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Sarcomas developed in patients with Lynch Syndrome are enriched in pleomorphic soft-tissue sarcomas and are sensitive to immunotherapy

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ABSTRACT

Background: Sarcomas do not belong to the Lynch Syndrome (LS)-tumour spectrum. A growing body literature has reported sarcomas in patients with LS. Clinical and tumour characteristics of these patients remain unknown.
Patients and methods: We set up the first national retrospective study, SarcLynch, describing the pathological and clinical characteristics of sarcomas developed in patients with LS. Patients were identified from two national networks and included from 23 centres in France.
Results: Eighty-one patients participated in the SarcLynch study. Sixty-seven (83 %) tumours were soft-tissue sarcomas (STS) and 14 (17 %) bone sarcomas. Among STS, 59 (88 %) showed a pleomorphic component, with undifferentiated pleomorphic sarcoma (UPS) (36 %) and pleomorphic rhabdomyosarcoma (pRMS) (21 %)

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being the most represented subtypes. Sarcoma was the first neoplastic event in 32 patients (40 %). Thirty-two patients (40 %) were carriers of *MSH2* germline pathogenic variants. Among patients who underwent an assessment of deficient mismatch repair (dMMR) by immunohistochemistry and/or molecular biology status, 75 % were dMMR by immunohistochemistry and 45 % were microsatellite instability high (MSI-H). Eight patients received immune checkpoint inhibitors and 4 (50 %) exhibited an objective response with 3 complete radiological response including 1 patient with pathological complete response. Duration of response ranged from 6 to 20 months.

Conclusions: SarcLynch, the largest multicentric series describing sarcomas developed in patients with LS, revealed an enrichment in patients with pleomorphic sarcomas – especially UPS and pRMS. This finding strongly supports screening for MMR status evaluation in these rare histotypes both for oncogenetic screening and therapeutic interest. Considering an objective response rate of 50 %, access to immunotherapy should be considered in these tumours.

1. Introduction

Lynch Syndrome (LS) is a rare genetic predisposition caused by a constitutive deficiency in the mismatch repair (MMR) system, consecutive to inherited monoallelic loss-of-function of one MMR gene including *MLH1, MSH2, MSH6, PMS2* or *EPCAM* [1]. This deficit in the MMR (dMMR) system preferentially affects repeated sequences such as microsatellites and leads to microsatellite instability (MSI). Consequently, due to a constitutional mutation of one MMR gene, tumours developed within the context of LS present a dMMR phenotype through the acquisition of a second hit on the MMR gene. However, MMR deficiency in tumours can occur outside LS by somatic inactivation of MMR genes, mostly hypermethylation of the *MLH1* promoter. In clinical practice the identification of dMMR phenotype is based on two methods: MSI analysis by molecular biology (usually Pentaplex-PCR method) and immunohistochemical (IHC) analysis for MMR proteins expression (with the loss of at least one MMR protein). Whatever its mechanism, the dMMR phenotype is currently a well identified predictive factor of response for immune checkpoint inhibitors (ICI) in many tumours [2,3]. For this reason, its evaluation as a biomarker for therapeutic purposes is recommended in many solid tumours. In addition, determination of MMR phenotype is mandatory in colorectal, small bowel, gastric and endometrial tumours both from a theragnostic perspective and to screen for LS. Patients with LS are at high risk of developing colorectal as well as endometrial cancers and less frequently, small-bowel, biliary tract and upper urinary tract cancers. However, tumour risk and cancer spectrum seem to differ among LS patients and it is likely that this population might also be at elevated risk of other cancers [4]. Recent agnostic indication of ICI for advanced dMMR/MSI solid tumours [5] and subsequent screening of MSI by NGS in a large panel of solid tumours has enabled LS diagnosis in tumours classically excluded from the LS-spectrum [6]. Among these tumours, 785 unselected soft-tissue sarcomas (STS) were included and revealed 45 MSI sarcomas (5.7 %) with only two patients with LS [6]. Consistently, whole germline genome sequencing in 1644 unselected patients with all-type of sarcomas revealed only 9 probands (0.5 %) as carriers of a germline pathogenic variant (GPV) in *MMR* genes [7]. By contrast, multiple case of sarcomas occurring within LS have been described [8]. Our recent review of literature reported 95 patients with LS who developed a sarcoma, of which 5 % had developed pleomorphic rhabdomyosarcomas (pRMS) [8], a rare STS histotypes usually responsible for 0.5 % of adult sporadic STS [9]. The majority of patients (57 %) exhibited a GPV in *MSH2* gene, when *MSH2* is known to account for 24 % of all LS [10]. In light of the poor knowledge available on this specific emerging subgroup of patients with sarcomas, we conducted the first national series to date – **SarcLynch** – aimed at describing the clinical and tumour characteristics in this newly identified population.

2. Patients and methods

2.1. Study design

SarcLynch is a national, retrospective and multicentre series aiming to describe the clinical and tumour characteristics of sarcomas developed in patients with LS. Patients included had 1) a proven LS (with a MMR constitutional pathogenic variant identified) or a “highly plausible LS” defined as being a member of a LS-confirmed family and having a personal history of another malignancy belonging to the LS spectrum with a dMMR phenotype and 2) a histologically confirmed diagnosis of sarcoma. Eligible patients were included independently of age at sarcoma diagnosis and date of diagnosis. Patients with unconfirmed diagnosis of sarcoma were excluded. This study was led in line with the French reference methodology MR-004 and registered under the following declaration number: Rn-IPH 2022-110. All included patients provided a non-opposition agreement according the Declaration of Helsinki.

2.2. Patients

Patients were identified through two distinct networks from 1982 to 2023: NetSarc and OFeLy. NetSarc is the French Sarcoma Group Network including French patients diagnosed with a sarcoma [11]. Patients who developed sarcomas and were recorded as being affected by “another genetic disease” were screened. Following national guidelines, all French sarcoma benefit at diagnosis from a reference pathologist assessment within NetSarc network. OFeLy is a French national network supported by the Genetic and Cancer Group (Unicancer) which is a French Oncogeneticists Network referencing most French patients and families with LS [12]. Patients with LS and past medical history of sarcoma were identified through this database. Anonymised patients were then cross-checked by date of birth, gender, treatment centre and histological subtype. Identified or suspected duplicates were included only once. For patients who developed multiple sarcomas, only the first sarcoma was considered in the analysis.

2.3. Mismatch repair evaluation

Mismatch repair status was locally assessed in participating centres. According to the French national guideline [13], and to avoid any ambiguity, the term "dMMR" will refer to any tumor exhibiting a concordant mismatch repair deficiency phenotype with the IHC (loss of at least one MMR protein) and molecular biology analysis of microsatellites (MSI). In contrast, "dMMR-IHC" specifically denotes tumors identified as MMR-deficient through immunohistochemistry (IHC), while "MSI" refers to those detected using molecular biology techniques. For tumors with discordant phenotypes, results of each technic will be mentioned, such as “dMMR-IHC/MSS” or “pMMR-IHC/MSI”.

2.4. Statistical analysis

The database was exported on 12 April 2024. Quantitative variables were summarised by the median and range (minimum-maximum) and qualitative variables with number and percentages. The number of missing data was presented for each type of variable. Overall survival rates were calculated from diagnosis and estimated by the Kaplan-Meier method with 95 % confidence interval (CI). First event definition was death from any cause. Statistical analyses were conducted using STATA software version 18.

3. Results

3.1. Baseline characteristics

One hundred and thirty-three patients were identified from 23 French centres. From this total, 52 were excluded: 5 duplicates, 19 uncertain diagnoses, 26 for absence of confirmed LS and 2 due to absence of consent (Supplementary Fig. S1). Eighty-one patients, of whom 3 who developed two sarcomas, were included in the study. One centre included 24 % of patients and the mean number of patients included by these centres was 3 (1–8). Median age at sarcoma diagnosis was 53 years (11–85 y.o). Seventy-three percent ($N = 54/74$, $NA = 7$) had a localised disease at the time of diagnosis. Among metastatic patients ($N = 20$), 9 (45 %) were metastatic at diagnosis. The most frequent primary tumours sites are depicted in Table 1. Two tumors arose in irradiated fields.

3.2. Oncological history and genetics

Seventy-five patients (93 %) had proven LS with a GPV identified and 6 presented a highly-plausible LS. Information on GPV was available for 80 patients, of whom 32 (40 %) concerned *MSH2*, 30 (38 %) *MLH1*, 14 (17 %) *MSH6*, 3 (4 %) *PMS2* and 1 (1 %) *EPCAM* genes. Seventy-two percent ($N = 54/75$, $UK = 6$) possessed a personal history of cancer, among whom 39 (72 %) had a colorectal cancer and 29 (54 %) another LS-associated cancer. Twenty-one patients (28 %) lacked personal or familial criteria for LS.

Sarcoma was the first neoplastic event in 32 patients (N = 32/81, 40 %). Three patients developed multiple sarcomas in the absence of familial history of sarcoma: one with an osteosarcoma in an irradiated field of a prior synovial sarcoma, another developed a liposarcoma then an UPS while another developed two distinct metachronous localised UPS. Thirteen percent ($N = 6/45$, $UK = 36$) possessed a familial history of sarcomas. No recurrent GPV was identified in patients with family history of sarcomas nor for the patients with personal history of multiple sarcomas.

3.3. Pathological information

Sixty-seven (83 %) patients exhibited a STS while 14 (17 %) had a bone sarcoma. Among the 67 STS cases, the most frequent histotypes were represented by UPS ($N = 24$, 36 %), pRMS ($N = 14$, 21 %), leiomyosarcoma ($N = 8$, 12 %), liposarcoma ($N = 7$, 10 %), myxofibrosarcomas ($N = 7$, 10 %) and other rare subtypes of STS ($N = 7$, 10 %) (Fig. 1). In total, fifty-nine (88 %) STS were pleomorphic STS (PSTS). Regarding bone sarcomas, 6 cases (43 %) comprised chondrosarcoma (including 4 dedifferentiated), 5 (36 %) were osteosarcoma, 2 (14 %) related to chordoma while 1 case (7 %) was an Ewing sarcoma. Three tumours were fusion-driven sarcomas (1 synovial sarcoma, 1 Ewing sarcoma and 1 alveolar rhabdomyosarcoma) and no gastrointestinal stromal tumours (GIST) were reported.

3.4. Biomarkers and immune scoring

Tumour MMR phenotype was assessed by Immunochemistry (IHC) ($N = 44$), molecular biology ($N = 31$) or both ($N = 31$). Thirty-three of the IHC-evaluated patients (75 %) were confirmed as dMMR-IHC and 11 (25 %) were proficient mismatch repair (pMMR-IHC). With molecular biology testing ($N = 31$), 14 (45 %) tumours were MSI and 17 (55 %) were microsatellite stable (MSS). Twenty-one tumours (68 %) displayed concordant results (13 dMMR-IHC/MSI and 8 pMMR-IHC/MSS) while 10 (32 %) demonstrated discordant results (9 dMMR-IHC/MSS and 1 pMMR-IHC/MSI) (Table 2). Program Death-Ligand 1 (PD-L1) tumour proportion score (TPS) was evaluated in 6 patients and was negative in all cases but one. PD-L1 combined positive score (CPS) was calculated for 5 patients and was higher than 10 for 3 of them. Tumour mutational burden (TMB) was evaluated by next generation sequencing (NGS) in 7 patients, with a median TMB of 12 mutations/megabase (6–16 mut/Mb) and three tumours with TMB higher than 10 mut/Mb (Supplementary Tables S1 and S2).

Table 1
Patients and tumour characteristics.

Characteristics	Total ($N = 81$)
Gender, n (%)	
Male	42 (52)
Female	39 (48)
Age at sarcoma diagnosis (year)	
Median (range)	53 (11–85)
UK	1
Genetic predisposition, n (%)	
Confirmed Lynch Syndrome	75 (93)
Highly-plausible Lynch Syndrome	6 (7)
Germline pathogenic variants, n (%)	
MLH1	30 (38)
MSH2	32 (40)
MSH6	14 (17)
PMS2	3 (4)
EPCAM	1 (1)
UK	1
Personal cancer history	
Yes, n (%)	54 (72)
Colorectal cancer, n (%)	39 (72)
Number of non-sarcoma cancers, median (range)	1 (0–4)
No, n (%)	21 (28)
UK, n	6
Tumor diagnosis, n (%)	
Soft-Tissue Sarcoma	67 (83)
Bone Sarcoma	14 (17)
FNCLCC grade, n (%)	
Grade 1	6 (8)
Grade 2	24 (34)
Grade 3	41 (58)
UK	10
Sarcoma primary site, n (%)	
Members	52 (66)
Trunk	11 (14)
Abdomen	8 (10)
Retroperitoneum	4 (5)
Head and neck	4 (5)
UK	2
MMR phenotype, n (%)	
dMMR	33 (79)
pMMR	9 (21)
UK	40
Secondary sarcomas, n (%)	
No	75 (93)
Yes	6 (7)
Irradiation field, n	2
Traumatic region, n	4
Metastatic disease, n (%)	
No	54 (73)
Yes	20 (27)
Metachronous	11 (55)
Synchronous	9 (45)
UK	7

UK: Unknown; dMMR: Deficient MisMatch Repair (dMMR-IHC and/or MSI); pMMR: Proficient MisMatch Repair.

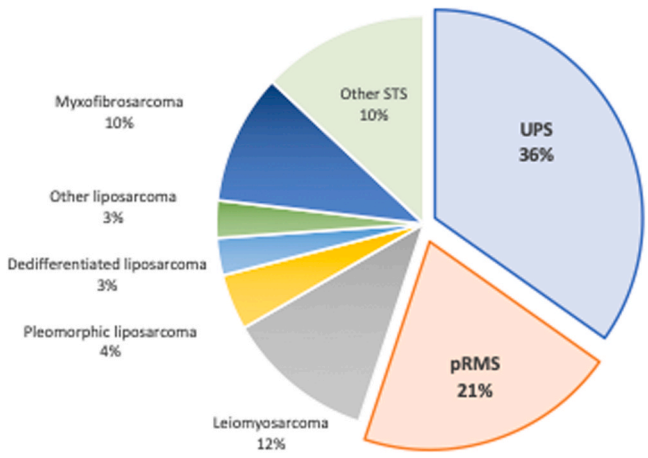

Fig. 1. Repartition of soft-tissue sarcoma histological subtypes. *UPS: Undifferentiated Pleomorphic Sarcoma; pRMS: Pleomorphic Rhabdomyosarcoma; STS: Soft-Tissue Sarcoma. Liposarcomas: 3 pleomorphic, 2 dedifferentiated, 1 myxoid and 1 well-differentiated. Other subtypes: 1 PEComa, 1 Clear Cell Sarcoma, 1 Malignant Peripheral Nerve Sheath Tumour (MPNST), 1 Alveolar Rhabdomyosarcoma, 1 Embryonal Rhabdomyosarcoma, 1 High-grade Endometrial Stromal Sarcoma and 1 Synovial sarcoma.*

Table 2
MMR phenotype assessment by immunohistochemistry and pentaplex PCR.

		MMR status by pentaplex-PCR		
		MSI	MSS	Total
IHC	dMMR-IHC	13	**9**	22
	pMMR-IHC	**1**	8	9
	Total	14	17	31

IHC = ImmunoHistoChemistry; dMMR-IHC = Deficient Mismatch Repair by IHC (loss of expression of at least one of the four MMR proteins: MLH1, PMS2, MSH2 or MSH6); pMMR-IHC = Proficient Mismatch Repair by IHC (expression of all 4 MMR proteins); MSI = Microsatellite Instable by Pentaplex-PCR; MSS = Microsatellite Stable by Pentaplex-PCR.

3.5. Efficacy of immune checkpoint inhibitors

Eight patients (10 %) received ICI: 7 with pre-treated metastatic or locally advanced diseases and 1 with newly diagnosed localised disease (Table 3; Figs. 2 and 3). All pre-treated patients had progressed when treated with standard of care chemotherapy and/or radiation therapy and immunotherapy was proposed as a palliative option. The objective response rate (ORR) according to iRECIST criteria was 50 % (3 complete response (CR) and 1 partial response (PR)) and disease control was 75 % (2 stable disease). Duration of response at time of analysis varied from 6 to 20 months. Median interval since start of ICI was 12 months (1–28 months). Among the 3 cases with CR, all were dMMR with at least one technique (IHC or molecular biology). Notably, the patient with a metastatic PEComa (perivascular epithelioid cell tumour) (Patient No. 1) had a severe performans status, classified as Eastern Cooperative Oncology Group 4 upon the introduction of pembrolizumab. He has now completed two years of treatment, including 11 months of CR and has maintained CR four months after discontinuation. The patient with a locally advanced pRMS (Patient No.2), whose initial recommendation for hand amputation was later refined following a 14-month regimen of pembrolizumab as guided by an objective radiological response, only required the amputation of the last finger which revealed a complete pathological response. Two sarcomas presented progressive disease despite a dMMR phenotype (one dMMR-IHC and one dMMR-IHC/MSI) and a slightly elevated TMB value (> 5 mut/Mb).

4. Discussion

To the best of our knowledge, we have reported on the largest series describing sarcomas developed in the context of LS, with 84 tumours observed in 81 patients. The vast majority of sarcomas were STS, largely (88 %) represented by pleomorphic STS. The proportion of pRMS (21 % of STS) is high, considering pRMS are an ultra-rare sarcoma occurring in less than 0.5 % of sporadic sarcomas [9]. This enrichment in pRMS, already described in the literature review carried out by our team, is confirmed and tends to be even more significant. Further molecular characterisation of pRMS in LS patients is required. Notably, no GIST was reported in our cohort and only a minority of patients developed a fusion-driven sarcoma (N = 3).

Our results are consistent with an American cohort ($N = 30$) [14] which described UPS as the first subtype of STS (40 %) in LS patients. Only two rhabdomyosarcomas were recorded without detail about the subtype (alveolar, embryonal, pleomorphic). This could be explained by the limited size of this series. In this study, 3 patients received ICI, of whom 2 with rhabdomyosarcomas (including 1 pRMS) presented a radiological response. However, our results diverge from the subgroup analysis of the Prospective Lynch Syndrome Database which identified

Table 3
Patients treated with immune checkpoint inhibitors (ICI) and clinical outcomes.

Patient	Gender	Age	Diagnosis	Stage	Biomarkers	ICI	BOR	DOT (mo)
1	M	50	PEComa	Metastatic	dMMR TMB 15 Mut/Mb	Pembrolizumab	CR	23
2	W	43	pRMS	Locally Advanced	pMMR-IHC/MSI TMB 16 Mut/Mb	Pembrolizumab	CR	17
3	M	19	pRMS	Metastatic	dMMR-IHC/MSS TMB 5.6Mut/Mb PD-L1 60 %	Nivolumab *	CR	28
4	W	57	UPS	Metastatic	NA	Dostarlimab	PR	13
5	W	51	Chordoma	Metastatic	pMMR	Pembrolizumab	SD	12
6	M	54	Chondrosarcoma	Metastatic	dMMR-IHC/MSS	Durvalumab Tremelimumab	SD	14
7	M	69	UPS	Localised	dMMR-IHC/NA TMB 6 Mut/Mb	Pembrolizumab**	PD	1
8	M	41	Chondrosarcoma	Metastatic	dMMR TMB 9 Mut/Mb	Pembrolizumab	PD	3

ICI = Immune Checkpoint Inhibitor; BOR = Best Overall Response; DOT = Duration Of Treatment; M = Male; W = Woman; dMMR = Deficient Mismatch Repair with both technics; pMMR = Proficient Mismatch Repair; MSI = MicroSatellite Instable; MSS = MicroSatellite Stable; TMB = Tumor Mutational Burden; CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; PEComa: Perivascular Epithelioid Cell Tumour; pRMS = Pleomorphic Rhabdomyosarcoma; UPS = Undifferentiated Pleomorphic Sarcoma; NA: Not Available.

* This patient received pazopanib as co-medication with Nivolumab.

** This patient received Trabectedin as co-medication.

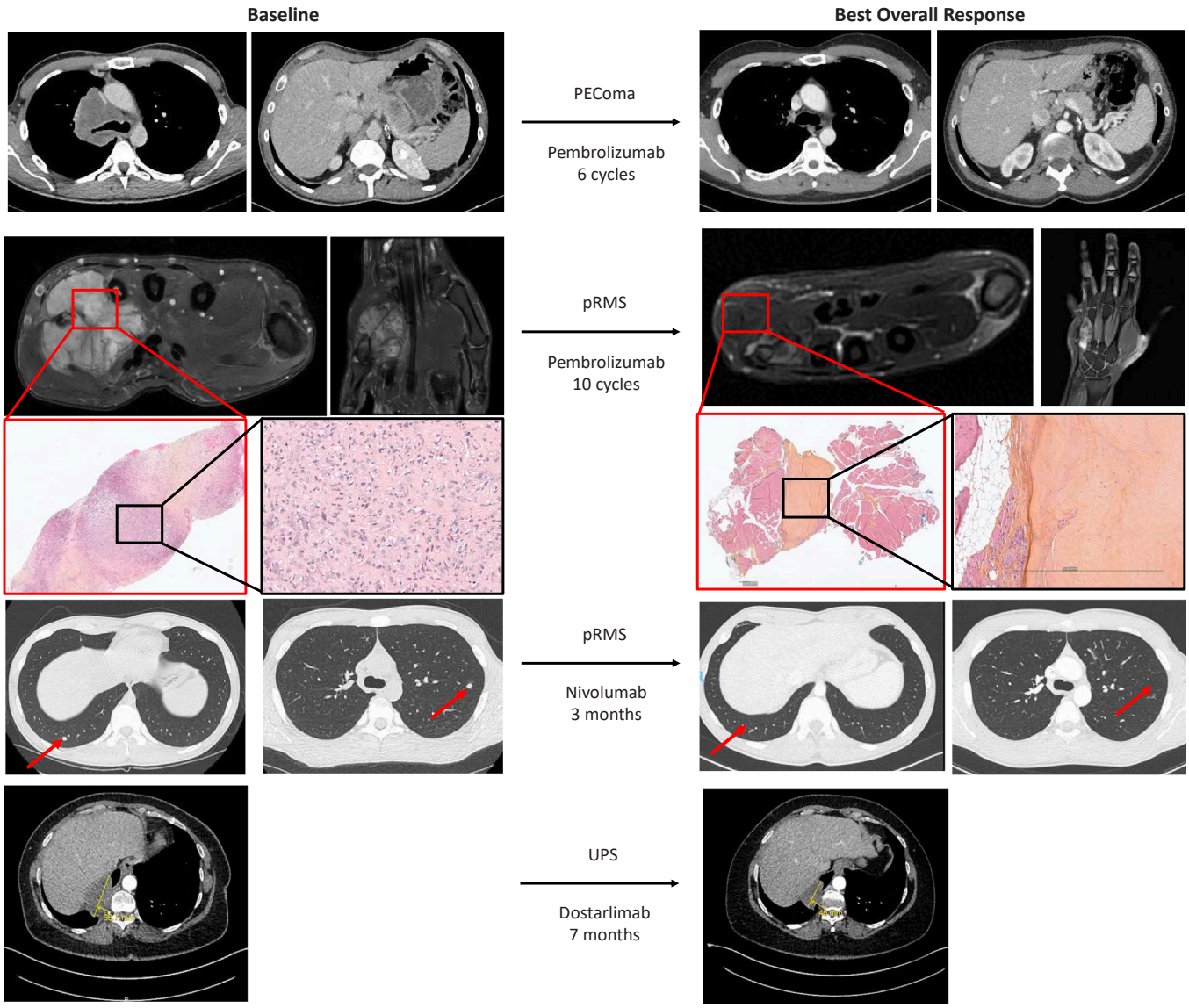

Fig. 2. Case series and representative iconographies of responder patients.

30 sarcomas [15]. With 15 cases of osteosarcoma and 16 STS, authors concluded that osteosarcomas were more prevalent in patients with LS compared to the general population but did not specify which type of STS occurred. This discrepancy might be explained by the low number of bone sarcomas in our cohort, the small proportion of STS in their cohort or a possible recruitment bias in both cohorts. Further prospective and larger cohorts will be needed.

Concerning the germinal pathogenic variants, results mirror those from the two series available to date. Both the American [14] and the Prospective Lynch Syndrome Database [15] cohorts reported a majority of patients are carriers of a *MSH2* GPV at 50 % and 57 % respectively. This result is tallied with the fact that patients with germline *MSH2* variants are the most exposed to developing extra-colonic cancers [16].

In this study, 40 % of patients developed a sarcoma as first oncologic event and not a carcinoma. Considering the lack of systematic oncogenetic screening for patients with sarcoma, we hypothesize that these patients are likely not to benefit from a Lynch Syndrome screening, as opposed to patients who first develop a colorectal carcinoma. Indeed, most patients did not fulfill revised Amsterdam nor Bethesda criteria at the time of diagnosis. In the same way, none of the 9 "Lynch-sarcomas" in the Ballinger study [7] satisfied these criteria while 4 met the criteria for Li-Fraumeni syndrome. Patients with LS who develop a sarcoma might have specific oncological histories.

In the literature, MMR deficiency is an infrequent phenotype accounting for 1–5.7 % of sarcomas [6,17,18]. However, the histotypes with the highest proportion of dMMR in the studies by Doyle and Lam were pRMS (33–100 %) and undifferentiated sarcomas (0–10 %), which are also the most prevalent subtypes in the SarcLynch study. These results suggest that a certain amount of dMMR undifferentiated sarcomas and pRMS (with or without LS) are currently undiagnosed in practice. We described 32 % discordant phenotypes between IHC and PCR, whereas such discordant phenotypes represent from 5 % up to 8 % in some large and old series of colorectal cancers, using relatively old or incomplete techniques for MMR/MSI determination ad/or no optimal IHC interpretation [19,20]. More recent studies from experienced teams reported discordance in 1–2,3 % of colorectal cancers [21–24]. In sarcomas, discordance may be related to the panel of microsatellites used which was initially validated in colorectal and endometrial cancers, conferring a lower sensitivity of National Cancer Institute-Pentaplex panel in extra-colonic tumours [25–27]. Indeed, for the 10 tumours with discordance, 9 were dMMR-IHC but MSS with Pentaplex-PCR. We have hypothesised that this panel may also lack sensitivity in sarcomas.

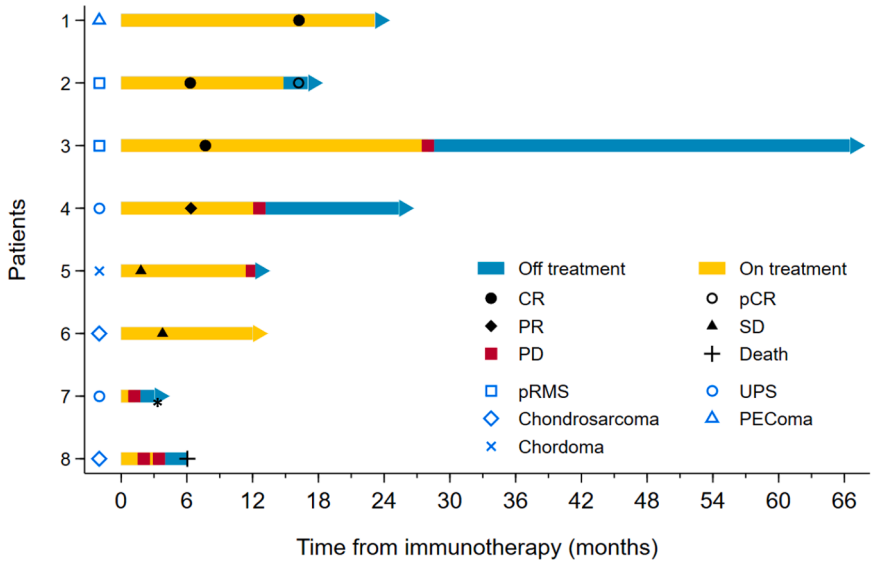

Fig. 3. Swimmer-plot of patients treated with immune checkpoint inhibitors. * *This patient had progressed on the first iconography but continued treatment considering initial clinical benefit. The immune checkpoint inhibitor was stopped at the second iconographic progression.*

Assessment with new techniques such as NGS, currently under investigation, may represent an adequate option [28].

The imputability of LS in sarcomagenesis can be strongly suspected in cases where the tumour presents a loss of expression of the MMR protein corresponding to the constitutionally mutated MMR gene. This situation is representative for the large majority of patients in SarcLynch who had IHC analysis ($N = 32/33$). On the other hand, for cases with a clearly pMMR phenotype, the association with LS remains difficult to establish. These could be sporadic sarcomas unrelated to LS (without a second tumour hit in the MMR gene) or sarcomas related to LS but with a technical defect for detecting MMR, considering that 6 out of the 9 patients who developed a pMMR sarcoma had also contracted another cancer from the LS spectrum. In our study, at least 34 cases of sarcomas could be considered as being associated with LS, bringing up the question of whether sarcoma belongs on the LS tumour spectrum. This retrospective series, biased by the inclusion of patients selected due to the presence of sarcoma, can only raise this question which remains entire.

Off-label use of ICI in heavily pre-treated, refractory and aggressive subtypes of PSTS demonstrated clinically impacting results, with 50 % ORR including 3 CR while in the literature, unselected sporadic sarcomas showed poor response to ICI, with disparity across histological subtypes [29–31]. Considering the limited number of patients ($N = 8$), we cannot conclude that certain subtypes of sarcomas would be better responders to ICI compared to another. In this setting, the predictive value of biomarkers such as CPS, TMB, tumour infiltrating lymphocytes and tertiary lymphoid structures need to be further characterised. However, in colorectal cancer, the first cause of resistance to ICI was a misdiagnosis of MMR deficiency [32]. This emphasises the importance of correctly assessing MMR deficiency in sarcomas. Interestingly, it is important to notice that dMMR phenotype was never ascertained in the main clinical trials investigating the efficacy of ICI in sarcomas [29,31, 33–36]. Access to ICI (dostarlimab vs standard of care) in first line for dMMR STS is currently evaluated in France thanks to a randomized, academic, phase II study (NCT06333314).

Our study has some limitations. Considering the low number of patients included, further prospective and larger assessments of LS in patients with "sporadic" sarcomas should be realised. Due to its retrospective design, several biomarkers classically assessed in routine for carcinomas associated with LS such as MMR phenotype assessment (by IHC and/or molecular biology) lacked for at least 46 % of patients. Concerning TPS/CPS score and TMB, they were almost never evaluated for these sarcomas. Finally, a substantial number of "Lynch-sarcomas" might be lacking in SarcLynch. Indeed, 24 % of the patients were included from a single centre, suggesting they might be underdiagnosed elsewhere, given the absence of dMMR/MSI screening in the guidelines.

5. Conclusion

SarcLynch is the most extensive series to date describing sarcomas which have developed in patients with LS. Its findings illustrate large numbers of UPS, a high representation of pRMS, a majority of LS involving *MSH2* GPV and, finally, a significant clinical benefit of immune checkpoint inhibitors in this selected population with an ORR of 50 % and long-lasting responses. The reality of the association between pRMS and LS will need to be confirmed in larger prospective or penetrance studies.

LS screening for patients with different kind of sarcomas cannot be recommended yet. However, our study suggests that MMR testing by immunohistochemistry would prove rather interesting for PSTS, especially for all UPS and pRMS, and to further address dMMR UPS/pRMS to oncogeneticists, both for therapeutic and oncogenetic purposes.

CRediT authorship contribution statement

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Declaration of Generative AI and AI-assisted technologies in the writing process

The Authors have declared no use of AI in scientific writing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115196.

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