Pediatric Phase I Trial Design Using Maximum Target Inhibition as the Primary Endpoint

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The extent to which a drug inhibits a target responsible for a therapeutic effect is a more rational primary endpoint for dose-finding studies of more selective anticancer drugs than the conventional endpoint of dose-limiting toxicity (DLT) used for cytotoxic agents. An adaptive phase I trial design incorporating maximum target inhibition as the primary endpoint was developed to define the optimal dose of talabostat, a dipeptidyl peptidase (DPP) inhibitor, in children with relapsed or refractory solid tumors. The relationship between dose and effect (percent inhibition of serum DPP-4) was assessed using a maximum effect model. Maximum target inhibition was defined as greater than 90% DPP-4 inhibition in five or more of six patients 24 hours post-dose. If DLT was to occur, the trial would adapt to a traditional phase I design with a more conservative dose escalation. At the 600 µg/m² dose level, serum DPP-4 inhibition at 24 hours was 85%. No talabostat-related DLT occurred. The maximum effect model predicted that 1200 µg/m² of talabostat would maximally inhibit DPP-4. This adaptive trial design appears to be feasible, safe, and efficient and warrants further evaluation for development of molecularly targeted agents.


Figure 1. Trial schema. Algorithm of the adaptable trial design used to define an optimal dose of talabostat based on the degree of target (dipeptidyl peptidase-4 [DPP-4]) inhibition. Maximum target inhibition (MTI) is defined as a greater than 90% decrease in DPP-4 activity relative to baseline, 24 hours after the first dose of talabostat. Two patients are enrolled at the starting dose. If dose-limiting toxicity (DLT) is not observed (boxes with a single line border) and one or both do not achieve MTI, the dose would be escalated. If MTI is achieved in both, the dose level would be expanded to six patients. If fewer than five of the six have MTI, the dose would be escalated. If five or more achieve MTI, the dose would be escalated one additional dose level to ensure that the optimal dose is on the plateau of the dose–response curve. If DLT is observed in one patient at any point, the dose escalation would switch to a traditional phase I (3 + 3 design), and a more conservative 40% dose escalation would be used (boxes with double line border), but DPP-4 inhibition would continue to be monitored. If two or more patients at a dose level experience a DLT, a maximum tolerated dose (MTD) would be defined.
Talabostat was given orally once daily for 102 days as a surrogate for FAP because of ease of sampling and similar $K_i$ for FAP and DPP-4. The assay has a lower limit of quantification of 0.6 ng/mL.

Statistical properties of the adaptable trial design were investigated by calculating probabilities of the three possible outcomes (MTD exceeded, MTI achieved in five or more of six patients, and dose escalation) using a range of probabilities of DLT and greater than 90% DPP-4 inhibition (Supplemental Table 1, available online).

At a given dose level, if the true probability of MTI is 0.90 and true DLT probability is 0.05, the probability of exceeding the MTD is 0.03, of achieving MTI in five or more of six patients is 0.76, and of dose escalation is 0.21. With a true probability of MTI of 0.90 and an unacceptable DLT probability of 0.33, the outcome probabilities become 0.61, 0.29, and 0.10, respectively, whereas if the DPP-4 inhibition probability is 0.50 with a 0.05 DLT probability, outcome probabilities are 0.02, 0.10, and 0.88, respectively. Thus, the design has a reasonable chance of correctly identifying the proper dose for attaining MTI.

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.

$AUC_{0,a}$ of talabostat increased in proportion to dose (mean $AUC_{0,a}$ was 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 ($C_{24h}$) was less than 0.6 ng/mL in five of the six patients. One patient, who received 350 µg/m², had a $C_{24h}$ 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 $K_i$ 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
post-350 µg/m² was 0.86 ng/mL, which should be inhibitory (15).

Intratient 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

**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, \( E(D) = \frac{D \cdot E_{\text{max}}}{D + ED_{50}} \), where \( E(D) \) is the observed effect at a given dose \( D \), \( E_{\text{max}} \) is the maximum effect (100% inhibition), \( ED_{50} \) 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 (\( n = 1.0, ED_{50} = 130 \mu g/m² \)). 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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