

How I treat MSI cancers with advanced disease



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ABSTRACT

Mismatch repair deficiency (dMMR) results in microsatellite instability (MSI) and is strongly associated with responsiveness to programmed death-1 receptor (PD-1)-blocking antibodies. Probably the main driver for the observed high efficacy of immune checkpoint inhibitors in dMMR tumours is the remarkably high tumour mutational burden. MSI can be detected using immunohistochemistry and/or PCR. In addition, next-generation sequencing is becoming increasingly available to clinical laboratories as a cost-effective and scalable method to evaluate multiple genetic aberrations including MSI. Efficacy of PD-1-blockade in MSI tumours is similar for patients with colorectal cancer (CRC; objective response rate (ORR) 36%) or a different cancer type (ORR 46% across 14 other cancer types). Based on these results, PD-1-blocking antibody pembrolizumab was the first tumour-agnostic treatment to be granted Food and Drug Administration approval based on the presence of MSI as a biomarker. Currently, there is no approved PD-1-blocking antibody for MSI cancers in Europe. Here, we present our experience with the screening for MSI and the treatment of patients with advanced disease of MSI CRC and non-CRC with immunotherapy.

Immunotherapy with immune checkpoint inhibitors has been very successful in a number of tumour types. The highest objective response rates (ORR) are observed among tumours with high tumour mutational burden (TMB), including melanoma, Merkel cell carcinoma (Merkel cell polyomavirus (MCPyV)-negative), cutaneous squamous cell carcinoma, a TMB-high subset of (non)-small-cell lung cancer and microsatellite instability (MSI) cancers. MSI tumours may be sporadic or result from germline mutations in mismatch repair (MMR) genes (Lynch syndrome), and have by far the highest TMB of all cancers, with often >1000 non-synonymous genomic mutations. It is very likely that the high TMB is the key driver for the observed high ORR in these tumours, creating a permissive inflamed tumour microenvironment. With the recent accelerated Food and Drug Administration (FDA) approval of pembrolizumab for the treatment of patients with advanced MSI tumours, regardless of tumour site or histology, programmed death-1 receptor (PD-1) blockade has become a highly relevant treatment option

for this patient population. The registration of pembrolizumab in this setting was based on data from 149 patients with MSI cancers enrolled across five uncontrolled, multicohort, single-arm trials. Ninety patients had colorectal cancer (CRC) and 59 patients were diagnosed with 1 of 14 other cancer types.^{1–3} The objective response rate (ORR) was 36% for patients diagnosed with CRC and 46% for patients with any of 14 other histology MSI tumours. The identification of MSI status for the majority of patients was prospectively determined using immunohistochemistry (IHC) tests for MMR proteins or local PCR tests for MSI status. To date, there is no approval of any PD-1-blocking antibodies for MSI cancers in Europe. Here, we present our experience at the Netherlands Cancer Institute (NKI) with screening for MSI, and treatment of patients with advanced disease of MSI non-CRC and CRC tumours with immunotherapy, either within clinical trials or patient access programmes.

Although not routinely tested, MSI can be found in other cancer types outside the more common Lynch syndrome-associated gastrointestinal and endometrial cancers, at a frequency of around 2%–4%.^{4,5} Traditionally, identification of MSI has relied on immunohistochemical detection of loss of MMR protein expression (MLH1, MSH2, MSH6 and PMS2) or PCR-based analysis using five microsatellite markers, including BAT-25 and BAT-26. Next-generation sequencing (NGS) is becoming increasingly available to clinical laboratories as a cost-effective and scalable method to evaluate multiple genetic aberrations in parallel, allowing linking of MSI status to TMB. Consequently, initiatives to incorporate MSI testing in NGS-based cancer gene panels have emerged,^{6,7} illustrated by two FDA-authorized NGS platforms now incorporating MSI-calling algorithms. These efforts allow the selection of individual patients with incurable metastatic disease for clinical immunotherapy trials via the screening for MSI.

COLORECTAL CANCER

MSI CRC comprises around 15% of all primary CRCs, of which 2%–3% are the

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result of germline mutations in one of the four MMR genes. In metastatic CRC (mCRC), less than 5% is MSI. Currently, several trials are ongoing in patients with MSI mCRC with either single-agent PD-1/programmed death receptor ligand-1 (PD-L1) inhibitors, or in combination with either cytotoxic T-lymphocyte associated protein-4 (CTLA-4) blockade, targeted therapies and/or chemotherapy. Since many of these studies include control arms, results are eagerly awaited and will hopefully lead to European Medicines Agency (EMA) approval of immune checkpoint blockade as a standard of care for patients with MSI mCRC. In the meantime, these patients are being treated with PD-1/PD-L1 inhibitors within clinical trials in the Netherlands. Another way of treating these patients with immunotherapy when they do not fulfil the criteria for clinical trials or when trials are not available is by acquiring PD-1 blockade through patient access programmes. Ultimately, checkpoint blockade in MSI mCRC provides clear benefit in a heavily pretreated population, and data from randomised controlled trials are needed for approval in Europe.

At the NKI, all patients with mCRC undergo MSI testing, using IHC for all four MMR proteins. Often, MSI testing has already been done at the time of diagnosis as this is advised in national guidelines in all patients under 70 years of age. In patients with MSI mCRC tumours harbouring BRAF mutations, immunotherapy is preferred over tyrosine-kinase inhibitors when possible. Patients with stage I–III colon cancers are routinely tested for MSI, and within the NKI and other participating centres in the Netherlands the possibility of neoadjuvant immunotherapy in a clinical trial setting is discussed.

NON-CRC

To date, PD-1-blocking antibodies are not approved for treatment of MSI cancers in Europe. Therefore, patients with advanced MSI cancers are entirely dependent on access to clinical trials or patient access programmes with immune checkpoint inhibitors. Given that the number of immunotherapy trials entering individuals based on high TMB⁸ or MSI status is increasing, it is becoming more customary and worthwhile to screen certain patient subgroups for MSI. At the NKI, we consider MSI screening for patients fulfilling the following criteria: (1) advanced disease, (2) no standard treatment options or only treatment options for which limited efficacy can be expected, (3) histologies outside tumour types for which PD-1/PD-L1-blocking antibodies have been approved (melanoma, lung cancer, bladder cancer, renal cell carcinoma and so on), (4) no severe autoimmune disease, and (5) WHO performance status and laboratory findings that allow participation in a clinical trial. In patients with gastrointestinal cancers other than CRC, subgroups of breast cancer, prostate and endometrial cancers who fulfil these criteria, it has become common practice to test for MMR deficiency. Also, MSI testing is performed in patients with non-metastatic gastro-oesophageal junction

and gastric cancers due to the availability of neoadjuvant immunotherapy trials (NCT03448835). With the emergence of neoadjuvant immunotherapy trials, for example breast cancer, it is expected that there will be a significant increase in MSI testing in a broad spectrum of tumour types in the early-stage disease setting.

The method of choice for screening for MSI depends on (cancer gene panel) sequencing options available in the hospital laboratory or at affiliated (commercial) institutes. Besides, certain trials offer screening for high TMB or MSI as part of the prescreening. However, given that IHC for MMR proteins and/or PCR for MSI detection is widely available, in most cases screening for MSI will start with IHC for the four MMR proteins and/or the PCR-based test. Of note, although these immunohistochemical and PCR assays are highly sensitive methods for the identification of MSI in CRCs, little is known about the likelihood of false-negative results and heterogeneity of the IHC staining in other tumour types. NGS studies in which IHC analyses for MMR protein expression are directly compared with NGS data suggest that MSI calling is highly concordant between these two assays.⁹

In addition, given that MSI is predictive of Lynch syndrome across a much broader tumour spectrum than is currently appreciated, germline assessment for Lynch syndrome should be considered for patients with an MSI tumour, regardless of cancer type or family history.¹⁰ At the NKI, patients with MSI tumours of any origin without an underlying (somatic) MLH1 hypermethylation are referred for genetic counselling.

FUTURE PERSPECTIVE

Immunotherapy with immune checkpoint inhibitors for patients in Europe with advanced MSI tumours will largely depend on EMA approval. Based on the current landscape of clinical trials in CRC versus non-CRC, the timing and details of this approval might come earlier for advanced CRC compared with the tumour-agnostic indication. Awaiting the data of ongoing trials, two fields of research are of particular interest for patients with MSI cancers. First, although the ORR with anti-PD-(L)1 monotherapy is high compared with other tumour subtypes, there is still a substantial proportion of patients with advanced MSI tumours that do not benefit from PD-(L)1-blocking antibodies. Progress in more fundamental immunological research should provide further insight into both the exact mechanism of tumour recognition as well as the immune cell types involved in tumour control of MSI cancers.¹¹ These data should thereby provide rationale for novel immunomodulatory approaches for MSI cancers. Second, neoadjuvant trials in melanoma^{12–14} and lung cancer¹⁵ have now shown that the response rate to immune checkpoint inhibition may be substantially higher when these treatments are given early in the disease course. Importantly, our preliminary data suggest that preoperative immunotherapy in patients with MSI colon cancer (NCT03026140) can result in an extremely

high major pathological response rate and has the potential to change the standard of care for early MSI-related cancers.

Contributors All authors contributed equally.

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