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Phase I trial of ixabepilone administered as three oral doses each separated by 6 hours every 3 weeks in patients with advanced solid tumors

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Summary

Background—Ixabepilone, which stabilizes microtubules, has low susceptibility to drug resistance mediated by P-glycoprotein or βIII-tubulin.

Materials and Methods—This study was designed to determine the maximum tolerated dose (MTD) of oral ixabepilone when administered every 6 h for three doses, every 3 weeks, to patients

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Ethical standards Informed consent was obtained from all patients. The protocol and patient informed consent were approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) at each site before any patients were enrolled at that site.

Conflict of interest P. L. Clemens, M. Messina, R. Kaleta, and F. Abrahao are employees of Bristol Myers Squibb and were involved in study conduct. There are no other conflicts of interest.

with refractory advanced cancers. Eighteen patients were treated with escalating doses of ixabepilone: three at cohort 1 (30 mg/dose; 90 mg on Day 1), nine at cohort 2 (40 mg/dose; 120 mg on Day 1), and six at cohort 3 (50 mg/ dose; 150 mg on Day 1). Serial plasma samples were collected during cycle 1 for pharmacokinetic (PK) measurements.

Results—Of the 18 treated patients, eight were male and ten were female. The median age was 59 years, and most had an excellent performance status (KPS 90–100; 61%). There were two dose limiting toxicities (DLT): Grade 4 febrile neutropenia at the 120 mg dose and Grade 4 neutropenic sepsis at the 150 mg dose. Because of the severity and duration of neutropenic sepsis at level 3, level 2 (120 mg) was defined as the MTD and this cohort was expanded to nine patients. High inter-individual variability in plasma drug concentrations was observed during the study, with particularly high levels in two patients with DLT.

Conclusions—On the basis of this safety profile, the MTD of oral ixabepilone was defined as 120 mg given as three 40 mg doses each separated by 6 h on Day 1 of a 3-week cycle. However, the PK variability observed makes further development of this oral formulation unlikely.

Keywords

Ixabepilone; Oral administration; Phase I trial

Introduction

Ixabepilone is a semi-synthetic epothilone B analog that binds to b-tubulin to stabilize preformed microtubules thereby leading to cell-cycle arrest and apoptosis of cancer cells [1, 2]. Ixabepilone binds to β-tubulin at a site distinct from the taxane-binding site [3, 4], which may explain why ixabepilone retains activity in tumors that are resistant or refractory to taxanes [5, 6]. Ixabepilone has low susceptibility to common resistance mechanisms that render other anticancer drugs ineffective, including overexpression of βIII-tubulin, P-glycoprotein and other efflux pumps that mediate multidrug resistance [6].

A series of phase 2 clinical trials demonstrate that ixabepilone has clinical activity in a wide array of advanced solid malignancies, including breast cancer [7–11], hormone-refractory prostate cancer [12, 13], pancreatic cancer [14], gastric cancer [15], non-small cell lung cancer [16], endometrial carcinoma [17], and ovarian cancer [18]. Ixabepilone plus capecitabine was found to be more effective than capecitabine alone in prolonging progression-free survival of patients with metastatic breast cancer after anthracycline and taxane therapy [19]. On the basis of these trials, intravenous ixabepilone is approved by the Food and Drug Administration for treatment of locally advanced or meta-static breast cancer in combination with capecitabine after failure of anthracycline and taxane therapy, and as mono-therapy following disease progression after an anthracycline, a taxane, and capecitabine [20]. The recommended dose of ixabepilone is 40 mg/m^2 via a 3-h IV infusion once every 3 weeks.

An oral formulation would provide a more convenient route of administration for patients than the IV infusion, and might allow more frequent dosing, offering the potential to optimize the therapeutic index of ixabepilone. Oral administration of ixabepilone produced antitumor activity in preclinical xenograft models equivalent to that achieved with parenteral drug administration [5]. Moreover, IV and oral administration of ixabepilone exhibited comparable safety profiles in animal toxicology studies. A capsule containing an enteric-coated bead formulation of ixabepilone was evaluated in a prior study that assessed the bioavailability of ixabepilone and intra- and inter-patient variability of exposure to the drug. The bioavailability of ixabepilone in this oral formulation was 43%. (BMS data on file: http://ctr.bms.com/OneBmsCtd/ResultDetailAction.do?prodid=48&trialid=1837).

The present study was designed to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs) and the recommended phase 2 dose (RP2D) of this oral ixabepilone formulation when administered as three doses each separated by 6 h every 21 days in patients with advanced solid tumors. Secondary objectives included the safety, pharmacokinetics, and antitumor activity of oral ixabepilone.

Patients and methods

Patient eligibility

Patients were recruited at the Stanford Cancer Center in Stanford, CA and at the Lombardi Comprehensive Cancer Center in Georgetown University, Washington, DC. The initial inclusion criteria for this trial were: presence of histologically- or cytologically-confirmed advanced or metastatic solid tumor that is unresponsive to currently available therapies or for which effective treatment is not available; measurable or non-measurable disease as defined by RECIST criteria [21]; ≥1 week after minor surgery; ≥3 weeks after major surgery, radiation therapy, or last dose of immunotherapy or chemotherapy; ≥2 weeks after weekly dosed chemotherapy, hormonal anti-cancer agents, or targeted therapies; Karnofsky performance status 70–100; available for treatment and follow-up at the participating center; recovery from toxicities due to previous therapies to ≤ grade 1 (except for alopecia); age ≥18 years. Exclusion criteria included: women of childbearing potential who are unwilling or unable to use an acceptable method to avoid pregnancy; women who are breastfeeding or pregnant; women with a positive pregnancy test; sexually active fertile men not using effective birth control; any history of radiation that includes ≥30% major bone marrow-containing areas; > three prior cytotoxic regimens in the metastatic setting; recent (≤3 months of enrollment) gastrointestinal disease/surgery that would impact absorption of the study drug; inability to swallow whole capsules; inability to tolerate venipuncture; symptomatic brain metastases; uncontrolled psychiatric or medical conditions; inadequate hematologic, hepatic or renal function; prior epothilones; exposure to any investigational drug or placebo within 4 weeks of enrollment; other concurrent chemotherapy regimens; treatment with CYP3A4 inhibitors or inducers within 2 weeks of the initiation of study treatment; long-term use of steroids (>30 days) within 2 weeks of starting treatment.

Informed consent was obtained from all patients. The protocol and patient informed consent were approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) at each site before any patients were enrolled at that site. This study was conducted in accordance with the principles of Good Clinical Practice and all local regulatory requirements.

Clinical study design

This study was an open-label, multicenter, single-arm, dose-escalation, phase 1 trial in which ixabepilone was administered on Day 1 as three oral doses each separated by 6 h every 3 weeks in patients with advanced cancer. A 3+3 dose-escalation design was used starting at dose level 1 (30 mg/dose; i.e., 90 mg on day 1). Dose escalation proceeded by 10 mg/dose for each successive cohort. Dose escalation to the next cohort was allowed if none of the first three patients had a dose-limiting toxicity (DLT). If a DLT was seen, then up to three additional patients were enrolled at that cohort, and the dose escalated only if no further DLTs were observed. The maximum tolerated dose (MTD) was based on cycle 1 data only; defined as the maximum dose that was given to six patients with not more than one patient experiencing a DLT and with ≥two patients experiencing a DLT at the next higher cohort.

DLTs included any of the following events: grade 4 neutropenia for ≥ five consecutive days; febrile neutropenia; grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding requiring platelet transfusion; grade 3/4 nausea, vomiting, or diarrhea despite adequate medical intervention or prophylaxis; any other drug-related clinically significant grade ≥3 nonhematological toxicity; or delayed recovery from drug-related toxicity that delays initiation of cycle 2 by ≥3 weeks.

The dose level used in subsequent cycles for any given patient was reduced by one dose level in the event of a DLT. Ixabepilone was discontinued in the event of grade 3 neuropathy lasting ≥7 days or any grade 4 motor or sensory neuropathy. Growth factors/colony stimulating factors were allowed at the discretion of the investigator, but their use was not to replace the dose reduction schema.

Pretreatment assessment and follow-up studies

Baseline imaging studies were obtained within 28 days of start of treatment. Within 14 days before start of treatment, a medical history was obtained and patients underwent a physical exam, laboratory testing, and an EKG for QTc evaluation. On the first day of each cycle, patients were examined, toxicities were assessed, and laboratory studies were performed. Adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; and their causal relationship to study treatment rated by the investigator. Tumor measurements were performed after every two cycles. All patients were considered evaluable for response regardless of their time on study. Tumor assessments were performed according to RECIST criteria guidelines: a response was considered confirmed if noted on two successive examinations made at least 4 weeks apart.

Ixabepilone treatment

Ixabepilone (in delayed-release capsules) was administered orally every 6 h for three doses on Day 1 of a 21-day cycle. Patients fasted for 4 h prior to the first dose and 2 h afterwards, and then for 2 h before and after the second and third doses. Water was allowed in the fasting periods except for 1 h before and after each dose. All doses were administered with eight ounces (240 mL) of water. All three doses in cycle 1 were administered in the research clinic. Treatment was repeated every 21 days providing absolute neutrophil count was >1,500 cells/mm^3, platelets >100,000 cells/mm^3, and all treatment-related non-hematological toxicity had resolved to baseline or ≤grade 1 (except for grade 2 alopecia or fatigue for which resolution was not required). If retreatment criteria were not met, treatment was delayed and patients were re-evaluated at least weekly. If recovery had not occurred by 3 weeks, then the patient was withdrawn from the study. For cycle 2 and subsequent cycles, only the first dose was administered in the clinic and the remaining two doses were taken in the patient's home.

Pharmacokinetic (PK) assessment

Serial PK samples were collected during cycle 1 before and after each of the three ixabepilone doses. Following the first dose, samples were taken at 30 min and then on the hour until 5 h. Two hours after the second dose, one sample was taken. Following the third dose, samples were taken at 30 min, on the hour until 6 h, 8 h, 36 h, 60 h, and finally 156 h (a total of 168 h after the first dose). Blood samples (4 ml each) were collected into labeled tubes containing potassium EDTA as anticoagulant from an indwelling catheter or by direct venipuncture for determination of plasma ixabepilone levels. After collection, each sample was gently inverted several times to ensure complete mixing with the anticoagulant, KEDTA, and placed on ice. Within 1 h of collection, samples were centrifuged at 1,000×g for 10 min at 4°C. Plasma was transferred to polypropylene tubes and stored at or below −20°C until shipped to the analytical site for analysis. Plasma ixabepilone concentrations

were analyzed using a validated liquid chromatography and tandem mass spectrometry assay [22]. PK data were not required for dose escalation decisions and PK parameters were not calculated. Rather, the data presented in this paper are the means of the actual ixabepilone drug concentrations for each cohort and time point.

Statistical considerations

All safety and efficacy data were evaluated by descriptive statistics using Statistical Analysis System (SAS) software language.

Results

Patients

A total of 23 patients with advanced cancers were enrolled between May, 2008 and June, 2009. This included three patients at dose level 1 (30 mg/dose; 90 mg on Day 1), nine patients at dose level 2 (40 mg/dose; 120 mg on Day 1), and six patients at dose level 3 (50 mg/dose; 150 mg on Day 1). The other five patients were not treated—four no longer met eligibility criteria and one withdrew consent. Patients at each dose level received a median of two cycles of ixabepilone. The maximum number of cycles of ixabepilone was 11 in the 90 mg cohort, four in the 120 mg cohort, and eight in the 150 mg cohort.

The study cohort had a median age of 59 years (range 27–75 years); most were female (10, 56%), most were white (16, 89%) and had a Karnofsky performance status of 90–100% (11; 61%). The study population had a variety of different advanced malignancies, most commonly colon cancer (4, 22%), as presented in Table 1.

Safety

Given the low patient numbers, AE's are not presented by cohort, but the two DLTs are reported in detail below. Table 2 lists the treatment-related adverse events in this trial. The most frequent hematologic adverse event regardless of CTC grade was anemia (22%). The most frequent non-hematologic adverse events regardless of CTC grade were fatigue (44%) and nausea (39%). Grade 3/4 non-hematological toxicity was typically uncommon; only fatigue, dysphagia, and mucosal inflammation were reported in more than one patient (two patients each; 11%). No grade 3 peripheral neuropathy was reported, and two patients (11%) developed grade 1 and 2 peripheral neuropathy at the 90 mg and 150 mg dose levels, respectively.

There were two DLTs reported and baseline characteristics for these two patients are presented in Table 3. One patient in the 120 mg cohort was hospitalized for grade 4 febrile neutropenia, which was associated with grade 4 leucopenia, grade 2 thrombocytopenia, grade 2 anemia, and grade 3 mucositis associated with grade 3 dysphagia. Following treatment, all of these events resolved after 6 days. The patient had their cycle 2 dose delayed and continued treatment with ixabepilone at the reduced dose of 90 mg until disease progression at cycle 4. One patient in the 150 mg cohort had grade 4 neutropenic sepsis, thrombocytopenia, and panenteritis and discontinued study treatment. This patient had prolonged persistent grade 3 neutropenia for 5 days despite growth factor support, was hospitalized for 2 months for complications of *E. coli* sepsis and aspiration pneumonia requiring intubation and tracheostomy placement. Because of the severity and duration of the neutropenic sepsis in one patient at dose level 3, and emerging PK data indicating high drug plasma concentrations in the two patients with DLT, dose level 2 (120 mg/ day every 21 days) was expanded to six patients after which it was defined as the MTD, and this cohort was further expanded to 9 patients.

Serious adverse events (SAEs) were reported in five patients (28%), including two receiving ixabepilone 90 mg, two receiving ixabepilone 120 mg, and one receiving ixabepilone 150 mg. Among the SAEs reported, Grade 3/4 mucosal inflammation was the only non-hematological toxicity experienced in more than one patient (two patients; 11%).

Four patients died during follow-up including two patients in each of the 90 mg and 120 mg cohorts, all from progressive disease. These deaths occurred 30–51 days after the last dose of ixabepilone.

Pharmacokinetics

Ixabepilone absorption following oral administration of the first dose reached peak plasma levels by 2–3 h. However, ixabepilone concentrations varied considerably among patients at each dose level. Peak concentrations following the third dose occurred as late as 8 h post-dose, the mean PK profiles across the three dose levels overlapped (Fig. 1) and the coefficient of variation exceeded 100% for ixabepilone concentrations at multiple time points throughout the profile at all 3 dose levels, Table 4. Most notably, ixabepilone concentrations in the two patients who experienced DLTs were over three-fold higher than that of other treated patients at the last time point collected (168 h post-first dose;156 h post-final dose).

Efficacy

Oral ixabepilone did not produce any objective responses in these advanced cancer patients. Five of the eighteen patients (28%) had stable disease after two cycles of therapy. Of these eighteen patients four patients received at least 4 cycles of study therapy, with the remaining patients receiving up to 11 cycles (range 4–11 cycles). These included one patient with adenoid cystic carcinoma of the tonsil treated with 90 mg; two patients with non-small-cell lung cancer and melanoma, respectively, treated with 120 mg; and two patients with colon and parotid cancer, respectively, treated with 150 mg. Of the other patients, twelve had progressive disease and one had a response that could not be confirmed.

Discussion

The oral dosing schedule used in the present study was selected because of unpublished data from Bristol-Myers Squibb favoring a multiple dosing schedule of ixabepilone in pre-clinical, xenograft models. These studies included simulations using a population pharmacokinetics model coupled with a semi-mechanistic exposure-response model for neutropenia. They compared the duration of time for Grade 3+ neutropenia (risk) with the duration in which plasma ixabepilone concentrations exceeded 30 nM (benefit; corresponding to effective drug levels in xenograft models). These models were derived for IV ixabepilone and then adjusted for oral dosing based on preliminary pharmacokinetic data from study CA163-088 (data not published but available on-line).

The bioavailability of ixabepilone in this oral formulation from study CA163-088 was 43%, with Cmax 50.0 ng/mL (mean CV 81%), AUC(0–24 h) 235.4 ng•h/mL (mean CV 65%), Tmax 2.0 h (Min 0.5, Max 24.0). Total variability of Cmax and AUC (0–24 h) was 91.4% and 81% respectively. The inter- and intra-patient variability of Cmax was 58.6% and 60.5% respectively. The inter- and intra-patient variability of AUC (0–24 h) was 67.6% and 37% respectively (BMS data on file; study report CA163-088 available at http://ctr.bms.com/OneBmsCtd/ResultDetailAction.do?prodid=48&trialid=1837)

In our current study, oral ixabepilone did not exhibit predictable pharmacokinetics over the dose range tested. Peak plasma ixabepilone concentrations were achieved 2–3 h after the first oral dose at each dose level, but as late as 8 h after the third dose. Variability was

observed at each dose level. Moreover, the two patients with DLTs had threefold higher ixabepilone drug concentrations at 168 h after the first dose than the other patients in those dose levels. The characteristics of these patients, including tumor type and prior treatments, did not suggest an explanation for such variability. As expected, oral administration using a split dose (each separated by 6 h) produced lower mean peak plasma concentrations than in prior Phase I studies with the I.V. formulation [23, 24].

Both DLTs involved grade 4 neutropenic fever or sepsis. Most other adverse events were mild or moderate (Grade 1 or 2); however, Grade 3/4 toxicities increased in frequency with ixabepilone dose. Grade 3/4 toxicity was reported in four of six patients (67%) at the highest dose level compared with two of nine patients (22%) at the middle dose level. The severity of the DLT in one patient at the 150 mg dose level, the high ixabepilone drug levels in the two patients with DLTs, and the variability in PK of this oral drug formulation resulted in expansion of the 120 mg dose level to nine patients, with only one DLT in this cohort. This dose level was thus declared the MTD.

Tumor remissions were not observed on this study. However, none of the patients had breast cancer and only one had ovarian cancer, tumor types which are known to be responsive to this agent [23].

It is worth noting that traditional limited definitions of MTD do not take into account the unacceptably large PK variability and unusually severe adverse events (AEs) in patients whose levels were unexpectedly high and prolonged. Based on the data from this trial and related studies, development of an oral formulation of ixabepilone is not currently being pursued.

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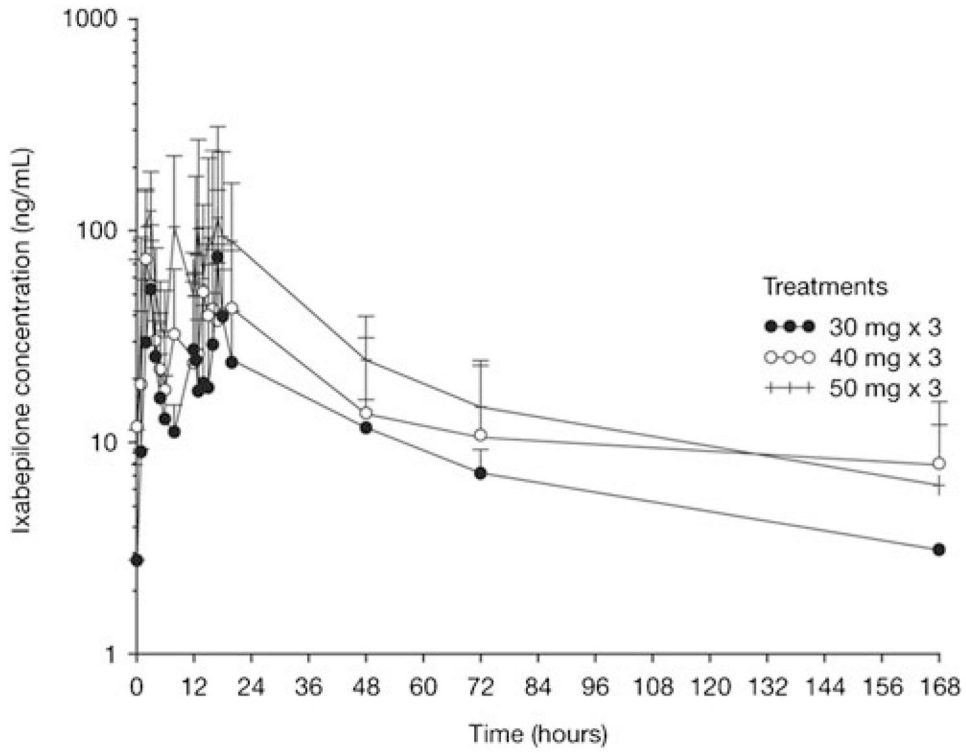

Fig. 1.

Mean (+SD) plasma concentration-time profiles for ixabepilone following administration of 3 equal oral doses separated by 6 h, by treatment (30, 40, or 50 mg each dose)

Table 1

Patient characteristics

Characteristic	Ixabepilone			
	Cohort 1 90 mg/day (*N*=3)	Cohort 2 120 mg/day (*N*=9)	Cohort 3 150 mg/day (*N*=6)	All patients (*N*=18)
Age, years				
Median (range)	59 (47–70)	69 (39–75)	56 (27–60)	59 (27–75)
≥65 years, *n* (%)	1 (33)	5 (56)	0 (0)	6 (33)
Gender, *n* (%)				
Male	1 (33)	4 (44)	3 (50)	8 (44)
Female	2 (67)	5 (56)	3 (50)	10 (56)
Race, *n* (%)				
White	2 (67)	8 (89)	6 (100)	16 (89)
Black/African-American	1 (33)	1 (11)	0 (0)	2 (11)
Karnofsky performance score, *n* (%)				
100	0 (0)	1 (11)	1 (17)	2 (11)
90	3 (100)	4 (44)	2 (33)	9 (50)
80	0 (0)	4 (44)	2 (33)	6 (33)
70	0 (0)	0 (0)	1 (17)	1 (6)

Table 2

Treatment-related adverse events

Adverse event	Grade 1–2 No. of patients (%)	Grade 3 No. of patients (%)	Grade 4 No. of patients (%)
Fatigue	7 (39)	0	1 (6)
Nausea	7 (39)	0	0
Anemia	3 (17)	1 (6)	0
Vomiting	4 (22)	0	0
Alopecia	3 (17)	0	0
Mucosal inflammation	1 (6)	2 (11)	0
Neutropenia	1 (6)	2 (11)	0
Diarrhea	1 (6)	1 (6)	0
Muscular weakness	1 (6)	0	1 (6)
Thrombocytopenia	1 (6)	0	1 (6)
Dysgeusia	2 (11)	0	0
Dysphagia	0	2 (11)	0
Neuropathy peripheral	2 (11)	0	0
Stomatitis	2 (11)	0	0
Escherichia infection	0	1 (6)	0
Febrile neutropenia	0	0	1 (6)
Fungal infection	0	1 (6)	0
Leukopenia	0	0	1 (6)
Neutropenic sepsis	0	0	1 (6)
Pneumonia, aspiration	0	0	1 (6)

Table 3

Baseline characteristic of two patients with dose limiting toxicities

	120 mg cohort	**150 mg cohort**
DLT (Grade 4)	Febrile neutropenia	Neutropenic sepsis
Age	69	60
Gender	M	M
Baseline Karnofsky Performance score	90	90
Baseline Weight (Kg)	87	72
Tumor type	Melanoma	Parotid Cancer
Number of prior systemic therapies	3	1
Prior anticancer therapies	Dacarbazine, XL518- Mek-inhibitor, paclitaxel	Cyclophosphamide/adriamycin

Table 4

Ixabepilone concentrations (ng/ml) by timepoint following first dose

Time (h)	30 mg×3		40 mg×3		50 mg×3	
	Mean	0%CV	Mean	0%CV	Mean	0%CV
0	NC	00NC	NC	00NC	NC	00NC
0.5	2.77	00NC	11.46	00NC	7.86	00NC
1	9.31	00NC	19.93	106.86	41.82	125.4
2	29.67	199.38	73.57	110.45	104.91	150.51
3	52.75	104.05	56.82	158.61	124.51	153.14
4	24.18	156.31	30.23	172.12	52.16	159.89
5	16.64	158.09	22.24	183.73	36.54	157.84
6	12.84	160.79	17.75	189.73	32.08	162.8
8	11.19	134.62	32.5	102.55	104.54	117.48
12	26.76	131.55	24.84	154.32	49.41	153.78
12.5	24.24	125.04	22.58	156.1	78.35	131.39
13	17.63	116.13	25.94	116.42	103.42	160.96
14	19.60	127.42	52.17	199.15	59.02	125.4
15	18.52	124.55	39.52	175.4	86.3	155.37
16	27.37	185.28	43.62	186.26	93.53	154.94
17	76.63	103.25	37.31	189.18	116.04	169.01
18	38.32	171.54	41.13	110.4	94.27	151.59
20	24.71	169.61	43.04	189.19	89.71	187.4
48	11.77	135.33	13.6	130.63	24.41	162.82
72	7.20	128.48	10.49	120.83	14.81	164.98
168	3.12	00NC	7.8	100.52	6.28	194.02