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Exploring the statistical and clinical impact of two interim analyses on the phase II design with option for direct assignment

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Abstract

Purpose—The primary goal of Phase II clinical trials is to understand better a treatment's safety and efficacy to inform a phase III go/no-go decision. Many Phase II designs have been proposed, incorporating randomization, interim analyses, adaptation, and patient selection. The phase II design with option for direct assignment (i.e. stop randomization and assign all patients to the experimental arm based on a single interim analysis (IA) at 50% accrual) was recently proposed [An et al, 2012]. We discuss this design in the context of existing designs, and extend it from a single-IA to a two-IA design.

Methods—We compared the statistical properties and clinical relevance of the direct assignment design with 2 IA (DAD-2) versus a balanced randomized design with 2 IA (BRD-2) and a direct assignment design with 1 IA (DAD-1), over a range of response rate ratios (2.0–3.0).

Results—The DAD-2 has minimal loss in power (<2.2%) and minimal increase in T1ER (<1.6%) compared to a BRD-2. As many as 80% more patients were treated with experimental vs. control in the DAD-2 than with the BRD-2 (experimental vs. control ratio: 1.8 vs. 1.0), and as many as 64% more in the DAD-2 than with the DAD-1 (1.8 vs. 1.1). We illustrate the DAD-2 using a case study in lung cancer.

Conclusion—In the spectrum of phase II designs, the direct assignment design, especially with 2 IA, provides a middle ground with desirable statistical properties and likely appeal to both clinicians and patients.

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Keywords

phase II; direct assignment; two interim analyses; biomarker

INTRODUCTION

There are typically three phases of clinical trials in the development of new treatments in oncology. In Phase I, the primary goal is to demonstrate the treatment's safety and identify a maximally tolerated dose in a small group of patients. In Phase II, the primary goal is to gain a better understanding of the treatment's safety and efficacy, to inform a go/no-go decision to phase III testing through a single arm or a small randomized trial in a homogenous group of patients, with the trial size varying from < 100 patients to as many as 300 patients. Finally, in Phase III, the primary goal is to compare the new treatment with the standard treatment in a large group of patients to demonstrate a clinical benefit. In this paper, we focus on designs for Phase II trials. Historically, Phase II trials in oncology have been single-arm trials where all patients receive the new treatment. More recently, randomization to either the new treatment or the standard treatment has become standard for Phase II trials [1]. In addition to being either single-arm or randomized trials, Phase II trials may also include planned interim analyses for safety and/or futility and/or efficacy. Bayesian methods have also been incorporated into Phase II design and analysis, allowing for flexible adaptive designs while requiring more resources than non-Bayesian designs.

Recently, a “hybrid” phase II design was proposed that blends attractive features of existing designs, including randomization, adaptive accrual and simple implementation. The proposed design (An et al, [2]) is initiated as a randomized trial with equal allocation between two treatment arms. At the time of a single interim analysis (IA), after one-half of planned accrual, the design includes an option, based on pre-specified rules, of terminating accrual entirely (for efficacy or futility), continuing as a randomized trial, or continuing as a single-arm trial (“direct assignment”). An et al ([2]) demonstrate that this design maintains comparable statistical properties in terms of power and type I error rate as those of a balanced randomized design with IA. Sensitivity analyses suggested minimal effects on statistical properties from the *timing* of single IA and *population shifts* in the case where the direct assignment option is adopted. This design with direct assignment option has ready applications to general settings of cytotoxic therapies.

In the setting of Phase II trials, many have argued that a single interim analysis may be inadequate, and that multiple looks improve both the statistical and ethical properties of the design. Further, a trial with interim analysis may terminate early, potentially resulting in cost savings and earlier delivery of effective treatments to patients (e.g. [4]–[7]). Additionally, the design of [2] with a single IA has mostly been studied so far for its statistical properties. In this paper, therefore, we study the design of [2] by incorporating two-IA, focusing more on the clinical relevance of this design as it relates to number of patients treated on the experimental regimen, and illustrate with an example using a real trial. Specifically, we first review the statistical properties of a design with the option for direct assignment and with two-IA (DAD-2) but then shift our focus to the impact on sample size and proportion of

patients receiving experimental vs. control treatment associated with a DAD-2 relative to both a balanced randomized design with two-IA (BRD-2) and a design with option for direct assignment and one-IA after 1/2 accrual (DAD-1). We then illustrate the DAD-2 with an example from a non-small cell lung cancer trial in which a retrospective analysis identified a treatment benefit in a subgroup of patients with elevated Cox2 enzyme levels [8].

METHODS

Design Framework

We consider a binary outcome. We specify two interim analyses (IA) after 1/3 and 2/3 of planned accrual. At the first IA (i.e. IA-1), there are 4 options: stop for efficacy, continue with direct assignment, continue with randomization, or stop for futility. If direct assignment is adopted at IA-1, then the trial continues with direct assignment to the end without a second IA, enrolling the planned accrual to active treatment for the remainder of the trial (i.e. $1/2 * (1/3 + 1/3) = \text{one-third of the total planned accrual}$). Otherwise if randomization continues at IA-1, then at the second IA (i.e. IA-2), there are again 4 options: stop for efficacy, continue with direct assignment, continue with randomization, or stop for futility.

Extending the framework of [1], the IA decisions are based on the p-values from a test comparing the experimental to control treatment using cumulative data. In particular, the first IA (IA-1) uses data from Stage I, the second IA (IA-2) uses data from Stages I and II, and the final analysis uses data from all available stages. We specify the overall type I error rate (α) and power ($1-\beta$); and the expected response rates in control (p^{control}) and in treated (p^{treat}) patients, with an associated treatment effect (response rate ratio, $\text{RRR} = p^{\text{treat}} / p^{\text{control}}$). The maximum sample size (N) is calculated based on α , β , and the expected treatment effect size, using a one-sided two sample test of proportions assuming 1:1 randomization and O'Brien-Fleming (OF) stopping rules for efficacy and futility. At any given IA, the cut-off boundary for deciding between direct assignment and randomization is taken to be the cut-off boundary for efficacy in the subsequent IA (or final analysis, in the case of the last IA). An advantage of using the known framework of OF stopping rules is that this design can be readily implemented using existing software.

As an example of the cut-off boundaries, consider the case of two-IA, $\alpha=0.10$, and $\beta=0.8$. We specify the cut-off for deciding between direct and randomized assignment at the first IA to be 0.043, which corresponds to the cut-off for efficacy at the second IA, and the cut-off for deciding between direct and randomized assignment at the second IA to be 0.087, corresponding to the cut-off for efficacy at the final analysis (Table 1).

Simulation Settings

We conducted simulation studies to evaluate the operating characteristics of the designs. In particular, we first recorded the probabilities of IA decisions (estimated by the proportion of trials adopting the decisions) for the DAD-2, to understand basic properties of the DAD-2. Then we compared the power and type I error rates for a DAD-2 with those for a BRD-2. Finally we compared the following accrual outcomes of a DAD-2 with those of a BRD-2 and a DAD-1, under the null and alternative hypotheses: the expected total accrual and ratio

of the number of patients treated with experimental versus control treatment if the experimental treatment is truly effective. Typically in Phase II studies, minimizing expected accrual is of primary interest, yet it might be simultaneously of interest to maximize the expected ratio of patients treated with experimental versus control treatment. To quantify this trade-off, we additionally considered the following composite measure: *Expected Accrual / Expected Ratio of Number Treated with Experimental vs. Control*, where lower values reflect lower expected accrual and proportionally more patients treated with experimental (vs. control), and are therefore desirable under the alternative hypothesis. We generated 6,000 trials and specified $\beta=0.80$, and $\alpha=0.10$ and 0.20 . Sample size calculations were based on a control response rate of $p^{\text{control}} = 0.20$ and experimental treatment response rates of $p^{\text{treat}} = 0.40$, with associated response rate ratio (RRR) of 2.0 (Table 1). We additionally considered other treatment effects by varying the experimental treatment response rates according to $\text{RRR} = 2.1$ to 3.0 . All tests of equal proportions were based on the normal-approximation z-test without correction for continuity.

RESULTS

Decision Probabilities

We estimated the probabilities of each decision (stop early for efficacy, continue with direct assignment option, continue with randomization, or stop early for futility), as well as the conditional probability of adopting direct assignment option given continuation, at both IA for DAD-2 only. Both the probability of stopping early for efficacy and the conditional probability of adopting the direct assignment option given continuation increase with increasing RRR, as expected. In particular, for $\alpha=0.10$ and at IA-1, the probability of stopping early for efficacy is 0.4% under the null, and under the alternatives, increases from 6.8% to 36.2% as RRR increases from 2.0 to 3.0 (Supplemental Table 1, rows labeled “IA-1”). At IA-2, the probability of stopping early for efficacy is 3.9% under the null; under the alternatives, the probability of stopping early for efficacy increases from 39.3% to 84.2% as RRR increases from 2.0 to 3.0. Under the null, 74.2% of trials continue past IA-1 and 34.1% of trials continue past IA-2. With larger expected treatment effects, trials are less likely to continue past either IA (90.1% to 63.7% of trials for continue past IA-1 for $\text{RRR}=2.0$ to 3.0 , and 48.5% to 15.3% of trials continue past IA-2 for $\text{RRR}=2.0$ to 3.0). Given that a trial will continue with either direct assignment or randomization, the conditional probability of adopting the direct assignment option increases from 5.8% to 65.9% at IA-1 (16.8% to 48.2% at IA-2) for RRR from 1.0 to 3.0 (Supplemental Table 1, rows labeled “Among trials that continue past IA-1 (IA-2)”). The decision probabilities follow similar trends for $\alpha=0.20$.

Statistical Properties

The statistical properties of a DAD-2 are similar to those of a BRD-2 (Table 2). For $\alpha=0.10$, the maximum power loss across RRR is 2.2% for a 2-IA direct design versus a BRD-2 (87.4% vs. 85.2% for BRD-2 vs. DAD-2, associated with $\text{RRR}=2.2$; results not shown in Table). The inflation of type I error rate is 1.6% for DAD-2 versus a BRD-2. Results for $\alpha=0.20$ similarly demonstrate that statistical properties are preserved with the DAD-2 as compared with a BRD-2.

Expected Accrual and Ratio of Number of Patients Treated with Experimental versus Control Treatments

Compared with either the BRD-2 or the DAD-1, the DAD-2 is associated with modest savings in total expected accrual and proportionally more patients treated with experimental than with control treatments (Table 2). For example, under the null and with $\alpha=0.10$, the total expected accruals are 65, 70, and 66 patients and the ratio of patients receiving experimental versus control treatments are 1.1, 1.1, and 1.0, for DAD-2, DAD-1, and BRD-2 respectively. For a RRR of 2.0 and with $\alpha=0.10$, the total expected accruals are 71, 74, and 74 patients and the ratio of patients receiving experimental versus control treatments are 1.6, 1.3, and 1.0, for DAD-2, DAD-1, and BRD-2 respectively. The *Expected Accrual / Expected Ratio of Number Treated with Experimental vs. Control* ratios are consistently lower for the DAD-2 relative to the other 2 designs (Figure 1).

EXAMPLE: NON-SMALL CELL LUNG CANCER (NSCLC) AND COX2 ENZYME AS A MARKER

A phase II study (C30203)[8] in advanced non-small cell lung cancer evaluated patients randomized to one of 3 treatment arms: Gemcitabine/Carboplatin + Zileuton (A), Gemcitabine/Carboplatin + Celecoxib (B), and Gemcitabine/Carboplatin + Zileuton + Celecoxib (C) over 6 treatment cycles. A predefined retrospective analysis (based on a relatively small sample size) suggested an overall survival benefit associated with B or C (vs. A) in patients with elevated levels of the Cox2 enzyme (4) determined by immunohistochemistry. We will therefore use this study as an illustrative example to discuss the DAD-2, and compare it to a BRD-2 and a DAD-1. In particular, we will consider the subgroup of patients with elevated Cox2 levels, and combine Arms B and C as the combined “experimental” treatment arm.

There were a total of 32 patients with elevated Cox2 levels, 11 of whom were on Arm A and 21 on Arms B-C combined. The 5-month overall survival (OS) rate in Arm A was 36.4%, compared with 90.5% for Arms B-C; we will design our trial based on these summary statistics. In particular, we generated 6,000 trials and specified $\beta=0.80$, and $\alpha=0.05$ and 0.10. We consider the smaller α -level (0.05) given the large expected treatment effect. Sample size calculations and stopping rules were based on a control response rate (i.e. 5-month OS rate) of $p^{\text{control}} = 0.35$ and experimental treatment response rates of $p^{\text{treat}} = 0.90$, with associated response rate ratio (RRR) of 2.57 (Table 3). In cancer clinical trials, typically one considers 3-, 6-, or 12-month OS, as well as more moderate treatment effects. Moreover, the small sample size means that the gains in expected accrual are likely to be minimal, and the time needed to accrue to a balanced randomized study without IA's might be less than the follow-up required for even a single IA. However, we chose this endpoint of 5-month OS merely to illustrate our design using summary data from an actual trial. In our simulations, we consider clinically-relevant scenarios.

The statistical properties (type I error rate and power) were preserved with the DAD-2 relative to the BRD-2 (Table 4). The maximum total sample size was 36 patients for $\alpha=0.05$, and 26 for $\alpha=0.10$ (Table 3). The decision probabilities are summarized in Supplementary

Table 2. Under the alternative and for $\alpha=0.05$ ($\alpha=0.10$), the total expected accrual for the DAD-2 was 28 (20) patients, compared with 29 (18) patients for the DAD-1 and 30 (21) for the BRD-2 (Table 4). The ratio of patients receiving experimental vs. control treatment was 1.54 (1.88) for the DAD-2, compared with 1.30 (1.39) for the DAD-1 and 1.00 (1.00) for the BRD-2 (Table 4). The ratio of total accrual / (experimental / control) was 18.2 (10.6) for the DAD-2, compared with 22.3 (12.9) for the DAD-1 and 30.0 (21.0) for the BRD-2 (Table 4).

Thus, if we had known a priori of the expected treatment benefit in the subgroup of patients with elevated Cox2 levels and adopted a DAD-2 rather than either a DAD-1 or a BRD-2 for this subgroup of patients, we would have treated proportionally more patients on experimental vs. control treatment, with a sample size similar to that of either a DAD-1 or a BRD-2

DISCUSSION

There are many choices for the design of a Phase II trial. Selecting a design that enrolls an appropriate patient population to yield valid results, and one that can be readily implemented in practice, is crucial for successful development of new treatments. The design with direct assignment option can enroll any pre-selected population of patients. Although the variance of any treatment effect estimate would be lower with a balanced randomized design versus an unbalanced design (such as the design with direct assignment option), the design with direct assignment option nevertheless has potential advantages over a balanced randomized design including reduced accrual requirements and treating proportionally more patients with experimental versus control treatment, while maintaining desirable statistical properties. Bayesian designs with outcome-adaptive randomization probabilities (e.g. [9–10]) also benefit from treating more patients with the superior treatment, while preserving some notion of power relative to designs with equal randomization. A key difference from the design with direct assignment option, however, is that with the Bayesian adaptive randomization designs, randomization of treatment continues throughout the duration of the trial (except in the rare instances where the adaptive randomization probabilities tend toward 0 in all but one treatment arm). While desirable in principle, these trials tend to require more resources for implementation, depending on how often the randomization probabilities are adapted. The design with direct assignment option, on the other hand, is relatively straightforward to implement while incorporating some of the benefits of adaptive features.

Maximizing the number of patients exposed to experimental treatment is not usually a major concern until the phase III setting. Our rationale for maximizing the number of patients exposed to experimental treatment in the phase II setting is based on the assumption that we have information on how a patient population might do with standard treatment. However, if patients treated in this trial are not similar to historical controls, then maximizing the number of patients exposed to experimental treatment might not be desirable since we lack prior data for how this patient population might do with either standard or experimental treatment.

Including an option for direct assignment not only preserves statistical properties and offers clinical appeal, but is also flexible. Our proposal for an option to direct assign is reminiscent of, but differs from, designs proposed by Colton ([11–12]), the two-armed bandit problems

(e.g. [13]), and Zelen's "play the winner" design ([14]). In reality, any design with interim monitoring or adaptive randomization could incorporate an option for direct assignment. In our earlier paper [2], we conducted a sensitivity analysis and found the effects of a population shift to be minimal on the statistical properties of our design. We acknowledge that this sensitivity analysis does not guarantee absence of potential sources of bias associated with non-randomization. However the concerns over selection bias are present in most adaptive designs as well as single-arm designs with comparison against historical controls, and in theory, any design. Thus it is important to conduct multiple phase II trials before proceeding to a phase III trial. Nonetheless, we advise against adopting the direct assignment option in situations where substantial population drifts are expected, or where eligibility criteria will change over the course of the trial.

There are several possible interesting extensions that could be the focus of future work. For example, one could consider extending to the setting of multiple (>2) treatments. Moreover, the timing of the interim analysis decision can be adaptive rather than at fixed timepoints (e.g. timing of second IA depends on data available at first IA). Extension from binary to time-to-event endpoints is another possibility. The design with direct assignment option could be conducted in the enrichment setting, or also be implemented as an all-comers design. We are currently exploring how to combine multiple biomarker-defined subgroups with different research hypotheses into a single trial design. All of these extensions, including from single to two interim analyses, raise the level of complexity of trial design. Nevertheless, with the potential savings in accrual and benefits from treating more patients with experimental than with control treatment that are associated with a direct assignment option, modifying existing designs to incorporate an option for direct assignment could be a next worthwhile step for developing the field of personalized cancer treatment. Another extension may have been to include 3 or more IA. However, the incremental benefit of additional interim analyses beyond 2 on expected accrual are likely to be small [4]. Moreover, since patient accrual may be suspended during each interim analysis (especially in cases where accrual rate is rapid), causing potential difficulties for subsequent patient enrollment, multiple interim analyses may not be desirable [15]. This trade-off in savings in expected accrual versus cost of extra time required for evaluation at IA (e.g. from an endpoint that requires a long time to observe) must be considered even with 2 IA. The DAD-1 may still be recommended in settings where the endpoint requires a long time to observe.

In this paper for the DAD-2, we specified the same decision set at each interim analysis. However, we also explored variations on this. In particular, we considered a DAD-2 where at the first IA there is no option to stop early for efficacy, as well as a DAD-2 where at the first IA, there is the option to stop early for efficacy but no option to adopt direct assignment. In either of these cases, though statistical properties were preserved, the total expected accrual and ratio of patients receiving experimental versus control treatment were less desirable as compared with the original DAD-2 (with options to stop for efficacy, continue with direct assignment, continue with randomization, or stop for futility available at both interim analyses).

In conclusion, among the choices available for Phase II trial designs, the direct assignment option design with 2 interim analyses (DAD-2) is an attractive option. The DAD-2 has comparable statistical properties as the balanced randomized design with 2 interim analyses (BRD-2). Moreover, of clinical interest, in terms of total expected accrual and expected ratio of patients treated with experimental versus control treatment, the DAD-2 does as well as, or better than, both the BRD-2 and the DAD-1. The benefits associated with the DAD-2 over either of the BRD-2 or the DAD-1 are more apparent with larger treatment effects. Therefore in the situation where preliminary evidence suggests a promising though not definitive treatment effect in a known (sub-) population of patients, and where the endpoint can be observed in a reasonably short amount of time, we recommend use of a design with option for direct assignment, and in particular with 2 interim analyses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Expected Accrual / Ratio of Expected Treated with Experimental vs. Expected Treated with Control vs. Response Rate Ratio, for the DAD-1 (solid teal), DAD-2 (dashed orange), and BRD-2 (dotted purple). Smaller values for Expected Accrual / Ratio of Expected Treated with Experimental vs. Expected Treated with Control are more desirable.

Table 1A

Sample Sizes and Stopping Boundaries for 1 interim analysis.

Alpha	Power	Accrual fraction for IA	Stopping Boundaries (p-values)			MaxN
			Early efficacy at IA1	Early futility at IA1	Overall efficacy	
0.10	0.8	1/2	0.02	0.4566	0.094	101
0.20	0.8	1/2	0.0699	0.5765	0.1803	65

To specify a one-IA design with direct assignment option, use the “overall efficacy” cutoff to decide between randomization and direct assignment at IA-1.

Table 1B

Sample Sizes and Stopping Boundaries for 2 interim analyses.

				Stopping Boundaries					
Alpha	Power	Accrual fraction for IA1	Accrual fraction for IA2	Early efficacy at IA1	Early futility at IA1	Early efficacy at IA2	Early futility at IA2	Overall efficacy	MaxN
0.10	0.8	1/3	2/3	0.004	0.736	0.043	0.293	0.087	98
0.20	0.8	1/3	2/3	0.026	0.813	0.109	0.432	0.166	63

To specify a two-IA design with direct assignment option at both IA, use the “early efficacy at IA2” cutoff to decide between randomization and direct assignment at IA-1 and the “overall efficacy” cutoff to decide between randomization and direct assignment at IA-2.

Table 2

Operating Characteristics for the 2-IA Direct Design (column is shaded for emphasis), the 1-IA Direct Design, and the 2-IA Balanced Randomized Design, at $\alpha=0.10$ and $\alpha=0.20$.

	RRR	$\alpha=0.10$			$\alpha=0.20$		
		2-IA Direct Design	1-IA Direct Design	2-IA Balanced Randomized Design	2-IA Direct Design	1-IA Direct Design	2-IA Balanced Randomized Design
Power (%)	2.0	77.4	78.3	78.7	75.2	78.8	76.8
	3.0	99.4	99.6	99.7	97.5	98.5	98.7
Type I Error Rate (%)	1.0	10.9	10.8	9.3	21.5	22.8	19.7
	1.0	65	70	66	42	48	42
Accrual (n)	2.0	71	74	74	42	46	44
	3.0	55	57	55	33	37	34
Experimental / Control	1.0	1.1	1.1	1.0	1.2	1.1	1.0
	2.0	1.6	1.3	1.0	1.5	1.2	1.0
	3.0	1.8	1.1	1.0	1.6	1.1	1.0
Accrual / (Experimental / Control)	1.0	57.8	64.0	65.4	34.5	43.1	42.4
	2.0	43.9	57.0	73.4	27.4	38.0	43.3
	3.0	29.4	49.3	54.7	20.1	32.5	33.1

Table 3A

Sample Sizes and Stopping Boundaries for 1 interim analysis, for c30203.

Alpha	Power	Accrual fraction for IA	Stopping Boundaries (p-values)			MaxN
			Early efficacy at IA1	Early futility at IA1	Overall efficacy	
0.05	0.8	1/2	0.0056	0.3280	0.0482	34
0.10	0.8	1/2	0.02	0.4265	0.094	24

To specify a one-IA design with direct assignment option, use the “overall efficacy” cutoff to decide between randomization and direct assignment at IA-1.

Table 3B

Sample Sizes and Stopping Boundaries for 2 interim analyses, for c30203.

				Stopping Boundaries					
Alpha	Power	Accrual fraction for IA1	Accrual fraction for IA2	Early efficacy at IA1	Early futility at IA1	Early efficacy at IA2	Early futility at IA2	Overall efficacy	MaxN
0.05	0.8	1/3	2/3	0.0007	0.5919	0.0161	0.1816	0.0451	36
0.10	0.8	1/3	2/3	0.0044	0.6724	0.0426	0.2721	0.0870	26

To specify a two-IA design with direct assignment option at both IA, use the “early efficacy at IA2” cutoff to decide between randomization and direct assignment at IA-1 and the “overall efficacy” cutoff to decide between randomization and direct assignment at IA-2.

Table 4

Operating Characteristics for the 2-IA Direct Design (column is shaded for emphasis), the 1-IA Direct Design, and the 2-IA Balanced Randomized Design, at $\alpha=0.05$ and 0.10, for c30203.

	RRR	$\alpha=0.05$			$\alpha=0.10$		
		2-IA Direct Design	1-IA Direct Design	2-IA Balanced Randomized Design	2-IA Direct Design	1-IA Direct Design	2-IA Balanced Randomized Design
Power (%)	2.57	81.5	75.3	82.0	81.1	78.2	8.6
Type I Error Rate (%)	1.0	5.5	4.7	4.9	80.1	10.6	9.2
Accrual (n)	1.0	22	23	23	16	16	17
Experimental/Control	2.57	28	29	30	20	18	21
	1.0	1.05	1.03	1.0	1.17	1.09	1
Accrual / (Experimental/Control)	2.57	1.54	1.30	1.0	1.88	1.39	1
	1.0	21.0	22.3	23.0	13.7	14.7	17.0
	2.57	18.2	22.3	30.0	10.6	12.9	21.0