC who have been treated with androgen-receptor pathway inhibitor (ARPI) therapy[1]*

- *Pluvicto becomes the first PSMA-targeted radioligand therapy to demonstrate clinical benefit in mCRPC patients before receiving taxane-based chemotherapy[1], addressing a significant unmet need[2]*

Alpha Particles
(Two protons and two neutrons)

Very destructive at short range

Significant percentage of double strand breaks resulting in high cell lethality

Short range….50-100 microns

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

First alpha emitter in medicine
Hats off to Roy Larsen and Oyvind Bruland at Algeta!!!

Radium-223 only goes to bone stroma!

Radium-223 moved the field forward but tumor targeted alpha therapy will be better

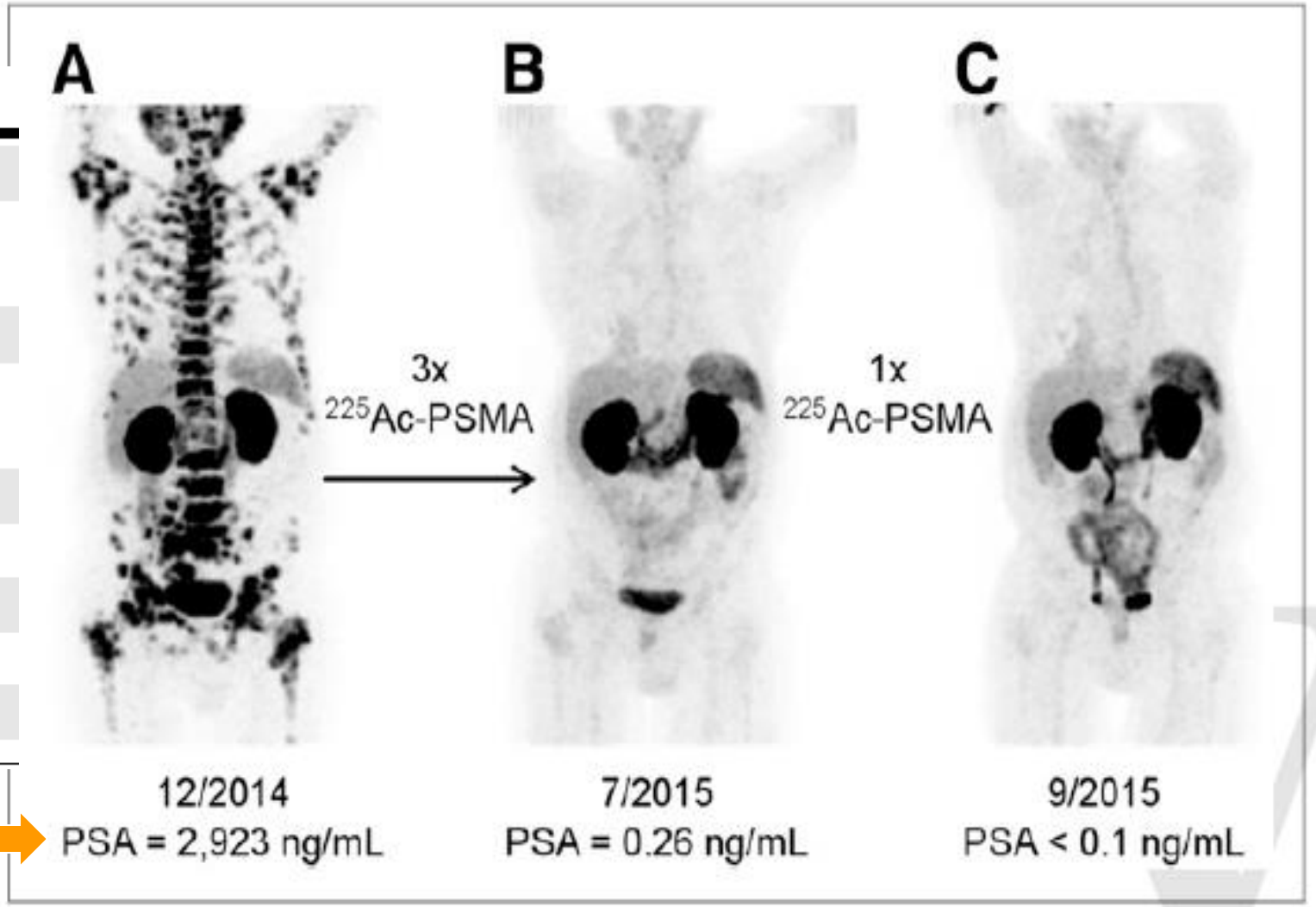
Radionuclide	Chelate	Half life	Total alpha	"Long lived" Intermediate	Final
Terbium-149	DOTA	4.1 hours	1 alpha		Nd-145
Astatine-211	Various	7.2 hours	1 alpha		Pb-207
Bismuth-212	C-DEPA/ DTPA/DO TA	61 minutes	1 alpha 1 beta		Pb-208
Lead-212	TCMC, DOTAM, and more	10.6 hours	1 alpha 2 beta		Pb-208
Bismuth-213	C-DEPA/ DTPA/DO TA	46 minutes	1 alpha 2 beta		Bi-209
Radium-223	None yet	11.4 days	4 alpha 2 beta		Pb-207
Radium-224	None yet	3.6 days	4 alpha	Lead-212	Pb-208
Actinium-225	DOTA Macropa	10.0 days	4 alpha 2 beta	Bismuth-213	Bi-209
Thorium-227	HOPO	18.7 days	5 alpha	Radium-223	Pb-207

Catalytic Images and Selected Data

Radio-conjugates: PSMA targeted alpha emitters (Actinium-225) as 9th line treatment

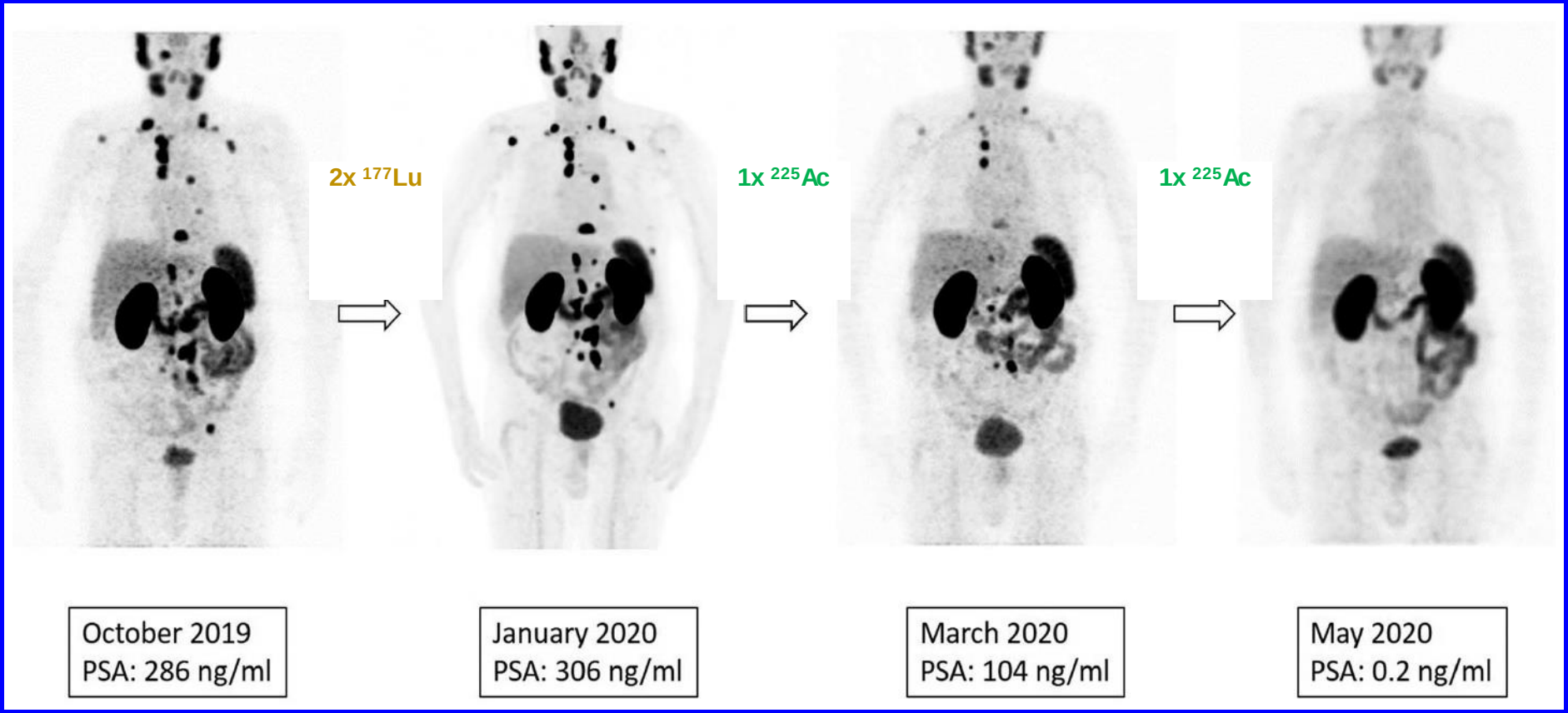
Kratochwil et a. J Nuc Med 57: 1-4, 2016

Patient A
Leuprorelin
Zoledronate
Docetaxel (50 cycles)
Carmustine/epirubicin in hyperthermia
Abiraterone
Enzalutamide
^{223}Ra (6 cycles)
Abiraterone reexposition
Estramustine



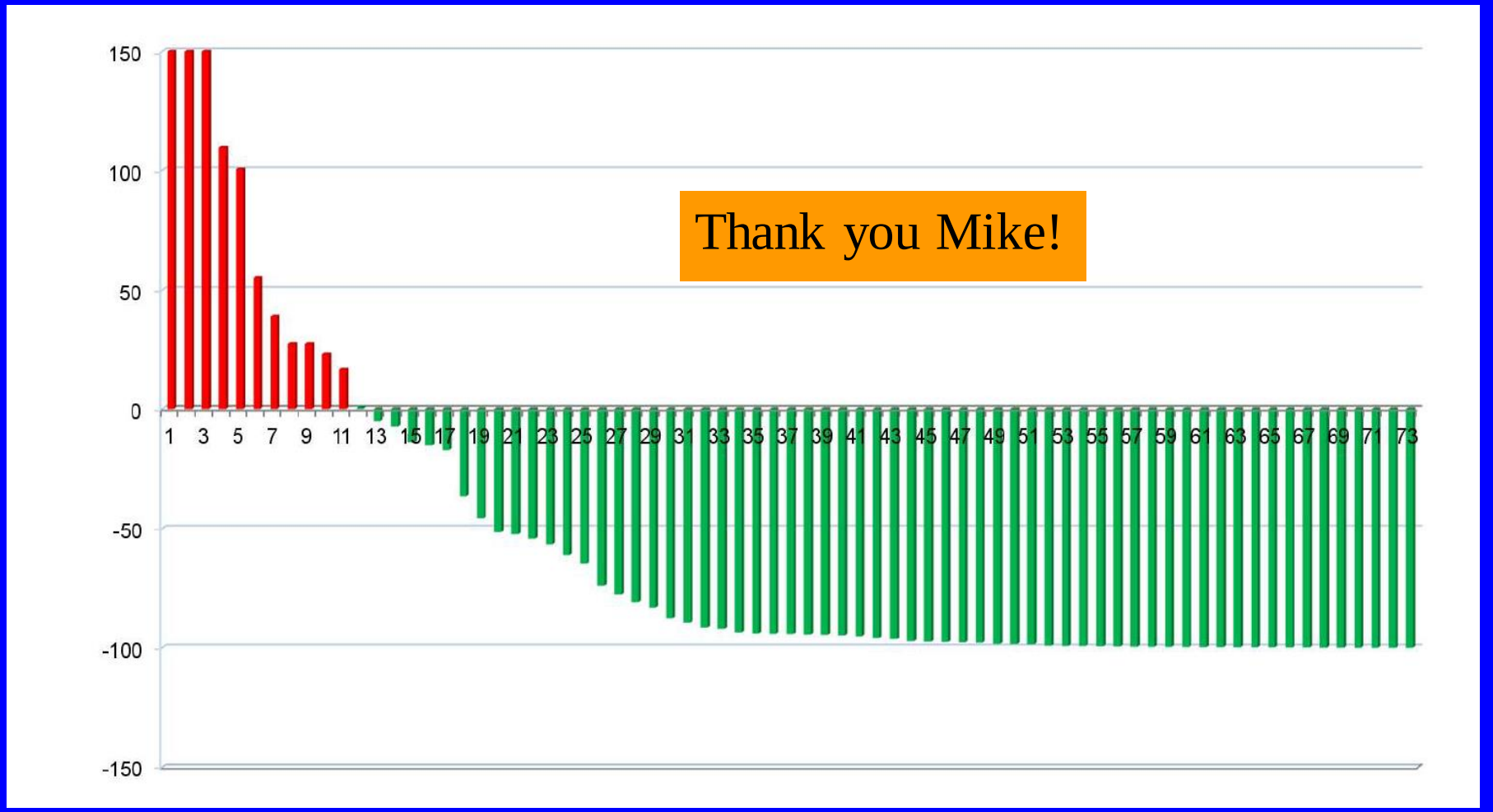
PSMA Ac-225 overcoming resistance to PSMA Lu-177

Sanli et al. (2021) Clin Nucl. Med 46(12):943-95

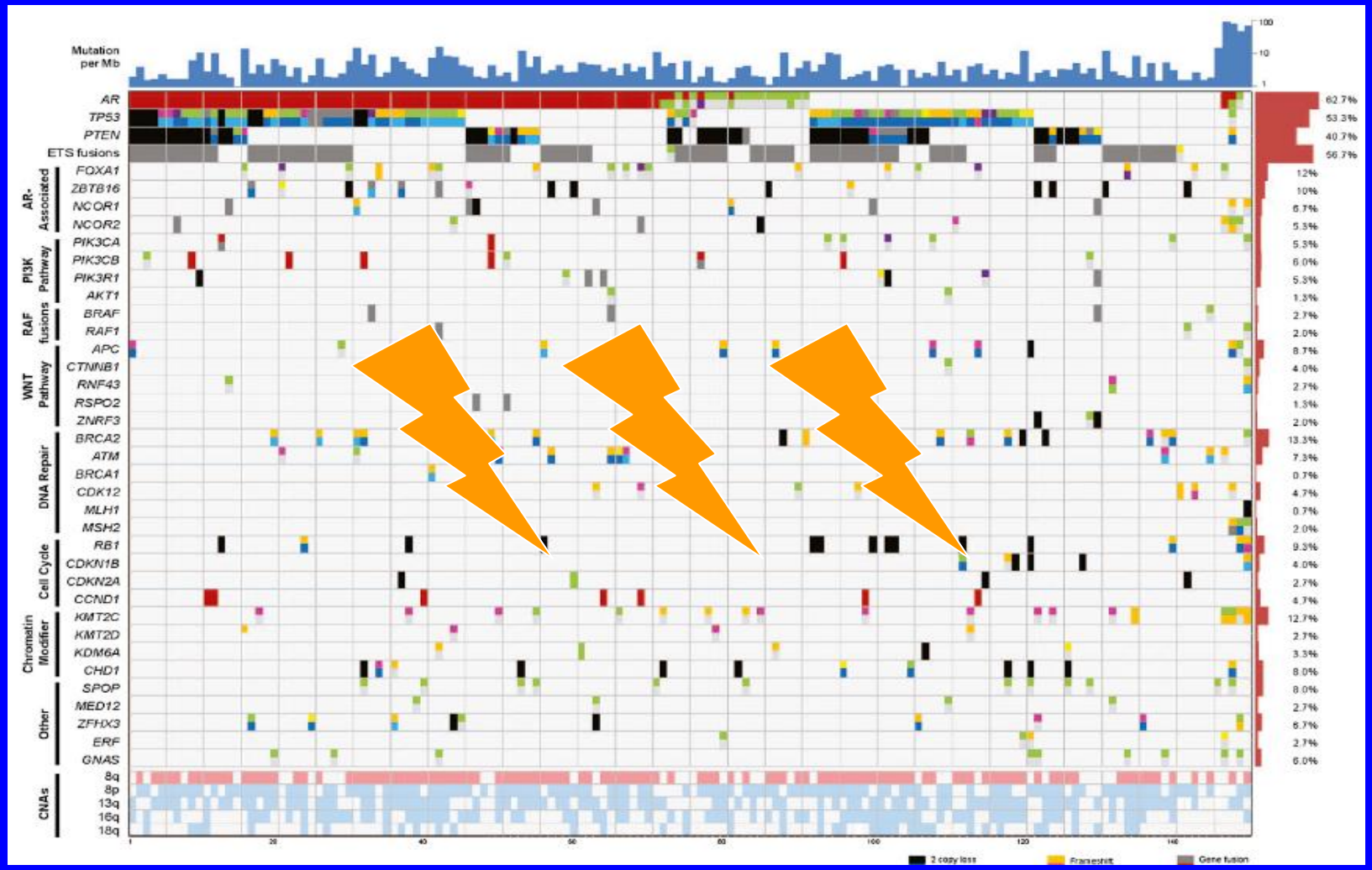


PSA waterfall after PSMA-617 Ac-225 in mCRPC patients without prior Abi/Enza

Sathegke et al. Journal of Nuclear Medicine May 2019, jnumed.119.229229



Challenges: Metastatic prostate cancer is a heterogeneous group of diseases but radiation can kill them all!



Robinson et al. Cell 161:1215, 2015

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