ORIGINAL ARTICLE

Phase I/II study of vemurafenib in patients with unresectable or recurrent melanoma with BRAF\(^{V600}\) mutations

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ABSTRACT

We investigated the efficacy and safety of vemurafenib in Japanese patients with unresectable or recurrent melanoma with BRAF\(^{V600}\) mutations. This was a two-step open-label multicenter phase I/II study. Step 1 evaluated the initial safety of vemurafenib 960 mg administrated p.o. twice daily in three patients. In step 2, eight patients received vemurafenib 960 mg administrated p.o. twice daily for 28-day treatment cycles; the primary outcome measure was response rate, as determined by independent review committee using Response Evaluation Criteria in Solid Tumors version 1.1. Adverse events (AE) experienced by five or more patients were arthralgia \((n = 10)\), myalgia \((n = 8)\), alopecia \((n = 7)\), and rash, maculopapular rash and decreased appetite \((n = 5\) each). Three patients had grade 3 AE. One serious AE occurred in one patient (abnormal hepatic function). Six patients required dose reduction because of AE. One patient died within 28 days after the last dose, but death was caused by disease progression and not associated with the study drug. In the eight patients in step 2, overall response rate was 75.0%, none had a complete response and six had a partial response (75.0%). Median response duration was 240.0 days, disease control rate 87.5%, median progression-free survival 416.0 days and median overall survival 443.0 days. In conclusion, vemurafenib treatment resulted in an overall response rate of 75% in Japanese patients with metastatic melanoma with BRAF\(^{V600}\) mutations. All toxicities were manageable.

Key words: BRAF, clinical trial, Japanese, melanoma, phase I/II, vemurafenib.

INTRODUCTION

Although melanoma accounts for only 4% of all skin cancers, 80% of the patients who die from skin cancers have melanoma,1 therefore, it is a highly malignant form of carcinoma. The prevalence of melanoma is markedly varied between races. The annual incidence of melanoma per 100 000 general population is estimated to be 15 in white Caucasians, two in Japanese and 0.5 in black Africans or Americans.2 The age-adjusted mortality rate of melanoma per 100 000 is approximately 0.5 in Japan. Melanoma is initially diagnosed in approximately 1500 patients per year and its rate is increasing.3 The differences in the incidence may be attributed to the amount of melanin pigment in skin; white people have less melanin pigment, resulting in a higher incidence of melanoma due to the increased effects of ultraviolet in sunlight compared with colored races.2

Pharmacological treatments for melanoma are determined according to whether there is distant metastasis. Surgical resection of the primary lesion is the first-line treatment in patients who do not have distant metastasis. In patients with distant metastasis or in whom distant metastasis has occurred after resection of the primary lesion, chemotherapy is the standard treatment. In the USA, various drugs have recently been approved for the treatment of melanoma, including ipilimumab (monoclonal antibody drug against CTLA-4), vemurafenib (BRAF inhibitor), and combination of dabrafenib (BRAF inhibitor) and trametinib (mitogen-activated protein kinase kinase [MEK] inhibitor). Compared with these, the drugs currently approved for the treatment of melanoma in Japan are limited; dacarbazine, ipilimumab, and a recently approved monoclonal antibody drug against PD-1, nivolumab. Therefore, there is a need for novel drugs.

Vemurafenib potently and selectively inhibits BRAF\(^{V600}\)-mutated kinase activity, and consequently blocks the downstream signaling of MEK and extracellular signal-regulated kinase (ERK),4–6 exerting potent inhibition of tumor growth. The most common BRAF mutation is the amino acid substitution of valine to glutamic acid at codon 600 (V600E). In tumor cells with BRAF\(^{V600}\) mutation, BRAF is constitutively active even as a monomer and leads to the hyperactivation of the downstream MEK and ERK signaling pathway, causing abnormal cell growth and prolonged survival.

The percentage of BRAF mutations in melanoma is reported to be approximately 40–50% in Europe and the USA,7 while indigenous Japanese have a range of 26.7–41.8%.8,9 In a phase III study involving mainly Caucasian populations, vemurafenib (960 mg,
administered p.o. twice daily) was compared with the standard chemotherapy at the time, dacarbazine (1000 mg/m² per 3 weeks, administered i.v.), in previously untreated patients with unresectable melanoma at stage IIIC or IV with \( \text{BRAF}^{\text{V600}} \) mutation (BRIM-3; ClinicalTrials.gov identifier, NCT01006980). Significantly better progression-free survival (PFS) and overall survival (OS), as well as good tolerability, of vemurafenib compared with dacarbazine have been reported.\(^{11,12}\)

This phase I/II study investigated the efficacy, safety and pharmacokinetic profiles of vemurafenib in Japanese patients with unresectable or recurrent melanoma with \( \text{BRAF}^{\text{V600}} \) mutations.

**METHODS**

**Study design**

This open-label multicenter phase I/II study was performed in two steps. Step 1 evaluated the initial safety of vemurafenib 960 mg (four 240-mg tablets per dose) administered p.o. twice daily to three patients with unresectable or recurrent melanoma with \( \text{BRAF}^{\text{V600}} \) mutation. When the Efficacy and Safety Evaluation Committee decided that there were no issues in the initial safety, the study proceeded to step 2, enrolling eight patients to evaluate the efficacy, safety and tolerability of vemurafenib 960 mg administered p.o. twice daily in the morning and evening for 28-day treatment cycles. Treatment continued until progressive disease (PD), unacceptable toxicity, consent withdrawal or for any reason as deemed by the investigator. Treatment interruption and/or dose reduction was performed according to the types and severity of adverse events (AE).

The study was conducted at three institutions in Japan between September 2012 and August 2013 in accordance with the Declaration of Helsinki, the study protocol, the Pharmaceutical Affairs Law and the Ministerial Ordinance on Good Clinical Practice for Drugs. The study protocol was approved by the institutional review boards of the participating institutions and written informed consent was obtained from each patient. The study was registered with the Japan Pharmaceutical Information Center (JapicCTI-121940) and sponsored by Chugai Pharmaceutical.

**Patient selection**

Eligible patients had histologically or cytologically confirmed unresectable or recurrent melanoma with positive \( \text{BRAF}^{\text{V600}} \) mutations in tissue from the primary tumor or metastasis, as determined by the cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems, Pleasanton, CA, USA) in the central laboratory. This real-time polymerase chain reaction test is used for the qualitative detection of the \( \text{BRAF}^{\text{V600E}} \) mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue. The results were used to help select patients with \( \text{BRAF}^{\text{V600E}} \) mutation-positive melanoma for treatment with vemurafenib. The cobas test is more sensitive than Sanger sequencing in the detection of V600E mutations (detecting V600E mutations in 90% of specimens with <5% mutant alleles), and it detects 70% of V600K mutations.\(^{13}\) The cobas test also detects other V600 variants.

Other inclusion criteria included age of 20 years or more when giving informed consent; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; life expectancy from main enrollment of 3 months or more; measurable disease by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1; adequate organ function including liver, kidney and bone marrow; and written informed consent. Major exclusion criteria were brain metastasis leading to any clinical symptoms or requiring any treatment; New York Heart Association class III or IV heart disease; marked prolongation of QTc interval (QTc interval, \( \geq 450 \text{ msec} \)); poorly controlled diabetes or hypertension; and prior treatment with a BRAF or MEK inhibitor.

**Outcomes and assessments**

In step 1, the primary outcome measure was initial safety (i.e. safety from days 1–28 of cycle 1) as determined by the Efficacy and Safety Evaluation Committee. After the third patient enrolled in step 1 completed cycle 1, the safety of each patient during the initial safety evaluation period was assessed, and it was determined whether to commence step 2. In step 2, the primary outcome measure was the overall response rate as determined by independent review committee using RECIST version 1.1. In steps 1 and 2, preliminary efficacy (i.e. tumor response, duration of response, disease control rate, PFS and overall survival in step 2), safety, pharmacokinetics and dose intensity were also evaluated. Safety was evaluated by assessment of AE, laboratory test values, physical findings, vital signs and electrocardiography. Full sampling for pharmacokinetic assessment was performed before dosing and at 1, 2, 4, 6, 8 and 12 h after dosing on days 1 and 15 of cycle 1 to measure plasma concentration of vemurafenib and pharmacokinetic parameters. The human plasma concentrations of vemurafenib were determined by validated high-performance liquid chromatography tandem mass spectrometry.

Tumor assessments were done by computed tomography or magnetic resonance imaging on day 1 of cycles 2, 3 and 4 and every two cycles thereafter, using RECIST version 1.1. These criteria define a complete response (CR) as the disappearance of all target lesions; any pathological lymph nodes (target or non-target) must be reduced in their short axis to less than 10 mm. A partial response (PR) is defined as a 30% or more decrease in the sum of diameters of the target lesions, taking as reference the baseline sum diameters. PD is a 20% or more increase in the sum of diameters of the target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest on study); in addition to the relative increase of 20%, the sum must also show an absolute increase of 5 mm or more (the appearance of one or more new lesions is also considered progression). Stable disease (SD) is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Adverse events were monitored up to the 28th day after the final dose, and assessed according to the National Cancer Institute Terminology Criteria for Adverse Events version 4.03. The prespecified criteria for temporary suspension, dose
reduction and permanent discontinuation of vemurafenib treatment are summarized in Table S1. For manageable skin tumors such as cutaneous squamous cell carcinoma, it was possible to continue treatment without temporary suspension and dose reduction.

Statistical analysis

In step 1, the target sample size was three patients. The rationale for the sample size was that in step 1 the main aim was to evaluate the initial safety in Japanese patients, and the number of patients was not defined according to statistical rationale. In step 2, the target sample size was eight patients. The rationale for the sample size was that a phase III study in which the efficacy of vemurafenib was compared with that of dacarbazine (BRIM-3; ClinicalTrials.gov identifier, NCT01006980) showed that the response rate of dacarbazine as standard of care was 5.5% (12/220 patients), and therefore the threshold response rate was set to 5%. Based on the fact that the response rate of the drug was 50.1% (176/351 patients) in the combined phase II study (ClinicalTrials.gov Identifier, NCT00949702) and BRIM-3, the expected response rate of the drug was set to 50%. With 80% power at a one-sided significance level of 2.5%, the number of patients with no dropout taken into account was estimated to be eight.

In the efficacy analysis, the response rate that is the primary end-point in step 2 and its 95% confidence interval (CI; Clopper–Pearson method) were calculated for the full analysis set. The response rate was the proportion of responders in the analysis population, responders being defined by RECIST version 1.1 as patients with the best overall response of CR or PR. For the secondary end-points, the disease control rate and its 95% CI (Clopper–Pearson method) were calculated for the full analysis set. The disease control rate was the proportion of patients with controlled disease in the analysis population; patients with controlled disease being defined by RECIST version 1.1 as those with a best overall response of CR, PR or SD. Duration of response, PFS and overall survival were listed for each responder in the analysis population; responders being defined by RECIST version 1.1 as patients with the best overall response of CR or PR. For the secondary end-points, the disease control rate and its 95% CI (Clopper–Pearson method) were calculated for the full analysis set. The disease control rate was the proportion of patients with controlled disease in the analysis population; patients with controlled disease being defined by RECIST version 1.1 as those with a best overall response of CR, PR or SD. Duration of response, PFS and overall survival were listed for each responder in the analysis population; responders being defined by RECIST version 1.1 as patients with the best overall response of CR or PR.

Safety

The safety profile was evaluated in all 11 patients. The mean dose intensity was 78.98%. Dose interruption or reduction was required in nine patients and six patients, respectively, with the most common reason for dose reduction being AE (Table S3).

A total of 144 AE and 127 adverse drug reactions (ADR) occurred among all 11 patients. Table 2 shows AE reported by more than three patients. The AE experienced by five or more patients were arthralgia (10 patients), myalgia (eight patients), alopecia (seven patients), and rash, maculopapular rash and decreased appetite (five patients each). Three patients had grade 3 AE, but there were no patients with grade 4 or 5 AE. The five grade 3 AE that occurred in the three patients are as follows: liver disorder and erythema multiforme in one patient; decreased neutrophil count and decreased white blood cell

RESULTS

Demographic and other baseline characteristics

A total of 24 patients were screened, and 11 patients were enrolled throughout steps 1 and 2. The data cutoff date for this report was June 6, 2014. Table S2 summarizes the baseline characteristics for all 11 patients. Reasons for screening failure were:

Table 1. Baseline demographics and clinical characteristics

| Sex (n [%]) | Step 1 (n = 3) | Step 2 (n = 8) | Total (n = 11) |
|---|---|---|---|
| Male | 2 (66.7) | 1 (12.5) | 3 (27.3) |
| Female | 1 (33.3) | 7 (87.5) | 8 (72.7) |

| Age (years) (n [%]) | Median age | ≥65 years | <65 years | Total |
|---|---|---|---|---|
| Median | 51.0 | 1 (33.3) | 2 (66.7) | 3 (37.5) |
| Mean | 61.57 | 6.901 | 6.415 | 6.713 |

| Weight (kg) Mean (SD) | Median (range) | LDH level at baseline |
|---|---|---|
| Normal (n [%]} | 3 (100) | 5 (62.5) | 8 (72.7) |
| Elevated (n [%]} | 3 (37.5) | 3 (27.3) |
count in one patient; and maculopapular rash in one patient. One serious AE occurred in one patient (abnormal hepatic function). One patient died due to disease progression within 28 days after the last dose of study drug; he was aged in his 30s at the time of registration and he died on the 116th day after the start of vemurafenib treatment. The investigator considered his death to have been caused by worsening of the primary disease that developed metastasis to the brain, and therefore not associated with the study drug. No treatment-related death was reported. Skin disorders such as cutaneous squamous cell carcinoma and keratoacanthoma were not observed.

No patients discontinued vemurafenib treatment due to an AE. Dose reduction due to AE was required in six patients (maculopapular rash in two patients, and erythema multiforme, abnormal hepatic function, liver disorder, arthralgia, myalgia, decreased neutrophil count, decreased white blood cell count, fatigue and muscle spasticity in one patient each).

### Pharmacokinetics

Full pharmacokinetic assessment was conducted in nine patients of a total of 11 patients. After a single dose, there was a rapid increase in plasma concentration, reaching $T_{\text{max}}$ at approximately 4–6 h before disappearing with a half-life of 10–15 h. After repeated dosing, plasma concentration reached $T_{\text{max}}$ at 1–4 h, and then showed biphasic elimination (Table 3). Steady state was reached on day 15 of cycle 1. Inter-individual variability in exposure parameters including $C_{\text{max}}$ and AUC was large at approximately 55% after a single dose, but smaller after repeated dosing.

### Efficacy

Table 4 shows the summary of the efficacy data in step 2 alone, and combined data of steps 1 and 2. In step 2, efficacy was evaluated in all eight patients. Efficacy data for all 11 patients are shown in Table S4. The response rate was 75.0% (95% CI, 34.9–96.8), no patient had a CR (0.0%) and six patients had a PR (75.0%). The lower limit of the 95% CI of the response rate exceeded the 5% threshold response rate, thus demonstrating a clinically significant effect. The median duration of response was 240.0 days (95% CI, 56.0–388.0), disease control rate 87.5% (95% CI, 47.3–99.7), median PFS 416.0 days (95% CI, 84.0–443.0) and median OS 443.0 days (95% CI, 116.0 days–not reached).

In steps 1 and 2, the response rate was 54.5% (95% CI, 23.4–83.3), with no patients having a CR and six patients having a PR; the disease control rate (CR + PR + SD) was 81.8% (95% CI, 48.2–97.7). The median PFS was 303.0 days (95% CI, 84.0–443.0) and median OS was 423.0 days (95% CI, 202.0–not reached). Figure 1 shows the best percent change from baseline in size of target lesions. Figure 2 shows positron emission tomographic (PET) scan images of a representative patient. Peritoneal metastasis observed at baseline had disappeared after 1 year of treatment with vemurafenib.

### DISCUSSION

In this study, the primary end-point was the response rate, as determined by the independent review committee. In step 2, in which eight patients were enrolled, the response rate was 75.0% (95% CI, 34.9–96.8), with the lower limit of 95% CI exceeding the 5% threshold level. Therefore, a clinically significant effect was obtained in Japanese patients with unresectable or recurrent melanoma with BRAFV600 mutation. With the addition of three patients enrolled in step 1, the response rate of the total 11 patients was 54.5% (95% CI, 23.4–83.3); this is comparable to that reported in a global phase III study (NO25028) (48.4%; 95% CI, 41.6–55.2), despite the small sample size in the present study. As of the submission of this report, two of the total 11 patients are still receiving treatment with vemurafenib. Of them, one patient received a PET/computed tomography scan examination (on day 375), which showed no accumulation of fluorine-18-fluorodeoxyglucose in any tumor sites, indicating that the tumor tissues have been necrotized or scarred.

In the present study, the percentages of patients diagnosed as having metastasis M1c and those with serum LDH level higher than the institution standard level at baseline, both of which are known as predictors of poor prognosis, were 82% (data not shown in the Results) and 27%, respectively. Those are consistent with the results reported in the phase III study (66% and 42%, respectively). Median PFS was 416.0 days (95% CI, 84.0–443.0) and median OS 443.0 days (95% CI, 116.0 days–not reached).

### Table 2. Adverse events reported by more than three patients ($n$ [%])

| Event                      | Total | Grade 1 | Grade 2 | Grade 3 |
|----------------------------|-------|---------|---------|---------|
| Arthralgia                 | 10 (90.9) | 9 (81.8) | 1 (9.1) |
| Myalgia                    | 8 (72.7) | 8 (72.7) |         |         |
| Alopecia                   | 7 (63.6) | 7 (63.6) |         |         |
| Rash                       | 5 (45.5) | 3 (27.3) | 2 (18.2) |         |
| Decreased appetite         | 5 (45.5) | 4 (36.4) | 1 (9.1)  |         |
| Maculopapular rash         | 5 (45.5) | 3 (27.3) | 1 (9.1)  | 1 (9.1) |
| Fatigue                    | 4 (36.4) | 2 (18.2) | 2 (18.2) |         |
| Photosensitivity reaction  | 4 (36.4) | 3 (27.3) |         | 1 (9.1) |
| Nasopharyngitis            | 4 (36.4) | 3 (27.3) |         | 1 (9.1) |
| Malaise                    | 4 (36.4) | 4 (36.4) |         |         |
| Erythema                   | 3 (27.3) | 3 (27.3) |         |         |
| Milia                      | 3 (27.3) | 3 (27.3) |         |         |
| Liver disorder             | 3 (27.3) | 1 (8.1)  | 1 (9.1)  | 1 (9.1) |
| Pyrexia                    | 3 (27.3) | 1 (8.1)  | 2 (18.2) |         |
| Headache                   | 3 (27.3) | 1 (9.1)  | 2 (18.2) |         |
| Hyperkeratosis             | 3 (27.3) | 2 (18.2) | 1 (9.1)  |         |
| Nausea                     | 3 (27.3) | 2 (18.2) | 1 (9.1)  |         |
| Vomiting                   | 3 (27.3) | 2 (18.2) | 1 (9.1)  |         |
| Dysgeusia                  | 3 (27.3) | 3 (27.3) |         |         |
| Insomnia                   | 3 (27.3) | 3 (27.3) |         |         |
| Oropharyngeal pain         | 3 (27.3) | 3 (27.3) |         |         |
| Purpura                    | 3 (27.3) | 3 (27.3) |         |         |
Pharmacokinetics were assessed in nine of the total 11 patients. Compared with the pharmacokinetic profiles of Caucasians reported in another clinical trial, the mean plasma concentration of vemurafenib in Japanese was slightly higher. However, the individual exposure to vemurafenib was considered to be almost the same as that of Caucasians.

The safety was evaluated in a total of 11 patients, and all patients experienced AE and ADR. The common AE included arthralgia, myalgia, alopecia, rash, maculopapular rash and decreased appetite. Three patients had grade 3 AE, but there were no patients with grade 4 or 5 AE. These safety profiles were not essentially different from those reported in the global phase III study. In that study, 129 of 336 patients (38.4%) had AE that led to dose reduction or discontinuation of treatment. In contrast, in the present study, no patients discontinued treatment because of AE. Therefore, treatment with vemurafenib appears to be tolerable, with appropriate dose adjustment, in Japanese patients. As clinically significant AE of vemurafenib, skin disorders such as cutaneous squamous cell carcinoma and keratoacanthoma have been noted, which have also been reported in patients treated with dabrafenib and sorafenib. The precise mechanisms of the development of these skin disorders by these BRAF inhibitors are still being investigated, however, some studies have suggested that BRAF inhibitors including vemurafenib may activate the mitogen-activated protein kinase pathway in wild-type BRAF cells, causing abnormal cell growth.

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![Figure 1. Best change in target lesion. *Tumor assessment was not done because of the early withdrawal (cycle 2, day 1). **Patients enrolled in step 1. PD, progressive disease; PR, partial response; SD, stable disease.](image1)

![Figure 2. Positron emission tomographic scans taken at baseline (day -32; left) and after 1 year of vemurafenib treatment (day 375; right) in a patient. A blue arrow shows peritoneal metastases.](image2)

| Table 3. Pharmacokinetic parameters after a single dose (cycle 1, day 1) and a repeat dose (cycle 1, day 15) |
|--------------------------------------------------------|
| n | AUC₀–₈₇ (µg/mL) | Cmax (µg/mL) | t₁/₂ (h) | Tmax (h) |
|---|----------------|-------------|----------|---------|
| Day 1 | 9 | 32.9 (19.1) | 6.40 (3.52) | 12.7 (2.32) | 3.88 (3.83–5.98) |
| Day 15 | 7 | 497 (135) | 73.3 (21.0) | 60.8 (50.1) | 2.12 (0.900–4.02) |

| Table 4. Summary of efficacy data |
|-----------------------------------|
| Step 2 (n = 8) (95% CI) | Steps 1 and 2 (n = 11) (95% CI) |
|---------------------------|-----------------------------------|
| Response rate (%) | 75.0 (34.9–96.8) | 54.5 (23.4–83.3) |
| Responders (n) | 6 | 6 |
| Disease control rate (%) | 87.5 (47.3–99.7) | 81.8 (48.2–97.7) |
| Median time to response (days) | 29.0 (27.0–29.0) | 29.0 (27.0–29.0) |
| Duration of response (days) | 240.0 (56.0–388.0) | 240.0 (56.0–388.0) |
| Median progression-free survival (days) | 416.0 (84.0–443.0) | 303.0 (84.0–443.0) |
| Median overall survival (days) | 443.0 (116.0–NR) | 423.0 (202.0–NR) |

CI, confidence interval; NR, not reached.

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study, differences in culture and lifestyles, resulting in varying length of exposure to sunlight, as well as medical environments may have contributed. The accurate incidence of these skin disorders in Japanese needs to be identified in future clinical studies. In patients who had cutaneous squamous cell carcinoma or keratoacanthoma in the global study, discontinuation or dose reduction of vemurafenib was considered unnecessary, and was successfully managed by surgical resection of the lesions.\textsuperscript{11} Therefore, in case Japanese patients had similar conditions, early diagnosis and surgical resection of lesions should be useful.

The present study enrolled patients based on the presence of 
\(BRAF^{V600E}\) mutation, however, variants of 
\(BRAF^{V600K}\) were not investigated. In addition to 
\(BRAF^{V600E}\), vemurafenib has been reported to be effective for 
\(BRAF^{V600E}\) and non-\(V600K/E\).\textsuperscript{22}

Although there was a small number of patients enrolled in the present study, vemurafenib 960 mg administered twice daily was shown to provide drug exposure in Japanese patients with metastatic melanoma with 
\(BRAF^{V600}\) mutation similar to that in Caucasians, and was well tolerated and exerted a clinically meaningful efficacy.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Criteria for temporary suspension, dose reduction and permanent discontinuation of vemurafenib treatment

Table S2. Baseline characteristics of all patients (\(n = 11\))

Table S3. Data on all serious adverse events (AE), AE leading to dose reduction and grade 3, 4 and 5 AE in all 11 patients

Table S4. Efficacy data for all patients (\(n = 11\))