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A Phase I Trial Of MK-2206 In Children with Refractory Malignancies: A Children's Oncology Group Study

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Abstract

Background—We report results of a phase I trial designed to estimate the maximum tolerated dose (MTD), describe dose-limiting toxicities (DLT), and characterize the pharmacokinetic profile of MK-2206, an AKT inhibitor, in children with refractory or recurrent malignancies.

Procedure—MK-2206 was administered either every other day (schedule 1), or once a week (Schedule 2) in a 28-day cycle. Dose escalations in increments of ∼30% were independently made in each part using the rolling-six design. Serial pharmacokinetic (PK) studies were obtained. Biological studies include analysis of PI3K/PTEN/AKT-cell signaling pathway in pre and post-therapy in PBMC and in tumors at diagnosis or recurrence.

Results—Fifty patients [26 males, median age 12.6 years (range, 3.1-21.9)] with malignant glioma (16), ependymoma (4), hepatocellular carcinoma (3), gliomatosis cereberi (2) or other tumors (22) were enrolled; 40 were fully evaluable for toxicity (schedule 1 n=23; schedule 2 n=17). Schedule 1 DLTs included: grade 3 dehydration in 1/6 patients at 28 mg/m^2; grade 4 hyperglycemia and neutropenia in 1/6 patients at 45 mg/ m^2; and grade 3 rash in 3/6 patients at dose level 4 (58 mg/m^2). Schedule 2 DLTs included: grade 3 alkaline phosphatase in 1/6 patients at 90 mg/m^2; grade 3 rash in 1/6 patients at 120 mg/ m^2, and grade 3 rash in 2/6 patients at 155 mg/m^2.

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Conclusions—The recommended pediatric phase 2 dose of MK-2206 is 45 mg/m^2/dose every other day or 120 mg/m^2/dose weekly. Pharmacokinetics appeared linear over the dose range studied.

Keywords

Phase I trial; MK-2206; AKT inhibitor; pediatric; relapsed solid tumors

Introduction

AKT, also known as protein kinase B, is a serine threonine protein kinase. The three AKT isoforms, AKT 1, 2, and 3, are expressed in all cell types and tissues. AKT is activated downstream of phosphatidylinositol 3-kinase (PI3K) which transmits signals from cytokines, growth factors and oncoproteins to multiple targets. Activation of PI3K localizes AKT to the plasma membrane, where AKT is activated by phosphorylation at Thr 308 and Ser 473. The most important negative regulator of PI3K/AKT signaling is the tumor suppressor phosphatase and tensin homologue deleted on chromosome 10 (PTEN).[1]

Once activated, AKT regulates multiple cellular processes including survival, proliferation, and growth. AKT activates mTORC1, which integrates many inputs including growth factor signaling, energy state of the cell, nutrients and O_2 availability.[1] Feedback interactions contribute to the overall regulation of the PI3K/AKT signaling.[2] The PI3K/AKT pathway is downstream of most of the common growth factor tyrosine kinase receptors (TKR) in cancer (*e.g.*, EGFR, HER2, IGFR) and is a likely driver of tumor progression in most carcinomas.[1] AKT protein kinase is activated in a substantial proportion of human solid tumors,[1,3] breast cancer,[4] prostate cancer,[3] glioblastoma,[5] colon,[6] ovarian,[7] gastric cancer,[8] non-small cell lung cancer [NSCLC],[3] pancreatic cancer,[9] malignant rhabdoid tumors,[10] neuroblastoma,[11] synovial sarcoma,[12] rhabdomyosarcoma,[13,14] GBM,[14] and medulloblastoma.[15]

MK-2206 is an oral allosteric AKT inhibitor that inhibits the activities of all three human AKT (recombinant full length) isoforms, AKT1, 2, and 3 with 50% inhibitory concentration (IC_{50}) values of 8, 12, and 65 nM, respectively. MK 2206 has demonstrated *in vitro* (IC 50s <1μM) and *in vivo* activity in many preclinical cancer models with weekly and every other day dosing. In a phase I study in adults with recurrent solid tumor, the maximum tolerated dose (MTD) of MK-2206 administered every other day was 60 mg per day. Dose-limiting toxicities (DLTs) included skin rash, and stomatitis. Other drug-related toxicities included nausea, pruritus, and diarrhea. Based on preclinical and clinical experience, some data suggest that higher doses of MK-2206 on a less frequent dosing schedule (e.g., weekly) may maximize peak target inhibition and may also alleviate DLTs associated with accumulated exposure to MK-2206. Thus, several studies are studying weekly as well as every other day dosing schedules.

We report the results of a phase I trial of MK 2206 in children with recurrent or refractory malignancies. The primary objectives were to estimate the MTD, describe dose limiting toxicities (DLTs) and characterize the pharmacokinetics of MK 2206 administered either once every other day (schedule 1), or once a week (Schedule 2) in a 28-day cycle. The

secondary objectives were to preliminarily define the antitumor activity of MK 2206 within the confines of a Phase I study and to evaluate the biological activity of MK 2206 by measuring PI3K/AKT/mTOR signaling in tumor and peripheral blood mononuclear cells.

Patients and Methods

Patient Eligibility

Eligible patients were ≥12 months and ≤ 21 years old, with a histologically verified diagnosis of recurrent or refractory solid tumors including CNS tumor (histology was not required for diffuse intrinsic pontine gliomas or optic pathway gliomas) with measureable or evaluable disease and Lansky or Karnofsky score ≥ 50. Patients were required to have recovered from acute toxic effects of prior therapy and not to have received: growth factors within 7 days of study entry (14 days for long-acting growth factor (e.g. Neulasta); myelosuppressive chemotherapy within 3 weeks (6 weeks if prior nitrosourea); biologic agent within 7 days; immunotherapy within 6 weeks; monoclonal antibodies within at least 3 half lives after the last dose; craniospinal or total body irradiation within 6 months; local palliative radiotherapy within 2 weeks or other substantial bone marrow irradiation within 6 weeks; stem cell infusion within 8 weeks; bone marrow transplantation within 3 months. Patients on corticosteroids must have been on a stable or decreasing dose for at least 7 days. Patients had to be able to swallow pills whole, could not be on enzyme- inducing anticonvulsants, insulin or growth hormone therapy or any medications that could prolong QTc or agents preventing graft versus host disease or organ rejection post transplant. Other requirements included adequate bone marrow (peripheral absolute neutrophil count ≥ 1000/ microliter, platelet count ≥ 100,000/ microliter, transfusion independent, hemoglobin ≥ 8.0 gm/dL), renal (serum creatinine based on gender/age, or GFR ≥ 70 ml/min/1.73m^2), liver (total bilirubin ≤ 1.5 × institutional upper limit of normal for age, ALT ≤ 110U/L and albumin ≥ 2 g/dL) and cardiac (QTc ≤ 450 msec) function. Pregnant or lactating females were excluded from the study. Patients of childbearing or child fathering potential had to agree to use a medically acceptable form of birth control, including abstinence, while on this study.

Informed consent was obtained from patients, parents or guardians, and assent was obtained as appropriate at the time of protocol enrollment. The institutional review boards of each COG institution approved the protocol before initial patient enrollment and continuing approval was maintained throughout the study.

Drug Administration and Study Design

MK-2206, supplied by Merck and Co (West Point, PA) and distributed by the NCI (Bethesda, MD) as 5, 25, and 200 mg tablets, was administered orally two hours before or two hours after food on one of two treatment schedules: (i) once every other day (schedule 1), or (ii) once a week (Schedule 2) in 28-day cycles.

The starting MK-2206 dosage was 28 mg/m^2/dose once every other day (schedule 1) or 90 mg/m^2/dose weekly (schedule 2) (approximately 80% of the MTDs in adults). Dosage levels

for subsequent patient cohorts were escalated in 30% increments. Patients could receive up to 12 courses in the absence of disease progression.

The two schedules were studied concurrently in separate cohorts using the rolling-six design. The MTD, defined as maximum dose at which less than one-third of patients experience DLT during Cycle 1 of therapy. Toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Hematologic DLT was defined as grade 4 neutropenia or thrombocytopenia not due to malignant infiltration and myelosuppression that caused a delay of ≥ 14 days between treatment cycles. Non-hematologic DLT was defined as any grade 3 or 4 non-hematological toxicity with the specific exclusion of Grade 3: nausea or vomiting of < 3 days duration; ALT/AST that returned to eligibility criteria levels within 7 days of drug interruption; fever or infection < 5 days duration; hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation; hyperglycemia (non-fasting) that returned to ≤ Grade 2 (with or without use of insulin or oral diabetic agents) prior to the next scheduled dose of drug, Any grade 2 non-hematological toxicity that persisted for ≥ 7 days and was considered sufficiently medically significant or intolerable which led to treatment interruption was also considered a DLT.

Pretreatment evaluations included a history, physical examination including a thorough neurological examination, performance status, disease evaluation, complete blood count (CBC), EKG, electrolytes, renal and liver function tests, urinalysis, urine glucose, pregnancy test for female patients of childbearing age. CBCs were obtained twice weekly during course 1, weekly during subsequent courses. History, physical examinations, and serum chemistries and urine glucose were obtained weekly in course 1 and prior to each subsequent course.

Disease evaluations were obtained at baseline, after courses 1, 3 and 5; then every 3 courses, thereafter. Tumor response was reported using the Response Evaluation Criteria in Solid Tumors (RECIST).[16]

Pharmacokinetic Studies

Sample Collection—For both dosing schedules, blood samples (3 mL) were collected in heparinized tubes from all patients prior to MK2206 dose on day 1, course 1 and at 0.5, 1.5, 3, 6-8, 24 (± 4) and 48 (±4) hours; prior to MK2206 on day 15; and 6-8 hours after the day 15 dose in consenting patients. For schedule 2 only (once weekly dosing), an additional sample was collected prior to dose on day 8. Plasma was separated by centrifugation at 2,000 ×g for 15 minutes, transferred into a polypropylene tube, and stored at -70°C until analysis. Plasma concentrations of MK-2206 were determined using a validated liquid chromatography, tandem mass spectrometry (LC/MS/MS) assay. Methods are detailed in Supplement 1. Full details are described in the supplementary material. The within-day and between-day precision (CV%) values and accuracy values met standard assay validation criteria.

Data Analysis—Pharmacokinetic parameters for MK-2206 were calculated using standard non-compartmental methods with WinNonlin Professional, version 4.1 (Pharsight Corporation, Mountain View, CA).

Biological Assay

The levels of activation of downstream signaling molecules (AKT, rpS6 and 4E-BP1), were determined in PBMC isolated from blood (5 ml) drawn at enrollment before beginning treatment (baseline), and 24 hours (±4 hours) post first dose of MK-2206.

Whole blood samples (5 mls) were collected in all consenting patients prior to treatment, at 24 (±4 hours) post first dose of MK-2206, and before the dose on Day 15, and 6 to 8 hours after the MK-2206 dose on day 15 in cycle 1

PBMCS were isolated from subjects' blood according to the protocol for Histopaque (Sigma-Aldrich, St. Louis, MO; cat#1077). PBMC pellets were frozen in liquid nitrogen and stored at -80°C analysis. Frozen cells were lysed with Cell Signaling lysis buffer (cat.#9803, and prepared for Western Blot analysis to detect AKT and pAkt (Ser473), GAPDH, rpS6 (Ser235,236) and 4E-BP1 proteins.

Results

Patient Characteristics

Fifty patients (28 on schedule 1 and 22 on schedule 2) were enrolled on the study. Table I summarizes the characteristics of the eligible patients. Patients who suffered a DLT at any point or those without DLT who received at least 85% of study drug were considered evaluable for toxicity. Five patients on schedule 1 and five on schedule 2 were in evaluable for toxicity for the following reasons: early progressive disease course 1 (n=6); repeat laboratory parameters outside of eligibility parameters prior to start of therapy (n=1); physician determination in patient's best interest (n=3). The median number of courses for schedules 1 and 2 was 6.5 (range, 1-12) and 6.5 (range, 1-12), respectively.

Toxicities

The observed DLTs are summarized in Table II. In schedule 1 (every other day dosing), at dose level 28 mg/m^2, among 6 evaluable patients, one experienced grade 3 dehydration. At 35 mg/m^2, none of the first 5 patients experienced DLTs. At dose level 45 mg/m^2, 1 of 6 patients developed grade 4 neutropenia and hyperglycemia. At dose level 58 mg/m^2, 3 of 6 evaluable patients developed grade 3 rash. Thus, the recommended phase II dose for the every other day dosing was 45 mg/m^2. Among the 17 evaluable patients in schedule 2 (once per week), at 90 mg/m^2, 1 of 6 patients had DLT of grade 3 alkaline phosphatase and diarrhea. At 120 mg/m2, 1 of 6 evaluable patients had a grade 3 maculopapular rash as a DLT. At dose 155 mg/m^2, 2 of 5 evaluable patients experienced a grade 3 maculopapular rash. Thus, the recommended phase II dose of weekly MK-2206 was 120 mg/m^2. Table III summarizes all other adverse events that were not DLTs that are at least possibly attributable to MK 2206 in all eligible patients. No patient required hospitalization for treatment-related complications.

Responses

No objective responses (OR) were reported. Prolonged SD (≥ 3 courses of therapy, up to 12 courses) was observed in 7 patients: 1 malignant paraganglioma (11 courses), 2

ependymomas (5 and 12 courses, respectively), 1 gliomatosis cereberi (11 courses), 1 metastatic juvenile pilocytic astrocytoma (12 courses), 1 malignant peripheral nerve sheath tumor (6 courses) and 1 clear cell sarcoma (12 courses).

Pharmacokinetics

Peak plasma concentrations were achieved 5.0 hrs (range, 1.5 – 7.1 hrs) after the oral dose. The MK-2206 half-life was 38.7 hrs. MK-2206 pharmacokinetics appeared to be linear over the dose range studied based on dose-proportional increases in C_{max} and AUC (Figure 2A) values, and similar Cl/F (Figure 2B) values across dose levels (Table IV). The Cl/F values appeared to be slightly higher for Schedule 1 compared with schedule 2. This is most likely due to the shorter sample collection interval for Schedule 1 (2 days) compared to Schedule 2 (7 days) and long half-life of 43 hours calculated for Schedule 2. Children of ages 12 or younger had similar CL/F as children older than age 12 (Figure 2C).

Pharmacodynamics

Three patients on schedule 1 who were treated at the MTD, 45 mg/m^2, had complete pre- and post-therapy sample collections. In these patients, there was evidence that pAKT decreased between the baseline sample and 6-8 hours post-dosing on day 1. In one of these samples, the GADPH loading was also decreased. Five patients on schedule 2 had complete collections: 3 at 120 mg/m^2, and 1 at 155 mg/m^2 and 1 at 90 mg/m2. There was evidence of decreased pAkt in one patient following day 1 dosing receiving a dose of 90 mg/m^2, although no concurrent change in p4E-BP1 or pS6 where this could be detected. Relative to control cell lines (Rh30 rhabdomyosarcoma and Abrams osteosarcoma) most samples after processing on both schedules had levels of Akt, 4E-BP1 and S6 proteins that were insufficient to determine drug-induced changes in phosphorylation.

Discussion

This pediatric phase 1 trial establishes the recommended phase 2 dose of MK 2206 as 45 mg/m^2 orally every other day or 120 mg/m^2 weekly. The key DLTs in both schedules were rash, similar to adults. In contrast to adult studies,[17],[18] dose-limiting stomatitis was not observed in this pediatric trial.

Pharmacokinetics appeared to be linear over the dose range studied for each schedule with moderate, interpatient variability in the peak plasma concentration and AUC values and a 43 hour half-life. There was no difference in BSA-adjusted Cl/F between younger (≤12 years) children (Cl/F, 17.6 ± 16.5 ml/hr/m^2) and older (>12 years) children (Cl/F, 15.8 ± 5.5 ml/hr/m^2). However, MK-2206 clearance appeared to be lower in children compared with adults since $AUC_{0\text{-}48h}$ values for a 45 mg/m^2 dose in children (Table 4) were 2-fold higher than those same values for an equivalent dose of 75 mg in adults. [19]

In our study, there were a limited number of patients with complete sample sets for correlative biology studies. However, at the MTD in both schedules, there was an indication that pAKT was decreased for at least 6-8 hours after dosing. In the published adult phase 1 study, paired tumor biopsy samples were obtained in 9 patients. All 9 showed evidence of

inhibition of pSer473 AKT when compared with paired pretreatment samples, with a median decrease in pSer473 AKT of 88.8% (range, 44.9% to 95.6%; p=0.015).[19]

This study demonstrates that MK-2206 is well tolerated in children at the doses and schedules studied. There were no objective responses; 7 patients experienced prolonged stabilization of disease for ≥ 3 cycles. Similarly, no objective responses were noted when MK 2206 underwent *in vitro* and *in vivo* testing (every other day schedule) in the Pediatric Preclinical Testing Program.[20] *In vitro*, the median relative IC_{50} for MK 2206 was 2.2 micromolar. *In vivo*, MK 2206 induced significant differences in event free survival (EFS) distribution in 41% of solid tumor xenografts. However, intermediate activity (EFS>2.0) was only achieved in 2 of 4 osteosarcoma xenograft models. Adult pre-clinical combination testing has demonstrated enhanced MK-2206 efficacy with drugs such as carboplatin, erlotinib, lapatinib, AZD6244 and others. Combination testing with MK2206 in the PPTP may delineate effective combinations that may warrant further testing in children. If data from pediatric preclinical or adult clinical combination studies prove promising, consideration may be given to combination clinical trials in children with recurrent malignancies.

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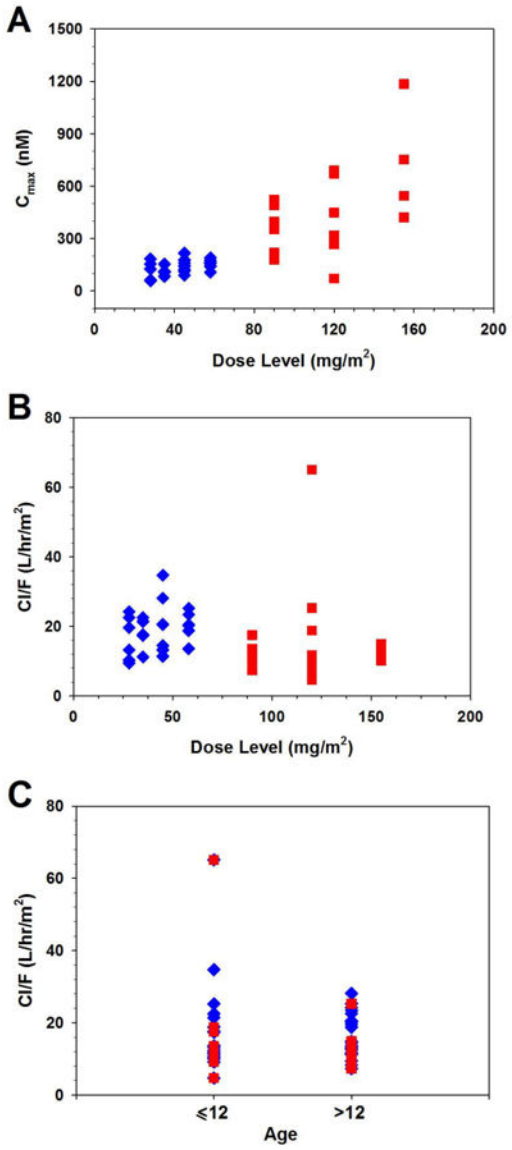

Figure 1. Graphs of C_{max} versus Dose (A) and Clearance versus Dose (B) and Age (C)

Table I

Patients Characteristics of Eligible Patients (n=50)

Characteristic	N=50
Male: female	26:24
Age, years	
Median	14.3
Range	3.1-21.9
Diagnosis	
Malignant glioma (including GBM, AA)	16
Ependymoma	4
Non-rhabdoid soft tissue sarcoma	4
Rhabdomyosarcoma	3
Hepatocellular carcinoma	3
Osteosarcoma	3
Ewing sarcoma	3
PNET (including medulloblastoma)	3
Neuroblastoma	3
Acinar cell carcinoma	1
Rhabdoid sarcoma	1
Anaplastic carcinoma	1
Malignant paraganglioma	1
Wilms tumor	1
Adrenal cortical carcinoma	1
Mixed germ cell tumor	1
Oligodendroglioma	1
Prior therapy	
Chemotherapy regimens: Median (range)	2 (0-8)
Radiotherapy	36
Courses of MK 2206	
Schedule 1: Median (range)	6.5 (1-12)
Schedule 2: Median (range)	6.5 (1-12)

Table II

Dose Limiting Toxicity Summary (course 1)

MK2206 Schedule	Dose Level	Number of Patients Entered	Number of Patients Evaluable	Number of Patients with DLT	DLT Types (n)
Schedule 1	28 mg/m^2	6	6	1	Dehydration (1)
	35 mg/m^2	6	5	0	
	45 mg/m^2	10	6	1	Hyperglycemia and neutropenia (1)
	58 mg/m^2	6	6	3	Rash (3)
Schedule 2	90 mg/m^2	6	6	1	Alkaline phosphatase and diarrhea (1)
	120 mg/m^2	10	6	1	Rash (1)
	155 mg/m^2	6	5	2	Rash (2)

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Table III

Other adverse events (non-DLTs) attributed (possibly, probably or definitely) to protocol therapy across both schedules and all dose levels.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Schedule 1	Maximum grade of toxicity across cycle 1 (Total, 23 cycles)				Maximum grade of toxicity across cycles 2-12 (Total, 47 cycles)			
Hematologic								
Anemia	1	1	1		2		1	
Lymphocyte count decreased	5	3	2	2	1	3	1	
Neutrophil count decreased	2	5				2		
Platelet count decreased	4				3			
White blood cell decreased	5	3	1		3	2		
Non-Hematologic								
Alanine aminotransferase increased	3	1					1	
Anorexia	4	3			1	2		
Aspartate aminotransferase increased	3	1					1	
Dry skin	2	1			1			
Fatigue	3	6			2	2		
Headache	3	1			1	1		
Hyperglycemia	8	1			2	1	1	
Hypermagnesemia	4				1			
Hypocalcemia	5				2			
Nausea	4						1	
Pruritus	2	2			1			
Rash maculopapular	3	2			1	1		
Sinus bradycardia	4							
Vomiting	6				1			
Weight loss	3	1			1	2		
Schedule 2	Maximum grade of toxicity across cycle 1 (Total, 17 cycles)				Maximum grade of toxicity across cycles 2-12 (Total, 62 cycles)			
Hematologic								
Anemia	3				2			
Lymphocyte count decreased	4	1		1	1		3	

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophil count decreased	1	2	3		1	2		
Platelet count decreased	2				1			
White blood cell decreased	3	3	1		4			
Non-Hematologic								
Anorexia	2					2		
Diarrhea	3	1			2			
Electrocardiogram QT corrected interval prolonged	3				1			
Fatigue	2	1			1	1		
Headache	3	1				1		
Hyperglycemia	2	1			3		1	
Hypocalcemia	1	1			2	1		
Hyponatremia	2							
Nausea	7	1			5			
Pruritus	1	3			2			
Rash maculopapular	4	2			1	2		
Vomiting	5	1			2			

*Non-hematologic toxicities are those that occurred in > 10% of patients

Table IV

Summary of MK 2206 Pharmacokinetic Parameters on Day 1, Cycle 1

Schedule	Dose (mg/m^2)	n	t_{max} (hr)	C_{max} (nM)	$AUC_{0\text{-}48h}$ (nM•hr)	Half Life (hr)	V_z/F (L/m^2)	Cl/F (L/hr/m^2)
1	28	6	4.7 (2.0)	108 (54)	3090 (1440)	32.3 (11.5)	806 (476)	16.5 (6.4)
	35	5	5.4 (1.4)	114 (25)	2820 (560)	45.7 (16.7)	1130 (320)	18.0 (4.4)
	45	9	4.7 (1.6)	151 (46)	4090 (1460)	32.8 (12.6)	758 (315)	17.6 (8.5)
	58	6	5.1 (1.7)	156 (28)	4230 (1460)	33.1 (6.2)	952 (178)	20.3 (4.0)
2	90	6	5.2 (1.8)	361 (140)	17300 (3200)	37.5 (4.0)	645 (214)	11.9 (3.5)
	120	9	5.1 (1.6)	418 (218)	24100 (13100)	44.2 (23.3)	1100 (1020)	18.0 (18.8)
	155	5	4.8 (1.7)	665 (321)	29300 (5700)	48.2 (15.0)	863 (304)	12.4 (1.8)