European Journal of Cancer 151 (2021) 72–83

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

The role of local therapy in the treatment of solitary melanoma progression on immune checkpoint inhibition: A multicentre retrospective analysis

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https://doi.org/10.1016/j.ejca.2021.04.003

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Received 8 January 2021; received in revised form 15 March 2021; accepted 5 April 2021
Available online 7 May 2021

KEYWORDS
Solitary progression;
Oligoprogression;
Immune checkpoint inhibition;
Metastatic melanoma;
Treatment;
Progression-free survival

Abstract ***Introduction:*** In patients with metastatic melanoma, progression of a single tumour lesion (solitary progression) after response to immune checkpoint inhibition (ICI) is increasingly treated with local therapy. We evaluated the role of local therapy for solitary progression in melanoma.

Patients and methods: Patients with metastatic melanoma treated with ICI between 2010 and 2019 with solitary progression as first progressive event were included from 17 centres in 9 countries. Follow-up and survival are reported from ICI initiation.

Results: We identified 294 patients with solitary progression after stable disease in 15%, partial response in 55% and complete response in 30%. The median follow-up was 43 months; the median time to solitary progression was 13 months, and the median time to subsequent progression after treatment of solitary progression (TTSP) was 33 months. The estimated 3-year overall survival (OS) was 79%; median OS was not reached. Treatment consisted of systemic therapy (18%), local therapy (36%), both combined (42%) or active surveillance (4%). In 44% of patients treated for solitary progression, no subsequent progression occurred. For solitary progression during ICI (n = 143), the median TTSP was 29 months. Both TTSP and OS were similar for local therapy, ICI continuation and both combined. For solitary progression post ICI (n = 151), the median TTSP was 35 months. TTSP was higher for ICI recommencement plus local therapy than local therapy or ICI recommencement alone (p = 0.006), without OS differences.

Conclusion: Almost half of patients with melanoma treated for solitary progression after initial response to ICI had no subsequent progression. This study suggests that local therapy can benefit patients and is associated with favourable long-term outcomes.

1. Introduction

Patients with metastatic melanoma can achieve long-term disease control after immune checkpoint inhibition (ICI) treatment [1]. Antibodies targeting cytotoxic T-lymphocyte–associated antigen (CTLA-4) and programmed cell death 1 (PD-1) can alone and combined result in durable responses [2,3].

Oligoprogression is defined as disease progression at a limited number of disease sites after initial response of polymetastatic disease to systemic treatment [4]. Although long-term benefit can be achieved in subsets of patients with oligometastatic disease, local treatment in polymetastatic disease is generally only performed for symptom control [5–7]. In clinical practice, oligoprogression is currently regularly treated with local therapy aiming to eliminate presumably drug-resistant subclones. This approach has been prospectively investigated in two small studies [8,9]. Limited evidence exists for this approach, and patients with progression were not systematically evaluated after termination of trial treatment.

A retrospective, single-centre study in 52 patients showed that, after initial response, local treatment of 1–3 progressive melanoma metastases present before ICI initiation resulted in longer median progression-free survival (PFS) than of 1–3 metastases developed during ICI (40 versus 7 months, $p < 0.01$) [10]. For the 38 patients with solitary progression (one progressive metastasis), similar results were found. In another retrospective, single-centre study, local therapy of 1–3 progressive melanoma metastases in 36 patients resulted in a median PFS of 32 months [11]. The outcome did not differ in the 30 patients with solitary progression compared with patients with oligoprogression, or for pre-existing versus newly developed metastases. In these small studies, alternative strategies such as systemic treatment or active surveillance were not described, and in the first study, intracranial oligoprogression was not considered.

Our retrospective, international, multicentre study aimed to determine the outcome of patients with metastatic

Table 1
Baseline patient and tumour characteristics of all patients and reported separately for patients with solitary progression during and post immune checkpoint inhibition (ICI).

Characteristics	Patients, *N* (%)		
	All patients (n = 294)	Solitary progression during ICI (n = 143)	Solitary progression post ICI (n = 151)
Gender (male)	177 (60)	89 (62)	88 (58)
Primary melanoma			
Cutaneous	246 (84)	119 (84)	127 (84)
Mucosal	5 (2)	3 (2)	2 (1)
Unknown primary	42 (14)	20 (14)	22 (15)
Missing data	1 (0)	1 (1)	NA
Mutational status			
BRAF V600E/K	118 (40)	61 (43)	57 (38)
NRAS	56 (19)	26 (18)	30 (20)
Non-BRAF V600E/K or NRAS	114 (39)	52 (36)	62 (41)
Unknown	6 (2)	4 (3)	2 (1)
Age at stage IV diagnosis in years (median, IQR)	62 (51–70)	62 (50–71)	60 (51–69)
LDH level at stage IV diagnosis			
<ULN	175 (60)	86 (60)	89 (59)
ULN – <2x ULN	56 (19)	34 (24)	22 (15)
2x ULN or more	6 (2)	2 (1)	4 (3)
Missing data	57 (19)	21 (15)	36 (24)
Brain metastasis at start ICI	62 (21)	32 (22)	30 (20)
Liver metastasis at start ICI	68 (23)	40 (28)	28 (19)
Bone metastasis at start ICI	62 (21)	27 (19)	35 (23)
Treated with targeted therapy before start ICI	51 (17)	26 (18)	25 (17)
Treated with other ICI line(s) before start of ICI on which solitary progression occurred	80 (27)	41 (29)	39 (26)
Last ICI received when solitary progression occurred			
Pembrolizumab	147 (50)	85 (59)	62 (41)
Ipilimumab	39 (13)	1 (1)	38 (25)
Ipilimumab + nivolumab	43 (15)	15 (11)	28 (19)
Nivolumab	49 (17)	31 (22)	18 (12)
Other	16 (5)	11 (8)	5 (3)
Best overall response to the last ICI received when solitary progression occurred			
Complete response	87 (30)	30 (21)	57 (38)
Partial response	163 (55)	92 (64)	71 (47)
Stable disease	44 (15)	21 (15)	23 (15)
Median follow-up from start date ICI in months (95% CI)	43 (40–46)	36 (32–40)	48 (44–52)
Median follow-up from first observation solitary progression in months (95% CI)	23 (20–25)	24 (20–28)	22 (19–24)

IQR: interquartile range; LDH: lactate dehydrogenase; n: number; ULN: upper limit of normal; 95% CI: 95% confidence interval. Start ICI refers to the ICI line on which solitary progression occurred. Number of percentages may not add up to hundred because of rounding.

melanoma experiencing solitary progression after initial response to ICI and to describe the role of local therapy in this setting. In addition, we investigated whether the treatment strategy and patient outcome differed depending on location or timing of solitary progression.

2. Patients and methods

2.1. Patient selection

Patients with stage IV, non-uveal melanoma treated with ICI for ≥12 weeks between 2010 and 2019 were retrospectively included from 17 centres in 9 countries. Patients achieving stable disease (SD), partial response (PR) or complete response (CR) as best overall response before solitary progression occurring during ICI treatment or after ICI cessation (post ICI) were included. Response evaluation was based on RECIST 1.1 when data were available, otherwise based on a local radiologist's assessment of contrast-enhanced computed tomography (CT) or positron emission tomography/CT scans. Because no internationally accepted standard for modality or timing of follow-up exists, there was heterogeneity in types of scans used across centres. Solitary progression was defined as a single newly developed or single progressive lesion, with stable or decreasing size of all other lesions. Patients were excluded if subsequent progression occurred before treatment of the solitary progressive lesion or if histology did not show viable melanoma cells.

The Netherlands Cancer Institute, coordinating study centre, obtained local institutional review board approval (reference: IRBd19151). In all participating centres, local ethical committee approval was obtained.

2.2. Data collection

Data were collected regarding patient, tumour and treatment characteristics, tumour response and survival status. The date of last follow-up was defined as the date of the last hospital visit or the date of death.

Patients with solitary progression were allocated into two groups, patients with solitary progression during ICI (including patients in whom ICI was discontinued because of development of solitary progression) and patients with solitary progression post ICI. All local and systemic treatments of a solitary progressive lesion were allowed. Surgical interventions were categorised as 'surgery', all radiotherapy schedules as 'radiotherapy' and other local treatment strategies (e.g. radiofrequency ablation) as 'other local treatments'. Surgical complications were registered as per the Clavien-Dindo classification [12]. For systemic treatment after solitary progression, the specific drug was annotated. Distinction was made between continuation of the ICI the patient was treated with at time of solitary progression, recommencing the ICI most recently discontinued before solitary progression or change of

Table 2
Characteristics of the solitary progressive lesions and the corresponding treatment strategies chosen reported separately for patients with solitary progression during and post immune checkpoint inhibition (ICI).

Characteristics	Patients, *N* (%)	
	Solitary progression during ICI (n = 143)	Solitary progression post ICI (n = 151)
Type of solitary progression		
In pre-existing metastasis	78 (55)	69 (46)
Newly developed metastasis	65 (46)	82 (54)
Site of solitary progression		
Brain	27 (19)	34 (23)
Lymph node	24 (17)	26 (17)
Cutis or subcutis	21 (15)	22 (15)
Lung	13 (9)	18 (12)
Bowel	10 (7)	15 (10)
Bone	11 (8)	9 (6)
Adrenal gland	10 (7)	8 (5)
Liver	6 (4)	1 (1)
Other[a]	21 (15)	18 (12)
Management of the solitary progressive lesion		
Local management	15 (11)	90 (60)
Local + continue ICI	94 (66)	NA
Local + recommence ICI	NA	21 (14)
Local + switch systemic management	6 (4)	3 (2)
Continue ICI	14 (10)	NA
Recommence ICI	NA	19 (13)
Switch systemic treatment	14 (10)	7 (5)
Active surveillance	NA	11 (7)
Time from solitary progression to management in days (median, IQR)	37 (14–65)	32 (15–56)
Outcomes of the solitary progressive lesion		
Remission	103 (72)	94 (62)
Stable	18 (13)	21 (14)
Progression	21 (15)	33 (22)
Missing data	1 (1)	3 (2)
Subsequent progression other than in the treated solitary progressive lesion	72 (50)	82 (54)
Subsequent progression		
Subsequent solitary progression	39 (26%)	30 (21%)
Subsequent progression at multiple sites	51 (75%)	46 (32%)
No subsequent progression	61 (40%)	67 (47%)
Clinical status at latest follow-up		
Progressive disease	24 (17)	27 (18)
Non-progressive disease	84 (59)	82 (54)
Missing data	35 (24)	42 (28)
Death	34 (24)	39 (26)
Death due to melanoma	29 (20)	32 (21)

IQR: interquartile range; n: number. Start ICI refers to the ICI line on which solitary progression occurred. Number of percentages may not add up to hundred because of rounding.

[a] Other sites of solitary progression: peritoneum, spleen, vagina, soft tissue other than muscle or subcutis, pancreas, muscle, kidney, gall bladder, pleura, heart, mesentery and leptomeninges.

systemic therapy. Active surveillance was defined as no treatment on detection of a solitary progressive lesion. Treatment strategies were accounted for until progression of this lesion, progression elsewhere or death. The date of progression at the site of the initial solitary progressive lesion or progression at other sites after its treatment was also recorded.

2.3. Statistical analysis

Descriptive statistics were used for patient, tumour and treatment characteristics. Median follow-up was calculated using the inverted Kaplan-Meier approach. PFS1 was defined as the time between ICI initiation and solitary progression, PFS2, as the time between solitary progression and the date of subsequent progression after treatment of solitary progression or last follow-up (Fig. S1). The sum of PFS1 and PFS2 is the time to subsequent progression after treatment of solitary progression (TTSP). Overall survival (OS) is the time between ICI initiation and death or the last follow-up. PFS1, PFS2, TTSP and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. PFS1 and PFS2 were correlated by Spearman's rho test. Univariable Cox regression analyses served to determine potential predictive variables for TTSP. Statistical analyses were performed using IBM SPSS Statistics, version 25.

3. Results

3.1. Baseline patient characteristics

We identified 294 patients (Tables 1 and S1) with solitary progression during (n = 143) or post ICI (n = 151) with anti−PD-1 in 67%, anti−CTLA-4 in 13%, anti−PD-1 plus anti−CTLA-4 in 15% and other combinations in 5%. At stage IV diagnosis, patients mostly had normal serum lactate dehydrogenase levels. Almost half of the patients had metastases in ≥3 organ sites at ICI start, and the best overall response before solitary progression was mostly PR (Table 1). The median follow-up was 43 months from ICI initiation and 23 months from first observation of solitary progression.

3.2. Solitary progression in all patients

Most patients received local and systemic treatment (42%) or local treatment only (36%) for solitary progression, whereas 18% received systemic treatment only, and 4% underwent active surveillance. Solitary

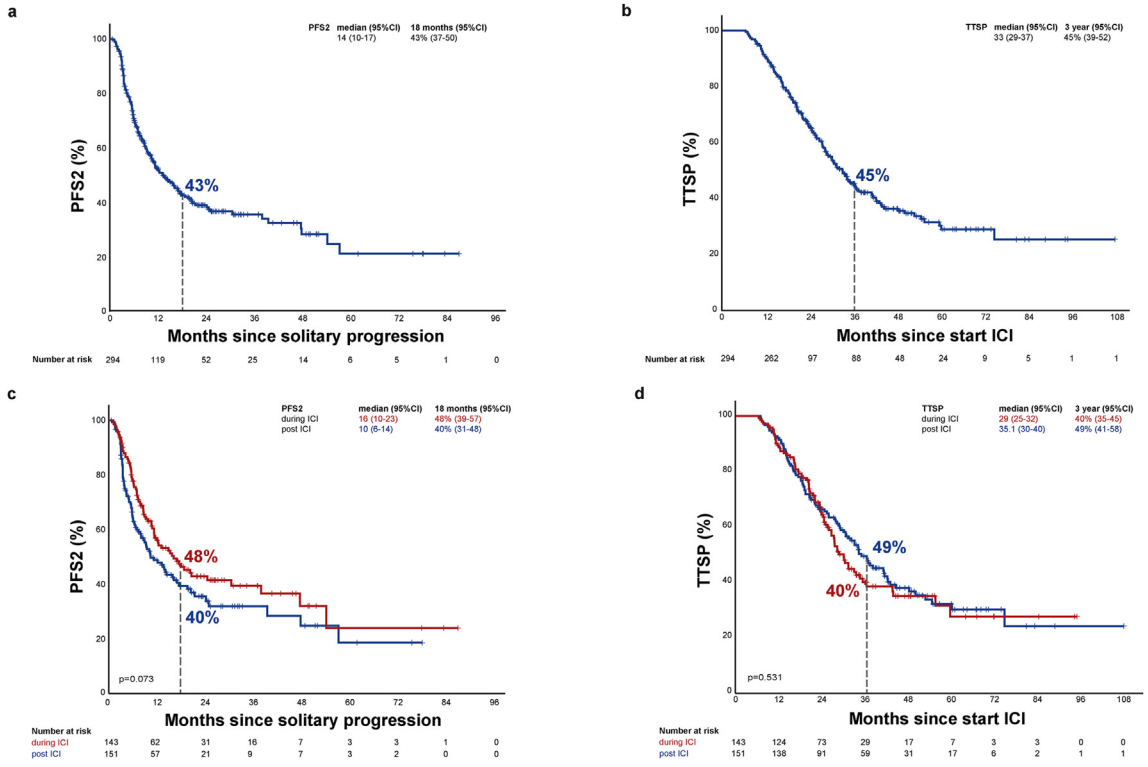


Fig. 1. Progression-free survival from first detection of solitary progression (PFS2) and time to subsequent progression after treatment of the solitary progressive lesion (TTSP) shown for all patients and for patients with solitary progression during immune checkpoint inhibition (ICI) versus post ICI. **a.** PFS2 in months for all patients. **b.** TTSP in months for all patients. **c.** PFS2 in months for patients with solitary progression during and post ICI. **d.** TTSP in months for patients with solitary progression during and post ICI. 95% CI: 95% confidence interval.

progression mostly occurred in the brain, lymph nodes, (sub)cutis and lungs (Table 2). The treatment modality for solitary progression did not differ between organ sites (p = 0.117, Fig. S2a). Most patients received local treatment (n = 229, 78%), namely, surgery (55%), radiotherapy (35%) or both (5%), and rarely other local treatments (4%). In total, 140 patients received surgery. Surgical resection was most often performed for progressive lymph node and (sub)cutaneous lesions. Hospital admission for surgery was generally short, with a median length of 3 days (interquartile range (IQR) 1–5), and the complication rate was low. Complications were scored as grade 1–2 (as per Clavien-Dindo classification) in 21 patients and as grade 3 in three patients, and one patient died because of complications after surgery (grade 5). Twelve patients received both surgery and radiotherapy; 80 patients were treated with radiotherapy only. The dosing regimens used, available for 84 patients, are described in Table S2. The median time from solitary progression detection until surgery was 40 days (IQR 19–64) and 36 days (IQR 22–63) until radiotherapy. Sixty-five patients did not receive local therapy because of change in systemic treatment (46%), SD during follow-up after solitary progression (14%), no local treatment options given the size or location of the lesion (12%), subsequent progression (8%), spontaneous regression of the lesion (5%) and other reasons (15%). In case of recommencement (n = 40) or switch (n = 30) of systemic therapy, the median time between first detection of solitary progression and start of systemic treatment was 35 days (IQR 14–81). Systemic therapy was switched to another ICI in 15 patients and to targeted therapy in 15.

Subsequent progression of the same solitary progressive lesion occurred in 16% of patients after local therapy, 12% after local plus systemic therapy and 35% after systemic therapy alone. Subsequent progression at any site occurred in 166 patients (57%); 69 again had solitary progression, and 97 had progression at multiple sites. In 33% of these 166 patients, the initial solitary progressive lesion progressed. Of the patients with progression at multiple sites, 36% received local therapy for the initial solitary progressive lesion, 39% received local plus systemic therapy, 19% received systemic therapy alone and 6% underwent active surveillance. Fig. S2b shows the treatment for solitary progression and subsequent follow-up per site.

3.3. Solitary progression during and post ICI

For solitary progression during ICI (n = 143), ICI's median duration before solitary progression was 11 months (IQR 8–16). For solitary progression post ICI (n = 151), median ICI duration was 4 months (IQR 2–13, n = 150), and median time between ICI cessation and solitary progression was 9 months (IQR 5–15, n = 150). In these patients, ICI was discontinued for toxicity in 44%, therapy completion in 34%, confirmed CR in 12%, the patient's and physician's decision in 5%, progression in 1% and other causes in 4%. For patients with solitary progression during ICI, main reasons for ICI cessation were progression in 39% of patients and therapy completion in 11%.

Solitary progression during ICI was mostly treated with combined local and systemic therapy (Table 2). ICI was continued in 76% of patients and terminated in 11%. Systemic therapy was switched in 14%, which occurred after a median time of 29 days (IQR 8.0–75.3) from solitary progression. Post ICI, solitary progression was commonly treated locally. Most patients (67%) did not recommence systemic therapy, 27% recommenced the same ICI and 7% commenced a different systemic treatment with a median time between switching or recommencing of 36 days (IQR 15–84).

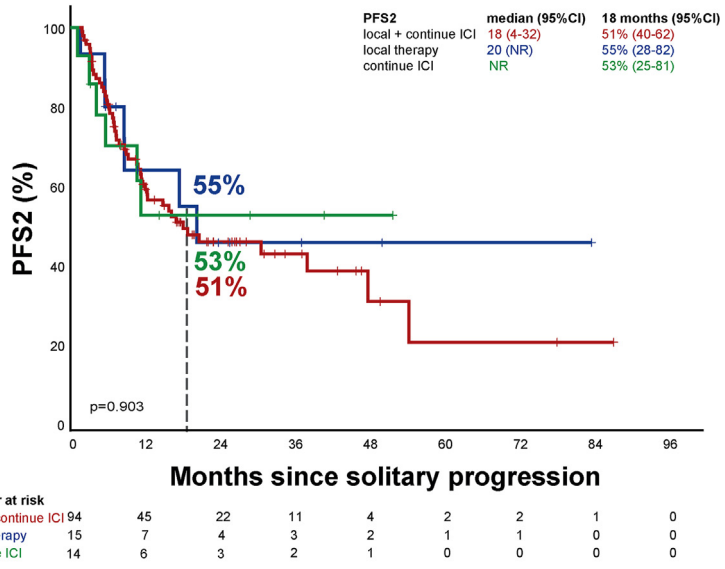
3.4. Outcomes of all patients

Median PFS1 was 13 months (95% confidence interval [CI] 11–14); the estimated 1-year PFS1 rate was 53% (95% CI 47–53, Fig. S3a). Median PFS2 was 14 months (95% CI 10–17, Fig. 1a); the estimated 18-month PFS2 rate was 43% (95% CI 37–50). The median TTSP for all patients was 33 months (95% CI 29–37, Fig. 1b). Three years after ICI initiation, the probability of not having subsequent progression after treatment of the solitary progressive lesion was 45% (95% CI 39–52). Median OS was not reached; the estimated 3-year OS was 79% (95% CI 73–84, Fig. S3b).

Patients with solitary progression in the bone or lymph node had the highest estimated 3-year TTSP rate (69% [95% CI 48–90] and 61% [95% CI 47–75], respectively), whereas this was lowest for patients with solitary progression in the liver or adrenal gland (29% [95% CI 0–62] and 20.8% [95% CI 14–40], respectively, Fig. S4a). TTSP was similar for patients treated with surgery versus radiotherapy (p = 0.353, Fig. S4b). TTSP and OS neither differed for patients with solitary progression of a newly developed or pre-existing metastasis (p = 0.167 and p = 0.353, Fig. S5).

Solitary progression in the brain (n = 61) more frequently concerned a newly developed than a pre-existing metastasis compared with other metastasis locations (72% vs 44%, p < 0.001, Table S3). Cerebral solitary progression was mostly only treated locally (38%) or with local treatment and ICI continuation combined (36%). Local therapy comprised radiotherapy (53%), surgery (21%) or both (12%). TTSP and OS did not differ for patients with solitary progression in the brain versus other organs (Fig. S6). Subsequent progression other than in the solitary progressive lesion occurred less often in patients with solitary progression in the brain than in other organs (41% vs 57%, p = 0.040).

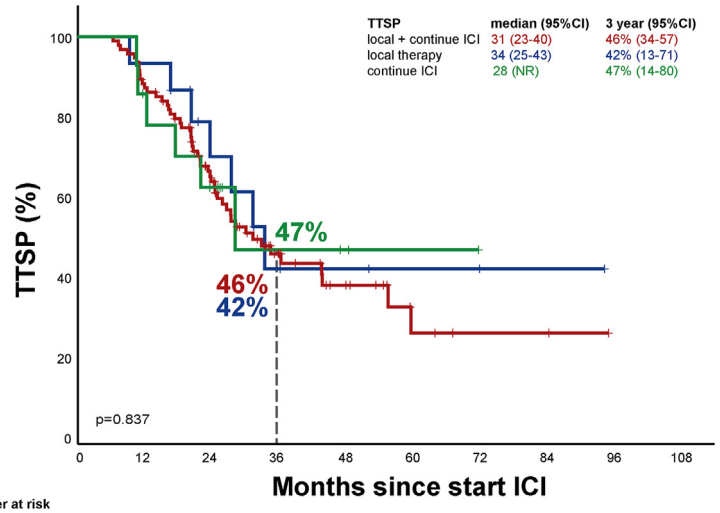
a



Number at risk

local + continue ICI	94	45	22	11	4	2	2	1	0
local therapy	15	7	4	3	2	1	1	0	0
continue ICI	14	6	3	2	1	0	0	0	0

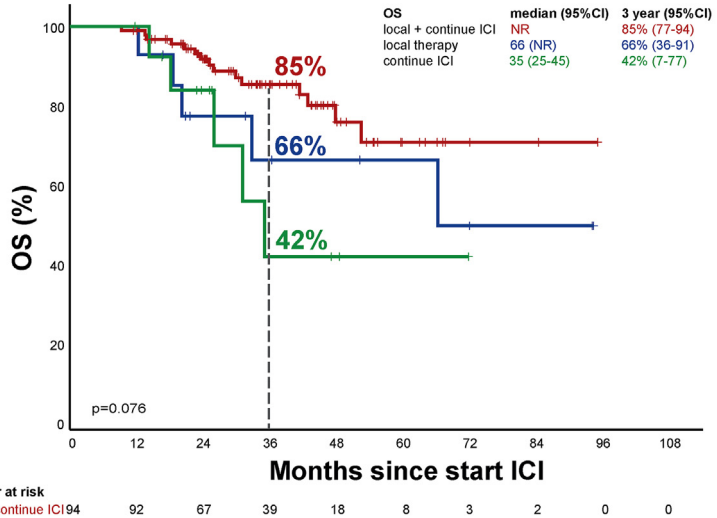
b



Number at risk

local + continue ICI	94	82	49	21	12	4	2	2	0	0
local therapy	15	14	8	4	3	2	1	1	0	0
continue ICI	14	11	7	3	2	1	1	0	0	0

c



Number at risk

local + continue ICI	94	92	67	39	18	8	3	2	0	0
local therapy	14	14	8	6	5	4	2	2	0	0
continue ICI	14	13	8	3	2	1	0	0	0	0

3.5. Outcomes of solitary progression during and post ICI

For solitary progression during ICI, the median PFS1 was 11 months (95% CI 9–12, Fig. S7a), the median PFS2 was 16 months (95% CI 10–23) and the median TTSP was 29 months (95% CI 25–32, Fig. 1c and d). Median OS was not reached; the estimated 3-year OS rate was 74% (95% CI 66–83, Fig. S7b). Post ICI, the median PFS1 was 17 months (95% CI 14–21, Fig. S7a), the median PFS2 was 10 months (95% CI 6–14) and the median TTSP was 35 months (95% CI 30–40, Fig. 1c and d). Median OS was not reached; the estimated 3-year OS rate was 82% (95% CI 76–89 Fig. S7b). Solitary progression during ICI had shorter PFS1 than post ICI (Fig. S7a). PFS2, TTSP and OS did not differ for patients with solitary progression during or post ICI (Fig. 1c and d, OS in Fig. S7b), and PFS1 and PFS2 did not correlate (Rs = −0.010, p = 0.905 and Rs = −0.010, p = 0.906, respectively).

For solitary progression during ICI, local therapy plus ICI continuation had similar PFS2, TTSP and OS as local treatment or ICI continuation alone (p = 0.837, p = 0.903 and p = 0.076, respectively, Fig. 2). Post ICI, TTSP was higher for ICI recommencement combined with local therapy than for local treatment or ICI recommencement alone (p = 0.006, Fig. 3b), whereas PFS2 and OS did not differ (p = 0.174 and p = 0.609, respectively, Fig. 3a and c). PFS2, TTSP and OS for all systemic treatment options with and without local therapy are shown in Fig. S8.

Solitary progression during ICI in the lung or adrenal gland was associated with a higher risk of progression after treatment of this lesion in univariable analysis (Table S4). CR before solitary progression and solitary progression in a lymph node were associated with a lower risk of progression after treatment of solitary progression post ICI in univariable analysis (Table S5).

4. Discussion

This first large, retrospective, international analysis of patients with metastatic melanoma and solitary progression after ICI response demonstrated good survival rates. Solitary progression during ICI was commonly treated with local and systemic therapy. Compared with single-modality treatment, local therapy plus ICI continuation had similar TTSP and OS rates. Post ICI, patients mostly received local therapy only. Local therapy plus ICI recommencement resulted in better TTSP than single-modality treatment; however, no OS difference was observed.

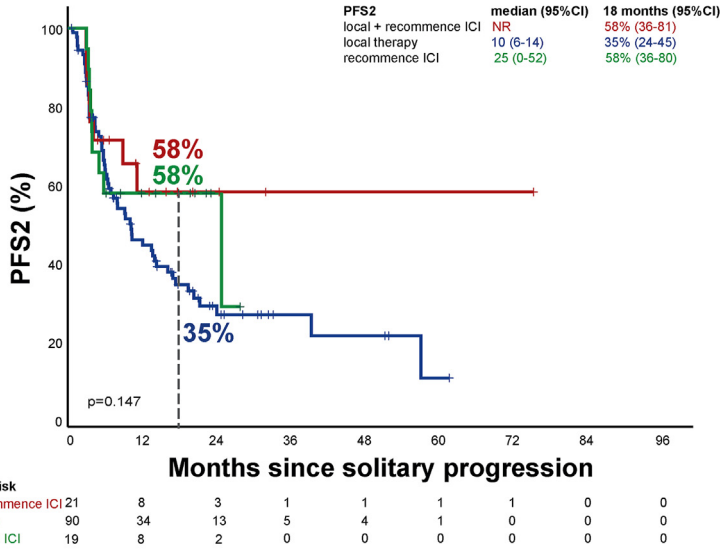
There is increasing interest in additional local treatment of resistant disease sites during systemic treatment. Patients with oligometastatic lung, colorectal, prostate and breast cancer had prolonged PFS and OS after local treatment, but in these studies, response to prior systemic treatment was mostly not a prerequisite [4,13,14]. Our data suggest that, in melanoma, solitary progression is not necessarily the tip of the iceberg for multimetastatic disease because progression at other sites occurred in only about half of the patients.

After treatment of solitary melanoma progression, 44% of patients had no subsequent progression, implying that solitary progression is not necessarily the harbinger of widespread progression. Patients with solitary progression during ICI had similar survival rates when ICI was continued without local therapy to patients treated with local therapy alone. In patients with solitary progression post ICI, previous CR to ICI was associated with a lower risk of progression after treatment of solitary progression, in line with studies demonstrating that patients with melanoma achieving CR have lower risk of disease progression after anti–PD-1 discontinuation [2]. We did not observe TTSP and OS differences for patients with solitary progression in pre-existing versus newly developed metastases, in line with one previous study [11]. Another study describing worse prognosis in patients with newly developed metastases included only 38 patients, all without intracranial solitary progression [10]. We did not find TTSP or OS differences when excluding patients with intracranial solitary progression (data not shown).

This study provides valuable insights into the role of local and systemic treatment strategies for solitary melanoma progression. However, inherent to our retrospective study design, selection bias cannot be excluded, comprehensive data on reasons for treatment choices were not available and some subgroups were small. Therefore, no definitive conclusions can be drawn regarding the role of local therapy in the treatment of solitary melanoma progression. Choices were likely based on factors including the patient's fitness, lesion accessibility, lesion growth rate, previous treatment and

Fig. 2. Progression-free survival from first detection of solitary progression (PFS2), time to subsequent progression after treatment of the solitary progressive lesion (TTSP) and overall survival (OS) for patients with solitary progression during immune checkpoint inhibition (ICI), reported separately as per the treatment strategy. **a.** PFS2 in months for patients with solitary progression during ICI, reported separately for patients who received local treatment, patients who received local treatment combined with ICI continuation and patients who continued ICI without the addition of local therapy. **b.** TTSP in months for patients with solitary progression during ICI, reported separately for patients who received local treatment, patients who received local treatment combined with ICI continuation and patients who continued ICI without the addition of local therapy. **c.** OS in months for patients with solitary progression during ICI, reported separately for patients who received local treatment, patients who received local treatment combined with ICI continuation and patients who continued ICI without the addition of local therapy. 95% CI: 95% confidence interval.

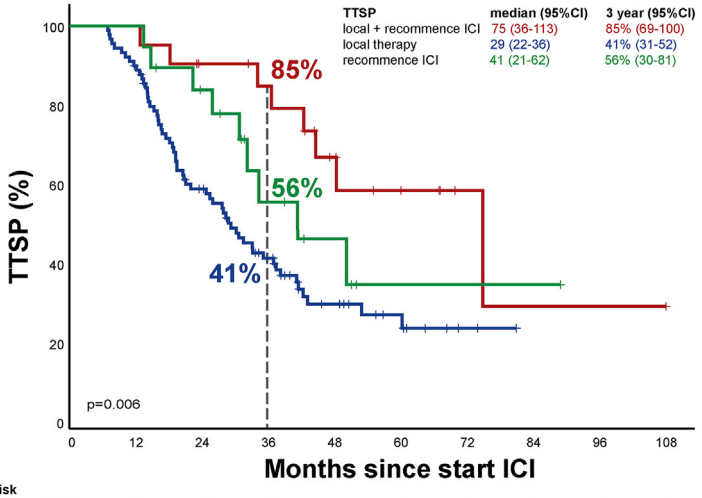
a



Number at risk

local + recommence ICI	21	8	3	1	1	1	1	0	0
local therapy	90	34	13	5	4	1	0	0	0
recommence ICI	19	8	2	0	0	0	0	0	0

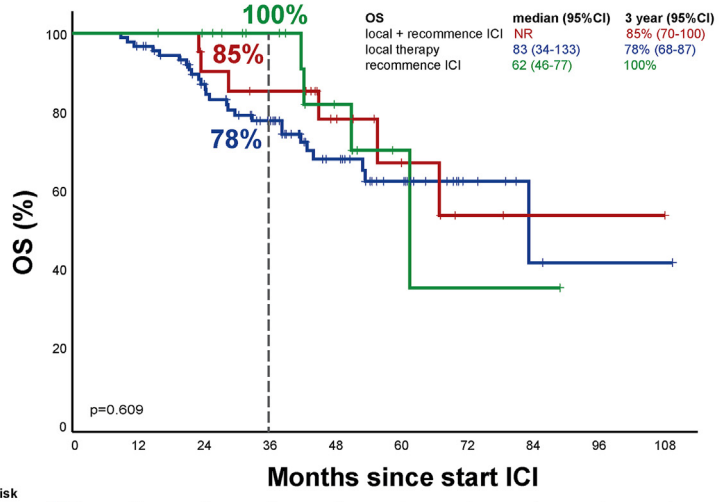
b



Number at risk

local + recommence ICI	21	21	17	15	9	6	2	1	1	1
local therapy	90	80	49	30	15	8	2	0	0	0
recommence ICI	19	19	14	7	4	1	1	1	0	0

C



Number at risk

local + recommence ICI	21	21	18	16	10	6	2	1	1	1
local therapy	90	86	68	51	29	17	6	2	1	1
recommence ICI	19	19	17	13	7	2	1	1	0	0

available trial options. Longer follow-up of our cohort is required to determine whether solitary progression is a predictor of future widespread progression and to determine whether TTSP differences will translate into OS differences for patients with solitary progression post ICI. Definitive answers can only come from a prospective randomised controlled trial, which is unlikely to be performed because of the rapidly changing treatment landscape and the number of patients needed. Despite the retrospective nature of our study, the results can aid in determining optimal treatment strategies in melanoma. The number of identified patients with solitary progression was not reported as a percentage of the total melanoma population treated with ICI in the included centres because, due to the retrospective study design, it was possible that not all patients with solitary progression were identified. Solitary progression is recognised in numerous cancer types sensitive to ICI, and analysis of local therapy outcomes in these tumour types will also be of interest.

Different cellular subclones of melanoma can coexist within one patient, and therefore, there may be differences in ICI sensitivity of various lesions within one patient [15]. Melanoma cells not eliminated by ICI therapy can, in time, result in (oligo)progression in patients initially responding to ICI. Furthermore, the composition of the tumour micro-environment has been suggested to be tissue-specific, which might result in organ-specific mechanisms of ICI resistance [16]. Patients with melanoma metastases in subcutaneous and lung tissue respond better to ICI than patients with metastases at other visceral sites, whereas patients with melanoma with liver metastases have a worse OS [17,18]. In our study, most solitary progressive lesions were found in the brain, lymph nodes and (sub)cutis. In a prior study including four patients, acquired resistance of melanoma to anti–PD-1 therapy was associated with loss-of-function mutations in Janus-kinase 1 and 2 in two patients, leading to resistance to interferon-gamma [19]. In another patient, a mutation in the β-2-microglobulin gene resulted in the loss of surface expression of major histocompatibility complex class 1, leading to acquired resistance of melanoma to anti–PD-1 therapy [19]. Future histological analysis of solitary progressive lesions might support understanding why a single metastasis acquires ICI resistance while other lesions in a patient do not.

In conclusion, our study demonstrates that in almost half of patients treated for melanoma solitary progression, no subsequent progression occurred. In patients with solitary progression post ICI, combining local therapy and ICI recommencement was associated with later onset of subsequent progression, but not with improved OS compared with single-modality treatment. This indicates that local therapy only is a reasonable option. There is less evidence supporting local therapy for solitary progression during ICI. In general, this study suggests that local therapy can benefit patients and may be associated with favourable long-term outcomes.

Funding

None declared.

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Manuscript review: All authors.

Conflict of interest statement

All authors declare no direct conflict with this work. For unrelated conflicts, K.P.M.S. has an advisory role

Fig. 3. Progression-free survival from first detection of solitary progression (PFS2), time to subsequent progression after treatment of the solitary progressive lesion (TTSP) and overall survival (OS) for patients with solitary progression post immune checkpoint inhibition (ICI), reported separately as per the treatment strategy. **a.** PFS2 in months for patients with solitary progression post ICI, reported separately for patients who received local treatment, patients who received local treatment combined with ICI recommencement and patients who recommenced ICI without the addition of local therapy. **b.** TTSP in months for patients with solitary progression post ICI, reported separately for patients who received local treatment, patients who received local treatment combined with ICI recommencement and patients who recommenced ICI without the addition of local therapy. **c.** OS in months for patients with solitary progression post ICI, reported separately for patients who received local treatment, patients who received local treatment combined with ICI recommencement and patients who recommenced ICI without the addition of local therapy. 95% CI: 95% confidence interval.

for Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, AbbVie and Pierre Fabre and has received honoraria from Merck Sharp & Dohme, Novartis and Roche. L.Z. has an advisory role for Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sanofi and Sun Pharma; has received research funding from Novartis; has received honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre and Roche and has received travel support from Amgen, Bristol Myers Squibb, Novartis, Pierre Fabre, Sanofi and Sun Pharma. E.W.K. has an advisory role for Bristol Myers Squibb, Merck, Novartis and Pierre Fabre; has received research funding from Bristol Myers Squibb and has received travel support from Roche. C.A. has received travel support from Amgen, Bristol Myers Squibb and Roche. D.B.J. has an advisory role for Array BioPharma, Bristol Myers Squibb, Incyte, Merck and Novartis; has received research funding from Bristol Myers Squibb and Incyte and has received travel support from Genentech. Adriana H. is an employee of AstraZeneca with stock options in the company, has received honoraria from Novartis; has an advisory role for L.E.K. Consulting and has received travel support from Roche. J.M. has received honoraria from Amgen, Bristol Myers Squibb, Merck-Pfizer, MSD, Novartis and Pierre Fabre; has an advisory role for Amgen, Merck-Pfizer, Merck Sharp & Dohme, Novartis and Pierre Fabre and has received travel support from Bristol Myers Squibb, L'Oreal, MSD, Pierre Fabre and Ultrasun. P.B. has received travel support from MSD. Y.J.L.J. has received travel support from Bristol Myers Squibb, MSD and Pfizer. V.A. has received honoraria from Bristol Myers Squibb, Genentech, Merck Serono, Merck Sharp & Dohme, Novartis and Pierre Fabre; has an advisory role for Bristol Myers Squibb, Merck Serono, Merck Sharp & Dohme, Novartis, Pierre Fabre and Roche and has received travel support from Bristol Myers Squibb, Merck Sharp & Dohme, OncoSec and Pierre Fabre. P.A.A. has an advisory role for 4SC, Alkermes, Amgen, Array BioPharma, Bristol Myers Squibb, Genentech, Genmab, Idera, Immunoscore, Incyte, Italfarmaco, MedImmune, Merck Serono, Merck Sharp & Dohme, Nektar, NewLink Genetics, Novartis, Pierre Fabre, Sandoz, Sanofi, Sun Pharma, Syndax and Ultimovacs; has received research funding from Array BioPharma, Bristol Myers Squibb and Genentech; has received travel support from Merck Sharp & Dohme and is a stockowner of PrimeVax. Andrew H. has received honoraria from Merck and Novartis and has an advisory role for Novartis and Pierre Fabre. A.M.M. has an advisory role for Bristol Myers Squibb, MSD Oncology, Novartis, Pierre Fabre and Roche. G.V.L. is a consultant advisor for Aduro Biotech, Inc., Amgen Inc., Array BioPharma Inc., Boehringer Ingelheim International GmbH, Bristol Myers Squibb, Highlight Therapeutics S.L., Merck Sharp & Dohme, Novartis Pharma AG, QBiotics Group Limited, Regeneron Pharmaceuticals, Inc. and SkylineDX B.V. C.L. had received honoraria from Amgen, Bristol Myers Squibb, Incyte, Merck Sharp & Dohme, Novartis, Pfizer, Pierre Fabre and Roche; has an advisory role for Amgen, Bristol Myers Squibb, Merck Serono, Merck Sharp & Dohme, Novartis, Roche and Sanofi; has received research funding from Bristol Myers Squibb and Roche and has received travel support from Bristol Myers Squibb and Merck Sharp & Dohme. A.A.M.v.d.V. has an advisory role for Bristol Myers Squibb, Eisai, Ipsen, MSD Oncology, Merck, Novartis, Pfizer, Pierre Fabre, Roche and Sanofi and has received research funding from Bayer and travel support from Bayer, MSD Oncology, Novartis and Roche. M.S.C. has an advisory role for Amgen, Bristol Myers Squibb, Eisai, IDEAYA Biosciences, Merck and Co, Merck Sharp & Dohme, Nektar, Novartis, Pierre Fabre, Roche, Sanofi and QBiotics and has received honoraria from Bristol Myers Squibb, Merck Sharp & Dohme and Novartis. S.S. has received honoraria from AstraZeneca, Bristol Myers Squibb, Merck and Merck Serono; has an advisory role for Amgen, Bristol Myers Squibb, MSD, Novartis and Roche outside the submitted work and has received research funding from Amgen, AstraZeneca, Endocyte, Genentech and Merck Sharp & Dohme. E.G.E.d.V. has an advisory role for Daiichi Sankyo, NSABP and Sanofi; has received research funding from Amgen, AstraZeneca, Bayer, Chugai Pharma, CytomX Therapeutics, G1 Therapeutics, Genentech, Nordic Nanovector, Radius Health, Regeneron, Roche, Servier and Synthon and is the chair of ESMO Cancer Medicines Working Group, chair of RECITS committee and member of the ESMO-MCBS working group. C.U.B. has received research funding from Bristol Myers Squibb, Novartis and NanoString; has an advisory role for Bristol Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, GlaxoSmithKline, AstraZeneca, Pfizer, Lilly, Genmab and Pierre Fabre and is a stockowner of Uniti Cars. M.J. has an advisory role for Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, AstraZeneca, Tesaro and Pierre Fabre.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.04.003.

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