Immunotherapy in Prostate Cancer

Athens – PROSCA 2022
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Conflicts of Interest

Advisory role (compensated, institutional):

Astra Zeneca, Astellas, Bayer, Janssen, Molecular Partners, MSD, Myriad, Pfizer, Roche, Sanofi Aventis (compensated, institutional)

Novartis, Janssen, Bayer, MSD, AstraZeneca, Merck, Astellas (compensated)

Research support (institutional):

TEVA, Janssen

Travel support:

Astellas, Bayer, Janssen, Sanofi Aventis

Speakers Bureau (compensated, institutional):

Astellas, Bayer, Janssen

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Overview

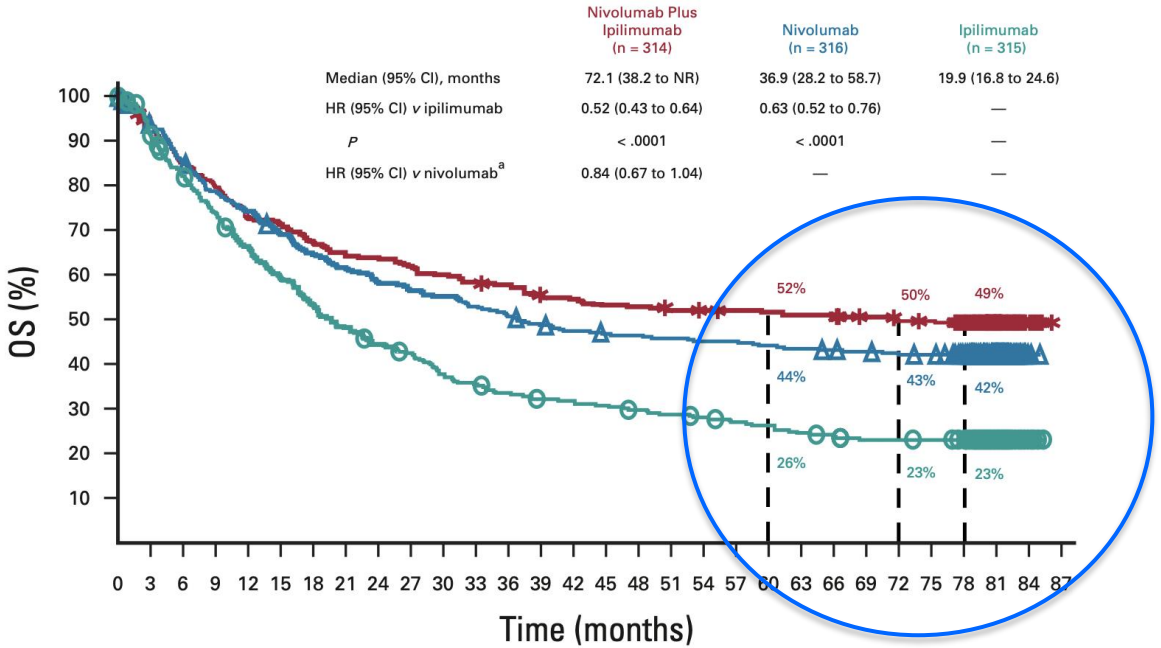
Background

Checkpoint inhibition in unselected patients

Identifying patients that may benefit from checkpoint inhibition 2022

Ongoing trials

What are we aiming for?

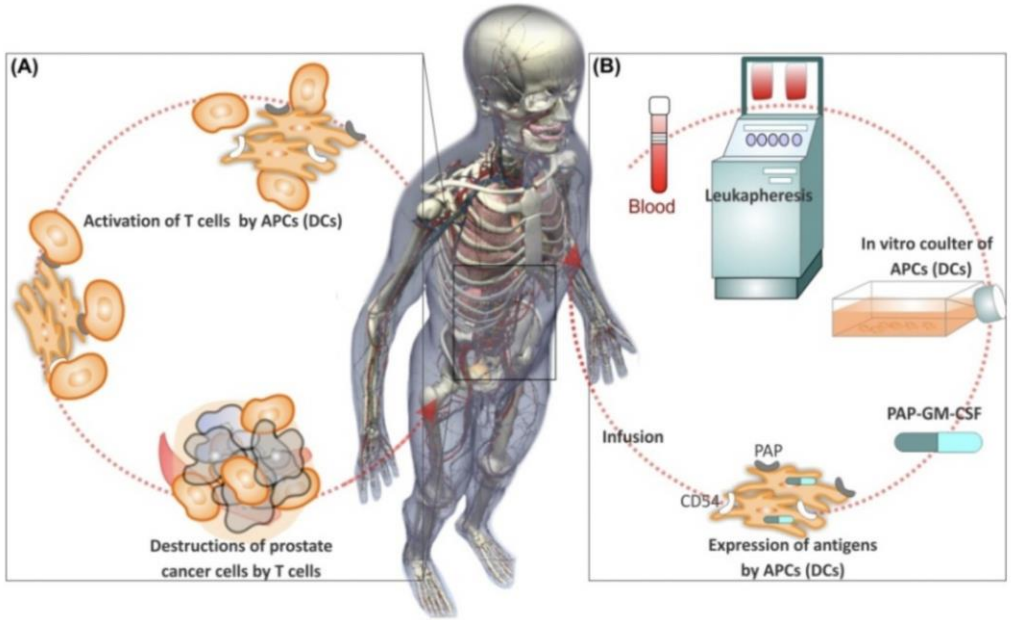


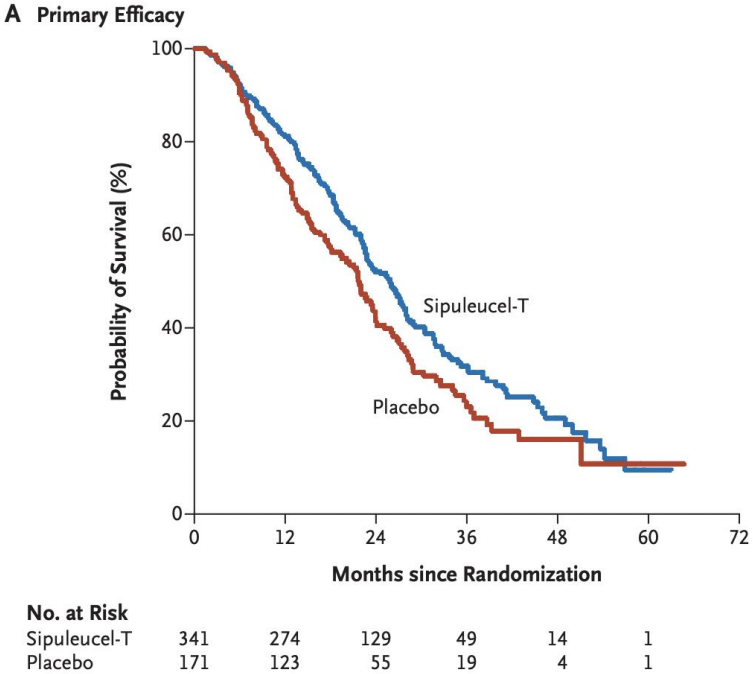
No. at risk:

Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	138	66	10	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	117	59	3	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	61	32	7	0

Wolchok et al J Clin Oncol 2021, 40:127-137

Breakthrough in 2010 with Sipuleucel-T?





- mCRPC mostly pre-chemotherapy
- Estimated OS >6 months
- No visceral metastases
- Mostly Gleason ≤7

Barar et al. BioImpacts, 2012, 2(3), 127-143
Kantoff et al. N Engl J Med 2010 Jul 29;363(5):411-22.

Overview

Background

- Sipuleucel-T only approved by FDA (cost approx. US 65´000)
- Long-term responders have been reported
- No robust biomarkers for response so far identified

Checkpoint inhibition in unselected patients

How can we use checkpoint inhibition in prostate cancer in 2022?

Ongoing trials

Immunotherapy Phase III Trial Graveyard in mCRPC

RTx to bone followed by **Ipilimumab** vs Placebo post-Docetaxel N=799

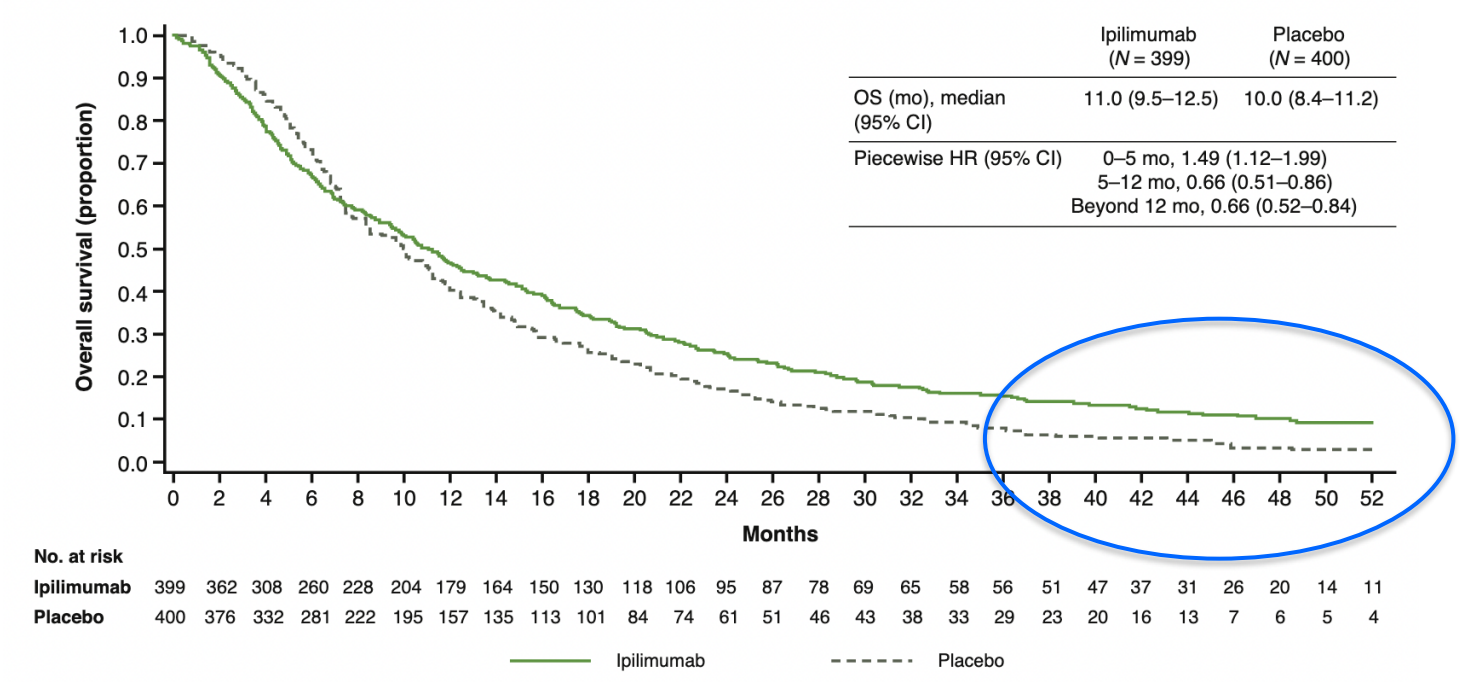
Ipilimumab vs Placebo pre-Docetaxel N=602

IMbassador 250 Enzalutamide ± **Atezolizumab** post Abiraterone N=759

KEYLYNK-010 **Pembrolizumab** plus Olaparib vs Abiraterone or Enzalutamide post ARPI and Docetaxel N=793

KEYNOTE-921 Docetaxel ± **Pembrolizumab** in 2n—line mCRPC N=1030

However…. Long-term Analysis of Ipilimumab Versus Placebo Following Radiotherapy



	Ipilimumab (*N* = 399)	Placebo (*N* = 400)
OS (mo), median (95% CI)	11.0 (9.5–12.5)	10.0 (8.4–11.2)
Piecewise HR (95% CI)	0–5 mo, 1.49 (1.12–1.99) 5–12 mo, 0.66 (0.51–0.86) Beyond 12 mo, 0.66 (0.52–0.84)	

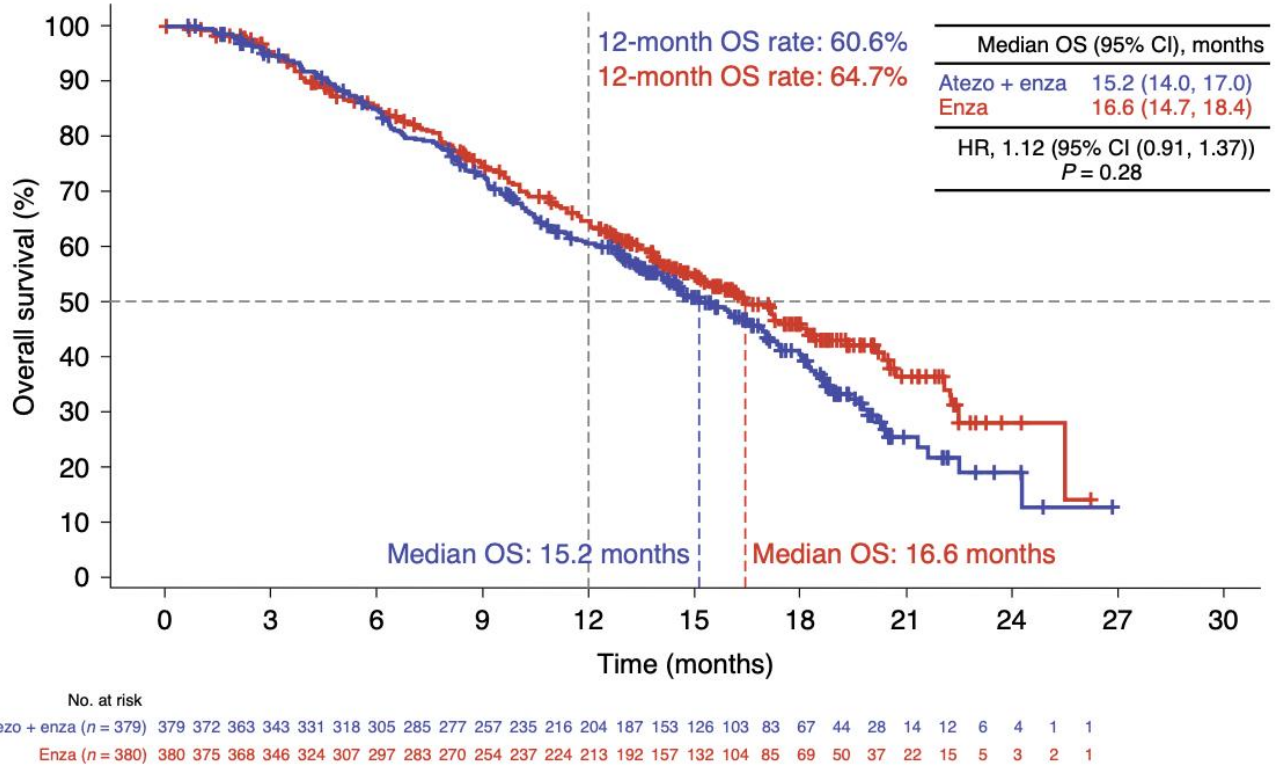
Fig. 1 – Overall survival. CI = confidence interval; HR = hazard ratio; OS = overall survival.

48m OS:
10.1% vs 3.3%

? Who are the patients with potential long-term benefit? Clinically applicable biomarkers remain elusive….

Fizazi et al. Eur Urol 2020, 822-830

Enzalutamide ± Atezolizumab (Imbassador 250)



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Enzalutamide ± Atezolizumab (Imbassador 250)

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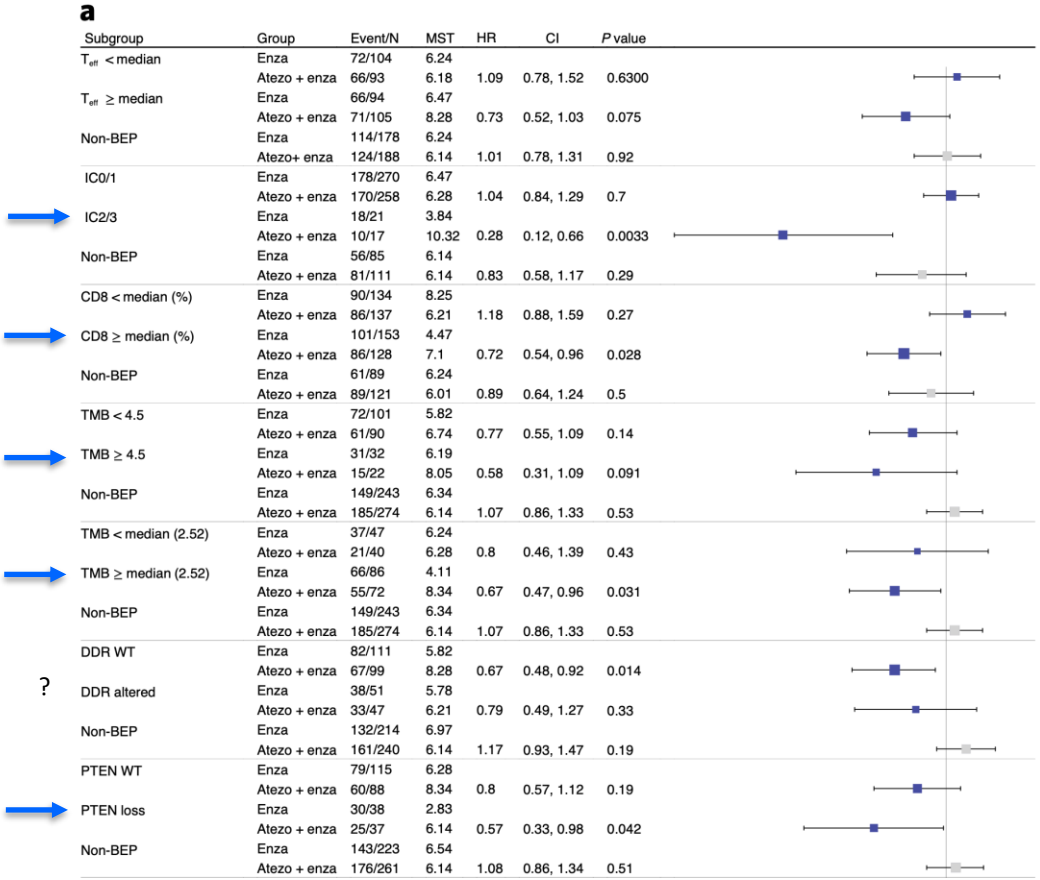
Subgroup	Group	Event/N	MST	HR	CI	*P* value
T_{eff} < median	Enza	72/104	6.24			
	Atezo + enza	66/93	6.18	1.09	0.78, 1.52	0.6300
T_{eff} ≥ median	Enza	66/94	6.47			
	Atezo + enza	71/105	8.28	0.73	0.52, 1.03	0.075
Non-BEP	Enza	114/178	6.24			
	Atezo+ enza	124/188	6.14	1.01	0.78, 1.31	0.92
IC0/1	Enza	178/270	6.47			
	Atezo + enza	170/258	6.28	1.04	0.84, 1.29	0.7
IC2/3	Enza	18/21	3.84			
	Atezo + enza	10/17	10.32	0.28	0.12, 0.66	0.0033
Non-BEP	Enza	56/85	6.14			
	Atezo + enza	81/111	6.14	0.83	0.58, 1.17	0.29
CD8 < median (%)	Enza	90/134	8.25			
	Atezo + enza	86/137	6.21	1.18	0.88, 1.59	0.27
CD8 ≥ median (%)	Enza	101/153	4.47			
	Atezo + enza	86/128	7.1	0.72	0.54, 0.96	0.028
Non-BEP	Enza	61/89	6.24			
	Atezo + enza	89/121	6.01	0.89	0.64, 1.24	0.5
TMB < 4.5	Enza	72/101	5.82			
	Atezo + enza	61/90	6.74	0.77	0.55, 1.09	0.14
TMB ≥ 4.5	Enza	31/32	6.19			
	Atezo + enza	15/22	8.05	0.58	0.31, 1.09	0.091
Non-BEP	Enza	149/243	6.34			
	Atezo + enza	185/274	6.14	1.07	0.86, 1.33	0.53
TMB < median (2.52)	Enza	37/47	6.24			
	Atezo + enza	21/40	6.28	0.8	0.46, 1.39	0.43
TMB ≥ median (2.52)	Enza	66/86	4.11			
	Atezo + enza	55/72	8.34	0.67	0.47, 0.96	0.031
Non-BEP	Enza	149/243	6.34			
	Atezo + enza	185/274	6.14	1.07	0.86, 1.33	0.53
DDR WT	Enza	82/111	5.82			
	Atezo + enza	67/99	8.28	0.67	0.48, 0.92	0.014
DDR altered	Enza	38/51	5.78			
	Atezo + enza	33/47	6.21	0.79	0.49, 1.27	0.33
Non-BEP	Enza	132/214	6.97			
	Atezo + enza	161/240	6.14	1.17	0.93, 1.47	0.19
PTEN WT	Enza	79/115	6.28			
	Atezo + enza	60/88	8.34	0.8	0.57, 1.12	0.19
PTEN loss	Enza	30/38	2.83			
	Atezo + enza	25/37	6.14	0.57	0.33, 0.98	0.042
Non-BEP	Enza	143/223	6.54			
	Atezo + enza	176/261	6.14	1.08	0.86, 1.34	0.51



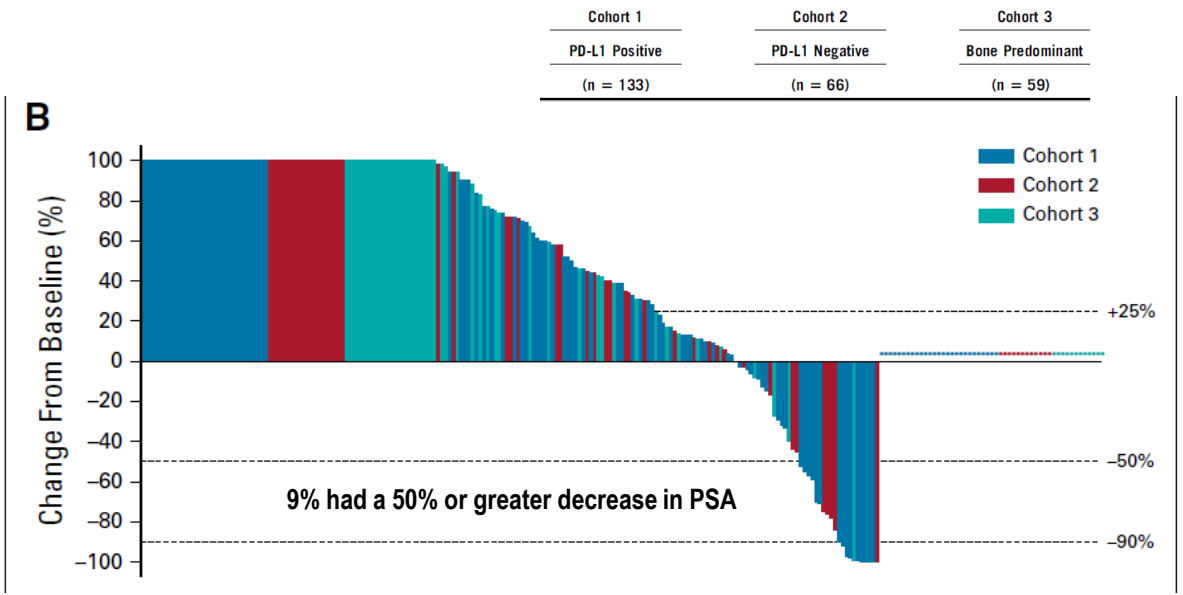
BEP= Biomarker evaluable population

Longer PFS in patients with:

- high PD-L1 IC2/3
- High- CD8 expression
- Established immune gene signatures
- Immune genes such as CXCL9 and TAP1…..
- 2 patients with MSI-high tumours were randomised to enzalutamide alone

Powles Nature Med 2022

Pembrolizumab in mCRPC: Keynote-199



Objective response rate (Cohort 1&2): **5%**

Little activity of pembrolizumab in unselected patients

Antonarakis J Clin Oncol 2019, 38:395-405

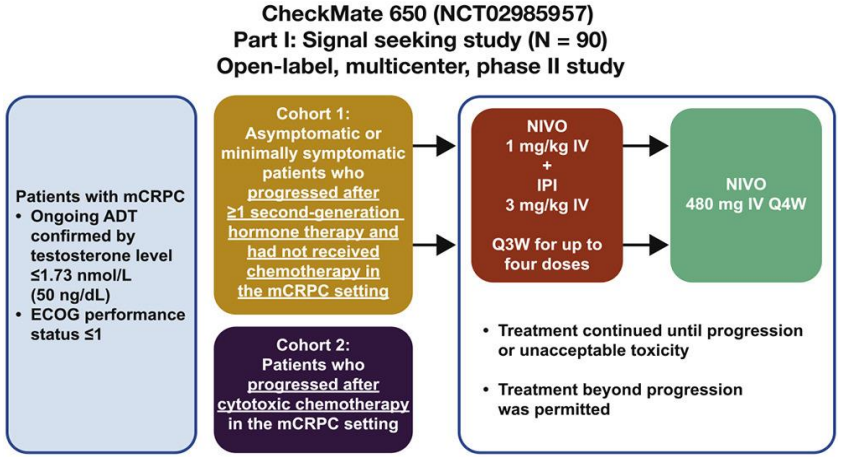
Biomarker Analysis of Keynote-199

TABLE A2. Tumor and PSA Response by Presence of Monoallelic and Biallelic Aberrations in *BRCA1/2*, *ATM*, or Other HRR Genes as Assessed by Whole-Exome Sequencing in Evaluable Patients in Cohorts 1, 2, and 3 Combined

Variable	*BRCA1/2* or *ATM* Aberrant (n = 19)	Aberrations in Other HRR Genes* (n = 10)	No Aberrations in HRR Genes (n = 124)
RECIST v1.1, central review			
ORR	2 (11)†	0	4 (3)
DCR (any duration)	4 (22)	0	22 (18)
Best response			
CR	0	0	2 (2)
PR	2 (11)	0	2 (2)
SD (any duration)	2 (11)	2 (20)	18 (15)
Non-CR/non-PD	1 (5)	0	7 (6)
PD	12 (63)	5 (50)	80 (65)
NE or missing	2 (11)	3 (30)	15 (12)
PSA response	2 (11)	1 (10)	4 (3)

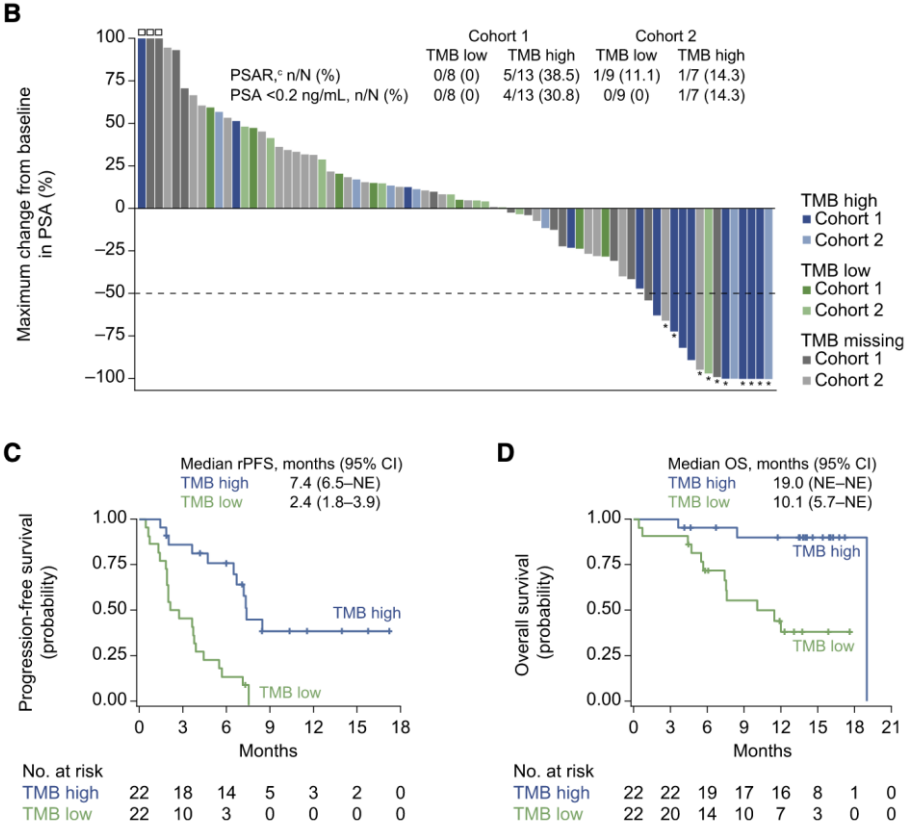
Antonarakis J Clin Oncol 2019, 38:395-405

CheckMate-650 – Combination Therapy?



Endpoints	Cohort 1 (n = 45)	Cohort 2 (n = 45)
Co-primary		
Investigator assessed ORR	25.0%	10.0%
rPFS	Median 5.5 months (95% CI, 3.5–7.1)	Median 3.8 months (95% CI, 2.1–5.1)
Secondary		
OS	Median 19.0 months (95% CI, 11.5–not evaluable)	Median 15.2 months (95% CI, 8.4–not evaluable)
Safety	Grade 3–4 treatment-related AEs in 42.2% of patients	Grade 3–4 treatment-related AEs in 53.3% of patients
Exploratory		
PSA response rate	17.6%	10.0%
Correlation of biomarkers with efficacy	Preliminary evidence of potential biomarkers of response	

Trial ongoing in randomised phase II part (4 arms)



Sharma et al., 2020, Cancer Cell 38, 489–499

Overview

Background

Checkpoint inhibition in unselected patients

- All phase III trials in **unselected** patients with mCRPC so far negative
- Promising biomarkers have been identified, validation pending

How can we use checkpoint inhibition in prostate cancer in 2022?

Ongoing trials

Tumour Agnostic Approval of Therapies

Molecular alteration	FDA	EMA
dMMR/MSI-high	Pembrolizumab tumour agnostic	Pembrolizumab: only selected in endometrium, CRC, small bowel, gastric, cholangio-carcinoma
dMMR	Dostarlimab tumour agnostic	Dostarlimab only in Endometrial-Ca (dMMR/MSI-high)
High TMB ≥10 mut/megabase	Pembrolizumab tumour agnostic	No approval for any therapies

Frequency of dMMR/MSI-high in Prostate Cancer

TABLE 1 Prevalence of germline and somatic MMR alterations

Study	Total patients	Disease state	Germline MMRd alterations, *N* (%)	Somatic MMRd or MSI-H, *N* (%)
Robinson et al.[10]	150	Metastatic	Not reported	3 (2)
Pritchard et al.[11]	692	Metastatic	4 (0.6)	Not reported
Abida et al.[12]	1033	Localized and metastatic	8 (0.8)	32 (3.1)
Latham et al.[13]	1048	Localized and metastatic	3 (0.3)	54 (5.2)
Nicolosi et al.[14]	3350	Localized and metastatic	58 (1.7)	Not reported

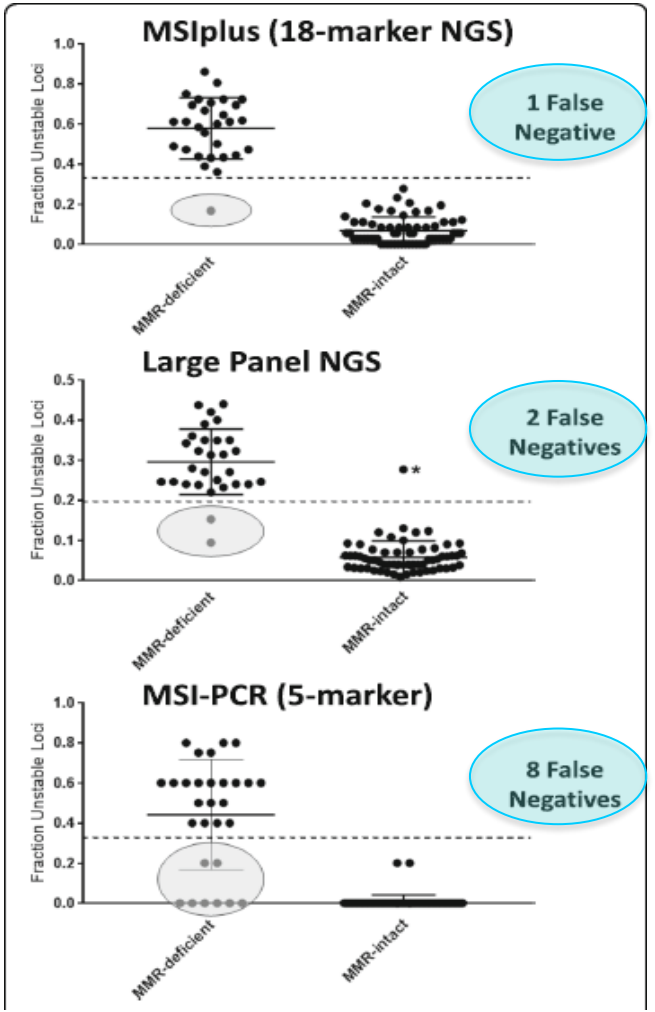
Abbreviations: MMRd, mismatch repair deficiency; MSI-H, microsatellite instability-high.

2-5% of patients with advanced prostate cancer have evidence of dMMR/MSI-high
The majority are somatic alterations

Graham et al. The Prostate. 2022;82:S37–S44

Testing Matters

- Testing for MSI: a prostate cancer specific assay is recommended including more than the traditional 5-marker PCR



NCCN v3.2022
Hempelmann et al. Journal for ImmunoTherapy of Cancer (2018) 6:29

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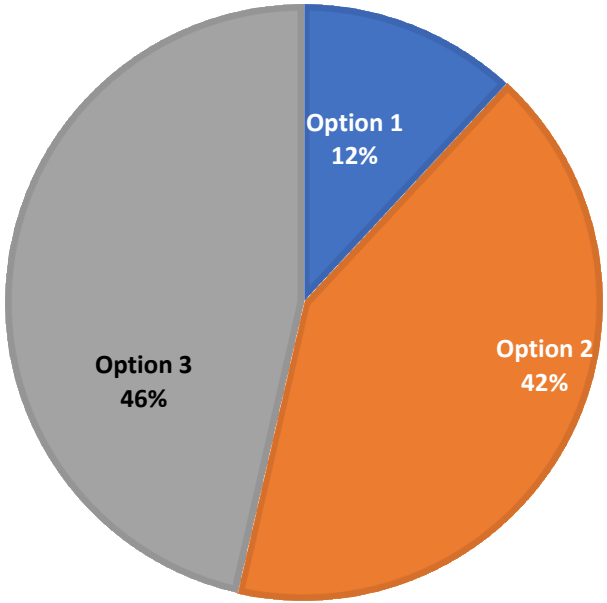
155. For evaluation of mismatch repair deficiency (MSI high) which tests do you recommend?

1. Immunohistochemistry (IHC) alone
2. Next-generation sequencing (NGS) analysis alone
3. A combination of IHC and NGS
4. Abstain/unqualified to answer



Option	Votes
Option 1	10
Option 2	35
Option 3	39
Option 4	20
Total votes	104

Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2022

Response to Checkpoint Inhibition

TABLE 2 Response to PD-1 blockade in MMRd prostate cancer

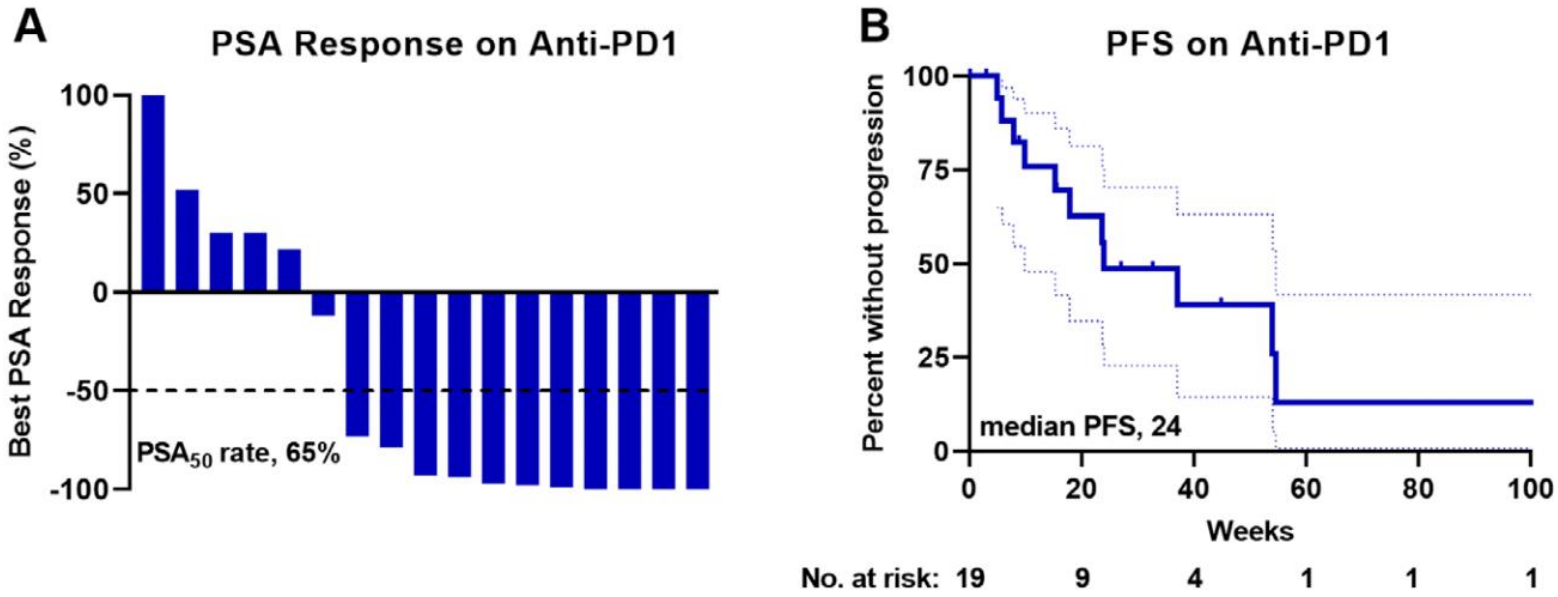
	Received PD-1 blockade and evaluable for response (*N*)	PSA50 response to PD-1 blockade, *n* (%)	Median clinical/radiographic PFS on PD-1 blockade months
Abida et al.[12]	11	6 (54.5)	NR
Antonarakis et al.[38]	4	2 (50)	9 (95% CI: 4–11)
Graham et al.[25]	15	8 (53)	Not reached (95% CI: 1.87–NR)
Barata et al.[43]	9	4 (44)	NR
Sena et al.[44]	17	11 (65)	5.5 (95% CI: 3.7–12.4)

Abbreviations: CI, confidence interval; MMRd, mismatch repair deficiency; NR, not reported; PFS, progression-free survival.

- Small series of patients
- Response rate similar to RR in patients with non-colorectal dMMR/MSI-high cancers

Graham et al. The Prostate. 2022;82:S37–S44

Example of Response to Checkpoint Inhibition

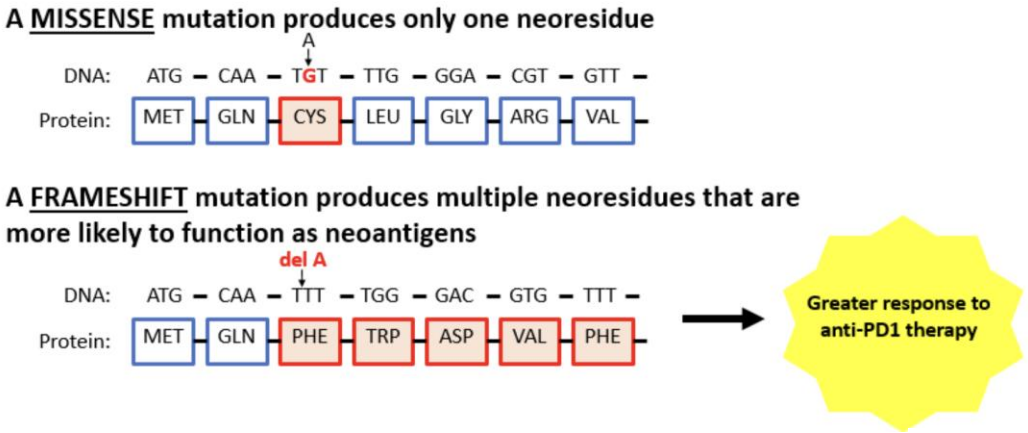


- Good rate of significant PSA declines
- But relatively short PFS of 6 months

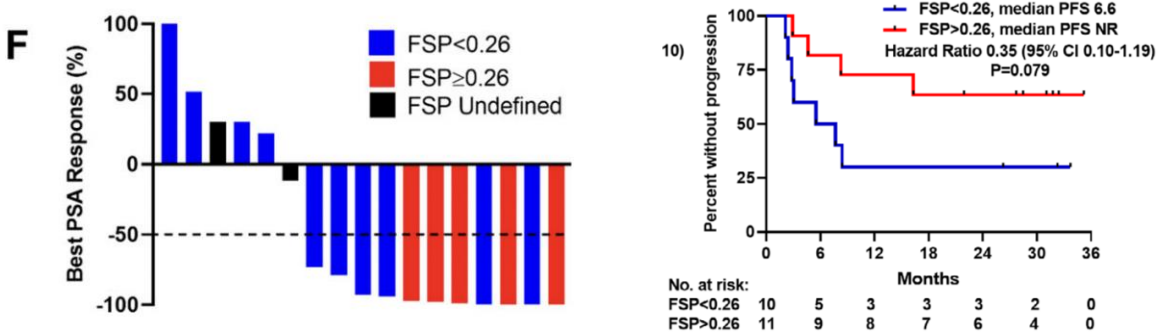
Sena et al. The Oncologist 2021;26:e270–e278

Response to Checkpoint Inhibition

Figure S1. Frameshift mutations are predicted to generate more neoantigens than missense mutations due to production of multiple neoresidues.



Tumor frameshift mutation proportion (FSP) correlats with PSA decline and with prolonged PFS (non-prostate cohort!)



Sena et al. The Oncologist 2021;26:e270–e278

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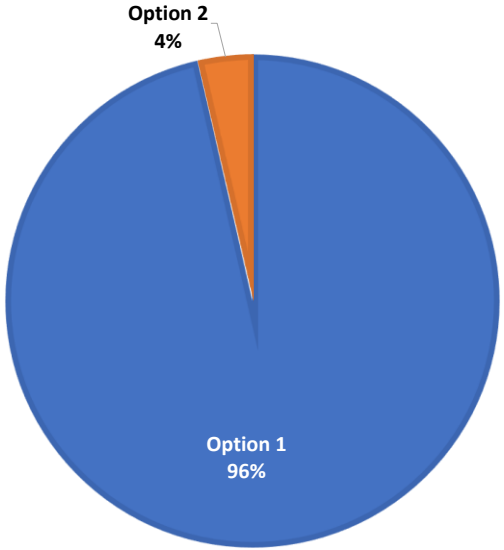
156. In the majority of patients with dMMR/MSI-high do you recommend treatment with an immune checkpoint inhibitor in the course of the disease?

1. Yes
2. No
3. Abstain/unqualified to answer

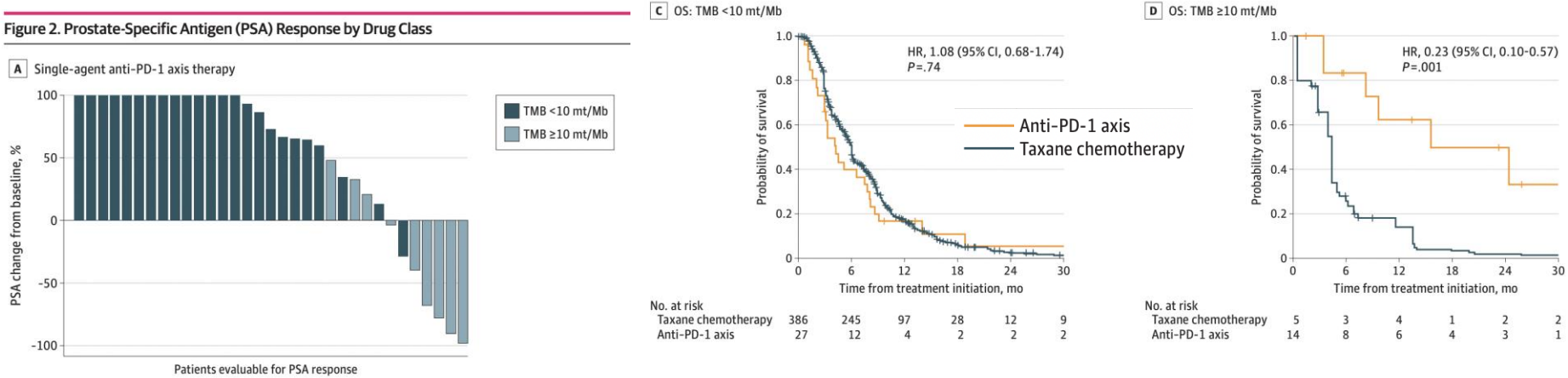


Option	Votes
Option 1	82
Option 2	3
Option 3	19
Total votes	104

Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2022

Tumour Mutational Burden

Data from US-wide Flatiron Health and Foundation Medicine deidentified clinicogenomic database



In this comparative effectiveness study, ICIs were more effective than taxanes in patients with mCRPC when:

- TMB was 10 mt/Mb or greater

Graf et al. JAMA Netw Open 2022 Mar 1;5(3):e225394

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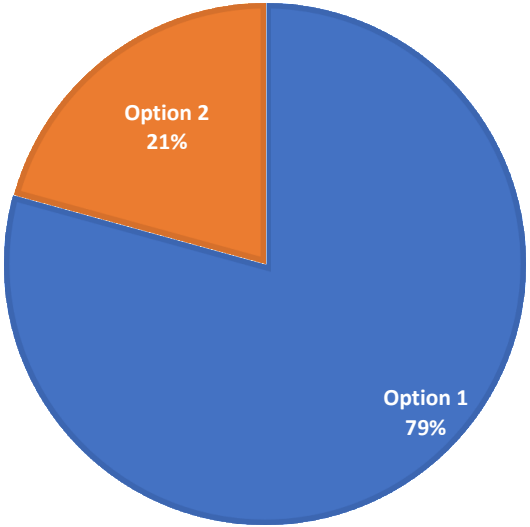
157. In the majority of patients with high tumour mutational burden (TMB ≥10 mutations/megabase) do you recommend treatment with an immune checkpoint inhibitor in the course of the disease?

1. Yes
2. No
3. Abstain/unqualified to answer



Option	Votes
Option 1	66
Option 2	18
Option 3	20
Total votes	104

Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2022

NCCN: Somatic Testing

- Can be helpful in decision making, for inclusion in clinical trials with molecular selection or to get access to targeted therapies
- Patients should be informed, that somatic testing result may indicate potential germline alteration
- Somatic testing may need to be repeated in case of tumour progression

<table>
<tr><th>Locally advanced</th><th>mHSPC or more advanced</th><th>mCRPC</th></tr>
<tr><td>Consider: BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2 und CDK12</td><td colspan="2">Recommended: BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2 und CDK12</td></tr>
<tr><td colspan="2">Consider: dMMR und MSI</td><td>Recommended: dMMR und MSI</td></tr>
<tr><td colspan="2"></td><td>Consider: TMB</td></tr>
</table>

NCCN v3.2022

Overview

Background

Checkpoint inhibition in unselected patients

How can we use checkpoint inhibition in prostate cancer in 2022?

- A small subset (2-5%) of patients with advanced prostate cancer have a molecular rationale for treatment with checkpoint inhibitors
- Based on very small series of patients, response rate seems promising but durability may be an issue

Ongoing trials

Phase III Trials to be Reported

Trial	Patient Population	Intervention	Read out
mHSPC			
Keynote-991	N=1232 mHSPC	ADT + Enzalutamide ± Pembrolizumab	07/2026
PROSTRATEGY	N=135 mHSPC	ADT + Docetaxel ADT + Docetaxel + Nivolumab ADT + Docetaxel alternating with Ipilimumab followed by Nivolumab	07/2022
mCRPC			
KEYNOTE-641	N=1200 mCRPC, first-line	Enzalutamide ± Pembrolizumab	11/2023
CheckMate7DX	N=984 mCRPC, post ARPI	Docetaxel ± Nivolumab	04/2024
CONTACT-02	N=580 mCRPC post ARPI	Cabozantinib plus Atezolizumab vs ARPI	03/2022

Ongoing Earlier Trials

Clinical Trial (Name, NCT, Phase)	Planned Number of Patients Patients' Characteristics	Pretreatment	Study Drug	Primary Endpoint	Estimated Completion Date
		Molecular-Selected Patients			
CHOMP trial NCT04104893 Phase II	$n = 30$ MMD or somatic biallelic inactivation of CDK12	One 2nd generation hormonal therapy for mCSPC, M0CRPC and/or mCRPC setting (i.e., abiraterone acetate, enzalutamide, apalutamide or darolutamide)	Pembrolizumab	PSA50 ORR	March 2023
PERSEUS1 NCT03506997 Phase II	$n = 100$ High mutational load (≥11 mutations per targeted panel) on NGS and/or DNA repair defect including MMD	≥1 approved treatment for mCRPC (i.e., abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, radium-233)	Pembrolizumab	PSA50 ORR	September 2023
INSPIRE NCT04717154 Phase II	$n = 75$ Immunogenic phenotype: MMD and/or high TMB (>7 mutations/Mb (cluster A); BRCA2 inactivation or BRCAness signature (cluster B); a tandem duplication signature and/or CDK12 biallelic inactivation (cluster C)	-	Nivolumab + ipilimumab for 4 cycles and nivolumab as maintenance (up to 1 year)	DCR	January 2026
IMPACT NCT03570619 Phase II	$n = 40$ Patients with metastatic cancers and CDK12 mutations: mCRPC (cohort A), metastatic solid tumors (non-prostate) (cohort B)	Patients must be ≥2 weeks from most recent systemic therapy or most recent radiation therapy	Nivolumab + ipilimumab for 4 cycles and nivolumab as maintenance (up to 1 year)	PSA50 ORR	September 2021
ImmunoProst trial NCT03040791 Phase II	$n = 38$ Patients with germline and somatic DRD (including HR and MMRd)	Documented prostate cancer progression, during treatment with docetaxel	Nivolumab	PSA response rate	January 2022
Neptunes NCT03061539 Phase II	$n = 175$ mCRPC patients with immunogenic biomarker positive disease (DRD–MMRd–high tumor-infiltrating lymphocyte)	1 or more lines of systemic treatment for mCRPC	Nivolumab + ipilimumab for 4 cycles and nivolumab as maintenance (up to 1 year)	PSA50 Radiological response conversion of CTC count	April 2022
NCT03248570 Phase II	$n = 50$ Patients with mCRPC with or without DNA damage repair defects	Patients must have received prior 2nd hormonal therapy (abiraterone, enzalutamide and/or apalutamide)	Pembrolizumab	rPFS	July 2023
NCT 04019964 Phase II	$n = 15$ Patients with at least one of the following genetic alterations: MMRd, MSIh, TMBh, inactivating mutation of CDK12	Prior local therapy with prostatectomy or EBRT/brachytherapy is required. Prior salvage or adjuvant radiation therapy is allowed but not mandated. Radiation therapy must have been completed for at least 6 months	Nivolumab	PSA50	January 2025

Rebuzzi et al. Cancers 2022, 14, 1245. https://doi.org/10.3390/cancers14051245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