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Original Research

High-dose interleukin-2 and interferon as first-line immunotherapy for metastatic melanoma: long-term follow-up in a large unselected Danish patient cohort

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Abstract ***Background and patients:*** Between January 2007 and April 2014, 464 Danish patients received high-dose (HD) interleukin-2 (IL-2) and interferon (IFN) as first-line treatment for metastatic melanoma. Our data represent the largest cohort of patients with metastatic melanoma worldwide, with relevant data on all patients and no patients lost to follow-up. Data have been gathered in a national database on the treatment of metastatic melanoma established since 2011.

Results: One hundred eighteen patients (25%) obtained an objective response rate (ORR) to treatment with a median progression-free survival (PFS) of 3.4 months and a median overall survival (OS) of 14.2 months. Furthermore, 2-, 3- and 5-year survival was 32.0%, 23.2% and 16.6%, respectively. Ipilimumab as second-line therapy has been used since July 2010. We divided patients in two subgroups before and after this date to evaluate the effects of new treatment strategies. Patient characteristics, ORR and PFS were comparable in the two subgroups. Survival was significantly improved after 2010, with an increase in median OS from 12.2 to 16.0 months and in 5-year OS from 12.5% to 20.7%.

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Conclusions: Our data confirm that HD IL-2/IFN as first-line therapy in metastatic melanoma leads to long-term survival in a subset of treated patients. Potentially, IL-2/IFN might represent a treatment option in patients with active melanoma after established initial treatment with checkpoint inhibitors and BRAF/MEK-targeted therapies.

1. Introduction

Interleukin-2 (IL-2) represents the first successful immunotherapeutic intervention in clinical oncology, which was approved by the US Food and Drug Administration (FDA) for treatment of metastatic melanoma in 1998. This was a major breakthrough because it was the first time that modulation of the immune system turned out to be an effective therapy for cancer. In March 2011, ipilimumab targeting cytotoxic T-lymphocyte Associated protein 4 (CTLA-4) was approved by the FDA. Since then, further two checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) have been approved (nivolumab and pembrolizumab [2014]). With the increasing use of combination immunotherapy targeting both CTLA-4 and PD-1, patients with BRAF wild-type metastatic melanoma may have an unmet need for further immunotherapy, if failing on combination immunotherapy. IL-2–based immunotherapy may be a treatment option in these patients. We present national 'real-world' data from a large unselected patient population receiving IL-2 and IFN as first-line treatment between January 2007 and April 2014.

2. Materials and methods

Based on our prior experience with IL-2–based therapy [1], we achieved national approval in 2008 to change the standard of care in Danish patients with metastatic melanoma to a regimen with high-dose (HD) IL-2 and interferon (IFN) alpha 2b, given intravenously in combination [2].

We developed specialised units within the Departments of Oncology at Odense University Hospital, Aarhus University Hospital (2008) and Copenhagen University Hospital, Herlev (2010), to standardise treatment for Danish patients with metastatic melanoma. All Danish patients with metastatic melanoma were referred to one of the three centres. Each centre followed a standard protocol of baseline evaluation for selection of patients eligible for HD IL-2/IFN therapy, treatment administration and follow-up, with evaluation at specified time points.

Baseline staging included patient history; physical examination, including Eastern Cooperative Oncology Group (ECOG) performance status (PS); imaging (computed tomography [CT] of the brain, neck, chest and abdomen); and blood chemistry (haemoglobin, white blood cell count (WBC), granulocyte counts, platelet counts, C-reactive protein (CRP), sodium, potassium, creatinine, alanine aminotranferase (ALAT), lactate dehydrogenase [LDH] and alkaline phosphatases). Patients with brain metastases were offered treatment if they were asymptomatic and had a limited number of metastatic lesions located in areas of the brain where the estimated risk of treatment-induced oedema would not be life-threatening. Based on Danish data [1], later confirmed in a larger European Organisation for Research and Treatment of Cancer (EORTC) dataset [3], we did not offer HD IL-2–based treatment to patients with high levels of WBC and high levels of LDH combined with an ECOG PS of 2 or more.

IL-2/IFN was administered according to a regimen developed by Keilholz *et al.* [4]. Until July 2009, the IFN dose was given as IFN alpha 2b (IntronA, Schering-Plough), 10 MU subcutaneous (s.c.), on days 1, 3 and 5. Thereafter, IFN was given as pegylated IFN alpha 2b, (PEG-Intron, Schering-Plough), 300 μg s.c., on day 1. The HD IL-2 regimen started in week 2 and consisted of aldesleukin (Proleukin, Novartis): 18 MU/m^2 in the first 6 h, 18 MU/m^2 in the next 12 h, 18 MU/m^2 in the subsequent 24 h and followed by 4.5 MU/m^2 per day for the next 3 days. IL-2 was administered as continuous intravenous infusions.

We retrospectively collected and gathered data in a national database which includes treatment details on Danish patients with metastatic melanoma. The database was established in 2011, including data on baseline characteristics, key biomarkers, given treatment and efficacy parameters. No data on toxicity were collected. Patient and disease characteristics were analysed using descriptive statistics and expressed as relative frequency (percentage) for discrete variables or medians for continuous variables.

Response to treatment was evaluated using Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 [5], based on CT imaging. CT was performed at baseline and repeated after 2 courses of HD IL-2/IFN. Patients responding to treatment (partial response [PR] or complete response [CR]) were offered 2 or 4 additional treatment courses. Patients with stable disease (SD) were offered 2 additional courses, except in cases where a marked imbalance between risk for toxicity and chance of efficacy was evident. Treatment was stopped for patients with progressive disease (PD) after 2 courses.

Patients in post-treatment follow-up had a repeated CT scan every 3 months for 2 years after treatment start and, thereafter, at 6-month intervals until 5 years. Follow-up for survival continued past this point, with repeat CT scans only on indication.

PFS and overall survival (OS) were evaluated using Kaplan–Meier analyses and expressed as medians and as 2-, 3- and 5-year survival. Differences between curves were evaluated using the log-rank test.

Evaluation of OS related to the following known prognostic markers was performed using the univariate log-rank test: gender, age (cut point: median age), primary melanoma site (cutaneous vs unknown primary), LDH (<upper limit of normal (ULN) vs 1–2 x ULN vs > 2 x ULN), WBC (<= ULN vs > ULN), granulocyte count (<= ULN vs > ULN) and M-stage (M1c vs M1a, M1c vs M1b).

With the availability of ipilimumab in July 2010 and later also with the approval of drugs targeting BRAF mutations, relevant second-line treatment option after IL-2 became available. To test the hypothesis of positive impact of these new treatment options, we divided our material into two subgroups, before and after July 1, 2010. We compared the aforementioned biomarkers in the two groups and subsequent analyses of response rate (RR), PFS and OS were performed.

3. Results

Between January 2007 and April 2014, 464 patients with metastatic melanoma initiated treatment with first-line HD IL-2/IFN. No patients were lost to follow-up. Final evaluation of included patients was performed as of December 31, 2017. The baseline characteristics are presented in Table 1. The median age was 59 years with no change in the median age over the time period of 7 years. The majority (62.3%) had M1c disease. Eighteen patients (3.9%) had brain metastases, and 43.5% patients had elevated LDH at baseline.

At the time of analysis, the median Kaplan–Meier estimated follow-up time was 77.1 months (6.4 years), with the last patient receiving the first dose of HD IL-2/IFN on April 1, 2014. No treatment-related deaths were observed during the treatment period.

Among 464 patients, 461 were evaluated for response according to RECIST (Table 2). One hundred eighteen patients obtained a response leading to an objective RR (ORR) of 25.3%. Forty-four of these patients (9.4%) obtained a CR, and 74 patients obtained a PR (15.9%).

The median PFS was 3.4 months with 8.0%, 7.1% and 6.0% maintaining response after 2, 3 and 5 years, respectively (Fig. 1). The median duration of CRs was 65.9 months. For patients obtaining PR or SD, the median duration was 7.4 and 4.2 months, respectively.

The median OS was 14.2 months, with 32.0%, 23.2% and 16.6% being alive after 2, 3 and 5 years, respectively (Fig. 1). The median OS of patients obtaining a CR was not reached. Furthermore, for patients obtaining PR or SD, the median OS was 20.4 and 16.3 months, respectively.

Table 1
Baseline demographics and disease characteristics of the treated population.

Patient characteristc	No.	%
Total no. of patients	464	
Sex		
Female	185	39.9
Male	279	60.1
Age: median (range)	59.0	(17.0–76.0)
Melanoma diagnosis		
Primary cutaneous melanoma	408	87.9
Metastatic melanoma, unknown primary	56	12.1
ECOG PS		
0	294	71.4
1	105	25.5
2	13	3.2
Unknown	52	11.2
M-stage (AJCC 7th edition)		
M1a	93	20.0
M1b	82	17.7
M1c	289	62.3
Metastatic disease biopsy verified		
Yes	368	79.3
No	96	20.7
Brain metastases		
Yes	18	3.9
No	446	96.1
LDH		
Normal	240	51.7
Elevated	202	43.5
Elevated > x 2 ULN	59	12.7
Unknown	22	4.7
White blood cell count		
Normal	386	86.2
Elevated	62	13.8
Unknown	16	3.4
Granulocyte count		
Normal	392	87.5
Elevated	56	12.5
Unknown	16	3.4

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; ULN, upper limit of normal; AJCC, American Joint Committee on Cancer.

Age, gender and known vs unknown primary melanoma did not impact OS (Table 3). Evaluation of OS according to M-stage revealed that both patients with M1a-stage cancer and patients with M1b-stage cancer have a significantly longer OS than those with M1c-stage cancer.

Evaluating baseline biomarkers revealed that LDH (normal vs 1–2 x ULN, >2 x ULN), ECOG PS (0 vs 1 vs 2), WBC (normal vs > ULN) and granulocyte counts (normal vs > ULN) had a significant influence on OS (Table 3; Fig. 2).

In the two subgroups before *(n = 232)* and after *(n = 232)* July 2010, we checked for differences in baseline clinical characteristics, finding no statistically significant difference between the two subgroups except for PS. The cohort treated before July 1, 2010, had a slightly poorer ECOG PS (Supplementary Table S1).

Table 2
RECIST response to treatment.

Response	Before July 2010 n = 232 patients	After July 2010 n = 232 patients	Total n = 464 patients
ORR, % (95% CL)	23.3%	27.6%	25.3%
Complete response (CR)	18 (7.8%)	26 (11.2%)	44 (9.4%)
Partial response (PR)	36 (15.5%)	38 (16.4%)	74 (15.9%)
Stable disease (SD)	94 (40.5%)	81 (34.9%)	175 (37.7%)
Progressive disease	81 (34.9%)	87 (37.5%)	168 (36.2%)
Not evaluable	3	0	3
Duration of response, months (median, 95% CL)			
CR	65.9 (23.5–NR)		
PR	7.4 (6.0–9.0)		
SD	4.2 (3.7–5.3)		

ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumours; CL, confidence limits.

Analysis of the two groups revealed that in the early patient cohort, 131 patients (56.9%) did not receive any further antineoplastic therapy after first-line IL-2 and IFN. This number was reduced to 68 (29.3%) in the 2nd period. Details on subsequent treatments are presented in Supplementary Table S2.

All PFS results at 2, 3 and 5 years were exactly identical before and after July 1, 2010 (Table 4). The median OS was increased from 12.2 to 16.0 months, with a subsequent improvement in 5-year OS also from 12.5% to 20.7%. In univariate analysis, this difference was significant with a hazard rate of 1.37, $(p = 0.002)$.

4. Discussion

We present retrospectively collected real-life data on an unselected patient cohort with metastatic melanoma treated with HD IL-2/IFN as first-line treatment in Denmark over a 7-year period. Denmark covers a population of approximately 5.5 million people. All patients received treatment according to nationally standardised guidelines.

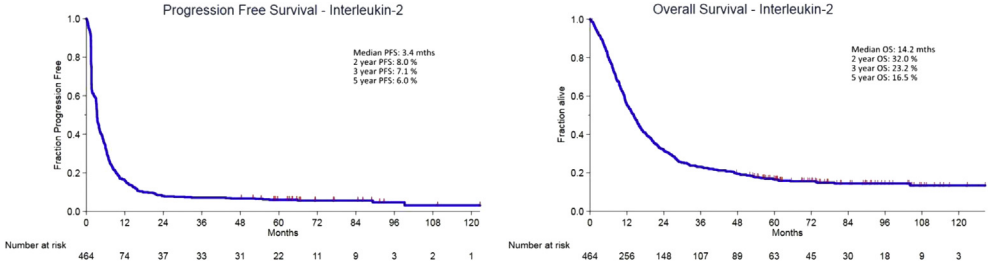

Fig. 1. (A) Progression-free survival (PFS) and (B) overall survival (OS) for 464 patients treated with HD IL-2/IFN as first-line treatment for metastatic melanoma with a median follow-up time of 6.4 years. HD, high-dose; IFN; interferon; IL-2, interleukin-2.

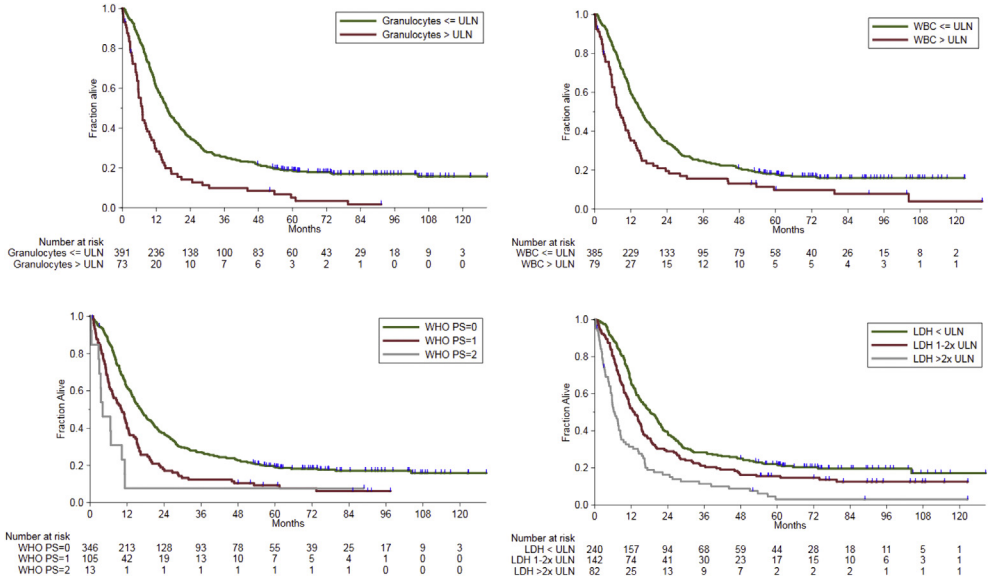

Fig. 2. Overall survival for known significant biomarkers (white blood cell and granulocyte count, ECOG performance status, and LDH). ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; WBC, white blood cell count; WHO, World Health Organisation; ULN, upper limit of normal.

Table 3
Univariate analyses of overall survival in relation to known biomarkers.

Univariate analyses	Overall survival	
	HR (95% CL)	p-value
Age, <= median vs > median	1.03 (0.85–1.26)	*p = 0.73*
Gender (female vs male)	1.08 (0.88–1.32)	*p = 0.48*
Cutaneous vs unknown primary	1.13 (0.82–1.55)	*p = 0.44*
Brain metastases	1.13 (0.69–1.84)	*P = 0.62*
ECOG PS 0 vs 1 vs 2	–	*p < 0.0001*
BRAF status WT vs mutated	1.04 (0.76–1.42)	*p = 0.81*
LDH < ULN vs 1-2 x ULN vs > 2 x ULN	–	*P < 0.0001*
WBC <ULN vs >ULN	1.71 (1.3–2.23)	*p < 0.0001*
Granulocyte count <ULN vs >ULN	2.32 (1.8–3.0)	*P < 0.0001*
Metastatic disease		
M1c vs M1a	0.51 (0.39–0.66)	*P < 0.0001*
M1c vs M1b	0.63 (0.48–0.83)	*P = 0.001*

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; HR, hazard rate; PS, performance status; WBC, white blood cell count; WT, wild-type; ULN, upper limit of normal; CL, confidence limits.

Table 4
Overall survival and progression-free survival before and after July 1, 2010.

Efficacy	Before July 2010	After July 2010	Total
Overall survival			
Median, (95% CL)	12.2 months (10.3–14.2)	16.0 months (13.9–20.0)	14.2 months (12.4–15.6)
2 years, (95% CL)	25.4% (20.0 –31.2)	38.7% (32.4 –45.0)	32.0% (27.8 –36.3)
3 years, (95% CL)	17.7% (13.1 –22.8)	28.7% (23.0 –34.6)	23.2% (19.4 –27.1)
5 years, (95% CL)	12.5% (8.6 –17.1)	20.7% (15.7 –26.3)	16.5% (13.2 –20.0)
Progression-free survival			
Median, (95% CL)	3.3 months (3.2–4.0)	3.4 months (3.0–3.9)	3.4 months (3.2 –3.7)
2 years, (95% CL)	8.2% (5.1 –12.2)	7.7% (4.8 –11.7)	8.0% (5.7–10.7)
3 years, (95% CL)	7.8% (4.8 –11.7)	6.5% (3.8 –10.1)	7.1% (5.0–9.7)
5 years, (95% CL)	6.0% (3.5 –9.6)	6.0% (3.4 –9.6)	6.0% (4.1–8.4)

CL, confidence limits.

The FDA approval of HD IL-2 for the treatment of metastatic melanoma in 1998 led to a large number of clinical trials evaluating different IL-2–based treatment regimens. Several questions were addressed in these trials, but only a few firm conclusions were drawn. Atkins *et al.* [6] emphasised the importance of obtaining a CR to significantly impact survival. A high CRR can be obtained by using a HD IL-2 regimen. The biochemotherapy (BCT) combination of IL-2 and cytotoxic chemotherapy leads to an increase in PRR only, offering a possible explanation as to why the higher RR obtained with BCT did not lead to survival improvement. This was confirmed by Atkins *et al.* [7], showing that 60% of the CRs were long-lasting and that these patients potentially had been cured for metastatic disease. The median duration of CR in our study was 65.9 months. The potential of IL-2 to induce long-lasting responses was also confirmed by Richards *et al.* [8] and Keilholz *et al.* [9].

The HD IL-2 regimen induces significant toxicity, and the strategy of centralising treatment is therefore important to secure optimal toxicity management. Probably, this also explains why we observed no treatment-related deaths. In a US cross-sectional study, Mehta *et al.* [10] showed a significant decline in treatment-related mortality of patients with renal cell cancer and metastatic melanoma treated with HD IL-2 with increasing number of patients treated, emphasising the importance of experienced and skilled staff taking care of these patients.

OS is the ultimate end-point. However, with the increase in available treatment options, subsequent treatments may influence survival, and this calls for the use of other end-points such as PFS and RR. In our study, we found an ORR, CRR and PRR of 25.3%, 9.4% and 15.9%, respectively. Atkins *et al.* [6,7] reported ORR, CRR and PRR of 16%, 6% and 10%, respectively, whereas Keilholz *et al.* [11] reported 18%, 6% and 12%, respectively. The corresponding figures in the meta-analysis by Bright *et al.* [12] were 19.7%, 4.8% and 12.5%, respectively. In the article by Atkins *et al.* [6], only 54% of the patients received IL-2 as first-line treatment, whereas the corresponding figure from Keilholz *et al.* [11] was 78%. This may explain the difference in response rates as all of our patients were treated with first-line therapy. The increase in clinical experience gained over the years may also have resulted in a higher dose intensity of IL-2 offered to our patient population, compared with the published data collected from multiple institutions. One study by Dorval *et al.* [13] evaluated IL-2/cisplatinum ± IFN with a limited number of patients (n = 117) revealing a non-significant increase in response rate, but no difference in OS. Therefore, the addition of IFN in our schedule may also have contributed to the higher response rates we found.

In our analysis, the median OS was 14.2 months. In general, a tendency for 'the tail of the survival curve' to become horizontal in patients receiving immunotherapy when having passed 3 years has been established in modern immunotherapy trials, indicating no further melanoma-related events. This has changed the focus from median survival to long-term survival rates instead. We found survival rates of 32.0%, 23.2% and 16.6% at 2, 3 and 5 years, respectively. Further, this compares favourably with the data from Keilholz *et al.* [14], reporting a 2-year survival of 23% and a 5-year survival of 13%. Payne *et al.* [15] reported a single-institution experience in renal cell carcinoma and

melanoma using IL-2, and in the subset of 314 patients with melanoma, they found a 2-year survival of 41% and a 5-year survival of 23%.

We divided the patient material into two subgroups before and after ipilimumab as second-line treatment became available. Using PFS as the end-point, we found overlapping survival curves. Combined with unchanged ORR, this indicates that the efficacy of the HD IL-2/IFN regimen did not change over time.

The analysis of the two subgroups with OS as the end-point reveals a significant increase. This may reflect the impact of subsequent medical therapies in 2nd and later lines. The median OS increased from 12.2 months to 16.0 months. Looking at the patients treated before July 2010, where the use of checkpoint inhibitors in second-line treatment was scarce, 12.5% of patients were alive after 5 years, demonstrating that long-lasting responses can be induced with HD IL-2/IFN. Turning to the group of patients treated after July 2010, the 5-year survival increased to 20.7%. This is in accordance with the retrospective data from Joseph *et al.* [16], finding 17% of patients who did not require further systemic therapy after treatment with IL-2. Furthermore, 7 of 48 patients receiving ipilimumab after progressing on IL-2 were alive after 2 years.

This shows that subsequent treatment with checkpoint inhibitors and/or BRAF/MEK-targeting agents after PD on HD IL-2 treatment may induce new responses and prolong OS. However, there is no indication of an additive effect of ipilimumab administered after HD IL-2 in our data, comparing with the published data on long-term efficacy of ipilimumab [17].

With respect to sequencing of HD IL-2 and ipilimumab, a randomised trial has been conducted by Patel *et al.* according to *ClinicalTrials.gov* (NCT01856023). No published data are available. Buchbinder *et al.* [18] published retrospective data on the use of second-line HD IL-2 treatment in patients progressing on ipilimumab. An ORR of 21% was obtained in the prior ipilimumab arm compared with 12% in the group with no prior ipilimumab. They concluded that HD IL-2 was active in patients with progression following ipilimumab and that toxicity was not worsened.

A recent publication from the same researchers [19] has confirmed that HD IL-2 has efficacy also after progression on drugs targeting PD-1/programmed death-ligand 1 (PD-L1), revealing efficacy data comparable with the data we present here with IL-2/IFN as first-line therapy.

We conclude that IL-2/IFN as an immune system stimulator combination used as first-line systemic treatment for metastatic melanoma can lead to complete and durable response in a small subset of patients. Our data cannot directly support the use of this treatment option after progression on modern immunotherapy and targeted therapies. However, in patients with no treatment options, HD IL-2/IFN may be a treatment option to be considered. The efficacy data presented combined with the well-described significant toxicities of HD IL-2–based regimens cannot justify a randomised trial evaluating HD IL-2/IFN against modern checkpoint inhibitors. It is also important to note that HD IL-2 should only be used in specialised centres, and this might influence the decision on whether or not to use this treatment option. Whether or not to use this treatment combination or perhaps including pegylated IL-2 (NKTR-214) [20] can only be definitively evaluated in a prospective clinical trial.

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Conflict of interest statement

Dr. Bastholt reports personal fees from Novartis, personal fees from Merck MSD, personal fees from Incyte, personal fees from Roche and personal fees from BMS, outside the submitted work; Dr. Svane reports personal fees from Novartis, personal fees from MSD, personal fees from Incyte, personal fees from Celgene, personal fees from Roche and grants from BMS, outside the submitted work; and Dr. Bjerregaard, Dr. Herrstedt and Dr. Hrobjartsson have nothing to disclose. Dr. Schmidt reports personal fees from BMS, personal fees from Novartis, grants and personal fees from MSD and personal fees from Incyte, outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.03.023.

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