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Citation for published version (APA):

Hendriks, L. E. L., Bootsma, G., Mourlanette, J., Henon, C., Mezquita, L., Ferrara, R., Audigier-Valette, C., Mazieres, J., Lefebvre, C., Duchemann, B., Cousin, S., le Pechoux, C., Botticella, A., De Ruysscher, D., Dingemans, A-M. C., & Besse, B. (2019). Survival of patients with non-small cell lung cancer having leptomeningeal metastases treated with immune checkpoint inhibitors. *European Journal of Cancer*, *116*, 182-189. https://doi.org/10.1016/j.ejca.2019.05.019

Document status and date:
Published: 01/07/2019

DOI:
10.1016/j.ejca.2019.05.019

Document Version:
Publisher's PDF, also known as Version of record

Document license:
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Please check the document version of this publication:

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Download date: 07 May. 2021

European Journal of Cancer 116 (2019) 182–189

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Survival of patients with non-small cell lung cancer having leptomeningeal metastases treated with immune checkpoint inhibitors

Lizza E.L. Hendriks [a,b,*], Gerben Bootsma [c], Jean Mourlanette [d], Clemence Henon [a], Laura Mezquita [a], Roberto Ferrara [a], Clarisse Audigier-Valette [e], Julien Mazieres [d], Corentin Lefebvre [d], Boris Duchemann [f], Sophie Cousin [g], Cecile le Pechoux [h], Angela Botticella [h], Dirk De Ruysscher [i], Anne-Marie C. Dingemans [b], Benjamin Besse [a,j]

[a] *Department of Medical Oncology, Gustave Roussy Cancer Campus, Institut d'Oncologie Thoracique (IOT), Gustave Roussy, Université Paris-Saclay, F-94805, Villejuif, France*
[b] *Department of Pulmonary Diseases, GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center+, Maastricht, the Netherlands*
[c] *Department of Pulmonary Diseases, Zuyderland Hospital, Location Heerlen, the Netherlands*
[d] *Department of Pulmonary Diseases, Centre Hospitalier Universitaire de Toulouse, Université Paul Sabatier, Toulouse, France*
[e] *Department of Pulmonary Diseases, Centre Hospitalier Toulon Sainte-Musse, Toulon, France*
[f] *Department of Pulmonary Diseases, Hopital Avicenne, Paris, France*
[g] *Department of Medical Oncology, Institut Bergonie, Bordeaux, France*
[h] *Department of Radiation Oncology, Gustave Roussy Cancer Campus, Villejuif, France*
[i] *Department of Radiation Oncology (MAASTRO Clinic), GROW School for Oncology and Developmental Biology, Maastricht University Medical Center+, Maastricht, the Netherlands*
[j] *Paris-Sud University, Orsay, France*

Received 15 March 2019; received in revised form 4 May 2019; accepted 12 May 2019
Available online 13 June 2019

* *Corresponding author*: Dept. of Pulmonary Diseases Maastricht University Medical Center+, PO Box 5800, 6202, AZ, Maastricht, the Netherlands. Fax: +31 0 433875051

E-mail addresses: lizza.hendriks@mumc.nl (L.E.L. Hendriks), G.bootsma@zuyderland.nl (G. Bootsma), Jean.mourlanette@orange.fr (J. Mourlanette), clemence.HENON@gustaveroussy.fr (C. Henon), laura.MEZQUITA@gustaveroussy.fr (L. Mezquita), Roberto.Ferrara@istitutotumori.mi.it (R. Ferrara), Clarisse.Audigier-Valette@ch-toulon.fr (C. Audigier-Valette), mazieres.j@chu-toulouse.fr (J. Mazieres), corentin.lefebvre@hotmail.com (C. Lefebvre), Boris.duchemann@aphp.fr (B. Duchemann), s.cousin@bordeaux.unicancer.fr (S. Cousin), Cecile.LEPECHOUX@gustaveroussy.fr (C. le Pechoux), angela.BOTTICELLA@gustaveroussy.fr (A. Botticella), Dirk.deruysscher@maastro.nl (D. De Ruysscher), a.dingemans@mumc.nl (A.-M.C. Dingemans), Benjamin.BESSE@gustaveroussy.fr (B. Besse).

https://doi.org/10.1016/j.ejca.2019.05.019
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KEYWORDS
NSCLC;
Immune checkpoint inhibition;
Leptomeningeal metastases

Abstract ***Introduction:*** Patients with non-small cell lung cancer (NSCLC) experience leptomeningeal metastases (LM) in 3–9% of cases. Because overall survival (OS) and performance status are very poor, they are mostly excluded from clinical trials. Here, we evaluated survival of patients with NSCLC having LM treated with immune checkpoint inhibitors (ICIs).
Methods: A prospectively collected list of patients with advanced NSCLC treated with ICIs between November 2012 and July 2018 in 7 European centres was merged. All patients with LM before ICI start were selected, data were retrospectively added and patients were classified according to the National Comprehensive Cancer Network (NCCN) LM prognostic classification (good/poor). Progression-free survival (PFS) and OS on ICIs were evaluated.
Results: Nineteen of 1288 (1.5%) patients had LM; 73.7% had synchronous brain metastases; 73.7% had neurological symptoms at the start of ICIs and 52.6% were in the NCCN LM good prognosis group. Programmed death ligand-1 (PD-L1) expression was known for 42.1% of patients (87.5% positive). Median follow-up was 13 months from the start of ICIs, and median (95% confidence interval [CI]) PFS on ICIs was 2.0 (1.8–2.2) months. Six-month PFS rate was 21.0% and was significantly higher in the NCCN good versus poor prognostic group: 40% vs 0% ($p = 0.05$). Twelve-month PFS rate was 0%. Median (95% CI) OS from the start of ICIs was 3.7 (0.9–6.6) months. Six-month OS rate was 36.8%, and 12-month OS rate was 21.1%; both were not statistically significantly different for the good versus poor NCCN prognostic group ($p = 0.40$ and $p = 0.56$, respectively).
Conclusion: Some patients with NSCLC having LM do benefit from ICI treatment; specifically, those in the NCCN LM good prognosis group can obtain a long survival.
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1. Introduction

Leptomeningeal metastases (LM) are diagnosed in up to 9% of patients with non-small cell lung cancer (NSCLC) [1,2]. Diagnosis is based on clinical evaluation, typical findings on brain/spinal cord magnetic resonance imaging (MRI) and presence of tumour cells in the cerebrospinal fluid (CSF) [3,4]. The National Comprehensive Cancer Network (NCCN) guideline advises to classify patients according to poor or good risk (Supplemental Table 1) and recommends best supportive care (BSC) for the poor risk group [3]. The European Association of Neuro-Oncology (EANO)–European Society for Medical Oncology (ESMO) guideline advises BSC in those with an expected survival of less than one month [4]. Treatment for patients with better prognosis consists of (combinations of) radiotherapy and systemic therapy with/without intrathecal chemotherapy [3,4]. Despite treatment, the median overall survival (OS) is 1–3 months for patients without, and up to 12 months for patients with, a targetable molecular alteration [5,6]. Immune checkpoint inhibitor (ICI) therapy has revolutionised the treatment for patients with NSCLC and has become standard of care in locally advanced and metastatic disease [7,8]. However, all NSCLC ICI trials have excluded patients with LM; hence, only a few case reports are available [9,10]. Two phase II trials included patients with only melanoma or mainly breast cancer [11,12]. To obtain more data on survival of patients with NSCLC having LM treated by ICI therapy, we performed a multicenter data collection.

2. Patients and methods

A prospectively collected list of patients with advanced NSCLC treated with ICIs between November 2012 and July 2018 in seven European centres (five French and two Dutch) was merged. All consecutive patients with advanced NSCLC were included when they were treated with programmed death ligand-1 (PD-L1) inhibitors with or without anti–cytotoxic T-lymphocyte antigen-4 (CTLA4) within routine clinical care, expanded access/compassionate use programs and clinical trials. Medical records were screened, and all patients diagnosed with LM (based on positive CSF analysis and/or imaging) before the start of ICIs were included. LM were classified according to EANO-ESMO criteria (Supplemental Table 2) [4].

Demographics, clinical, pathological/molecular and survival data were retrospectively extracted from the medical records between October 2018 and December 2018. PD-L1 expression was assessed on tumour cells by immunohistochemistry in each local institution. Expression of at least 1% was considered positive. Radiological assessments of the brain and extracranial disease were performed at discretion of the treating physician (usually every six to nine weeks), and response was determined locally at each institution by the

investigator. Patients were classified as poor or good prognosis according to the NCCN criteria (Supplemental Table 1) [3].

This study was approved by the Institutional Review Board of Gustave Roussy (Commission Scientifique des Essais Thérapeutiques) and the ethical committee of Maastricht University Medical Center+ (number 2018–0805): informed consent was considered not necessary by the ethics committee.

2.1. Statistical analysis

OS was calculated from the date of the first ICI administration until death due to any cause. Progression-free survival (PFS) was calculated from the date of the first ICI administration until progressive disease (PD: cranial and/or extracranial or symptomatic when imaging was not available), or death due to any cause. Statistics were performed using SPSS (IBM statistics, version 23). Descriptive statistics of demographic and clinical variables were obtained. Six- and 12-month PFS and OS rates were compared for different groups using the Fisher exact test. Survival curves were estimated using the Kaplan–Meier method.

3. Results

3.1. Patient selection and characteristics of patients with leptomeningeal metastases

Data of 1288 patients with NSCLC treated with ICIs were screened. Nineteen (1.5%) had LM (with/without brain metastases) at the start of ICI therapy (Table 1): mean age was 59.3 years (range, 41.1–69.1), 13 (68.4%) were female, 17 (89.5%) had adenocarcinoma and eight (42.1%) had known PD-L1 status (7/8 positive, PD-L1 expression level: 20–95%). Six patients had a targetable driver mutation (3 EGFR, 1 ALK, 1 BRAF, 2 MET); all these patients received ICI after exhaustion of targeted therapies. Fourteen (73.7%) patients had brain metastases also, and 14 (73.7%) had neurological symptoms at the start of ICI therapy (varying from slight headache to severe neurological symptoms). Ten out of 19 (52.6%) were in the good prognostic NCCN LM group. Details on LM diagnosis, treatment and symptoms and PFS/OS per patient are depicted in Table 2. Patient 3 (also reported previously) [10] was treated with intrathecal methotrexate before the start of ICIs, and patient 17 received intrathecal methotrexate concurrent with nivolumab.

3.2. Outcome

Time from LM diagnosis to the start of ICI therapy ranged from 0 to 16.6 months: for five and eight patients, respectively, LM diagnosis was within one and ≥ six months of the start of ICI therapy (Fig. 1). Median follow-up from the start of ICI therapy was 13 months. Except for one patient (patient 13, died of trauma), all patients showed disease progression. The clinical condition of three patients deteriorated very rapidly; they died before brain or extracranial imaging could be performed. For one patient, the neurological condition improved, nine deteriorated (Table 2). Seven patients

Table 1
Patient characteristics.

Nr	Age at the start of ICI therapy, years	Gender	Smoking status/PY	Histology/molecular status	PD-L1 status/antibody	Nr of organs with metastases at the start of ICI therapy	ICI treatment line	Type of ICI
1	68.1	F	Former/40	SCC/unk	unk	3	3	Nivolumab
2	65.8	F	Former/35	AC/*KRAS*	20%/28	2	3	Pembrolizumab
3	53.6	M	Former/35	AC/*KRAS*	unk	3	2	Nivolumab
4	63.5	F	Unk/unk	AC/*KRAS*	80%/22C3	3	2	Pembrolizumab
5	69.1	M	Former/20	AC/*ALK*	unk	3	4	Nivolumab
6	52.0	F	Former/7	AC/*EGFR*	0/unk	5	4	Nivolumab
7	55.3	F	Unk/unk	AC/*EGFR*	Pos/22C3	3	5	Pembrolizumab
8	55.3	F	Current/30	AC/*KRAS*	unk	6	2	Nivolumab
9	51.0	F	Former/15	AC/*MET*	80%/28	2	5	Pembrolizumab
10	41.1	M	Former/15	AC/WT	unk	4	3	Nivolumab
11	66.4	F	Former/50	AC/WT	95%/22C3	4	2	Pembrolizumab
12	65.4	M	Former/unk	AC/WT	90%/28	2	2	Pembrolizumab
13	56.8	F	Current/40	AC/WT	unk	3	2	Nivolumab
14	69.1	F	Never	AC/*EGFR*	unk	3	7	Nivolumab
15	66.0	F	Former/unk	AC/WT	unk	6	2	Nivolumab
16	52.2	F	Current/unk	AC, WT	unk	5	2	Nivolumab
17	53.6	F	Current/20	AC/*BRAF*	80%/unk	3	3	Nivolumab
18	57.2	M	Current/40	SCC/unk	unk	5	2	Nivolumab
19	64.8	M	Current/35	AC/*EGFR*ampl	unk	7	6	Nivolumab

Abbreviations: nr: number; ICI: immune checkpoint inhibitor; PY: packyears; PD-L1: programmed death ligand-1; F: female; M: male; SCC: squamous cell carcinoma; AC: adenocarcinoma; KRAS: Kirsten rat sarcoma viral antigen; EGFR: epidermal growth factor receptor; BRAF: v-RAF murine sarcoma viral oncogene homologue B; ampl: amplification; unk: unknown.

Table 2
Leptomeningeal metastases details and PFS and OS from immune checkpoint inhibitor initiation per patient.

Nr	LP/results	MRI brain[a]	EANO-ESMO diagnosis group	BM at the start of ICI therapy	Cranial rtx before ICI	Time from cranial rtx to ICI, months	Time from LM diagnosis to the start of ICI therapy, months	KPS at the start of ICI therapy	MRI brain baseline ICI/follow-up ICI	LM symptomatic at the start of ICI therapy/symptoms	Use of steroids/dose prednisolone per day	NCCN risk group	Neurological status during ICI	ICI PFS, months	ICI OS, months[b]
1	No	Yes	IIB probable	No	Yes	0.5	1.2	100	Yes/yes	No	No	Good	Stable	10.4	11.6+
2	Yes/neg	Yes	IIB probable	No	No	N/A	16.6	80	No/yes	Yes/visual disturbances	Yes/10 mg	Good	Stable	7.3	13.0+
3	Yes/pos	Yes	1 A	Yes	No	N/A	8.5	80	Yes/no	Yes/facialis paralysis	Yes/20 mg	Good	Improve	6.4	10.7
4	No	No (PET-CT)	IIunk probable	Yes	Yes	18.9 (BM)	15.8	90	Yes/no	Yes/headache	No	Good	Stable	6.1	12.9+
5	Yes/pos	Yes	IC	No	No	N/A	2.3	80	Yes/no	Yes/light headache, vertigo	No	Good	Worse	2.8	3.7
6	Yes/neg	Yes	IIB probable	Yes	Yes	5.6 (BM)	4.0	70	No/no	Yes/visual disturbances, nausea, vomiting	No	Poor	Stable	2.5	10.6
7	Yes/neg	Yes	IIB probable	Yes	No	N/A	0..2	90	Yes/no	Yes/sensory disturbances upper extremities	No	Good	Stable	2.1	15.6
8	No	Yes	IIA probable	Yes	Yes	0	0.1	60	Yes/no	Yes/headache, nausea	Yes/unk	Poor	Worse	2.0	2.0
9	Yes/pos	Yes	IA	Yes	Yes	1.6	1.6	80	Yes/no	Yes/sensory loss toes, pain legs	Yes/20 mg	Good	Worse	1.9[d]	2.0
10	Yes/pos	Yes	IB	Yes	Yes	5.5	7.6	50	Yes/no	Yes/visual disturbances, dysartria, absences	Yes/80 mg	Poor	Worse	1.8	2.5
11	No	Yes	IIA probable	Yes	Yes	5.5	6.0	80	Yes/no	Yes/light headache	Yes/1.5 mg	Good	Stable	1.8	4.0
12	Yes/pos	Yes	IB	Yes	Yes	1.2	6.1	80	No/no	Yes/headache, vomiting, hearing loss, walking problems	Yes/100 mg	Poor	Worse	1.7[d]	1.8
13	No	Yes	IIB probable	Yes	Yes	0.1	0.1	60	Yes/yes	Yes/facialis paralysis, headache, cerebellar symptoms	No	Poor	Stable	1.7	1.7[e]
14	No	Yes	IIB probable	Yes	Yes	9.1 (BM)	1.2	70	Yes/yes	No	Yes/40 mg	Good	Worse	1.7	5.8
15	No	Yes	IIA probable	Yes	Yes	0.7	1.3	70	No/no	Yes/severe headache	No	Poor	Worse	0.9	1.7
16	No	Yes	IIC probable	Yes	Yes	12.0	12.5	60	Yes/no	No	No	Poor	Stable	0.8[d]	0..9

(*continued on next page*)

Table 2 (*continued*)

Nr	LP/results	MRI brain[a]	EANO-ESMO diagnosis group	BM at the start of ICI therapy	Cranial rtx before ICI	Time from cranial rtx to ICI, months	Time from LM diagnosis to the start of ICI therapy, months	KPS at the start of ICI therapy	MRI brain baseline ICI/follow-up ICI	LM symptomatic at the start of ICI therapy/symptoms	Use of steroids/dose prednisolone per day	NCCN risk group	Neurological status during ICI	ICI PFS, months	ICI OS, months[b]
17	Yes/pos	Yes	ID	No	No	N/A	0.1	80	Yes/no	Yes/light headache	No	Good	Worse	0.7	1.9
18	Yes/neg	Yes	IIA possible	No	No	N/A	0.7	50	Yes/no	No	No	Poor	Stable	0.5[d]	1.1
19	Yes/neg	Yes (−)/yes	IIB probable	Yes	No	N/A	14.5	80	Yes/yes	No	Yes/20 mg	Poor	Worse[c]	0.2[c]	29.8[e]

Abbreviations: nr: number; LP: lumbar puncture; MRI: magnetic resonance imaging; ESMO: European Society for Medical Oncology; BM: brain metastases; rtx: radiation; ICI: immune checkpoint inhibitor; mg: milligram; NCCN: National Comprehensive Cancer Network; PFS: progression free survival; OS: overall survival.

[a] MRI brain performed for LM diagnosis.

[b] Still alive.

[c] 7 days after the start of ICI therapy, neurological deterioration was observed on computed tomography compared with computed tomography 1.1 months before the start of ICI therapy: new brain lesions and progression of existing ones were found. High-dose steroids (80 mg/day) were started, and whole-brain irradiation is initiated at 30 Gy, 3 months later he had on imaging stable disease extracranial, and partial response on MRI brain, afterwards ongoing stable disease extracranial and response cranial, hospitalised 6 months after the start of ICI therapy because of cerebrovascular accident. Nivolumab was discontinued, and the patient never progressed (and had regular imaging including brain MRI).

[d] Documented as progressive disease by physician based on deteriorating clinical condition, no imaging.

[e] died of non–cancer-related cause.

had baseline and follow-up brain imaging (five had MRI follow-up): three had progressive central nervous system disease (PD) as the best cranial response (two stable disease (SD) extracranial and 1 PD extracranial) and 2 SD. The two patients with SD as the best LM response did not experience LM PD on MRI during follow-up but had extracranial PD.

Median (95% confidence interval [CI]) PFS on ICIs was 2.0 (1.8–2.2) months. Six-month PFS rate was 21.0% (4/19 patients, 95% CI: 1–41%) and was significantly higher for the NCCN LM good versus poor prognostic group (40% [95% CI: 3–77%] vs 0% [95% CI: not evaluable (NE)], $p = 0.05$). Twelve-month PFS rate was 0%. Survival curves are depicted in Fig. 2A. Five patients were treated with ICIs for ≥six months, four of whom were in the good prognostic group. None of the patients treated with ≥ six months of ICIs had a targetable driver mutation. PD-L1 status was known only for two (20% and 80%, respectively). The five others who were PD-L1 positive all progressed within 0.7–2 months.

Except for three patients, all died. Median OS from LM diagnosis was 10.0 (95% CI: 5.6–14.3) months. Median OS from the start of ICI therapy was 3.7 (95% CI: 0.9–6.6) months (Fig. 2B). Six-month OS from the start of ICI therapy was 36.8% (7/19 patients, 95% CI: 13–61%), and 12-month OS was 21.1% (4/19 patients, 95% CI: 1–41%); both were not statistically significantly different for the poor versus good NCCN prognostic group ($p = 0.22$ and $p = 0.33$, respectively). Two out of four patients with ≥12-month survival had a PFS on ICI therapy for ≥6 months; three were PD-L1 positive (other unknown). Three received another line of systemic treatment.

4. Discussion

Data on survival of patients with NSCLC having LM treated with ICIs are scarce. To the best of our knowledge, with 19 included patients, we report here the largest, detailed multicentre series to date. Because ICI efficacy is so far unknown for LM, most of them received ICIs when alternatives were no longer available. In general, survival was poor, although some patients, especially those with an NCCN good prognosis classification, benefited from ICI treatment (6-month PFS 21.0%, 40% versus 0% for good versus poor prognosis classification). Furthermore, some patients with LM can obtain a relatively long survival (also after PD on ICI therapy) because 6- and 12-month OS rates were 36.8% and 21.1%, respectively. The median OS was comparable to a single-arm phase II pembrolizumab trial, including 20 patients with LM (1 NSCLC; 3.7 vs 3.6 months), but 6-month (22.0%) and 12-month OS (0%) rates were lower than our data [11]. Compared with our data, a similar median (5.1 months), six- (43.8%) and 12-month (31.3%) OS rates

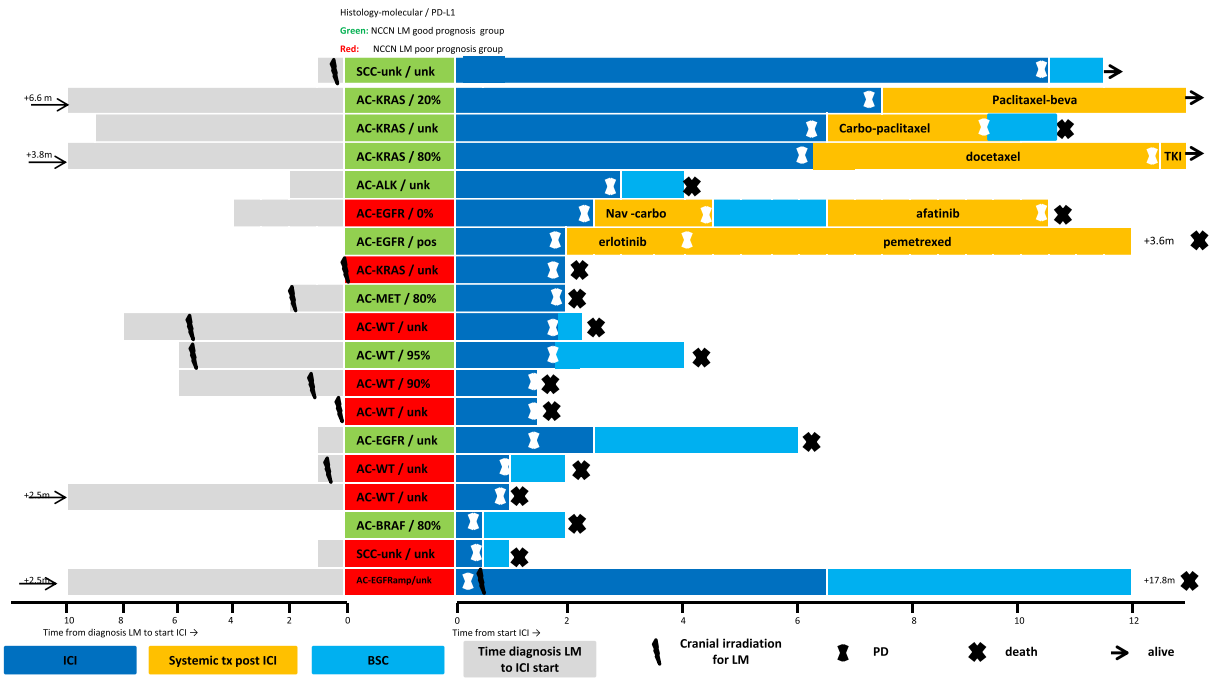

Fig. 1. Swimmer plot of patients with NSCLC having leptomeningeal metastases treated with immune checkpoint inhibitors. Abbreviations: PD-L1: programmed death-ligand 1; NCCN: National Comprehensive Cancer Network; LM: leptomeningeal metastases; SCC: squamous cell carcinoma; unk: unknown; AC: adenocarcinoma; KRAS: Kirsten rat sarcoma viral antigen mutation; beva: bevacizumab; carbo: carboplatin; TKI: tyrosine kinase inhibitor; ALK: anaplastic lymphoma kinase translocation; nav: navelbin; m: months; EGFR: epidermal growth factor receptor mutation; WT: wild type; BRAF: v-raf murine sarcoma viral oncogene homologue B; amp: amplification; ICI: immune checkpoint inhibitor; tx: therapy; BSC: best supportive care; PD: progressive disease; NE: not evaluable.

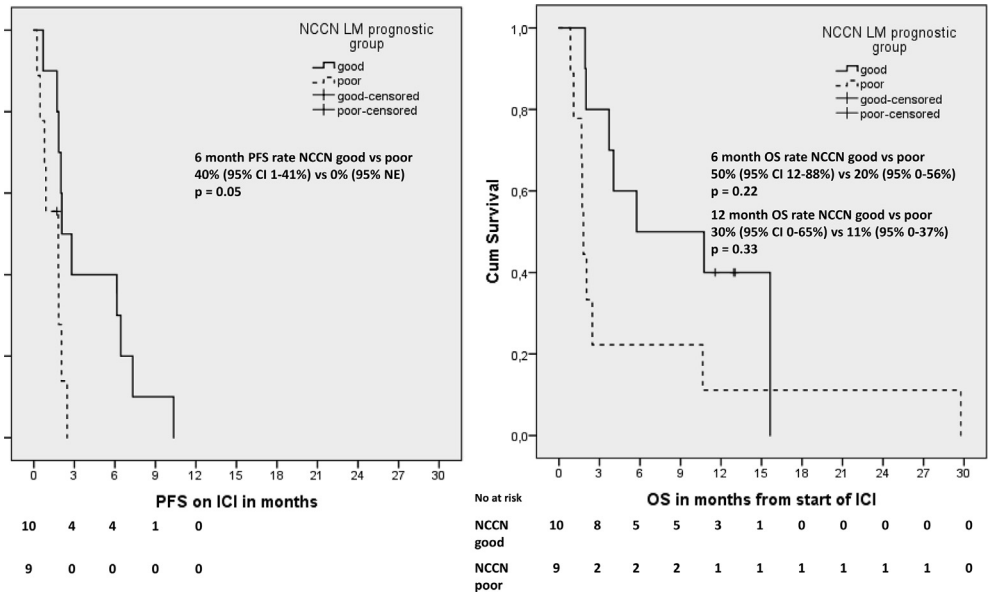

Fig. 2. (A) Progression-free survival on immune checkpoint inhibitor therapy; (B) overall survival from the start of immune checkpoint inhibitor therapy. Abbreviations: NCCN: National Comprehensive Cancer Network; LM: leptomeningeal metastases; PFS: progression-free survival; ICI: immune checkpoint inhibitor; OS: overall survival.

were found in a melanoma nivolumab trial in the cohort with progressing and/or symptomatic brain metastases, and/or LM [12]. A retrospective series including 25 patients with melanoma having LM, 10 of whom were treated with the CTLA4 inhibitor ipilimumab, showed survivals from diagnosis of LM ranging from 1.4 to 54.2 months for patients treated with ipilimumab (ipilimumab treatment was often preceded or followed by BRAF-inhibition and/or whole brain radiotherapy (WBRT)) [13].

Because 73.7% had neurological symptoms at the start of ICI therapy and only five patients underwent follow-up brain MRI during ICI treatment, differentiation between ICI toxicity and brain/LM progression was difficult. In the phase II trials reported to date with mainly patients with breast cancer and melanoma, toxicity was usually low grade and manageable. Headache was the most common neurological grade 3 toxicity in six and 10%, respectively [11,12]. In the present study, not all patients had a lumbar puncture for CSF analysis, although all patients with only imaging available had symptoms suggestive of LM. Furthermore, it is possible that some patients with LM were missed when screening the total ICI database because some could have had asymptomatic LM that were invisible on MRI before ICI therapy. Other drawbacks are inherent to the retrospective data collection (although the overview of patients receiving ICI was prospectively collected), making Response assessment in neuro-oncology (RANO) response evaluation [14] not feasible. All patients could be classified as having good or poor risk, but PD-L1 status (associated with outcome on ICI) was not available for all. The included population was heterogeneous (e.g. different previous treatments, driver mutations), making comparisons across groups more difficult.

Trials specifically evaluating patients with LM are often difficult to perform because the clinical condition of these patients often deteriorates rapidly, and the population is very heterogeneous. Currently, several early-phase ICI trials for patients with LM are ongoing, addressing PD-L1 inhibition (intravenous or intrathecal) with or without CTLA4 inhibition or radiotherapy (Supplemental Table 3). Because first-line ICI combined with chemotherapy proved superior to chemotherapy alone [15], it would be interesting to evaluate this combination in patients with LM.

5. Conclusion

In conclusion, most patients with NSCLC having LM do not benefit from ICI treatment, although some, especially those in the NCCN LM good prognosis group, can obtain a long survival.

Conflicts of interest statement

L.E.L.H. has received research funding from Roche and Boehringer Ingelheim; has been a member of the advisory board of Boehringer Ingelheim and Bristol-Myers Squibb (BMS), (both institution and self), has received travel/conference reimbursement from Roche and BMS (self); has been part of a mentorship program with key opinion leaders funded by AstraZeneca; has received fees for educational webinars Quadia (self). and reports no conflict of interest related to this work. L.M. has been a member of the speakers' bureau of BMS and a member of the advisory board of Roche diagnostics. C A-V. has been the principal investigator of industry trials (AstraZeneca, Boehringer Ingelheim, BMS, Novartis and Roche) and has been a member of the advisory board of AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, Novartis, MSD, Pfizer and Roche and speakers' bureau of AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, Novartis, Pfizer and Roche. J.M. has received institutional research funding from Roche, BMS and AstraZeneca; has served consulting/advisory roles for Novartis, Roche/Genentech, Pfizer, BMS, Lilly and ImClone Systems, MSD and AstraZeneca; and has received travel/accommodation fees from Pfizer, Roche and BMS. C.l.P. has been a member of the advisory board of AstraZeneca and reports no conflict of interest related to this work. D.D.R. has been a member of the advisory board of BMS, AstraZeneca, Roche/Genentech, Merck/Pfizer and Celgene; has received research grants from AstraZeneca, BMS and Boehringer Ingelheim. All income from the advisory board and from the research grants went integrally to the institution. A.-M.C.D. has been a member of the advisory board of BMS, MSD, Roche, Eli Lilly, Takeda, Pfizer and Boehringer Ingelheim and has received research grant from BMS (institution). BD has given expert testimony to BMS and Roche (payment to self) and has received travel and accommodation fees from BMS and Roche (payment to self)..).B.B. has received institutional grants for clinical and translational research from AbbVie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgene, Eli Lilly, GSK, Ignyta, Ipsen, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda and Tiziana Pharma and has no conflict of interest related to this work. G.B., C.H., R.F., C.L. S.C., A.B., and J Mourlanette (JM = Julien Mazieres) have no conflict of interest to declare.

Funding

L.E.L.H. was the recipient of a DUERTECC/EURONCO grant for 2017–2018.

Writing assistance

None.

Data statement

Not publicly available (retrospective database collection).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.05.019.

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