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Original Article

Efficacy of Anti-PD-(L)1 Immunotherapy in Patients with DNA Mismatch Repair–deficient Metastatic Castration-resistant Prostate Cancer

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Abstract

Background and objective: Up to 5% of patients with metastatic castration-resistant prostate cancer (mCRPC) harbour loss-of-function alterations in mismatch repair genes (dMMR) resulting in microsatellite instability (MSI-H). Data on the efficacy of immune checkpoint inhibitors (ICIs) in dMMR mCRPC are limited, and reimbursement for these agents is not universally available.

Methods: We performed an international, multicentre, retrospective study to investigate the efficacy of anti-PD-(L)1 monotherapy in dMMR mCRPC. dMMR was defined as MMR protein loss on immunohistochemistry (IHC), and/or a deleterious alteration in an MMR gene or MSI-H status according to polymerase chain reaction analysis or next-generation sequencing. The primary endpoint was progression-free survival (PFS).

Key findings and limitations: Between July 2016 and July 2024, 93 patients with a median age of 70 yr (range 46–90) started anti-PD-(L)1 treatment. Patients were classified as dMMR on the basis of IHC results (n = 37, 40%), genomic alterations in MMR genes

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Microsatellite instability
Mismatch repair deficiency

(*n* = 55, 59%), and/or an MSI-H phenotype (*n* = 64, 69%). Among evaluable patients according to Response Evaluation Criteria in Solid Tumours v1.1, the objective response rate was 46% (*n* = 84; 95% confidence interval [CI] 35–58%). A prostate-specific antigen decline ≥50% was observed in 60% of evaluable patients (*n* = 68; 95% CI 48–72%). Median PFS across the entire cohort was 7.7 mo (95% CI 5.3–12.4), with 1-yr, 2-yr, and 3-yr PFS rates of 39%, 27%, and 26%, respectively. Median overall survival was 27.0 mo (95% CI 17.7–43.5). PFS was significantly longer for patients with positive dMMR status on two or more tests than for patients with just one positive dMMR test.

Conclusions and clinical implications: These data confirm the efficacy of anti-PD-(L)1 therapy in patients with dMMR mCRPC and warrant consideration of reimbursement for anti-PD-(L)1 agents in dMMR mCRPC by health authorities.

ADVANCING PRACTICE

What does this study add?

While the role of immune checkpoint inhibitors (ICIs) in tumours with deficient DNA mismatch repair (dMMR) has been well established across various cancers, there is a paucity of data on their efficacy in dMMR metastatic castration-resistant prostate cancer (mCRPC). This international, multicentre study provides compelling evidence that anti-PD-(L)1 monotherapy is a highly effective treatment option for patients with dMMR mCRPC. In addition, our data show that patients with consensus dMMR positivity according to two or more tests derive more benefit from ICIs than those with only one positive test, indicating that patients should be preferably selected for ICI therapy using a combination of dMMR tests.

Clinical Relevance

While the role of immune checkpoint inhibitors (ICIs) in tumours with deficient DNA mismatch repair (dMMR) has been well established across various cancers, there is a paucity of data on their efficacy in dMMR metastatic castration-resistant prostate cancer (mCRPC). This international, multicentre study provides compelling evidence that anti-PD-(L)1 monotherapy is a highly effective treatment option for patients with dMMR mCRPC. Associate Editor: Elena Castro.

Patient Summary

Our study looked at the efficacy of immunotherapy in a selected group of patients with prostate cancer deficient in DNA mismatch repair. We found that immunotherapy is a highly effective treatment option for these patients.

1. Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is generally insensitive to immune checkpoint inhibitors (ICIs), partly because of its relatively low tumour mutation burden (TMB) [1–5]. Up to 5% of patients with mCRPC have deficient DNA mismatch repair (dMMR) because they harbour loss-of-function alterations in mismatch repair genes, resulting in a microsatellite unstable hypermutated (MSI-H) phenotype that is thought to be more sensitive to ICIs in comparison to unselected mCRPC cohorts [6,7].

The anti-PD-1 inhibitor pembrolizumab is currently approved by the US Food and Drug Administration (FDA) but not the European Medicines Agency for the treatment of patients with dMMR solid tumours who lack satisfactory alternative treatment options. This approval was based on results from KEYNOTE-158 [8], in which pembrolizumab induced an objective response rate (ORR) of 31% in a cohort of 321 patients with noncolorectal solid tumours. Median progression-free survival (PFS) was 3.5 mo, and 1-yr, 2-yr, and 3-yr PFS rates were 34%, 27%, and 24%, respectively. The study included only eight patients with mCRPC, of whom two experienced an objective response.

While KEYNOTE-158 demonstrated the efficacy of anti-PD-1 therapy in dMMR solid tumours, the efficacy may differ among tumour types because of differences in tumour biology. Prostate cancers generally harbour a highly immunosuppressive tumour microenvironment with high myeloid infiltration, which possibly influences susceptibility to ICIs [9,10]. Literature on the efficacy of anti-PD-(L)1 monotherapy in dMMR mCRPC is limited to small studies

with a follow-up that seldom exceeded 1 yr [6,11–20]. The aim of this retrospective multicentre study was to improve insights into the efficacy of anti PD-(L)1 monotherapy in dMMR mCRPC.

2. Patients and methods

2.1. Study design and participants

In this international, multicentre study, we investigated the efficacy of anti-PD-(L)1 monotherapy in patients with dMMR mCRPC. Clinical data of patients with dMMR mCRPC were requested via the Dutch Drug Rediscovery Protocol and retrospectively collected from 18 hospitals in seven countries (NCT02925234). Eligible patients were treated with anti-PD-(L)1 monotherapy for dMMR mCRPC. Tumours were considered dMMR if one of the following criteria applied: (1) loss of MMR protein expression (MLH1, MSH2, MSH6, and/or PMS2) on immunohistochemistry (IHC); (2) a somatic or germline pathogenic or likely pathogenic genomic alteration in an MMR gene; and (3) MSI-H status according to polymerase chain reaction (PCR) analysis or any next-generation sequencing (NGS) test. NGS could be performed on tumour tissue or circulating tumour DNA (ctDNA). While we applied less stringent criteria for dMMR than in KEYNOTE-158 [8], we favoured this inclusive approach to reflect real-world use of anti-PD-(L)1 therapy for dMMR mCRPC and to gain more insight into appropriate selection criteria for dMMR with regard to ICI treatment.

This study was reviewed and deemed exempt by the local ethics committee (Radboudumc; reference no. 2023-16941). The study was conducted in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki.

2.2. Study endpoints

The primary endpoint was PFS according to physician assessment. Secondary endpoints included ORR according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, biochemical response rates (decrease in prostate-specific antigen [PSA] of $\geq$50% [PSA_{50}] or $\geq$90% [PSA_{90}]), and overall survival (OS). To assess the impact of the dMMR detection method on clinical outcomes, subgroup analyses were performed for patients with one, two, or three or more of the following features: (1) MMR protein loss on IHC; (2) a loss-of-function alteration in an MMR gene; (3) MSI-H status; and (4) a nonsynonymous TMB (nsTMB) >20 mutations/Mb, with a similar cutoff used for ctDNA and tissue [21]. Exploratory endpoints included associations between baseline characteristics and clinical outcomes. Sample size calculations are described in the Supplementary material.

2.3. Statistical analyses

Response rates and corresponding 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. PFS and OS were estimated using the Kaplan-Meier method. Cox proportional-hazards models were used to assess the association between baseline characteristics and clinical outcomes (PFS and OS). Data analysis was performed in R v4.4.0.

3. Results

3.1. Baseline characteristics

Between July 2016 and July 2024, 93 patients with a median age of 70 yr (range 46–90) started anti-PD-1 (94%) or anti-PD-L1 (6%) treatment. Twenty-four patients (27%) had visceral metastases, 52 (58%) had received prior taxane therapy, and 77 (87%) had received prior androgen receptor pathway inhibitors. The median number of prior therapies in the CRPC setting was 1 (range 0–7).

Patients were classified as dMMR on the basis of IHC (n = 37, 40%), genomic alterations in MMR genes (n = 55, 59%), and/or an MSI-H phenotype (n = 64, 69%). dMMR classification was based on a combination of findings for the majority of patients (n = 55, 59%), on IHC alone for ten patients (11%), on genomic alterations alone for ten patients (11%), and on MSI-H alone for 16 patients (17%) (Supplementary Fig. 1). For four germline carriers, dMMR or MSI-H status of the prostate cancer was not confirmed. Finally, in two patients (2%) the exact method of detection was not available. These patients were included in a clinical trial that mandated IHC loss of MMR protein expression and/or evidence of MSI-H according to PCR or NGS [22]. NGS was performed on tumour tissue for 61 patients (80%) and on ctDNA for 15 patients (20%). Median nsTMB was 31 mutations/Mb (range 2–268) among the 65 patients with data available.

The cohort included five patients with discordant dMMR testing results. One patient had a pathogenic alteration in *MSH2* and loss of MSH2 protein expression but a microsatellite stable (MSS) phenotype. Two patients had a germline MMR alteration but no evidence of MSI-H or MMR protein loss. Two patients had a pathogenic alteration in *PMS2* and MSS tumours.

A summary of the baseline characteristics is shown in Table 1.

3.2. Efficacy of anti-PD-(L)1 therapy in dMMR mCRPC

After a median follow-up of 16.3 mo (range 1.0–82.6), median PFS was 7.7 mo (95% CI 5.3–12.4) and the 1-yr, 2-yr, and 3-yr PFS rates were 39%, 27%, and 26%, respectively. Median OS was 27.0 mo (95% CI 17.7–43.5) and the 1-yr, 2-yr, and 3-yr OS rates were 71%, 53%, and 41%, respectively (Fig. 1).

Objective responses were observed in 39/84 patients with RECIST-evaluable disease (46%, 95% CI 35–58%), including ten patients with a complete response (12%) and 29 with a partial response (35%). The median duration of response among these patients was 41.0 mo (95% CI 11.7–not reached; Supplementary Fig. 2). Unconfirmed PSA_{50} and PSA_{90} responses were observed in 41 (60%) and 32 (47%) of 68 PSA-evaluable patients, respectively. Efficacy outcomes are summarised in Table 2.

The median duration of ICI treatment was 5.2 mo (range 1.0–43.4). Among the 76 patients who had discontinued

Table 1 – Patient characteristics for the study cohort (n = 93)

Parameter	Result	n[a]
Median age, yr (range)	70 (46-90)	90
Median WHO performance status score (range)	1 (0–3)	72
Median Gleason grade group at diagnosis (range)	5 (1–5)	80
M1 disease at initial diagnosis, n (%)	48 (57)	84
Histology, n (%)		78
Adenocarcinoma	76 (97)	
Ductal/intraductal histology	2 (3)	
Visceral metastases, n (%)	24 (27)	90
Liver metastases, n (%)	17 (19)	90
Prior local therapy, n (%)		87
Radical prostatectomy	20 (23)	
Radiotherapy	17 (20)	
None	50 (57)	
Median time from ADT initiation to CRPC, mo (range)	15 (2–176)	84
Median number of prior CPRC therapies (range)	1 (0–7)	89
Prior systemic therapies, n (%)[b]		89
Taxane	52 (58)	
Androgen receptor pathway inhibitor	77 (87)	
Radionuclide therapy	7 (8)	
Checkpoint inhibitor	3 (3)	
PARP inhibitor	4 (4)	
Other immunotherapy agent (sipuleucel-T, HPN424)	9 (10)	
Other	4 (4)	
Radiotherapy in the 3 mo before ICI therapy, n (%)	18 (21)	87
dMMR detection method, n (%)[c]		93
IHC	37 (40)	
Genomic alteration in an MMR gene	55 (59)	
Somatic ± germline alteration	51 (55)	
Germline only alteration	4 (4)	
MSI-H[d]	64 (69)	
Not known[e]	2 (2)	
Germline alteration, n (%)	11 (20)	55
MMR gene/protein affected according to IHC or NGS, n (%)		93
MLH1	11 (12)	
MSH2	51 (55)	
MSH6	43 (46)	
PMS2	7 (8)	
Unknown/none of the above[e,f]	18 (19)	
Median nsTMB, mutations/MB (range)[g]	31 (2–268)	65
nsTMB >10 mutations/Mb, n (%)[g]	51 (78)	65
nsTMB >20 mutations/Mb, n (%)[g]	45 (69)	65

ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; dMMR = DNA mismatch repair–deficient; IHC = immunohistochemistry; ICI = immune checkpoint inhibitor; MSI-H = microsatellite instability; NGS = next-generation sequencing; nsTMB = nonsynonymous tumour mutational burden; PCR = polymerase chain reaction.

[a] Number of patients with data available per variable.

[b] This includes therapies given in both the castration-sensitive and castration-resistant settings.

[c] Most patients had more than one test indicating dMMR positivity.

[d] MSI-H status was assessed via PCR assay or any NGS test (Supplementary Table 3).

[e] For two patients the exact method of dMMR detection was unknown, as they were included in a clinical trial that allowed inclusion on the basis of IHC loss of MMR protein expression and/or evidence of MSI-H according to PCR assay or any NGS test.

[f] For 16 patients with evidence of MSI-H on NGS, no genomic alteration could be identified.

[g] nsTMB was calculated using a variety of NGS panels for tumour tissue or circulating tumour DNA.

treatment at data cutoff, reasons for discontinuation included disease progression (n = 55, 72%), non–cancer-related death (n = 2, 3%), adverse events (n = 10, 13%), favourable response/treatment considered finished (n = 8, 11%), and decision to administer radiotherapy for oligoprogressive disease not meeting RECIST progression criteria (n = 1, 1%). At data cutoff, 17 patients were still receiving treatment, including two patients who continued treatment after receiving radiation therapy at the site of progression. Thirty-two patients (34%) started another line of systemic therapy after treatment discontinuation, whereas 49 (53%) did not (yet) start subsequent therapy. Data on subsequent treatment lines is missing for 12 patients (13%).

3.3. dMMR detection method and clinical outcomes

Given that ambiguous IHC results or MSI-indeterminate findings are not uncommon, we hypothesised that use of dMMR consensus on two or more tests would improve the accuracy of selecting patients likely to respond to ICI therapy. We thus performed a subgroup analysis for patients with one, two, or three or more of the following features: (1) loss of MMR protein expression; (2) a loss-of-function alteration in an MMR gene; (3) MSI-H status; and (4) nsTMB >20 mutations/Mb. Twenty-six patients (28%) had one positive test, 29 (31%) two positive tests, and 38 (41%) had three or four positive tests (Fig. 2A). PFS was significantly longer for the group with dMMR consensus on two or more tests than for the group with only one positive test (2 tests: hazard ratio [HR] 0.47, 95% CI 0.25–0.86; p = 0.015; ≥3 tests: HR 0.36, 95% CI 0.20–0.65; $p = 7.1 \times 10^{-4}$). In addition, OS was longer for the group with dMMR consensus on three or more tests than for the group with only one positive test (HR 0.50, 95% CI 0.28–0.89; p = 0.019). ORR and PSA responses also appeared to be favourable in patients with a higher number of positive tests (Fig. 2B–D and Table 2).

Closer examination of clinical outcomes for patients with only one positive test revealed that those with loss of MMR protein expression had outcomes comparable to those in the overall cohort (ORR 60%, median PFS 8.0 mo), while patients with MSI-H status or an altered MMR gene as the sole positive test had poorer outcomes. For the group of ten patients with MSI-H status as only positive test, the ORR was 10% and median PFS was 2.7 mo. Notably, MSI-H status was detected via ctDNA analysis in eight of these ten patients. Among the seven patients with an MMR gene alteration as the only feature, two of the four RECIST-evaluable patients had an objective response (ORR 50%), but median PFS for the seven patients was only 2.2 mo (Supplementary Table 1). Of note, this subgroup included four germline carriers with unconfirmed dMMR status of the prostate cancer. Among the five patients with discordant test results, only one patient had PFS >6 mo. Supplementary Tables 1–3 provide an overview of clinical outcomes by assay. An overview of dMMR tests per patient is shown in Fig. 3 and Supplementary Table 4.

3.4. Association between baseline characteristics and survival

Exploratory analyses were carried out to investigate the relationship between baseline characteristics and clinical outcomes (Supplementary Table 5). After adjusting for the number of positive dMMR tests (1, 2, or ≥3), younger age and the presence of visceral or liver metastases were associated with shorter PFS (p < 0.05) but not OS. By contrast, favourable World Health Organisation performance status

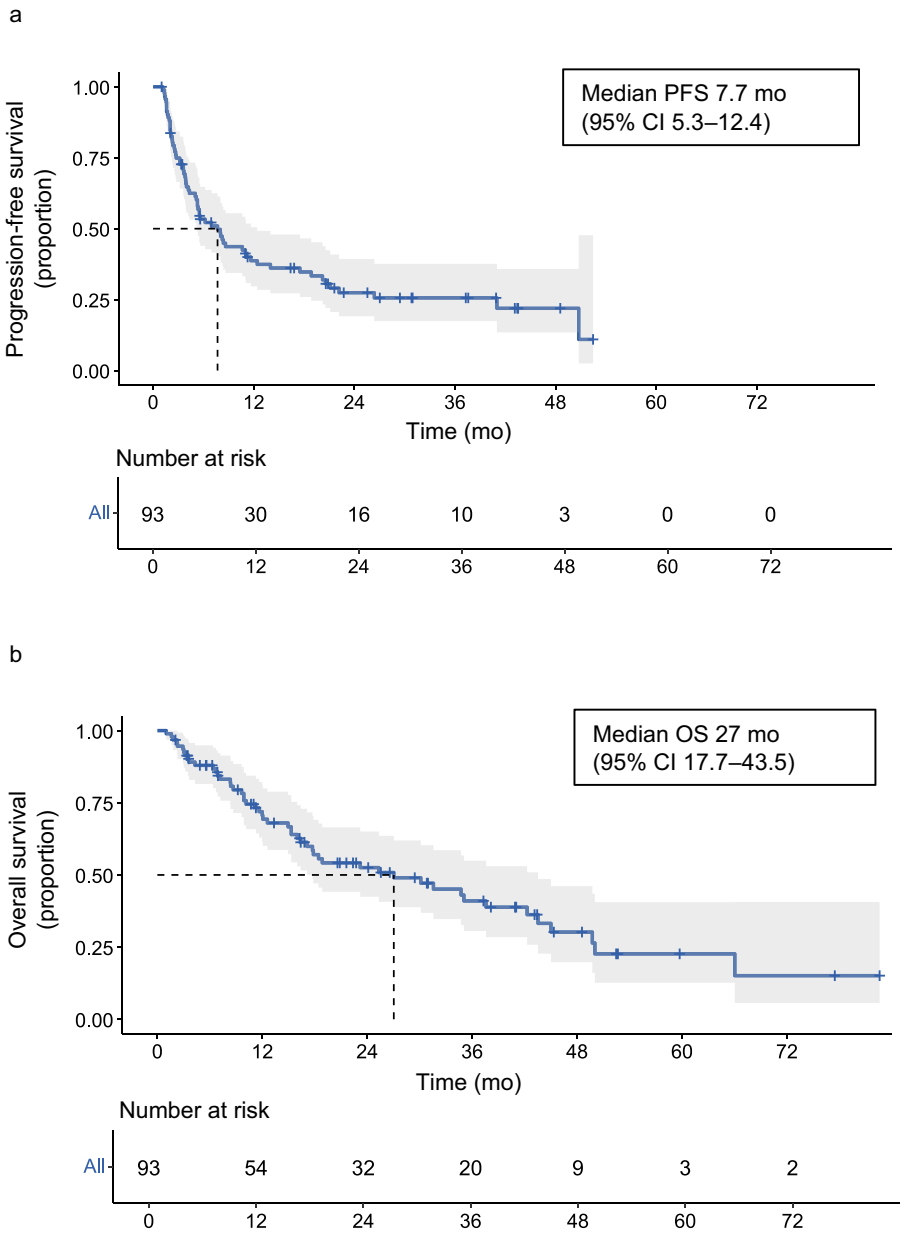

Fig. 1 – (A) Progression-free survival (PFS) and (B) overall survival (OS) in the overall cohort.

Table 2 – Efficacy of anti-PD-(L)1 therapy

Parameter	Total cohort		1 positive test		2 positive tests		≥3 positive tests	
	Result	*n*	Result	*n*	Result	*n*	Result	*n*
ORR, % (95% CI)	46 (35–58)	84	33 (15–57)	21	39 (22–59)	28	60 (42–76)	35
BOR, *n* (%)		84		21		28		35
Complete response	10 (12)		0 (0)		2 (7)		8 (23)	
Partial response	29 (35)		7 (33)		9 (32)		13 (37)	
Stable disease	23 (27)		7 (33)		9 (32)		7 (20)	
Progressive disease	22 (26)		7 (33)		8 (29)		7 (20)	
PSA_{50}, % (95% CI)	60 (48–72)	68	47 (23–72)	17	52 (31–73)	23	75 (55–89)	28
PSA_{90}, % (95% CI)	47 (35–60)	68	29 (10–56)	17	39 (20–61)	23	64 (44–81)	28
PFS, mo (95% CI)	7.7 (5.3–12.4)	93	3.4 (2.3–8.1)	26	5.6 (4.0–NR)	29	14 (8.4–NR)	38
OS, mo (95% CI)	27 (17.7–43.5)	93	15.3 (9.9–NR)	26	25.3 (15.0–NR)	29	43.5 (31.6–NR)	38

BOR = best objective response; CI = confidence interval; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; PSA_{50} = ≥50% decrease in PSA; PSA_{90} = ≥90% decrease in PSA.

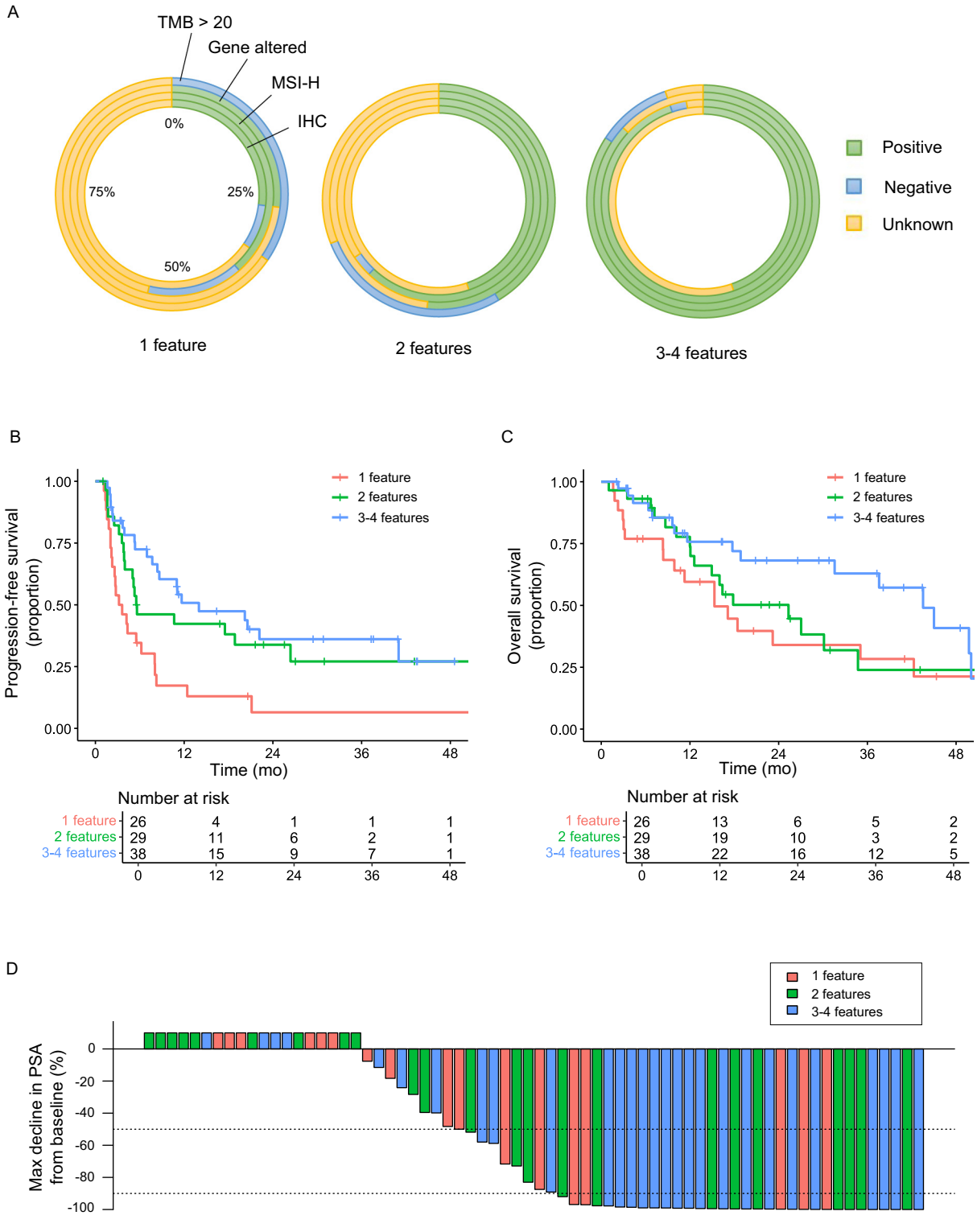

Fig. 2 – Clinical outcomes in subgroups with one, two, and three or more positive dMMR features. (A) The cohort was split into subgroups according to the number of dMMR-associated features. These features include: (1) loss of MMR protein expression on IHC; (2) a somatic or germline pathogenic or likely pathogenic alteration in one of the MMR genes; (3) microsatellite instability according to polymerase chain reaction analysis or next-generation sequencing (MSI-H); and (4) a nonsynonymous TMB >20 mutations/Mb. The diagram shows how many patients had a positive, negative, or unknown test result for each of these four features in the subgroups with one (*n* = 26), two (*n* = 29), or three or more (*n* = 38) dMMR-associated features. The two patients with missing data are included in the subgroup with one positive test. (B) Progression-free survival by subgroup. (C) Overall survival by subgroup. (d) Waterfall plot depicting the maximum percentage decline in PSA levels during treatment for those who were evaluable for PSA response. On-treatment PSA values were only collected for those with a PSA decline. For patients without a reduction in PSA levels during treatment, a value of +10% was imputed. dMMR = deficient MMR; IHC = immunohistochemistry; MMR = DNA mismatch repair; PSA = prostate-specific antigen.

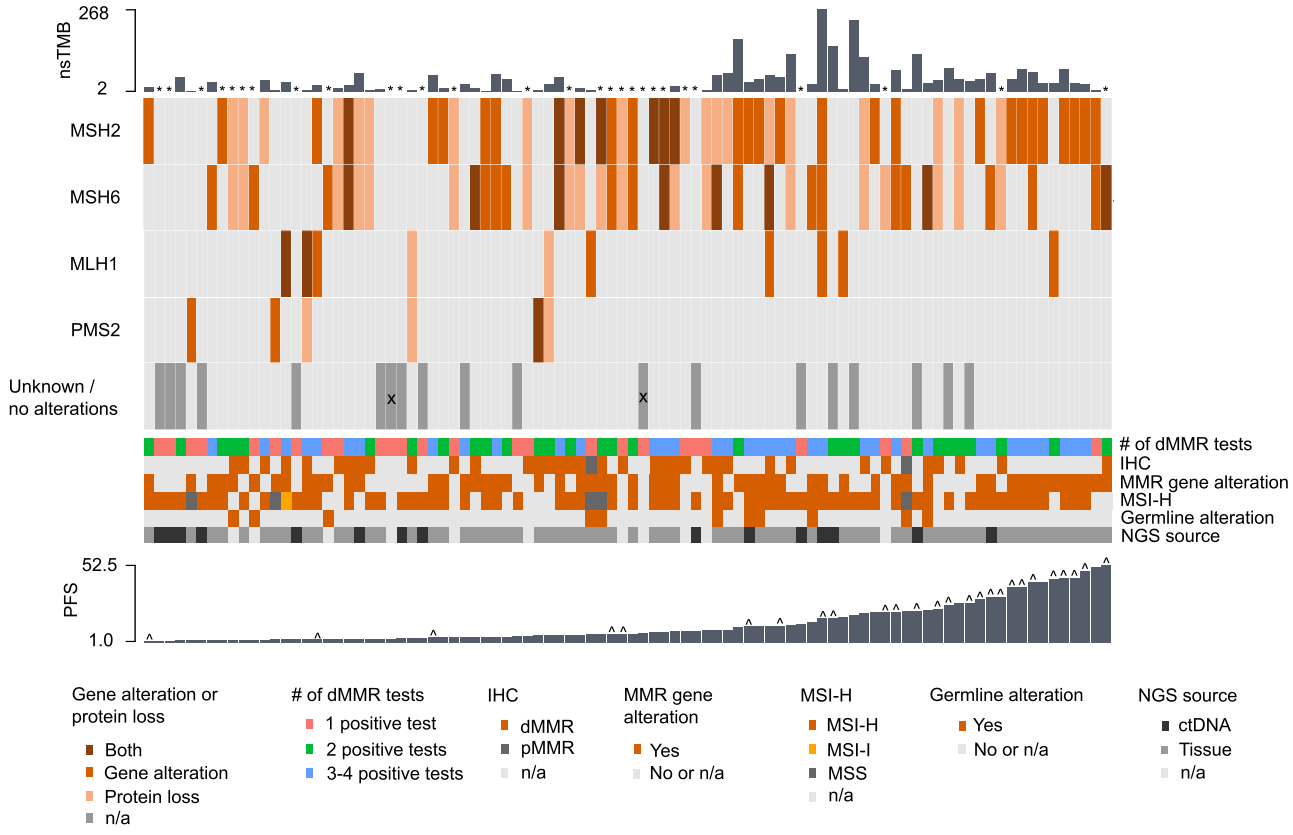

Fig. 3 – Overview of molecular characteristics and dMMR detection methods. At the top, nonsynonymous tumour mutational burden (nsTMB, mutations/Mb) is shown per patient for those with available data. Patients with missing data are denoted by an asterisk. Below, the affected MMR genes/proteins are shown. This includes data obtained by NGS and IHC as indicated by the different colours,. Next, the methods of dMMR detection are annotated. For two patients, the exact method for dMMR detection was unknown (denoted by X). Of note, information on nsTMB, MSI-H status, and gene alterations was obtained from a variety of NGS platforms as detailed in Supplementary Table 3. If NGS was performed, the "NGS source" bar indicates if it was performed on tumour tissue or ctDNA. Patients are ordered by increasing PFS at data cutoff, as shown at the bottom. Patients with ongoing PFS at data cutoff are denoted by carets (^) on top of the PFS bars. ctDNA = circulating tumour DNA, dMMR = deficient DNA mismatch repair; IHC = immunohistochemistry; n/a = not assessed; NGS = next-generation sequencing; MMR = mismatch repair; MSI-H = microsatellite instability; MSI-I = MSI-indeterminate; MSS = microsatellite stable; pMMR = proficient mismatch repair; PCR = polymerase chain reaction; PFS = progression-free survival.

and nsTMB >20 mutations/Mb were associated with longer PFS and longer OS ($p < 0.05$). Patients with alterations in *PMS2* or a lack of PMS2 expression had significantly poorer PFS and OS. However, it should be noted that the number of patients with PMS2 inactivation was low ($n = 7$) and included two patients with a discordant second dMMR test result. Neither the number of prior therapies in the mCRPC setting nor the prior use of taxanes was significantly associated with PFS or OS in the overall cohort. However, after exclusion of patients with only one positive dMMR test, we found a significant association for both parameters, with a higher number of prior therapies and prior use of taxanes associated with shorter PFS (Supplementary Table 6).

4. Discussion

This international, multicentre study assessed the efficacy of anti-PD-(L)1 therapy in a large cohort of 93 patients with dMMR mCRPC. Our data confirm the efficacy of anti-PD-(L)1 therapy in patients with dMMR mCRPC and demonstrate outcomes comparable to those in other noncolorectal dMMR solid tumours [8]. Particularly remarkable, given the typically poor prognosis of mCRPC, is the observation that 26% of patients remained progression-free after 3 yr of follow-up.

Various clinical trials have investigated the efficacy of ICIs in unselected patients with mCRPC without success [1–5,23]. The phase 2 KEYNOTE-199 trial, which is the largest trial investigating anti-PD-1 monotherapy in mCRPC, demonstrated that pembrolizumab monotherapy led to objective responses in only 3–5% of patients with mCRPC [3]. These results indicate that ICIs should be withheld from the majority of mCRPC patients and should only be administered to selected subgroups that are more susceptible to ICIs, such as those with dMMR mCRPC. While data on the efficacy of anti-PD-(L)1 monotherapy in dMMR mCRPC have been limited to small cohort studies [6,11–20], more robust data are available on the efficacy of dual ICIs in this subgroup. The phase 2 INSPIRE trial recently showed that the combination of ipilimumab and nivolumab is highly efficacious, with an ORR of 75% and PFS of 32.7 mo in a dMMR mCRPC cohort [24]. While PFS with dual ICIs in INSPIRE appears to be longer than with anti-PD(L)1 monotherapy in the present study, an important downside of dual ICI therapy is its high toxicity, with 48% of patients experiencing grade ≥3 treatment-related adverse events in INSPIRE.

Anti-PD-(L)1 monotherapy provides an effective, but less toxic, alternative.

Given the low incidence of dMMR mCRPC, comparative analysis of the efficacy of ICIs within the context of a randomised controlled trial will be challenging. Despite the retrospective nature of our study, we believe these data provide compelling evidence that anti-PD-(L)1 monotherapy is a highly effective treatment option for patients with dMMR mCRPC and strongly support its consideration for reimbursement by European health authorities.

Anti-PD-(L)1 therapy is currently only approved by the FDA for patients with dMMR mCRPC who lack other satisfactory treatment options. However, responses to anti-PD-(L)1 therapy appear to be favourable in comparison to standard-of-care second- and later-line treatment options [25,26]. In our opinion, the high efficacy of anti-PD-(L)1 therapy in dMMR mCRPC, as observed in this study, justifies the use of ICIs before other treatment options have been exhausted and highlights the need for collaborative international efforts to investigate ICIs in earlier settings, including front-line mCRPC and metastatic castration-sensitive prostate cancer. Our observation that the number of prior therapies and prior taxane lines are negatively associated with PFS, albeit only in those with two or more dMMR features, further supports this position.

Our data suggest that the use of a single dMMR test does not accurately identify patients with dMMR. In particular, use of (germline) MMR gene alterations or MSI-H phenotype as a sole selection criterion was associated with poor response to ICIs. It is well known that Lynch syndrome carriers can develop MMR-proficient MSS tumours. Elze and colleagues [27] recently showed that only 28% of prostate cancers developing in germline carriers are dMMR. Somatic loss-of-function alterations in MMR genes, however, also do not necessarily result in dMMR because such alterations are not always biallelic or clonal. In addition, loss of *MSH6* and *PMS2* may not always cause dMMR because functional redundancy exists in MMR proteins [28].

While MSI-H status has traditionally been evaluated via PCR-based approaches that used only five microsatellite loci, several groups have aimed to improve MSI-H detection using NGS-based approaches that allow simultaneous analysis of a large panel of microsatellite loci. NGS-based approaches have shown high sensitivity and specificity in comparison to PCR [29–31]. Prior studies demonstrated that NGS-based MSI-H detection can also be reliably performed using ctDNA, with a detection limit of 10% ctDNA [32]. Nevertheless, MSI-H detection is not always reliable as a sole biomarker, as PCR-based approaches are not optimised for mCRPC [33] and NGS cutoffs for MSI-H are poorly defined, particularly when using ctDNA. This may lead to misclassification of a significant proportion of patients [34,35]. We used different methods to detect MSI-H in our cohort, including ctDNA-based approaches. Our results highlight the need for further optimisation of NGS thresholds for MSI-H [30].

While patients selected using IHC as the sole test appeared to fare better than patients selected using another single assay, IHC may also sometimes result in false-positive or false-negative findings. First, some loss-of-function alterations lead to nonfunctional MMR proteins that are still detected on IHC [36]. In addition, it has been shown that colorectal cancer specimens sometimes demonstrate loss of MSH6 protein expression without underlying dMMR after systemic therapy [37]. Moreover, IHC interpretation requires an experienced pathologist to avoid inaccurate findings [38]. Therefore, the European Society for Medical Oncology recommends performing confirmatory testing if there is any uncertainty regarding the IHC result. This includes not only disagreements or difficulties in interpreting IHC, but also loss of only one heterodimer subunit, such as only MSH2 or MSH6 and not both (Supplementary Table 3) [39].

While not specific for dMMR tumours, we included high TMB as a biomarker because it adds confidence to the diagnosis of dMMR. Most dMMR mCRPC tumours have a TMB >10 mutations/Mb [6,7,24]. The relative high percentage of patients with TMB <10 mutations/Mb in our cohort suggests that some patients might not have had true dMMR status. While patients with dMMR mCRPC do not necessarily exhibit a TMB of >20 mutations/Mb, we favoured this higher cutoff as it may provide additional predictive value for response to ICIs [40].

On the basis of the higher ICI efficacy in patients with two and especially three or more positive dMMR features versus those with only one, we suggest preferential selection of patients with mCRPC for ICI therapy according to dMMR consensus based on a combination of at least two features. If access to NGS is limited, IHC assessment of MMR proteins alone by an experienced pathologist might be a reasonable alternative.

Limitations of our study include its retrospective design and missing data. Specifically, we lacked complete information on MMR protein expression, MMR gene alterations, MSI-H status, and TMB for all patients, as well as data on the zygosity of MMR gene alterations. In addition, the broad definition of dMMR and the use of various assays for TMB and MSI-H detection, including both tumour- and ctDNA-based methods, can be considered a limitation of the study. Owing to the broad definition of dMMR, we may have included sporadic MSS tumours in Lynch syndrome carriers, and MSS tumours harbouring pathogenic alterations in one of the MMR genes. As a result, clinical outcomes for the overall cohort are likely to underestimate the efficacy of anti-PD-(L)1 in truly deficient dMMR tumours. Nevertheless, we believe that our more inclusive approach offers valuable insights into the efficacy of ICIs in a real-world population of patients with mCRPC classified as having dMMR tumours, while also providing clinically relevant information on dMMR testing.

5. Conclusions

In conclusion, these multicentre real-world data confirm the efficacy of ICIs in patients with dMMR mCRPC. We are hopeful that the results of this study will encourage health authorities to consider reimbursement for anti-PD-(L)1 therapies for dMMR mCRPC in countries outside the USA.

Author contributions: Sandra van Wilpe had full access to all the data in

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Appendix A. Supplementary data

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