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Therapy with pembrolizumab in treatment-naïve patients with non-metastatic, mismatch repair deficient colorectal cancer

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Key words: Colorectal cancer; unresectable; mismatch repair deficient; checkpoint inhibition; pembrolizumab.

Abbreviations

CRC: Colorectal cancer**, CT:** Computed tomography, **ctDNA:** circulating tumor DNA, **DCCG:** Danish Colorectal Cancer Group, **dMMR:** Deficient mismatch repair**,** , **FDA:** U.S. Food and Drug Administration, **5-FU:** 5-fluorouracil, **ICI:** immune checkpoint inhibitors, **IHC:** Immunohistochemistry, **mCRC:** Metastatic colorectal cancer**, MDT:** Multidisciplinary team meeting, **MRI:** magnetic resonance imaging, **MSI:** Microsatellite instable, **PCR:** Polymerase chain reaction, **PD-1:** programmed cell death-1, **PET:** Positron emission tomography, **pMMR:** Proficient mismatch repair

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Abstract

Therapy with immune checkpoint inhibitors (ICI) is effective in patients with metastatic mismatch-repair deficient (dMMR) colorectal cancer (CRC); however, data on treatment with neoadjuvant ICI in patients with locally advanced CRC are limited. From March 2019 to June 2020, five Danish oncological centers treated 10 patients with a treatment-naïve dMMR CRC with pre-operative pembrolizumab, 9 with a non-metastatic, unresectable colon cancer and 1 with a locally advanced rectum cancer. All 10 patients were evaluated regularly at a multidisciplinary team (MDT) meeting, and they all had a radical resection after a median of 8 cycles (range 2−13) of pembrolizumab. A microscopic evaluation of the resected tumors revealed no remaining tumor cells in 5 patients, while 5 still had tumor cells present. The patients were given no additional therapy. No recurrences were reported after a median follow-up of 26 months (range 23–38.5 months).

Biopsies from Danish patients with CRC are routinely screened for dMMR proteins. In 2017, data from the Danish Colorectal Cancer Group showed that 19% (565/3000) of the patients with colon cancer and 1.5% (19/1279) of those with rectum cancer had an dMMR tumor. Among the patients with MMR determination, 26% (99/384) patients had a T4 dMMR colon cancer; thus, the 10 patients treated with neoadjuvant pembrolizumab comprised about 9% of the patients with a T4 dMMR colon cancer (9/99) and 5% of patients with dMMR rectal cancer (1/19). Therapy with pembrolizumab was feasible and effective. Larger prospective trials are needed to confirm our findings.

Highlights

1. Annually, T4 dMMR CRC is diagnosed in 26% of Danish colon cancer patients, and dMMR rectum cancer is diagnosed in 1.5%.
2. Initial therapy with pembrolizumab resulted in tumor shrinkage in 9 out of 10 patients with non-metastatic dMMR CRC.
3. Radical surgical removal of the primary tumor was performed in all 10 patients.
4. At microscopy, no viable tumor cells were present in 5 patients (50%), while 5 (50%) had remnant tumor cells.
5. No patients had a recurrence at 26 months of follow-up (range 23–38.5 months).

Introduction

Most antineoplastic therapies for patients with colorectal cancer (CRC) were developed before 2004 and consisted of 5-fluorouracil (5-FU)-based chemotherapy alone or in combination with leucovorin, irinotecan, oxaliplatin, agents targeting angiogenesis and agents targeting the epidermal growth factor receptor in patients with RAS-wildtype metastatic CRC (mCRC). Inhibition of BRAF signaling in patients with a $BRAF^{V600E}$ has emerged as the most recent development in the management of CRC [1-4]. The 5-year survival rate for patients with mCRC remains disappointingly low, around 10%[5]. Thus, there is a desperate need for more efficient medical treatment options for these patients. Patients with mismatch repair deficient (dMMR) or microsatellite instable (MSI) CRC constitute a distinct biomarker-defined population and patients with dMMR CRC may benefit less from chemotherapy in comparison to patients with a proficient MMR (pMMR) CRC[5-10].

In 2015, Le et al.[11] were the first to report that treatment with the programmed cell death-1 (PD-1) inhibitor pembrolizumab, an immune checkpoint inhibitor (ICI), was clinically beneficial in patients (n = 10) with treatment-refractory progressive dMMR mCRC but had no effect in patients with pMMR mCRC (n = 18). In 2017 and 2018, phase 2 studies were published demonstrating clinical benefit of PD-1 blockade with nivolumab alone or in combination with ipilimumab in previously treated patients with dMMR mCRC[12, 13]. In 2020, a phase 2 study demonstrated clinical benefit in patients with chemo-refractory dMMR mCRC who received pembrolizumab[14], and the results were published from a randomized phase 3 study with pembrolizumab versus first-line standard chemotherapy in patients with dMMR mCRC[15]. Patients initiating therapy with pembrolizumab had a significantly longer progression-free survival[15] and an improved quality of life[16, 17]. In May 2017, the U.S. Food and Drug Administration (FDA) approved pembrolizumab for use in patients with any MSI/dMMR tumor that had progressed on prior treatment and MSI/dMMR CRC progressing after standard therapy. This was the first time a cancer drug had

been approved by the FDA based on tumor-agnostic treatment rather than tissue type or tumor site[18]. The FDA approved nivolumab and ipilimumab for patients with dMMR mCRC in 2018 and pembrolizumab as first-line therapy in June 2020. At the European Society for Medical Oncology conference in 2018, Chalabi et al. presented the first results of the NICHE trial. Seven patients with dMMR resectable colon cancer were treated with 1 cycle of nivolumab on days 1 and 15 and ipilimumab on day 1 before surgery[19]. An update on 20 patients was reported in 2020[20]. All 20 patients obtained a major response; however, 8/20 (40%) still had viable tumor cells[19, 20]. In the NICHE-2 trial, 95% of the patients had a major pathological response, 67% with a complete pathological response[19-21]. In June 2022, Cercek et al. reported from a phase 2 trial that 12 patients with rectal cancer had a complete response after neoadjuvant PD-1 blockade with dostarlimab, chemoradiation, and surgery[22]. In the present study, we investigated the efficacy of pembrolizumab in treatment naïve patients with unresectable non-metastatic dMMR CRC.

Material and methods

A survey was conducted among all 10 oncological centers in Denmark treating patients with CRC regarding the use of ICI in treatment-naïve patients with unresectable dMMR CRC during the period from March 2019 to June 2020. The MMR status was determined by IHC, which has been a procedure in Denmark since 2009. A screening of dMMR by the identification of sporadic or germline deficiency of at least 1 of the 4 MMR proteins MLH1, PMS2, MSH2, and MSH6 was evaluated according to the national guidelines[23]. A tumor was categorized as pMMR when all 4 MMR proteins were normally expressed and the MMR status was thus determined by immunohistochemistry (IHC), while MSI can be determined by a polymerase chain reaction (PCR).

All 10 centers responded: 5 centers had treated 2 patients each with pembrolizumab, 2 mg/kg every 3 weeks, while 5 had not used ICI therapy. One patient had a locally advanced rectum cancer and 9 patients had unresectable, non-metastatic, T4 colon cancer. They comprised all the

known Danish patients during this almost 1-year period with treatment-naïve CRC who were offered ICIs as initial therapy. The initial biopsy from the primary tumor of the 10 patients was besides MMR expression by IHC, analyzed for mutations in the *RAS* and *BRAF* oncogenes by next generation sequencing[24]. Patients were categorized as having a potential sporadic or germline dMMR based on the mutation status of dMMR proteins and $BRAF^{V600E}$ gene and the methylation status of the MLH1 promotor[25]. Resectability was assessed at multidisciplinary team (MDT) meetings with experts in radiology, surgery, pathology, and oncology and was based on a combined clinical assessment and imaging by a computed tomography (CT) scan or a combined CT and positron emission tomography (PET) scan of the thorax and abdomen. The patient with a rectal cancer also had a magnetic resonance imaging (MRI) performed. During pembrolizumab therapy, a CT scan or a combined PET and CT scan was performed after every 2 to 4 cycles, and resectability was re-assessed at a MDT meeting. When considered resectable, a standard hemicolectomy and assessment of the resected specimen was performed according to Danish guidelines, with a histopathological description of remaining tumor cells and lymph node involvement[23]. Follow-up was from date of surgery to November 10, 2022.

Results

This exploratory national survey disclosed a total of 10 treatment-naïve patients with dMMR tumors, 9 patients with non-metastatic, unresectable T4 colon cancer and 1 with a doubtful resectable rectal cancer, treated with pembrolizumab 2 mg/kg every 3 weeks. Table 1 gives the detailed clinical and pathological features, treatment, and outcome in the 10 patients. All patients had a confirmed adenocarcinoma on a pre-treatment biopsy. Fifty percent of the patients were females. The potential germline group comprised 3/10 (30%) of the patients – all males. One patient differed from the other patients with a sporadic tumor due to young age (43 years), location of the tumor in the sigmoid, and a $KRAS^{G12A}$ mutation and $BRAF^{V600E}$ wild type. She likely had a sporadic tumor due to the presence of a MLH1-promotor methylation. The median age was 64 years (range 36–79). The median age in

the 6 patients with clearly sporadic dMMR tumors was 72 years (range 57−79) and 44 years (range 36−47) in the 3 patients with potential germline tumors. All the clearly sporadic $BRAF^{V600E}$ mutated tumors were located proximal to the splenic flexure. Two of the potential germline tumors were located distal to the splenic flexure, and 1 with a deficiency of both MSH2 and MSH6, was located proximal to the splenic flexure.

The patients received a median of 8 cycles of pembrolizumab (range 2−13) during a median of 6 months (range 1.5−11 months) before surgery. Clinical assessment on a CT scan was possible in 9 patients before and after treatment with pembrolizumab. In 1 patient assessment of the CT scan was not possible after pembrolizumab therapy and before surgery due to the insertion of a colonic stent. This patient had a clinical T4 tumor before treatment and a pathological T2 tumor with only a few viable cells in the resected tumor. In the 9 assessable patients, the median size of the primary tumor decreased from 80 mm (range 40−100 mm) to 37 mm (range 0−100 mm), a median decrease in size of 56%. One patient had a tumor of 100 mm. At the initial MDT meeting, the patient was assessed as doubtfully resectable, why neoadjuvant treatment was recommended. After 13 cycles of pembrolizumab it was decided to perform a laparoscopy even though the tumor was without shrinkage, to determine whether resection could be performed or not. Resection was possible and the resected tumor was without any viable tumor cells at microscopy. Fifty percent of the patients had no viable tumor cells in the resected primary tumor, while 50% still had viable tumor cells, their tumors ranging from T1 to T4 after ICI and before surgery. The pre-treatment clinical CT evaluation suggested that 9 out of 10 patients had more than 3 affected lymph nodes (N2) and 1 less than 3 (N1). In the resected specimen, the median number of examined lymph nodes was 43 (range 20−63), with only 1 patient still having remnant viable tumor cells in one lymph node. Figure 1 illustrates the monthly metabolic activity and tumor size on a PET and CT scans during pembrolizumab therapy in 1 patient. Pembrolizumab was tolerated well. A surgical complication was observed in 1 patient who had an anastomosis leak following the initial surgery and a splenic rupture at re-surgery but recovered

without complications. Two patients had a grade 2 adverse event, 1 with a skin rash and pruritus and 1 with a mild myositis, both patients were successfully treated with oral glucocorticoids. There were no other observed short- or long-term side effects. All patients were recurrence free after a median of 26 months after surgery (range 23–38.5 months).

To estimate the target population for ICI treatment of Danish patients with T4 CRC, data on MMR status and T category were extracted from the nationwide Danish Colorectal Cancer Group database. In 2017, a total of 4856 patients were diagnosed with CRC, and MMR determination was performed in 88% of the patients, 87% had colon cancer (3000/3429) and 89% had rectum cancer (1279/1427). Data from a total of 3429 patients with colon cancer and 1427 patients with rectal cancer were extracted. The database contains detailed reports on MMR status that also allow identification of hereditary CRC, which is observed in approximately 5% of the patients[24-27]. Table 2 provides detailed information on the distribution of tumors in the colon and rectum in patients with and without determination of MMR status according to the clinical T category. In the total population of patients with colon cancer, the proportion of patients with a T4 tumor was 14% (487/3429) with an MMR determination in 79% (384/487), and with a T4 dMMR tumor in 26% of the patients (99/384). Of the 99 patients with a T4 dMMR tumor, 73% (72/99) were in the proximal colon, 8% (8/99) in the distal colon, and 18% (18/99) had an unreported location. The proportion of patients with a rectum cancer and dMMR was 1.5% (19/1279). As 99 patients were diagnosed with a T4 treatment-naïve dMMR colon cancer and 19 with a dMMR rectum cancer, the 10 patients treated with neoadjuvant pembrolizumab comprised about 9% of patients with T4 dMMR colon cancer (9/99) and 5% of patients with dMMR rectal cancer (1/19).

Discussion

After many years of disappointing results in the treatment of CRC, new therapeutic possibilities involving immunotherapy finally appeared in 2015 when data from an explorative study of 10 patients

with mCRC treated with ICI showed benefit in a distinct dMMR biomarker-defined population[11]. As patients with dMMR CRC may benefit less from chemotherapy than patients with pMMR[5-9], these results gave rise to new treatment possibility in CRC with a determined dMMR status. Because of routine screening, an MMR status is accessible in 88% of Danish patients with a newly diagnosed CRC[26, 27]. A therapeutic approach using ICI instead of conventional systemic therapy was encouraged by the initial results of studies in the metastatic setting, as well as the initial report from the NICHE study[19]. In the metastatic setting, partial response rates are obtained in about 30−48% of patients after monotherapy with a PD-1 inhibitor, and with a manageable toxicity profile[11-15, 28]. In the Keynote-177 trial, 56% of the patients had a grade 3 or higher adverse event in the pembrolizumab group, in comparison to 78% in the chemotherapy group[17, 29].

Only 4 other studies have examined the pathological response after ICI therapy in patients with non-metastatic CRC[19-22, 30]. In 2021, Ludford et al.[31] presented the results of a phase 2 study, treating 35 patients with non-metastatic local advanced dMMR tumors; 27 of the patients were diagnosed with CRC and received 6 months of pembrolizumab. Twelve patients with CRC underwent a resection, and 10/12 (83%) had no viable tumor cells left in the excised tumor[30]. All 10 patients in the present study underwent radical excision of the primary tumor. No viable tumor cells were seen in 50% (5/10) of the patients, while 50% (5/10) of the patients still had remnant viable tumor cells. Our findings are comparable with the findings from the phase 2 trial by Cercek et al.[22] and the NICHE-2 trial[21], but some differences are obvious. The ICI used, duration of therapy, and tumor type may explain why the complete pathological responses varied from 50% in our study (pembrolizumab monotherapy, median treatment duration 8 cycles, CRC) to 67% in the NICHE-2 trial (nivolumab and ipilimumab, treatment duration of 6 weeks, colon cancer) and 100% in the Cercek study (chemoradiotherapy and dostarlimab, treatment duration 6 months, rectal cancer). The mutational tumor characteristics also differed. Six of 10 patients in this report had a MLH1/PMS2 deficiency combined with a $BRAF^{V600E}$ mutation indicative of a sporadic dMMR colon cancer versus none of the

patients with a *BRAF* ^{V600E} mutation in the Cercek study. In the present report, 3/10 (30%) patients were potential germline, which was comparable to the NICHE-2 trial, where 35/112 (31%) of the patients had a potential germline dMMR colon cancer. In the study by Cercek et al. 8/14 (57%) of the patients with a rectal cancer were potential germline.

Interestingly, all 10 patients were recurrence free 26 (23–38.5) months after surgery regardless of the response to therapy before surgery. The radiological evaluation of the 10 patients demonstrated a decrease in tumor size from 0–100%; however, the decrease of tumor size was not correlated to the pathological responses. Evaluating response after ICI by measuring the size of the tumor on a CT and/or PET scan may be of doubtful value in predicting a pathological response. With 50% of the patients still having remnant viable tumor cells, the final management of these patients should still be surgery until further prospective studies with longer follow-up time are available. It is, however, tempting to speculate whether this immunological approach may have an organ-sparing potential. Thus, selection of patients should possibly be further improved by the use of biomarkers such as circulating tumor DNA (ctDNA) that may predict pathological response.[32] Limitations of this study include the small sample size of only 10 patients, the explorative retrospective nature of the study, and the inherent bias in the selection of patients offered ICI. The known molecular MMR heterogeneity of CRC with a skewed distribution of dMMR tumors toward the proximal vs. the distal colon in the T4 dMMR Danish patient population (73% vs. 9%) and only 1.5% in the rectum was reflected in the present study. Among the 10 patients reported here, 7 patients had a primary tumor located proximal to the splenic flexure including 6 patients with a sporadic dMMR tumor with a *BRAF*^{V600E} mutation. Furthermore, based on the nationwide Danish Colorectal Cancer Group data from 2017, the 10 patients treated with ICI reported here comprised about 9% of the possible Danish target population with colon cancer and 5% with rectum cancer. Prospective trials are needed to determine the optimal type and duration of ICI, timing of surgery, and identification of possible predictive biomarkers for response. The immunological rationale for neoadjuvant immunotherapy

involves activation of many different types of T-cells before surgical removal of the lesion, leaving many and more diverse T-cells to search for remnant tumor cells[33]. A radical excision of the primary tumor was carried out in all our initially unresectable patients treated with pembrolizumab. Fifty percent of the patients still had remnant tumor cells in the resected specimen, but no recurrences were seen in any of the patients. It is not known what implication a few viable remaining tumor cells in the tumor has once the immune system has been activated toward them. Our data and future data collected in more patients in larger studies should possibly include patients with a longer follow-up for a proper validation of the treatment.

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Author contributions

RLE: Treated 2 of the patients and discussed the initial idea of the scope of the paper with BVJ. Collection of data and review of results. Written first draft of the paper and discussion of results and manuscript with co-authors. JSL: Treated 1 of the patients. Discussed results and co-authored first draft of the manuscript. LLK: Pathologist with a special interest in the interpretation of dMMR results. Draft of manuscript commented, and results discussed. Review of the final draft. RA: Treatment of one of the patients. Review of the manuscript. EH: Comments of dMMR analysis and comments of the results and manuscript. PI: Provided data on the distribution of dMMR in Denmark from the Danish Colorectal Cancer Group database in 2017 and 2018. Discussion of results and review of the manuscript. JL: Surgical treatment of 2 of the patients. Discussion of results and review of the manuscript. DLN: Discussion of results and review of the manuscript. PP: Discussion of results and review of the manuscript. LØP: Treated 2 of the patients. Discussion of the results and review of the manuscript. CQ: Treated 1 of the patients. Discussion of the results and review of the manuscript. JVS: Expert in CRC. Discussion of results and review of the manuscript. MMS: Treated 1 of the patients. Discussion of the results and review of the manuscript. KØ: Treated 1 of the patients. Discussion of the results and review of the manuscript. BVJ: Treated 2 of the patients and fostered the initial idea of the scope of the paper. Discussion of the results and review of the manuscript. The work reported in the paper was performed by the authors, unless clearly specified in the text.

Conflict of interest

RLE: Personal, Amgen (2021) Expert board on targeted therapy. Institutional, BMS: drug-funding for an investigator-initiated trial. The other authors have no conflicts to declare.

Data Availability Statement

Data of MMR status and T category of 2017 population of patients with a newly diagnosed CRC were extracted from the nationwide Danish Colorectal Cancer Group database. Data from the patients were extracted from the patient reports by the medical doctors treating the patients. Further details are available from the corresponding author upon request.

Ethics Statement

This work was conducted in accordance with the requirements of the Danish data registry agency, approval number P-2021-184. All patients signed a written informed consent in accordance with the requirements of the Danish data registry agency, approval number P-2021-184.

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Figure legends:

Figure 1: PET/CT scans of a patient with initial unresectable, non-metastatic T4a N2 dMMR rectosigmoid colon cancer during 5.5 months of therapy with 9 cycles of pembrolizumab 2 mg/kg every 3 weeks every 3 weeks.

Table 1. Clinico-pathological features, treatment, and outcome of initial therapy with pembrolizumab.

MMR Deficiency group	Sporadic						Potential sporadic [1]	Potential germline		
Patient identification no	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Age (Years)	57	74	79	71	74	74	43	36	47	44
Male/ Female	F	F	F	M	F	M	F	M	M	M
Performance status	0	1	1	0	1	1	0	0	0	0
Location of colon tumor	Ascending	Ascending	Ascending	Right flexure	Right flexure	Transverse	Sigmoid	Ascending	Rectosigmoid	Rectum
Clinical TN category	T4b N2	T4b N2	T4a N2	T4b N2	T4b N1	T4b N2	T4b N2	T4a N2	T4a N2	T3c N2
MMR deficiency	MLH1/PMS2	MLH1/PMS2	MLH1/PSM2	MLH1/PSM2	MLH1/PSM2	MLH1/PSM2	MLH1/PSM2	MSH2/MSH6[1]	MSH6	MSH2/MSH6
$BRAF^{V600E}$ mutation	V600E	V600E	V600E	V600E	V600E	V600E				
KRAS mutation							KRAS G12A		NRAS G12A	
Pmab treatment										
- No of treatments	9	5	9	9	8	7	13	6	9	2
- Months to surgery	6.5	2.5	7	7.5	5.5	4.5	11	7	5.5	1.5
Tumor diameter (mm)										
- before Pmab	79	40[2]	80	93	81	70	100	70	67	100
- before surgery	49	0	30	37	80	NA[3]	100	17	21	88
Decrease in tumor size (%)	38%	100%	63%	60%	1%	NA	0%	56%	69%	12%
Pathological TN category	T0N0	T0N0	T1N0	T4N0	T3N1	T2N0	T0N0	T0N0	T0N0	T3N0
No of malignant/benign LN	0/47	0/53	0/22	0/20	1/29	0/68	0/33	0/58	0/39	0/63
Viable tumor cells	Not present	Not present	Present	Present	Present	Present	Not present	Not present	Not present	Present
Months after surgery without recurrence	23.5	32.5	26	23.5	23	36	25.5	34	38.5	26

Pmab: Pembrolizumab. NA: Not assessable. LN: Lymph node. No: Number. TN: Tumor and Nodal status.
1) MLH1-promotor methylated, hence most likely sporadic based on molecular analysis.
2) Thick but not measurable intestinal wall with a 40−mm lymph node conglomerate.
3) Not assessable due to a stent.

Table 2. MMR-status in relation to clinical T category and location of tumor.

Clinical T category	T1		T2		T3		T4		Tx [4]		All T categories [5]	
Proximal colon [1]	107	**8%**	290	**21%**	523	**37%**	207	**15%**	272	**19%**	1399	**100%**
MMR status	99	93%	280	97%	499	95%	188	91%	246	90%	1312	94%
dMMR	35	35%	85	30%	182	36%	72	38%	85	35%	459	35%
Distal colon [2]	286	**20%**	267	**18%**	445	**31%**	135	**9%**	321	**22%**	1454	**100%**
MMR status	259	91%	254	95%	427	96%	119	88%	293	91%	1352	93%
dMMR	5	2%	8	3%	25	6%	9	8%	9	3%	56	4%
Colon UN [3]	33	**6%**	61	**11%**	156	**27%**	145	**25%**	181	**31%**	576	**100%**
MMR status	27	82%	36	59%	102	65%	77	53%	94	52%	336	58%
dMMR	3	11%	5	14%	10	10%	18	23%	14	15%	50	15%
All colon	426	**12%**	618	**18%**	1124	**33%**	487	**14%**	774	**23%**	3429	**100%**
MMR status	385	90%	570	92%	1028	91%	384	79%	633	82%	3000	87%
dMMR	43	11%	98	17%	217	21%	99	26%	108	17%	565	19%

Data from the national clinical DCCG database 2017. "MMR status" indicates the number of cases where MMR status (pMMR or dMMR) was known and where the proportion is expressed in relation to the total number of cases. "dMMR" indicates the number of cases where there was defective expression of one or more mismatch repair proteins. The proportion is stated in relation to the number of cases where MMR status was known.

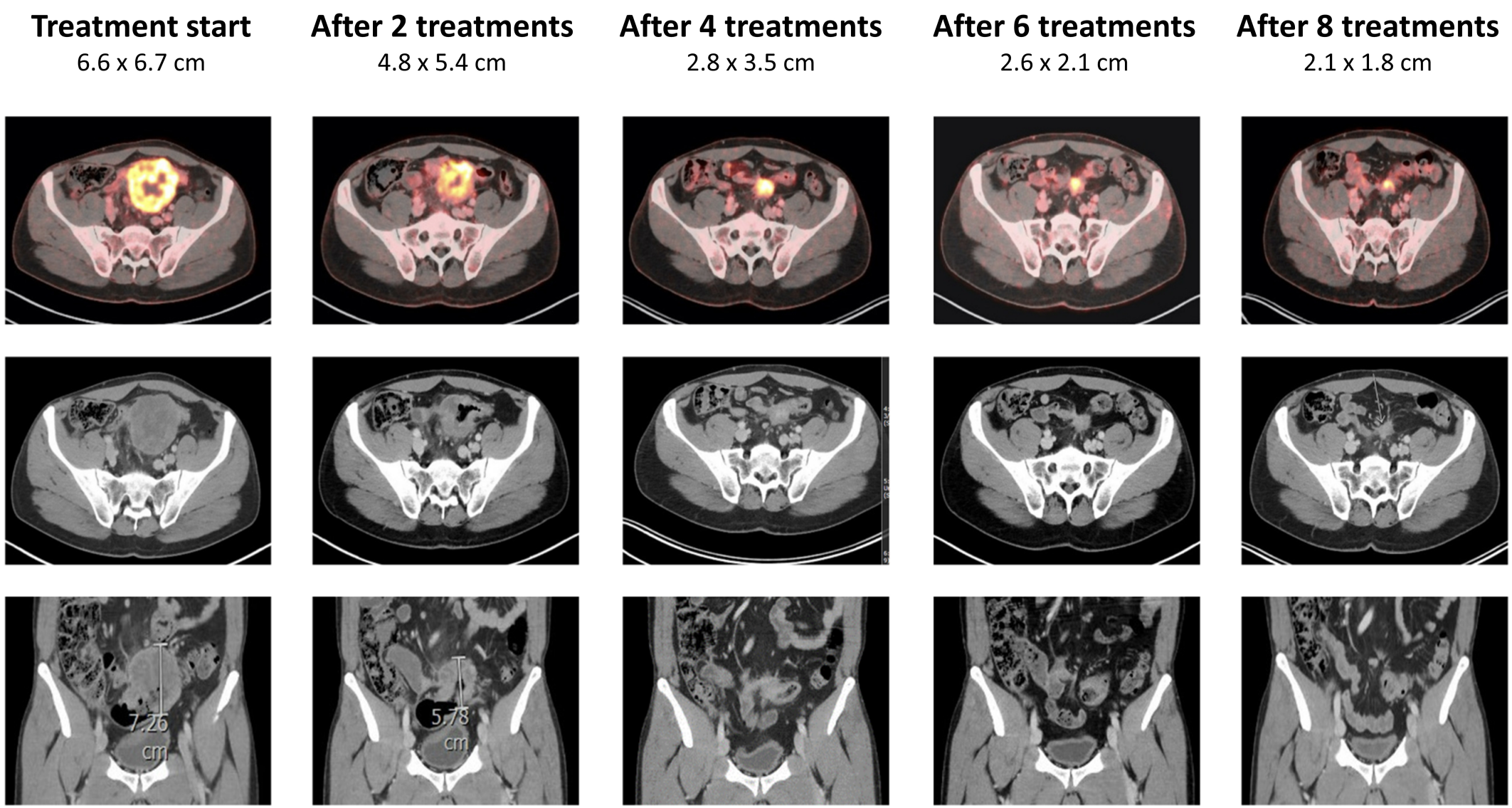
1) Coecum, ascending, right flexure, transverse colon.

2) Left flexure, descending, sigmoid colon.

3) Location unknown/not reported.

4) T category unknown/not reported.

5) In rectum cancer 1.5% of the patients had a dMMR tumor (19 out of 1279 patients tested for MMR expression)



Real world national survey March 2019 to June 2020

Treatment naïve, non-metastatic, unresectable dMMR colorectal cancer

- Colon cancer (n=9); T4a (n=3), T4b (n=6)
- Rectum cancer (n=1); T3c (n=1)

Pembrolizumab median of 8 cycles (range 2-13 cycles)

Surgery:
- All 10 patients had a R0 resection

Pathology:
- Viable tumor cells in resected specimen: N=5
- No viable tumor cells in resected specimen: N=5

Median follow-up after immunotherapy with pembrolizumab and surgery without a relapse:

26 months (range 23-38.5 months)

Danish Colorectal Cancer Group (DCCG) database

Number of CRC patients in Denmark (2017) in total: N=4856
- Colon cancer (n=3429)
- Rectum cancer (n=1427)

Number of CRC patients in Denmark (2017) with a MMR determination: N=4279

Number of patients with a dMMR T4 colon cancer: 26% (99/384)

Number of patients with a dMMR rectum cancer: 1.5% (19/1279)

The 10 patients with dMMR non-metastatic CRC in Denmark is thus about 9% of the colon cancer patient population and 5% of the rectum cancer patient population