



Aviscumine (ME-503)-Skin Reaction as significant Factor for its Efficacy Expanded Evaluation of the Results from the Phase II Trial NCT00658437 in Patients with Unresectable stage IV Metastatic Melanoma

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Received date: January 7, 2017, Accepted date: January 30, 2017, Published date: February 13, 2017

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Abstract

Aviscumine (ME-503), a recombinant lectin, enhances inflammatory cytokine (esp. IL-1 β) release, activation of Langerhans cells, and T-cell responses. An extended evaluation of phase II data of the patient cohorts with/without skin reactions within the first treatment cycle after SC injection regarding the efficacy of avis cumine are presented. 31 patients (ITT total population) (ECOG: 0 or 1) with progressive stage IV malignant melanoma after failure of standard therapy were enrolled onto a single-arm, multi-centre, open-label, phase II trial (NCT00658437). Patients received 350 ng avis cumine twice weekly by SC injection until progression. Tumor response was assessed every eight weeks, survival of patients was followed up to one year after the end of therapy. 21 patients with skin reactions vs. 9 patients without skin reactions as adverse events were assessed for efficacy in an expanded evaluation.

Comparing the median overall survival data (mOS) in patients (n=9) without injection site reactions (mOS: 5.1 months; 95% CI 2.1-6.9; 1-year survival rate: 0%) with survival data in patients (n=21) showing injection site reactions (mOS: 14.6 months; 95% CI 11.0-19.8; 1-year survival rate: 62%) a clear difference in favor of the patients with skin reactions is seen. The difference in overall survival between these two groups of patients was high significant (p<0.0001). In the total ITT population (n=31) the mOS was 11.0 months (95% CI 6.9-19.8) and the 1-year survival rate was 45%.

Preliminary conclusions from our small cohorts suggest a strong clinical impact of avis cumine in patients with previously treated metastatic melanoma if those patients show injection site reactions as adverse events after SC injection within the first treatment cycle. Patients without any injection site reactions apparently failed to prove clinical benefit.

Keywords: Aviscumine; Cancer immunotherapy; CY-503; ME-503; Metastatic malignant melanoma stage IV; Phase II trial; Ribotoxic stress; Skin reaction

Abbreviations: APC: antigen-presenting cell; CTLA4: Cytotoxic T-lymphocyte-associated protein 4; DC: dendritic cell; EGFR: epidermal growth factor receptor; irAEs: immune-related adverse events; PD1: Programmed cell death 1; RIP II: class II ribosome-inactivating protein.

Introduction

Aviscumine (ME-503; formerly CY-503) is a class II ribosome-inactivating protein (RIP II) with immune modulatory properties including activation of natural killer cells, and antigen-presenting cells, induction of T-cell responses, and stimulation of proinflammatory

cytokine release (esp. IL-1 β) [1,2]. After internalisation into the target cell (e.g. monocytes/macrophages, dendritic cells), and subsequent cleavage of the N-glycosidic bond of the adenine-4324 residue in the eukaryotic 28S ribosomal RNA the holoprotein induces catalytic inactivation of the ribosomes and inhibition of protein synthesis („ribotoxic stress“) [3]. The holoprotein induces a priming signal that results in the transcription of pro-IL-1 β and pro-IL-18 in macrophages/monocytes, (immature) dendritic cells, Kupffer cells, keratinocytes, chondrocytes, epithelial cells. IL-1 β release is due to the activity of caspase-1 (interleukin 1 converting enzyme), a scaffolding complex that mediates pro-IL-1 β cleavage to active IL-1 β . This mode of action of avis cumine is characteristic for RIP II [4,5].

Recently we published results from a single-arm, multi-centre, open-label, phase II trial to investigate the efficacy and safety of subcutaneously administered avis cumine monotherapy in 32 patients with unresectable stage IV metastatic melanoma after failure of one or

more previous anti-neoplastic therapies. Interestingly, grade 1 or 2 AE occurred in 72% of patients and were mostly injection site reactions [6]. A similar rate of injection site reactions (grade 1/2) was observed after SC injection of aviscumine in an earlier phase I trial [7].

Skin reactions or skin toxicity as adverse events occurring during drug treatments are not so rare. These are common adverse effects of cetuximab and other EGFR- targeting agents and mainly develop within the first 3 weeks of treatment [8-13].

Furthermore, skin reactions are observed in the context of different immunotherapies. A common site of immune-related adverse events (irAEs) of ipilimumab is the skin. The dermatologic irAEs (44.9% any grade) typically occurring as a maculopapular rash, which can be accompanied by pruritus, pruritus with no skin lesions, alopecia, and vitiligo [14], often manifest earlier in treatment than other irAEs [15]. Moreover, skin reactions after vaccination are frequent adverse events. So all patients experienced grade 2 local skin reactions during immunotherapy with dendritic cells [16]. A multi-epitope peptide vaccine induced skin reactions (grade 1/2) in all treated patients [17].

In this paper we present an extended evaluation of the phase II data regarding the efficacy of the immune modulator aviscumine in the total patient population vs. patient cohorts with/without skin reactions after SC injection. We examine whether induction of an injection site reaction was positively associated with any outcome measure.

Methods

Details regarding the patients, the study design, the study outcomes and the statistical analysis have been published previously [6]. An extended evaluation of the study outcomes in two patient cohorts is replenished with this publication. The study was carried out in compliance with current Good Clinical Practice, Ethics Committee recommendations, informed consent regulations, the Declaration of Helsinki and with the laws and regulations of Germany. Approval was received from the local ethics committee (responsible: Ethik-Kommission der Ärztekammer Hamburg) and from the German health authority before recruitment started. All patients gave their written informed consent.

21 patients with injection site reactions and 9 patients without injection site reactions as adverse events met the eligibility criteria and were included in the efficacy analysis. The survival of patients was followed for up to 12 months.

OS and PFS were estimated by constructing Kaplan-Meier curves. Patients lost to follow-up or not progressed at time of analysis were censored. Median overall survival (mOS) was deduced from the Kaplan-Meier curve. The 1-y survival rates were estimated from the individual survival data of the patients.

Variability estimates are expressed as 95% confidence intervals (CI). Categorical variables are expressed as absolute values and percentages. Survival was estimated with the Kaplan–Meier product limit estimator, and median (95% CI) survival times are reported. OS was calculated from randomization until the occurrence of the pertinent event or last observation. Cox’s regression models were calculated for OS, with adjustment for following subgroups: ECOG performance status (0,1), grade (M1c, visceral), sex (male, female), age (≤ 60 years, >60 years), and number of previous treatments (<2 , ≥ 2). Survival data were compared between both cohorts of patients. Fisher’s exact test was used to calculate two-sided significance values, with $p < 0.05$ deemed significant.

Results

Between April 2008 and May 2009 32 pretreated patients (safety population) with confirmed metastatic malignant melanoma (stage IV) were included in the study

published in 2014 [6]. 21 out of the patients showed injection site reactions grade 1 or 2 (Table 1).

	Grade1	Grade2	Total
Injection site reaction	n (%)	n (%)	n (%)
Application site erythema	3 (9.4)	1 (3.1)	4 (12.5)
Application site pain	1 (3.1)	1 (3.1)	2 (6.3)
Application site pruritus	1 (3.1)	1 (3.1)	2 (6.3)
Application site rash	1 (3.1)	-	1 (3.1)
Application site swelling	1 (3.1)	-	1 (3.1)
Application site reaction*)	10 (31.3)	5 (15.6)	15 (46.9)

Table 1: Drug-related injection site reactions (n=26) Terms are from MedDRA (version 14.0) preferred terms, and grades are Common Toxicity Criteria of the National Cancer Institute (version 3.0). The drug-related injection site reactions occurred in 21 treated patients. No grade 3 or 4 observed*) local reactions, not further defined.

For the expanded evaluation of the efficacy of aviscumine, 30 patients (21 patients with injection site reactions and 9 patients without injection site reactions) met the eligibility criteria and were evaluated. The mean duration of treatment was 104.7 (SD 98.0) days. Patients received a mean of 6.4 (range 1–8) injections per cycle and 26.4 injections (range 1–127) overall. The most frequent reason for discontinuation of therapy was disease progression. The aviscumine-induced injection site reactions started after the first SC injection of the drug in 71.4% (15/21) of patients.

Response	“Non-Skin Reaction” Pts (n=9)	“Skin-Reaction” Pts (n=21)
Best overall*		
Complete	0	0
Partial	0	1 (4.8%)
Stable disease	0	10 (47.6%)
Progressive disease	8 (88.9%)	10 (47.6%)
Not determinable	1 (11.1%)	0
Disease control rate†	0	11 (52.4%)

Table 2: Overall response and disease control rates *, summary from site and central review; †Calculated as (complete response+partial, response+stable disease) / number of patients.

Two out of 21 patients (9.5%) showed injection site reactions after the second and third SC injection, respectively. All injection site reactions appeared in the first cycle and resolved during the continuation of treatment. 10 patients out of 21 patients of the responder group showed stable disease during the trial, one patient

showed partial response. The disease control rate (DCR) was 52.4% (11 of 21 patients) (Table 2). No effect could be detected in all patients (n=9) without any injection site reactions.

Kaplan-Meier analysis of OS was conducted in both cohorts of patients. The observed mOS in the cohort of patients with injection site reactions was 445 days (95% CI 335–604) vs. 155 days (95% CI 65-210) in patients without injection site reactions (Figure 1). The hazard ratio for death was 0.14 (95% CI 0.04-0.58), indicating a strong survival benefit in this trial in favor of the patients showing injection site reactions. OS data and 1-year-survival rates in the cohort of patients with injection site reactions were analysed between patient subgroups (Table 3).

Subgroup	Median OS (months) (95% CI)	1-y-OS (%)	no./total no.
Gender			
Female	14.5 (11.3-15.3)	66.7	12/15
Male	12.4 (8.7-14.6)	55.6	9/15
Performance status			
ECOG 0	14.3 (8.7-15.3)	53.8	13/17
ECOG 1	14.1 (11.0-15.5)	75	8/13
Metastasis stage			
M1c	14.1 (8.9-15.2)	57.1	14/22
Visceral*)	14.3 (11.0-15.3)	61.1	18/26
Age			
≤ 60 yrs	11.3 (8.7-15.5)	33.3	6/8
> 60 yrs	14.3 (10.4-15.3)	73.3	15/22
Pre-treatments			
≤ 1 pretreatment	14.4 (11.3-15.3)	70	10/15
>1 pretreatment	14.3 (8.7-15.3)	54.5	11/15

Table 3: Survival by subgroup in “skin reaction” population

For these analyses, the last observational time-point was used as end date for the overall survival instead of the censored value. OS=overall survival, CI=confidence interval, *) visceral=stage M1b and M1c.

There was no difference in mOS between ECOG 0 and ECOG 1 subgroups (mOS: 14.3 and 14.1 months, respectively) or in patients with different pretreatments (mOS: 14.4 and 14.3 months, respectively). The mOS for patients with visceral disease was 14.3 months compared to 14.0 months for M1c patients. The 1-year overall survival in both subgroups was 61.1% (visceral) and 57.1% (M1c), respectively. As already presented in the previous paper [6] a correlation between anti-aviscumine antibody titers and OS could not be detected (Cox regression analysis for OS: p>0.05).

Discussion

Injection site reactions are common adverse events after SC injection of aviscumine and develop within the first cycle of treatment [6,7]. Of the 31 patients (ITT population) with stage IV malignant

melanoma who received aviscumine 21 patients (68%) had injection site reactions, and this incidence was similar to the previous report of a phase I trial with patients suffering from different solid tumors [7]. The characteristic aviscumine-induced injection site reactions are erythema, pain, pruritus, rash, swelling, reddening, itching, induration at the application sites and generally resolve during the continuation of treatment. All these adverse events were grade 1/2 (as per Common Terminology Criteria for AEs, Version 4.02). Avcumine treatment at a dose of 350 ng resulted in a mOS of 11 months and a 1-year survival rate of 45% in patients with unresectable metastatic malignant stage IV melanoma who had undergone previous treatment [6].

Interestingly, the mOS of patients showing injection site reactions was 14.6 months, and the 1-year survival rate was 62%. In contrast the mOS of patients without injection site reactions was only 5.1 months and the 1-year survival rate was 0%.

Cox regression analysis showed that patients survived significantly longer after they developed injection site reactions (P<0.0001; HR, 0.14; 95% CI, 0.04 to 0.58). That means that aviscumine-induced injection site reactions were associated with an improved survival. Otherwise patients without any injection site reactions apparently failed to prove clinical benefit.

Clinical activity of aviscumine was observed in all subgroups of patients, including patients with stage M1c disease, if injection site reactions occurred within the first treatment cycle. The clinical activity was the same in ECOG 0 and in ECOG 1 patients. The mOS was 14.3 months and 14.1 months, respectively. The 1-year overall survival rate for patients with visceral disease (M1b and M1c) was 61.1% in comparison to 57.1% for M1c patients. These findings are interesting, because performance status is the most important individual-level prognostic variable, followed by presence of visceral disease for stage IV melanoma patients [18]. 18 out of 21 patients (86%) had visceral metastasis, which is associated with poor survival [18,19]. Avcumine was also effective in elderly patients (aged >60 years). The mOS was 14.3 months; the 1-year-survival rate was 54.5%.

52.4% of the patients treated with aviscumine and suffering from injection site reactions within the first treatment cycle met the criteria for a confirmed DCR, whereby most patients had NC. The high rate of NC may be viewed as an indicator of a meaningful therapeutic effect. Disease control due to NC is characteristic for immunotherapeutics and other biologics in cancer [20].

Ipilimumab (3 mg/kg), an anti-CTLA4 antibody, was shown to improve overall survival in patients with unresectable metastatic melanoma (stage III and IV) in two phase III trials. Compared with a peptide vaccine the 1-year survival rate was 45.6%, the mOS was 10.1 months and the DCR was 28.5% [21].

Furthermore, in the context of published clinical experience with comparable patient populations, the 1-year overall survival rate of 62%, a mOS of 16.8 months and a DCR of 38% associated with nivolumab, an anti-PD-1 antibody, are particularly important [22]. In case of another anti-PD-1 antibody, pembrolizumab, the DCR is with 50% (10 mg/kg) or 51% (2 mg/kg) slightly higher [23]. The injection site reactions as drug-related adverse events were immune-related and consistent with the proposed mechanism of action of aviscumine.

The ribotoxic stress induced by aviscumine causes T-cell responses, activation of natural killer cells, and antigen-presenting cells (e.g. monocytes/macrophages, dendritic cells), and stimulation of proinflammatory cytokine release [1,2]. IL-1β is one of the most

relevant cytokines. It is constitutively produced by monocyte-derived DCs and monocytes [24]. Whole epidermal cell suspensions comprised of Langerhans cells, keratinocytes, and melanocytes produce IL-1 [25]. We assume that the injection site reactions may be mainly due to the release of inflammatory stimuli such as IL-1 β .

Ipilimumab-induced dermatologic irAEs (44.9% any grade) typically occurring as a maculopapular rash, which can be accompanied by pruritus, pruritus with no skin lesions, alopecia, and vitiligo [14], often manifest earlier in treatment than other irAEs [15]. The median time to onset of moderate, severe, or life-threatening immune-mediated dermatitis was 3 to 4 weeks and ranged up to 17.3 weeks from initiation of ipilimumab [26]. The rash observed with ipilimumab appears to be similar to maculopapular rashes to commonly used medications (ie, antibiotics, nonsteroidal anti-inflammatory drugs) and atopiform dermatitis [27].

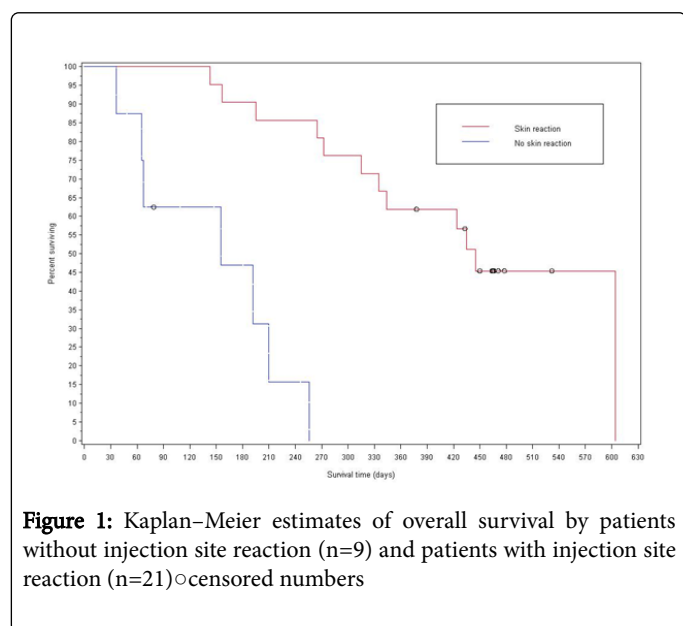


Figure 1: Kaplan–Meier estimates of overall survival by patients without injection site reaction (n=9) and patients with injection site reaction (n=21)○censored numbers

Moreover, all patients experienced grade 2 local skin reactions (irritation, erythema and swelling) at the intradermal injection sites during DC immunotherapy [16]. A multiepitope peptide vaccine induced injection site reaction, pruritus/itching, rash (grade 1/2) in all treated patients [17]. Skin reactions as common adverse effects of cetuximab and other EGFR-targeting agents differ from that observed with aviscumine. EGFR-inhibitors are associated with characteristic papulopustular (acneiform) rash in 68% to 75% of patients, an adverse event believed to be a class effect of these agents [28,29]. The characteristic drug-induced acneiform rash arises during treatment and generally resolves completely in the first weeks following the cessation of therapy. In the BOND study, a positive association between the development of cetuximab-associated skin reactions and clinical activity was demonstrated [8]. Similar associations were subsequently reported in colorectal and other cancers [13,30-33].

First-cycle rash was associated with long survival of patients with advanced NSCLC who received cisplatin and vinorelbine plus cetuximab as a first-line treatment [33]. In locoregionally advanced squamous cell carcinoma of the head and neck cetuximab-treated patients with prominent cetuximab-induced rash (grade 2 or above) have better survival than patients with no or grade 1 rash [32]. Our retrospective analysis leaves open the question of whether the

occurrence of injection site reactions is indicative of a mechanism functionally linking the anticancer activity of aviscumine with the occurrence of injection site reactions or, alternatively, whether aviscumine might coincidentally induce injection site reactions in an otherwise unrecognized subgroup of patients with good prognosis.

Conclusion

The relatively high DCR and relatively long OS in patients with unresectable metastatic melanoma (stage IV) correlated with the appearance of injection site reactions as adverse events after SC injection within the first treatment cycle. The skin reaction seems to be mainly dependent on the release of IL-1 β from APCs in the subcutaneous area. Patients without any skin reactions apparently failed to prove clinical benefit. It is possible that aviscumine-induced injection site reactions occurring during the first treatment cycle are a biomarker of an immunological response that is conducive for optimal outcome. The data here shown strengthen the consideration of a combination with the new immune checkpoint blockers.

Due to relatively small sample size in this study, these findings require validation in a larger patient cohort.

Authors' contributions

HL, KW, PM, RG, UT participated in the study conception and design. PM was the principal investigator. FS, KK, RG, TW, UT were investigators. VJ carried out the independent evaluation of tumor images. HL, KW, UT drafted the manuscript. The approval of the manuscript was done by FS, HL, KK, KW, PM, RG, TW, UT, VJ. All authors approved and read the final manuscript.

Acknowledgement

The authors thank Michael Bulitta and Daniel Schmitz, CRMB, Rheinbach, Germany for data analysis.

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