

The Phase 1 Trial from study participant's point of view

**OBJECTIVE: To help advocates (representing primary stakeholders)
to see why we can do better than 3+3**

- **for ethical reasons - honoring why patients enroll in trials ², and**
- **to personalize the dose-finding problem. ³ One size does not fit all.**

Topics

Why patients enroll in phase 1 trials?

How does the standard 3+3 dose-finding clinical trial work?

Why the MTD is not your MTD

What is Adaptive Dose Titration?

Premises:

- Raising advocate awareness
- Shared stakeholder goals

Goals of adaptive dose titration - summarized

Why patients would prefer titration

Patient concerns with 3+3

Docetaxel example:

range of individual MTDs

- Individual MTDs vary widely
- A Histogram
- Dose Titration vs 3+3:
comparing participant's dose experience

Ethical questions

Informed Consent in dose finding studies

Side-by-side consent language:

3+3 | Titration

- Why is this study being done?
- What are the study groups?
- Benefits / What possible benefits can I expect from taking part in this study?

In Summary

By Karl Schwartz

Patient advocate

www.lymphomation.org

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 1

Why do patients enroll in Phase I Clinical Trials?

- **Most patients take part with an expectation or hope for benefit - not out of altruism** ²
"more than 80% of patients enroll in early-phase clinical oncology trials motivated by the potential of a clinical benefit, with approximately half expecting tumor shrinkage"
- **Due to advances in basic science and how study drugs are designed to target disease pathways, there is an increasing potential for tumor responses in early-phase studies.**
- **Advances in immunotherapy are showing an increasing prospect for very durable tumor responses for single agents across cancer types.**

Perspective: We should honor patient motivations, hopes, and expectations and recognize that the prospect for benefit in early phase studies is improving.

Consent language for 3+3 studies must better inform patients about the potential for receiving sub-therapeutic doses if they are assigned to the initial dose cohorts.

To implement the position statement made by ASCO that phase 1 studies have **therapeutic intent**, the Titration method should be adopted whenever feasible.

Julie Vose and 1 other Retweeted



Mike Thompson, MDPH @mtmdphd · Jan 7

...position of @ASCO that phase 1 cancer clinical trials have **therapeutic intent** & should be covered by Medicare ow.ly/9IFu30aGyh3



1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 2

How does the standard 3+3 dose-finding trial work?

3+3 Dose Group Escalation (based on NCI Consent Language)

Different doses of the study drug will be given to several study participants. The first several study participants will receive the lowest dose.

If the drug does not cause serious side effects, it will be given to other study participants at a higher dose.

The doses will continue to increase for every group of study participants until side effects occur that require the dose to be lowered. Then the study is stopped. You (*will/will not*) be able to receive additional doses of the drug.

The **standard 3+3 dose escalation** method tests different doses on groups of patients (dose-level groups). The dose-level group you are assigned to is based on chance. Your dose will not be increased or decreased.

The **titration** method tests different doses on each participant as described:

Dose Titration method: (from proposed consent language)

In this study, you will belong to a group of your own. With safety in mind, we will start you at a dose that we think is probably too low for you. If you tolerate this dose without bad effects, we will increase your dose. If at some point we reach a dose where you have some bad effects that you can tolerate, we will suggest staying at that dose. If you have bad effects that you cannot tolerate, we will decrease your dose back to the previous level.

In this study, you may benefit from what we learn from the participants who enrolled before you. (For example, we might learn that there is some dose that most participants find too toxic. If this happens, we might stop increasing your dose before reaching that level, even if you seem to be tolerating the drug very well.) In the same way, your experience trying different doses of the study drug will help the participants who enroll after you.

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT>

Why “the” MTD (arrived at with the 3+3) probably isn’t your MTD?

From life experiences we observe that our spouse sleeps soundly after a pot coffee at 6PM, while we stare all night at the ceiling. Is it that our wife absorbs less of it, or that her brain is not sensitive to caffeine? Or is it that you eliminate the caffeine slower?

Factors influencing the heterogeneity (individual variation) of treatment effects (HTE) at the same doses:

Category

Non-biologic

disease and patient characteristics

Factors

age, sex, hepatic/renal function, diet/exercise practices, illness severity, smoking, and alcohol consumption habits

Pharmacokinetic (PK)

*what the body does to a drug
or the fate of a drug within the body*

absorption, distribution, metabolism, excretion (ADME)

Our unique **ADME** genes can influence the fate of the drug in our body ... in our being a poor, intermediate, efficient, or ultra-rapid metabolizers of a drug - affecting efficacy or the risk of bad drug reactions (neuropathy for example) - requiring individualized dosing.

Pharmacodynamic (PD)

what a drug does to the body

Our unique PD pathways genes can influence how our body responds to the drug through different pathways: receptors, ion channels, enzymes, and the immune system

These factors can help explain the relationship between the dose and response (the drug's good or bad effects.) Finally, the **pharmacologic response** depends on the drug binding to its target. The concentration of the drug at the receptor site influences the drug's effect.

NOTE: All the factors above -related to dosing- may be optimal, but will only influence efficacy if the target the drug binds to is also right (e.g., is important to the survival and persistence of the cancer cell). A drug target may be crucial to the persistence of one type of cancer and not to another.

Adapted from: *Potential genetic causes of heterogeneity of treatment effects.* - PubMed <http://bit.ly/2DQV7FC>

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede ‘the’ Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT>

What is the Adaptive Dose Titration?

It is the continual adjustment of a dose of a study drug in each study participant. Dosages are adjusted until the desired clinical effect is achieved in order to find his or her individual MTD (iMTD) and the range of iMTDs appropriate for the next phase of study.

Premises - what is needed to advance it?

Raising awareness

There are ethical and scientific shortcomings with the 3+3 method.

Patient awareness is needed to alter entrenched practices and biases that are no longer justified due to advances in basic science and rational study drug design.

Shared stakeholder goals

The adaptive dose titration method:

- Can yield higher response rates to support FDA approval.
- Can lower the risk of high grade adverse events that can occur when the MTD is higher than the individual's MTD.
- The improved prospect for benefit can foster timely accrual
- Is aligned with the ideals and patient-centered goals of personalized medicine: *"the right drug, at the right dose, for the right patient."*
- Can be a more efficient design for testing study drugs for rare cancers, or less common molecular subtypes of common cancers, by gaining optimal information from each study participant.
- Can improve the efficiency in gaining knowledge by assessing, safety, efficacy, and related biomarkers in all phases of study (dose-finding, expansion, and beyond)

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 5

Goals of adaptive dose titration - summarized

To harmonize clinical research goals with the hopes and wishes of the study participants.

- To find **each** participant's individual maximum tolerated dose (iMTD) in order to increase the potential for efficacy.
- To optimize each patient's prospect for clinical benefit.

Public citation library: https://www.zotero.org/groups/1150255/the_mtd_kills

- To potentially reduce the risk of higher grade adverse events.
- To identify the starting **and** highest recommended phase 2 dose (RP2D) for the next phase of study.
- To learn how the next patients may be monitored for good or bad effects as the dose is adjusted towards the iMTD.
- To optimize how each participant's outcome (tumor and side effects, biomarker changes) adds knowledge to the dose-finding question
- To merge dose-finding with the dose-expansion phase of study as the doses are adjusted and the clinical effects – including clinical responses - are monitored.

(All participant outcomes counted in a seamless phase 1 / 2)



1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 6

Why the patient will prefer adaptive dose titration trials:

*There is a correlation between the MTD and tumor responses
– most of the time (for cytotoxic agents) tumor response occur at 80% or more of their subsequent
recommended dose for phase II trials.¹*

- **The dose you receive is based your iMTD (*not when you happen to enter the study*)**
- **The doses you receive will change based on your ability to tolerate the dose, including how it makes you feel (your preference to go higher or lower) – increasing patient autonomy.**
- **The increasing doses you receive increases the potential for a tumor response.**
- **Your individual MTD (iMTD) can be very different than Joe's MTD**
- **The highest dose of a study drug you receive will be based on your individual MTD.
Potentially increasing the prospect for benefit and reducing the risk of serious side effects.**

Patient concerns with 3+3

** KEY basis for ethical concern: There is a correlation between the MTD and tumor responses – most of the time (for cytotoxic agents) tumor response occur at 80% or more of their subsequent recommended dose for phase II trials.¹*

- **The dose you receive in 3+3 is based on chance
(*when you happen to enter the study*)**
- **The dose you receive will not change even if much higher doses are found to be safe as increasing doses are tested in different groups of patients.**
- **The dose you receive (by chance) can be subtherapeutic
well below the MTD or your MTD & therefore less likely to lead to a tumor response.**
- **The dose you start with (by chance) could be much higher than your unknown MTD – which can lead to a higher grade adverse event.**

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 7

Dr. Norris: Docetaxel Example - range of individual MTDs

Method summary: These are simulated, *individual* MTD's (iMTD) randomly drawn for 24 patients from a simulation model.

It was built by combining 2 published models for the cytotoxic chemotherapy drug, docetaxel.

One of the models described how docetaxel is processed by the body. The other model described how it causes neutropenia.

These models also described how individuals differ in regard to how their bodies processed docetaxel, and how their bone marrow responds to it.

The iMTD are in arbitrary units

Frequency of Individual Maximum Tolerated Dose (iMTD) in BIN order				
Dose Bin Labels	DOSE RANGE for BIN Labels	Patient Number	individual Maximum Tolerated Dose (iMTD)	Frequency
0	0-0.25	15	0.1939304	1
0.25	0.25-0.5	17	0.325614	5
0.25	0.25-0.5	10	0.3691172	
0.25	0.25-0.5	23	0.4529213	
0.25	0.25-0.5	13	0.490257	
0.25	0.25-0.5	11	0.4960891	
0.5	0.5-0.75	9	0.5804417	3
0.5	0.5-0.75	4	0.658602	
0.5	0.5-0.75	2	0.7087201	
0.75	0.75-1.0	18	0.769855	4
0.75	0.75-1.0	24	0.8162474	
0.75	0.75-1.0	16	0.8430098	
0.75	0.75-1.0	22	0.985511	
1	1.0-1.25	14	1.00756	6
1	1.0-1.25	6	1.044504	
1	1.0-1.25	5	1.054882	
1	1.0-1.25	19	1.05695	
1	1.0-1.25	7	1.141596	
1	1.0-1.25	20	1.229229	
1.25	1.25-1.5	3	1.278496	
1.25	1.25-1.5	8	1.437727	2
1.5	1.5-1.75	21	1.654841	2
1.5	1.5-1.75	12	1.656257	
1.75	1.75-2	1	1.879306	1

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 8

The range of individual MTDs (continued):

The MTD_i values were determined by 'solving for' the dose that caused the neutrophil (ANC) count to dip to 500 in each cycle. (*This ANC count is on the borderline of Grade III-IV toxicity in the CTCAE grading system.*)

Among the 24 simulated patients:

- **Just over half had an iMTD between 0.5 & 1.25**
- **About a quarter could tolerate more than 1.25, and a quarter could not even tolerate 0.5.**

This example should be understood as an illustration only. But there is ample evidence that iMTD varies meaningfully among cancer patients.

Two decades of observational evidence across many types of cancer show that patients who have more adverse effects with chemo also have better outcomes*

* *Public citation library:*

https://www.zotero.org/groups/1150255/the_mtd_kills

Frequency of Individual Maximum Tolerated Dose (iMTD) in BIN order				
Dose Bin Labels	DOSE RANGE for BIN Labels	Patient Number	individual Maximum Tolerated Dose (iMTD)	Frequency
0	0-0.25	15	0.1939304	1
0.25	0.25-0.5	17	0.325614	5
0.25	0.25-0.5	10	0.3691172	
0.25	0.25-0.5	23	0.4529213	
0.25	0.25-0.5	13	0.490257	
0.25	0.25-0.5	11	0.4960891	3
0.5	0.5-0.75	9	0.5804417	
0.5	0.5-0.75	4	0.658602	
0.5	0.5-0.75	2	0.7087201	4
0.75	0.75-1.0	18	0.769855	
0.75	0.75-1.0	24	0.8162474	
0.75	0.75-1.0	16	0.8430098	
0.75	0.75-1.0	22	0.985511	6
1	1.0-1.25	14	1.00756	
1	1.0-1.25	6	1.044504	
1	1.0-1.25	5	1.054882	
1	1.0-1.25	19	1.05695	
1	1.0-1.25	7	1.141596	
1	1.0-1.25	20	1.229229	2
1.25	1.25-1.5	3	1.278496	
1.25	1.25-1.5	8	1.437727	2
1.5	1.5-1.75	21	1.654841	
1.5	1.5-1.75	12	1.656257	1
1.75	1.75-2	1	1.879306	

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

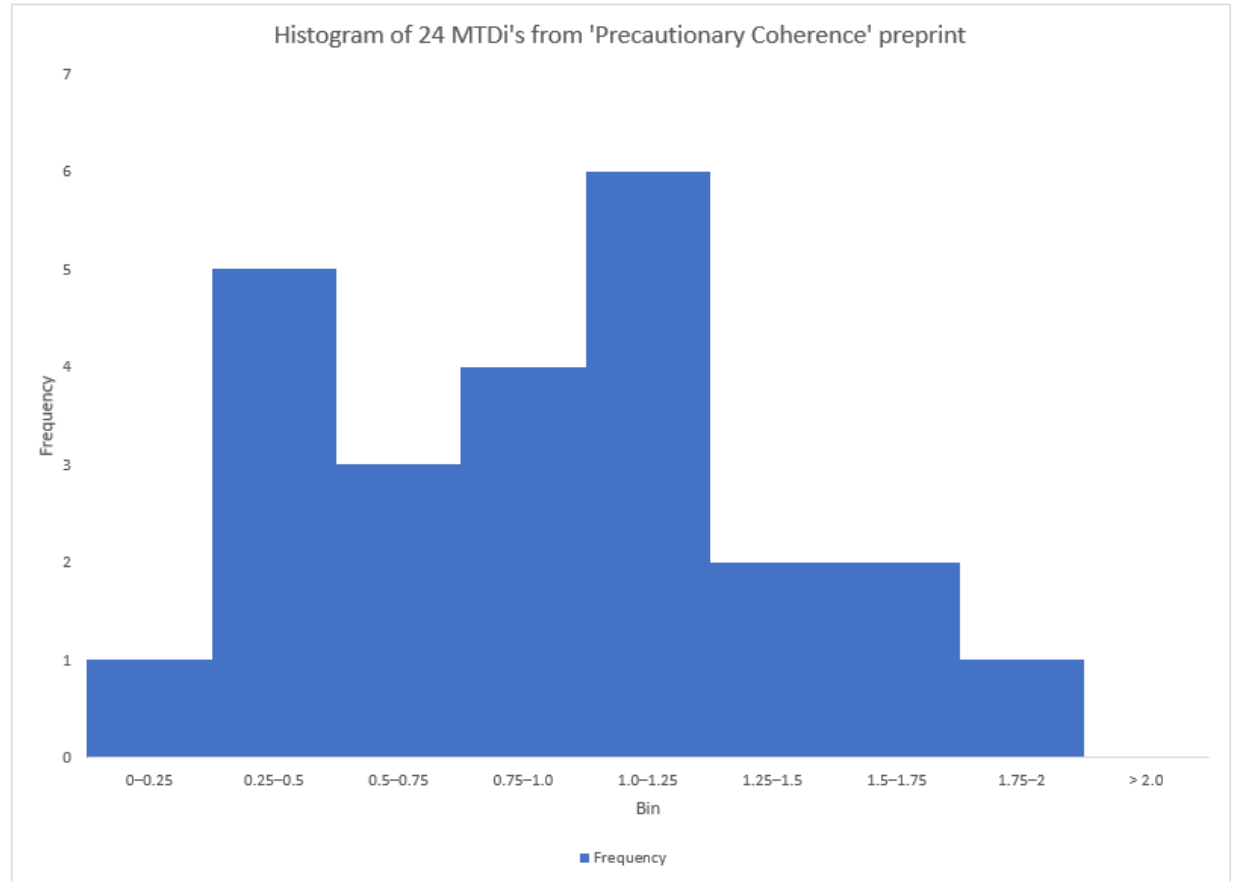
2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 9

A Histogram:

The value of a histogram is that it effectively groups similar individual outcomes together in the several 'bins'.

Dose BIN Label	Dose Range	Frequency of identified MTDs in simulated dose cohorts
0	0-0.25	1
0.25	0.25-0.5	5
0.5	0.5-0.75	3
0.75	0.75-1.0	4
1	1.0-1.25	6
1.25	1.25-1.5	2
1.5	1.5-1.75	2
1.75	1.75-2	1
2	> 2.0	0



How can we reconcile the MTD with this visualization showing the range of individual MTDs (iMTD)?

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 10

Dose Titration vs Standard 3+3: Individual experience in simulated dose-finding studies

based on the simulated individual-MTD results above

Note the **low % of iMTD** - the fixed **subtherapeutic** dosages for patients in the initial dose cohort (13%, 35%, and 20% respectively) using standard 3+3.

Participant No.	Individual Maximum Tolerated Dose (iMTD)	% of iMTD the patient received in 3+3	Dose Limiting Toxicity (DLT) Assessment Period									
			1	2	3	4	5	6	7	8	9	10
1	1.88	13%	0.25	0.35	0.49	0.68	0.96	0.96	1.35	1.35	1.35	1.35
2	0.71	35%	0.25	0.35	0.49	0.68	0.96	0.68	0.68	0.68	0.68	0.68
3	1.28	20%	0.25	0.35	0.49	0.68	0.96	0.96	1.35	0.96	0.96	0.96
4	0.66	53%	0.25	0.35	0.49	0.68	0.96	0.49	0.49	0.49	0.49	0.49
5	1.05	33%	0.25	0.35	0.49	0.68	0.96	1.35	0.96	0.96	0.96	0.96
6	1.04	34%	0.25	0.35	0.49	0.68	0.96	1.35	0.96	0.96	0.96	0.96
7	1.14	43%	0.25	0.35	0.49	0.68	0.96	1.35	0.96	0.96	0.96	0.96
8	1.44	34%	0.25	0.35	0.49	0.68	0.96	1.35	1.35	1.35	1.35	1.35
9	0.58	84%	0.25	0.35	0.49	0.68	0.96	0.49	0.49	0.49	0.49	0.49
10 *	0.37	184%	0.25	0.35	0.49	0.68	0.49	0.35	0.35	0.35	0.35	0.35
11 *	0.50	137%	0.25	0.35	0.49	0.68	0.49	0.68	0.49	0.49	0.49	0.49
12	1.66	41%	0.25	0.35	0.49	0.68	0.96	0.68	0.96	0.96	1.35	1.35
13	0.49		0.68	0.68	0.68	0.68	0.68	0.68	0.68	0.68	0.68	0.68
14	1.01											

← dose titration
← standard 3+3 group

Note:
Participants #10 & #11 could be listed as "184% -> 0%" and "137% -> 0%", respectively.

... In the usual 3+3 scheme, they get their DLTs, but never get a chance to benefit from the drug at a reduced dose.

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 11

Ethical questions: respect for persons and beneficence

"more than 80% of patients enroll in early-phase clinical oncology trials motivated by the potential of a clinical benefit, with approximately half expecting tumor shrinkage" ²

"Autonomy (or respect for people) demands that the ability of competent subjects to make their own decisions be recognized and respected, while also protecting the autonomy of the vulnerable by preventing the imposition of unwanted decisions."

Beneficence refers to a moral obligation to act for the others' benefit, helping them to further their important and legitimate interests, often by preventing or removing possible harms.

The Principle of Beneficence in Applied Ethics (Stanford Encyclopedia of Philosophy) <http://stanford.io/2rPNOJA>
the Belmont Report | HHS.gov <http://bit.ly/2EiGskh>

Questions:

Accepting the premise that the "limited chance of benefit" in phase 1 trials is improving with rationally designed agents and that the potential degree of benefit is also increasing:

- **Can we reconcile the 3+3 with the ethical principles of respect for persons and beneficence?**
- **Have researchers informed patients about the titration method?
Have they asked advocates which study method they would prefer?**
- **Should we honor the true motivations of the patients who enroll in studies ²
by adopting the titration method to identify the optimal dose in each participant?**

¹ Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

² A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

³ Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 12

Informed Consent in dose finding studies

The NCI Informed Consent template has been revised for the year 2018.

This section proposes language modification for this and the prior NCI template in order to show how perspectives on consent language specific to phase 1 studies are evolving.

Yellow highlighting will show key differences in language and/or proposed changes to the consent language for 3+3 phase 1 studies.

Includes language for 2017 and 2018 NCI Consent Templates:

- **Why is this study being done?**
- **What are the study groups?**
- **Benefits / What possible benefits can I expect from taking part in this study?**

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 13

Why is this study being done?

NCI 2017 Template Language for phase I dose-finding studies

3+3 Dose group escalation

The purpose of this study is to test the safety of a study drug called (drug name). This drug has been tested in animals but not yet in people.

This study tests different doses of the study drug **to see which dose is safer in people**. There will be about (insert number) people taking part in this study.

There will be about (insert number) people taking part in this study.

Dose Titration design (proposed)

The purpose of this study is to test the safety **[and anti-tumor activity]** of different doses of study drug (*drug name*). This drug has been tested in animals but not yet in people.

This study tests different doses of the study drug in patients **to find the highest dose with manageable toxicity that can be safely given to each patient and to identify the recommended range of doses for further testing**.

There will be about (*insert number*) people taking part in this study.

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 14

Why is this study being done?

NCI 2018 Template Language for phase I dose-finding studies

3+3 Dose group escalation

This study will answer the following question *(based on the primary study endpoint)* such as: to find the highest tolerated dose of the study drug (name) that has manageable toxicity in groups of 3 patients.

We will then continue to test the dose in the next phases of clinical trials.

Dose Titration design (proposed)

This study will answer the following questions: to find the highest tolerated dose [and anti-tumor activity] of the study drug (name) that has manageable toxicity in each patient.

We will then continue to study the range of doses in the next phases of clinical trials.

The titration method allows the research to assess both safety and efficacy as the dose reaches each participant's iMTD.

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 15

What are the study groups?

NCI 2018 Template Language for phase I dose-finding studies

3+3 Dose group escalation

Different people taking part in this study will get different doses of the study drug.

(~Insert treatment schedule, including route of administration~)

The first (*N*) people taking part in this study will get the lowest dose. If the drug does not cause serious side effects, the next group of people in the study will get a higher dose. The study doctor will watch each group carefully as they increase the dose. The doses will continue to increase for every new group until people have serious side effects that require the dose to be lower. Once this dose is found, the study is stopped. **You (will/will not*) be able to get additional doses of the drug.** This drug is not approved by the FDA for treatment of your disease.

Confirm: the “additional doses of the study drug” will be that assigned to each patient’s dose-level group.

Dose Titration design (proposed)

In this study, you will belong to a group of your own. With safety in mind, we will start you at a dose that we think is probably too low for you. If you tolerate this dose without bad effects, we will increase your dose. If at some point we reach a dose where you have some bad effects that you can tolerate, we will suggest staying at that dose. If you have bad effects that you cannot tolerate, we will decrease your dose back to the previous level.

In this study, you may benefit from what we learn from the participants who enrolled before you. (For example, we might learn that there is some dose that most participants find too toxic. If this happens, we might stop increasing your dose before reaching that level, even if you seem to be tolerating the drug very well.) In the same way, your experience trying different doses of the study drug will help the participants who enroll after you.

(~Insert treatment schedule, including route of administration~)

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede ‘the’ Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 16

What are the study groups (expansion study)?

NCI 2018 Template Language for phase I **dose-expansion** studies

3+3 Dose group escalation

There are two parts in this study, a dose escalation part and a dose expansion part. Your doctor will tell you which part you are in.

In the dose escalation part of this study, different people will get different doses of the study drug (*name*). (*Insert schedule here if different from treatment schedule used in dose expansion – see example below*).

The first (*input number*) people taking part in this study will get the lowest dose. If the drug does not cause serious side effects, the next group of people in the study will get a higher dose. The study doctor will watch each group carefully as they increase the dose. The doses will continue to increase for every new group until people have serious side effects that require the dose to be lower. Once this dose is found, the dose escalation is stopped.

In the dose expansion part of this study, the highest dose with manageable side effects will be given to (*insert number*) more people. This will help study doctors better understand the side effects that may happen with this drug.

(~Insert appropriate treatment schedule, including route of administration.) Each cycle lasts 21 days. This study has 4 cycles. (~ Include the following sentence if you are including a study calendar.~) See the study calendar for more information.

You (*will/will not*) be able to get additional doses of the drug. This drug is not approved by the FDA for treatment of your disease.

Dose Titration

An expansion phase is not needed for dose titration.

Each patient will continue as described in the dose-finding consent for Titration (above).

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 17

What possible benefits can I expect from taking part in this study?

NCI 2018 Template Language for phase I dose-finding studies (molecular target)

3+3 Dose group escalation

There is some evidence (**select and modify as appropriate: in animals, in living human cells, in living animal cells, in people with another cancer**) that this treatment can (**shrink or stabilize**) cancer (**insert targeted mutation as appropriate, e.g. with a change in the EGFR gene**), but we do not know if this will happen in people.

Also, we do not know the good and bad effects of the study drug at the dose you will receive. The dose is determined by the group you are assigned to and will not change while you are in the study. The dose can affect the prospect for good effects and the risk of side effects.

It is unlikely that this (**insert intervention**) will help you live longer. This study may help the study doctors learn things that may help other people in the future.

The **highlighted text is proposed**. It is not currently in the recommended consent language.

Dose Titration (proposed)

There is some evidence (**select and modify as appropriate: in animals, in living human cells, in living animal cells, in people with another cancer**) that the study drug can (**shrink or stabilize**) cancer (**insert targeted mutation as appropriate, e.g. with a change in the EGFR gene**), but we do not know if this will happen in people **or at which dose**.

The dose of the study drug can affect the prospect for good effects and the risk of side effects.

It is unlikely that this (**insert intervention**) will help you live longer. This study may help the study doctors learn things that may help other people in the future.

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 18

In Summary

Group Escalation

Dosages are increased or decreased for each group of patients. The dose remains the same for each patient while on study.

Dose Titration

the continual adjustment of a dose. Dosages are adjusted in each patient until desired clinical effect is achieved.

Outcomes

Group Dose Limiting Toxicity (DLT)
The Maximum Tolerated Dose (MTD)
One size fits all MTD
Slower accrual | Less knowledge per patient

Individual Dose Limiting Toxicities (iDLT)
Your Maximum Tolerated Dose (iMTD)
Range of iMTD doses for next phase of study
Faster accrual | Optimal knowledge per patient

Prospect for benefit / Respect for persons

Groups of patients can receive sub-therapeutic doses. ("Stepping stones")

Honors why patients enroll in studies
The dose-related potential for efficacy is improved for each participant.
(Therapeutic intent)

Applications

The MTD: limits potential dose-related response
The MTD: can increase risk of higher grade adverse events

Your MTD: Full potential for response
Your MTD: Titration (starting at lower dose) reduces risk of serious adverse events

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 19

Karl Schwartz Advocacy CV

<http://www.lymphomation.org/ks-cv-advocacy-2017-july.pdf>

1 Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002 — NEJM <http://bit.ly/1V6aVDd>

2 A study of motivations and expectations of patients seen in phase 1 oncology clinics <http://bit.ly/2C1lgAl>

3 Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials <http://bit.ly/2na6gHT> 20