First in Human Phase I Trial of 852A, a Novel Systemic Toll-like Receptor 7 Agonist, to Activate Innate Immune Responses in Patients with Advanced Cancer

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Toll-like receptors (TLR) are a highly conserved group of pathogen recognition receptors. To date, 10 human TLRs have been described and their central role in the activation of innate immune responses has been clearly defined (1). 852A (3M-001) is a small-molecule imidazoquinoline, in patients with advanced cancer. Preclinical studies showed that 852A stimulates plasmacytoid dendritic cells to produce multiple cytokines, such as IFN-α, interleukin-1 receptor antagonist, and IFN-inducible protein-10. Our goal was to define the tolerated dose, pharmacokinetics, pharmacodynamics, and immunologic effects of 852A in humans.

Experimental Design: Eligible adult patients with refractory solid organ tumors received i.v. 852A thrice weekly for 2 weeks. Patients who had responses or stable disease were eligible for additional cycles.

Results: Twenty-five patients (median age, 55.0 years; 72% male) were enrolled in six cohorts at dose levels of 0.15 to 2.0 mg/m². Serum drug levels showed dose proportionality and no evidence of drug accumulation. The maximum tolerated dose was 1.2 mg/m²; higher doses were limited by fatigue and constitutional symptoms. Increases in IFN-α, interleukin-1 receptor antagonist, and IFN-inducible protein-10, immunologic activity, and clinical symptoms were observed in all patients receiving dose levels ≥0.6 mg/m². Significant correlations were found between pharmacodynamic biomarkers and pharmacokinetic variables, and an objective clinical response was seen.

Conclusions: 852A was safely administered i.v. at doses up to 1.2 mg/m² thrice weekly for 2 weeks with transient or reversible adverse effects. This novel Toll-like receptor 7 agonist is biologically active and holds promise for stimulating innate immune responses. Future trials are warranted to assess its therapeutic role in patients with cancer.

Toll-like receptors (TLR) are a highly conserved group of pathogen recognition receptors. To date, 10 human TLRs have been described and their central role in the activation of innate immune responses has been clearly defined (1). 852A (3M-001) is a small-molecule imidazoquinoline that is related to imiquimod but is a more potent and more selective activator of TLR7. In vitro studies have shown that 852A directly activates antigen-presenting cells, such as dendritic cells, resulting in (a) the production of various cytokines, including IFN-α and tumor necrosis factor-α, which may inhibit tumor growth or viability, (b) the expression of chemokines, including both IFN-inducible protein-10 (IP-10) and the chemokine receptor CCR7, which is important for dendritic cell migration to lymphoid tissue, and (c) the expression on antigen-presenting cells of costimulatory molecules required for T-cell activation (2–6).

The efficacy of a TLR agonist in the treatment of cancer has been shown in superficial basal cell carcinoma, where the use of topical imiquimod 5% cream (a compound from the same drug class) resulted in histologic clearance rates between 79% and 82% in phase III randomized placebo-controlled studies (7). In addition, antitumor activity has been shown using this topical agent in a variety of other tumor types (8–11). These studies, combined with preclinical data on 852A and the knowledge that cytokine therapy is effective treatment for certain cancers (12), provide the rationale for testing a systemically delivered TLR agonist as an anticancer agent. 852A has ~40 times greater aqueous solubility than imiquimod at physiologic pH, allowing easier formulation as an injectable systemic agent. In
addition, 852A underwent slower elimination and less extensive metabolism than imiquimod in animal pharmacokinetic studies or when incubated in the presence of human liver enzymes. These features, along with the increased potency and greater relative TLR7 selectivity of 852A, made it an attractive candidate for drug development.

Materials and Methods

**Phase 1 study.** Men or women ≥18 years of age, with an Eastern Cooperative Oncology Group performance status ≤2, with preserved bone marrow (WBC >3,000/μL, absolute neutrophil count >1,500/μL, platelets >100,000/μL, hemoglobin >10.0 g/L, renal (creatinine ≤1.8 mg/dL), and hepatic function (≤2.5× upper limits of normal) were eligible to participate in the study. A 4-week prior antitumor therapy washout period (6 weeks for nitrosourea or mitomycin C) was required before the first dose of study drug. All patients consented to participate in the study approved by the Committee on the Use of Human Subjects in Research at the University of Minnesota according to the Declaration of Helsinki.

Study 1493-852A was a dose-escalation study in which 852A (N-[4-(4-amino-2-ethyl-1H-imidazo[4,5-c]quinolin-1-yl) butyl]methanesulfonamide; 3M Pharmaceuticals) was prepared as a 0.2% sterile solution and delivered i.v. thrice weekly for 2 weeks to patients with refractory solid organ tumors. Body surface area (BSA) dosing was used (Mosteller formula; ref. 13), and the following dose levels were administered: 0.15, 0.3, 0.6, 1.2, 1.55, and 2.0 mg/m².

Statistical methods. All enrolled patients receiving at least one dose of 852A were included in the intent to treat population. Completion of one 2-week course of study drug was required to be included in the determination of the MTD, unless a patient discontinued due a DLT before completion of the first treatment cycle. Descriptive statistics were used for clinical variables. Tumor response was documented using Response Evaluation Criteria in Solid Tumors published methods (17). Tumor evaluation by standard Response Evaluation Criteria in Solid Organ Tumors (17) was conducted 4 weeks after the last dose. Patients showing clinical benefit, defined as stable disease or better, were eligible to receive additional 2-week cycles of treatment.

Preclinical studies of nuclear factor-κB activation in TLR-transfected HEK293 cells. TLR activity was assessed in human HEK293 cells cotransfected with human TLR7, TLR8, or TLR9 and a nuclear factor-κB-luciferase reporter construct as previously described (18). TLR-transfected cells were stimulated with 852A (0.1, 0.3, 1, 3, 10, 33, and 100 μmol/L), imiquimod (0.1, 0.3, 1, 3, 10, 33, and 100 μmol/L), 3M-002 (a TLR agonist, 10 μmol/L), CpG2059 (a TLR agonist, 10 μmol/L), or vehicle control (0.3% DMSO) in triplicate. After incubation for 24 h, cells were lysed and analyzed for luciferase production. Mean relative luciferase units were used to calculate the fold increase over the control.

Preclinical studies of cytokine production in human PBMC and plasmacytoid dendritic cell from healthy subjects. Human peripheral blood mononuclear cells (PBMC) were isolated from healthy subjects and cultured ex vivo as described (18). Plasmacytoid dendritic cells (pDC) were enriched or depleted from PBMC preparations using BDCA-4 antibody according to the manufacturer’s instructions (Miltenyi Biotec). The cells were cultured at 2 × 10⁸/mL in 0.25 mL RPMI 1640/10% FCS/1% penicillin/streptomycin and for 24 h with 852A (0.5-1,193 ng/mL or 0.002-3.3 μmol/L) or vehicle (0.03% DMSO), and supernatants were analyzed for IFN-α by ELISA (IFN-α ELISA, PBL). The minimum level of detection for the assay was 20 pg/mL. The purity of the pDC-depleted culture was verified using a combination of fluorochrome-labeled antibodies (BD Biosciences), Lin1 cocktail, CD123 (clone 9F5), and CD11c (clone S-HCL-3), which showed that enriched pDC cultures were 67%, 81%, and 83% pDC (Lin1⁻/CD123⁺, CD123⁻, and CD11c⁻).

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 scale (14). Grade ≥3 toxicities were considered dose-limiting toxicities (DLT) with the exception of transient constitutional symptoms and hematologic toxicities. Patients who discontinued therapy for reasons other than toxicity were replaced.

Serum and urine samples were collected over 24 h for pharmacokinetic assessments. Concentrations of 852A were measured by liquid chromatography coupled to a tandem mass spectrometry system (15). The lower limits of quantitation were 0.1 ng/mL in serum and 0.2 ng/mL in urine. For pharmacodynamic assessments, blood was collected before dosing and 2, 4, 6, 9, and 12 h following dosing. The following pharmacodynamic markers were measured, IFN-α, interleukin-1 receptor antagonist (IL-1RA), interleukin-12 p40 subunit (IL-12p40), and IP-10, by ELISA according to the manufacturer’s recommendations (R&D Systems). All analytic methods were validated with respect to accuracy, precision, and stability.

Natural killer (NK) cell activity was evaluated before and after 852A treatment by measuring CD69 (FITC conjugated, clone L78) expression by flow cytometry (16). NK cells were identified from peripheral blood mononuclear cells (PBMC) as CD56⁻⁺ (clone NCAM 16.2) and CD3⁻ (peridinin chlorophyll protein conjugated, clone SK7). All antibodies were from BD Biosciences.

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The following 852A pharmacokinetic variables were calculated: serum concentration at 5 min (C5min), area under the serum concentration versus time curve from time zero to the time of last measurable concentration (AUC⁰-t), total body clearance per kg body weight (CL/kg), volume of distribution per kg body weight (Vd/kg), apparent elimination half-life (t1/2), and amount excreted in urine as

![Fig. 1. 852A is a TLR7 agonist that stimulates IFN-α from pDC. A. HEK293-nuclear factor-κB-Luc cells were transiently transfected with a mammalian expression vectors encoding human TLR7, TLR8, or TLR9. The cells were stimulated with 852A, imiquimod, 3M-002, CpG2059, or vehicle at the concentrations indicated (log scale). After incubation, the cells were lysed and analyzed for luciferase production. The results are reported as fold change relative to vehicle control. For 852A, 1 μmol/L = 361 ng/mL. B. Human PBMC, pDC enriched from PBMC, and pDC deficient in pDC were evaluated for IFN-α production following stimulation with 852A (n = 5).](http://www.aacrjournals.org/clin cancerres.aacrjournals.org) Clin Cancer Res 2007;13(23) December 1, 2007 7120 www.aacrjournals.org

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unchanged drug. The early serum concentration data were extrapolated to calculate the initial serum concentration at time zero (C0). Calculation procedures were as described previously (15).

Biomarkers were assessed by calculating the maximum change in concentration from the predose 1 baseline for each patient (Rmax). Spearman rank correlation coefficients were determined to assess the relationship between summary pharmacokinetic measurements and dose and between summary pharmacokinetic measurements and maximum change in biomarkers.

Results

In vitro studies to show the specificity and action of 852A. Concentrations of 852A >3.3 μmol/L (1,205 ng/mL) were capable of activating nuclear factor-κB in HEK293 cells transfected with TLR7 (Fig. 1A). 852A activated TLR8-transfected cells only at the highest concentration evaluated (100 μmol/L) and did not activate TLR9-transfected cells at any concentration. Those cells did respond to known TLR8 and TLR9 agonists and did not activate TLR9-transfected cells at any concentration. Nuclear factor-κB induction in TLR7-transfected cells was greater after 852A than after imiquimod exposure at all concentrations evaluated. In addition, other than at 100 μmol/L, the relative TLR7 to TLR8 activity was always greater with 852A than with imiquimod (Fig. 1A).

Concentrations of 852A as low as 14.9 ng/mL (0.041 mol/L) were effective at inducing the production of IFN-α from human PBMC cultures (Fig. 1B). pDC depletion of the cell cultures resulted in a loss of IFN-α production after 852A exposure, and enrichment of the pDC population resulted in increased levels of IFN-α production relative to the PBMC parent population. The minimum effective concentration of 852A required to induce IFN-α from the pDC-enriched population was 14.9 ng/mL. IP-10, IL-1RA, and IL-12p40 were measured in the PBMC culture supernatants as well. IP-10 and IL-1RA were induced at the same concentration of 852A that was required to induce IFN-α (data not shown). In contrast, 30 to 100 times more 852A were required to induce IL-12p40 (data not shown).

Clinical trial results. Twenty-five of 32 screened patients were enrolled in the study, with a median age of 55.0 years (mean age of 56.4 years) and a range from 39 to 80 years. There were 7 (28%) female and 18 (72%) male patients enrolled. Most patients had a baseline Eastern Cooperative Oncology Group status of 0 (48%) or 1 (44%). Diagnosis distribution showed a predominance of renal cell carcinoma [n = 10 (40%)] and melanoma [n = 4 (20%)]. Other diagnoses included non–small cell lung cancer (n = 4), squamous cell lung cancer (n = 2), atypical carcinoid (n = 2), ovarian cancer (n = 1), and breast cancer (n = 1). Most patients had received prior radiation (14 of 25, 56%) and/or chemotherapy (19 of 25, 76%).

Of the 25 patients enrolled in this study, 24 (96%) had at least one grade ≥3 adverse event during the study and the number of patients treated at each dose is listed (Table 1). Of these, the most frequently observed adverse events were fever (24%) and fatigue (16%). Adverse events indicative of pharmacologic activity were consistently observed at doses ≥0.6 mg/m2, with a dose-related increase both in frequency and severity. With the exception of local injection site irritation and pain observed in one patient at the 0.15 mg/m2 dose, grade 3 drug-related adverse events were only observed at doses ≥0.6 mg/m2 as summarized Table 1. There were no clinically meaningful decreases in RBC counts or platelets. Transient (<48 h after dose) decreases in circulating WBC populations were observed at doses ≥0.6 mg/m2, including decreases in absolute neutrophil count and total lymphocyte count (data not shown). The rapid transient nature is consistent with a pattern of immune activation rather than myelosuppression.

Five patients experienced nine DLTs in this study, one of six (17%) receiving 1.2 mg/m2, two of four (50%) receiving 2.0 mg/m2, and two of two (100%) receiving 1.55 mg/m2; all five discontinued dosing. DLTs (some patient had more than one) included fatigue (four patients), muscle weakness (three), vomiting (one), and nausea (one). An additional patient (0.6 mg/m2) was considered initially to have had a DLT of decreased absolute neutrophil count; this patient resumed

Table 1. Summary of drug-related adverse events (Common Terminology Criteria for Adverse Events grade ≥3) during the study

<table>
<thead>
<tr>
<th>852A dose (mg/m²)</th>
<th>0.15 mg/m² (n = 3)</th>
<th>0.3 mg/m² (n = 3)</th>
<th>0.6 mg/m² (n = 7)</th>
<th>1.2 mg/m² (n = 6)</th>
<th>1.55 mg/m² (n = 4)</th>
<th>2.0 mg/m² (n = 4)</th>
<th>Total (N = 25)</th>
</tr>
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<tbody>
<tr>
<td>CTCAE grade</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>No. subjects with grade ≥3 drug-related adverse event</td>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Fever</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>1</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>0</td>
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<tr>
<td>Vomiting</td>
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<td>0</td>
<td>0</td>
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<tr>
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<td>Deep vein thrombosis</td>
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<td>0</td>
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<tr>
<td>Injection site pain and irritation</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Neutrophil count decreased</td>
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<tr>
<td>Peroneal nerve palsy</td>
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</table>

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.
dosing after determination that the transient decrease did not fully meet DLT criteria. All patients recovered from their DLTs after cessation of 852A dosing.

Pharmacokinetics, pharmacodynamics, and immunologic effects of 852A. Serum 852A concentrations increased proportionally over a 13-fold range of doses and showed a similar biphasic profile for all dose levels (Fig. 2A). Similar concentration-versus-time profiles were observed after dose 1 and dose 6 at each dose level. Pharmacokinetic variables C0, C5min, and AUC(0-t) were found to be approximately proportional to administered dose on each dosing day. CL/kg (~0.3 L/h/kg), Vd/kg (~4 L/kg), and t1/2 (~10 h) showed little change with dose, which suggests that the drug exhibited linear kinetics over the dose range studied. Approximately 30% to 40% of the administered dose was recovered unchanged in the urine following dose 6 of each dose level.

Increases in IFN-α, IL-1RA, and IP-10 biomarkers were observed in all patients receiving dose levels ≥0.6 mg/m² (Table 2). For IL-1RA and IP-10, increases seemed to be greater following dose 1. There was no increase over baseline in IL-12p40 following any dose (data not shown).

IFN-α responders were defined as patients having IFN-α concentrations after 852A exposure that were greater than twice the lower limit of detection (>6 IU/mL). Following the first dose of 852A, most patients were classified as IFN-α responders in the 0.6 mg/m² (86%), 1.2 mg/m² (83%), 1.55 mg/m² (100%), and 2.0 mg/m² (100%) dose groups, whereas no patients were classified as responders in the 0.15 and 0.3 mg/m² dose groups. The median time for maximum response following 852A injection was between 4 and 6 h after dose (data not shown). As several patients in the higher dose groups discontinued due to DLT, biomarker data following dose 6 were limited but suggested an increase in response with multiple doses in patients receiving 1.2 mg/m² 852A or higher. Unlike IFN-α responders, determining the number of IP-10 and IL-1RA responders was less clear due to variable background cytokine levels in each patient. However, statistically significant Spearman rank correlations (P < 0.05) were observed when the Rmax values for IFN-α, IL-1RA, and IL-10 were compared with the pharmacokinetic variables C5min and AUC(0-t). Figure 2B shows the representative correlations for IFN-α.

NK cells were evaluated after the first i.v. dose of 852A to see if NK cell activation occurred in vivo. PBMCs were tested 4 h after the first dose of 852A. Because 852A induced lymphopenia, presumably due to lymphocyte activation and egress of lymphocytes into tissues, expression of CD69 was measured on gated NK cells as a more definitive marker of NK cell activation. CD69 expression on NK cells did not increase in patients receiving 0.15 to 0.3 mg/m². In contrast, 1 of 5 (20%) evaluable patients receiving 0.6 mg/m² and 5 of 12 (42%) of patients receiving ≥1.2 mg/m² had increased CD69 expression over their baseline sample. The CD69 expression (as a surrogate of NK cell activation) was greatest in those patients who had the greatest demargination of NK cells from the peripheral circulation (Fig. 3). In preclinical studies, in vitro stimulation of PBMC with 852A induced NK activation consistent with the clinical results indicated above (19).

Six of the 25 patients enrolled in the study showed disease stabilization after receiving 2 weeks of 852A, and they received additional treatment cycles. These included one patient in the 0.3 mg/m² cohort, three in the 0.6 mg/m² cohort, and two in the 1.2 mg/m² cohort. Subsequently, five of the six patients experienced disease progression. The remaining patient, a 65-year-old woman with atypical carcinoid of the mediastinum who received 0.6 mg/m², continued to show clinical benefit defined as improved symptoms [decrease in pleural effusion with no need for oxygen, better Eastern Cooperative Oncology Group performance status (2 to 0) and tumor partial response (Fig. 4) that lasted 24 months].

Discussion

The results from this study show that 852A can be safely administered i.v. at doses up to 1.2 mg/m² thrice weekly for 2 weeks with predictable pharmacokinetics. At doses of ≥0.6 mg/m², consistent pharmacologic activity was seen based on cytokine levels that correlated with clinical signs of immune

Fig. 2. Pharmacokinetics and biological activity of 852A. A, median serum 852A concentrations are shown as a semilogarithmic plot following dose 1 (closed symbols and X) and dose 6 (open symbols) versus time (h) following 852A administration. B, semilogarithmic plots of the IFN-α correlation (Rmax) with the 852A AUC(0-t) (top) or C5min (bottom) following dose 1 (■) and dose 6 (○).
The ability to induce immune activation in vivo suggests that this innate arm of the immune system is still responsive even in patients with advanced refractory disease. All DLTs attributed to study drug were reversible and most were transient, consistent with immune system activation. The transient changes observed in WBC counts, absolute neutrophil counts, and total lymphocyte counts most likely reflect margination of the PBMCs following cytokine secretion. In mice treated with resiquimod, a drug in the same class as 852A, leukocytes rapidly leave the bloodstream and remain in peripheral organs following systemic delivery of the compound (20). In support of this premise, there was no evidence of an increase in infections during the study, suggesting that the transient change in white blood counts was not clinically relevant. However, further investigation is warranted to characterize the egress of effector cells and to determine if TLR7 agonists can drive cellular infiltration into cancer tissues. The observed increases in the biomarkers associated with TLR7 agonists (IFN-α, IL-1RA, and IP-10) and the lack of response for the biomarker associated with TLR8 agonists (IL-12p40) are consistent with the proposed pharmacologic activity of 852A as a selective TLR7 agonist. Whereas pDCs are the primary source of type I IFN, additional preclinical studies using intracellular cytokine staining suggest that monocytes also contribute IP-10 and IL-1RA. In the presence of type I IFN receptor blockade, both IP-10 and IL-1RA were no longer induced by 852A stimulation of PBMCs in vitro. Thus, 852A can elicit both direct and indirect effects much like TLR9 agonist CpG oligonucleotides (21). The apparent decreases in IL-1RA and IP-10 after dose 6 compared with dose 1 may represent suppressed cytokine signaling after repeated dosing or may reflect decreases in circulating monocytes, mechanisms that need to be studied further.

A correlation was seen between the blood levels of 852A required to induce serum cytokines in vivo and the levels capable of inducing cytokines in human PBMC cultures. Further support of the 852A mechanism comes from the pDC experiments. pDCs are presumed to be the primary source of IFN-α production from PBMC after TLR7 stimulation based on their expression of this receptor (22, 23). Our experiments clearly showed that IFN-α production from PBMC was dependent on pDC concentration. Although type I IFN is important in immune responses, there are several reasons why treatment with 852A is expected to be different from treatment to activate (e.g., fever). The ability to induce immune activation in vivo suggests that this innate arm of the immune system is still responsive even in patients with advanced refractory disease.
administration, and IFN-α activation compared with that which can be achieved with treatment with 852A induces a unique pattern of immune stimulation with 852A. In the clinical trial, a clear trend toward peak expression of CD69 on NK cells was observed after 24 h of the innate immune response (26). In the preclinical studies, the recently established as an important mechanism to coordinate indirect activation by TLR agonists via dendritic cells has been shown. The type I IFN produced by pDC may localize in tissues differently than with systemic recombinant IFN-α administration, and pDCs make over 10 type I IFNs that are not all functionally equivalent. Based on these data, treatment with 852A induces a unique pattern of immune activation compared with that which can be achieved with IFN-α alone (24, 25).

The effect of 852A on NK cells was monitored because their indirect activation by TLR agonists via dendritic cells has been recently established as an important mechanism to coordinate the innate immune response (26). In the preclinical studies, the peak expression of CD69 on NK cells was observed after 24 h of stimulation with 852A. In the clinical trial, a clear trend toward dose-dependent NK cell activation was identified, although increased cytokine production was observed in more patients than was apparent NK cell activation. This finding may be explained by the short duration of exposure to 852A (4 h) in subjects before analysis. In addition, the preferential loss of activated NK cells from the peripheral blood following 852A dosing also may have affected the measurements of NK cell activation.

This study also provides the first information on the pharmacokinetic and pharmacodynamic of multiple doses of 852A in patients. For the dosing regimen tested, 852A showed predictable dose proportionality and no drug accumulation in the serum. Urinary excretion seemed to be an important route of elimination, as about 30% to 40% of the administered dose was excreted unchanged. Imiquimod, in contrast, has a 1/2 approximately one fourth of that of 852A, extensive metabolism, and a urinary excretion of unchanged drug about one tenth that of 852A and also shows accumulation on multiple dosing. Taken together, these characteristics support the selection of 852A to test the systemic administration of an imidazoquinoline (27, 28).

A second pharmacokinetic study of 852A in humans has now been completed (15). That study examined the pharmacokinetics of single doses of 852A in healthy volunteers following i.v., s.c., and oral administrations. The bioavailability following s.c. administration was ~80%, and serum levels by 30 min were comparable with i.v. administration. This finding suggests that s.c. administration would be suitable for future studies of 852A in patients.

A key result of this trial was the disease stabilization observed following only 2 weeks of 852A therapy in six of the patients. Although the disease progressed in five of these patients after additional treatment cycles, our clinical experience provides promising evidence that systemic TLR agonists may play a therapeutic role against cancer. This suggests that further study of the antitumor application of 852A is warranted. S.c. dosing may simplify drug delivery and prolonged dosing may increase efficacy.

In summary, we report the systemic administration in patients of 852A, a selective small-molecule TLR7 agonist. Safe dosing was defined for the population studied. 852A induced immune activation, as assessed both clinically and with laboratory assays. Our data support a model in which the mechanism of action of TLR7 agonists is mediated by pDC, consistent with the expression pattern of TLRs and the pattern of cytokines induced in vivo (29, 30). Disease stabilization in some patients and one objective response by Response Evaluation Criteria in Solid Organ Tumors criteria provide proof of principle that 852A can be a systemic antitumor agent.

Acknowledgments

We thank the patients and the research staff who participated in these studies and the following 3M personnel for their assistance: Jamie Lowe (project management), Cathryn Lloyd (clinical monitor), Kari Larson and Jamie Broos (data management), and Laura Bean Warner and Tze-Chiang Meng (manuscript preparation).

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First in Human Phase I Trial of 852A, a Novel Systemic Toll-like Receptor 7 Agonist, to Activate Innate Immune Responses in Patients with Advanced Cancer

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