# Noval approaches in mCRPC Immunotherapy and more

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Icons, September 2018, Turkey

# Disclosures

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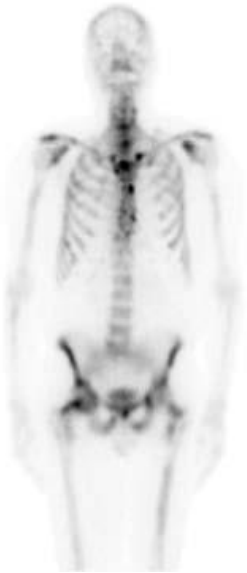
BMS, Astellas. JNJ, Pfizer, Merck, AZ,

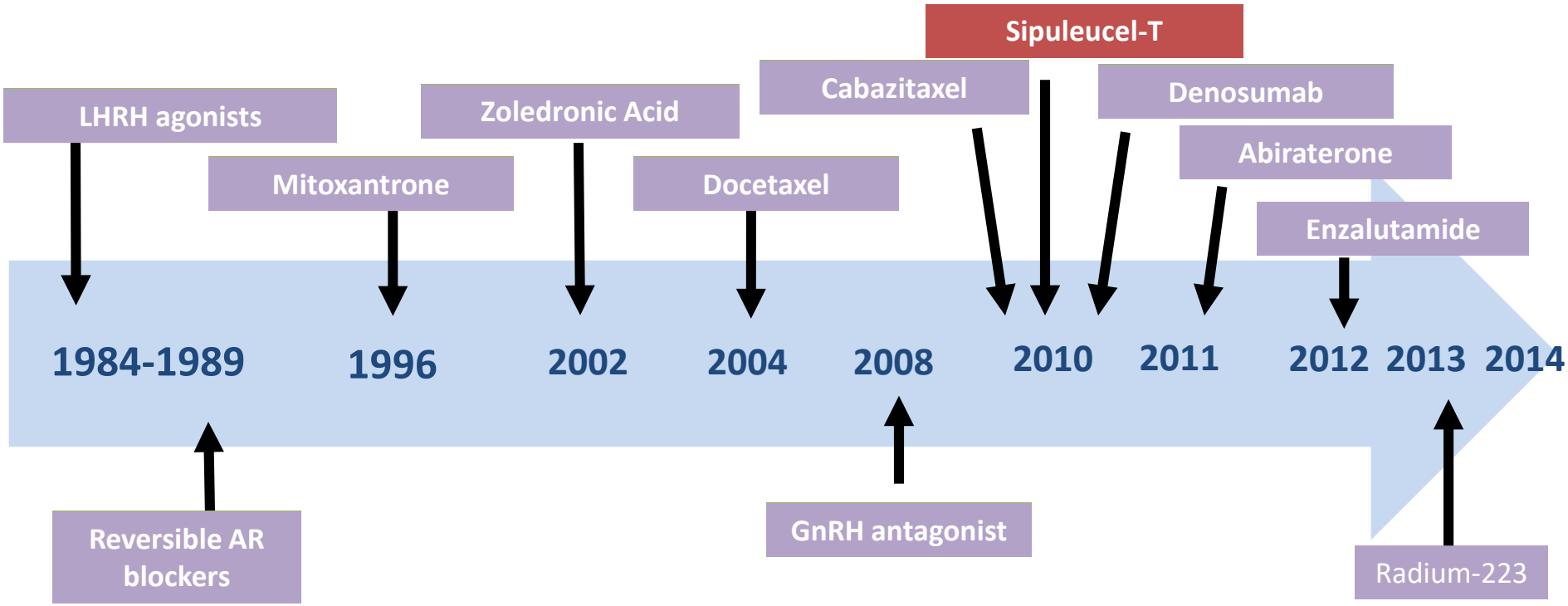
Bayer, Teva, Roche, Novartis.

**Research grant**: Sanofi

# Treatment Options for metastatic prostate cancer



# Approved Therapies mCRPC



# I-0 in Prostate cancer

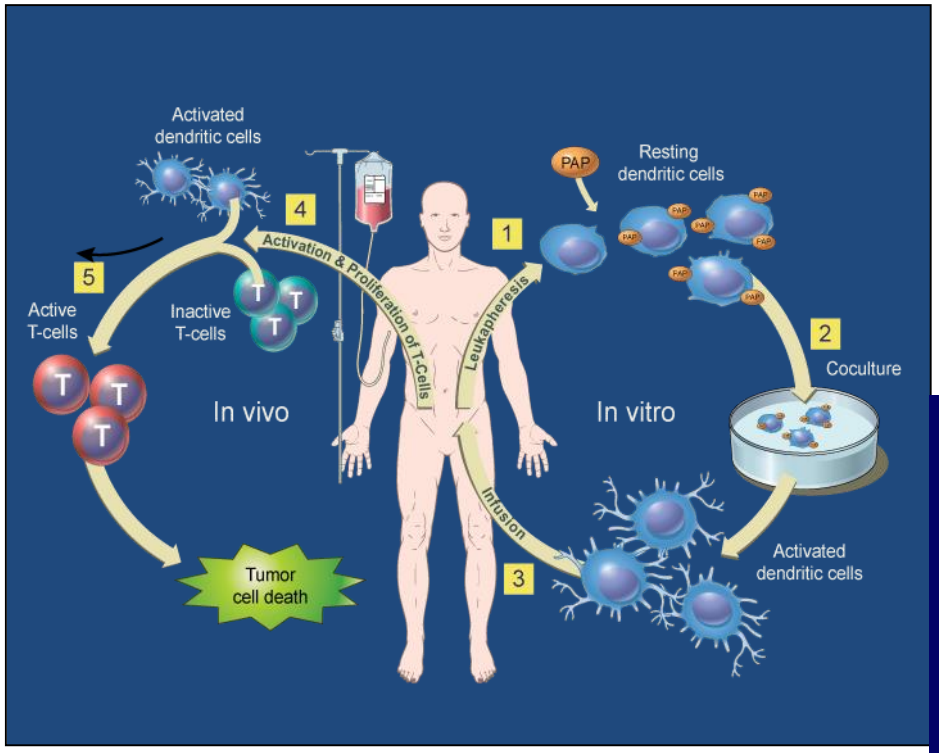
- Recent clinical trials have shown that only 5 -15% of patients with advanced prostate cancer have a favorable response to PD-1 inhibitor treatment [1,2] .
- For responding patients response rates are high.

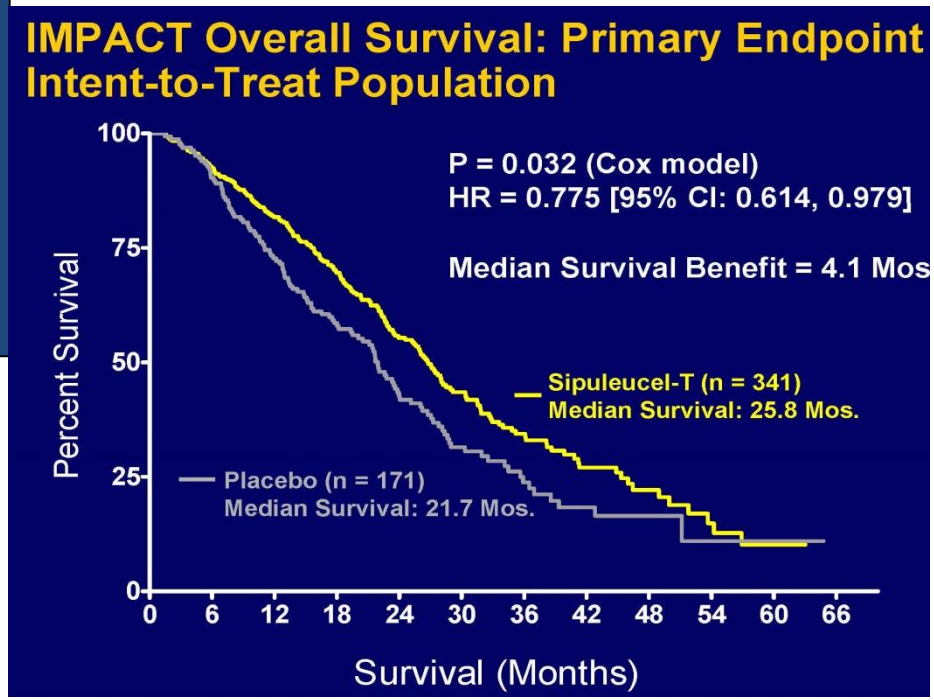
- PCa has a small subclass of patients with dMMR , and represent only 2-5% of all castration resistant prostate cancers.

- This small group of dMMR may represent a subclass that is more responsive to immune checkpoint inhibition.

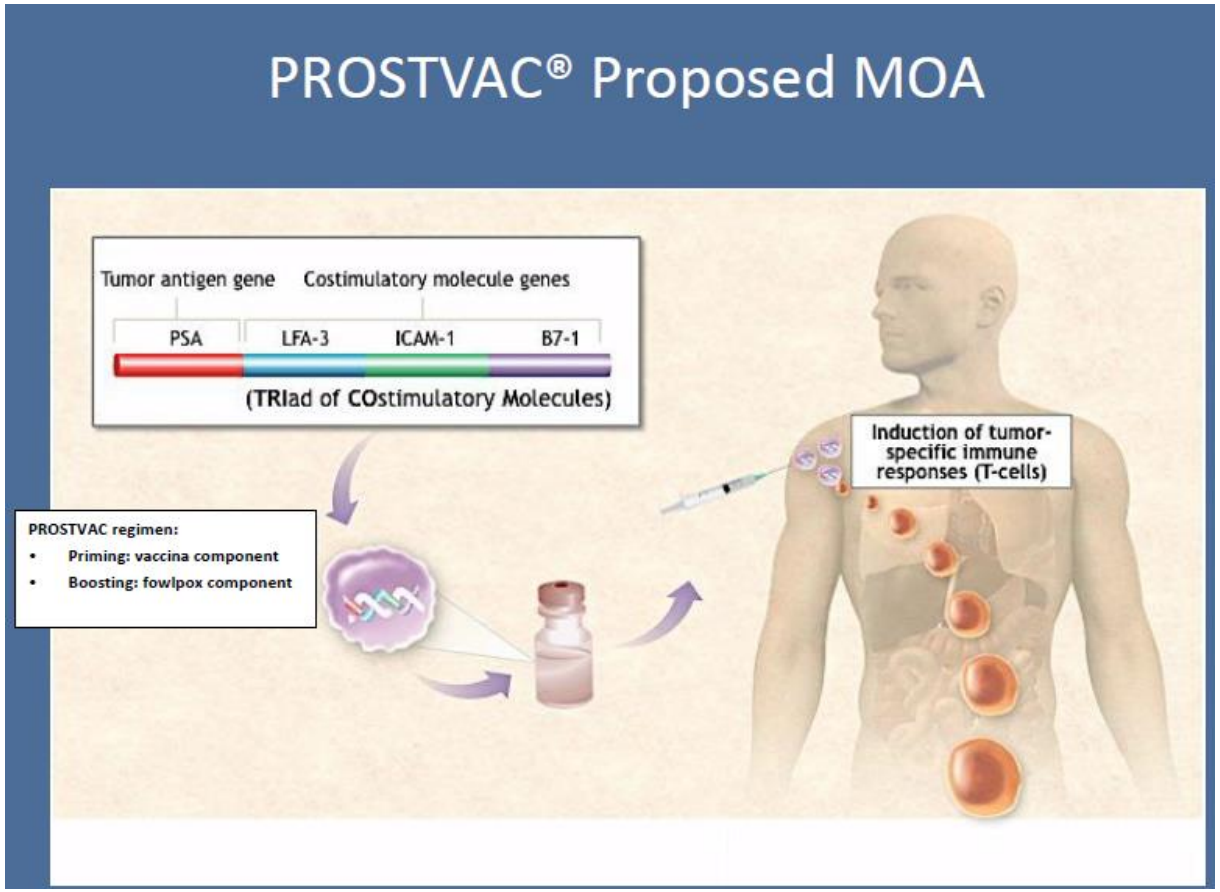
1.De Bono JS, Goh JCH, Ojamaa K, et al. KEYNOTE-199: pembrolizumab for docetaxel-refractory metastatic castration-resistant prostate cancer. J Clin Oncol 2018; 36: Suppl: 5007. abstract.
**2.** Boudadi K, Suzman DL, Anagnostou V, et al. Ipilimumab plus nivolumab and DNA-repair defects in AR-V7-expressing metastatic prostate cancer. Oncotarget 2018; 9: 28561-71

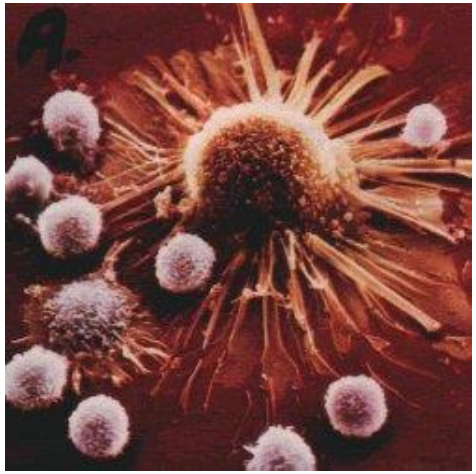
# Sipuleucel-T Immunotherapy in Metastatic CRPC



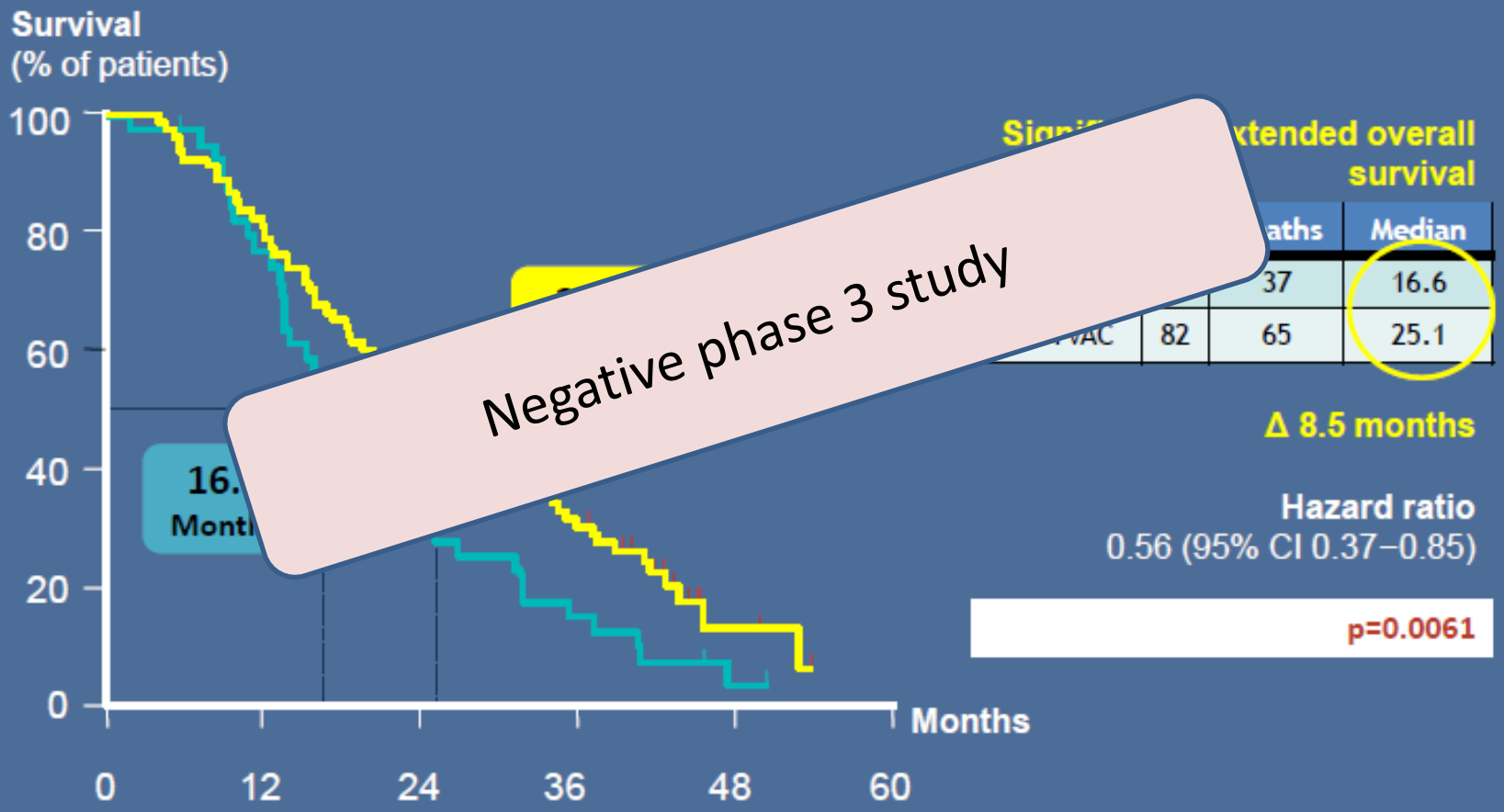



# I-O in PCa


PROSTVAC® Proposed MOA
Tumor antigen gene
Costimulatory molecule genes
PSA
LFA-3
ICAM-1
B7-1
(TRIad of COstimulatory Molecules)
PROSTVAC regimen:
• Priming: vaccina component
• Boosting: fowlpox component
Induction of tumor-specific immune responses (T-cells)



# PROSTVAC® Phase 2 Results




Kantoff et al. *J Clin Oncol*, March 2010

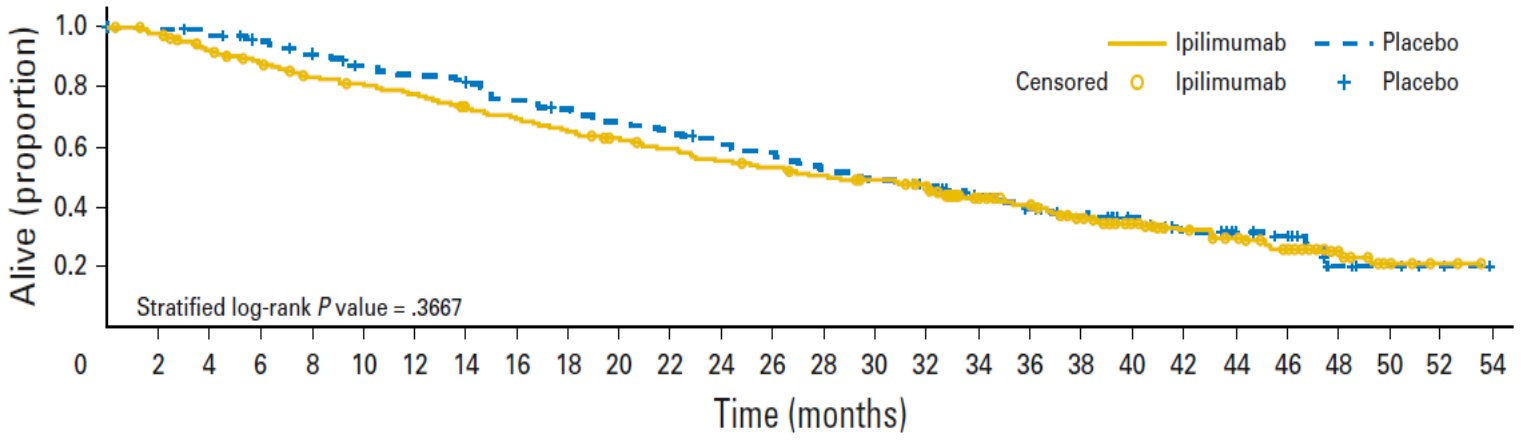
VOLUME 35 · NUMBER 1 · JANUARY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

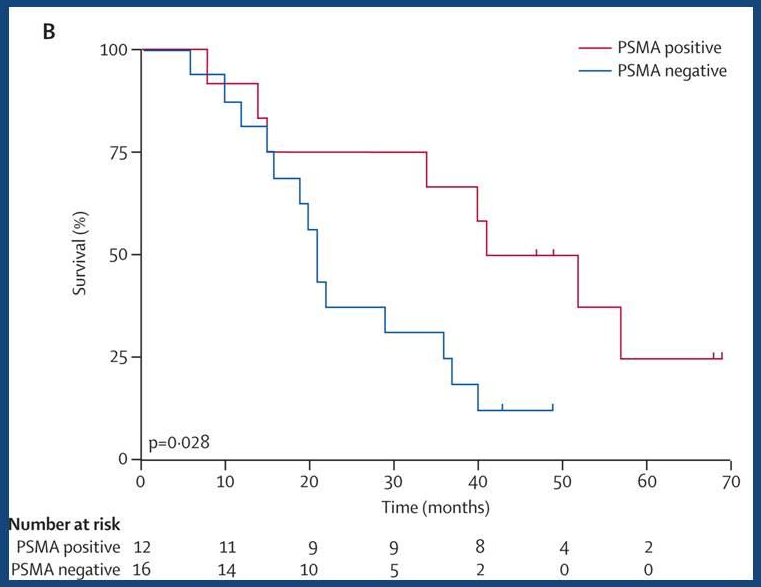
ORIGINAL REPORT

# Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer

*Tomasz M. Beer, Eugene D. Kwon, Charles G. Drake, Karim Fizazi, Christopher Logothetis, Gwenaelle Gravis,*

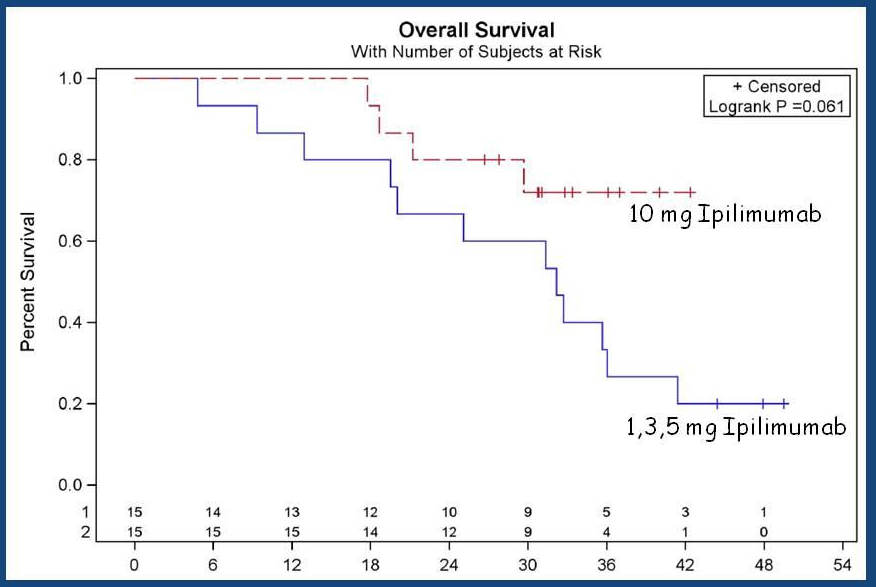


## GVAX + Ipilimumab




*The Lancet Oncology* 2012 13, 509-517

## PROSTVAC + Ipilimumab




*The Lancet Oncology* 2012;13(5):501-8

# Immunotherapy of Castrate Resistant Prostate Cancer

Vaccines:

- Sipuleucel-T: phase III study: 4 months survival benefit
- GVAX: 2 phase III studies: no survival benefit versus docetaxel
- Prostvac: phase III study: no survival benefit versus placebo

Immune Checkpoint Inhibitors:

- Ipilimumab: 2 phase III studies: no survival benefit versus placebo

Conclusions: monotherapy has modest effect, low mutational burden
ICI's has significant clinical benefit in some patients

# mCRPC is geomically heterogeneous disease

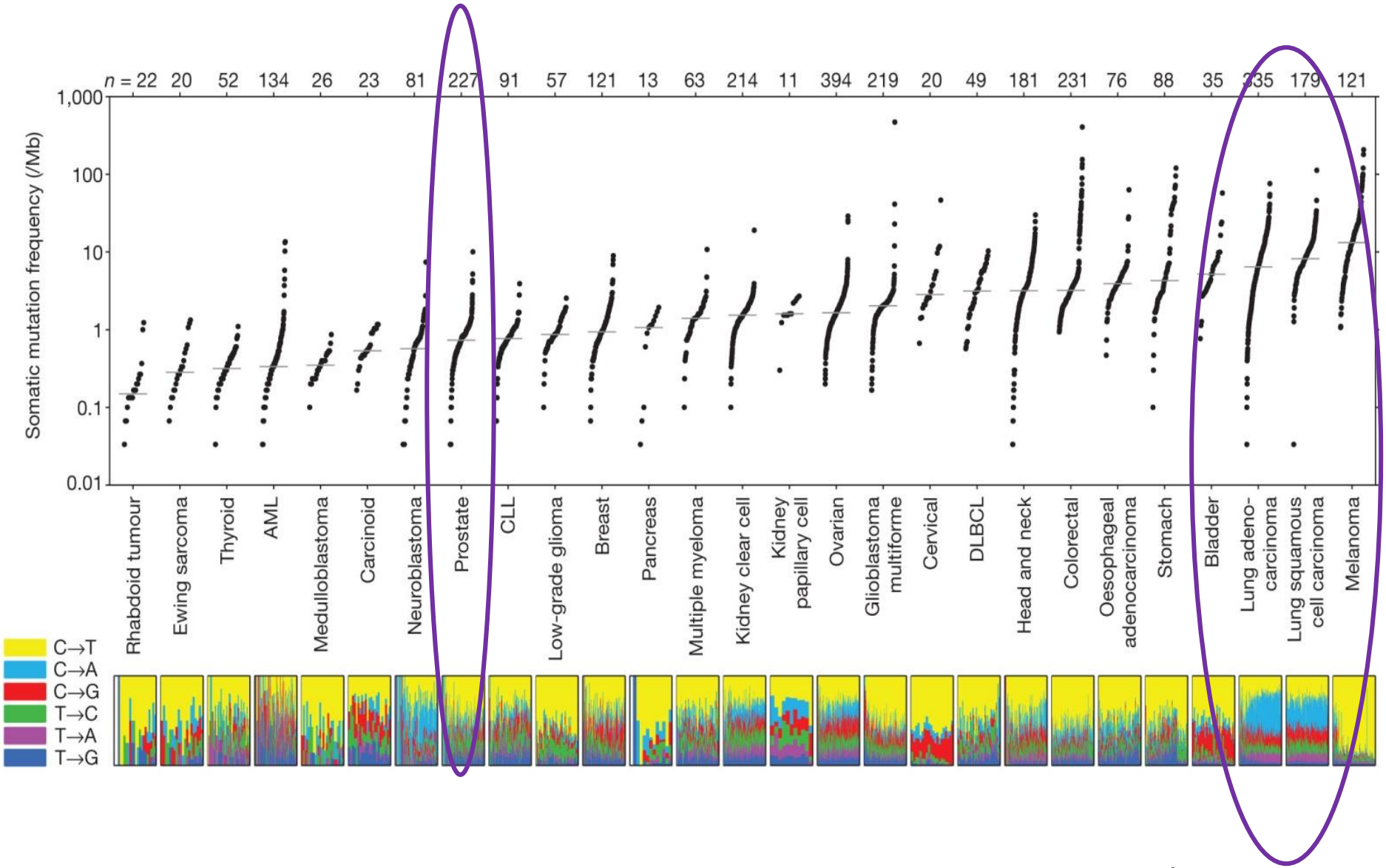
Includes DNA repair defective subtypes:

- **MMR-** variable prevalence has been reported in different APC studies
- **HR repair defects**
- **CDK 12**
- **ATM loss**

- Initial clinical data suggest that 5%–12% of patients with mCRPC may benefit from immune checkpoint blockade [1,2]

1. Graff JN, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. *Oncotarget*. 2016;7(33):52810–52817.
2. Hansen A, et al. Pembrolizumab for patients with advanced prostate adenocarcinoma: Preliminary results from the KEYNOTE-028 study. *Ann Oncol*. 2016;27(6):243–265.

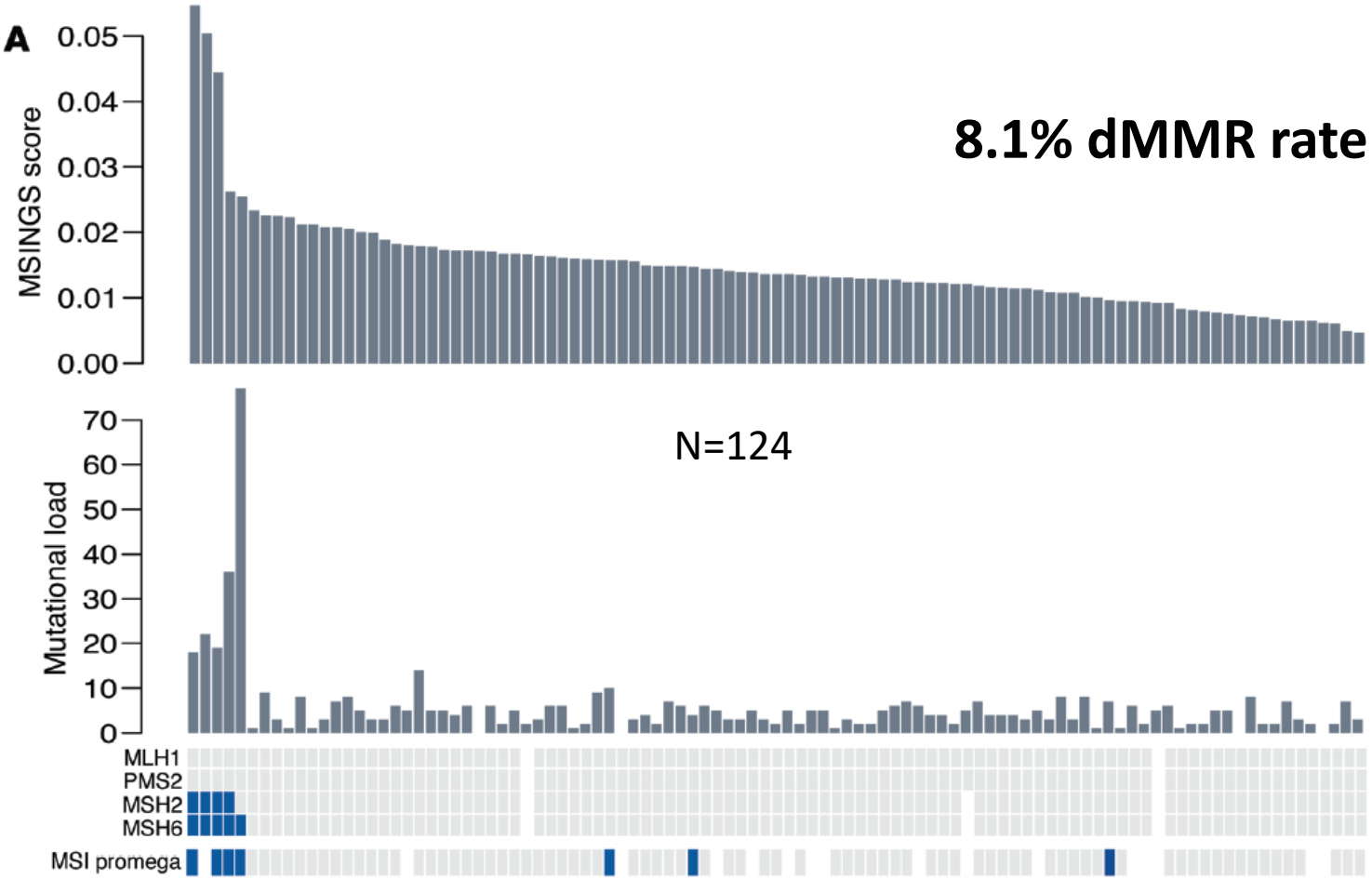
# Somatic mutations by tumor type




MS Lawrence *et al. Nature* **2013**

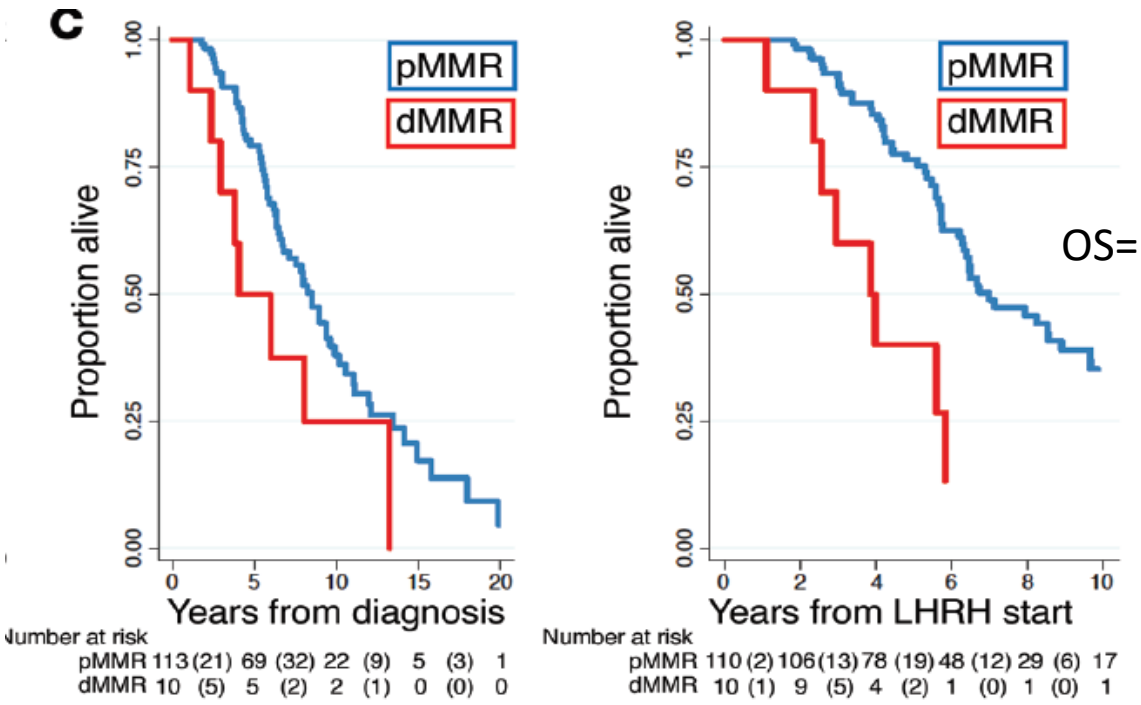
# Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer

Daniel Nava Rodrigues,[1,2] Pasquale Rescigno,[1,2,3] David Liu,[4,5] Wei Yuan,[1] Suzanne Carreira,[1] Maryou B. Lambros,[1] George Seed,[1] ...de Bono




Aug, 2018

# Impact of mismatch DNA repair defects on outcome from prostate cancer




OS= 3.8 vs 7.0 years

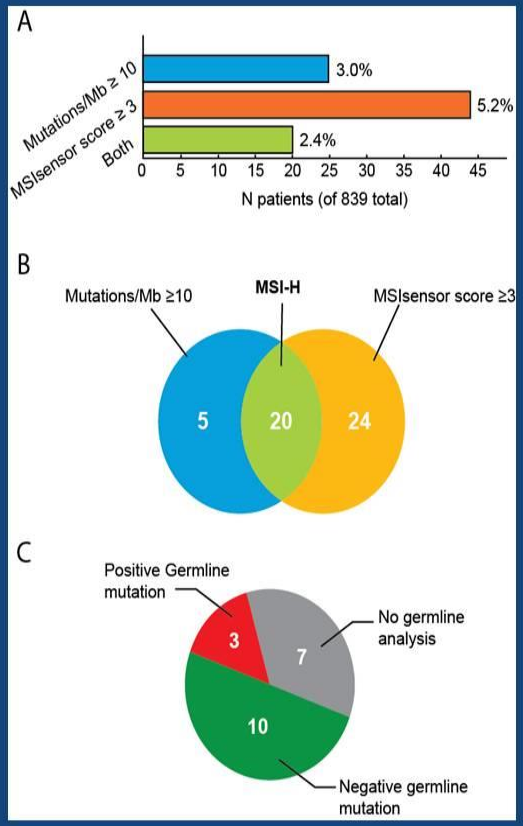
- 56% of the patients had metastatic disease at diagnosis.
- dMMR can be focal in primary disease, but that having dMMR in primary disease strongly associates with developing  MMR CRPC.
- higher likelihood of PD-L1 positivity in dMMR mCRPC
- PD-L1 expression was associated with increased T cell infiltration in mCRPC samples

Rodrigues, de Bono et al, JCI 2018

# Microsatellite instability in prostate cancer and response to immune checkpoint blockade

Wassim Abida*, Michael L. Cheng, Joshua Armenia, Sumit Middha, Karen A. Autio, Dana E. Rathkopf, Michael J. Morris, Daniel Costin Danila, Susan F. Slovin, Emily Carbone, Melanie Hullings, Jaclyn Frances Hechtman, Victor E. Reuter, Michael F. Berger, Philip W. Kantoff, Charles L. Sawyers, Nikolaus Schultz, David B. Solit, Anuradha Gopalan, Howard I. Scher

# Prevalence of MSI-H cases in the 839 patient dataset (MSKCC, New York)



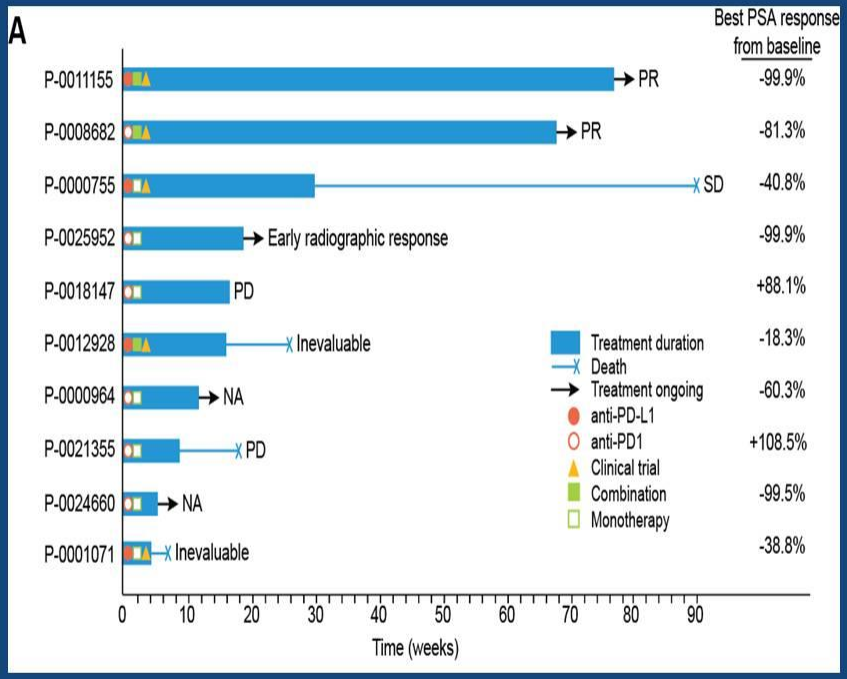

Radboudumc experience (N=124) 7% MSI high (N=9) → 6 pts received nivolumab





Presented By Winald Gerritsen at 2018 ASCO Annual Meeting

## Biochemical Responses, Duration of response (MSKCC data)




10 patients:

5 pts: > 50% PSA decline
7 pts: > 25% PSA decline

3 pts: PD

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

# Cyclin-Dependent Kinase 12, Immunity, and Prostate Cancer

Emmanuel S. Antonarakis, M.D.

- A new molecular subclass of advanced prostate cancers
- Defined by biallelic somatic loss-of-function mutations of the tumor-suppressor gene *CDK12*,which encodes cyclin-dependent kinase 12 .

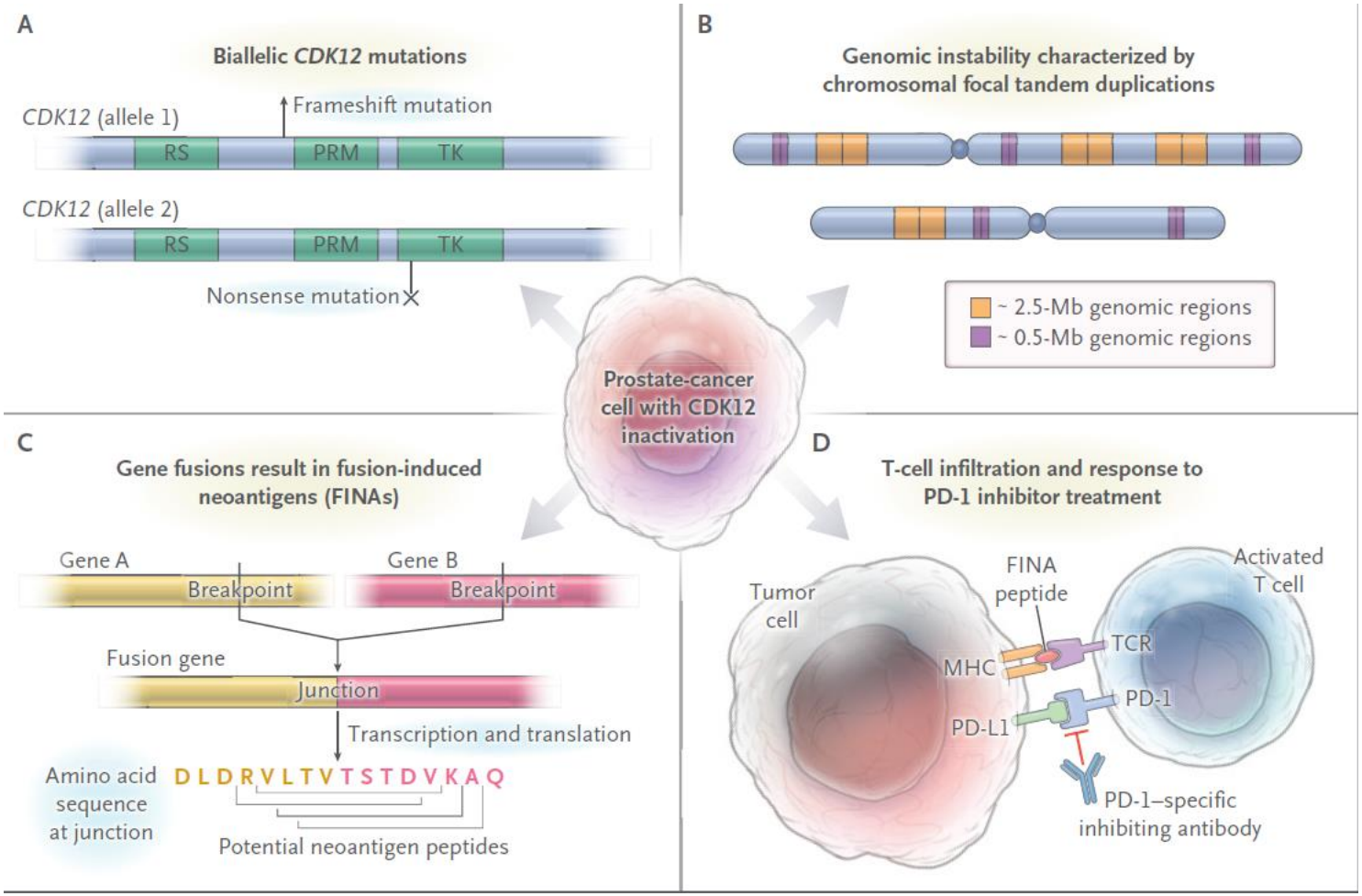
- Biallelic inactivation of *CDK12* was found in 6.9% obtained from patients with metastatic castration-resistant prostate cancer and in only 1.2% in the primary prostate cancers.

Wu YM, Cieślik M, Lonigro RJ, et al. Inactivation of CDK12 delineates a distinct immunogenic class of advanced prostate cancer. Cell 2018; 173(7): 1770-1782.e14.

# Cyclin-Dependent Kinase 12, Immunity, and Prostate Cancer

NEJM Sep, 2018

Emmanuel S. Antonarakis, M.D.




**The neoantigen- prediction methods confirmed a higher level of fusion-induced neoantigens (FINAs) in *CDK12*-variant prostate cancers than in all the other molecular subclasses of prostate cancer.**

# CDK 12 Variant

- *CDK12*-variant tumors had higher overall levels of T-cell infiltration  than all other genomic subtypes of prostate cancer (except those deficient in MSI) and also had increased expression levels of certain chemokines and their receptors.

- Preliminary data from patients with *CDK12*-inactivated advanced Pca suggested impressice response to PDL-1 inhibitors.

- *CDK12*-variant prostate  cancer may become the second genomically defined tumor subtype that may benefit from anti– PD-1 therapy.

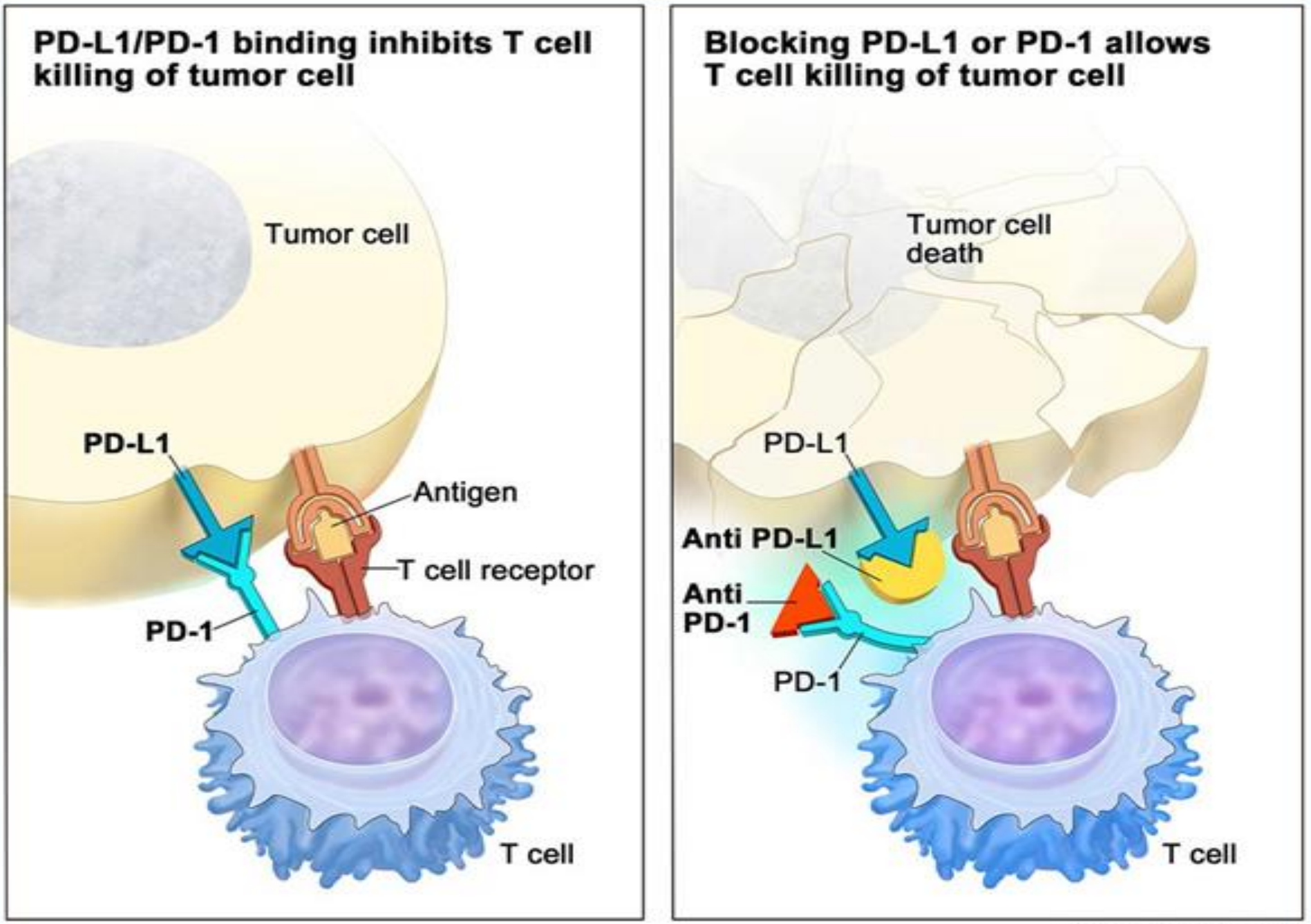
# Future directions with CDK12

- Furthermore, *CDK12* loss*CDK12* alterations in many tumor types, including gastrointestinal, bladder, uterine, and ovarian cancers.

- Because CDK12 mediates DNA repair by means of homologous recombination in addition to replication-associated repair, combination therapy comprising a PD-1 inhibitor and a PARP inhibitor may also be an effective approach in patients with CDK12-deficient cancers.

- In cancers with wildtype *CDK12* status, treatment with a CDK12 inhibitor may induce a sensitivity to immune checkpoint blockade therapy,  generating a new form of synthetic lethality.

Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 2017; 23: 703-13.



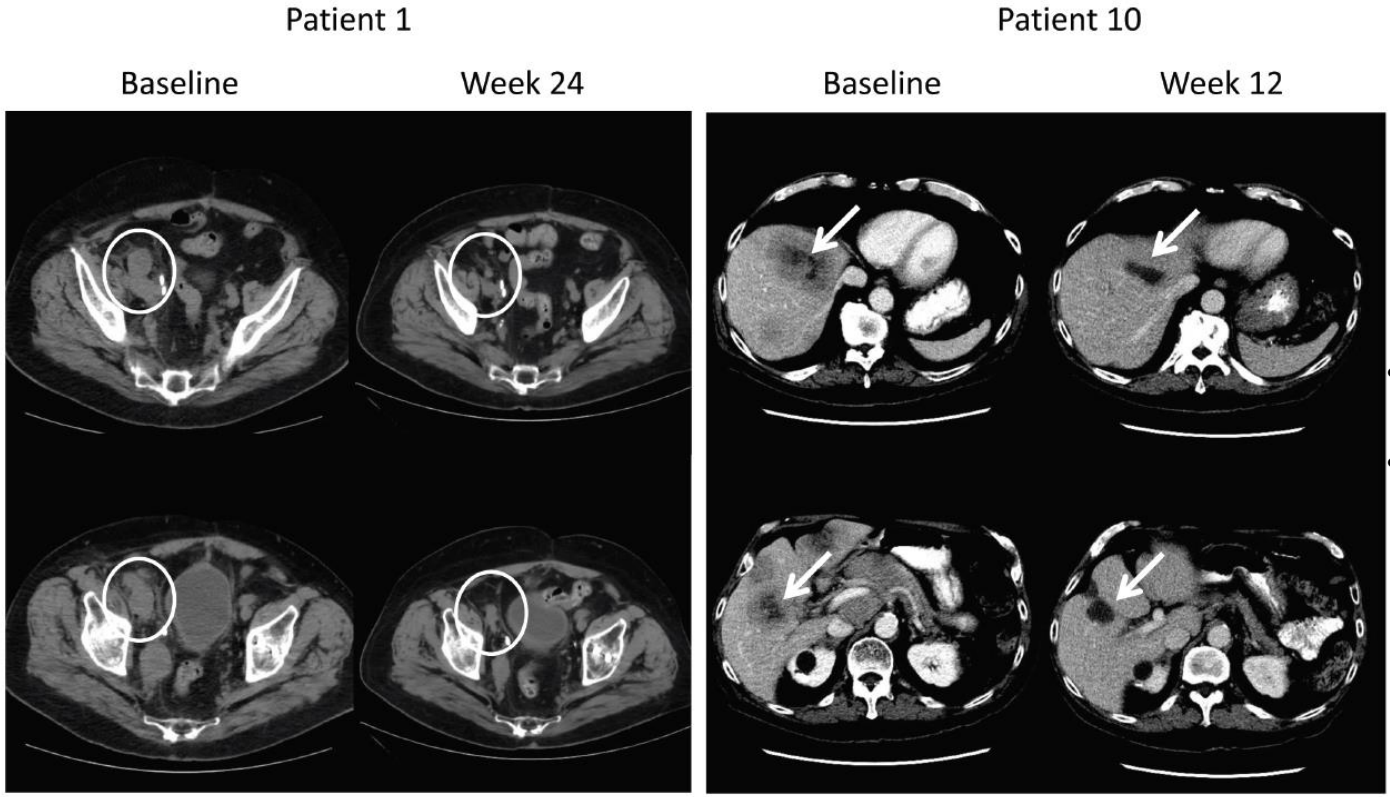
www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 33

Research Paper: Immunology

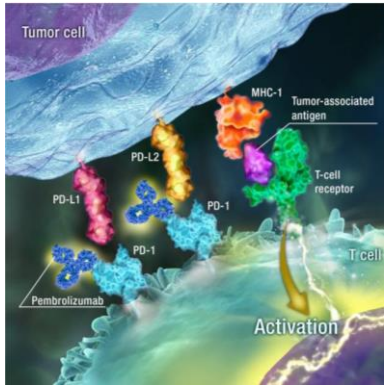
# Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer

Julie N. Graff[1,2], Joshi J. Alumkal[1], Charles G. Drake[3], George V. Thomas[4], William L. Redmond[5], Mohammad Farhad[5,6], Jeremy P. Cetnar[1], Frederick S. Ey[1], Raymond C. Bergan[1], Rachel Slottke[1] and Tomasz M. Beer[1]

*Published*: July 12, 2016




- 3/10 with rapid PSA response
- 1 with MMR



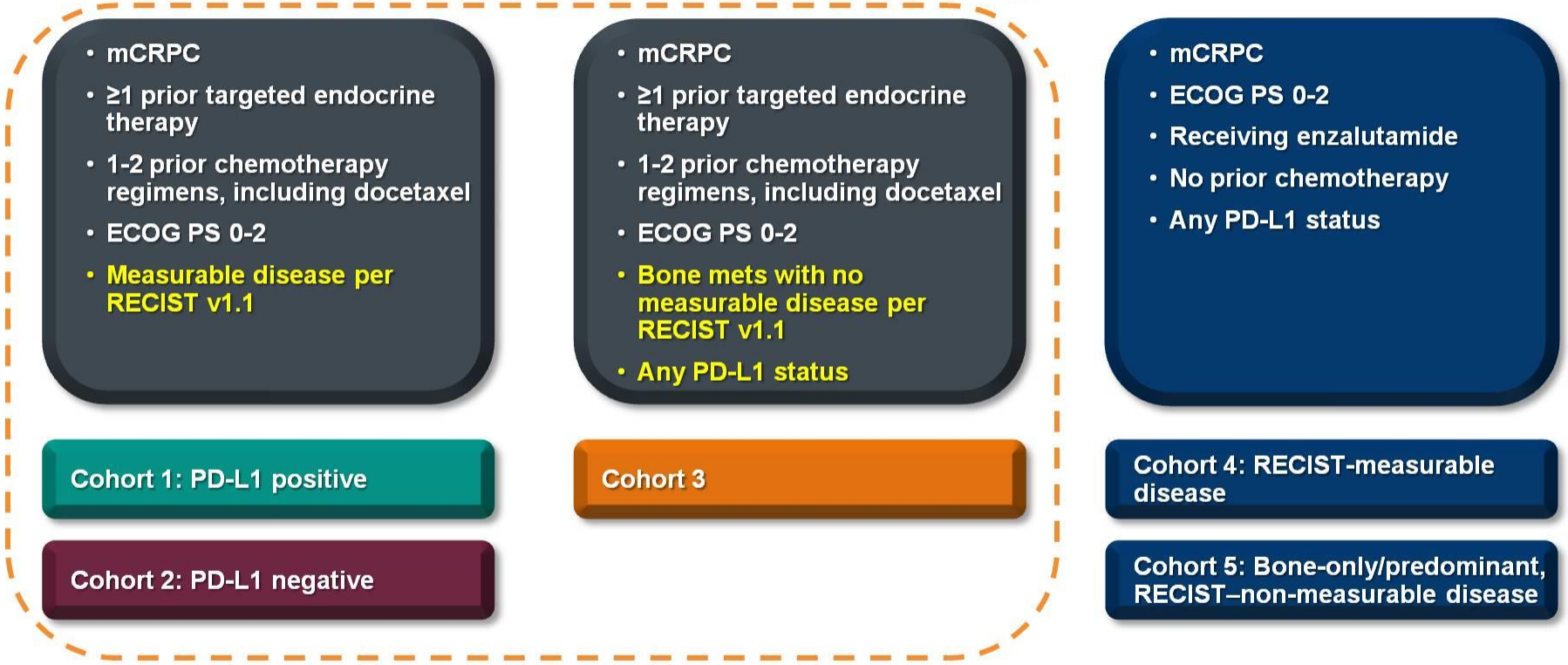

# KEYNOTE-199: Pembrolizumab For Post-Docetaxel Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Johann S. de Bono,[1] Jeffrey Goh,[2] Kristiina Ojamaa,[3] Marine Gross-Goupil,[4] Josep Piulats,[5] Charles G. Drake,[6] Christopher J. Hoimes,[7] Haiyan Wu,[8] Ping Qiu,[9] Christian Poehlein,[9] Emmanuel S. Antonarakis[10]

[1]Royal Marsden and The Institute of Cancer Research, London, UK; [2]Royal Brisbane & Women's Hospital, Herston, and University of Queensland, St. Lucia, QLD, Australia; [3]East Tallinn Central Hospital, Tallinn, Estonia; [4]Institut Bergonié, Bordeaux, France; [5]Instituto Catalan de Oncologia, Hospital Duran i Reynals, Hospitalet de Llobregat, Barcelona, Spain; [6]Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA; [7]Case Western Reserve University Hospitals Seidman Cancer Center, Cleveland, OH, USA; [8]MSD China, Beijing, China; [9]Merck & Co., Inc., Kenilworth, NJ, USA; [10]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

Presented By Johann De Bono at 2018 ASCO Annual Meeting

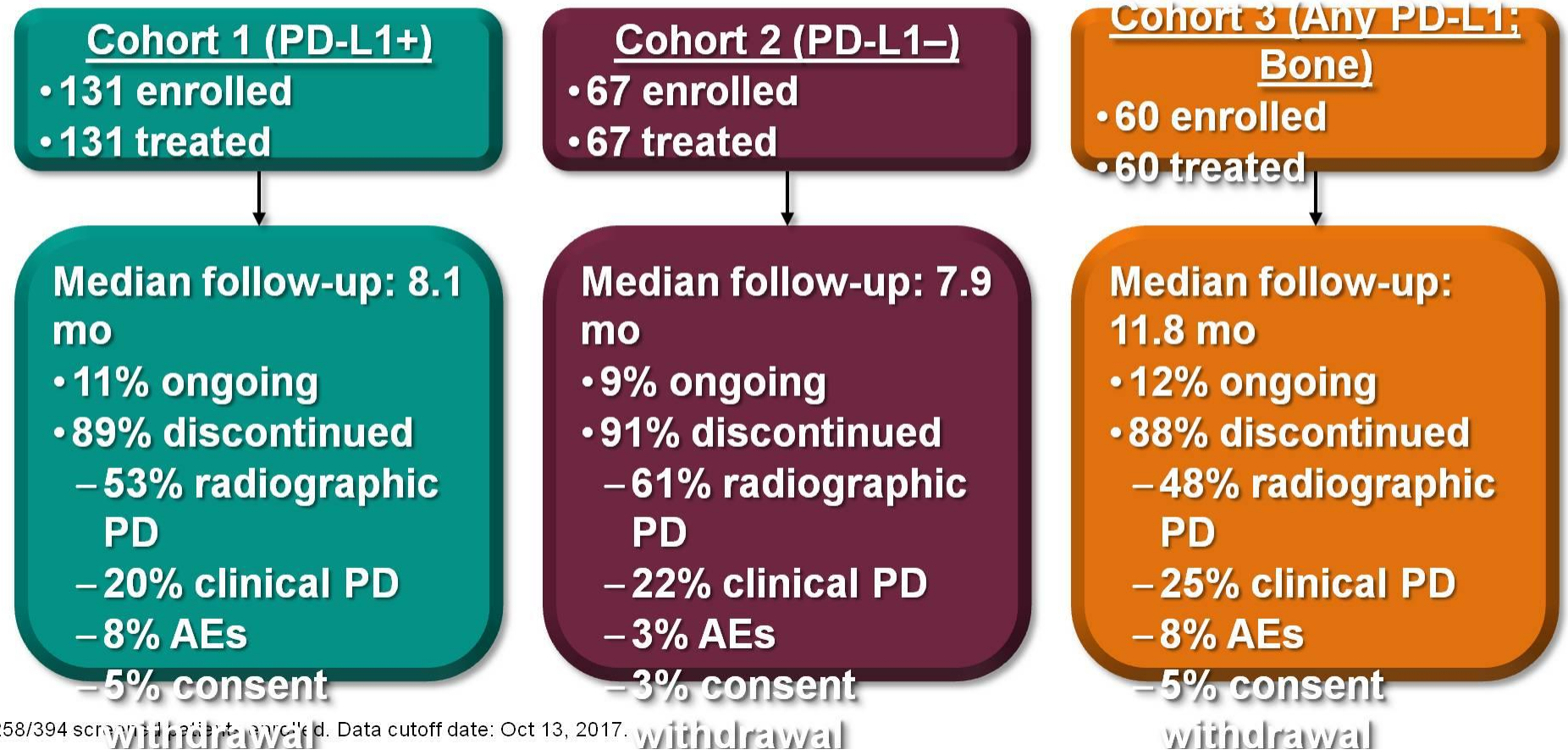
# KEYNOTE-199 Study Design




**Treatment in all cohorts:** pembrolizumab 200 mg Q3W for 35 cycles or until confirmed PD, intolerable toxicity, investigator decision, or patient withdrawal

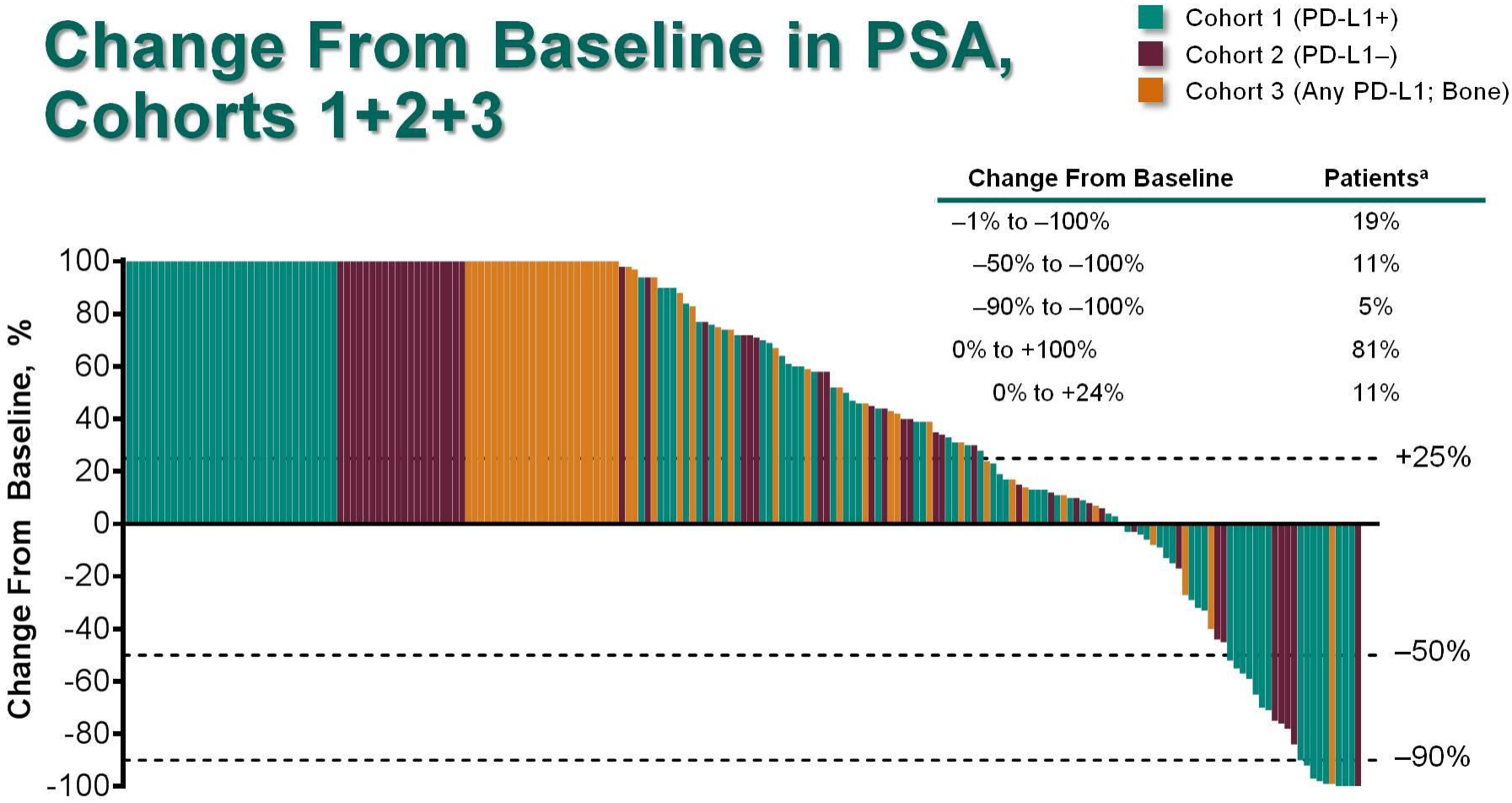
ClinicalTrials.gov, NCT02787005.

# Disposition of Study Treatment




258/394 screened patients enrolled. Data cutoff date: Oct 13, 2017.

# Change From Baseline in PSA, Cohorts 1+2+3




[a]Percentages are calculated out of the **193 patients** who had ≥1 post-baseline PSA assessment.
Data cutoff date: Oct 13, 2017.

# Best Response
## RECIST v1.1, Central Review

| | Cohort 1 N = 131 | Cohort 2 N = 67 | Cohort 3 N = 60 | Cohorts 1+2 N = 198 | Cohorts 1+2+3 N = 258 |
|---|---|---|---|---|---|
| CR | 2 (2%) | 0 | — | 2 (1%) | 2 (<1%) |
| PR | 5 (4%) | 2 (3%) | — | 7 (4%) | 7 (3%) |
| SD (any duration) | 22 (17%) | 14 (21%) | — | 36 (18%) | 36 (14%) |
| SD ≥6 mo | 5 (4%) | 2 (3%) | — | 7 (4%) | 7 (3%) |
| NonCR/NonPD[a] | 0 | 0 | 22 (37%) | 0 | 22 (9%) |
| PD | 76 (58%) | 42 (63%) | 33 (55%) | 118 (60%) | 151 (59%) |
| Not evaluable[b] | 4 (3%) | 1 (1%) | 1 (2%) | 5 (3%) | 6 (2%) |
| Not assessable[c] | 22 (17%) | 8 (12%) | 4 (7%) | 30 (15%) | 34 (13%) |

[a]Patients without disappearance of all existing lesions or development of new lesions. 13 of these patients had nonCR/nonPD for ≥6 months.
[b]Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable for response. [c]Patients without ≥1 post-baseline imaging assessment.
Data cutoff date: Oct 13, 2017.

# Genomic Analysis of Responders: Whole Exome Sequencing

- 6 of 9 responders with available data: 5/7 from cohort 1 (PD-L1+), 1/2 from cohort 2 (PD-L1–)
- **4 of 6 with mutations in DDR genes**: 3/5 from cohort 1 (PD-L1+), 1/1 from cohort 2 (PD-L1–)

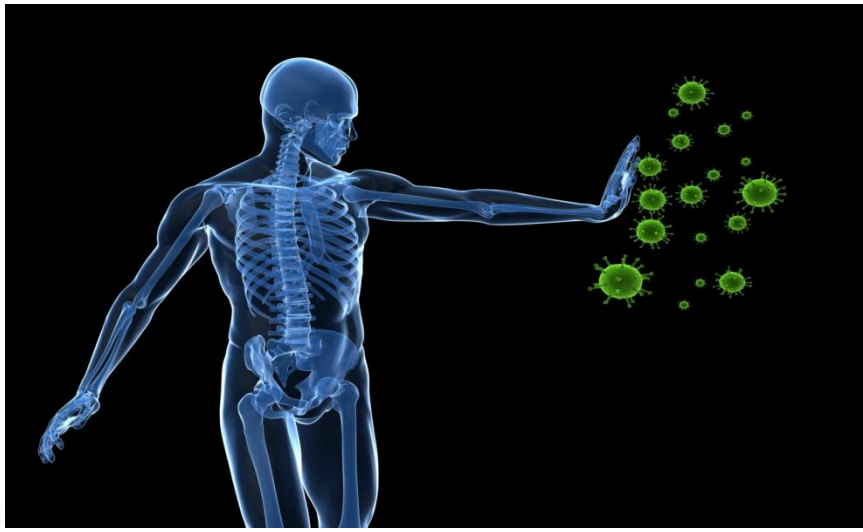
| Patient 1 (Cohort 1) | Patient 2 (Cohort 1) | Patient 3 (Cohort 2) | Patient 4 (Cohort 1) |
|---|---|---|---|
| *ATM* splice site acceptor deletion | *TP53* R273P substitution | *BRCA2* V1176Gfs*8 insertion | *NBN* Q494P substitution |
| *BRCA2* A1162V substitution | | | *TP53* S241F substitution |
| *CDK12* G1461Afs* deletion | | | |
| *FANCA* substitution | | | |
| *FANCD2* R263H substitution | | | |
| *MLH3* T930Qfs*35 deletion | | | |
| *RAD54L* R511H substitution | | | |

DNA damage repair (DDR) genes examined: *ATM*, *ATR*, *BAP1*, *BARD1*, *BLM*, *BRAP*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK12*, *CENPQ*, *CHEK1*, *CHEK2*, *EPCAM1*, *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC6*, *FAM175A*, *FAM175B*, *FANCA*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCL*, *GEN1*, *HDAC2*, *MLH1*, *MLH3*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PIF1*, *PMS2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*, *RDM1*, *TP53*, and *XRCC2*.
Data cutoff date: Oct 13, 2017.

# Response by Presence of Somatic Aberrations in DNA Repair Genes: Cohorts 1+2+3

| | *BRCA1/2* or *ATM* 19/153 | Other DDR Genes[a] 10/153 | Negative 124/153 |
|---|---|---|---|
| RECIST v1.1 | | | |
| ORR | 2 (11%)[b] | 0 | 4 (3%) |
| DCR (any duration) | 4 (22%) | 0 | 22 (18%) |
| CR | 0 | 0 | 2 (2%) |
| PR | 2 (11%) | 0 | 2 (2%) |
| SD (any duration) | 2 (11%) | 2 (20%) | 18 (15%) |
| NonCR/nonPD | 1 (5%) | 0 | 7 (6%) |
| PD | 12 (63%) | 5 (50%) | 80 (65%) |
| NE or missing | 2 (11%) | 3 (30%) | 15 (12%) |
| PSA responders | 2 (11%) | 1 (10%) | 4 (3%) |

[a]*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51C*, *RAD51B*, *RAD51D*, and *RAD54L*. [b]1 patient each from cohorts 1 and 2.
Presence of somatic alterations in DNA repair genes was derived from whole exome sequencing. Data cutoff date: Oct 13, 2017.



## Summary and Conclusions

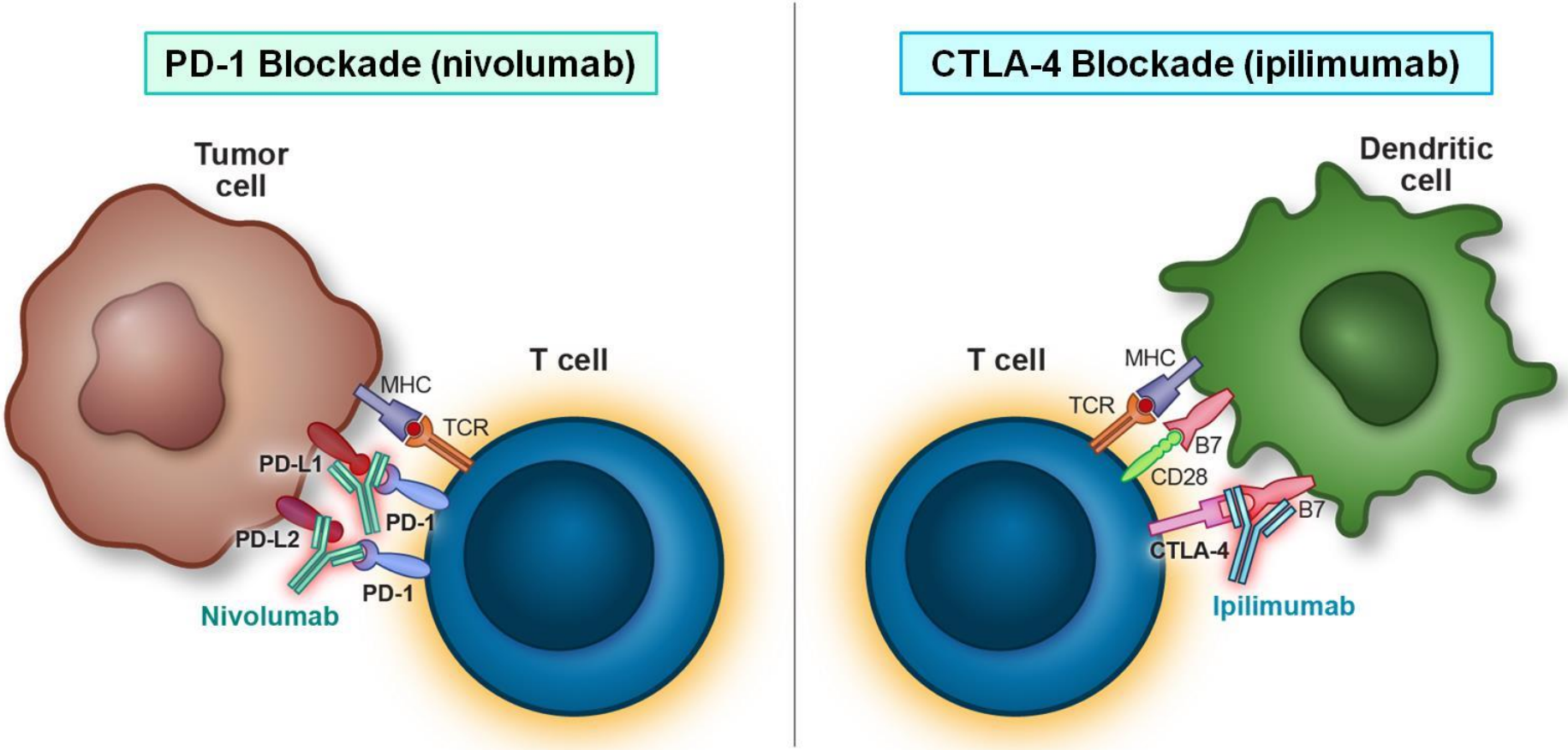
- Pembrolizumab has antitumor activity and acceptable safety in patients with mCRPC treated with docetaxel
  - Activity observed in PD-L1–positive and PD-L1–negative cohorts
  - Activity observed in patients with RECIST-measurable disease and in those with bone-predominant disease
- Biomarker work ongoing, but suggests that DNA repair defects may be associated with antitumor activity
  - Low number of responses overall makes interpretation difficult
- Further evaluation of pembrolizumab as monotherapy and as part of combination therapy is ongoing

# Combination therapy

**Overview of immunotherapy of prostate cancer: combination therapy**

| Anti-PD-1/ anti-PDL-1 | combined with | remarks |
|---|---|---|
| nivolumab | vaccines | |
| nivolumab | ipilimumab | Neoantigen DNA vaccine, Prostvac, Biomarker driven, Immunogenic signature |
| pembrolizumab | vaccines (DNA) | |
| pembrolizumab | activated T-cells | HER2Bi-armed |
| pembrolizumab | enzalutamide/olaparib | |
| atezolizumab | Sipuleucel-T | |
| Durvalumab | Tremulimumab | |
| Regn2810 | Ipilimumab (intraprostatic) | + stereotactic RT |

# Nivolumab plus Ipilimumab Mechanism of Action



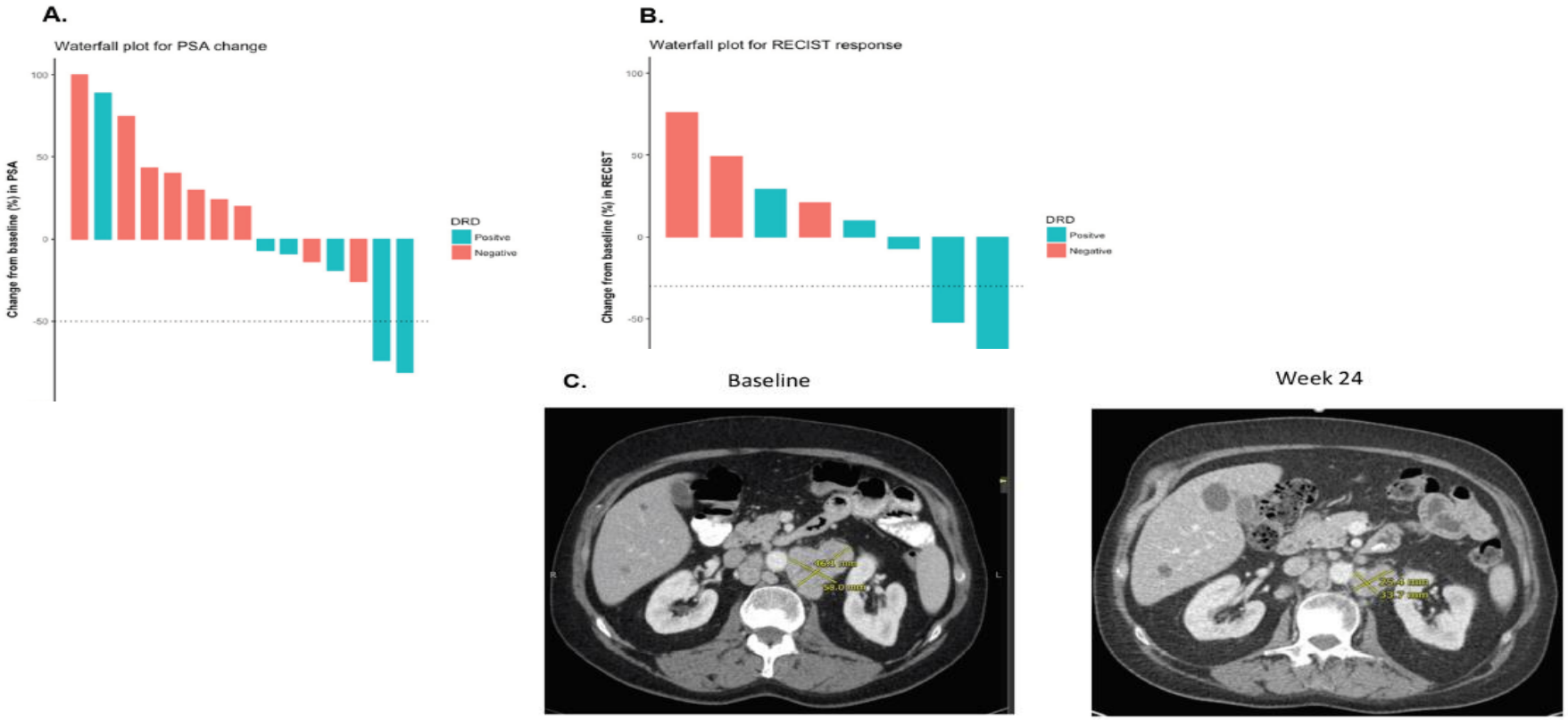

Sznol M, et al. *J Clin Oncol*. 2013;31. Abstract CRA9006.[61]
Motzer RJ. ESMO 2014.[64]

www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 47), pp: 28561-28571

Research Paper

# Ipilimumab plus nivolumab and DNA-repair defects in AR-V7-expressing metastatic prostate cancer

Karim Boudadi[1], Daniel L. Suzman[4], Valsamo Anagnostou[1], Wei Fu[1], Brandon Luber[1], Hao Wang[1], Noushin Niknafs[1], James R. White[1], John L. Silberstein[3], Rana Sullivan[1], Donna Dowling[1], Rana Harb[1], Thomas R. Nirschl[1], Brendan A. Veeneman[5,9], Scott A. Tomlins[5,6], Yipeng Wang[7], Adam Jendrisak[7], Ryon P. Graf[7], Ryan Dittamore[7], Michael A. Carducci[1], Mario A. Eisenberger[1], Michael C. Haffner[2], Alan K. Meeker[2], James R. Eshleman[2], Jun Luo[3], Victor E. Velculescu[1], Charles G. Drake[8] and Emmanuel S. Antonarakis[1,3]



# Ipi+Nivo demonstrated encouraging efficacy in AR-V7 + PCa with DRD mutations, but not in the overall study population

**Table 2: Summary of DNA-repair deficiency (DRD) status among the 15 patients treated with ipilimumab plus nivolumab**

| Patient no. | DRD status | DNA-repair gene | Pathogenic DNA-repair mutations | Germline vs. somatic | Loss of heterozygosity (LOH) | MSI markers shifted | Mutational load (muts/Mb) | Source of tumor DNA |
|---|---|---|---|---|---|---|---|---|
| 1 | – | - | - | - | - | N/A | 1.1 | Plasma |
| 2 | – | - | - | - | - | N/A | 2.4 | Prostate |
| 3 | + | *BRCA2* | E1646Qfs*23 | Germline | No | 0/5 | 1.6 | Liver mass |
| 4 | + | *BRCA2*<br>*MSH6* | P3189H<br>E192X | Somatic<br>Somatic | Yes<br>No | 0/5 | 7.8 | Lymph node |
| 5 | – | - | - | - | - | N/A | 3.1 | Plasma |
| 6 | + | *ATM* | D2708N | Somatic | No | 0/5 | 1.6 | Lymph node |
| 7 | – | - | - | - | - | 0/5 | 1.4 | Epidural mass |
| 8 | + | *BRCA2*<br>*FANCM* | D3095E<br>R579H | Germline<br>Somatic | Yes<br>No | 0/5 | 0.8 | Prostate |
| 9 | + | *ATM* | E2039X | Somatic | No | 0/5 | 1.1 | Plasma |
| 10 | – | - | - | - | - | N/A | 1.1 | Plasma |
| 11 | – | - | - | - | - | 0/5 | 1.3 | Prostate |
| 12 | – | - | - | - | - | 0/5 | 0.8 | Prostate |
| 13 | – | - | - | - | - | 0/5 | 1.3 | Lymph node |
| 14 | + | *ERCC4* | D762V | Somatic | No | 0/5 | 5.6 | Lymph node |
| 15 | – | - | - | - | - | 0/5 | 1.8 | Liver mass |

# Future directions:

**TPS3126**

## An Open-Label, Phase II Study of Nivolumab in Combination With Either Rucaparib, Docetaxel, or Enzalutamide in Men With Castration-Resistant Metastatic Prostate Cancer (CheckMate 9KD)

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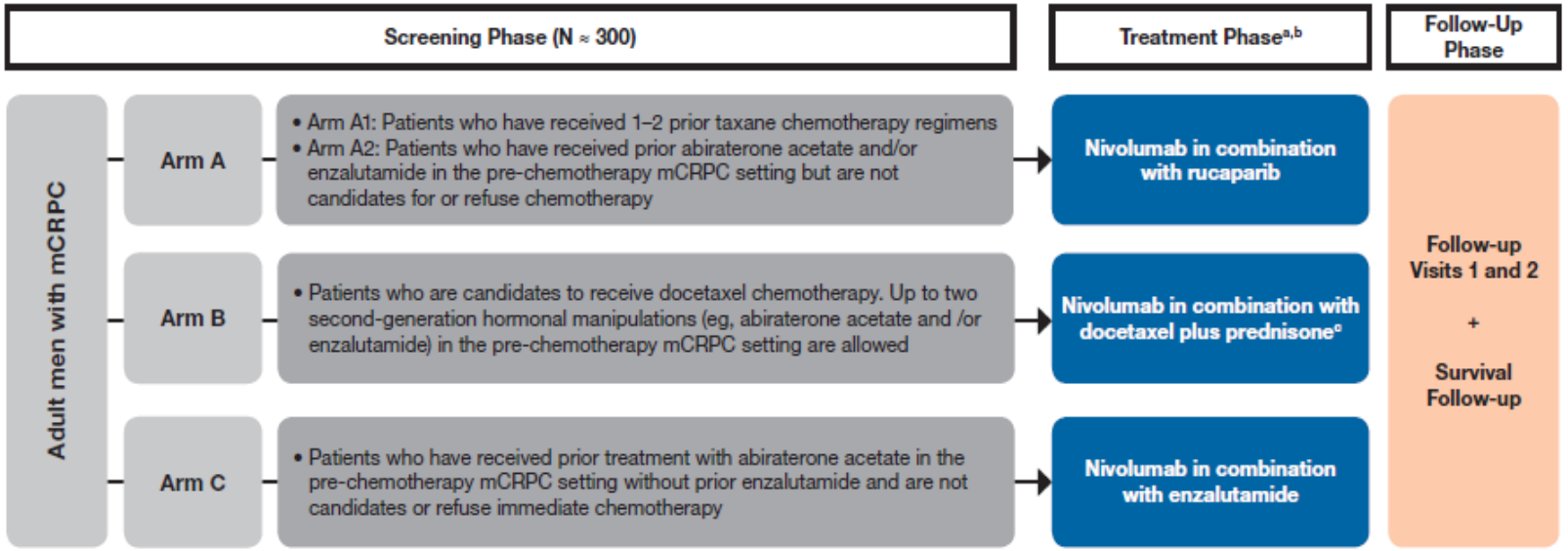



[a]Nivolumab will be given for up to 2 years. Rucaparib or enzalutamide administration will continue until progression
[b]Dose delays for all four investigational products are permitted for toxicity and other protocol-specified criteria. Dose reductions are permitted for rucaparib, docetaxel, and enzalutamide, but not for nivolumab
[c]Docetaxel is given up to a maximum of 10 cycles. Nivolumab will be administered as monotherapy after cycle 10

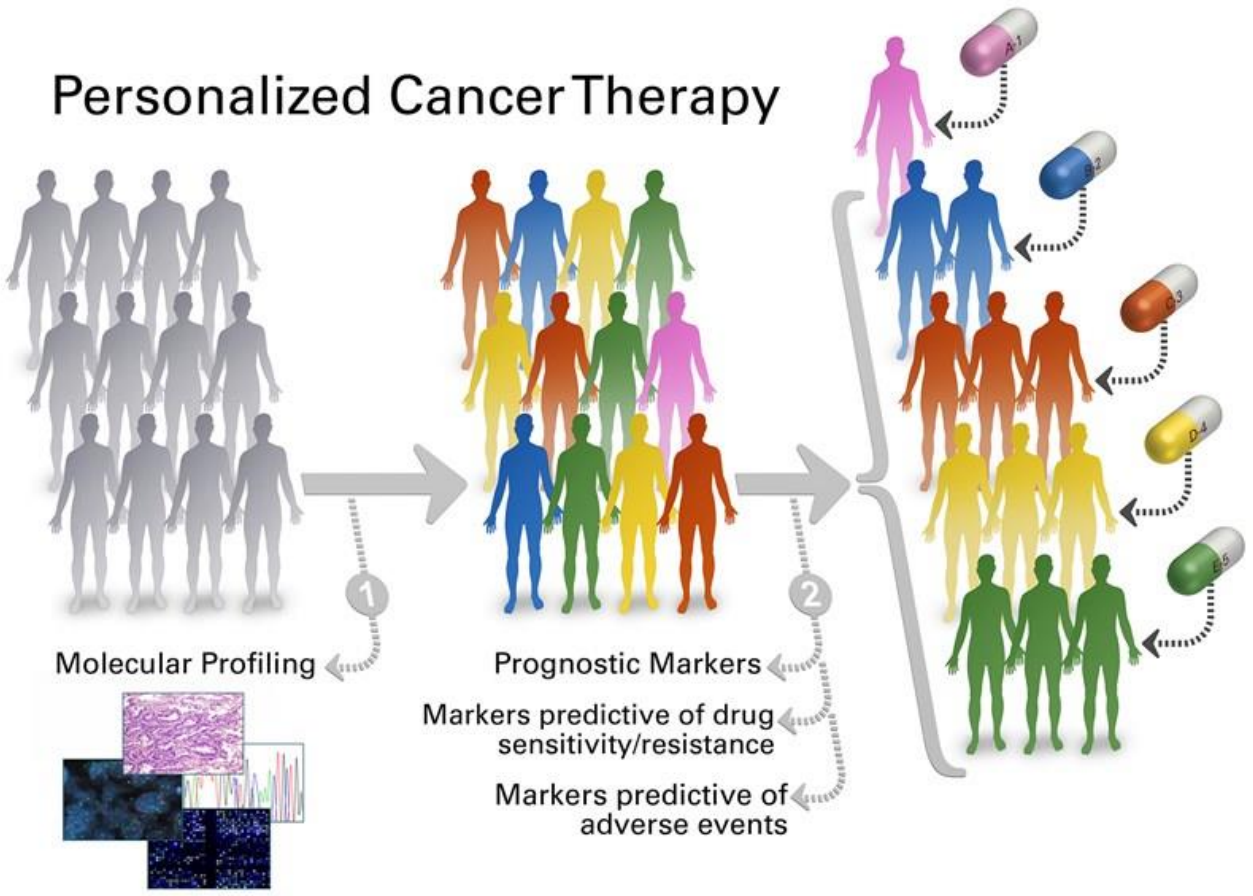
# JNJ study

Niraparib capsule is taken daily orally. There is no known food effect.

JNJ-283 is IV q 4 week. It is mixed in NS, takes 50-70 min to infuse. No pre-medication needed unless IRR (protocol section 6.2.2.2).
Frequent vitals taken during infusion (refer to protocol section 6.1.1 for details)

# Immunotherapy For All?

# Conclusion:




**Sensitivity to ICI may be extended beyond MSI-H patients to other type of DNA –repair alterations, particularly HRD mutations.**

Thank you!