Conventional anticancer drug dose-finding (phase I) trials define the recommended dose as the maximum tolerated dose (MTD) based on the incidence of dose-limiting toxicity (DLT). DLT may not be the optimal endpoint for new classes of more selective, potentially less toxic molecularly targeted drugs because the MTD may substantially exceed the dose required to achieve maximum target inhibition (MTI) (1–6). Determining optimal dose by quantifying target modulation is a rational alternative but depends on identification of the appropriate drug target, availability of a validated real-time assay for quantifying target modulation, tissue selection (tumor or surrogate) for analysis, and timing of tissue sampling relative to drug administration.

We developed an adaptable trial design that incorporates MTI as the primary endpoint to define optimal dose but that can also define MTD if DLT is observed before reaching a dose that achieves MTI (Figure 1). We applied this design to define the optimal dose or MTD of the dipeptidyl peptidase (DPP) inhibitor talabostat mesylate (Point Therapeutics, Inc, Boston, MA) (7,8), which was administered in combination...
Prior knowledge
The conventional primary endpoint in dose-finding studies is dose-limiting toxicity (DLT). However, newer more selective anticancer drugs may require a different primary endpoint defined by the extent to which a drug inhibits a therapeutic target. Talabostat mesylate inhibits fibroblast activation protein (FAP), which may play a role in tumorigenesis and tumor stromal remodeling.

Study design
A phase I trial design incorporating maximum target inhibition as the primary endpoint was used to find the optimal dose of talabostat in children with relapsed or refractory solid tumors. Inhibition of dipeptidyl peptidase-4 (DPP-4) was used as a surrogate for FAP inhibition. The trial was designed to revert to a traditional phase I trial if DLT were to occur.

Contribution
DPP-4 activity was completely inhibited at doses lower than that predicted by the maximum effect model. There were no grade 3 or 4 toxic effects or talabostat-related DLT.

Implications
Maximum target inhibition is a rational primary endpoint for selective anticancer drugs. An adaptive trial design incorporating this model can be a feasible and safe means of dose finding for molecularly targeted agents.

Limitations
The trial was stopped because clinical development of talabostat was discontinued, so the effects could not be investigated in a larger sample of patients. DPP-4 was used as a surrogate for FAP because of ease of sampling, so FAP inhibition was not measured directly.

Six patients, median age 15 years (range 4.5–18 years), were enrolled at doses of 100 (n = 2), 200 (n = 2), and 350 (n = 2) µg/m²/d (Figure 2). Two patients who received two cycles and one who received three cycles had intrapatient talabostat dose escalation for a total of 10 cycles and a maximum talabostat dose of 600 µg/m²/d. No grade 3 or 4 toxic effects and no talabostat-related DLT occurred. The trial stopped before completion because clinical development of talabostat was discontinued, but data from these six patients illustrate the utility of this adaptable phase I trial design.

AUC₀−₉₉⁹₉₉ of talabostat increased in proportion to dose (mean AUC₀−₉₉₉₉₉ = 7.0 ng·h/mL at 100 µg/m², 20 ng·h/mL at 200 µg/m², and 34 ng·h/mL at 350 µg/m²). Mean half-life of talabostat was 2.8 hours. DPP-4 activity was completely inhibited (median = 98%) 1 hour after the first dose of talabostat on nine of the 10 treatment cycles at doses ranging from 100 to 600 µg/m². One patient experienced nausea and delayed gastric emptying, as evidenced by an undetectable plasma concentration 1 hour post-dose. Plasma talabostat concentration 1 hour post-dose on cycle 1 (100–350 µg/m²) ranged from 0.64 to 10.1 ng/mL (n = 5). At the 600 µg/m² dose level, serum DPP-4 inhibition was 85% on two cycles administered to one patient (Figure 2). Talabostat plasma concentration 24 hours post-dose (C₉₉) was less than 0.6 ng/mL in five of the six patients. One patient, who received 350 µg/m², had a C₉₉ of 0.86 ng/mL. The maximum effect model predicted that a dose of 1200 µg/m² would be required to achieve MTI.

Characterization of the dose–effect relationship by application of basic pharmacodynamic principles was the basis of this dose-finding study. A surrogate tissue (serum) and target (DPP-4) were selected as the endpoint because of the ease of sampling and similar Kᵣ for FAP and DPP-4. To assess whether the target was maximally inhibited throughout the dosing interval, we measured DPP-4 inhibition 24 hours post-dose. The maximum effect model predicted that 1200 µg/m² would be required to achieve MTI on a once-daily schedule. This dose was not tolerable in adults (14); therefore, a change to twice-daily dosing was planned. The mean plasma talabostat concentration 10 hours
Intrapatient dose escalation with DPP-4 inhibition measured on every treatment cycle provides additional valuable dose–effect data characterizing the dose–effect curve within individual patients as well as the population to more efficiently evaluate multiple dose levels. One limitation of the study was that FAP inhibition was not directly measured. A second limitation was early closure of the study because of drug availability. However, treatment of six patients on four dose levels provided sufficient data to project optimal dose. This adaptable trial design appears to be feasible, safe, and efficient. Further evaluation of this trial design in the development of molecularly targeted agents with validated biomarkers is warranted.

**Supplementary Data**

Supplementary data can be found at http://www.jnci.oxfordjournals.org/.

**References**

9. Cheng JD, Weiner LMTumors and their microenvironments: tilling the soil.

**Figure 2.** Dose–effect curve and pharmacokinetic parameters for oral talabostat at doses ranging from 100 to 600 µg/m². Talabostat effect is percent inhibition of serum dipeptidyl peptidase-4 (DPP-4) enzyme activity measured 24 hours after the first dose of talabostat. A maximum effect model, \( E(D) = \frac{D \cdot E_{\text{max}}}{D + \text{ED}_{50}} \), where \( E(D) \) is the observed effect at a given dose \( D \), \( E_{\text{max}} \) is the maximum effect (100% inhibition), \( \text{ED}_{50} \) is the dose achieving 50% of the \( E_{\text{max}} \), and \( n \) is the slope, was fit to the dose–effect data with MLAB (Civilized Software, Silver Spring, MD; http://www.civilized.com/). A) The curve represents the fitted maximum effect model (\( n = 1.0, \text{ED}_{50} = 130 \mu g/m^2 \)). The maximum effect model predicts that the maximum target inhibition would be achieved at doses exceeding 1200 µg/m². Each symbol represents an individual patient. B) Pharmacokinetic parameters for each patient and dose. Talabostat pharmacokinetic parameters include \( C_{\text{max}} \), maximum concentration; \( T_{\text{max}} \), time to peak concentration; \( \text{AUC}_{0-\infty} \) area under the concentration × time curve extrapolated to infinity; CL/F, apparent clearance.

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<th>24 h</th>
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post-350 µg/m² was 0.86 ng/mL, which should be inhibitory (15).


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**Affiliations of authors:** Pharmacology and Experimental Therapeutics Section, Pediatric Oncology Branch (HM, AA, PW, RFM, BCW, EF) and Biostatistics and Data Management Section (SMS), National Cancer Institute, Bethesda, MD; Department of Hematology/Oncology, Children’s National Medical Center, Washington, DC (HM); The Children’s Hospital of Philadelphia, Philadelphia, PA (FMB, EF).