First-line temozolomide combined with bevacizumab in metastatic melanoma: a multicentre phase II trial (SAKK 50/07)

von Moos, R; Seifert, B; Simcock, M; Goldinger, S M; Gillessen, S; Ochsenbein, A; Michielin, O; Cathomas, R; Schläppi, M; Moch, H; Schraml, P H; Mjhic-Probst, D; Mamot, C; Schönewolf, N; Dummer, R
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Abstract

BACKGROUND: Oral temozolomide has shown similar efficacy to dacarbazine in phase III trials with median progression-free survival (PFS) of 2.1 months. Bevacizumab has an inhibitory effect on the proliferation of melanoma and sprouting endothelial cells. We evaluated the addition of bevacizumab to temozolomide to improve efficacy in stage IV melanoma. PATIENTS AND METHODS: Previously untreated metastatic melanoma patients with Eastern Cooperative Oncology Group performance status of two or more were treated with temozolomide 150 mg/m(2) days 1-7 orally and bevacizumab 10 mg/kg body weight i.v. day 1 every 2 weeks until disease progression or unacceptable toxicity. The primary end point was disease stabilisation rate [complete response (CR), partial response (PR) or stable disease (SD)] at week 12 (DSR12); secondary end points were best overall response, PFS, overall survival (OS) and adverse events. RESULTS: Sixty-two patients (median age 59 years) enrolled at nine Swiss centres. DSR12 was 52% (PR: 10 patients and SD: 22 patients). Confirmed overall response rate was 16.1% (CR: 1 patient and PR: 9 patients). Median PFS and OS were 4.2 and 9.6 months. OS (12.0 versus 9.2 months; P = 0.014) was higher in BRAF V600E wild-type patients. CONCLUSIONS: The primary end point was surpassed showing promising activity of this bevacizumab/temozolomide combination with a favourable toxicity profile. Response and OS were significantly higher in BRAF wild-type patients.
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<td>Complete List of Authors:</td>
<td>von Moos, Roger; Kantonsspital Graueünden, Department of Medicine Oncology Seifert, Burkhardt; University Hospital Basel, Oncology Simcock, Mathew; Swiss Group for Clinical Cancer Research, Statistics Goldinger, Simone; University Hospital Zurich, Oncology Gillessen, Silke; Kantonsspital, St. Gallen CH Ochsenbein, Adrian; University of Berne, Department of Clinical Research Michielin, Olivier; CHUV, Oncology Cathomas, Richard; Kantonsspital Graubünden, Medical Oncology Schlæppi, Marc; Kantonsspital St.Gallen, Oncology / Hematology Moch, Holger; University Hospital of Zurich, Institute of Surgical Pathology, Department of Pathology Hans Schraml, Peter; University Hospital Zurich, Oncology Mihic-Probst, Daniela; University Hospital Zurich, Institute of Surgical Pathology, Department of Pathology Mamot, Christoph; Kantonsspital Aarau, Oncology Schönewolf, Nicola; University Hospital of Zürich, Department of Dermatology Dummer, Reinhard; University Hospital of Zurich, Department of Dermatology</td>
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dacarbazine in phase III trials with median progression free survival (PFS) of 2.1 months. Bevacizumab has an inhibitory effect on the proliferation of melanoma and sprouting endothelial cells. We evaluated the addition of bevacizumab to temozolomide to improve efficacy in stage IV melanoma.

Patients and Methods: Previously untreated metastatic melanoma patients with ECOG performance status ≤2 were treated with temozolomide 150mg/m2 days 1-7 orally and bevacizumab 10mg/kg body weight IV day 1 every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was disease stabilisation rate (CR, PR or SD) at week 12 (DSR12); secondary endpoints were best overall response, PFS, overall survival (OS) and adverse events.

Results: Sixty-two patients (median age 59 years) enrolled at 9 Swiss centres. DSR12 was 52% (PR: 10 patients, SD: 22 patients). Confirmed overall response rate was 16.1% (CR: 1 patient, PR: 9 patients). Median PFS and OS was 4.2 and 9.6 months. OS (12.0 vs. 9.2 months; p=0.014) was higher in BRAF V600E wild-type patients.

Conclusion: The primary endpoint was surpassed showing promising activity of this Bevacizumab/temozolomide combination with a favourable toxicity profile. Response and OS were significantly higher in BRAF wild-type patients.
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A multicentre phase II trial (SAKK 50/07)


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Running Title: First line temozolomide and bevacizumab in metastatic melanoma

Key Words: metastatic melanoma, antiangiogenic therapy, bevacizumab, temozolomide, first line treatment

Trial Registration: This trial is registered with ClinicalTrials.gov with the identifier NCT00568048.

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R. Dummer: Had consultancy of advisory role and research funding at Astrazenica and Novartis.
R. Cathomas: Consultancy/advisory role at Sonofie Aventis
A. Ochsenbein: Consultancy/advisory role at Roche and Essex

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Abstract (200 words of 200 maximum)
ABSTRACT

Background: Oral temozolomide has shown similar efficacy to dacarbazine in phase III trials with median progression free survival (PFS) of 2.1 months. Bevacizumab has an inhibitory effect on the proliferation of melanoma and sprouting endothelial cells. We evaluated the addition of bevacizumab to temozolomide to improve efficacy in stage IV melanoma.

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Conclusion: The primary endpoint was surpassed showing promising activity of this Bevacizumab/temozolomide combination with a favourable toxicity profile. Response and OS were significantly higher in BRAF wild-type patients.
INTRODUCTION

Cutaneous melanoma today is considered a genetically heterogeneous disease characterised by a wide variation of genetic alterations, including the most frequent mutation in the BRAF gene [1]. This has resulted in molecular definition of melanoma subtypes [2]. Chemotherapy for metastatic melanoma remains disappointing. The median survival time is 6-9 months, depending on the bulk and location of disease at the time of tumour recurrence, and has not improved significantly in the last few decades with the currently available chemotherapy regimens. Dacarbazine, the generally accepted standard, has response rates in phase III trials of 9.8-12% [3,4]. Temozolomide is at least as effective in conventional dosing as it can cross the blood brain barrier and can be given orally [3]. Two phase II trials that combined extended dose temozolomide with thalidomide or with pegylated interferon α2b showed response rates of approximately 30% [5,6]. In analogy to the EORTC 18032 study [4] we decided to use the extended dosing temozolomide of 150 mg/m² day 1-7 every 14 days.

Bevacizumab is a monoclonal antibody against vascular endothelial cell growth factor (VEGF), that has shown significant survival advantage when combined with chemotherapy in advanced colorectal and non-small cell lung cancer [7,8]. A significant advantage in progression-free survival (PFS) was attained in advanced breast [9] and non-small cell lung cancer [10] when administering bevacizumab in combination with chemotherapy and in renal cell cancer when combined with interferon [11,12]. Bevacizumab recognizes all isoforms of VEGF but does not recognise other peptide growth factors tested (fibroblast growth factor, epidermal growth factor, hepatocyte growth factor, platelet-derived growth factor and nerve growth factor). It may exert a direct anti-angiogenic effect by binding and clearing
VEGF from the tumour environment. Additional anti-tumour activity may be obtained via the effects of bevacizumab on tumour vasculature, interstitial pressure and blood vessel permeability that can lead to enhanced chemotherapy delivery to tumour cells. VEGF receptors were found in melanocytes as well as in malignant melanoma cells and the surrounding stromal cells [13]. It could be shown in several melanoma cell lines that treatment with Dacarbazine can cause higher secretion of IL8 and VEGF. Metastatic cell lines secreting high levels of IL8 and VEGF were more resistant to Dacarbazine treatment [14]. Exogenously added VEGF (10 ng/ml) was able to stimulate up to 40% increased proliferation of A375 melanoma cells following a 48 hour period of quiescence, suggesting that VEGF indeed plays a role in autocrine, as well as paracrine stimulation of melanoma growth [15]. It was shown in human melanoma xenografts that anti-VEGF therapy inhibits melanoma growth [16]. However, tumour cells appear to express endothelial markers that do not respond to normal angiogenic control. In a recently published study it was shown that VEGF-A driven autocrine loop promotes human melanoma cell ability to invade the extracellular matrix, which strongly supports the hypothesis that activation of VEGFR-2 plays a primary role in this process [17]. Immunohistochemical studies have found that expression of VEGF in melanoma metastases is higher than in primary tumours and increased serum concentrations of VEGF have been found to correlate with tumour progression and survival [18]. A case series [19] as well as a few phase II studies of bevacizumab in combination with different non standard chemotherapy (nab-paclitaxel, paclitaxel as single agent or in combination with carboplatin) have been published so far [20-23]. One trial has combined bevacizumab with interferon α2b, another study tested the combination with everolimus [24,25]. The results of these trials are encouraging and warrant further evaluation of combination therapy of bevacizumab with other agents.
Considering all the points mentioned and in view of the fact that the combination of VEGF antibodies and standard chemotherapy can improve time to progression (TTP) and overall survival (OS) in different tumour entities, it appeared to us a logical step to investigate the combination of chemotherapy and bevacizumab in melanoma patients as well. Because temozolomide is a standard chemotherapy regime in metastatic melanoma, has a favorable side effect profile and non-overlapping toxicity with bevacizumab, we decided to test this combination in our trial. Especially, we were interested to evaluate the efficacy of this therapeutic approach in patients with BRAF positive compared to BRAF negative metastatic melanoma.

PATIENTS AND METHODS

Adult patients who had histologically confirmed stage IV metastatic melanoma; had measurable disease according to RECIST; had ECOG performance status of 2 or less; had haemoglobin ≥ 90 g/l (may be transfused to maintain or exceed this level), neutrophils ≥ 1.5 x 10⁹/l, platelets ≥ 100 x 10⁹/l, bilirubin ≤ 1.5 x ULN, ALAT and AP ≤ 2.5 x ULN (≤ 5 x ULN acceptable in patients with liver metastases), serum creatinine < 177 µmol/l and had not received prior systemic chemotherapy were included. Prior cytokine or vaccine adjuvant therapy was allowed if it was completed more than 4 weeks prior to trial registration. Prior vaccine therapy for stage IV as well as therapy of locoregional disease with perfusional therapy (limb and liver) was allowed as well. The main exclusion criteria were: patients with ocular melanoma, brain metastases [magnetic resonance imaging (MRI) mandatory], uncontrolled hypertension, use of full-dose oral or parenteral anticoagulants, thrombolytic agents or use of aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day). Major surgery within 30 days or minor surgery within 24 hours prior to registration, serious non-healing wound, active peptic ulcer, non-healing bone fracture or bleeding skin metastases were also considered.
as exclusion criteria. Patients with history of abdominal disease such as fistula, gastrointestinal perforation or intra-abdominal abscess, not able to swallow tablets, receiving a treatment in a clinical trial within 30 days prior to registration, receiving concurrent treatment with other experimental drugs or other anti-cancer therapy, who had previous therapy with bevacizumab or other angiogenic inhibitors were not allowed to enter the trial. Pregnant or lactating women were excluded. The trial was approved by the local ethics review boards as well as by Swissmedic and was registered at the National Institute of Health (www.clinicaltrial.gov; identifier number: NCT00568048). All patients gave informed consent prior to any trial procedure.

BRAF MUTATION STATUS – PCR-BASED METHOD

In order to determine the mutation status for the amino acid exchange at position V600E of exon 15 of the BRAF gene, quantitative real-time PCR was performed by means of Taqman 7900HT Fast Real-Time PCR Systems (Applied Biosystems) subsequent to DNA-extraction from paraffin-embedded melanoma-tissue [26]. The exact method has been described elsewhere and has been used in a variety of tumour types [27].

TREATMENT

Participating patients received a two drug regimen containing temozolomide 150 mg/m² on days 1-7 every 14 days orally and bevacizumab 10 mg/kg body weight intravenous over 90 minutes for the first infusion, 60 minutes for the second and 30 minutes for the third and subsequent infusions every 14 days. In case of grade 3 hematological toxicity two dose reduction for temozolomide was requested (dose -1: 112.5 mg/m², dose -2: 75 mg/m²). Therapy was given until progression, unacceptable toxicity or intolerability of either of the drugs. Prophylactic antiemetic treatment with a
5-HT3-antagonist was administered before temozolomide on day 1. From day 2, prophylaxis was replaced by metoclopramide 10 mg or domperidone 10 mg. Because continued administration of temozolomide has been associated with severe lymphocytopenia with increased risk for opportunistic infections, in particular pneumocystis jirovecii pneumonia, prophylaxis with trimethoprim-sulfamethoxazole was recommended.

**CLINICAL ASSESSMENT**

Screening assessments included full physical examination and medical history, MRI of the brain, computed tomography (CT) as indicated for tumour assessment, hematology, chemistry testing and urinalysis. Physical examination, updates of the medical history, haematology (haemoglobin, neutrophils, platelets) and urine analysis were performed before each cycle. Tumour response was assessed by investigators according to the RECIST criteria 1.0 at the end of every 3 cycles (i.e., every 6 weeks). Investigators were required to document all sites of disease at baseline. The longest diameter measurement of all lesions large enough to be reliably detected at baseline was summed at each tumour evaluation (i.e., sum of the longest diameters [SLD]). The first two tumour assessments after trial registration were reviewed by an independent, blinded, radiologist. The first documented partial response (PR) and complete response (CR) were confirmed by the next assessment six weeks later. Adverse events (AE) were graded according to National Cancer Institute’s Common Terminology Criteria of Adverse Events (CTCAE), version 3.0.

**STATISTICAL DESIGN AND ANALYSIS**

This single arm open label multicentre phase II trial used the Simon’s optimal two-stage design with the primary endpoint being disease stabilisation rate at 12 weeks
(DRS12) after trial registration. The trial therapy would be considered promising if the proportion of patients with disease stabilisation [CR, PR or stable disease (SD)] was 35% or more and uninteresting if 20% or less. Allowing for one interim analysis with 80% power and a 5% significance level, the total sample size was 62 patients. This translates into the trial therapy being considered promising if, during the final analysis, 18 or more patients experience disease stabilisation at week 12.

AEs were summarised by event type and grade over the total number of patients (worst recorded AE grade per patient).

For secondary endpoints three time-to-event analyses were performed: PFS, duration of response stabilisation (RD) and OS. PFS was defined as the time from trial registration until either a disease progression or death with patients censored at the time of starting a second line therapy or the last time they were known to be alive without progression. RD included only patients with disease stabilisation (CR, PR or SD) and was read as the time from disease stabilisation until disease progression or death; patients were censored at the last time they were known to be alive and without disease progression if no event was observed. All time-to-event analyses were carried out using the intention-to-treat principle and estimated with the Kaplan-Meier method.

Other secondary endpoints included best overall response and confirmed response as well as the effect the BRAF mutation had on the primary and secondary endpoints. Between-group comparisons were carried out using the chi-squared test for categorical/binary endpoints and the log-rank test for time-to-event endpoints.

The data was analysed in SAS (Statistical Analysis Systems, version 9.2).
RESULTS

Between January 2008 and April 2009, 62 patients (40 male, 22 female) were enrolled. None of the patients were found ineligible or withdrew participation before the start of treatment. The median age at enrolment was 59 years (range: 29 - 82) and the median follow-up time was 20.1 (range: 1.7 – 32.0) months. All patients underwent at least one cycle of therapy. Further characteristics of these patients are presented in Table 1.

Disease stabilisation rate at 12 weeks

The unreviewed clinical DSR12 according to the investigators was 58% including 1 patient with a CR, 11 patients with a PR and 24 patients with SD. The independently reviewed DSR12 was 52% (10 PR, 22 SD).

Overall best response

The independently reviewed and confirmed objective response rate was 16.1% with 1 patient with CR and 9 patients with PR. Patients with elevated LDH (28 patients) did not have a higher response rate than patients with LDH within normal range (33 patients) (6.6% versus 9.8%, p value: 0.4899). No correlation between experiencing hypertension and response rate could be seen. At the end of the observation period 1 out of 32 patients with reviewed disease stabilisation at 12 weeks had not experienced progression and was censored. Median RD was 6.1 months [95% confidence interval (CI): 5.3, 8.1]. Maximum percentage change in the SLD from trial registration is depicted by a waterfall plot: Figure 1.

Progression free - and overall survival

Median PFS was 4.2 months (95% CI: 2.7, 5.4) (Figure 2) and median RD was 4.4
months (95% CI: 4.1, 5.7). At 6 months 33% (95% CI: 21.7, 44.8) of the patients survived without experiencing disease progression. The 6 months survival probability was 77.4% (95% CI: 64.9, 86.0) and the median OS was 9.6 months (95% CI: 8.0, 11.9) (Figure 2). Non-statistically significant differences in median OS was observed when stratified by LDH level: normal 11.5 months (95% CI: 8.3, 13.6) vs. elevated 8.8 months (95% CI: 6.5, 11.8); p = 0.1746 (Figure 3).

Toxicity
The toxicity analysis was based on all treated patients (n = 62). The majority of observed AEs were mild to moderate (i.e., grades 1 or 2) in severity. Thirty-two percent of all patients experienced a serious adverse event during the trial. The most common haematological grade 3 and 4 AEs were thrombocytopenia (6 patients, 9.7%) and neutropenia (4 patients, 6.5%). Non-haematological AEs grade 3 were hypertension (7 patients, 11.3%), fatigue (5 patients, 8.1%), haemorrhage (3 patients, 4.8%), nausea (3 patients, 4.8%) and vomiting (2 patients, 3.2%). Other toxicities were rare (Table 2). Of the 56 patients who died since study entry, 51 deaths were attributed to disease progression, one was the patient decision, two are unknown and two deaths were attributed to the trial drugs, one patient died with extensive abdominal tumour burden and bowel perforation, another patient died with pulmonary infection without leuco- or lymphopenia.

BRAF analysis
Of the 44 BRAF status results available for analysis; 22 patients had the BRAF V600E mutation and 22 were BRAF wild-type. Based on the independent response review, a statistically significant association was found between BRAF status and the unconfirmed 12 weeks response favouring a response in the wild-type group; p =
Median PFS time in the mutated group was 4.0 months (95% CI: 1.7, 5.4) vs. 5.4 months (95% CI: 2.6, 8.2) in the wild-type group; p = 0.0556. Median duration of disease stabilisation was 4.2 (95% CI: 3.0, 5.5) vs. 4.1 (95% CI: 2.7, 6.9) months between the mutated (n = 15) and wild-type (n = 17) groups respectively; p = 0.7292. A statistically significant difference was found between the groups regarding OS; median OS being 9.2 months (95% CI: 6.5, 11.9) in the mutated group compared with 12.0 months (95% CI: 7.4, 16.4) in the wild-type group (p = 0.0137) (Figure 4).

Other prognostic biomarkers for metastatic melanoma such as LDH, performance status and age did not differ significantly between the BRAF mutated versus BRAF wild-type groups. Due to low numbers, no multivariable analyses are performed regarding BRAF status.
DISCUSSION

No significant advances in the treatment of metastatic melanoma have been achieved in the last three decades. Despite several promising results in phase II trials, all phase III trials have reported negative results.

This multicentre single arm phase II trial surpassed its primary endpoint of 18 or more patients with a DSR12 with an impressive 32/62 patients having confirmed, reviewed disease stabilisation as defined in our trial. Our response rate of 16.1% is in the same range as reported for single agent temozolomide conventional [3] (13.5%) and extended dosing schedule [4] (14.5%), despite having studied a population at higher risk by including patients with LDH > 2 ULN (16%) and/or ECOG performance status of 2: (7%). The median PFS of 4.2 months compares favourably with the PFS seen in single agent temozolomide trials (1.9 - 2.3 months). The median OS of temozolomide+bevacizumab was in the range of single agent temozolomide (9.6 months versus 7.7 - 9.1 months) [3,4]. The extent of response rate as well as PFS is comparable to other trials that have added bevacizumab to conventional chemotherapy in melanoma patients [22,23]. In the only randomised phase II trial of its kind, carboplatin and paclitaxel (CPP) showed a PFS of 4.2 months versus 5.6 months (p = 0.14) when adding bevacizumab (CPB) [22]. In another single arm phase II trial with CPB dosing paclitaxel weekly the PFS was in the same range (6.5 months) [23]. Even though the absolute numbers of PFS are slightly higher in the combination chemotherapy backbone with CPB, the extent of improvement with bevacizumab when combined with temozolomide seems to be higher compared to other chemotherapy backbone. In addition, the side effects of single agent oral temozolomide are lower and seem to be better tolerable for the patients. In contrast to most melanoma trials our patients with elevated LDH showed higher response
rates and a statistically equal OS to the group with normal LDH value. This raises the hypothesis whether patients at high risk with rapidly progressive disease may particularly profit more from the addition of bevacizumab, which is in line with the results of the BEAM trial [22].

Patients with a BRAF wild-type had better progression free- (borderline significance), overall- survival and response rate than patients with BRAF mutation. It remains to be determined whether this mutation is only a prognostic or also a predictive biomarker. Since there are new promising targeted therapies for BRAF mutant patients such as PLX4032 in phase III trials it appears appealing to re-evaluate these findings in BRAF wild-type patients.

The treatment was generally well tolerated. The incidence of serious adverse events in our trial was 32%, which is comparable to the 30% observed in single agent temozolomide [4]. Bevacizumab specific side effects were in the range known from other trials; no new or unexpected toxicities occurred. The good tolerability is of utmost importance in a disease where survival is mostly short and the quality of life of the remaining weeks is crucial for the patients.

In summary, the results of our trial suggest that the combination of an alkylating agent such as temozolomide with an agent that specifically targets VEGF might be a valid and interesting therapeutic strategy for patients with metastatic melanoma. A phase III trial stratifying for LDH level as well as for BRAF status is urgently warranted in a disease where no satisfactory first line treatment exists.
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REFERENCES


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### Table 1: Patient baseline characteristics

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<td>19 (30.7)</td>
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<tr>
<td>Wild-type</td>
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Table 2: Adverse events (worst grade observed per patient)

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<td>Pulmonary infection without leuco- or lymphopenia</td>
<td>-</td>
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<td>Thrombosis/thrombus/embolism</td>
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<td>Trismus</td>
<td>1 (2)</td>
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<tr>
<td>Vomiting</td>
<td>2 (3)</td>
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Only grade 3 and 4 adverse events shown
CTCAE: Common terminology criteria for adverse events (version 3.0).
**Figure 1:** Waterfall plot of maximal percentage change in sum of longest diameter of target tumour lesion(s) size from baseline

**Figure 2:** Kaplan-Meier plot of progression free survival and overall survival

**Figure 3:** Kaplan-Meier plot of overall survival stratified by normal LDH and elevated LDH

**Figure 4:** Kaplan-Meier plot of overall survival stratified by BRAF wild-type and BRAF mutation
Waterfall plot of maximal percentage change in sum of longest diameter of target tumour lesion(s) size from baseline

260x204mm (100 x 100 DPI)
Kaplan-Meier plot of progression free survival and overall survival

Patients at Risk:
PFS 62 38 20 8 3 1 0 0 0 0 0
OS 62 60 48 35 22 11 5 2 1 1 1 0

Kaplan-Meier plot of progression free survival and overall survival
260x214mm (100 x 100 DPI)
Kaplan-Meier plot of overall survival stratified by normal LDH and elevated LDH

- Log rank test p value: 0.1746
  - — = LDH normal
  - --- = LDH elevated

Patients at risk: (stratified by LDH indication)

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<th>Elevated</th>
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Kaplan-Meier plot of overall survival stratified by normal LDH and elevated LDH
260x214mm (100 x 100 DPI)
Kaplan-Meier plot of overall survival stratified by BRAF wild-type and BRAF mutation

Log rank test p value: 0.0137

- - - = BRAF Wild type
--- = BRAF mutation

Time from registration (months)

Proportion remaining alive

Patients at risk (stratified by BRAF indication)

Mutated  22  21  17  12  5  1  0  0  0  0  0  0
Wild type 22  22  19  14  11  6  4  2  1  1  1  0

Kaplan-Meier plot of overall survival stratified by BRAF wild-type and BRAF mutation

260x214mm (100 x 100 DPI)
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Dr. mad. S. Goldinger
Staatsklinikum USZ
Salzburger Str 142 862

Turin, 21 DEC 2009
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Date: 1/4/2010
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Leiter der Klinik
Medizinische Klinik I
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\[ \text{Leitender Arzt Onkologie} \]
\[ \text{Loètzbstrasse 770, CH-7000 Chur} \]
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Name of entity: ____________________________

Title or role held: __________________________

Select one: ☐ Employment ☐ Leadership

Select one: ☐ Myself ☐ Immediate Family Member

Select one: ☐ Compensated ☐ Uncompensated

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Kantonsspital Graubünden
Dr. med. Richard Cathomas
Leitender Arzt Onkologie
Loëstrasse 170, CH-7000 Chur.
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S. Salen, 22.12.09
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