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Phase I study of nelfinavir in liposarcoma

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Abstract

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Conflict of interest None.

Purpose—HIV protease inhibitors are associated with HIV protease inhibitor–related lipodystrophy syndrome. We hypothesized that liposarcomas would be similarly susceptible to the apoptotic effects of an HIV protease inhibitor, nelfinavir.

Methods—We conducted a phase I trial of nelfinavir for liposarcomas. There was no limit to prior chemotherapy. The starting dose was 1,250 mg twice daily (Level 1). Doses were escalated in cohorts of three to a maximally evaluated dose of 4,250 mg (Level 5). One cycle was 28 days. Steady-state pharmacokinetics (PKs) for nelfinavir and its primary active metabolite, M8, were determined at Levels 4 (3,000 mg) and 5.

Results—Twenty subjects (13 males) were enrolled. Median (range) age was 64 years (37–81). One subject at Level 1 experienced reversible, grade 3 pancreatitis after 1 week and was replaced. No other dose-limiting toxicities were observed. Median (range) number of cycles was 3 (0.6–13.5). Overall best responses observed were 1 partial response, 1 minor response, 4 stable disease, and 13 progressive disease. Mean peak plasma levels and AUCs for nelfinavir were higher at Level 4 (7.3 mg/L; 60.9 mg/L × h) than 5 (6.3 mg/L; 37.7 mg/L × h). The mean ratio of M8:nelfinavir AUCs for both levels was ~1:3.

Conclusions—PKs demonstrate auto-induction of nelfinavir clearance at the doses studied, although the mechanism remains unclear. Peak plasma concentrations were within range where anticancer activity was demonstrated in vitro. M8 metabolite is present at ~1/3 the level of nelfinavir and may also contribute to the anticancer activity observed.

Keywords

Nelfinavir; Phase I; Liposarcoma; Pharmacokinetics

Introduction

Liposarcomas are the most common adult soft-tissue sarcoma. Despite its common preadipocyte or adipocyte origin, its principal subtypes (well-differentiated/dedifferentiated, myxoid/round cell, and pleomorphic) represent distinct diseases with different morphology, genetics, and natural history [1]. Surgery and radiation remain the principle treatments for localized tumors. Outcomes for recurrent or metastatic liposarcoma are poor because of their relative insensitivity to chemotherapy.

HIV protease inhibitors (PIs) prevent cleavage of gag and gag-pol protein precursors in HIV-infected cells; this inhibition of cleavage prevents HIV maturation and thereby blocks the infectivity of nascent virions [2]. HIV PI use is linked to a clinical syndrome of peripheral lipoatrophy and central fat accumulation associated with insulin resistance and hyperlipidemia, known as “HIV protease inhibitor-related lipodystrophy syndrome” [3]. Complicating its characterization and incidence, lipoatrophy has also been linked to nucleoside reverse transcriptase inhibitor (NRTI) use [4]. NRTI-related lipoatrophy has been proposed to result from NRTI-induced damage to mitochondrial DNA [5]. In contrast, inhibition of adipocyte differentiation via inhibition of PPAR γ initially was theorized to underlie the pathobiology of “HIV PI-related lipodystrophy syndrome,” based upon the observation that the HIV PIs indinavir and zidovudine reduce peroxisome proliferator-activated receptor- γ (PPAR γ) levels during preadipocyte differentiation [6, 7]. More recently, alteration of sterol regulatory element-binding protein-1 (SREBP-1) expression has been advanced as the basis of this pathology [8]. SREBP-1 is a basic helix-loop-helix leucine zipper transcription factor that promotes lipogenic gene expression and adipogenesis [9]. Both gene and protein expression of major adipocyte differentiation markers and cytokines in subcutaneous abdominal adipose tissue from HIV-1 infected subjects who developed peripheral lipoatrophy while on HIV PIs was compared with seronegative healthy

controls [8]. Interestingly, SREBP-1 gene expression was decreased by a median of 93 %, whereas SREBP-1 protein concentration was increased 2.6-fold.

There are three SREBP isoforms: SREBP-2, SREBP-1a, and SREBP-1c; the latter two are alternative splice products of a single gene [9]. SREBP-1c is the primary isoform in adipose tissue, but is also present in liver, adrenal gland, ovary, kidney, and prostate [10, 11]. SREBPs are produced as inactive precursors bound to the endoplasmic reticulum (ER) by a hydrophobic tail by SREBP cleavage-activating protein (SCAP) [12]. In the presence of cholesterol, SCAP functions as a sterol-sensing domain and binds insulin-induced gene-1 or gene-2 (Insig-1 or -2) to the ER [13]. Insigs block the proteolytic processing of SREBP required for its activation [13]. Upon cholesterol depletion, SCAP and Insig fail to interact, and the SREBP-SCAP complex is transported to the golgi apparatus, where it is processed in two sequential cleavage steps by site-1 protease (S1P) and site-2 protease (S2P) to release the transcriptionally active NH2 terminus of SREBP into the nucleus. There it binds the promoters of target genes as dimers in a process known as “regulated intramembrane proteolysis (RIP)” (Fig. 1), [14, 15].

Based upon their adipocytic origin and their basal expression of SREBP-1c, we hypothesized that liposarcoma would be a good model to test our hypothesis that HIV PIs are active anticancer agents. We previously demonstrated that the most potent HIV PI identified in clonogenic assays, nelfinavir (Viracept®, Pfizer), led to a dose-dependent increase in precursor SREBP-1 protein expression in the absence of increased gene expression [16]. This observation is strikingly similar to the results observed in HIV-infected individuals on HIV PIs [8]. Additionally, increased SREBP-1 expression mediated inhibition of proliferation through p21-mediated G1 cell cycle block and induction of Fas- and Bax-dependent apoptosis [16]. Consequently, we developed the present phase 1/2 trial of nelfinavir in recurrent, non-surgically amenable liposarcomas. We report here the results of the phase 1 portion of this study.

Materials and methods

Subject eligibility

Subjects were required to have histologically confirmed liposarcoma of any subtype, which was recurrent, metastatic, or unresectable. Subjects must have been ≥ 18 years and possessed an ECOG performance status 0–2. Women of child-bearing potential and men must have agreed to use adequate contraception prior to study entry as the effects of nelfinavir on the developing human fetus was unknown. There was no limit to prior chemotherapy, and prior radiation was allowed; however, all prior therapy must have been completed >3 weeks prior to enrollment. All subjects must have had measurable disease. Organ function requirements included an absolute neutrophil count ≥ 1,000/ μ L, platelet count ≥ 75,000/ μ L, bilirubin ≤ 2.0 g/dL, and alanine aminotransferase/aspartate aminotransferase ≤ 2.0 times the upper limit of normal.

Subjects were excluded for prior or current use of an HIV PI, concurrent use of other investigational agents, strong inhibitors of CYP3A4 including grapefruit juice, St. John's Wort, and enzyme-inducing anticonvulsants. Additionally, subjects with uncontrolled intercurrent illness or subjects who had not recovered from toxicities associated with previous chemotherapy or radiation therapy were excluded.

This trial was conducted under a food and drug administration (FDA) Investigational New Drug Application (IND 70,194) held by the City of Hope (COH). This trial was approved by the COH Institutional Review Board. All subjects received and signed an informed consent document.

Trial design

This was a single-institution, phase I trial to determine the toxicities and maximum tolerated dose (MTD) of nelfinavir in subjects with liposarcoma. An additional objective was to evaluate the pharmacokinetics of nelfinavir. The objectives of the phase II portion of this trial were to assess the response rate and progression-free survival of subjects treated with nelfinavir and to evaluate expression of proteins in surrogate abdominal adipose tissue identified in preclinical studies to be necessary for nelfinavir cytotoxicity. The phase II results will not be reported here.

Nelfinavir was administered orally, twice daily with a meal or light snack at the assigned dose level. One cycle was defined as 28 days. A drug diary was maintained by the subject and reviewed after each cycle. Monitoring for treatment-related toxicity included history, physical examination, and performance status prior to each cycle; serum chemistries, complete blood counts, and lipid panel were performed prior to week 3 of the first cycle and prior to each cycle.

Pharmacokinetic analyses were performed in subjects treated at dose Levels 4 and 5 (3,000 and 4,500 mg twice daily, respectively). Serial blood samples were collected on day 8 of the first cycle at the following times: predose (within 15 min before the morning dose) and at 0.5, 1, 2, 4, 6, and 8 h after the morning dose. For each sample, approximately 4 mL blood was collected in a Vacutainer® tube containing EDTA (purple top). Blood samples were kept on ice and centrifuged within 1 h of collection (1,000×g, 15 min). Plasma was transferred to appropriately labeled polypropylene tubes and stored at -20 °C or lower until subsequent analysis.

Analysis of plasma concentrations of nelfinavir and its active metabolite (M8) along with ritonavir levels was performed using a validated LC-MS/MS in the COH Analytical Pharmacology Core, as previously described [15]. Briefly, nelfinavir, M8, and internal standard (reserpine) were extracted from human plasma by protein precipitation and organic extraction. After evaporation of the organic phase under nitrogen, the residue was reconstituted in mobile phase and analyzed. Quantification was done using multiple reaction monitoring, in positive ionmode, on a Waters Quattro Premier XE triple quadrupole tandem mass spectrometer. The assay had a lower limit of quantitation of 1 nM nelfinavir and M8 from a starting volume of 200 µL of plasma. The inter- and intraday precision and accuracy of the method were within ±10 % across the range of the standard curve.

Pharmacokinetic parameters were calculated from plasma concentration-time data for nelfinavir and M8 using standard non-compartmental analyses. Maximum observed plasma concentrations (C_{max}) and the time to reach maximum plasma concentrations (T_{max}) for nelfinavir and M8 were determined from the concentration-time data. Area under the plasma concentration-time curve over the dosing interval (AUC_{0-}) and extrapolated to infinity ($AUC_{0-\infty}$) was estimated using the linear/log trapezoidal approximation. Finally, the ratio of metabolite to parent (M/P; i.e., M8/nelfinavir) was determined based on the AUC values.

A modified 3 + 3 Fibonacci phase 1 dose escalation schema was employed [17]. The initial dose level (Level 1) was the FDA-approved dose for HIV infection (1,250 mg twice daily). Subsequent levels evaluated were the following: Level 2, 1,500 mg; Level 3, 2,125 mg; Level 4, 3,000 mg; Level 5, 4,250 mg.

Tumor burden was measured radiographically using response evaluation criteria in solid tumors (RECIST) prior to treatment and after every third treatment cycle [18]. Toxicity was graded according to the NCI common terminology criteria for adverse events (CTCAE),

version 3.0. To be evaluable for toxicity, a subject must have completed at least one cycle of treatment or experienced a dose-limiting toxicity (DLT). DLT was defined as any grade 3 toxicity not reversible to grade 2 within 1 week, or any grade 4 toxicity. Hyperlipidemia, hyperglycemia, diarrhea, and nausea/vomiting were not included as DLTs unless they were grades 3 or 4 uncontrolled with maximal medicinal therapy (atorvastatin and gemfibrozil for hyperlipidemia and up to 3 oral hypoglycemics for hyperglycemia). All subjects not evaluable for toxicity were replaced. The MTD was defined as the highest dose at which <33 % of subjects experienced DLT at least possibly attributable to nelfinavir, when at least six subjects were treated at that dose level. Intrasubject dose escalation by one dose level was permissible if no grade 2 or higher toxicity was observed after at least one cycle.

Results

Subject characteristics

From August 10, 2006, to June 18, 2009, 20 subjects were enrolled. The characteristics of the subjects are listed in Table 1. All subjects were eligible; however, 1 subject at dose Level 1 developed grade 3 pancreatitis after 2 weeks of treatment requiring hospitalization, which reversed within 3 days. Acute pancreatitis is a rare, known toxicity described for nelfinavir [19]. This subject was replaced because one cycle of treatment was not completed, and the prespecified DLT was not reached (grade 3 toxicity not reversible to grade 2 within 1 week).

Toxicity

No other dose-limiting toxicities, grade 3 or 4, were observed at any of the dose levels tested. Hematologic toxicities were predominantly grade 1, with only one subject experiencing grade 2 anemia and lymphopenia during the first cycle. In subsequent courses, there were 2 subjects with grade 2 anemia and 1 with grade 2 decrease in neutrophils. 11 subjects experienced grade 1 or 2 diarrhea during the first course, and 7 subjects encountered grade 1 diarrhea in subsequent courses. Observed liver toxicities were grade 1 for all dose levels, except for one subject with grade 2 alkaline phosphatase elevation and one grade 2 AST increase (Table 2).

MTD was not reached at dose Level 5, because at this dose level, PK data demonstrated auto-induction of nelfinavir clearance. Subjects at higher dose levels did not experience more severe hematologic or gastrointestinal toxicities (Fig. 2).

Results

Table 3 lists the responses in the 20 patients who completed therapy. Using RECIST criteria, CT partial response (PR) was observed in 1 subject, 1 subject demonstrated reduction in tumor size, but less than a PR, and stable disease (SD) was observed in 4 other subjects. A total of 13 subjects developed progressive disease at initial evaluation, and 1 was not evaluable secondary to grade 3 pancreatitis during cycle 1. Average length of treatment ranged from 0.6 to 13.5 months (median 3 months). Notably, the subject who achieved a PR, a 63-year-old male with dedifferentiated liposarcoma, received treatment for a total of 13.5 months (Fig. 3). He was taken off study due to development of acute myeloid leukemia (AML) with 11q23 (MLL), which was consistent with development of secondary AML related to his prior significant exposure to anthracycline and alkylator chemotherapies for therapy of his liposarcoma.

Pharmacokinetics

The starting dose of nelfinavir was 1,250 mg twice daily (Level 1). The maximal dose evaluated was 4,250 mg twice daily (Level 5). Steady-state pharmacokinetics for nelfinavir

and its primary active metabolite, M8, were determined at Levels 4 (3,000 mg twice daily) and 5. PK data are available from six subjects at dose Level 4 and three at dose Level 5 (Fig. 2). Interestingly, mean peak plasma levels and AUCs for nelfinavir were higher at the 3,000 vs. 4,250 mg BID dose levels. Because the PK data demonstrated auto-induction of nelfinavir clearance, further dose escalation past Level 5 was considered futile despite the absence of MTD toxicities observed at this dose, and further dose escalation was halted. Furthermore, time to peak plasma concentration of nelfinavir and M8 occurred later (4–6 h) with 3,000 mg vs. 2 h for the 4,250 mg dose. The mean ratio of M8:nelfinavir AUCs for both dose levels was ~1:3. Peak plasma concentrations were within the range where anticancer activity was demonstrated in vitro (5–10 μ M) [15].

Nelfinavir is extensively metabolized by *CYP* isoenzymes *CYP3A4*, *CYP2C9*, *CYP2C19*, and *CYP2D6*. The *CYP2C19* pathway generates M8, which is as pharmacologically active as the parent drug in suppressing HIV replication. Further, M8 possesses anticancer activity comparable to its parent molecule [15]. HIV (PIs) are not only substrates of *CYP* enzymes, but are also known to induce or inhibit some isoforms, in particular *CYP3A4*. The effect of nelfinavir on *CYP3A4* metabolism is believed to be the result of competitive inhibition by its metabolites on *CYP3A4* [20, 21]. Although the mechanism of auto-induction of nelfinavir clearance at higher dose levels is unclear, it may be due to this *CYP* induction, as has been observed in other protease inhibitors, such as ritonavir [22].

Discussion

The clinical syndrome of HIV protease inhibitor-induced lipodystrophy syndrome is associated with use of HIV protease inhibitors. Affected individuals develop peripheral fat wasting and central fat accumulation in association with insulin resistance and hyperlipidemia. Preclinical studies have demonstrated that HIV proteases promote apoptosis of terminally differentiated adipocytes. Nelfinavir is thought to inhibit site-2 protease (S2P), which blocks RIP processing of precursor SREBP-1 to its transcriptionally active form. Mature SREBP-1 is unable to translocate to the nucleus to transactivate lipogenic gene transcription, and liposarcoma cellular proliferation is reduced. Further, the accumulation of precursor SREBP-1 in the ER leads to significant ER stress and results in apoptosis [15]. In vivo evaluation of nelfinavir in a murine liposarcoma xenograft model led to inhibition of tumor growth without significant toxicity [15]. These clinical and preclinical observations led us to conduct a phase I trial of the HIV protease inhibitor, nelfinavir, for liposarcomas.

This trial demonstrates the feasibility of treating subjects with unresectable liposarcomas with nelfinavir. The study design was based on dosing nelfinavir in subjects infected with HIV, using a modified Fibonacci dose escalation. Overall, nelfinavir was well tolerated even at the highest dose levels, with no observed grade 3 or 4 treatment-related toxicities, except for one subject who developed reversible grade 3 pancreatitis during the first course. Most frequently occurring toxicities were grade 1 hematologic effects and diarrhea. Additionally, MTD was not reached, as auto-induction of nelfinavir metabolism was seen at dose Level 5.

Mean peak plasma levels and AUCs for nelfinavir were higher at Level 4 (7.3 mg/L; 60.9 mg/L $\times$ h) than 5 (6.3 mg/L; 37.7 mg/L $\times$ h), and the mean ratio of M8:nelfinavir AUCs for both levels was ~1:3. Therefore, pharmacokinetics demonstrate auto-induction of nelfinavir clearance at the doses evaluated. Peak plasma concentrations were within range where anticancer activity was demonstrated in vitro. Nelfinavir auto-induction may be due to its metabolism by *CYP* isoenzymes. More specifically, nelfinavir metabolites induce *CYP3A4* at higher doses; therefore, nelfinavir induces its own metabolism. Because auto-induction was observed, further dose escalation was discontinued.

In this study, there was evidence of clinical benefit, defined as complete response, PR, plus SD. Clinical benefit was observed in 6 of 20, or 30 % of subjects. Although liposarcomas comprise varying histologies and prognoses, with the unique exception of myxoid/round cell liposarcoma, the other histologic subtypes are considered relatively chemotherapy resistant [23]. Nelfinavir was very well tolerated, even at the highest dose levels with minimal toxicities, and therefore, it warrants further testing in the phase II setting.

Nelfinavir is a promising antineoplastic agent currently being explored in a number of other ongoing clinical trials because it has also been found to downregulate the phosphatidylinositol 3-kinase (PI3 K)-Akt pathway, inhibits signal transducer and activator of transcription 3 (STAT3) signaling, and induces malignant cell death by inducing ER stress through accumulation of misfolded proteins [24–28]. This pathway is activated in many human malignancies, and preclinical data also suggest that nelfinavir may also have radiosensitization effects. Phase I or II studies using nelfinavir in rectal, recurrent adenoid cystic head and neck, renal cell, and relapsed progressive hematologic malignancies are underway. Additionally, nelfinavir is being evaluated as an adjunct to standard chemoradiation in pancreatic, glioblastoma, cervical, and non-small-cell lung cancer [29–31].

Based upon a clinical benefit in nearly one-third of subjects, and its minimal toxicity profile, we have proceeded with the planned phase II trial of nelfinavir for liposarcomas. Auto-induction was seen at dose Level 5; thus, the phase II portion on this trial is ongoing with dose Level 4 (3,000 mg BID) to evaluate for efficacy of nelfinavir in liposarcoma. Because nelfinavir was very well tolerated with minimal toxicities, future studies using it in combination with chemotherapy or radiation may be warranted.

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Fig. 1.

Current model of nelfinavir in liposarcoma. SREBP and ATF6 are synthesized as ER transmembrane proteins and transported to the Golgi upon appropriate stimulus. Luminal S1P cleaves first, followed by intramembrane S2P to liberate the transcriptionally active amino-terminal segments of nSREBP and nATF6 from the Golgi membrane to migrate to the nucleus to activate transcription of lipogenic target genes such as FASN or UPR target genes (*solid arrow*); NFV inhibits liposarcoma proliferation and promotes apoptosis through inhibition of RIP processing of SREBP and ATF6. Inhibition of S2P cleavage by NFV leads to retention of precursor SREBP and ATF6 proteins in the ER or Golgi and block of transcriptional activation of target genes (FASN). Accumulation of unprocessed SREBP and ATF6 induces ER stress, which leads to caspase-dependent apoptosis (*dotted arrow*). NFV, nelfinavir; ER, endoplasmic reticulum; nSREBP-1, nuclear active SREBP; nATF6, nuclear active ATF6; FASN, fatty acid synthase; UPR, unfolded protein response; S1P, site-1 protease; S2P, site-2 protease; RIP, regulated intramembrane proteolysis (Adapted from Guan et al. [15])

Fig. 2.

Pharmacokinetic data for nelfinavir and active metabolite M8. Pharmacokinetic results of dosing nelfinavir 3000 and 4250 mg BID demonstrate higher mean peak nelfinavir and M8 concentrations and corresponding AUC values. BID, twice daily (Elsevier, license# 2982560891165)

Fig. 3. Serial chest CT scans of a patient in a clinical trial of nelfinavir for liposarcoma: Partial remission was documented in a 64-year-old male with a dedifferentiated liposarcoma unresponsive to combination chemotherapy treated with nelfinavir 1500 mg orally twice daily beginning February 8, 2007 (Adapted from Chow et al. [32])

Table 1

Clinical characteristics for subjects receiving Nelfinavir for liposarcoma

Characteristic	No. of subjects (<i>N</i> = 20)	%
Age, years		
Median	62	
Range	45–81	
Sex		
Male	13	65
Female	7	35
Histology		
Well-differentiated liposarcoma/atypical lipomatous tumor	7	35
Dedifferentiated liposarcoma	10	50
Myxoid	2	10
Pleomorphic	1	5

Table 2

Acute toxicity

System	Course 1				Subsequent courses			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Blood/bone marrow								
Hemoglobin	3	1	–	–	2	2	–	–
Leukocytes (total WBC)	2	–	–	–	1	–	–	–
Lymphopenia	–	1	–	–	1	–	–	–
Neutrophils	–	–	–	–	–	1	–	–
Platelets	1	–	–	–	1	–	–	–
Other	1	–	–	–	–	–	–	–
Cardiac arrhythmia ventricular arrhythmia	1	–	–	–	–	–	–	–
Constitutional								
Fatigue	1	–	–	–	1	1	1	–
Weight loss	–	–	–	–	1	–	–	–
Dermatology/skin								
Rash/desquamation	1	–	–	–	1	–	–	–
Other	1	–	–	–	1	–	–	–
Gastrointestinal								
Anorexia	–	–	–	–	1	–	–	–
Diarrhea	9	2	–	–	7	–	–	–
Nausea	2	–	–	–	1	–	–	–
Vomiting	1	–	–	–	1	–	–	–
Hemorrhage/bleeding	1	–	–	–	–	–	–	–
Hepatobiliary/pancreatitis	–	–	1	–	–	–	–	–
Lymphatics/limb edema	1	–	–	–	–	–	–	–
Laboratory								
ALT, SGPT	3	–	–	–	1	–	–	–
AST, SGOT	3	–	–	–	1	1	–	–
Album, serum-low	1	–	–	–	–	–	–	–
Alkaline phosphatase	2	1	–	–	2	–	–	–
Bicarbonate, serum-low	1	–	–	–	–	–	–	–
Cholesterol, serum-high	2	–	–	–	3	1	–	–
Glucose, serum-high	1	1	–	–	3	–	–	–
Lipase	–	–	1	–	–	–	–	–
Potassium, serum-low	2	–	–	–	1	–	–	–
Triglyceride, serum-high	2	–	–	–	2	–	–	–
Neurology dizziness	1	–	–	–	–	–	–	–
Pain	–	2	–	–	2	–	–	–
Pulmonary dyspnea	–	–	–	–	1	–	–	–
Hypoxia	–	–	–	–	1	–	–	–
Other	–	–	–	–	–	1	–	–

Table 3

Subject response to Nelfinavir

Subject	Age	Dx	Dose level	Best response	Duration of therapy (mos.)
1	81	ALT	1250 mg BID	SD	5.5
2	61	ALT		SD	6.0
3	72	Dediff		Not evaluable	
4	37	ALT		SD	2.8
5	63	Dediff	1500 mg BID	PR	13.5
6	45	Myxoid		PD	2.4
7	70	Dediff		PD	2.1
8	66	Dediff	2125 mg BID	PD	0.6
9	54	Dediff		PD	1.9
10	67	Myxoid		PD	1.7
11	42	Pleomorphic	3000 mg BID	PD	1.0
12	62	ALT		SD	5.9
13	69	ALT		MR	5.8
14	66	Dediff	4250 mg BID	PD	2.9
15	81	ALT		PD	3.1
16	64	ALT		PD	4.0
17	62	Dediff		PD	3.1
18	62	Dediff	3000 mg BID	PD	3.0
19	45	Dediff		PD	2.0
20	64	Dediff		PD	1.5

ALT atypical lipomatous tumor, *dediff* dedifferentiated lip osarcoma, *BID* twice daily, *SD* stable disease, *PR* partial response, *MR* minor response, *PD* progressive disease