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Phase I, open-label study of pasireotide in patients with *BRAF*-wild type and *NRAS*-wild type, unresectable and/or metastatic melanoma

Reinhard Dummer,[1] Olivier Michielin,[2] Mirjam Chantal Nägeli,[1] Simone M. Goldinger,[1] Federico Campigotto,[3] Ulrike Kriemler-Krahn,[4] Herbert Schmid,[4] Alberto Pedroncelli,[4] Sara Micaletto,[1] Dirk Schadendorf[5]

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[1]Department of Dermatology, University Hospital Zurich, Zurich, Switzerland
[2]Multidisciplinary Oncology Center, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[3]Global Medical Affairs, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA
[4]Clinical Development, Novartis Pharma AG, Basel, Switzerland
[5]Department of Dermatology, University Hospital Essen, Essen, Germany & German Cancer Consortium, Heidelberg, Germany

Correspondence to
Professor Reinhard Dummer, Department of DermatologyUniversity Hospital Zurich Zurich Switzerland ; reinhard.dummer@usz.ch

ABSTRACT

Introduction Somatostatin analogues exert antitumour activity via direct and indirect mechanisms. The present study was designed to assess the safety and efficacy of pasireotide in patients with *BRAF*-wild type (WT) and *NRAS*-WT metastatic melanoma.

Patients and methods Patients with unresectable and/or metastatic melanoma or Merkel cell carcinoma were eligible. Pasireotide was administered at different doses for ≤8 weeks in dose-escalation phase, followed by long-acting pasireotide 80 mg or lower dose in case of toxicity in follow-up phase up to six additional months. Primary endpoint was safety in the first 8 weeks of dose-escalation phase.

Results The study was terminated early due to slow recruitment. Of the 10 patients with metastatic melanoma enrolled, only four reached the high dose level: two patients reached 3600 µg in dose-escalation and follow-up phases and two patients reached 3600 µg in dose-escalation and long-acting pasireotide 80 mg in follow-up phases and were stable for >5 months. Most common adverse events (AEs) during dose-escalation phase in ≥2 patients (20%) were: diarrhoea (50%), nausea (50%), fatigue (20%), hyperglycaemia (20%), hypophosphatemia (20%), chills (20%) and tumour pain (20%). Grade 3 or 4 study drug-related AEs were diarrhoea and nausea, reported in one patient. Partial response was documented in one patient and stable disease in another.

Conclusions Pasireotide was well tolerated, and safety results were similar to those previously reported in other indications. Further studies are needed to evaluate its antitumour activity alone and in combination with other drugs in melanoma.

Key questions

What is already known about this subject?

- Until now, the treatment options for patients with *BRAF*-wild type (WT) and *NRAS*-WT melanoma are limited.
- Mitogen-activated protein kinase (MAPK) and PI3K pathways are the major signalling pathways in melanoma, which regulate cell growth, proliferation, survival and transformation. Somatostatin receptors (SSTRs) and insulin growth factor receptors are overexpressed in human melanoma cells and are upstream of the Ras/MAPK signalling pathway.
- Somatostatin analogues (such as pasireotide) exert antitumour activity in different tumours like pituitary, prostate, gastric, lung, pancreas, colorectal or thyroid origin, both via direct (mediated through SSTRs) and indirect mechanisms (insulin-like growth factor 1 (IGF-1) signalling pathway).

What does this study add?

- This is the first phase I study to assess the safety and efficacy of pasireotide in patients with unresectable and metastatic *BRAF*-WT and *NRAS*-WT melanoma.
- We observed that pasireotide was well tolerated, and the safety profile was similar to the prior reports in other indications.
- Of 10 patients included in the study, stable disease and partial response were observed in one patient each.

How might this impact on clinical practice?

- Though the antitumour activity in these late-staged patients was limited, pasireotide could be potentially used in combination with other therapeutic agents in the treatment of patients with *BRAF*-WT and *NRAS*-WT melanoma.
- Further prospective randomised studies are warranted to evaluate the efficacy of pasireotide in *BRAF*-WT and *NRAS*-WT melanoma.

INTRODUCTION

Melanoma is the most aggressive and sometimes treatment-resistant form of skin cancer. *BRAF*-wild type (WT) and *NRAS*-WT tumours are observed in approximately 28%–32% of melanomas.[1 2] The constitutive activation of the mitogen-activated protein kinase (MAPK) signalling pathway in *BRAF*-WT and *NRAS*-WT melanoma may be due to the loss of function mutations and deletions in *NF1* (a tumour suppressor gene encoding the RAS GTPase-activating protein). *NF1* mutations are identified in up to 70% of *BRAF*-WT and

NRAS-WT melanomas.[3] The other activating mutations of *KIT*, amplification of *KIT*, *CCND1* and *TERT* are also observed in this population.[4 5]

Somatostatin and its analogues (SSAs) bind to somatostatin receptors $(SSTR)_{1-5}$ with variable affinities and may directly inhibit the cell growth by the inhibition of cell proliferation through the cell cycle control and induction of apoptosis.[6] The data from preclinical and clinical studies demonstrate that SSAs exert antitumour effects in different tumour types including those of pituitary, prostate, gastric, lung, pancreas, colorectal or thyroid origin.[7–11] One or more subtypes of SSTRs are also highly expressed in melanoma cell lines[12] and tumour samples obtained from patients with melanoma (with some subtypes being more abundant than other subtypes [$SSTR_1$>$SSTR_2$>$SSTR_3$>$SSTR_4$>$SSTR_5$]).[13] The insulin-like growth factor receptors (IGFRs) are also overexpressed in human melanoma cells, and the IGF-1 signalling pathway via IGF-1R is shown to play a key role in melanoma progression.[14 15]

Pasireotide, a second-generation SSA, has a broader affinity for SSTRs compared with the first-generation SSAs, octreotide and lanreotide. The binding affinity of pasireotide is highest for $SSTR_5$ (IC_{50}: 0.16±0.01 nmol/L) and $SSTR_2$ (IC_{50}: 1±0.1 nmol/L) with moderate affinity to $SSTR_3$ (IC_{50}: 1.5±0.3 nmol/L) and $SSTR_1$ (IC_{50}: 9.3±0.1 nmol/L), and low affinity towards $SSTR_4$ receptors (IC_{50}: >100 nmol/L).[16] Pasireotide also inhibits IGF-1 plasma levels more effectively than octreotide.[17] Pasireotide demonstrated antitumour activity in phase 3 clinical studies by significantly reducing growth hormone (GH) and IGF-1 levels and shrinking tumours in patients with acromegaly.[18] Long-acting pasireotide showed a trend towards higher tumour control rate at month 6 (although not statistically significant) and was associated with a longer progression-free survival than long-acting octreotide in patients with metastatic neuroendocrine tumours (NETs).[19] In a recent phase 2 study in patients with lung NETs, pasireotide alone had significant antitumour efficacy of the same magnitude as everolimus, and the combination of both compounds resulted in a potentiation of the antitumour effect.[20]

Therefore, SSTRs and the IGF-1 signalling pathways, which are upstream of the Ras/MAPK signalling pathway,[21] may potentially be targeted using pasireotide in *BRAF*-WT and *NRAS*-WT melanoma. In the present study, we assessed the safety profile and the preliminary antitumo activity of pasireotide in patients with *BRAF*-WT and *NRAS*-WT metastatic melanoma.

PATIENTS AND METHODS

Adult patients (aged ≥18 years) with histologically/cytologically confirmed, unresectable (stage III) and/or metastatic (stage IV) melanoma or metastatic Merkel cell carcinoma (MCC) excluding patients with *BRAF* and *NRAS* mutations were eligible. Only patients with measurable disease according to Response Evaluation Criteria in Solid Tumour version 1 (RECIST 1.0) and the presence of ≥1 lesion suitable for standardised uptake value measurements on 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) were included in the study. The other key eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ function. Patients with unknown *BRAF*-mutation or *NRAS*-mutation status, primary uveal melanoma, prior treatment with SSA or hypersensitivity to SSA and those receiving >3 prior lines of systemic therapy, prior radiotherapy, an investigational drug or any antineoplastic therapy within 4 weeks prior to baseline were excluded from the study.

The study was conducted in accordance with US Food and Drug Administration (USFDA) guidelines, Good Clinical Practice, the Declaration of Helsinki and applicable local health authority requirements. All patients provided written informed consent. The study was approved by the institutional review boards and registered on Clinicaltrials.gov as NCT01652547.

Study design

This was an open-label, single-arm, multicentre, intrapatient, dose-escalation, phase I study to evaluate the preliminary safety, pharmacokinetics (PK) and antitumour activity of pasireotide (SOM230) subcutaneous (SC) at doses of 300 µg, 600 µg, 900 µg and 1200 µg three times a day in patients with metastatic melanoma or metastatic MCC. As per the protocol amendment 4, patients were allowed to switch to 80 mg long-acting pasireotide intramuscular every 28 days (or a lower dose in case of toxicity) for an additional 6 months, during the follow-up phase (online supplementary figure 1). It is to be noted that this study was not designed to determine the maximum tolerated dose (MTD). The maximum allowable dose in this study was 1200 µg three times a day (total daily dose of 3600 µg, which is still below the MTD for the SC formulation in healthy volunteers 1950 µg twice a day=total daily dose of 3900 µg).

Assessments

The primary objective of the study was to assess the safety profile of pasireotide SC during the 8-week dose-escalation phase. The secondary objectives included the assessment of safety at study completion, disease control rate (DCR; defined as the proportion of patients with a best overall response (ORR) of complete response (CR) or partial response (PR) or stable disease), PK and the effect of pasireotide on melanoma response biomarkers (S100b, melanoma-inhibitory activity (MIA)) and treatment response and/or secretion biomarkers over time.

Safety was monitored by clinical assessments including laboratory evaluations, ECGs, vitals, physical examination, gall bladder ultrasound, and recording adverse events (AEs) through the electronic case report form at each visit. The site investigator used RECIST version 1.0,[22] assisted by the CT or MRI, to assess ORR, defined as the proportion of patients with a best overall CR or PR,

measured on days 57, 113, 169 and at the end of treatment. In addition, ORR was also assessed using adapted European Organization for Research and Treatment of Cancer criteria by 18-FDG-PET on days 29 and 57. The serum samples were estimated for PK parameters on days 1 and 8 during the four cycles of the dose-escalation phase and at monthly visits during the follow-up phase using non-compartmental analysis by Phoenix (V.6.3, Pharsight, Mountain View, California, USA). Pharmacokinetic parameters included pasireotide maximum/minimum concentration on days 1 and 8 for each cycle (C_{max} and C_{min}) and area under the curve from 0 to 2 hours (AUC_{0-2h}) at steady state. The secretion biomarkers assessed over time included S100b and MIA, IGF-1, IGF-2, IGF-binding protein 2 (IGFBP2) and IGFBP3.

Statistical analysis

A sample size of 18 eligible patients was considered to be sufficient to assess the safety of pasireotide SC in this patient population. With 18 patients, there was an 85% of probability of detecting an AE with a 10% incidence rate. However, due to the slow recruitment and change in the treatment landscape, this study was terminated early without full enrolment of 18 patients according to the planned sample size. Safety, PK and efficacy results were presented for the 10 enrolled patients.

Patients who received at least 1 dose of study medication and had at least one post-baseline safety assessment were used for all safety analyses. Patients who received at least 1 dose of study drug were used for all efficacy analyses. The study endpoints were reported according to the following two study phases: the dose-escalation phase and the overall phase. The patient characteristics, safety, efficacy and laboratory endpoints were summarised with descriptive statistics and 95% CI as appropriate. The data were analysed using SASV.9.3.

RESULTS

Patient characteristics

Ten patients with *BRAF*-WT and *NRAS*-WT melanoma received the pasireotide treatment. Patients with MCC could not be recruited. All the patients were Caucasians with the median age of 71.5 years (range, 60–77 years); 80% of the patients were males. All the patients (unresectable stage III/IV melanoma) were heavily pretreated, underwent prior surgical treatment for their disease and received prior antineoplastic therapies as shown in table 1.

The patient disposition is illustrated in online supplementary figure 2. The safety, efficacy and PK analyses included those 10 patients who were treated with pasireotide.

Among the 10 patients, five completed the dose-escalation phase; the follow-up phase was reduced from 6 months to 3 months after the decision to terminate the study early, and the patients were offered to receive further pasireotide treatment in a rollover study. Three of those five patients (30%) completed the follow-up phase. One patient completed the study as per protocol: 8 weeks of dose-escalation phase and an additional 6-month follow-up. Two of those three patients (20%) completed the follow-up phase receiving 80 mg long-acting pasireotide for at least 3 months. Three of the five patients received pasireotide SC three times a day.

Table 1 Baseline characteristics

Baseline characteristic	All patients, n=10
Age (years)	
Median (range)	71.5 (60–77)
Gender, n (%)	
Male	8 (80.0)
Female	2 (20.0)
Race, n (%)	
Caucasian	10 (100.0)
Ethnicity, n (%)	
Other	10 (100.0)
Baseline weight (kg)	
Mean (SD)	77.0 (13.4)
Height (cm)	
Mean (SD)	170.6 (8.7)
Prior antineoplastic therapy, n (%)	
Prior surgery	10 (100)
Prior radiotherapy	4 (40)
Prior anticancer medications	6 (60)

Safety

Dose-escalation phase

The median duration of pasireotide exposure in this phase was 6.7 weeks (range, 1.6–8.1 weeks); one patient was exposed to pasireotide SC for >8 weeks in the dose-escalation phase. The most commonly reported AEs (incidence ≥20%) were diarrhoea (50%), nausea (50%), fatigue (20%), hyperglycaemia (20%), hypophosphatemia (20%), tumour pain (20%) and chills (20%) (table 2). The most frequently reported study drug-related AEs (incidence ≥20%) were diarrhoea (50%), nausea (50%), hyperglycaemia (20%) and fatigue (20%). Grade 3 or 4 study drug-related AEs (diarrhoea and nausea) were observed in one patient. Study drug-related serious AEs (SAEs) were nausea, vomiting and diarrhoea in one patient, which occurred at pasireotide SC 300 µg.

One patient died due to disease progression 5 days after the premature termination of study treatment, and one patient died due to disease progression 12 days after the withdrawal of consent. Both patients were treated only for a very short period of time (16 days and 11 days of treatment, respectively).

Table 2 Adverse events (≥20% incidence), regardless of study drug relationship, by preferred term and dose level*–dose-escalation phase (safety set)

	Pasireotide SC, n=10				
Preferred term	300 µg tid n (%)	600 µg tid n (%)	900 µg tid n (%)	1200 µg tid, n (%)	All patients n (%)
Diarrhoea	4 (40)	1 (10)	0	0	5 (50)
Nausea	3 (30)	2 (20)	1 (10)	0	5 (50)
Fatigue	2 (20)	0	0	0	2 (20)
Hyperglycaemia	2 (20)	0	0	0	2 (20)
Hypophosphatemia	1 (10)	1 (10)	1 (10)	0	2 (20)
Tumour pain	2 (20)	0	0	0	2 (20)
Chills	0	1 (10)	1 (10)	0	2 (20)

*List of all AEs that started at each specific dose level. A patient with multiple occurrence of an AE preferred term in each dose level is counted only once for that preferred term.
AEs, adverse events; SC, subcutaneous; tid, three times a day.

Overall safety

Overall, the median duration of exposure to pasireotide SC was 7.6 weeks (range, 1.6–32.1 weeks); one patient was exposed to pasireotide SC for >28 weeks. Of the five patients in the follow-up phase, one patient received pasireotide SC and completed the follow-up phase, two discontinued the pasireotide SC treatment, and two received long-acting pasireotide 80 mg for at least 3 months in the follow-up phase. The most commonly reported AEs (incidence ≥20%) were diarrhoea (50%), nausea (50%), fatigue (30%), hyperglycaemia (30%), hypophosphatemia (30%), chills (20%), tumour pain (20%) and decreased weight (20%) (table 3). Study drug-related AEs were reported in 80% of patients, and they included diarrhoea (50%), nausea (50%), hyperglycaemia (30%), fatigue (20%), hypophosphatemia (20%) and weight decrease (20%). The hyperglycaemia occurring in two patients was managed by concomitant medications including gliclazide and metformin hydrochloride. Grade 3 or 4 drug-related AEs were observed in 20% of patients (diarrhoea and nausea in one patient, and hypophosphatemia in one patient). SAEs, suspected to be study drug related, included nausea, vomiting and diarrhoea in one patient.

Table 3 Adverse events (≥20% incidence) regardless of study drug relationship by preferred term (safety set) – overall (dose-escalation phase+follow-up phase)

Preferred term	All patients, n (%)
Diarrhoea	5 (50)
Nausea	5 (50)
Fatigue	3 (30)
Hyperglycaemia	3 (30)
Hypophosphatemia	3 (30)
Chills	2 (20)
Tumour pain	2 (20)
Weight decreased	2 (20)

Efficacy

Among the total 10 patients included in the study, the best ORR (defined as PR or better) was observed in one (10%) patient (95% CI 0.3 to 44.5), and best overall DCR (defined as stable disease or better) was observed in two (20%) patients (95% CI 2.5 to 55.6), both by CT or MRI and 18-FDG-PET. Stable disease and PR were observed in one patient each. The best ORR for patients with the measurable disease at baseline is presented in (online supplementary table 1). Four patients reached high dosing (two patients reached 3600 µg in the dose-escalation phase and the follow-up phase, and two patients reached 3600 µg in the dose-escalation phase and long-acting pasireotide 80 mg in the follow-up phase and were stable for more than 5 months). One patient achieved stable disease in target lesions (patient number 3). However, it was not considered to be stable disease by RECIST criteria due to the worsening of one of the non-target lesions, and the response was considered as progressive disease (PD).

Pharmacokinetics

The mean plasma concentration of pasireotide versus time profiles on day 8 suggested that the AUC_{0-2h}, C_{max} and C_{min} increased with the increasing dose. The accumulation ratio of AUC_{0-2h} was 147% for 300 µg three times a day, and 1%–44% for 600 µg three times a day, 900 µg three times a day and 1200 µg three times a day, respectively.

Biomarkers

In patients with observed responses (defined as CR, PR or stable disease), the serum levels of S100B and MIA were sustainably low over the course of the study, whereas in some of the patients who had PD, there was a considerable increase in S100B and MIA serum levels with time. During treatment with pasireotide, there was a decrease in the serum level of growth factors (IGF-1 and IGF-2) and melanoma response biomarkers (MIA and S100B) (figure 1). Furthermore, there was a decrease in IGFBP3 levels (online supplementary figure 3) and an increase in IGFBP2 serum levels with time.

Ki-67, a marker of proliferation, was assessed before and during pasireotide treatment in four patients. Three of the four tumour samples showed decreases in Ki-67 staining following pasireotide treatment (figure 2).

Individual patient response summary

The patient characteristics and response to treatment of those five patients who completed the treatment in the dose-escalation phase will be described in more detail, as they provide the most relevant information of the potential effect of pasireotide on patients with advanced melanoma. Of these five patients who completed the dose-escalation phase, four patients (patient numbers 3, 4, 8 and 9) received high dose of 3600 µg pasireotide,

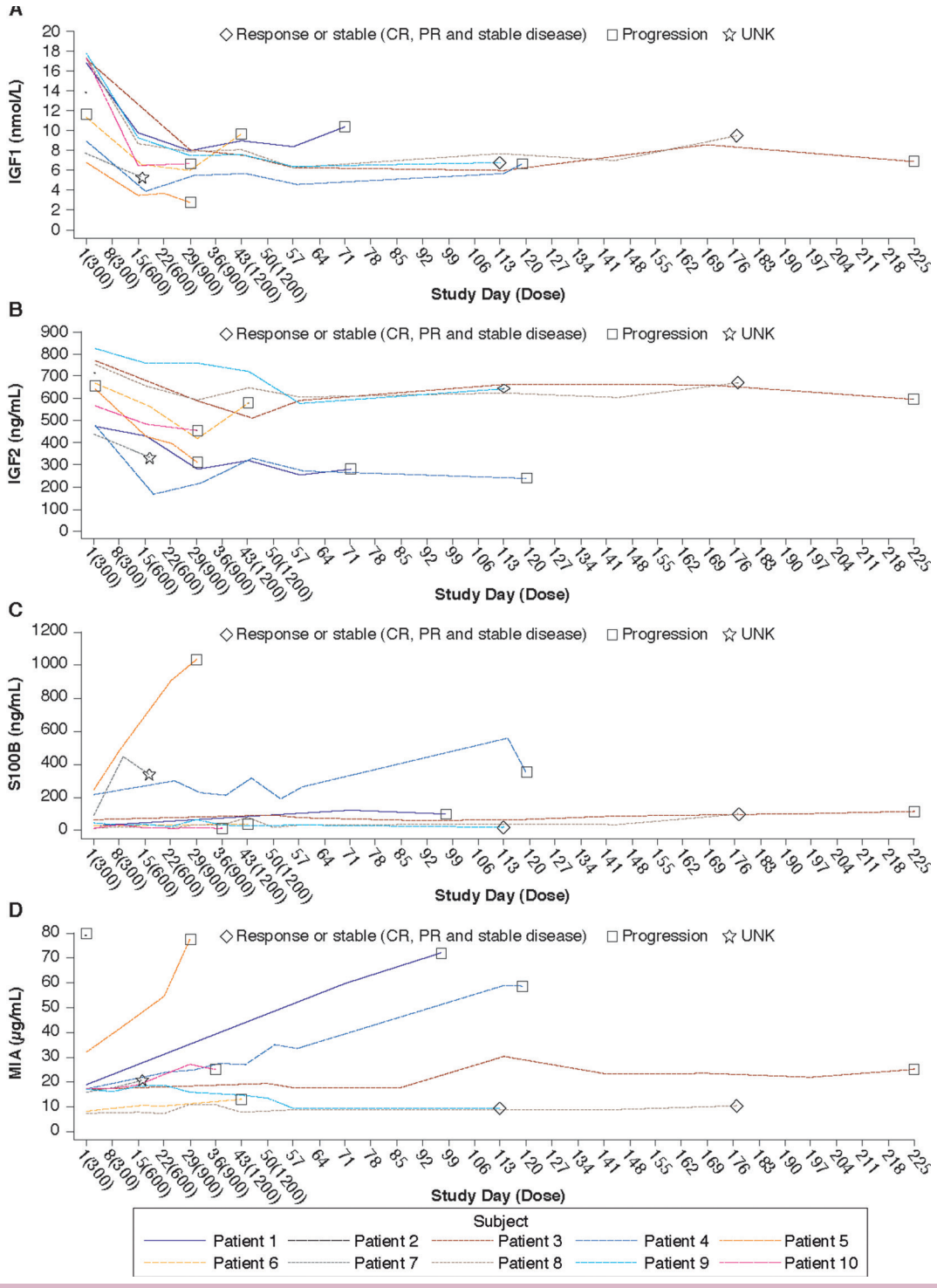

Figure 1 Individual line plots for biomarkers (A) IGF-1, (B) IGF-2, (C) S100B and (D) MIA. *For patient number 2, samples were collected only for these biomarkers on predose day 12, and on day 1, there were no 'on treatment' samples for this patient. CR, complete response; FAS, full analysis set; MIA, melanoma-inhibitory activity; PR, partial response; UNK, unknown.

while the highest dose received by the remaining one patient (patient number 1) was lower with 1800 µg. The treatment time for the remaining patients may not have been long enough and/or the applied dose may not have been high enough in this dose-escalation study to result in significant responses in efficacy.

Patient number 1 was a 64-year-old Caucasian male diagnosed with cutaneous acral-lentiginous melanoma (without *BRAF* and *NRAS* mutation; stage IVa). The presence of three target and three non-target lesions were identified in this patient. This patient did not receive pasireotide treatment as per the dosing schedule

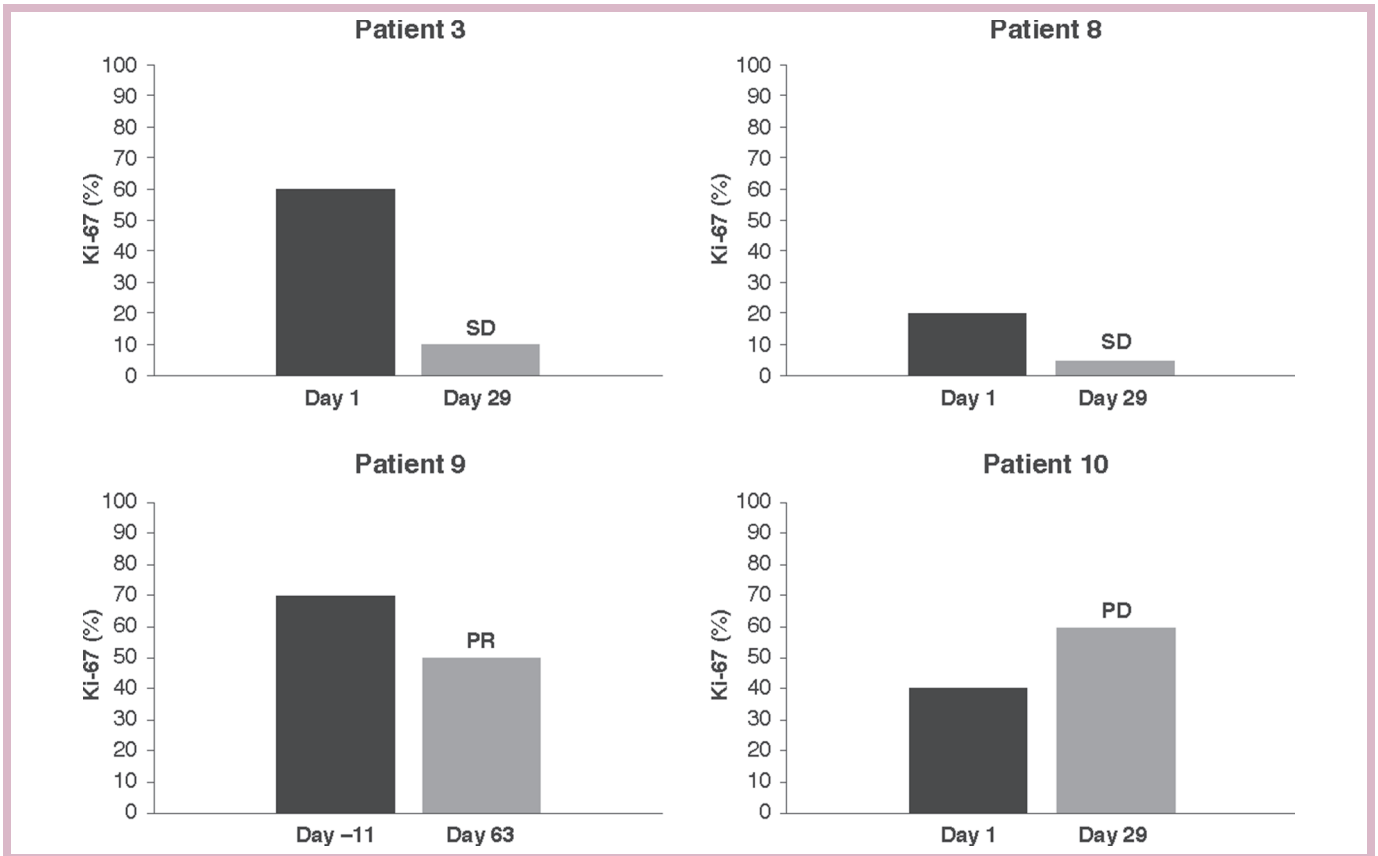

Figure 2 Effect on Ki-67 biomarker levels before and after pasireotide. For those patients with the histological data of Ki-67 before and after treatment, n=4. Individual patient response summary; the responses (PR/stable disease/PD) are based on CT/MRI at specific time points, corresponding to the grey bar. PD, progressive disease; PR, partial response.

mentioned in the study protocol as he did not receive more than 1800 µg and completed four cycles of treatment. The patient received the first dose of pasireotide 300 µg in the dose-escalation phase. The dose was gradually escalated up to 1800 µg as per protocol; the response observed was stable disease in the dose escalation phase. However, due to the occurrence of grade 3 diarrhoea and nausea, study drug was temporarily interrupted for 7 days and then reduced to 900 µg. The patient completed the dose escalation phase and was treated for another 12 days in the follow-up phase. The overall lesion response was considered as PD in the follow-up phase, which led to the permanent discontinuation of this patient from the study.

Patient number 3 was a 63-year-old Caucasian female diagnosed with *BRAF*-WT and *NRAS*-WT stage IVa cutaneous nodular melanoma. The presence of one target lesion and three non-target lesions were identified in the patient. This patient received pasireotide as per the dosing schedule mentioned in the study protocol and completed 10 cycles of treatment with an exception of a dosing error, occurred during the eighth cycle. The results of CT/MRI scans (on days 29, 57, 113, 169 and 225) and 18-FDG-PET (on days 29, 57, 113 and 169) revealed the presence of stable target lesions throughout the study. However, during cycle 3, worsening of the non-target lesion in the lung and the generation of a cutaneous lesion in the left upper thigh occurred, which was considered as PD. During cycle 4, the CT/MRI and FDG/PET scan revealed worsening of the non-target lesion (pulmonal noduli), and the response was considered as PD. The investigator decided not to discontinue the treatment, as the patient was benefitting from treatment. Further evaluations until the end of study revealed stable disease. This patient also showed significantly lower levels of S100B. At the end of the study, the patient was treated with compassionate use of pasireotide without any safety follow-up.

Patient number 4 was a 77-year-old Caucasian male diagnosed with *BRAF*-WT and *NRAS*-WT stage IVc cutaneous melanoma. The presence of five target lesions and two non-target lesions were identified in the patient. The patient received pasireotide as per the dosing schedule mentioned in the study protocol and completed six cycles of treatment. Due to the lack of efficacy, this patient switched to the twice-daily regimen and received a dose of 2400 µg pasireotide but then discontinued due to disease progression. CT/MRI scans and 18-FDG-PET results showed stable disease for target and non-target lesions during cycle 3 (day 30) and PD during cycle 5 (day 58), due to worsening of the non-target lesions. On day 114, CT scan showed worsening of the target lesions, continued worsening of the non-target lesion (left deep lymph node) and two new lesions (at left adrenals and

liver), and the tumour response was assessed as PD. No FDG-PET was performed. This patient showed significant improvement in ascites, which appeared to be an independent effect of the drug that considerably improved his quality of life. However, due to disease progression, he was discontinued from pasireotide treatment and prescribed with paclitaxel in a therapeutic setting (after 7 days of the last study drug dose). After discontinuation, the ascites recurred, and pasireotide was readministered that led to a significant reduction in weight (from 85 kg to 63 kg) and improvement in ascites (from grade 2 to grade 1). This patient also showed significantly increased serum levels of S100B and MIA with respect to time.

Patient number 8 was a 72-year-old Caucasian male diagnosed with *BRAF*-WT and *NRAS*-WT stage IVa cutaneous melanoma and had six target lesions and no non-target lesions. This patient received pasireotide treatment as per the dosing schedule mentioned in the study protocol and completed eight cycles of treatment. During all the evaluations from cycles 1 to 8, the tumour response for this patient was considered as stable disease by CT/MRI (on days 29, 57, 85 and 114) and FDG/PET (on days 29 and 57), and no new lesions were observed. The patient also showed low S100B and MIA serum levels throughout the study. This patient completed treatment and was further enrolled on the rollover study CSOM230B2412.

Patient number 9 was a 67-year-old Caucasian male diagnosed with *BRAF*-WT and *NRAS*-WT stage IV melanoma, identified with the presence of one target lesion and one non-target lesion. The patient received pasireotide as per the dosing schedule of the study protocol and completed eight cycles of treatment. No new target lesions were observed during the tumour assessment. CT/MRI (on days 57 and 114) and FDG/PET scans (on days 29 and 60) assessed the tumour response as PR. This patient also showed low levels of S100B and MIA serum levels during the study. The patient completed treatment and enrolled in the rollover study CSOM230B2412.

DISCUSSION

This is the first study to demonstrate that pasireotide is safe and well tolerated in patients with *BRAF*-WT and *NRAS*-WT melanoma. The safety profile of pasireotide was consistent to that previously reported in other indications with the exception of a lower incidence of hyperglycemia, observed in this patient population.[23–25] A PR and stable disease that were observed in this study comprising a small sample size (n=10) suggest further investigation should be conducted. Of note, patients enrolled in this study had significant disease burden (stage IIIC and IV melanoma) and seven patients discontinued treatment prematurely (five patients discontinued in the dose-escalation phase and two in the treatment follow-up phase). Most of those who discontinued earlier were not treated for long and did not reach high doses. Six of them discontinued due to disease progression (four PDs in the dose-escalation phase and two in the treatment follow-up phase).

MAPK and PI3K pathways are the major signalling pathways in melanoma, which regulate cell growth, proliferation, survival and transformation. These pathways may be activated by the IGF-1 signalling via IGF-1R. Additionally, MAPK pathway may be activated in melanoma directly via activating mutations in the signalling components including *NRAS*, *BRAF*, MEK 1/2 and c-KIT mutations or via mutations in the tumour suppressor genes like *NF-1*. IGFRs are overexpressed in human melanoma cells, and the IGF-1 signalling pathway via IGF-1R is shown to play a key role in melanoma progression.[14 15] Due to the well-established inhibitory effect of pasireotide on GH/and IGF-1, which was also observed for patients with melanoma in the current study, there may be an opportunity for combining pasireotide with other anticancer agents targeting different oncogenic pathways in melanoma. *KIT* inhibitors have shown some efficacy in a subset of patients with *BRAF*-WT and *NRAS*-WT melanoma harbouring *KIT* mutations, particularly those with exon 11 or 13 mutations.[26] However, this therapeutic option will be applicable only to the 10%–22% of patients with *KIT* mutant *BRAF*-WT and *NRAS*-WT melanoma.[4 5]

In the present study, the antisecretory effect of pasireotide was confirmed by decreased serum levels of IGF-1 and IGF-2 and a corresponding decrease in IGFBP3 levels (independent of response). Pasireotide is believed to decrease IGF-1 levels primarily through its ability to decrease GH secretion in the pituitary gland, thereby decreasing the synthesis of IGF-1 in the liver.[27] The observed suppression of IGF-2 levels suggests that pasireotide regulates autocrine/paracrine growth signals in the tumour, since IGF-2 is also known to be secreted by tumours and surrounding cells.[28] IGFBP3 is the major carrier of the IGF ligands and is also responsive to GH. The decrease in IGFBP3 provides additional evidence that pasireotide had an antisecretory effect. IGFBP2 serum level was increased after the treatment with pasireotide, which is supported by similar results observed in patients with acromegaly.[17] Additionally, there was a decrease in the serum level of melanoma response biomarkers (S100B and MIA) in patients who had response (defined as PR, CR and stable disease), whereas patients with disease progression had high S100B and MIA serum levels. These results are supported by the observation that disease progression is directly proportional to the elevated S100B and MIA.[29 30]

Possible limitations of this study include the following: insufficient study drug exposure as patients were dropping out during the dose-escalation phase due to disease progression. Some patients received a lower dose for a shorter period of time and disease progression occurred early. Nevertheless, the patients who continued to the follow-up phase received high doses of pasireotide for more than 5 months and showed stable disease/PR or stable disease in target lesions. Further prospective randomised studies are warranted to evaluate the efficacy

of pasireotide in *BRAF*-WT and *NRAS*-WT melanoma. Pasireotide may also be potentially used in combination with other therapeutic agents in the treatment of patients with *BRAF*-WT and *NRAS*-WT melanoma.

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Competing interests RD has intermittent, project-focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda and Pierre Fabre outside the submitted work. OM has occasional, project-focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, outside of the scope of the submitted work. SG reports grants and other from Novartis, during the conduct of the study; personal fees and other from Intermittent advisory board relationships with Novartis, Roche, MSD and BMS, outside the submitted work. DS reports grants, personal fees and other from Novartis, during the conduct of the study; personal fees from Amgen, GSK, BMS, Roche, Amgen, Merck, Astra Zeneca, Merck-Serono and Pfizer, outside the submitted work. FC reports other from Novartis Pharmaceuticals Corporation, outside the submitted work. UK-K reports personal fees from Novartis Pharma AG, outside the submitted work. HS reports other from Novartis Pharma AG, outside the submitted work. AP reports other from Novartis Pharma AG, outside the submitted work.

Patient consent Not required.

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