Immunotherapy for Prostate Cancer

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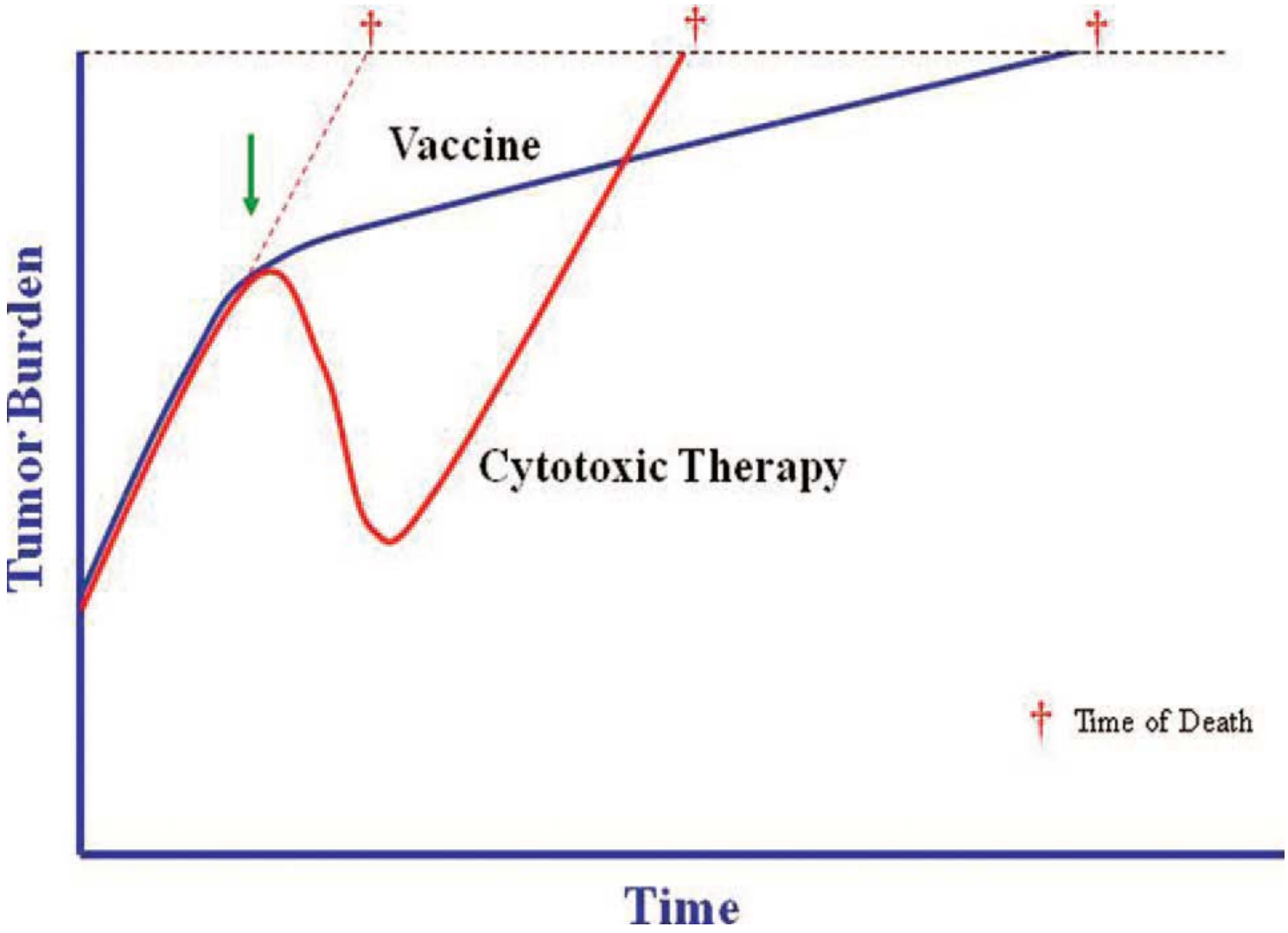
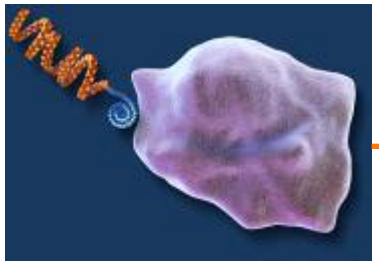
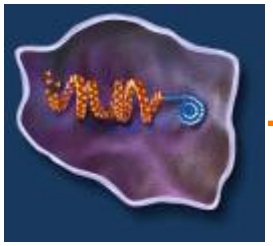


Maddan, et al. *The Oncologist.* 2010.

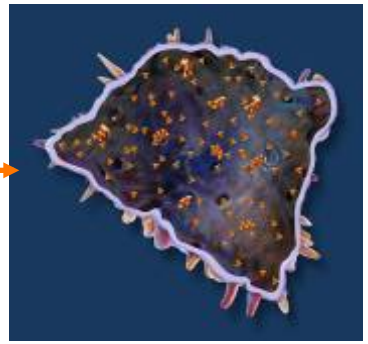
Sipuleucel-T: Autologous APC Cultured with PAP-cytokine Fusion Protein



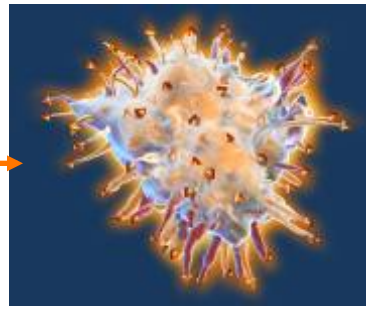
Recombinant Prostatic Acid Phosphatase (PAP) antigen combines with resting antigen presenting cell (APC)



APC takes up the antigen

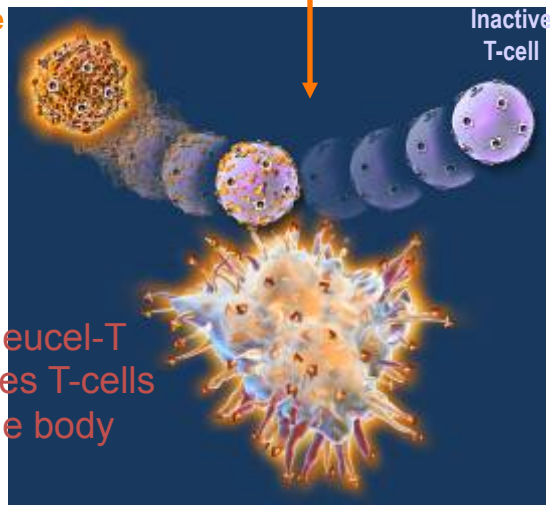


Antigen is processed and presented on surface of the APC

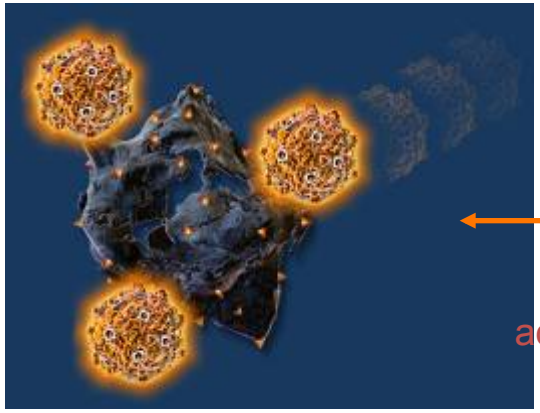


Fully activated, the APC is now sipuleucel-T

INFUSE PATIENT



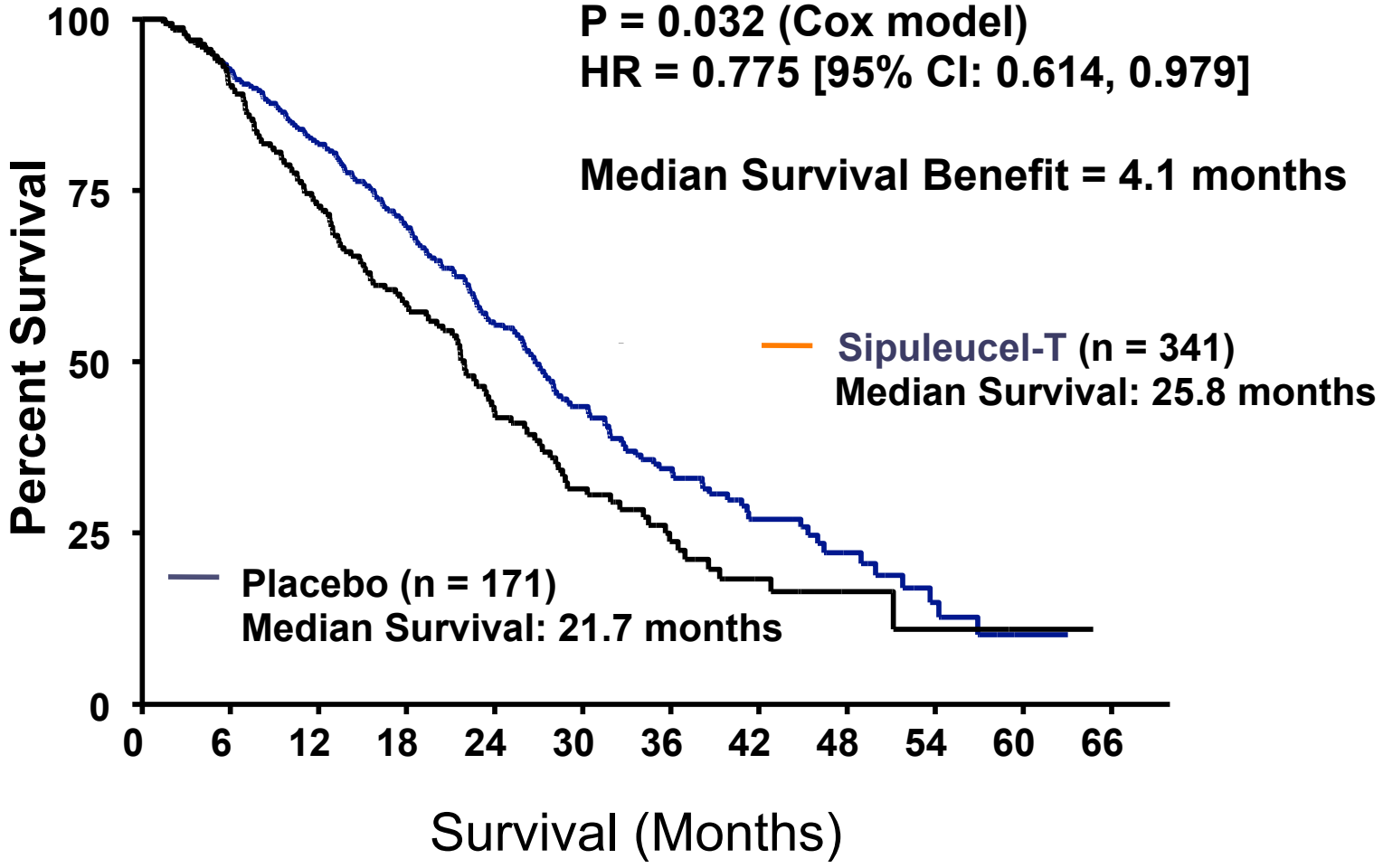
Sipuleucel-T activates T-cells in the body



T-cells proliferate and attack cancer cells

The precise mechanism of sipuleucel-T in prostate cancer has not been established.

IMPACT Overall Survival
Intent-to-Treat Population



Optimal timing for treatment of metastatic castration-resistant prostate cancer (mCRPC): sequencing and identifying parameters of early progression with sipuleucel-T

E. David Crawford, M.D.[1], Adam S. Kibel, M.D.[2], Neal D. Shore, M.D., F.A.C.S.[3]

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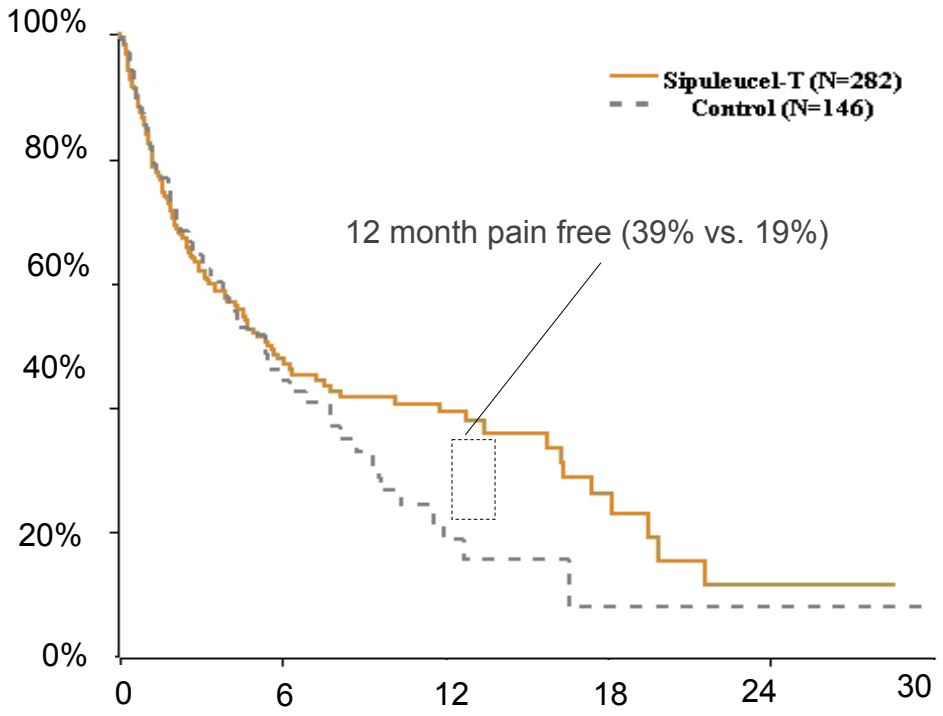
Patients in the lowest PSA quartile had greatest OS benefit with sipuleucel-T

Baseline PSA ng/mL	≤22.1 (n=128)	>22.1 to 50.1 (n=128)	>50.1 to 134.1 (n=128)	>134.1 (n=128)
Median OS, months				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference, months	**13.0**	**7.1**	**5.4**	**2.8**
HR (95% CI)	0.51 (0.31 – 0.85)	0.74 (0.47 – 1.17)	0.81 (0.52 – 1.24)	0.84 (0.55 – 1.29)

- Although all PSA quartile groups in IMPACT showed a benefit from sipuleucel-T treatment, those in the lowest PSA quartile benefitted the most in terms of OS
- The magnitude of treatment effect in patients in the lowest quartile appeared to be greater than those in the highest quartile (13.0 vs. 2.8 months median OS benefit, respectively)

1. Crawford ED et al. AUA 2013. Abstract #960; 2. Schellhammer PF et al. *Urology*. 2013 Jun;81(6):1297-302

Analysis of Three Randomized Trials, Time to Disease Related Pain



Study	HR (95% CI)[1]	*P*-value[2]
D9902A	1.392 (0.652, 2.973)	0.390
Integrated[3]	0.844 (0.635, 1.122)	0.241

PDL-1 Expression in Prostate cancer

- Hormone sensitive radical prostatectomy specimens express high levels of PDL-1 52.2% of cases (Gevensleben et al Clin Cancer Res 2016)
- Patients progressing on enzalutamide have significantly increased PDL-1/2 dendritic cells in blood compared to those progressing on treatment. (Bishop et al. Oncotarget, 2016)
- Nivolumab treatment in men with CRPC demonstrated no objective responses in 17 patients; 2 patients who had tissue stained for PDL-1 demonstrated no immunoreactivity (Topalian NEJM2012)
- 3/20 samples (15%) had focal areas of PD-L1 positivity, although in only two of the three positive samples was plasma membrane staining clearly observed on malignant epithelial cell. (Martin et al. Prostate Cancer and Prostatic Disease 2015)

Microsatellite Instability

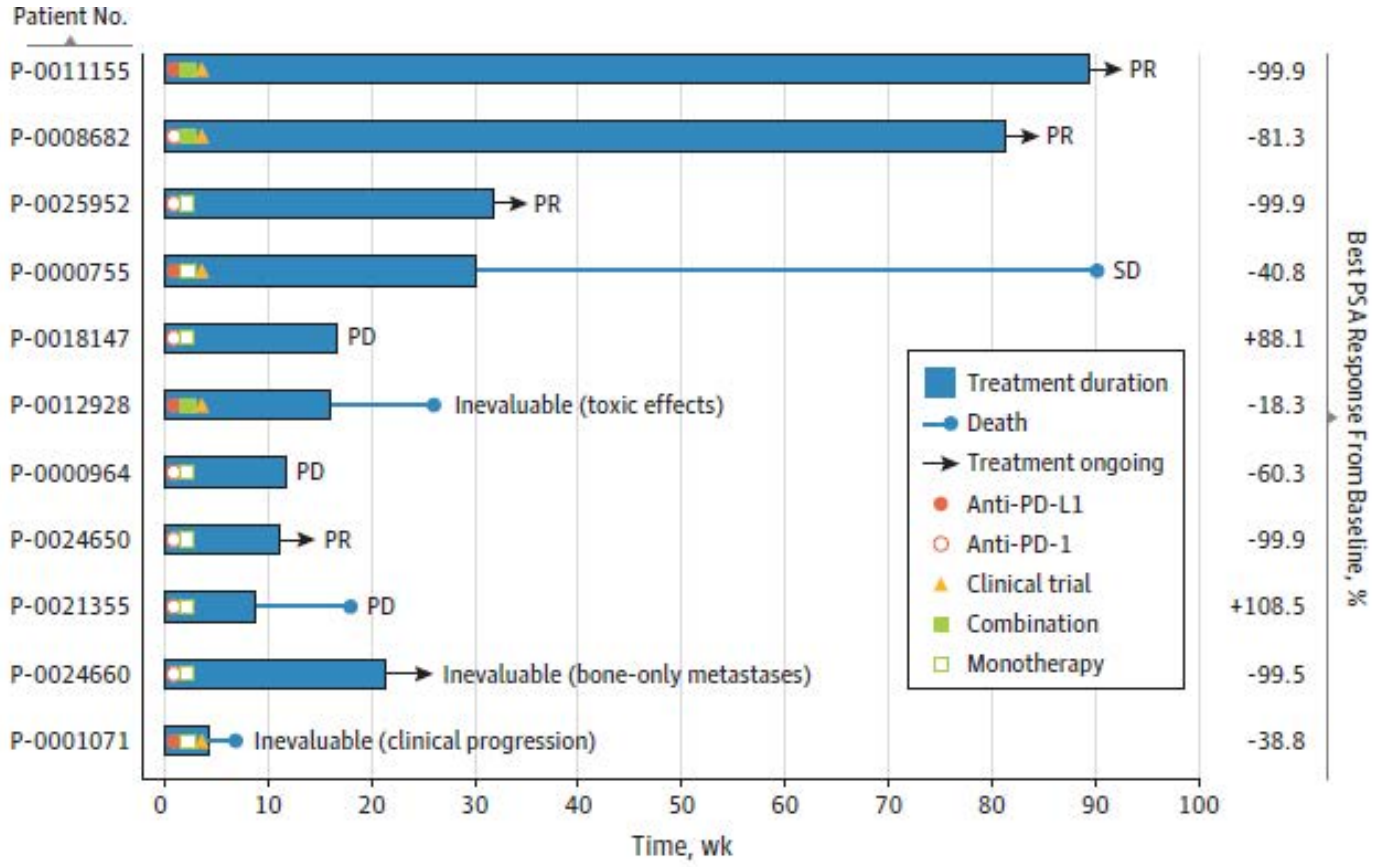
- Defined as the condition of genetic hypermutability (predisposition to mutation) that results from impaired DNA mismatch repair (MMR).
- MMR corrects errors that spontaneously occur during DNA replication, such as single base mismatches or short insertions and deletions
- The proteins involved in MMR correct polymerase errors by forming a complex that binds to the mismatched section of DNA, excises the error, and inserts the correct sequence in its place
- The abberant process leads to DNA fragments with Microsatellite instability structure consists ofrepeated nucleotides, most often seen as GT/CA repeats.[

MSI in Prostate Cancer

- 1033 patients who had adequate tumor quality for MSI sensor analysis 32 (3.1%) had MSI-H/dMMR prostate cancer.
- 23 of 1033 patients (2.2%) had tumors with high MSI sensor scores, and an additional 9 had indeterminate scores with evidence of dMMR.
- Seven of the 32 MSI-H/dMMR patients (21.9%) had a pathogenic germline mutation in a Lynch syndrome–associated gene.
- Six patients had more than 1 tumor analyzed, 2 of whom displayed an acquired MSI-H phenotype later in their disease course.

Abida et al JAMA Oncol. 2019;5(4):471-478. doi: 10.1001/jamaoncol.2018.5801
Published online December 27, 2018.

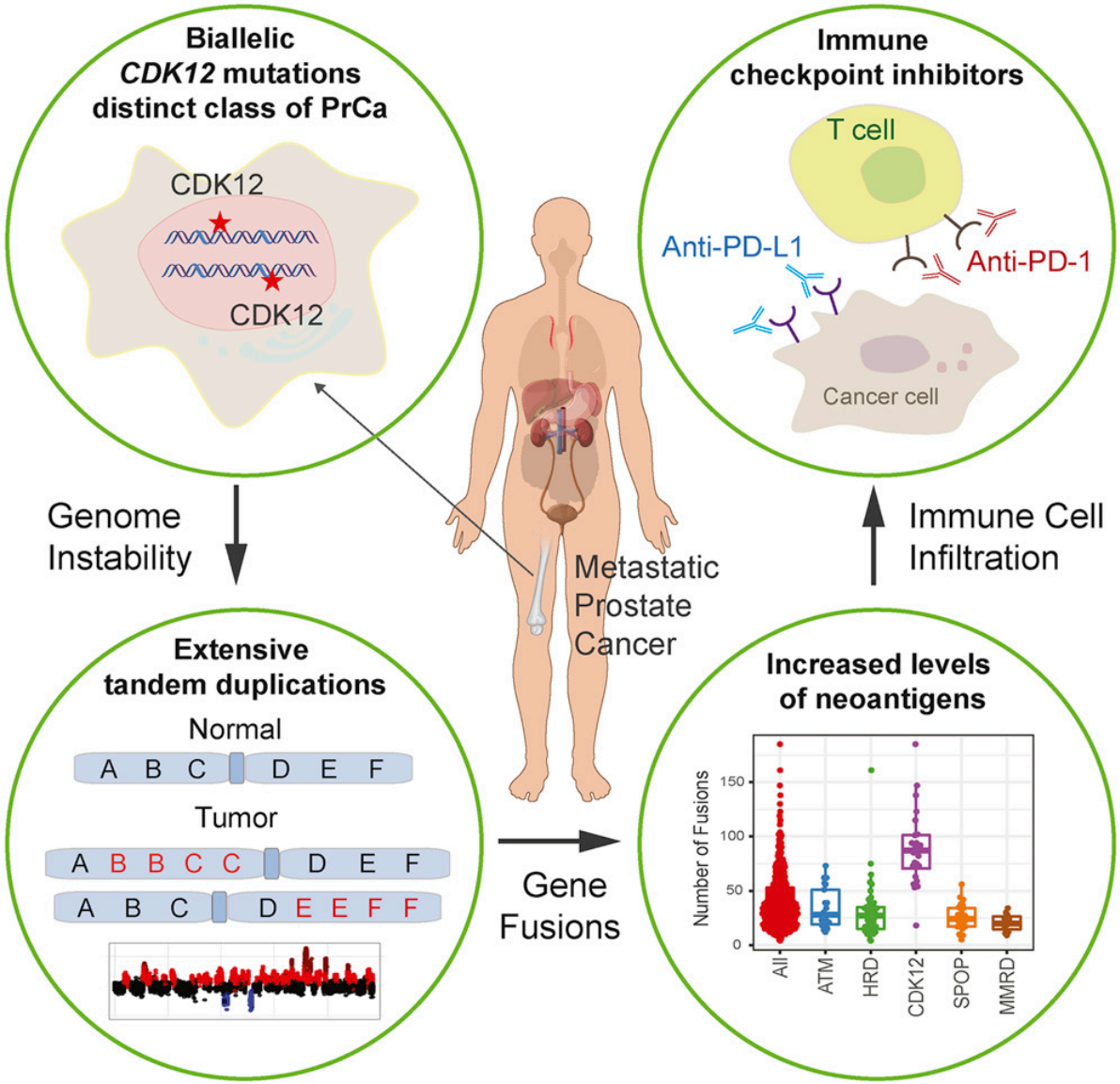
MSI in Castration Resistant Prostate Cancer

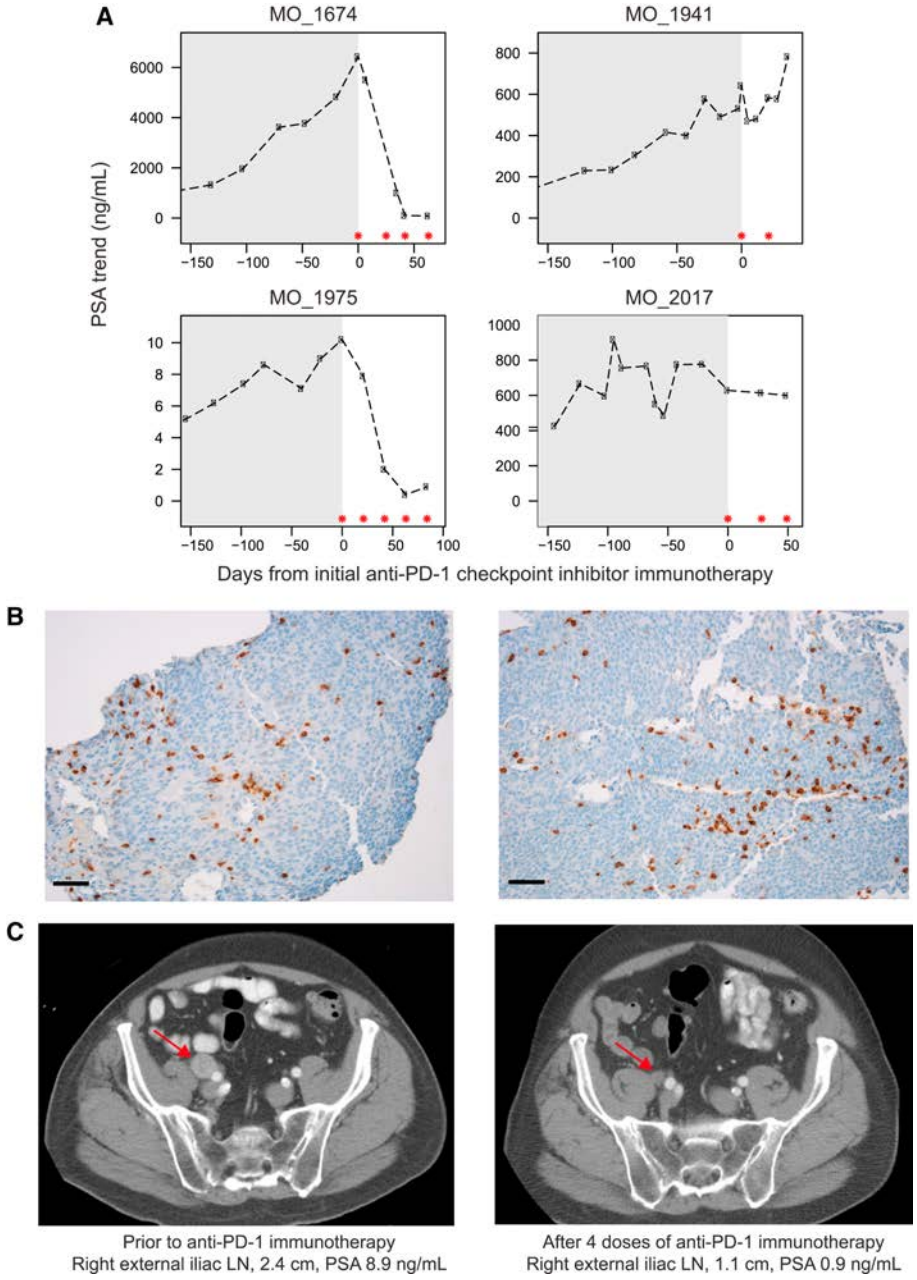


Programmed death-1 blockade in mismatch repair deficient cancer independent of tumor histology.

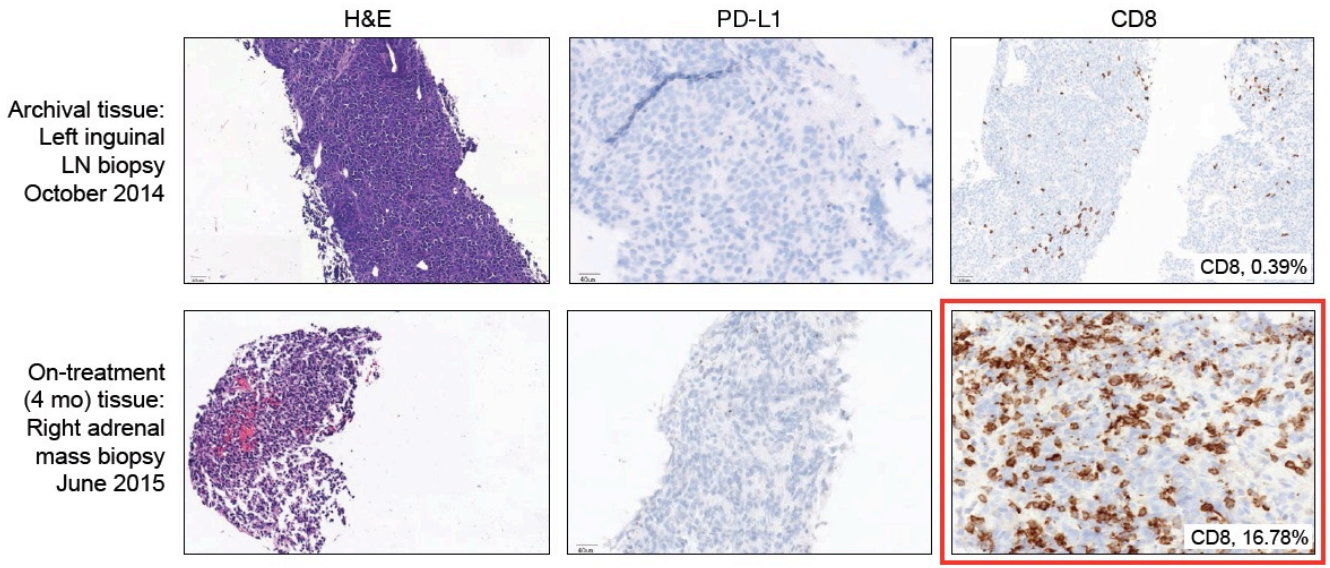
- 29 patients were enrolled and treated on this study, including the following histologies: (endometrial: 9; pancreatic: 4; ampullary: 4; biliary: 3; small bowel: 3; gastric: 3; thyroid: 1; prostate: 1)
- The one prostate cancer patient demonstrated an objective reponse.

Diaz LA et al. J Clin Oncol 34, 2016 (suppl; abstr 3003


Biallelic
CDK12 mutations
distinct class of PrCa
CDK12
CDK12
Immune
checkpoint inhibitors
T cell
Anti-PD-L1
Anti-PD-1
Cancer cell
Genome
Instability
Metastatic
Prostate
Cancer
Immune Cell
Infiltration
Extensive
tandem duplications
Normal
A B C D E F
Tumor
A B B C C D E F
A B C D E E F F
Gene
Fusions
Increased levels
of neoantigens
Number of Fusions
150
100
50
0
All
ATM
HRD
CDK12
SPOP
MMRD

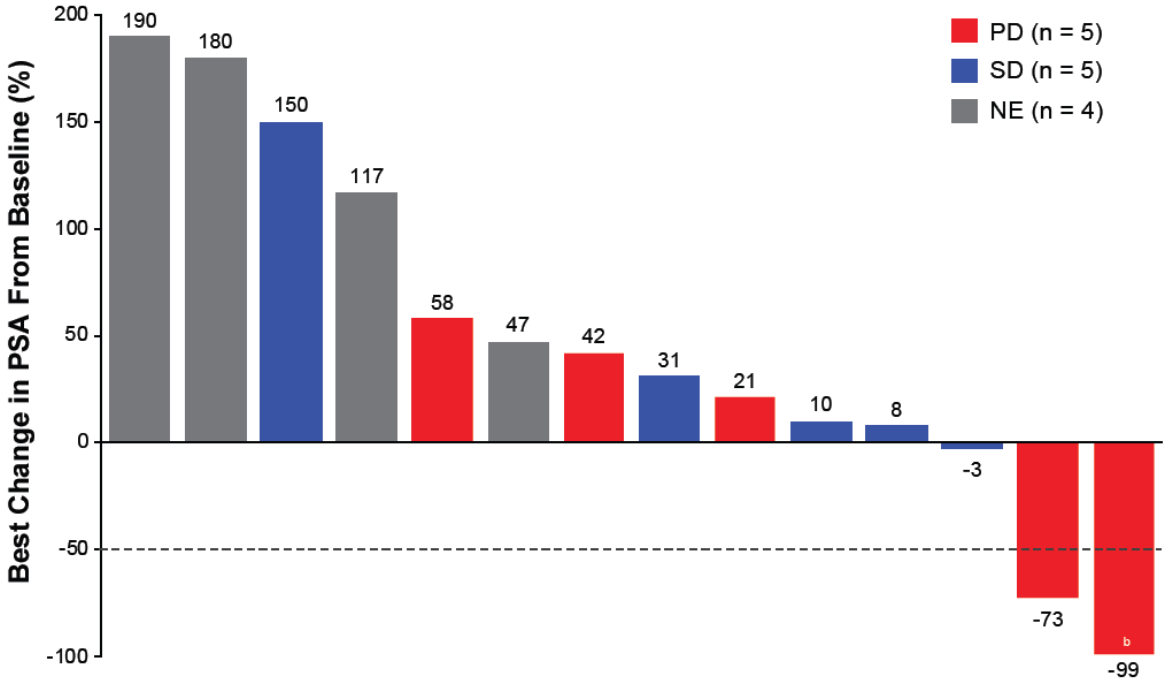

A
MO_1674
MO_1941
MO_1975
MO_2017
PSA trend (ng/mL)
Days from initial anti-PD-1 checkpoint inhibitor immunotherapy
B
C
Prior to anti-PD-1 immunotherapy
Right external iliac LN, 2.4 cm, PSA 8.9 ng/mL
After 4 doses of anti-PD-1 immunotherapy
Right external iliac LN, 1.1 cm, PSA 0.9 ng/mL

Atezolizumab in CRPC

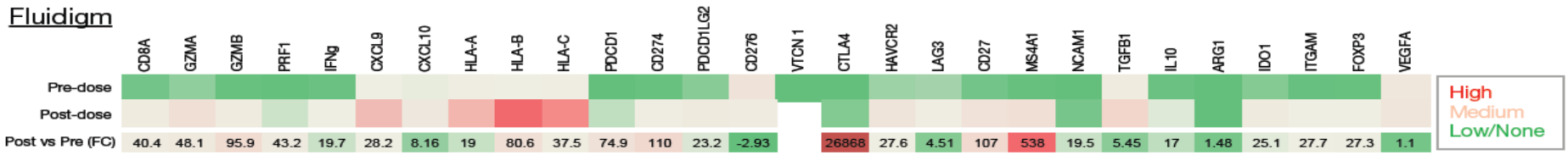


- PD-L1 expression was negative in both archival tissue and tissue collected after 4 months of atezolizumab treatment
- CD8 expression was higher in tissue collected on treatment than in archival tissue

Atezolizumab in CRPC: PSA Declines



Atezolizumab in CRPC



- This patient had a microsatellite stable (MSS) tumor and average/low TMB (4.8 mutations/megabase), comparable with data from MSS prostate tumors from the FMI Database Insights (mean TMB, 5.3 mutations/megabase)
- This patient's tumor also had a mutation in *ATM*, a component of the DNA damage response (DDR) pathway

Responding Patients: Pembrolizumab in Prostate Cancer

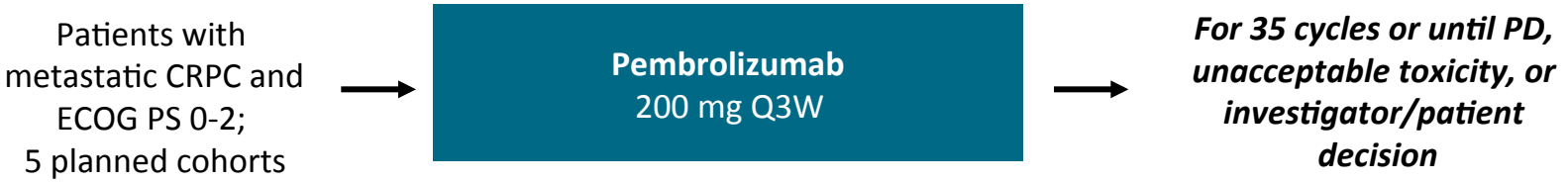
Table 2: Responding Patients*

Patient number	Date of cycle 1	PSA (ng/ml) baseline to nadir	Measurable Disease at Baseline	Best Radiologic Response	MSI	Prior Treatment for mCRPC
1	April 2015	70.65 → 0.08	Yes	PR	present	abi, enz
7	October 2015	46.09 → 0.02	No	N/A	n/a	abi, enz
10	January 2016	2502.75 → < 0.01	Yes	PR	absent	enz

* All responding patients remain on study.
PR – partial response; N/A – not applicable (i.e. no baseline biopsy done); MSI – microsatellite instability; abi – abiraterone; enz – enzalutamide

KEYNOTE-199: Study Design

- Multicohort phase II study (data cutoff: October 13, 2017)



Assessments: imaging Q9W during Yr 1, then Q12W. Measurable disease per RECIST v1.1.
PD-L1 assessment with PD-L1 IHC 22C3 pharmDx assay; CPS ≥ 1 considered positive.

≥ 1 prior targeted endocrine therapy, 1-2 prior CT regimens including docetaxel (current analysis)
Cohort 1: measurable disease, PD-L1 positive (n = 131)
Cohort 2: measurable disease, PD-L1 negative (n = 67)
Cohort 3: bone metastases, no measurable disease, any PD-L1 status (n = 60)

Receiving enzalutamide, no prior CT, any PD-L1 status:
Cohort 4: measurable disease
Cohort 5: bone metastases, no measurable disease

- Primary endpoint: ORR per RECIST v1.1 by BICR in cohorts 1 and 2 (separately and combined)
- Secondary endpoints: DCR, DoR per RECIST v1.1, PCWG3-modified RECIST; OS, safety
- Exploratory endpoints: biomarker signature for benefit with PD-1 blockade

de Bono JS, et al. ASCO 2018. Abstract 5007.

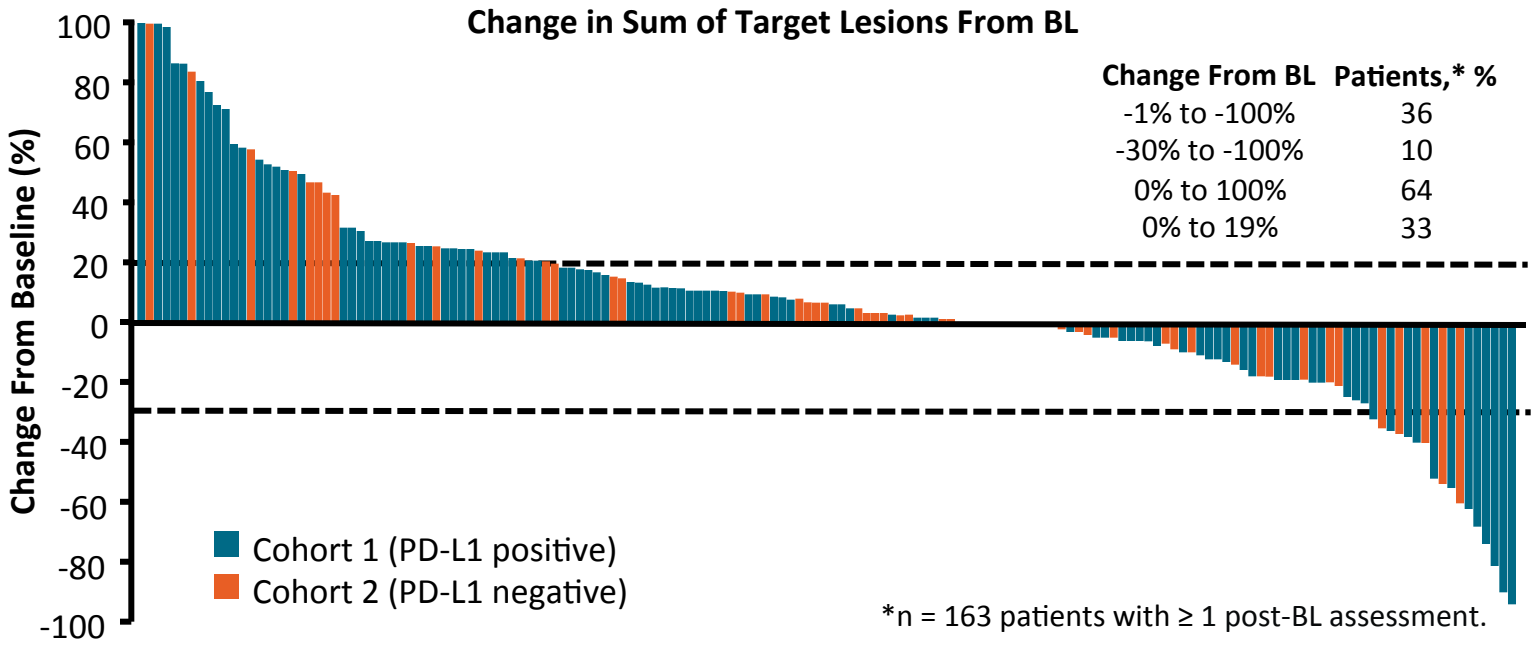
Slide credit: clinicaloptions.com

KEYNOTE-199: Baseline Patient Characteristics

Characteristic	Cohort 1: PD-L1 Positive (n = 131)	Cohort 2: PD-L1 Negative (n = 67)	Cohort 3: Bone Mets (n = 60)
Median age, yrs (range)	68 (48-85)	68 (53-84)	70 (53-90)
ECOG PS 0/1/2, %	31/56/12	39/54/6	43/47/10
Gleason score ≥ 8, %	63	64	57
Mean PSA, ng/mL (SD)	308.4 (655.9)	346.4 (646.2)	175.5 (375.1)
Visceral disease, %	66	45	12
Prior therapies, %			
▪ ≥ 2 CT	32	27	25
▪ ≥ 2 antiendocrine therapies	26	22	25
▪ Enzalutamide only	30	40	30
▪ Abiraterone only	44	37	45
▪ Enzalutamide + abiraterone	26	22	25

de Bono JS, et al. ASCO 2018. Abstract 5007.

KEYNOTE-199: Antitumor Activity (Cohorts 1 + 2)



- In 193 patients from all 3 cohorts, 11% experienced a ≥ 50% PSA reduction from BL

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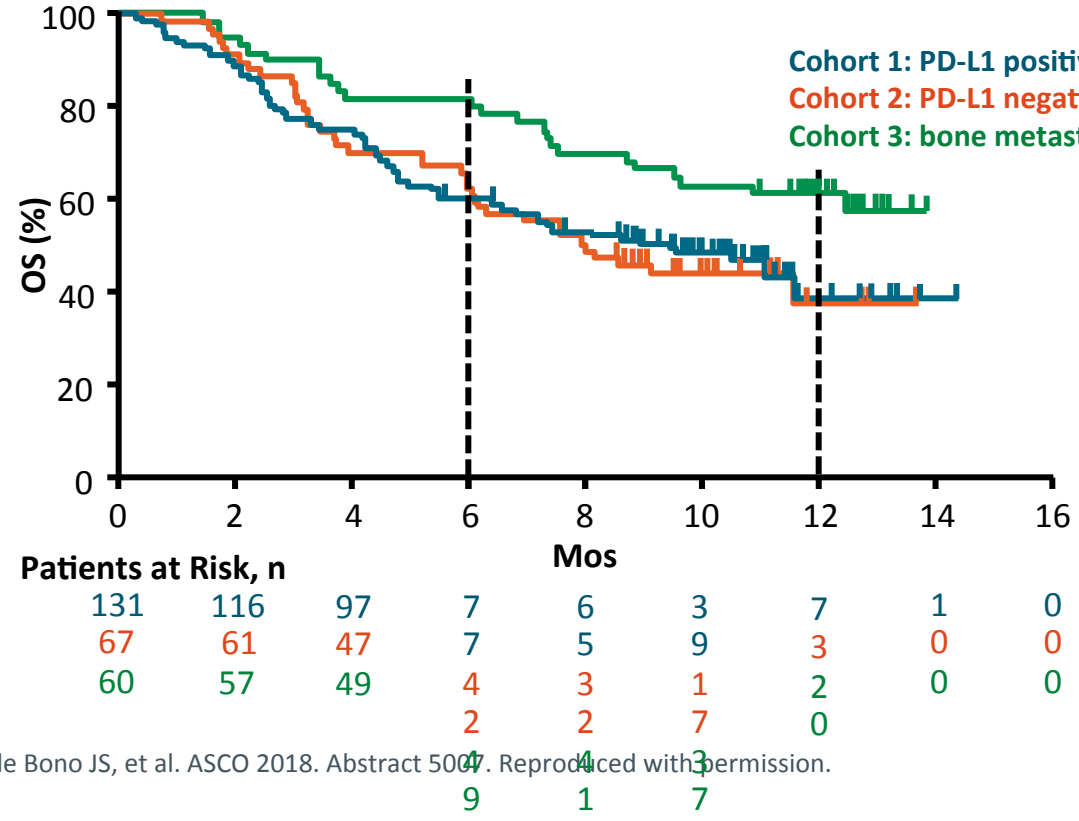
KEYNOTE-199: Response

Response Outcome	Cohort 1: PD-L1 Positive (n = 131)	Cohort 2: PD-L1 Negative (n = 67)	Cohort 3: Bone Metastases (n = 60)	Cohorts 1 + 2 (n = 198)	Cohorts 1 + 2 + 3 (n = 258)
ORR,* n (%)	7 (5)¶	2 (3)¶	--	9 (5)¶	9 (4)
▪ 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 mos	5 (4)	2 (3)	--	7 (4)	7 (3)
▪ Non-CR/non-PD†	0	0	22 (37)	0	22 (9)
▪ PD	76 (58)	42 (63)	33 (55)	118 (60)	151 (59)
▪ NE	4 (3)	1 (1)	1 (2)	5 (3)	6 (2)
▪ NA‡	22 (17)	8 (12)	4 (7)	30 (15)	34 (13)
DCR ≥ 6 mos,§ n (%)	12 (9)	4 (6)	13 (22)	16 (8)	29 (11)
mDoR, mos (range)	8.4 (1.9-10.6+)	NR (4.4-7.2+)	--	8.4 (1.9-10.6+)	--
Median follow-up, mos	8.1	7.9	11.8	--	--
Ongoing responses, %	11	9	12	--	--

*CR + PR by RECIST v1.1. †Patients with persistent existing lesions or who developed new lesions. ‡Patients with 1 post-BL assessment.
§Patients with CR or PR of any duration, SD or non-CR/non-PR for ≥ 6 mos by RECIST v1.1. ¶Primary endpoint.

de Bono JS, et al. ASCO 2018. Abstract 5007.

KEYNOTE-199: OS by Cohort*



	Events, %	Median OS, Mos (95% CI)	6-Mo OS, %	12-Mo OS, %
Cohort 1: PD-L1 positive	53	9.5 (6.6-NR)	60	39
Cohort 2: PD-L1 negative	57	8.0 (5.9-NR)	63	38
Cohort 3: bone metastases	40	NR (9.6-NR)	82	61

*Distinct cohorts, not a randomized comparison.

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KEYNOTE-199: Response by Somatic DNA Aberration (Cohorts 1 + 2 + 3)

Response Outcome, n (%)	*BRCA1/2* or *ATM* (n = 19)	Other DDR Genes* (n = 10)	Negative (n = 124)
ORR	2 (11)	0	4 (3)
▪ CR	0	0	2 (2)
▪ PR	2 (11)	0	2 (2)
▪ SD (any duration)	2 (11)	2 (20)	18 (15)
▪ PD	12 (63)	5 (50)	80 (65)
DCR (any duration)	4 (22)	0	22 (18)
PSA responders	2 (11)	1 (10)	4 (3)

**BARD1, BRIP1, CDK12, CHEK1, CHEK1, FANCL, PALB2, PPP2R2A, RAD51C, RAD51B, AD51D, RAD54L.*

de Bono JS, et al. ASCO 2018. Abstract 5007.

Abstract 5027:Pembrolizumab + Olaparib

- NCI had previously reported possible synergy with considerable publicity invoking “STING” pathway as an explanation
- N=41; mCRPC treated previously with docetaxel and ≤2 next generation hormonal treatment treated with pembrolizumab 200 mg Q3 weeks + Olaparib 400 mg PO BID
- No patient selection
- PSA response 5/41 (12%)
- Measurable disease 4/28 (14%)
- 6 month rPFS =48%

Abstract #5029 Pembrolizumab + docetaxel in mCRPC

- N=72; mCRPC with prior progression on abi or enza now treated with docetaxel and pembro
- PSA response 22/71 (31%)
- Measurable disease 8/35 (23%)
- 6 month rPFS =45%
- AEs: two deaths from pneumonitis

Abstract #5010 Pembrolizumab + enzalutamide in mCRPC

- Prior work with Julie Graff and initial report showing 3/10 responders with some spectacular
- N=69; mCRPC with prior progression on abi now treated with enza + pembro
- PSA response 18/67 (27%)
- Measurable disease 10/25 (40%)
- 6 month rPFS =50%
- AEs: 0 deaths

Conclusons

- Treatment with immune therapy should be used early in the course of CRPC
- PSA declines may not be seen in pateints treated with immune therapy