Treatment reality of patients with BRAF-mutant advanced/metastatic melanoma in Switzerland in the era of choice

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Cutaneous melanoma represents a major cause of cancer death in Europe. Without adequate therapy, the 5-year survival rate is 15–20% in distant metastatic disease. Evaluating the *status quo* of treatment standards in advanced melanoma and rationale for therapy decisions in Switzerland between January 2016 and September 2018. In this retrospective, anonymized registry, data of male and female patients with unresectable advanced/metastatic BRAF-positive cutaneous melanoma treated in first-, second- and third-line with registered substances were analyzed using descriptive statistics. Forty-one patients (56.1% male) were included providing a total of 70 treatment lines (first-line: $n = 41$; second-line: $n = 18$; and third-line: $n = 11$). Within the patients presenting with stage III or IV melanoma, immunotherapy with checkpoint inhibitors was more frequently administered as first-line treatment than targeted therapy (TT) (70.7% vs. 29.3%). Across all lines, patients received TT in 47.1% (predominantly combined BRAF-MEK-inhibition) and immunotherapy in 52.9% of the cases (anti-PD-1 monotherapy in 62.2% and anti-PD-1/anti-CTLA-4 combinations in 37.8%). Most commonly, the treatment type was switched from TT to immunotherapy or vice versa upon disease progression. The most frequent rationales for prescribing either TT or immunotherapy were physician's preference (40.0%) or remission pressure (28.6%), respectively. Disease progression led to treatment discontinuation more frequently than undesired events. Patients in Switzerland with unresectable advanced or metastatic BRAF-mutant melanoma predominantly receive guideline-recommended treatments. IO was used as predominant front-line therapy, with TT/immunotherapy switch being the predominant treatment principle. Sequencing studies are underway to identify the optimal treatment regimen for those patients. *Melanoma Res* 32: 366–372 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

At an incidence of approximately 150 000 new cases and approximately 26 000 deaths for both men and women in 2020, cutaneous melanoma represents a major cancer disease and prominent cause of cancer death in Europe [1]. In Switzerland, an average of roughly 320 people died of cutaneous melanoma each year between 2012 and 2016 [2]. However, these figures may represent an underestimate for new cases [3]. The prognosis ranges from 5-year survival of more than 90% in patients who present with localized disease and primary tumors up to 1.0 mm in thickness and between 20 and 70% in stage III depending primarily on the nodal tumor burden to less than 10% in long-term survival for patients with distant metastatic melanoma [3,4]. At diagnosis, approximately 10–20% of the patients present with advanced or metastatic melanoma [5,6], and around 45% of melanoma harbor an activating mutation of the BRAF gene, coding for a serine-threonine kinase in the mitogen-activated protein kinase (MAPK) signaling pathway [7]. The treatment of advanced or metastatic melanoma, including BRAF-mutant melanoma, has rapidly evolved during the last years with the introduction of multiple new drugs of two predominant treatment types – checkpoint inhibition (IO) and targeted therapy (TT). IO aims at overcoming or circumventing the immune evasion mechanisms of tumor cells with inhibitory antibodies blocking the immune checkpoints programmed death 1 [pembrolizumab (Pem) and nivolumab (Niv)] or cytotoxic T-lymphocyte-associated protein 4 [ipilimumab (Ipi)]. In case of $BRAF^{V600}$-mutant melanoma, TT can be administered to directly act on the altered protein and the activated MAPK signaling cascade with the combination of

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BRAF- plus MEK-inhibitors, namely vemurafenib + cobimetinib (Vem+Cob), dabrafenib + trametinib (Dab+Tra) and encorafenib + binimetinib (Enc+Bin) [3,8].

Most therapeutic options currently recommended for first-line treatment of advanced or metastatic melanoma have been approved by the Swiss Agency for Therapeutic Products (Swissmedic, Bern, Switzerland) in 2015 and 2016.

Objective

This analysis depicts the *status quo* of the current treatment standards in advanced melanoma and summarizes the rationales for therapy decisions in Switzerland in the era of the modern treatment options before the commercial availability of Enc+Bin.

Methods

In this retrospective, cross-sectional documentation based on anonymized data at five specialized hospitals in Switzerland, data of male or female patients, at least 18 years of age, with histologically confirmed unresectable advanced or metastatic $BRAF^{V600E/K}$-positive malignant cutaneous melanoma (stage IIIB/C or IV) according to the eight American Joint Committee on Cancer classification [9] treated between January 2016 and September 2018 in the first-, second- and third-line setting with substances registered in Switzerland at the time of treatment was collected retrospectively and analyzed using descriptive statistics. The key exclusion criteria were: (i) noncutaneous melanoma, (ii) other stages III–IV malignancies, (iii) prior/concomitant systemic treatment of any other malignancy and (iv) participation in a clinical trial or an early access program while being treated in the first-, second- and third-line setting.

Data from participating centers were combined, analyzed, summarized and reported. Datasets included demographic and baseline characteristics, effectiveness and safety observations, measurements using descriptive statistics (frequency, mean, SD, median, minimum, maximum, 25% quartile and 75% quartile – quantitative data), and contingency tables (absolute and relative frequencies – qualitative data) as appropriate. The treatments administered at first-, second- and third-line were analyzed *in toto*, by treatment line and by treatment type (IO, TT, chemotherapy and others) together with the respective reasons. The safety parameters were analyzed by treatment line (overall and by treatment type). Further details are specified in the statistical analysis plan.

An informed consent process was not required in this anonymized, retrospective data analysis. The study was submitted to the responsible ethics committee (EC) at the Kanton Zürich, Switzerland. However, the project was not in the scope of the Federal Act on Research involving Human Beings and, therefore, did not require approval by the EC.

Results

Patient population

Treatment sequences of 41 patients were documented. All 41 met all inclusion criteria and had at least one line of melanoma therapy. Eighteen patients continued to be treated in a second-line setting and 11 patients received a third-line treatment, accounting for 70 documented treatment lines in total. Upon initiation of the first-line treatment, 56.1% of the patients were male and 43.9% were female. The mean age for both sexes was 57.9 years at this time. Around 70–95% of the patients presented with stage IV melanoma at the start of each treatment line. In all treatment lines, around 40% of the patients had normal lactate dehydrogenase (LDH) and in 18.2–27.8% of the patients LDH was elevated (up to 55% of data was missing) at the start of the treatment lines. For the key patients' characteristics at the time of initiation of each treatment line, see Table 1.

Treatment

IO was more frequently administered as a first-line treatment than TT (70.7% IO vs. 29.3% TT). Across all lines, patients received TT in 47.1% and IO in 52.9% of the cases. Chemotherapy was not administered in any of the treatment lines (0.0%). The overall absolute frequencies of the active components used are depicted in Fig. 1. BRAF-inhibitors were administered as a monotherapy in two out of 33 cases; whereas in all other patients, combinations of BRAF- and MEK-inhibitors were administered. With this investigation having been performed before the commercial availability of Enc+Bin, Dab+Tra was the TT of choice when compared with Vem+Cob (63.6 vs. 30.3%). Patients treated with IO received a combination treatment with Ipi plus Niv (37.8%) or IO monotherapy regimens (62.2%). None of the patients were treated with T-VEC (0.0%). Upon initiation of a subsequent treatment line, the type of treatment was usually switched from either IO to TT or vice versa. In a total of three cases, patients received TT twice in a row and in a single case, the patient was treated with TT in all three treatment lines. In those patients having received consecutive TT, the active substances were mostly switched. In patients receiving IO, one patient was treated with IO consecutively.

According to the physician's assessment, their preference for a specific treatment (40.0%), and high remission pressure (28.6%; i.e. rapid tumor progression, tumor load/location and high LDH-levels) are the most frequent reasons for choosing a certain treatment. However, the main reason differed between the two treatment types (TT and IO) with remission pressure being named most often for TT (54.5%) and physician's preference for IO (54.1%). Treatment details are outlined in Table 2.

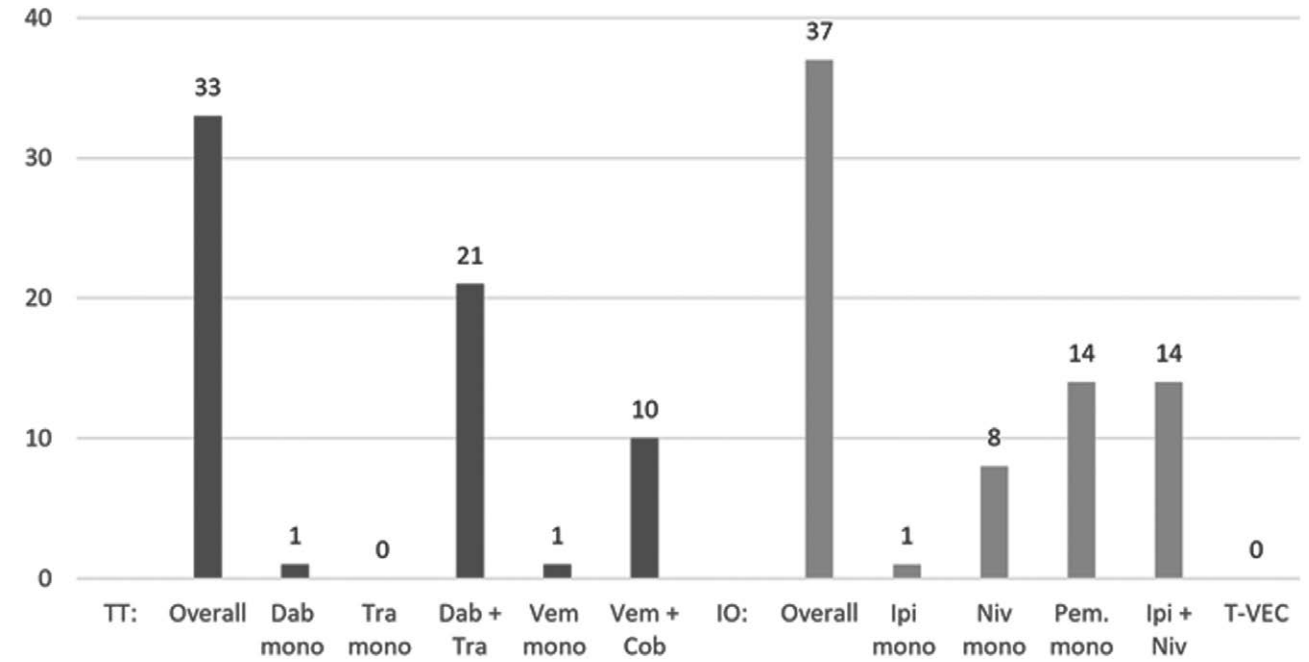
The main reasons for prescribing a specific drug are outlined in Table 3. The treatment choice between Dab+Tra vs. Vem+Cob was mainly driven by the toxicity profile, tolerability and – also for the TT monotherapy regimens – physician's preference. The choice for Niv monotherapy and Niv+Ipi was mainly based on physician's preference and effectiveness in case of the combination with Ipi. Ipi in monotherapy was selected due to its safety

Table 1. Key patient characteristics at the time of initiation of each treatment line

	At initiation of first-line ($n = 41$)	At initiation of second-line ($n = 18$)	At initiation of third-line ($n = 11$)
Male sex, *n* (%)	23 (56.1)	12 (66.7)	7 (63.6)
Age, median (range)	56 (24–84)	56 (24–84)	56 (35–84)
ECOG, *n* (%)			
0	25 (61.0)	Not assessed	Not assessed
1	13 (31.7)		
≥2	1 (2.4)		
Involvement of ≥3 organs, *n* (%)			
Yes	7 (17.1)	11 (61.1)	5 (45.5)
No	34 (82.9)	7 (38.9)	6 (54.5)
LDH, *n* (%)			
Normal	19 (46.3)	8 (44.4)	4 (36.4)
High	9 (22.0)	5 (27.8)	2 (18.2)
1x ULN ≤ LDH < 2x ULN	5 (12.2)	5 (27.8)	2 (18.2)
LDH ≥ 2x ULN	4 (9.8)	0 (0.0)	0 (0.0)
Unknown	13 (31.7)	5 (27.8)	5 (45.5)
Stage			
III	12 (29.3)	1 (5.6)	1 (9.1)
IV	29 (70.7)	17 (94.4)	10 (90.9)
M1a	5 (12.2)	2 (11.1)	0 (0.0)
M1b	6 (14.6)	3 (16.7)	2 (18.2)
M1c	8 (19.5)	5 (27.8)	2 (18.2)
M1d	10 (24.4)	7 (38.9)	6 (54.5)

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Fig. 1.



Treatment types and active components, all treatment lines (absolute numbers are presented). Cob, cobimetinib; Dab, dabrafenib; IO, checkpoint inhibition; Ipi, ipilimumab; Niv, nivolumab; Pem, pembrolizumab; Tra, trametinib; TT, targeted therapy; T-VEC, Talimogen laherparepvec; Vem, vemurafenib.

profile and tolerability, whereas the monotherapy with Pem was chosen mainly due to its treatment schedule (every 3 weeks) and physician's preference.

Treatment discontinuation

Most treatments were discontinued by the time of data documentation. Across all treatment lines, the predominant reason for discontinuation was the development of disease progression followed mainly by toxicities (Table 4). In particular, the combination regimens Ipi+Niv as well as Vem+Cob were discontinued in half of the cases due to toxicities. The specific toxicities leading to treatment discontinuation by drug(s) are listed in Table 5. For TT, the events were mostly specific for the active substances, whereas inflammatory events were exclusively described for IO.

Table 2. Main reason for treatment choice by treatment type

Analysis set	First-line		Second-line		Third-line	
	Targeted therapy ($n = 12$)	Checkpoint inhibition ($n = 29$)	Targeted therapy ($n = 12$)	Checkpoint inhibition ($n = 6$)	Targeted therapy ($n = 9$)	Checkpoint inhibition ($n = 2$)
Reason	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Remission pressure (rapid PD, tumor load/location, LDH)	7 (58.3)	0 (0.0)	7 (58.3)	1 (16.7)	4 (44.4)	1 (50.0)
Toxicity profile	0 (0.0)	1 (3.4)	0 (0.0)	1 (16.7)	1 (11.1)	0 (0.0)
Patient's preference	1 (8.3)	6 (20.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Physician's preference	3 (25.0)	19 (65.5)	3 (25.0)	1 (16.7)	2 (22.2)	0 (0.0)
Comorbidities	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (8.3)	3 (10.3)	2 (16.7)	2 (33.3)	2 (22.2)	1 (50.0)

Table 3. Main reason for choosing specific drugs (by patient)

	Targeted therapy regimen				Checkpoint inhibition regimen			
Reason	Dab+Tra ($n = 21$)	Vem+Cob ($n = 10$)	Dab ($n = 1$)	Vem ($n = 1$)	Ipi+Niv ($n = 14$)	Ipi ($n = 1$)	Pem ($n = 14$)	Niv ($n = 8$)
Physician's preference	8	1	1	1	5		3	7
Safety profile, better tolerability	5	4				1	1	
Effectiveness	4				7			
(Fast) Progression	1				1			
Patient had the other combination	1							
Unknown, missing, not applicable	2	2			1		1	
Disponibility		3						
Treatment schedule, e.g. q3w							5	
Easy access							1	
Experience							1	
New admission							1	
Previously treated with pembrolizumab in combination							1	
Response/toxicity ratio								1

Cob, cobimetinib; Dab, dabrafenib; Ipi, ipilimumab; Niv, nivolumab; Pem, pembrolizumab; Tra, trametinib; Vem, vemurafenib.

Table 4. Main reasons for treatment discontinuation by treatment line and type

	First-line		Second-line		Third-line	
n (%)	Targeted therapy ($n = 12$)	Checkpoint inhibition ($n = 29$)	Targeted therapy ($n = 12$)	Checkpoint inhibition ($n = 6$)	Targeted therapy ($n = 9$)	Checkpoint inhibition ($n = 2$)
Patients with treatment discontinuation	11 (91.7)	29 (100.0)	8 (66.7)	6 (100.0)	7 (77.8)	2 (100.0)
Any reason for treatment discontinuation	11 (100.0)	29 (100.0)	7 (87.5)	6 (100.0)	6 (85.7)	2 (100.0)
Progression	4 (36.4)	10 (34.5)	3 (37.5)	5 (83.3)	4 (57.1)	1 (50.0)
Toxicity	3 (27.3)	7 (24.1)	3 (37.5)	1 (16.7)	1 (14.3)	0 (0.0)
Best benefit reached	1 (9.1)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of planned cycles reached	0 (0.0)	9 (31.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient's decision	1 (9.1)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)
Other	1 (9.1)[a]	0 (0.0)	1 (12.5)[b]	0 (0.0)	0 (0.0)	1 (50.0)[c]

Each of the following reasons was named once:
[a]Switch to checkpoint inhibition decided;
[b]CR reached, decision to switch to IO; and
[c]Perilesional edema + bleeding from a brain metastasis.

Discussion

In this study, we examined the real-world treatment of unresectable advanced or metastatic $BRAF^{V600E/K}$-positive cutaneous melanoma in patients treated at five major hospitals in Switzerland before commercial availability of Enc+Bin. The aim of our data analysis was to better understand the treatment landscape and the decision-making process in Switzerland. The results of this study include information on patient profiles, treatment patterns and outcomes of patients treated in the real-world setting.

In the first-line setting, a higher number of patients was treated with IO compared to TT, reflecting the recent treatment recommendations laid out in the European

Table 5. Toxicities leading to treatment discontinuation by drug(s)

	Dab+Tra ($n = 21$)	Vem+Cob ($n = 10$)	Ipi+Niv ($n = 14$)	Pem ($n = 14$)
	Toxicity ($n = 2$)	Toxicity ($n = 5$)	Toxicity ($n = 7$)	Toxicity ($n = 1$)
Pyrexia, fever, chills	Grade 2	Grade 2		
Cutaneous events	Grade 4	Grade 4		
Diarrhea		Grade 3		
Cardiomyopathia		Grade 3		
Hepatopathia		Grade 3		
Pancreatitis			Grade 3	
Pneumonitis			Grade 3[a]	
Hepatitis			Grade 3	
Adrenal insufficiency			Grade 3	
Gastroduodenitis, jejunitis			Grade 3	
Interstitial nephritis			Grade 3	
Arthralgia and muscle pain				Grade 4

Cob, cobimetinib; Dab, dabrafenib; Ipi, ipilimumab; Pem, pembrolizumab; Tra, trametinib.
[a]Two cases.

Society for Medical Oncology Clinical Practice Guidelines for cutaneous melanoma stating that – in case it is considered safe for the first few months and depending on treatment goals, comorbidities and patient preference – patients should be considered for IO first for the first few months in order to target potential long-term disease control, preserving TT for the next treatment line [8,10]. This preferential tendency of IO over TT in the upfront setting is mainly based on clinical study results investigating first-line regimens, which suggest that TT may have a better outcome within the initial treatment phase, while IO regimens might provide the potential for a better long-term outcome [11–24]. However, the guidelines also note that the best sequencing approach has not been established yet. Clinical trials investigating TT/IO sequencing approaches, such as the DREAMseq phase III study (NCT02224781) or the Sequential Combo Immuno and Target Therapy (SECOMBIT) phase II study (NCT02631447), address previously unanswered questions on the optimal treatment sequence [25–26]. An additional phase II study (EBIN, NCT03235245) is currently underway. So far, current data of the DREAMseq trial (median follow-up 27.7 months) point towards the conclusion that the IO combination Niv+Ipi followed by TT with Dab+Tra might be the preferred treatment sequence vs. the reciprocal arm based on the observation that Niv+Ipi followed by Dab+Tra was associated with greater overall survival (OS) at 2 years – and likely beyond – than the reverse treatment order [25]. In addition, current data obtained in the SECOMBIT trial (median follow-up 32.2 months) showing a better trend for Niv+Ipi followed by the TT combination Enc+Bin (or even a 'sandwich' design: Enc+Bin followed by Niv+Ipi followed by Enc+Bin) in both progression-free survival of the whole treatment sequence and OS [26]. More mature and detailed data as well as further information on potential limitations of these trials (such as dropouts within the treatment sequence, patient baseline characteristics at the time of second treatment and information on subsequent and dropout therapies) are awaited to gain further and more robust insights regarding treatment sequencing.

While for patients treated with TTs the administration of BRAF-inhibitors in monotherapy occurred in a single case only regarding the present data set, the combination of Dab+Tra was predominantly prescribed, followed by the combination of Vem+Cob. The combination Enc+Bin was not registered in the observed time period. In contrast, IO was more frequently administered as a monotherapy. Chemotherapy was not administered to any of the patients.

Our data suggest that the main driver for administering TTs was the need of a rapid, reliable and sustained remission (remission pressure). Results from several phase III trials have demonstrated that combined BRAF- and MEK-inhibition achieves numerically higher overall response rates but shorter duration of response as indirectly compared with immune checkpoint inhibitors that show a tendency towards more durable responses [11,14–24,27,28]. In the IO group, the treatment choice was influenced by the treating physician's preferences. Favorable OS data of the combination regimen Ipi+Niv may constitute an underlying reason for this decision-making [29]. Taken together, our data underline that modern treatment options are the standard of care in major hospitals in Switzerland.

For IO, immune-related adverse reactions represented the leading cause for treatment discontinuation, especially for the combination Ipi+Niv. TTs, however, predominantly induced substance-specific toxicities, such as pyrexia or cutaneous events. The availability of numerous combinations makes switching to an alternative TT combination (with intermediate or subsequent IO treatment), a common therapeutic strategy in cases where specific toxicities required treatment discontinuation. Our data showing more frequent cases of rechallenge treatment sequences with TT underline that this approach is being used. The registration of Enc+Bin is associated with a favorable and distinct toxicity profile [11,14–22,28] and, thus, leads to a further promising option for future melanoma patients. As mentioned earlier, the sequential use of TTs and IOs is currently being investigated. While combinatory approaches of IO plus TT showed high toxicity rates and partially failed to show improved efficacy [30–32], currently leading to a controversial debate concerning the value and patient selection with regard to this treatment approach.

Methodological limitations

The underlying study included efficiency endpoints whose interpretation is troubled by a series of limitations. Only patients who had completed at least one treatment line, which had been started after January 2016 were eligible for inclusion with the documentation period ending in April 2019; therefore, biasing the treatment duration, time-to-progression and response rates. Hence, these data are not shown here. Another general limitation is introduced by the nature of this study with its retrospective, uncontrolled, open design, nonstandardized treatment allocations and conditions, as well as its nonstandardized, observational character. Therefore, the study data are presented in a descriptive way only, showing the real-life situation during the specified documentation period. Observed treatment trends and tendencies must be interpreted with caution, as these might be influenced by underlying patient and disease characteristics. In addition, our data only reflects the situation in Switzerland, whereas results obtained in similar studies might inform the situation in other countries.

Conclusion

Patients in Switzerland with unresectable advanced or metastatic BRAF-mutant melanoma receive guideline-recommended treatments. IO was used as the predominant front-line therapy, with TT/IO switch being the predominant treatment principle. Sequencing studies are underway to identify the optimal treatment regimen for advanced BRAF-mutant melanoma.

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This project and the analysis were designed and conducted by Pierre Fabre. All named authors participated in the development of this manuscript and in the decision to submit this manuscript for publication. The authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with Ethics Guidelines – ethics approval and consent to participate.

An informed consent process was not required in this anonymized, retrospective data analysis. The study was submitted to the competent ethics committee, Kantonale Ethikkommission Zürich, Switzerland (EC review number: 2018-01822) confirming that the Human Research Act does not apply to this project and that the project does not require ethics committee approval.

Consent for publication: in this anonymized, retrospective data analysis no consent, including consent for publication and reporting individual patient data, was required from the patients.

Availability of data and materials: the anonymized data from the clinical study is archived according to the ICH-GCP requirements at Pierre Fabre Pharma GmbH, Freiburg, Germany and will not be made public.

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Conflicts of interest

J.M. has intermittent project focused consultant or advisory relationships with Merck/Pfizer, Merck Sharp & Dohme, Amgen, Novartis, Sanofi, Bristol Myers Squibb, and Pierre Fabre and has received travel support from Ultrasun, L'oreal, Merck Sharp & Dohme, Bristol Myers and Squibb und Pierre Fabre outside of the submitted work. D.Z. has received Ad-Board honoraria from Merck, Janssen, Bristol Myers Squibb, Sanofi, and Pierre Fabre. D.B. was an employee at Pierre Fabre at the time the research was performed. R.Z. received financial support for congress participation from Pierre Fabre. S.B. and C.L.G. declare that they have no conflicts of interest.

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