Reintroduction of immune-checkpoint inhibitors after immune-related meningitis: a case series of melanoma patients

Stefania Cuzzubbo,1,2 Pauline Tetu,3,4 Sarah Guegan,5,6 Renata Ursu,2 Catherine Belin,2 Lila Sirven Villaros,1,2 Julie Mazoyer,2 Coralie Lheure,7 Celeste Lebbe,3,4 Barouyr Baroudjian,3 Antoine F. Carpentier1,2

ABSTRACT
Immune-checkpoint inhibitors (ICIs) targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death ligand-1 (PD-L1) are associated with several immune-related neurological disorders. Cases of meningitis related to ICIs are poorly described in literature and probably underestimated. Several guidelines are available for the acute management of these adverse events, but the safety of resuming ICIs in these patients remains unclear. We conducted a retrospective case series of immune-related meningitis associated with ICIs that occurred between October 1 2015 and October 31 2019 in two centers: Saint-Louis and Cochin hospitals, Paris, France. Diagnosis was defined by a (1) high count of lymphocytes (>8 cells/mm3) and/or high level of proteins (>0.45 g/L) without bacteria/virus or tumor cells detection, in cerebrospinal fluid and (2) normal brain and spine imaging. Patients were followed-up for at least 6 months from the meningitis onset. Seven cases of immune-related meningitis are here reported. Median delay of meningitis occurrence after ICIs onset was 9 days. Steroid treatment was introduced in four patients at a dose of 1 mg/kg (prednisone), allowing a complete recovery within 2 weeks. The other three patients spontaneously improved within 3 weeks. Given the favorable outcome, ICIs were reintroduced in all patients. The rechallenge was well tolerated and no patients experienced meningitis recurrence. In conclusion, in our series, the clinical rate of recurrence of the specific or distinct irAE. Some studies reported a 40%–60% rate of recurrence of the specific or distinct AE after the reintroduction of ICIs.5–8 As a consequence, only few patients with irAEs-N resume ICI treatment in current practice because of life-threatening risk related to neurological syndromes.

INTRODUCTION
Immune-checkpoint inhibitors (ICIs) targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1) and PD ligand 1 are today a standard of care in the treatment of several cancers. Initially approved for unresectable metastatic melanoma and non-small cell lung cancer, ICIs are now increasingly used to treat a high variety of solid-organ and hematological cancers. They are nevertheless associated with several immune-related (ir) disorders that can potentially involve every organ or system but gastrointestinal, dermatological, hepatic, endocrine and pulmonary toxicities predominate.1 Neurological ir adverse events (irAEs-N) are rare, with an overall incidence of 3.8% for anti-CTLA4 antibodies, 6.1% for anti-PD1 antibodies and 12.0% for the combination of them. However, the incidence of severe irAEs-N is below 1% for all types of treatment. Although rare irAEs-N require prompt recognition and treatment to avoid substantial morbidity.23 Several guidelines are available for the acute management of irAEs,4 but their long-term management is less standardized. Specifically, no clear data are available on the safety of resuming ICIs after an irAE. Some studies reported a 40%–60% rate of recurrence of the specific or distinct AE after the reintroduction of ICIs.5–8 As a consequence, only few patients with irAEs-N resume ICI treatment in current practice because of life-threatening risk related to neurological syndromes.

Given the benefits of ICI therapy in patients with cancer, additional research is necessary to guide clinicians in practical decisions. Considering the heterogeneity of irAEs, even within neurological irAEs, recommendations for resuming ICIs should be specifically defined for each type of them. Herein, we report a retrospective series of seven consecutive patients who developed ir-meninigitis with the aim of defining the long-term management and exploring the safety of ICIs reintroduction in these patients.

METHODS
We collected the cases of ir-meninigitis associated with ICIs in adult melanoma patients of Saint-Louis and Cochin hospitals, Paris, between October 1 2015 and October 31
Adverse Events, V.4.03.9 Duration of corticosteroids was of at least 6 months after meningitis occurrence. The decision of ICI reintroduction was made on a case-by-case basis.

We collected clinical characteristics of patients. IrAEs were defined using the National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.03. Duration of corticosteroids was collected, and patients were considered "off steroids" when hydrocortisone equivalent dose was ≤ 30 mg/day. We also collected tumor evaluations according to the ir-response criteria at 3 months after the ICI readministration and at the latest follow-up.

RESULTS
We, here, report seven consecutive cases of ir-meninigitis. Table 1 summarizes demographic and clinical characteristics of patients. Median delay of meningitis onset after the first dose of ICI was 9 days (range: 6–95 days). CSF study displayed lymphocytic meningitis in six out of seven patients, and an isolated high protein level in patient 5, but lumbar puncture was realized 45 days after the onset of neurological symptoms in this patient. CSF microbiological studies were negatives in all patients and no evidence of tumor meningitis was found in CFS study or brain and spine MRI. MRI did not find any signs of myelitis nor encephalitis, and therefore, a diagnosis of isolated ir-meninigitis was made.

After diagnosis of ir-meninigitis, a steroid treatment (prednisone 1 mg/kg) was introduced in patients 1, 2, 4 and 6 (all with irAEs-N grade 2), allowing a complete clinical recovery within 2 weeks. After 1-2 weeks of full dose, corticosteroids were gradually tapered until discontinuation after 6 weeks. The other three patients (all with grade 1 AEs) spontaneously improved within 3 weeks (table 2).

Given the favorable outcome of ir-meninigitis, ICI treatment was reintroduced in four patients (cases 2, 3, 5, 7) after 4–54 days from irAE-N. For the other three patients, despite a quick recovery of meningitis, ICI was not resumed immediately because of the high grade of nAE (grade 3) in patient 1, and of multiple co-occurring non neurological irAEs in patients 4 and 6. These patients were followed by whole body imaging every 3 months and ICIs were reintroduced at time of disease progression.

The rechallenge was well tolerated in six out of seven cases: no meningitis nor other irAEs occurred. Patient 3 developed a severe interstitial lung disease, without meningitis recurrence, leading to permanent discontinuation of ICI treatment (table 3). Table 3 shows the cancer status at 3 months from the rechallenge of ICIs and at the latest follow-up.

DISCUSSION
A broad spectrum of neurological irAEs has been described in the literature, potentially involving all areas of the central and peripheral nervous system. Cases of ir-meninigitis have been less frequently reported. However, their frequency is likely underestimated because their presentation can be paucisymptomatic. The occurrence of an unusual headache during ICI treatment should raise the suspicion of meningitis and lead to appropriate treatment.

| Table 1 Demographic and clinic characteristics of patients |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
| Sex, age (years) | M, 71 | F, 29 | F, 51 | F, 46 | F, 64 | M, 27 | F, 20 |
| Stage of melanoma | IIIb | V600E mutant | IIIc | Wild type | IV | V600E mutant | IIIc |
| ICI regimen at the irAE-N onset | Nivolumab 3 mg/kg | Ipilimumab 1 mg/kg +nivolumab 3 mg/kg | Spartalizumab 400 mg/28 days | Ipilimumab 1 mg/kg +nivolumab 3 mg/kg | Nivolumab 3 mg/kg | Ipilimumab 1 mg/kg +nivolumab 3 mg/kg |
| Concomitant cancer | 0 | 0 | 0 | 0 | 0 | 0 |
| No of ICI doses before irAE-N | 1 | 1 | 4 | 2 | 1 | 2 | 1 |
| Delay of neurological symptoms onset from ICI onset (days) | 6 | 6 | 95 | 50 | 6 | 9 | 17 |

F, female; ICI, immune-checkpoint inhibitor; irAE-N, neurological immune-related adverse event; M, male.
investigations. Notably, differential diagnosis with bacterial/viral meningitis and meningeal carcinomatosis must be considered in first place, hence lumbar puncture and brain/spine MRI with and without contrast generally lead to the correct diagnosis.

As reported for other irAEs-N, we did not observe any exclusive association between ir-meningitis and a class of ICIs.2,8 Clinical signs of meningitis occurred early with a median delay of 9 days after the ICI onset and a median number of ICI cycles of 2, compared with 6 weeks and three cycles observed in all kinds of irAEs-N respectively.2,8 Ir-meningitis had a favorable evolution with a fast and full recovery in all patients. According to published recommendations,12 steroid treatment was introduced in more severe cases (grade ≥2) and maintained at full dose (prednisone 1 mg/kg/day) for one or 2 weeks depending on the clinical recovery of meningitis and then tapered over 6 weeks given the half-life of ICI drugs.

The safety of ICI reintroduction after an irAE is still a matter of debate. Some studies showed a quite poor tolerance of resuming ICI after a severe irAE, reporting an occurrence of the same or a distinct AE in 40%–55% of patients.5–7 The risk of irAEs-N recurrence is likely similar to other ir-AEs, but, very few cases of reintroduction of ICIs after an irAE-N have been reported so far, probably because of concerns on potential severity and life-threatening risk associated to irAEs-N. Dubey et al reported a series of 10 patients retreated with ICIs after a severe irAEs-N. The irAE-N recurrence rate was 60% and the authors suggested a correlation with a short steroid treatment (less than 2 weeks) after the initial AE in these patients.8

Only few cases of ICI rechallenge after an ir-meningitis are reported in literature. Spain et al reported a melanoma patient with meningitis associated with ir-hepatitis. The rechallenge with the same regimen resulted in severe ir-colitis.13 Fellner et al reported another case of reintroduction of ICIs after meningitis related to ipilimumab–nivolumab combination therapy. In this case, only nivolumab was resumed, with a good tolerance.14 In both cases, ICI drugs were reintroduced at the moment of cancer recurrence according to checkmate-067 trial results, in which 68% of patients who discontinued ICI treatment due to toxicity experienced a long response (median time of 13 months).15

In our series of seven consecutive patients, ICI treatment was early reintroduced in four patients (all with irAE-N grade ≤2), as soon as the meningitis symptoms had completely recovered. Tolerance of reintroduction was good in three out of four patients. One patient

| Table 2  | Characteristics of ir-meningitis and management with steroids |
|---------|-----------------------------------------------------------------|
| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
| Severity grade of meningitis | 3 | 2 | 1 | 2 | 1 | 2 | 1 |
| Symptoms | Fever, confusion, partial seizure. | Headache, nausea, photophobia. | Headache, four limbs pain. | Headache, vomiting. | Headache, vomiting. | Headache, fever. | Fever, headache |
| Lumbar puncture | | | | | | | |
| cells/mm³ | 40 (90% L) | 8 (100% L) | 19 (90% L) | 25 (90% L) | 0 | 9 (90% L) | 320 (90% L) |
| Protein level | 0.99 g/L | 0.30 g/L | 0.39 g/L | 0.43 g/L | 0.59 g/L | 0.54 g/L | <0.45 g/L |
| Steroid treatment* | | | | | | | |
| Initial dose | 1 mg/kg/day | 1 mg/kg/day | 0 | 1 mg/kg/day | 0 | 1 mg/kg | 0 |
| Length at full dose | 7 days | 7 days | 0 | 7 days | 0 | 14 days | 0 |
| Length of tapering | 42 days | 42 days | 42 days | 42 days | 42 days | 42 days |
| Delay of complete recovery | | | | | | | |
| From irAE-N onset | 18 days | 17 days | 10 days | 21 days | 65 days | 49 days | 10 days |
| From steroids onset | 2 days | 14 days | – | 2 days | – | 14 days | – |
| Other irAEs occurrence | None | None | None | Hypophysitis (gr. 2), diabetes (gr. 2), hepatitis (gr. 1) | None | Hypophysitis (gr. 2), hepatitis (gr. 4), colitis (gr. 2) small fibers neuropathy (gr.1) | None |

*Prednisone equivalent doses.
irAE, immune-related adverse event; irAE-N, neurological immune-related adverse event; L, lymphocytes.
Cuzzubbo S, et al. J Immunother Cancer 2020;8:e001034. doi:10.1136/jitc-2020-001034

Table 3 Tolerance of ICI reintroduction

| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Delay of resumption of ICI after meningitis (days) | 373 | 54 | 24 | 118 | 4 (No ICI discontinuation) | 126 | 19 |
| ICI regimen at the rechallenge | Ipilimumab 1 mg/kg +nivolumab 3 mg/kg | Ipilimumab 1 mg/kg +nivolumab 3 mg/kg | Spartalizumab 400 mg | Nivolumab 3 mg/kg | Nivolumab 3 mg/kg | Spartalizumab 400 mg +ribociclib 600 mg/day | Nivolumab 3 mg/kg |
| Steroid treatment at the time of ICI resumption* | 0.5 mg/kg/day | 0 | 0 | 0 | 0 | 0 | 0 |
| Meningitis recurrence | No | No | No | No | No | No | No |
| Other irAEs occurrence at rechallenge with ICIs | No | No | Interstitial lung disease (grade 3) | No | No | No | No |
| Cancer status at 3 months from rechallenge with ICIs | PD | PR | PD | PD | PR | PD | PR |
| Cancer status at latest follow-up (months from rechallenge) | Death caused by cancer progression | Maintained CR (32 months) | Maintained PR (25 months) | Death caused by cancer progression | Maintained PR (6 months) | Death caused by cancer progression | Maintained PR (17 months) |

*Prednisone equivalent doses.
CR, complete response; ICI, immune-checkpoint inhibitor; irAE, immune-related adverse event; PD, progression disease; PR, partial response.

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CONCLUSIONS

Cases of meningitis related to ICIs are poorly described in literature. In our cases, the clinical course was favorable and steroids were not always required. In case of isolated ir-meningitis, an early reintroduction of ICI treatment at the same regimen appears to be safe, even in case of combination therapy (anti-CTLA-4/PD-1). On the contrary, a longer discontinuation of ICI drug (until disease progression) and a regimen shift from dual to monotherapy is recommended in case of multiple irAEs. We are aware that our study has some limitations since only one patient experienced a high grade ir-meningitis. A careful analysis of the risk/benefit ratio should be done on a case-by-case basis.

Acknowledgements The authors thank MelBase biobank coordination team for technical support and medical data and PATIO group for the constructive exchanges.

Contributors SC conceptualized the study, collected and analyzed data, and wrote the preliminary version of the paper. AFC conceptualized the study and wrote the preliminary version of the paper. PT, SG, CB, LSV, JM, CLh, CLe and BB contributed to the collection of patient data. All authors participated in critical review and revision of the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests BB is a consultant for BMS, MSD and Pierre Fabre; CLh received grants or honoraria from Roche, BMS, MSD, GSK, Novartis and Amgen; AFC is a consultant for BMS.

Patient consent for publication Not required.

Ethics approval MelBase protocol was approved by the French ethics committee (CPP Ile-de-France XI, no 12027, 2012).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article.

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ORCID iD Stefania Cuzzubbo http://orcid.org/0000-0003-0288-4607

REFERENCES

1 Baroudjian B, Arangalage D, Cuzzubbo S, et al. Management of immune-related adverse events resulting from immune checkpoint blockade. Expert Rev Anticancer Ther 2019;19:209–22.
2 Cuzzubbo S, Javeri F, Tissier M, et al. Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. *Eur J Cancer* 2017;73:1–8.

3 Cuzzubbo S, Bellin C, Chouahnia K, et al. Assessing cognitive function in patients treated with immune checkpoint inhibitors: a feasibility study. *Psychooncology* 2018;27:1861–4.

4 Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of clinical oncology clinical practice guideline. *JCO* 2018;36:1714–68.

5 Pollack MH, Betof A, Dearden H, et al. Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. *Ann Oncol* 2018;29:250–5.

6 Simonaggio A, Michot JM, Voisin AL, et al. Evaluation of readministration of immune checkpoint inhibitors after immune-related adverse events in patients with cancer. *JAMA Oncol* 2019;5:1310–7.

7 Santini FC, Rizvi H, Plokdowski AJ, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol Res* 2018;6:1093–9.

8 Dubey D, David WS, Reynolds KL, et al. Severe neurological toxicity of immune checkpoint inhibitors: growing spectrum. *Ann Neurol* 2020;87:659–69.

9 Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for immunotherapy of cancer (SITC) toxicity management Working group. *J Immunother Cancer* 2017;5:95.

10 Wolchok JD, Hoos A, O’Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009;15:7412–20.

11 Astaras C, de Micheli R, Moura B, et al. Neurological adverse events associated with immune checkpoint inhibitors: diagnosis and management. *Curr Neurol Neurosci Rep* 2018;18:3.

12 Spain L, Tippu Z, Larkin JM, et al. How we treat neurological toxicity from immune checkpoint inhibitors. *ESMO Open* 2019;4:e000540.

13 Spain L, Walls G, Messiou C, et al. Efficacy and toxicity of rechallenge with combination immune checkpoint blockade in metastatic melanoma: a case series. *Cancer Immunol Immunother* 2017;66:113–7.

14 Fellner A, Makranz C, Lotem M, et al. Neurologic complications of immune checkpoint inhibitors. *J Neurooncol* 2018;137:601–9.

15 Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015;373:23–34.