Immunotherapy for Prostate Cancer

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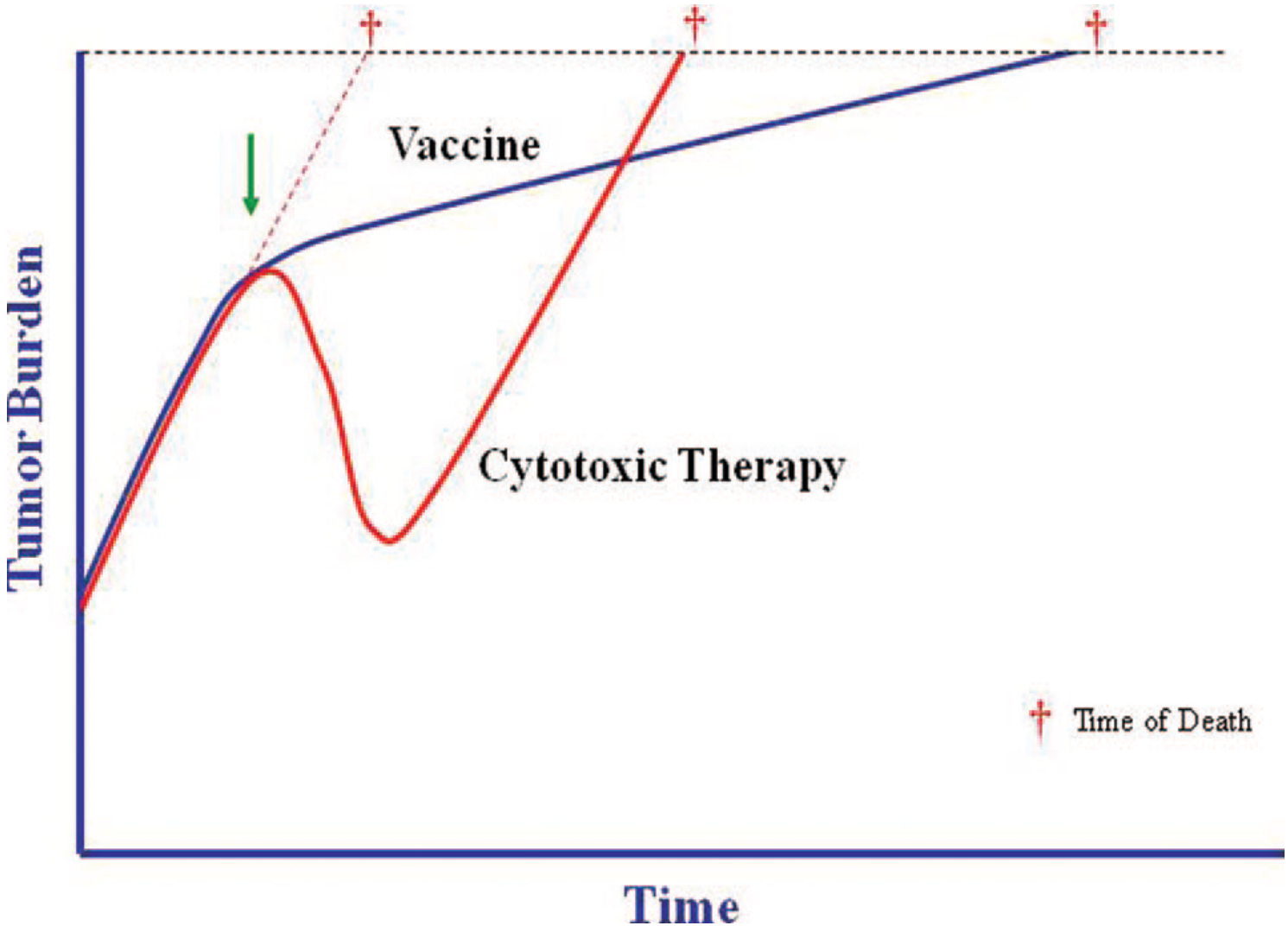
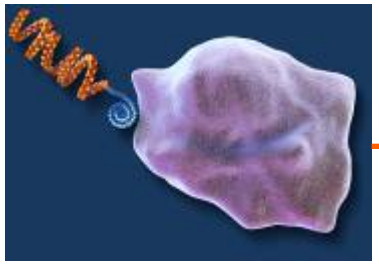
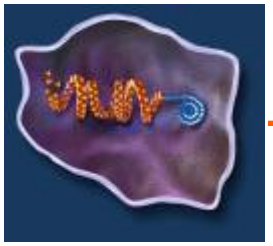


Maddan, et al. *The Oncologist.* 2010.

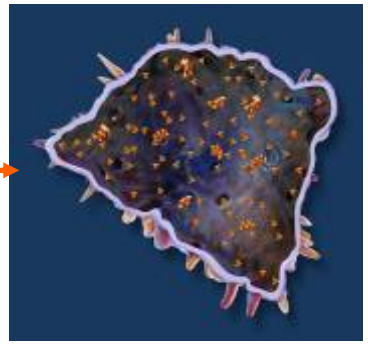
Sipuleucel-T: Autologous APC Cultured with PAP-cytokine Fusion Protein



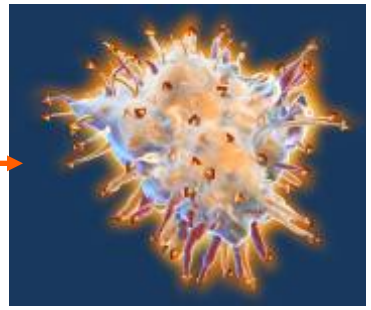
Recombinant Prostatic Acid Phosphatase (PAP) antigen combines with resting antigen presenting cell (APC)



APC takes up the antigen

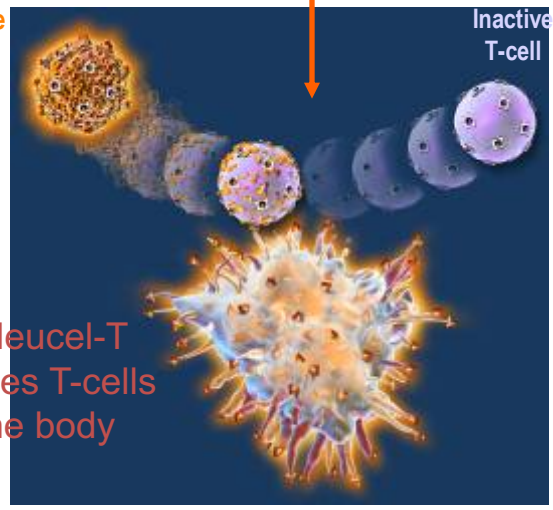


Antigen is processed and presented on surface of the APC

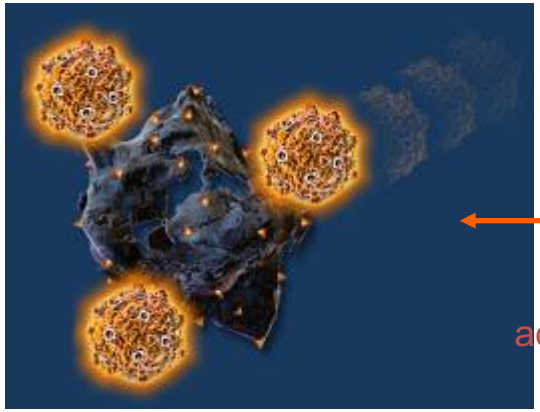


Fully activated, the APC is now sipuleucel-T

INFUSE PATIENT



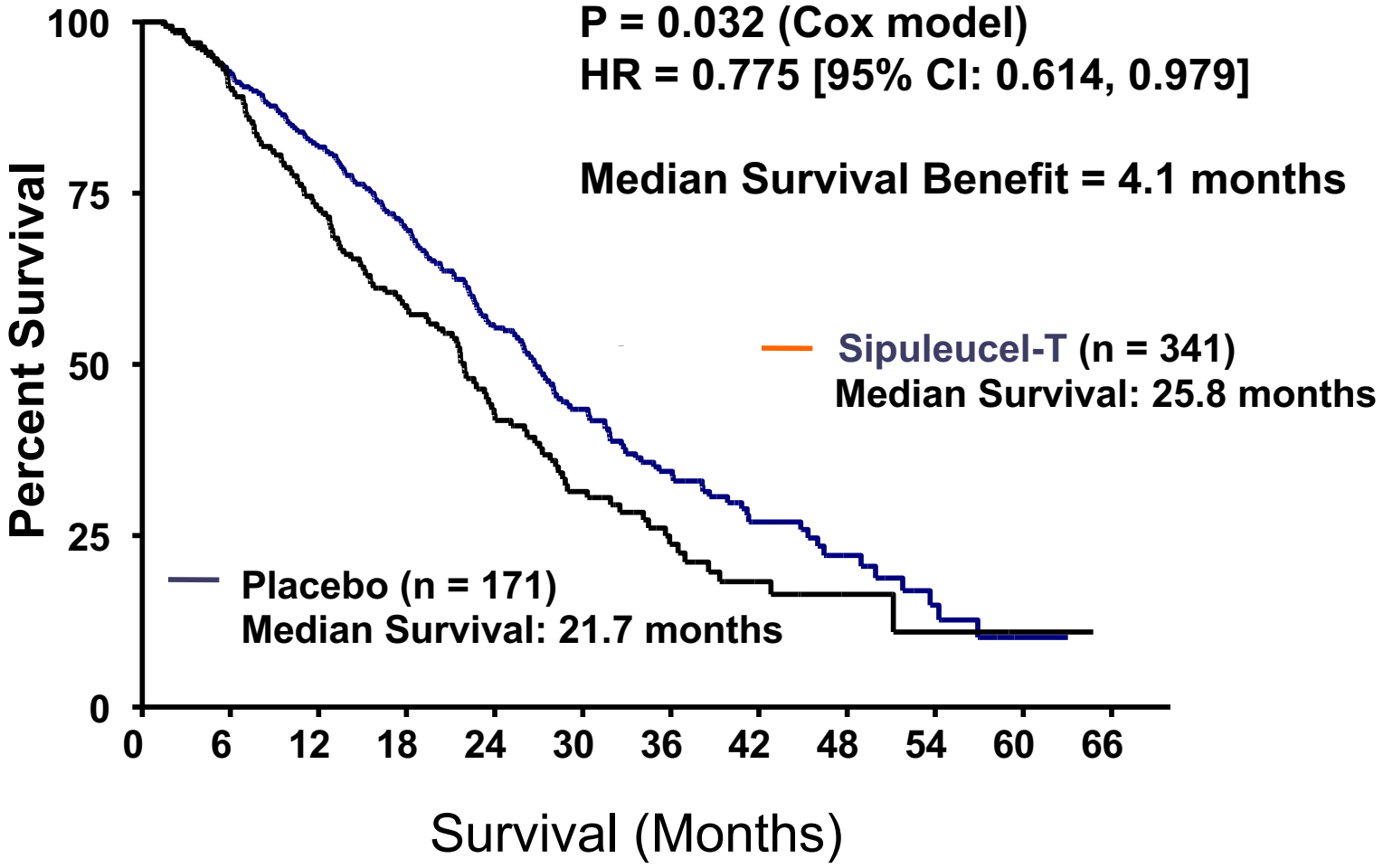
Sipuleucel-T activates T-cells in the body



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]

[1]University of Colorado Anschutz Medical Campus, Aurora, Colorado; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Atlantic Urology Clinics, Myrtle Beach, SC

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

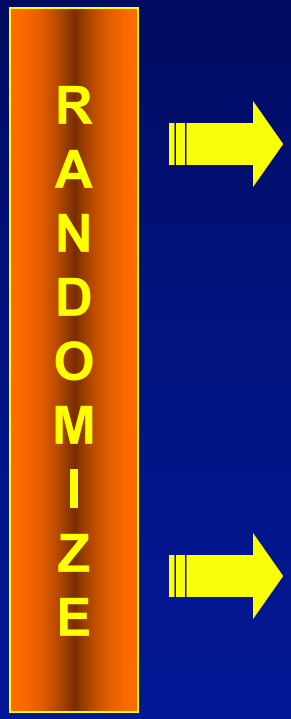
Baseline PSA ng/mL	≤22.1 (n=128)	>22.1 to 50.1 (n=128)	>50.1 to 134.1 (n=128)	>134.1 (n=128)
Median OS, months				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference, months	**13.0**	**7.1**	**5.4**	**2.8**
HR (95% CI)	0.51 (0.31 – 0.85)	0.74 (0.47 – 1.17)	0.81 (0.52 – 1.24)	0.84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

Randomized Phase II trial of Sipulecel T + MDV3100

- Chemotherapy naïve
- Visceral disease permitted
- No prior ketoconazole/abiraterone



- **Sipuleucel T x 3 doses**
- **MDV 3100 1600 mg concomitantly**

- **Sipuleucel T x 3 doses**
- **MDV 3100 after completion of Sipeuleucel T**

Methods

- Time-to-events at 36 months were defined as:
  - OS: proportion of patients alive
  - PSA progression-free survival (from start of enzalutamide)
    - either 1st PSA increase of ≥25% and ≥2 ng/mL above the nadir confirmed by a 2nd value ≥3 weeks later (for patients with PSA decline from BL) or PSA progression ≥25% and ≥2 ng/mL after 12 weeks of enzalutamide treatment (for patients with no PSA decline from BL)
  - Disease-free survival (from start of enzalutamide)
    - PSA progression-free survival OR
    - Free from a clinically significant disease-specific event, i.e. new spinal cord/nerve root compression; pathologic fracture; metastatic disease in a new anatomic location, disease progression on radiographic imaging and RECIST criteria
  - Receipt of abiraterone, radium-223, docetaxel, or cabazitaxel from enrollment
  - Treatment with radiation from enrollment
- Statistical analyses
  - Kaplan-Meier method for median and 95% CIs for OS and all time-to-event endpoints
  - Cox regression model versus lowest PSA quartile for OS and all time-to-event endpoints, with PSA sub-group as an independent variable and treatment arm as covariate

RECIST = response evaluation criteria in solid tumors

Selected patient demographics and disease baseline characteristics

	BL PSA, ng/mL N=13/group			
	Q1 ≤3.9	Q2 >3.9–≤9.4	Q3 >9.4–≤47.3	Q4 >47.3
Median (range) age, years	66 (43–81)	74 (55–88)	70 (58–86)	71 (55–85)
Race, n (%) Caucasian Black or African American	13 (100) 0	12 (92) 1 (8)	13 (100) 0	12 (92) 1 (8)
ECOG PS, n (%) 0 1	11 (85) 2 (15)	11 (85) 2 (15)	9 (69) 4 (31)	10 (77) 3 (23)
Gleason score ≥8, n (%)	11 (85)	7 (58)	9 (75)	8 (62)
Prostate-specific antigen, ng/mL	1.6 (0.2–3.8)	6.3 (4.0–9.2)	23 (9.6–47)	71 (47–112)
Lactate dehydrogenase, U/L	214 (106–244)	185 (129–315)	188 (86–275)	192 (154–655)
Alkaline phosphatase, U/L	79 (52–271)	90 (50–161)	103 (52–675)	114 (59–392)
Hemoglobin, g/dL	12.7 (10.0–15.1)	13.2 (10.3–16.4)	13.0 (10.6–14.9)	13.3 (10.9–15.8)
Serum albumin, g/dL	4.1 (3.6–4.5)	4.1 (3.3–4.8)	3.9 (3.4–4.7)	4.2 (3.6–4.8)

Values for laboratory parameters are median (range); ECOG = European Cooperative Oncology Group; PS = performance status; Q = quartile

Duration of exposure to enzalutamide

Per-protocol enzalutamide exposure, weeks	Concurrent Arm (sipuleucel-T + enzalutamide) (N=25)	Sequential Arm (sipuleucel-T → enzalutamide) (N=27)
Mean (SD)	39.9 (16.7)	37.7 (16.1)
Median (range)	51.9 (11.3–56.1)	40.7 (11.1–58.0)

SD = standard deviation

Median OS by BL PSA quartile

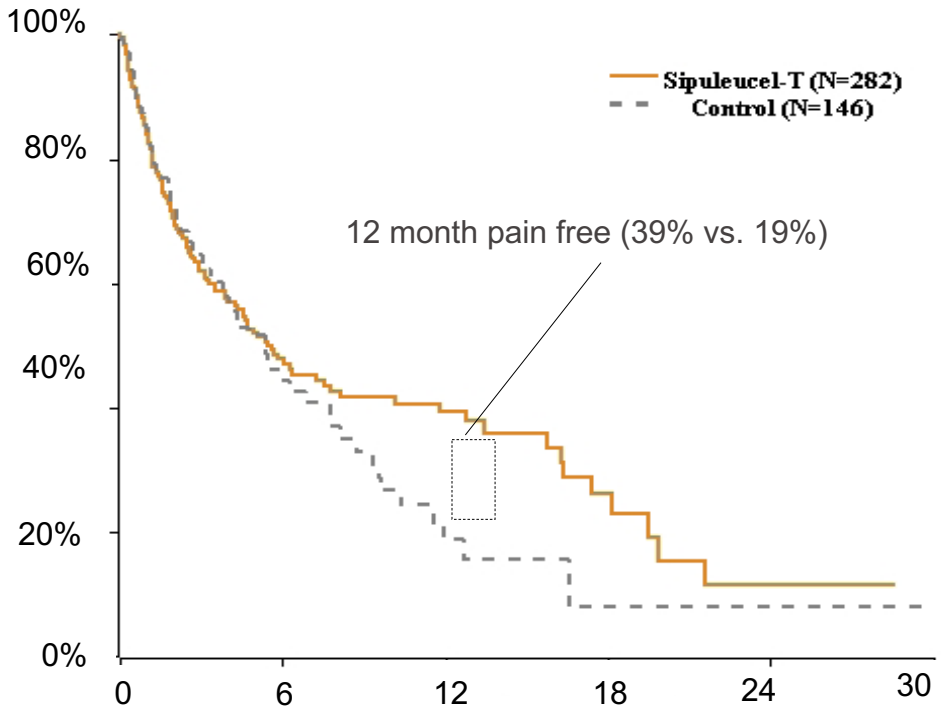
	BL PSA, ng/mL N=13/group			
	Q1 ≤3.9	**Q2 >3.9–≤9.4**	**Q3 >9.4–≤47.3**	**Q4 >47.3**
Median (95% CI), months	NE (31.3–NE)	NE (18.3–NE)	23.9 (17.4–37.5)	24.3 (8.3–32.5)
Hazard ratio (95% CI) vs lowest PSA quartile	1.0	1.6 (0.4–5.9)	4.3 (1.3–14.5)	5.3 (1.6–17.0)
p-value	–	0.479	0.020	0.005

CI = confidence interval; NE = not estimable

Conclusions

- Survival and clinical outcomes with sipuleucel-T + concurrent or sequential enzalutamide are significantly better in mCRPC patients with low baseline PSA
  - sipuleucel-T + concurrent or sequential enzalutamide earlier in the course of mCRPC may be more beneficial, although a stage migration effect cannot be excluded
- Sipuleucel-T + concurrent or sequential enzalutamide treatment is well tolerated
- Long-term studies on whether sequencing impacts survival may be of interest

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

Results of PROSPECT: A Randomized Phase 3 trial of PROSTVAC-V/F in men with asymptomatic or minimally symptomatic metastatic, castration-resistant prostate cancer

Gulley JL[1], Novikov A[2], Borre M[3], Vogelzang N[4], Ng S[5], Agarwal N[6], Parker CC[7], Pook DW[8], Rathenborg P[9], Flaig TW[10], Carles-Galceran J[11], Saad F[12], Langkilde NC[13], Shore N[14], Priou F[15], Gerritsen W[16], Chen L[17], Heery CR[17], Kantoff P[18]

[1]NCI, Bethesda; [2]North-West State Medical University, St. Petersburg; [3]Universitetshospital, Aarhus; [4]Comprehensive Cancer Centers of Nevada, Las Vegas; [5]St John of God Hospital, Subiaco; [6]University of Utah, Salt Lake City; [7]The Royal Marsden, Sutton; [8]Monash Medical Centre, East Bentleigh; [9]Herlev Hospital, Herlev; [10]University of Colorado, Aurora; [11]Hospital Universitario Vall d'Hebron, Barcelona; [12]Centre Hospitalier de l'Universite, Montreal; [13]Sygehus, Aalborg; [14]Carolina Urologic Research Center, Myrtle Beach; [15]Centre Hospitalier Départemental La Roche sur Yon, Lyon; [16]Radboudumc, Nijmegen; [17]Bavarian Nordic, Morrisville; [18]Memorial Sloan Kettering Cancer Center, New York

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: James L Gulley, NCI

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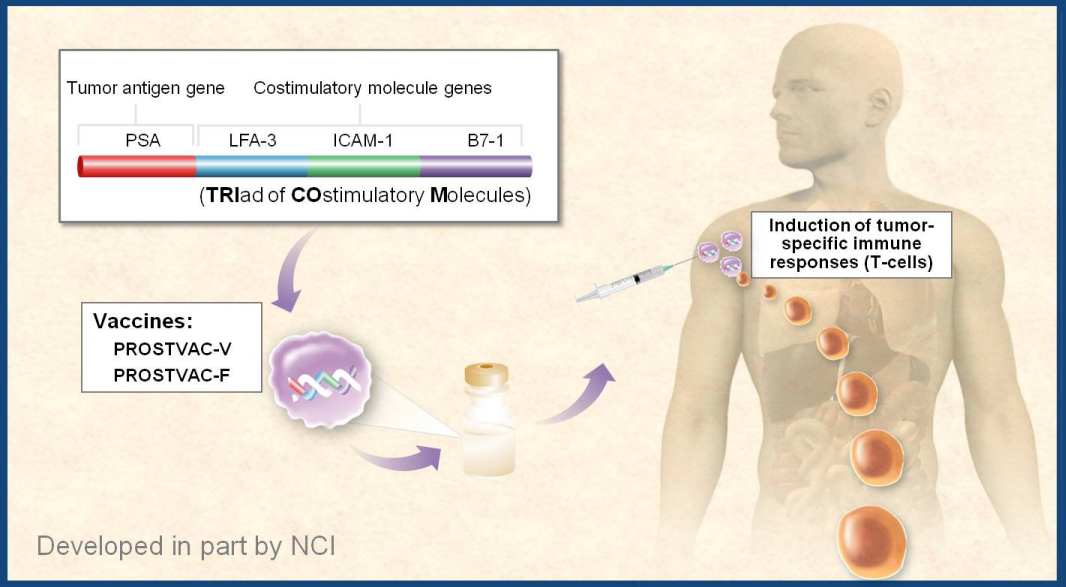

NIH Medical Arts and Photography

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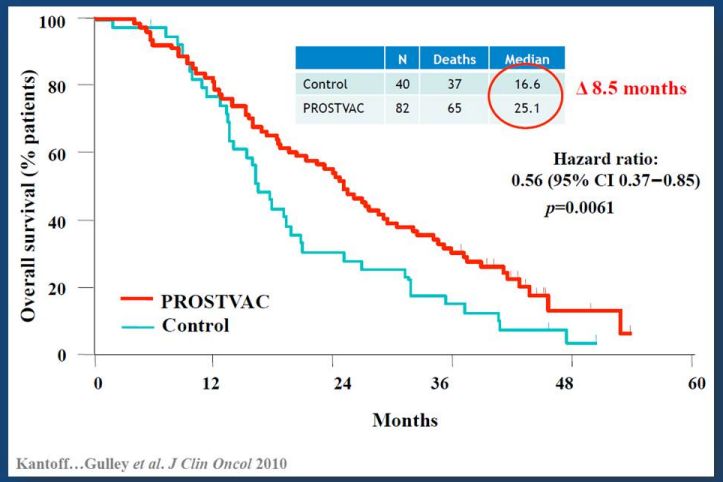
PROSTVAC Clinical Development

- Therapeutic cancer vaccine platform and early clinical development at NCI
- Randomized Phase 2 clinical trial sponsored by Therion Inc suggested OS prolongation



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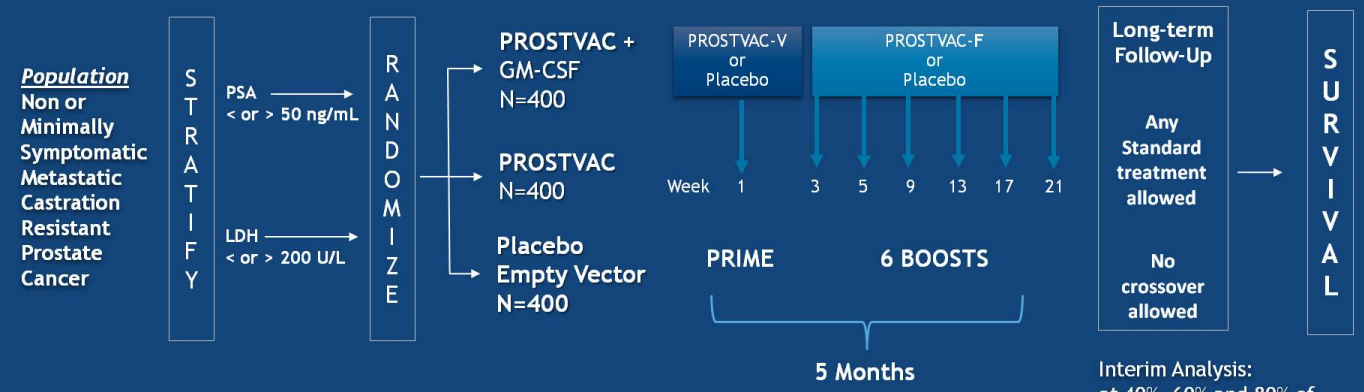
PROSPECT Phase 3 Design



- **Primary Endpoint:** **Overall Survival**
- Secondary Endpoint: Event-Free Survival at 6 Months

Interim Analysis:
at 40%, 60% and 80% of the expected events

Two comparisons:
PROSTVAC vs Pbo
PROS + GM vs Pbo

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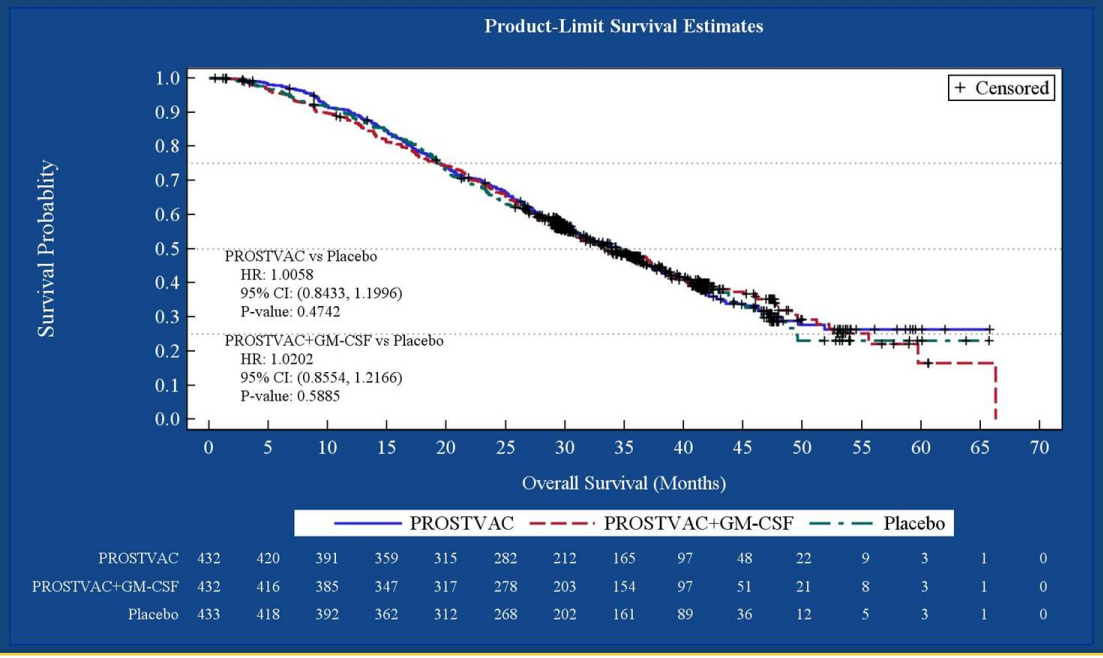
Overall Survival ITT



Sep 2017
Interim Analysis #3
DMC recommended closure of the study on grounds of futility

Median OS	
PROSTVAC	34.4
PROSTVAC+ GM-CSF	33.2
Placebo	34.3

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Conclusions

- PROSPECT failed to confirm the OS benefit suggested by the prior Randomized Phase 2 clinical trial
- No evidence of benefit in any relevant subgroup
- PROSTVAC AE profile similar to placebo arm, with no evidence of myo-pericarditis observed
- OS observed in all arms was approximately one year longer than anticipated, based upon historical controls and prior randomized phase 2 trial; likely due to improved standard of care as study enrollment began in 2011
- Further studies will help determine the utility of vaccine with other agents than can impact the function of immune effector cells in the TME

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PDL-1 Expression in Prostate cancer

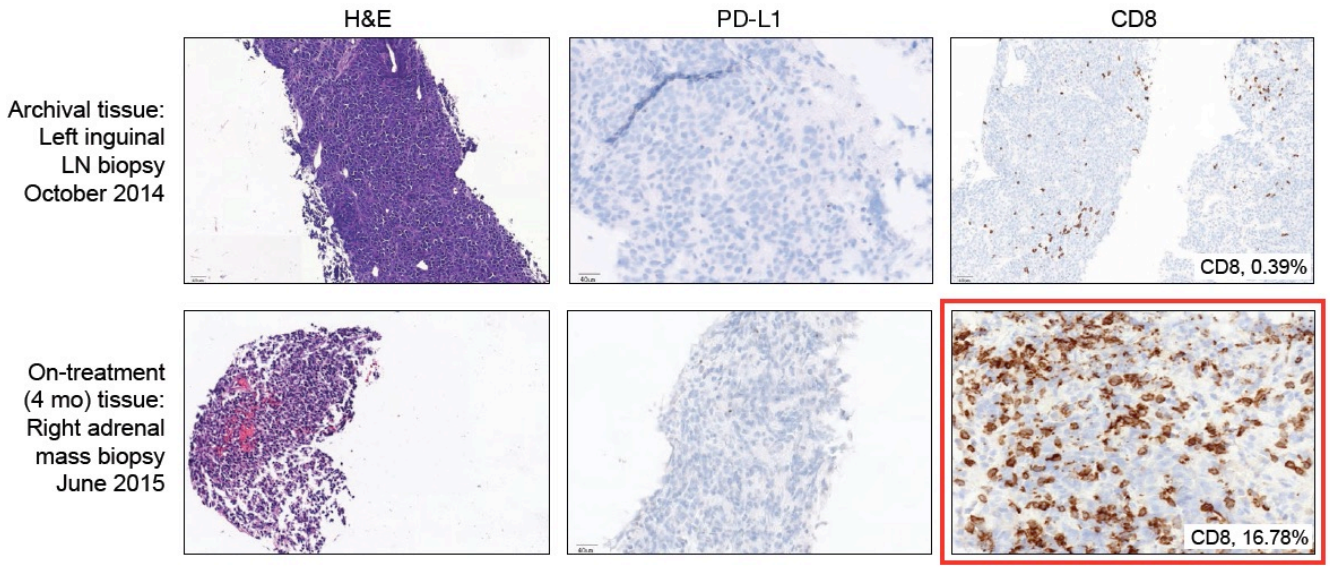
- Hormone sensitive radical prostatectomy specimens express high levels of PDL-1 52.2% of cases (Gevensleben et al Clin Cancer Res 2016)
- Patients progressing on enzalutamide have significantly increased PDL-1/2 dendritic cells in blood compared to those progressing on treatment. (Bishop et al. Oncotarget, 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)

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.

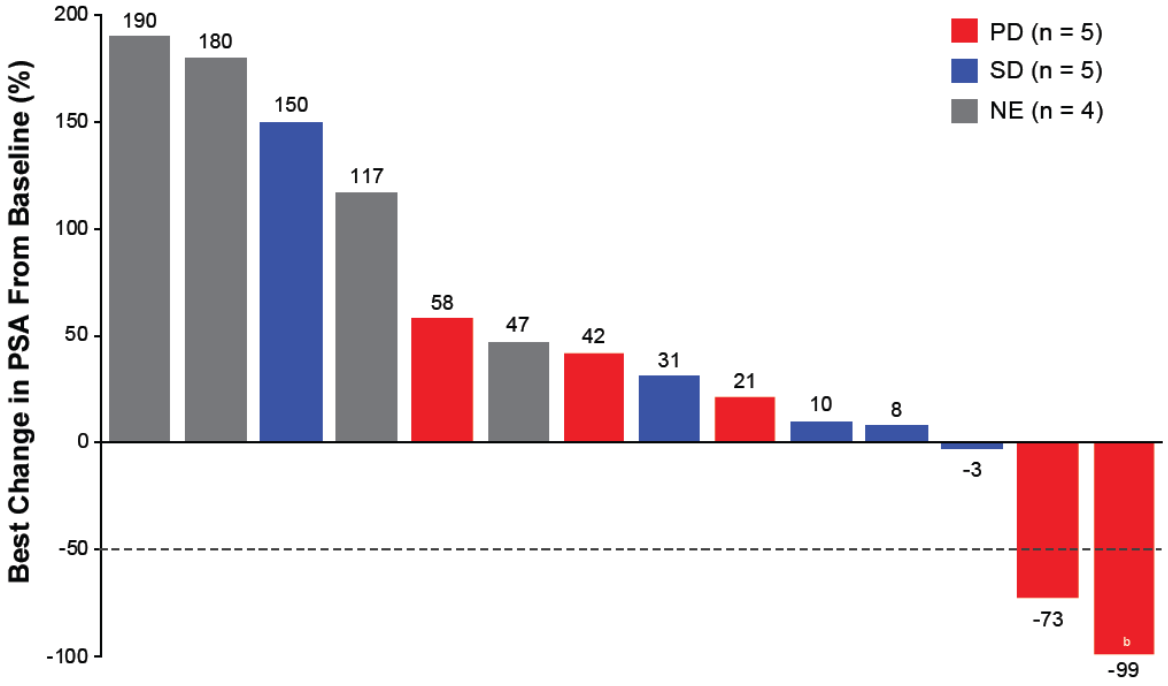
Diaz LA et al. J Clin Oncol 34, 2016 (suppl; abstr 3003

Atezolizumab in CRPC

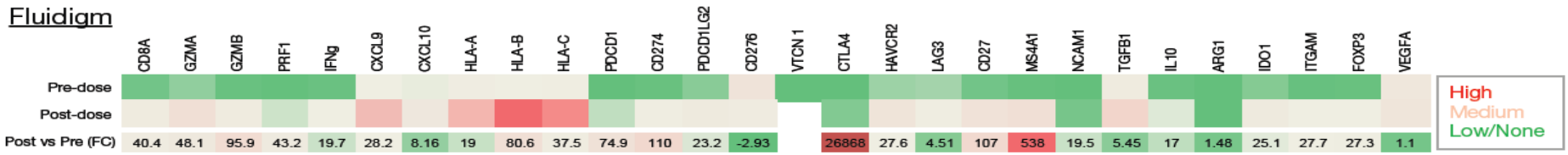


- PD-L1 expression was negative in both archival tissue and tissue collected after 4 months of atezolizumab treatment
- CD8 expression was higher in tissue collected on treatment than in archival tissue

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

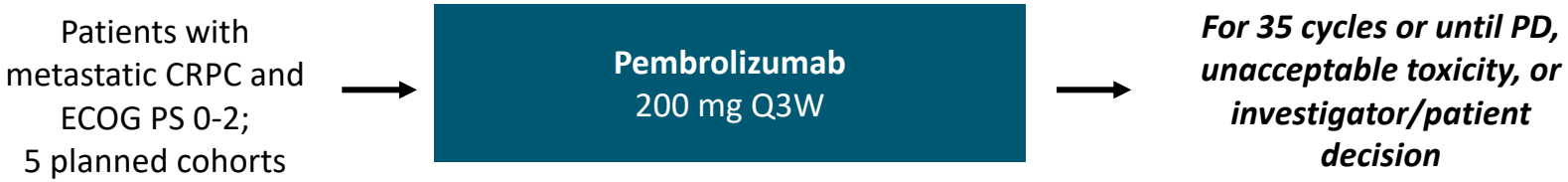
Table 2: Responding Patients*

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.

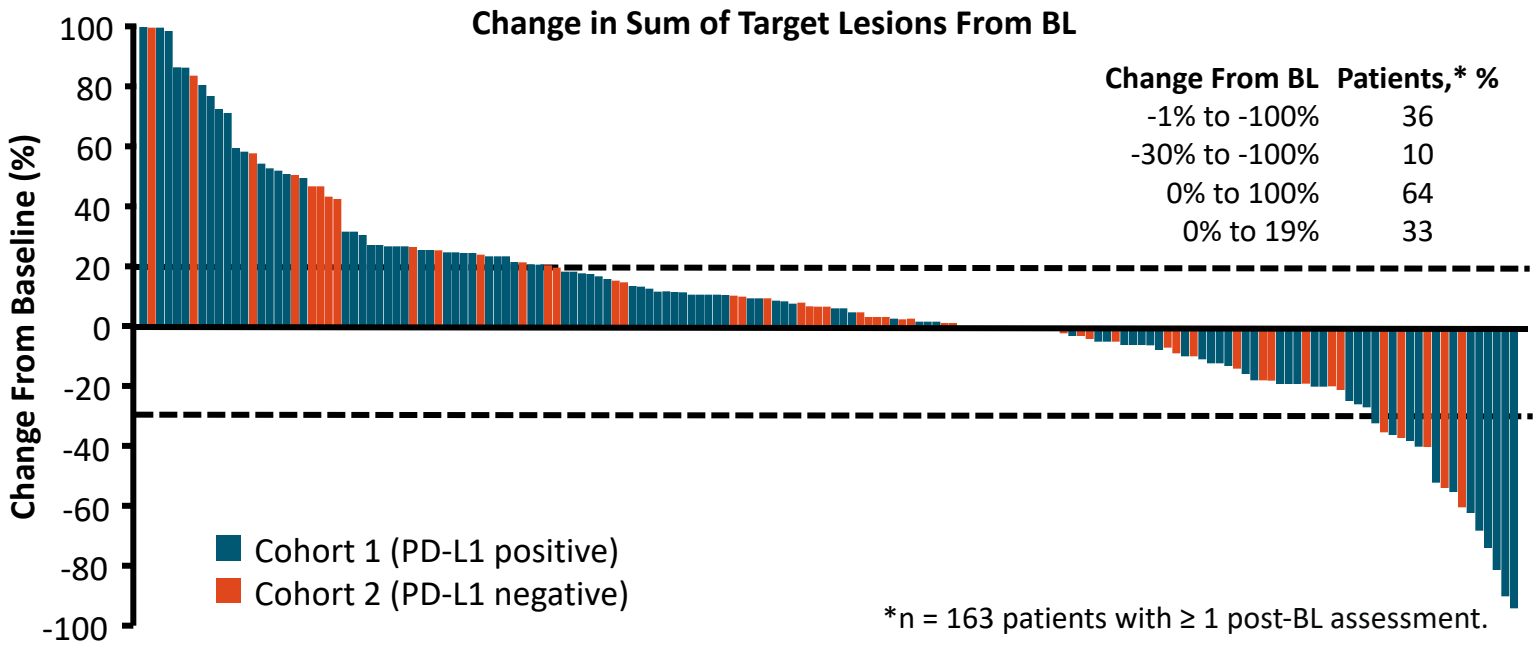
Slide credit: clinicaloptions.com

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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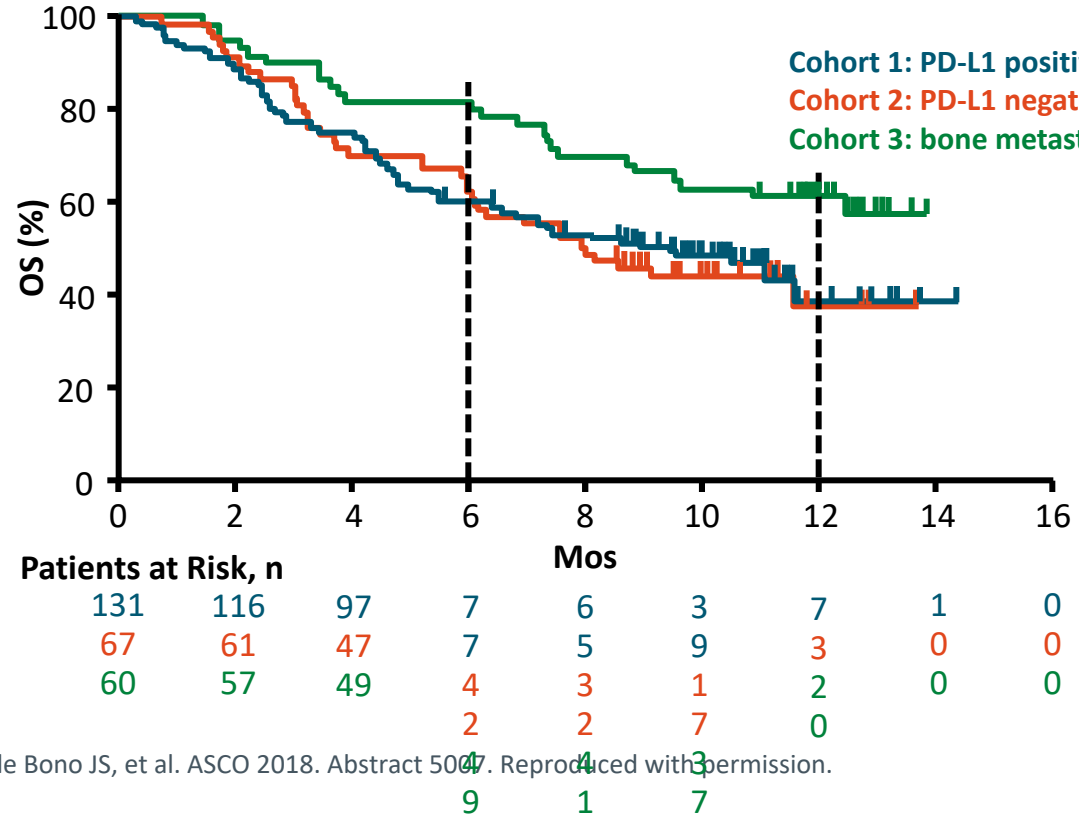
KEYNOTE-199: Response

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.

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