

An Open-Label, Multicenter, Phase I/II Study of JNJ-40346527, a CSF-1R Inhibitor, in Patients with Relapsed or Refractory Hodgkin Lymphoma

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Abstract

Purpose: This phase I/II study investigated JNJ-40346527, a selective inhibitor of the colony-stimulating factor-1 receptor (CSF-1R) tyrosine kinase as treatment for relapsed or refractory classical Hodgkin lymphoma (cHL).

Experimental Design: Patients ≥ 18 years with histopathologically confirmed initial diagnosis of cHL that had relapsed or was refractory after ≥ 1 appropriate therapies were assigned to sequential cohorts of oral daily doses of JNJ-40346527 (150, 300, 450, 600 mg every day, and 150 mg twice a day). For the dose-escalation phase, the primary endpoint was to establish the recommended phase II dose. Secondary endpoints included safety, pharmacokinetics, and pharmacodynamics.

Results: Twenty-one patients [(150 mg: 3; 300 mg: 5; 450 mg: 3, 600 mg: 3) every day, and 150 mg twice a day: 7] were enrolled, 10 men, median age 40 (range, 19–75) years, median number of prior systemic therapies 6 (range, 3–14).

No dose-limiting toxicities were observed; maximum-tolerated dose was not established. Best overall response was complete remission in 1 patient (duration, +352 days) and stable disease in 11 patients (duration, 1.5–8 months). Median number of cycles: 4 (range, 1–16). Most common ($\geq 20\%$ patients) possibly drug-related adverse events (per investigator assessment) were nausea ($n = 6$), headache, and pyrexia ($n = 5$ each). JNJ-40346527 exposure increased in near dose-proportional manner over a dose range of 150 to 450 mg every day, but plateaued at 600 mg every day. Target engagement was confirmed ($>80\%$ inhibition of CSF-1R phosphorylation, 4 hours after dosing).

Conclusions: JNJ-40346527, a selective inhibitor of CSF-1R was well tolerated, and preliminary antitumor results suggested limited activity in monotherapy for the treatment of cHL. *Clin Cancer Res*; 21(8); 1843–50. ©2015 AACR.

Introduction

First-line standard treatment comprising radiotherapy, combination chemotherapy, or combined modality therapy provides long-term survival in more than 80% of patients with classical Hodgkin lymphoma (cHL; refs. 1, 2). However, depending on initial stage and first-line therapy, approximately 10% to 30% of patients presenting with cHL are expected to become refractory to initial therapy or to relapse (3, 4). Even at first relapse, approximately 50% of patients can be cured with high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT; ref. 5).

Despite these advances, patients relapsing after ASCT have a poor prognosis and treatment is often palliative (6, 7). Moreover, in the increasing number of older patients who do not tolerate current first-line approaches and are not suitable for HDCT and ASCT at relapse, the prognosis is dismal (8). Recently, in a phase II study with patients with post-ASCT recurrence of HL, treatment with brentuximab vedotin, an antibody–drug conjugate (ADC) that selectively delivers an antimicrotubule agent into CD30-expressing cells, showed an overall response rate of 75%, with 34% complete responses (CR) and a median remission duration of 20 months for complete responders (9). Furthermore, the median overall survival (OS) was 40.5 months and the estimated 3-year survival rate was 54% (10). However, median PFS for all patients was 5.6 months and long-term remissions were reported in a small proportion of patients who did not require additional treatment (10). Therefore, there is still an unmet medical need for new targeted therapies that are able to suppress the oncogenic drivers of malignant cHL cells with tolerable side effects in patients with HL relapsing after ASCT or patients not suitable for ASCT.

Colony-stimulating factor-1 receptor (CSF-1R), also known as cFMS [cellular homolog of the feline McDonough sarcoma virus oncogene (v-fms); refs. 11, 12] is an exclusive type III receptor tyrosine kinase for CSF-1 and interleukin (IL)-34, with high expression limited to macrophage lineage and closely related to tyrosine-protein kinase kit (ckit) and fms-related tyrosine kinase-3 (flt-3). Macrophage infiltration correlates with poor prognosis,

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Translational Relevance

In preclinical studies, JNJ-40346527, a selective inhibitor of colony-stimulating factor-1 receptor (CSF-1R), reduced the viability of Hodgkin lymphoma (HL) cell lines, which aberrantly express lineage-inappropriate CSF-1R. Furthermore, classical HL patient's samples demonstrated expression of CSF-1R and its ligand, confirming activation of the CSF-1R pathway in classical HL. These findings provide a rationale for the use of JNJ-40346527 in the treatment of classical HL. JNJ-40346527 demonstrated an acceptable safety and tolerability profile in patients with relapsed or refractory classical HL in this open-label, phase I/II, multicenter study. Although preliminary antitumor results suggested limited activity in monotherapy for the treatment of classical HL, the other study objectives of determining the recommended phase II dose, pharmacokinetic exposure, and biomarkers of target engagement were met. Thus, further evaluation of this drug in other cancers is warranted.

and has been observed in several types of human cancers (13–15). CSF-1 is implicated in tumor macrophage recruitment, survival, proliferation, and differentiation, osteoclast maturation/differentiation, primary tumor growth, metastasis, and patient outcome in several tumors and bone metastasis (16–20). Tumor-associated macrophages (TAM) provide factors that promote tumor growth, angiogenesis, and metastasis, and high proportions of macrophages/TAMs are associated with adverse treatment outcome in cHL (14, 15, 21–23). Animal studies demonstrated that inhibition of macrophage infiltration in experimental tumors in mice, via CSF-1R blockade, had a significant effect on tumor growth (20, 24).

The cHL is characterized by the presence of Reed–Sternberg tumor cells that are outnumbered by the surrounding inflammatory milieu of macrophages, B and T cells, eosinophils, and other lymphoid cells (25). The hallmark of hematopoietic malignancies, including cHL, is reprogramming of the normal gene expression pattern (26, 27). In cHL, the B cell–derived clonal Reed–Sternberg cells lose expression of B cell–specific genes and acquire the expression of B lineage inappropriate genes, such as oncogenic tyrosine kinase receptors. Both CSF-1R and its ligand, CSF-1, are expressed in cHL cell lines and patient samples (11, 12, 17, 28). Reduced proliferation of several HL cell lines following inhibition of CSF-1R suggests that this pathway is used by cHL cells for growth (11). JNJ-40346527, an orally available selective inhibitor of CSF-1R, reduced the viability of HL cell lines that aberrantly express lineage-inappropriate CSF-1R confirming that the CSF-1R pathway is active in cHL cell lines (29). Furthermore, PCR and TaqMan analysis of HL patient's samples showed expression of CSF-1R. JNJ-40346527 also acts to prevent osteoclastogenesis and macrophage activation, survival, and differentiation in an arthritis model (unpublished data). In HL, secretion of macrophage migration inhibition factor may contribute to the proliferation of HL cells and therefore, the inhibition of HL tumor promoting macrophages could provide a second mechanism by which the compound would inhibit the tumor growth (15). These preclinical findings provided a rationale that inhibition of CSF-1R by JNJ-40346527 may result in sustained anti-proliferative activity.

The doses evaluated in this study were based on the results of phase I studies of JNJ-40346527. In a single-dose phase I study of JNJ-40346527 [doses ranging from 10 mg every day to 450 mg twice a day (total daily dose of 900 mg)], the absorption of JNJ-40346527 was rapid (median t_{max} ranging from 1 to 3.5 hours) and both C_{max} and AUC values increased with dose up to the 450 mg every day dose (unpublished data). Furthermore, in the multiple-dose phase I study of JNJ-40346527 [doses ranging from 50 mg every day to 300 mg twice a day (total daily dose of 600 mg) for 14 consecutive days], on day 14, C_{max} appeared to increase dose proportionally following every day dosing (50–300 mg), while AUC on day 14 appeared to increase dose proportionally across all dose regimens (50 mg every day to 300 mg twice a day; unpublished data). This study investigated JNJ-40346527, as treatment for relapsed or refractory cHL by means of dose, safety, response rates, pharmacokinetics (PK), and pharmacodynamics correlative studies.

Materials and Methods

Patient population

Patients of either sex ≥ 18 years of age with a histopathologically confirmed initial diagnosis of cHL who had relapsed or refractory disease after at least one appropriate therapy (chemotherapy, radiation, allogeneic, or ASCT) were included in the study. The patients had to have received an ASCT, if eligible for transplant. If allogeneic transplant was received before enrollment, the patient had to be off immunosuppressive medication for at least 1 month. Additional inclusion criteria were an Eastern Cooperative Oncology Group Performance status (ECOG PS) score of 0–2, at least 3 weeks since the last chemotherapy or radiation and adequate bone marrow [absolute neutrophil count (ANC) $\geq 1,000/\text{mm}^3$ (or $\geq 1.0 \times 10^9/\text{L}$), a platelet count $75,000/\text{mm}^3$ (or $\geq 75 \times 10^9/\text{L}$), and a hemoglobin level greater than 8.5 g/dL (or $\geq 85 \text{ g/L}$)], liver [serum total and direct bilirubin levels $\leq 2.0 \times$ upper limit of normal (ULN), and serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels $\leq 3.0 \times$ ULN], and kidney [serum creatinine levels $\leq 1.5 \times$ ULN or calculated glomerular filtration rate (GFR) of $>60 \text{ mL/min/1.73 m}^2$] function. Main exclusion criteria were as follows: known brain metastases or leptomeningeal disease, prior treatment with a CSF-1R inhibitor, major surgery within 3 weeks before screening, and other malignancies within 5 years.

The Independent Ethics Committee or Institutional Review Board at each study site approved the protocol, and the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. All patients or their legally acceptable representatives provided their written consent before entering the study.

Study design and treatment schedule

This open-label, multicenter dose-escalation phase I/II study of JNJ-40346527 in patients with relapsed or refractory cHL consisted of screening (day –28 to –1), an open-label treatment (treatment to continue until disease progression or unacceptable toxicity), and a follow-up phase. Patients self-administered JNJ-40346527 orally once daily (preferably in the morning shortly after breakfast) or twice daily on a continuous dosing schedule at approximately the same time each day.

Each 21 consecutive days constituted one treatment cycle. The study used a traditional 3+3 dose-escalation design. Dose-limiting toxicities (DLT) were assessed during the first treatment cycle. Dose levels assessed were 150, 300, 450, and 600 mg every day and 150 mg twice a day. If one of the first 3 patients had a DLT, the cohort was expanded to 6 patients. Dose escalations continued until the maximal-tolerated dose (MTD) was determined (defined as the highest dose at which less than one third of the patients in a dose level cohort experience DLT), the highest dose cohort was reached, or an appropriate dose for phase II was determined on the basis of PK, pharmacodynamics, and response data. The DLT evaluation period began with the first dose of JNJ-40346527 and ended after 21 days of dosing (1 cycle, including any treatment delays within the cycle) immediately before the initiation of the second cycle. The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.03) were used to grade toxicity. DLT were defined as follows: any grade 3 or grade 4 nonhematologic toxicity, including persistent grade ≥ 2 nausea or vomiting despite prolonged antiemetic treatment; grade 4 neutropenia ($ANC < 500/mm^3$) > 7 days febrile neutropenia [$ANC < 1,000/mm^3$ with a single temperature of $> 38.3^\circ C$ or sustained temperature of $\geq 38^\circ C$ for over 1 hour] or sepsis; or grade 4 thrombocytopenia (platelet count, $< 25,000/mm^3$) > 5 days and not responding to transfusion support. Excluded for DLT were grade 3 nausea or vomiting or diarrhea responding to treatment, isolated grade 3 gamma glutamyl transferase (GGT) elevations, grade 3 fatigue/asthenia.

Patients who experienced a DLT were not substituted with another patient. Patients who discontinued the first cycle without experiencing a DLT were replaced to ensure 3 safety and PK evaluable patients per dose cohort. All available data were reviewed by the study evaluation team (SET). The SET consisted of the principal investigators (or their designees), the sponsor's medical monitors, and the sponsor's clinical pharmacologist. No inpatient dose escalation was permitted. Treatment was continued until disease progression or unacceptable toxicity (based on investigator decision) occurred. Only patients who discontinued study treatment before disease progression or because of treatment-related grade 3 or higher toxicity participated in the follow-up phase.

Study endpoints

Safety evaluations. Safety evaluations included all adverse events (AE), clinical laboratory tests, vital sign measurements, physical examinations, electrocardiograms, and ECOG PS.

Efficacy evaluations. Patients were evaluated using computed tomography (CT) scans with IV contrast of the neck, chest, abdomen, and pelvis and whole body positron emission tomography (PET) scans. Disease response was assessed according to the Revised Response Criteria for Malignant Lymphoma (Cheson criteria; ref. 30). The analysis of response rate included data from physical examination, CT and [^{18}F]-fluorodeoxyglucose (FDG)-PET or magnetic resonance imaging (MRI) scan (if applicable to evaluate sites of disease that cannot be adequately imaged using CT). Patients who completed two cycles of therapy were restaged and those who achieved a response or stable disease (SD) could continue treatment until disease progression. The evaluations were performed throughout the study for each patient [baseline, end of cycle 2 (= 6 weeks), end of cycle 6 (= 18 weeks),

thereafter per hospital standard practice with a minimum every 3 months) using the same method of assessment.

Pharmacokinetic evaluation. Blood samples for PK studies were collected on days 1 and 21, predose and 30 minutes 1, 2, 3, 4, 6, 8, and 24 hours after dose, and on days 7 and 14, predose and 4 hours after dose during the first cycle from all patients for the measurement of plasma concentrations of JNJ-40346527 using a validated liquid chromatographic tandem mass spectrometric method. The following PK parameters were calculated using noncompartmental methods with WinNonlin Version 5.2.1 (Pharsight Corporation): maximum observed plasma concentration (C_{max}), trough plasma concentration before dosing or at the end of the dosing interval (C_0), observed plasma concentration at 4 hours after dosing (C_4), time to reach C_{max} (t_{max}), area under the plasma concentration-time curve from time 0 to time 24 hours after dosing (AUC_{24}).

Pharmacodynamic evaluation. Blood samples (whole blood and plasma) were collected on days 1, 7, 14, and 21. Biomarkers included CSF-1 in plasma or tumor tissue and phosphorylated CSF-1R/total CSF-1R in peripheral blood mononuclear cells (PBMC).

To measure phosphorylated CSF-1R/total CSF-1R, PBMC lysates were prepared from blood collected from patients stimulated with either CSF-1 (8 $\mu g/mL$ in PBS) or vehicle control. Immunoprecipitation (IP) coupled with Western-based approach was used to measure ratio of phospho-CSF-1R (pCSF-1R) to CSF-1R in the PBMCs. Briefly, IP for each sample and control was carried out using biotinylated human M-CSF-1R capture antibody for CSF-1R and biotin-conjugated antiphosphotyrosine capture antibody was used for pCSF-1R (31). Resolved proteins were transferred to a nitrocellulose membrane and CSF-1R blots were probed with CSF-1R antibody at 1:2,000 in milk buffer and pCSF-1R blots were probed with phospho-M-CSF receptor (Tyr723) antibody at 1:1,000 dilution. Chemiluminescence was detected using the ChemiDoc XRS+ System with supercooled CCD camera. Band intensities were measured at approximately 150 to 165 kDa, the estimated molecular weight for CSF-1R after accounting for glycosylation, and quantified with the Image Lab image acquisition and analysis software (Bio-Rad).

Statistical design and analysis

Sample size determination. The sample size estimated for the phase I portion of the study was based on the utilization of a traditional 3+3 design. The sample size estimated for a phase II part assumed a 30% overall response rate. A sample size of 27 response-evaluable patients at specified dose level (including patients treated at the same dose during phase I and in the expansion cohort, if deemed appropriate) would provide a two-sided 95% confidence interval (CI; 14%–50%). To account for a dropout rate of approximately 10%, up to 30 patients treated in total at the recommended phase II dose (including patients treated at the same dose during phase I and in the expansion cohort) were planned to be enrolled.

Safety evaluations, PK parameters, and pharmacodynamic biomarker parameters were summarized descriptively.

The "Treated Population," used for all safety analyses and for efficacy analysis consisted of all patients who received ≥ 1 dose of the study drug. The "Response-Evaluable Population" consisted of all patients who received ≥ 1 dose of study drug and had a

Table 1. Baseline demographics

| Treated, n | 150 mg QD 3 | 300 mg QD 5 | 450 mg QD 3 | 600 mg QD 3 | 150 mg BID 7 | Combined 21 |
|--|----------------|----------------|----------------|----------------|-----------------|----------------|
| Age, y | | | | | | |
| Mean (SD) | 48.0 (24.9) | 33.4 (10.0) | 49.0 (18.5) | 29.3 (10.5) | 38.6 (18.6) | 38.9 (16.7) |
| ≤45, n (%) | 2 (66.7) | 4 (80.0) | 1 (33.3) | 3 (100.0) | 5 (71.4) | 15 (71.4) |
| >45, n (%) | 1 (33.3) | 1 (20.0) | 2 (66.7) | 0 | 2 (28.6) | 6 (28.6) |
| HL stage at entry, n (%) | | | | | | |
| Stage I | 0 | 0 | 0 | 0 | 0 | 0 |
| Stage II | 1 (33.3) | 0 | 0 | 0 | 0 | 1 (4.8) |
| Stage III | 0 | 0 | 0 | 1 (33.3) | 3 (42.9) | 4 (19.0) |
| Stage IV | 2 (66.7) | 5 (100.0) | 3 (100.0) | 2 (66.7) | 4 (57.1) | 16 (76.2) |
| HL subtype, n (%) | | | | | | |
| Nodular sclerosis | 2 (66.7) | 5 (100.0) | 3 (100.0) | 2 (66.7) | 7 (100.0) | 19 (90.5) |
| Mixed cellularity | 1 (33.3) | 0 | 0 | 1 (33.3) | 0 | 2 (9.5) |
| Patients with prior systemic therapy | | | | | | |
| Median (range) | 4.0 (3; 12) | 9.0 (5; 13) | 8.0 (4; 14) | 6.0 (4; 12) | 6.0 (3; 10) | 6.0 (3; 14) |
| 1–5, n (%) | 2 (66.7) | 1 (20.0) | 1 (33.3) | 1 (33.3) | 3 (42.9) | 8 (38.1) |
| > 5, n (%) | 1 (33.3) | 4 (80.0) | 2 (66.7) | 2 (66.7) | 4 (57.1) | 13 (61.9) |
| Patients who received ASCT/alloTx, n (%) | 2 (66.7) | 5 (100.0) | 2 (66.7) | 3 (100.0) | 6 (85.7) | 18 (85.7) |
| Prior radiotherapy, n (%) | 3 (100.0) | 4 (80.0) | 3 (100.0) | 3 (100.0) | 4 (57.1) | 17 (81.0) |

NOTE: Percentages are calculated with the number of patients in all treated patient populations with nonmissing values for that parameter as the denominator. One patient each in the 150 mg QD, 600 mg QD, and 150 mg BID cohorts had a prior surgery on HL lesions, such as lymph nodes, etc. Abbreviations: ASCT/alloTx, autologous or allogeneic stem cell transplant; BID, twice a day; QD, once a day; SD, standard deviation.

posttreatment disease assessment. The "PK Population" consisted of all patients who had sufficient and interpretable PK assessments to calculate the noncompartmental PK parameters.

Results

Demographics

A total of 21 patients were enrolled during the dose-escalation phase I part of the study. In the 300-mg every day cohort, there were 2 patients enrolled who showed rapid PD during the first cycle and discontinued after 15 and 6 days, respectively. Patients were still counted for the overall safety tabulations, but excluded for DLT assessment as they discontinued so rapidly. In the 150-mg twice a day cohort, 3 patients were included for DLT assessment and 4 additional patients to further assess safety, PK, and pharmacodynamics. The median age of the patients was 33 years (range, 19–75 years; Table 1). Most patients ($n = 16$; 76.2%) had stage IV HL and nodular sclerosis ($n = 19$; 90.5%) at study entry (Table 1).

All patients discontinued the study; 18 (85.7%) patients discontinued because of progressive disease, and 1 (4.8%) patient discontinued with CR after 1 year of treatment, 1 patient by investigator decision (SD with increase in lesions' sizes and

increased PET activity), and 1 patient due to AEs [lung embolism (noted at cycle 1 day 1), which was a preexisting event at study entry]. The median duration of treatment was 9.9 weeks (range, 0–49 weeks), during which patients received a median of four cycles of treatment (range, 1–16 cycles; Supplementary Table S1).

The median number of prior therapies was 6 (range, 3–14). There were 9 of 21 patients who were refractory to last treatment. No noteworthy prior/concomitant medications were taken. Of the 21 patients, 13 received brentuximab vedotin before they entered the study (response after brentuximab vedotin: $n = 1$ with CR, $n = 2$ with PR, $n = 5$ with SD; $n = 3$ with PD, and $n = 3$ were not evaluable).

Pharmacokinetics

On the basis of trough plasma JNJ-40346527 concentrations on days 7, 14, and predose and 24-hour concentrations on day 21, JNJ-40346527 appears to have reached steady-state by day 21 for all doses. C_{max} and AUC_{24} of JNJ-40346527 increased with increasing dose from 150 mg every day to 450 mg every day on day 21 (Table 2 and Fig. 1). However, exposure was paradoxically lower at 600 mg every day compared with 450 mg every day. Mean AUC_{24} values were comparable between 300 mg every day and 150 mg twice a day on day 21 while mean C_{max} was lower

Table 2. PK parameters

| Day | PK parameters | 150 mg QD (n = 3) | 300 mg QD (n = 5) | 450 mg QD (n = 3) | 600 mg QD (n = 3) | 150 mg BID (n = 7) |
|-----|----------------------------|-------------------|-------------------|-------------------|-------------------|--------------------|
| 1 | ^a T_{max} (h) | 4.1 (1.0–4.5) | 3.0 (2.0–4.0) | 2.1, 2.1 | 3.0 (2.0–4.0) | 1.0 (1.0–6.0) |
| | C_{max} (ng/mL) | 278 (71.4) | 552 (198) | 552, 655 | 358 (244) | 313 (86.9) |
| | AUC_{24} (ng.h/mL) | 1,931 (404) | 3,935 (2,001) | 2,536, 4,135 | 2,657 (1,255) | NC |
| 7 | C_0 (ng/mL) | 78.3 (23.5) | 131 (70.4) | 314 (134) | 123 (54.0) | 270 (157) |
| | C_4 (ng/mL) | 285 (140) | 388 (271) | 952 (275) | 433 (359) | 363 (120) |
| 14 | C_0 (ng/mL) | 108 (15.6) | 138 (30.7) | 285 (115) | 156 (83.3) | 229 (40.4) |
| | C_4 (ng/mL) | 317 (72.7) | 394 (193) | 980 (205) | 672 (424) | 367 (124) |
| 21 | T_{max} (h) | 1.0, 3.1 | 4.1 (4.0–5.9) | 3.0 (2.0–4.5) | 3.9 (3.0–4.0) | 2.5 (1.9–8.0) |
| | C_{max} (ng/mL) | 304, 321 | 598 (156) | 1,157 (409) | 843 (394) | 483 (182) |
| | AUC_{24} (ng.h/mL) | 3,417, 3,436 | 7,588 (2,248) | 12,804 (4,875) | 6,961 (2,656) | 7,471 (2,349) |
| | C_0 (ng/mL) | 100, 101 | 160 (63.2) | 277 (89.0) | 129 (45.4) | 196 (41.0) |

Abbreviations: AUC_{24} , area under the plasma concentration-time curve from time 0 to time 24 hours after dosing; C_0 , trough plasma concentration before dosing or at the end of the dosing interval; C_4 , observed plasma concentration at 4 hours after dosing; C_{max} , maximum observed plasma concentration; T_{max} , time to reach C_{max} ; NC, not calculated.

^aMean (SD) for all parameters; median (range) for T_{max} .

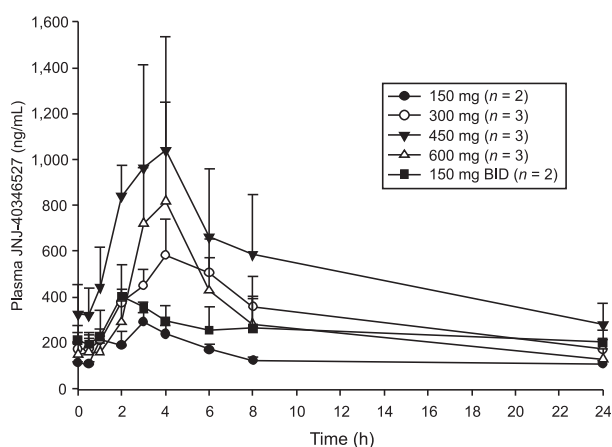


Figure 1. Comparative mean (SD) pharmacokinetic profiles of JNJ-40346527 on day 21 for all cohorts.

following twice a day dosing. Among all dose levels, PK at 150 mg twice a day was associated with the lowest C_{max} to C_{min} ratio (approximately 2.5) and less fluctuations on drug concentrations over the dosing interval. This appears to be consistent with the

sustained pFMS inhibition (>90%) observed at the 150 mg twice a day dose level. Therefore, 150 mg twice a day dose included 3 patients for DLT assessment and 4 additional patients to further assess safety, PK, and pharmacodynamics.

Biomarkers

From pCSF-1R analysis, more than 80% to 90% inhibition of pCSF-1R was observed at 4 hours after treatment on days 1, 7, 14, and 21 in most patient samples in all cohorts (Fig. 2A and B), confirming target engagement by JNJ-40346527. The pCSF-1R inhibition seemed to drop at trough (i.e., 24 hours after dosing on day 21) at every day doses, but sustained inhibition was observed at the 150 mg twice a day dose level at both peak and trough, and therefore this was recommended as the most optimal phase II dose.

Safety

Overall, 90.5% (19 of 21) treated patients experienced one or more AEs. The most frequently reported AEs (occurring in $\geq 20\%$ of the patients) included pyrexia ($n = 11$; 52.4% patients), nausea and headache (each $n = 7$; 33.3% patients), vomiting ($n = 6$; 28.6% patients), and anemia ($n = 5$; 23.8% patients). Grade 3 TEAEs were reported in 7 (33%) patients [anemia and lymphopenia ($n = 3$; 14.3%); gastric obstruction, peripheral edema,

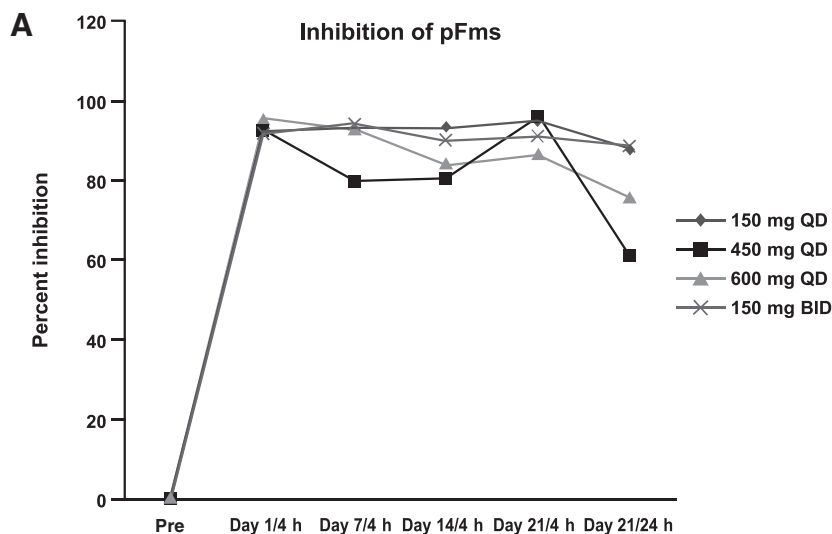
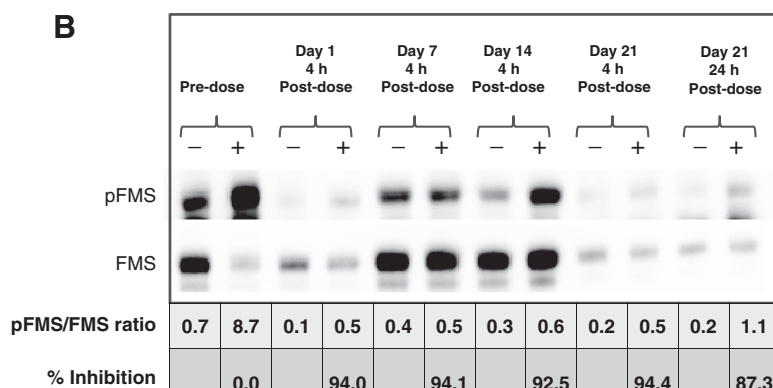


Figure 2. A, inhibition of CSF-1R phosphorylation. B, representative Western blot analysis.



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Table 3. Treatment-emergent drug-related adverse events by worst toxicity grade in at least 2 patients in any group (treated patients)

| | TEAE toxicity | | | | | Combined |
|---|---------------|----------|----------|---------|---------|-----------|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | |
| Treated patients | | | | | | 21 |
| Patients with drug-related TEAEs, <i>n</i> (%) | 8 (38.1) | 6 (28.6) | 3 (14.3) | 0 | 0 | 17 (81.0) |
| Drug-related TEAEs in ≥2 patients, <i>n</i> (%) | | | | | | |
| Nausea | 3 (14.3) | 3 (14.3) | 0 | 0 | 0 | 6 (28.6) |
| Headache | 4 (19.0) | 1 (4.8) | 0 | 0 | 0 | 5 (23.8) |
| Pyrexia | 4 (19.0) | 1 (4.8) | 0 | 0 | 0 | 5 (23.8) |
| Vomiting | 3 (14.3) | 1 (4.8) | 0 | 0 | 0 | 4 (19.0) |
| Anemia | 0 | 2 (9.5) | 1 (4.8) | 0 | 0 | 3 (14.3) |
| Abdominal pain, upper | 2 (9.5) | 1 (4.8) | 0 | 0 | 0 | 3 (14.3) |
| Constipation | 2 (9.5) | 0 | 0 | 0 | 0 | 2 (9.5) |
| Fatigue | 0 | 2 (9.5) | 0 | 0 | 0 | 2 (9.5) |
| Blood CPK increased | 1 (4.8) | 1 (4.8) | 0 | 0 | 0 | 2 (9.5) |
| Enzyme abnormality | 1 (4.8) | 1 (4.8) | 0 | 0 | 0 | 2 (9.5) |

Abbreviations: CPK, creatine phosphokinase; TEAE, treatment-emergent adverse events.

abnormal hepatic function, hyperlipasemia, and hypoalbuminemia (*n* = 1; 4.8%)] and grade 4 (laryngeal inflammation) and 5 (oropharyngeal pain) TEAEs in 1 (4.8%) patient each. Total 81.0% (17 of 21) treated patients experienced 1 or more drug-related AEs (Table 3). No DLTs were identified. The MTD was not reached. Serious AEs were recorded in 4 patients; 2 patients had SAEs of dyspnea, one of which was grade 4. One patient had lung disorder that was reported as an AE leading to death due to disease progression (grade 5), and 1 patient had gastric obstruction (grade 3).

A grade 3 or 4 laboratory abnormality was reported in 12 (57.1%) patients. Most common was decreased lymphocyte counts that occurred in 9 (42.9%) patients. None of these abnormalities led to dose reduction or treatment discontinuation, except a grade 2 elevation of creatine kinase that led to a dose reduction. Two (9.5%) patients discontinued treatment, both due to non-drug-related TEAEs (grade 3 limb edema and grade 3 lung disorder). There were 3 deaths that occurred, the cause of death in all the cases was disease progression and lung disorder was reported to be the cause of death in 1 patient. This patient progressed on the lung lesion and developed an interstitial pneumonitis; no infection could be documented. Of the other 2 patients who died, one had been admitted to the intensive care unit with worsening of dyspnea and fever, 10 days before death. The event of dyspnea led to patients' persistent/significant disability; however, the patient was discharged on the next day. For the third patient, at the time of death, the events of enzyme abnormality (alkaline phosphatase levels elevated) and hypoalbuminemia had not resolved while, the event of oral candidiasis was reported as resolving.

Two of the deaths occurred within 30 days of the last dose of study treatment.

Efficacy

One patient treated with 150 mg every day, had a best overall response of CR with a PFS of 352+ days. This male patient had multiple relapsed disease and received HDCT and ASCT after initial combined modality treatment. At post-ASCT relapse, he was treated with IGEV (ifosfamide, gemcitabine, vinorelbine, steroids; ref. 32) followed by involved-field radiotherapy and achieved a PET-positive PR. The patient then entered the current trial. During the treatment period, the tumor shrank and became PET negative. Overall, 11 (55.0%) patients had SD and 8 (40.0%) patients had progressive disease (PD; Table 4). PFS for all treated patients ranged from 2 days to 352+ days.

Discussion

JNJ-40346527, a CSF-1R inhibitor, demonstrated an acceptable safety and tolerability profile in patients with relapsed or refractory cHL in this open-label, phase I/II, multicenter study. One patient (5.0%) treated with 150 mg every day had a best overall response of CR across all treatment groups with PFS of 1 year, and 11 (55.0%) patients had SD. Baseline characteristics of patients (median of 6 prior regimen including brentuximab vedotin for 13 of 21 patients and 9 of 21 refractory to last prior therapy) suggest we enrolled a very poor-risk group of patients, which could have contributed to the failure in achieving target

Table 4. Best overall response by Cheson criteria (response-evaluable patient population)

| | 150 mg QD | 300 mg QD | 450 mg QD | 600 mg QD | 150 mg BID | Combined |
|--------------------------------------|-----------|-----------|-----------|-----------|------------|------------|
| Patients ^a , <i>n</i> | 3 | 5 | 3 | 3 | 6 | 20 |
| Objective response rate ^b | 1 | 0 | 0 | 0 | 0 | 1 (5.0%) |
| Complete response | 1 | 0 | 0 | 0 | 0 | 1 (5.0%) |
| Partial response | 0 | 0 | 0 | 0 | 0 | 0 |
| Stable disease | 1 | 2 | 2 | 2 | 4 | 11 (55.0%) |
| Progressive disease | 1 | 3 | 1 | 1 | 2 | 8 (40.0%) |

NOTE: Percentages calculated with the number of evaluable patients as denominator.

Abbreviations: BID, twice a day; QD, once a day.

^aPatients who received at least 1 dose of the study treatment, and had baseline and at least one posttreatment tumor assessment.

^bObjective response rate = complete response or partial response.

efficacy outcomes. No DLTs were reported and MTD was not reached.

The doses to be evaluated in the present study (150–600 mg/day) are within the dose range that was deemed safe and well tolerated in healthy participants (unpublished data). These doses have also been demonstrated to be pharmacologically active *ex vivo* with maximal inhibition of CSF-1R phosphorylation (>95%) being achieved at a dose of 450 mg or higher in the single-dose study and at a dose of 150 mg once daily or higher in the multiple-dose study. Both PK and pharmacodynamic analyses showed that there was target engagement at all dose levels, with optimal inhibition of pCSF-1R at 150 mg twice a day. The primary goal of the pharmacodynamic biomarker analysis was to assess inhibition of CSF-1R–mediated biologic effects by JNJ-40346527 (as an indicator of target engagement by the compound) to analyze differences between responders and nonresponders, and to determine whether the markers could be used to classify patients as potential responders before treatment. Tumor tissue analyses were not performed because pre- and posttreatment tumor biopsies were not obtained and only 1 patient reported a CR before the study being terminated. The 150 mg twice a day dose was selected as the recommended phase II dose based on the PK and pharmacodynamic results over 24 hours after dosing. On the basis of these results, increasing dose or changing administration schedule was not expected to result in an increased target engagement, inhibition of phosphorylation and thus higher efficacy.

High-dose chemotherapy supported by ASCT is considered the standard of care in patients with HL, which has relapsed, or is refractory to conventional chemoradiotherapy. Patients with relapsed HL after ASCT and patients not suitable for ASCT at first relapse have a poor prognosis, hence new approaches are needed (33). Although, brentuximab vedotin has shown high efficacy and excellent tolerability in this group of patients (10), patients relapsing after or refractory to brentuximab vedotin still have few therapeutic options. In other B-cell neoplasms, targeted small-molecule inhibitors have shown high efficacy; however, an effective small-molecule inhibitor for the treatment of relapsed HL has not been reported yet (34, 35). An interplay of several mechanisms underlies the development of cancer, and various multitargeted small-molecule tyrosine kinases are now in routine use for the management of different solid tumor indications that were earlier considered to be unresponsive to systemic therapy (36–38). CSF-1R/CSF-1 signaling strongly correlates for instance with poor prognosis in breast cancer, and inhibition of this signaling pathway impaired CSF-1–induced cell proliferation in cell lines (39–41). Despite successful inhibition of proliferation and invasion in HL cell lines, this study did not show high efficacy in late-stage cHL patients who had undergone several prior treatments before enrollment. This is possibly, in part, due to the high tumor burden and dedifferentiation of HL tumor cells in these patients. Interestingly, the patient with the CR had a low tumor burden before study entry and might thus have been more responsive to the treatment.

Limitation of single-target molecules that are upstream in the signaling cascade is that tumors can activate alternate parallel or downstream messengers that can compromise the efficacy (42). Furthermore, resistance to these single-target molecules is a problem. Further clinical studies are required to assess the effect of

these novel single-target molecules, perhaps in combination with other agents, for the management of cancer, and correlation of pharmacodynamics and biomarker studies is essential to decipher the signaling mechanism, to ensure optimal efficacy with manageable toxicity profile (42, 43).

In conclusion, the advent of CSF-1R inhibitors that possess the novel dual ability to regulate the tumor cells and the surrounding macrophage behavior could revolutionize the understanding and treatment of difficult to treat resistant cancers such as cHL. Although, the objective of at least 30% overall response rate was not met and further dose increases were not expected to improve PK and pharmacodynamic outcomes, JNJ-40346527 demonstrated an acceptable safety and tolerability profile and the other study objectives of determining the recommended phase II dose, PK exposure, and biomarkers of target engagement were met. Because of the favorable toxicity profile of JNJ 40346527 and the demonstration of its pharmacologic activity in terms of CSF-1R-inhibition in relapsed HL, further evaluation of this drug in other cancers is warranted.

Disclosure of Potential Conflicts of Interest

B. von Tresckow reports receiving a commercial research grant from and is a consultant/advisory board member for Novartis, and reports receiving travel reimbursement from Takeda. M.S. Topp is a consultant/advisory board member for Affimed and Amgen. S. Seetharam has ownership interest (including patents) in Johnson & Johnson. No other potential conflicts of interest were disclosed.

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