A phase 1 trial of the anti-inhibitory KIR mAb IPH2101 for AML in complete remission

Norbert Vey,1,3 Jean-Henri Bourhis,4 Nicolas Boissel,5 Dominique Bordessoule,6 Thomas Prebet,1,3 Aude Charbonnier,1 Anne Etienne,1,2 Pascale Andre,7 François Romagne,7 Don Benson,8 Herve Dombret,5 and Daniel Olive1-3,9

1Institut Paoli-Calmettes, Marseille, France; 2Aix-Marseille Université, Marseille, France; 3Centre de Recherche en Cancérologie de Marseille, Marseille, France; 4Institut Gustave Roussy, Villejuif, France; 5Hôpital Saint Louis, Paris, France; 6Centre Hospitalier Universitaire de Limoges, Limoges, France; 7Innate Pharma, Marseille, France; 8The Ohio State University and Comprehensive Cancer Center, Columbus, OH; and 9Infrastructures Biologie Sante et Agronomie Cancer Immunomonitoring Platform

IPH2101 is an anti-killer inhibitory receptor (anti-KIR) mAb that can block KIR-mediated inhibition of natural killer (NK) cells to enhance cytotoxicity against acute myeloid leukemia blasts. We have conducted a phase 1 study of IPH2101 in elderly patients with acute myeloid leukemia in first complete remission. Patients received escalating doses (0.0003-3 mg/kg) of IPH2101 following a 3 + 3 design. Safety, toxicity (primary end points), pharmacokinetics, outcome, and immunologic correlates were evaluated. Twenty-three patients (median age, 71 years), were enrolled. Adverse events were mild and transient, consisting mainly of infusion syndrome and erythema. The maximum tolerated dose was not reached, although full KIR saturation (> 90%) was sustained for more than 2 weeks at 1 and 3 mg/kg. There was a clear correlation between mAb exposure and KIR occupancy. Neither hematologic toxicity nor significant changes in the numbers and distribution of lymphocyte subsets, NK cell receptor expression, or in vitro cytotoxicity were seen. At the highest dose levels (0.3, 1, and 3 mg/kg), transient increases in TNF-α and MIP-1β serum concentrations and NK cell CD69 expression were observed. Overall and relapse-free survival in the present study compared favorably to reports in comparable patient populations. We conclude that IPH2101 administration is safe and can block KIR for prolonged periods of time with limited side effects. Registered with the European Union Drug Regulating Authorities Clinical Trials (EUDRACT) as 2005-005298-31. (Blood. 2012;120(22):4317-4323)

Introduction

Despite the possibility of complete remission (CR) with intensive therapy, acute myeloid leukemia (AML) remains virtually incurable in older patients and new treatments are needed.1-3 Potential new treatments under investigation include noncytotoxic therapies such as immunotherapy.4

Natural killer (NK) cells are critical effectors of the innate immune system that are regulated by a balance of signaling via activating and inhibitory receptors and endowed with potent anticancer effects.5,6 A role for NK cells in tumor control has been shown in AML. For example, NK cell number and function have been shown to be correlated with relapse-free survival (RFS).5,7 Killer inhibitory receptors (KIRs) are inhibitory receptors that prevent NK cell activation on binding with their ligands, principally HLA-C molecules.8 The clinical relevance of KIR inhibition has been shown in the allogeneic haplo-mismatched stem cell transplantation (allo-SCT) model. KIR/KIR-ligand mismatch between donor and recipient is associated with improved RFS and overall survival (OS),9 suggesting that in the absence of KIR/KIR-ligand binding, alloreactive NK cells may eradicate residual leukemia.10

We hypothesized that pharmacologic targeting and modulation of KIR using an anti-KIR mAb might reproduce the KIR-mismatched situation in the allo-SCT setting and improve NK cell antileukemic effects. IPH2101, also called anti-KIR (formerly, 1-7F9), is a fully human IgG1 mAb that binds specifically and with high affinity to a set of inhibitory KIRs, namely KIR2DL1, KIR2DL-2, and KIR2DL-3 (and KIR2DL-2DS1 and KIR2DL-2DS2), expressed on half of the total NK cell population. The KIR2DL1, KIR2DL-2, and KIR2DL-3 set collectively recognizes virtually all HLA-C alleles. By preventing the KIR/HLA-C interaction, IPH2101 augments NK cell–mediated killing of autologous human AML blasts that express HLA-C in a dose-dependent manner.10 In vivo efficacy has also been demonstrated in a NOD-SCID mouse model of NK cell–mediated tumor rejection.10

In the present study, we evaluated the clinical and biologic effects of IPH2101 in elderly patients with AML in first CR.

Methods

Patients

Four French centers enrolled patients in the IPH2101-101 study, which is registered at European Union Drug Regulating Authorities Clinical Trials (EUDRACT) as 2005-005298-31 and was approved by the ethical review board. Presented in part at the American Society of Clinical Oncology 2009 Annual Meeting, May 18, 2009, Orlando, FL, and the American Society of Hematology 2009 Annual Meeting, December 7, 2009, New Orleans, LA.


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boards of all participating institutions. All participants gave written informed consent in accordance with the Declaration of Helsinki.

In patients with overt leukemia, expression of NK receptors may be impaired, and NK cells display reduced cytotoxicity against autologous AML blasts.1 Because these factors might confound identification of mechanism of action-related adverse events resulting from administration of anti-KIR mAb, we selected elderly patients in first CR of AML for this phase 1 trial, for whom no standard of care postremission treatment exists.

Inclusion criteria were: age 60-80 years, diagnosis of AML according to World Health Organization (WHO) criteria1 in first CR;3 30-120 days after last chemotherapy dose; KIR expression on NK cells; Eastern Cooperative Oncology Group (ECOG) performance status = 2; serum creatinine < 2 mg/dL; total bilirubin < 1.5 x the upper limit of normal; and transaminase < 3 x the upper limit of normal. Exclusion criteria were: acute promyelocytic leukemia or AML with favorable prognosis based on cytogenetics, G-CSF or any cytokine treatment, systemic steroid treatment within the last 30 days before screening, history of active autoimmune disease, monoclonal gammopathy, or active infectious disease.

Treatment
IPH2101 was administered as an IV slow injection for doses up to 0.015 mg/kg and as a 1-hour infusion for doses more than 0.015 mg/kg. Treatment took place close to an intensive care unit. A minimum of 2 working days was required between the first treatment dose of consecutive patients.

Study design
A classic, modified Fibonacci phase 1 design was used, with a minimum of 3 patients included at each dose level in a standard 3 + 3 trial design. Briefly, consecutive cohorts of 3 patients received escalating doses of IPH2101. Starting dose was established with the Minimal Anticipated Biologic Effect Level (MABEL)-like approach calculation at 0.0003 mg/kg. A 1-log increment was scheduled for escalation to dose level 2. Half-log increments were planned for the subsequent dose escalation (supplemental Table 1, available on the Blood Web site; see the Supplemental Materials link at the top of the online article). Dose escalation was determined based on 4-week safety and pharmacokinetic (PK)/pharmacodynamic (PD) evaluation.

The objective of the dose-escalation scheme was to explore at least one dose level above the dose that gives full KIR saturation (ie, > 90% KIR occupancy) for at least 4 weeks to evaluate the safety of prolonged KIR blockade in vivo. Patients were followed until negative (< 30%) KIR occupancy.

When KIR occupancy became negative, patients without significant adverse events (AEs) and still in CR were offered participation in an extension study of repeated doses of IPH2101 (protocol IPH2101-102, EUDRACT 2006-003004-41). Patients who had given written informed consent could receive up to 6 cycles of IPH2101 given every 28 days at the same dose as in the dose-escalation trial.

PK analysis
PK analysis was performed by ELISA on samples collected at time 0 (pre-dose), 10 minutes, 1, 3, 6, 12, and 24 hours after dosing, and at 1, 2, 3, 4, 6, 8, 10, and 12 weeks after dosing. The lower limit of quantification was 5.0 ng/mL. PK parameters were calculated using noncompartmental analysis with WinNonlin Enterprise Version 5.2 software (model 202 constant rate IV infusion).

PD analysis
Absolute numbers of peripheral NK, B, and T lymphocytes and activation status were assessed by flow cytometry on whole blood with True Count beads (BD Biosciences). Expression of NK receptors KIR2DL1/S1, KIR2DL2/3/5/2, KIR3DL1/S1, KIR2DS4, CD85j, CD161, CD94, NKG2A, NKP46, NKP30, CD244, DNAM-1, NKG2D, NKG2C, and CD16, as well as NK- and T-cell activation markers (ie, NKP44, CD25, CD69, CD107 and perforin) were measured. Saturation of KIRs targeted by IPH2101 was evaluated by staining with PE-conjugated IPH2101, leading to free KIR detection. KIR saturation was evaluated as the ratio between fluorescence intensities obtained at a given time point and predose. Values more than 90% were considered to correspond to full saturation. All directly labeled mAbs were purchased from BD Biosciences or Beckman Coulter. IFN-γ, IL-6, IL-1, and macrophage inflammatory protein-1 β (MIP-1β) serum levels were measured by ELISA assay.

Response evaluation
Response was assessed using the criteria of Cheson et al.12 Progression-free survival (PFS) was assessed as the time difference between administration of IPH2101 and diagnosis of progression or death from any cause. RFS was assessed from the date of attainment of CR to date when relapse was diagnosed. OS was assessed from the administration of IPH2101 to date of death from any cause. PFS, RFS, and OS were calculated using the Kaplan-Meier method.

Statistical methods
Analyses were performed with StatView Version 5.0 software. P < .05 was considered significant. PFS, LFS, and OS were calculated using the Kaplan-Meier method.

Results
Patients
From January 2007 to February 2009, 23 patients were enrolled in our study. Patient characteristics are presented in Table 1. At inclusion, the median number of circulating NK cells was 127/μL (range, 20-843). The median percentage of NK cells expressing inhibitory KIR (recognized by IPH2101) was 40.4% (range, 15%-58.4%; supplemental Table 2) and was not different from healthy subjects (data not shown). Staining with KIR2DL1-specific and KIR2DL2/3-specific mAbs was also performed predose together with determination of C1 and C2 MHC status, which allowed for the calculation of the number of cells that could become “alloreactive” on treatment in individual patients. This number varied from 10 cells/μL and 213 cell/μL, respectively (mean, 51; supplemental Table 3). Data from a representative patient are provided in supplemental Figure 1. The median number of circulating T cells and the median percentage of T cells expressing IPH2101 are depicted in supplemental Table 4.

Nine patients were included in the extension trial after a median of 18 weeks (range, 6-36) after initial IPH2101 injection and received a median of 5 cycles (range, 1-6). Five patients were discontinued before completion of the 6 planned cycles, 4 for progression (n = 5) and 1 for consent withdrawal.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
<td>Patients, no</td>
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<tr>
<td>Median age, y (range)</td>
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<tr>
<td>Sex ratio, M/F</td>
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<td>FAB category, n (%)</td>
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<tr>
<td>M0</td>
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<td>M1</td>
<td>4 (17%)</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Interval CR inclusion, mo, median (range)</td>
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</table>

Safety

IPH2101 administration was generally well tolerated and the maximum tolerated dose was not reached. Three patients were included at each dose level, except for dose levels 4 and 5, in which 1 additional patient was included. One patient in dose level 4 relapsed on day 15 after treatment and 1 patient in dose level 5 had no detectable anti-KIR. Both patients were replaced because they were deemed not informative for safety evaluation. During the dose escalation, a total of 27 treatment-related AEs were reported in 15 patients. Grade 3-4 treatment-related AEs were limited to 1 patient who experienced transient grade 3 lipase elevation that resolved without medical intervention; this event was not thought to be clinically significant and was not considered a dose-limiting toxicity. One patient at dose level 3 mg/kg had grade 2 bradycardia and hypotension on the day of IPH2101 administration. This event, concomitant with fever and chills, resolved within an hour of treatment with paracetamol, was caused by a vagal reaction, and did not recur on redosing in the extension trial. The most frequently reported treatment-related AEs were pruritus (17%), rash (17%), and fever (13%), all grades 1-2 (Table 2). Fever was observed only at the 3 highest dose levels and occurred shortly after drug administration, which is consistent with an infusion syndrome (ie, fever and chills). Skin disorders were reported from 3-22 days after IPH2101 administration.

Among the 12 serious AEs that were not related to treatment, 11 were AML relapses (as per protocol definition), including 5 patients in whom relapse led to premature discontinuation from the study. The other was pancreas adenocarcinoma diagnosed incidentally a few days after IPH2101 administration.

A similar tolerance profile was seen in 9 patients who received repeated dosing of IPH2101, with skin reactions representing the most frequent AEs (supplemental Table 5).

PK and PD

A total of 23 patients received at least one dose of IPH2101, and 20 patients were evaluable for PK analysis. One patient at the 0.3 mg/kg dose level was excluded because he had no measurable concentrations (ie, below the lower limit of quantification) after dosing, and 2 patients on the 0.003 mg/kg dose level because they had less than 3 measurable concentrations in their PK profiles. Mean concentration-time profiles of IPH2101 are depicted in Figure 1A and descriptive statistics on PK parameters of IPH2101 are presented in supplemental Table 6. Mean concentration levels declined in a bi-exponential fashion after the end of the infusion, however, with lower mean clearance ranging from 0.016-0.020 L/h. The terminal half-life of IPH2101 at the highest 3 dose levels (0.3-3 mg/kg) ranged from 12.4-16.2 days.

Full KIR occupancy (> 90%) was achieved during the first 24 hours in all patients on the 0.003 mg/kg dose. A clear relationship between exposure and KIR occupancy was observed, including exposure response for maximum concentration and maximal occupancy (as predicted from the preclinical PK/PD model) and exposure response in duration of PK and occupancy, with moderate interpatient variability. The doses that elicited full occupancy were: 1 week = 0.075 mg/kg, 2 weeks = 1 mg/kg, and for at least 4 weeks = 3 mg/kg (Figure 1B). At 3 mg/kg, KIR saturation (> 30% KIR occupancy) persisted for 24-32 weeks.

Immunologic effects

IPH2101 treatment had no significant effect on the number or distribution of lymphocyte subsets (Figure 2A). A slight nonsignificant decrease in NK cells was observed in the peripheral blood at day 1 that was restored by week 4. There was no alteration in expression of major inhibitory and activating NK receptors up to 10 weeks after treatment (Figure 2B), nor in the CD56bright population, although for this tiny subpopulation, results must be confirmed with greater number of patients (data not shown). Similarly, NK cell function tested by ex vivo cytokotoxicity and degranulation was not impaired (Figure 2C). We were able to follow the IPH2101-targeted population in the patients undergoing high-dose therapy by indirect staining with an anti-IgG4. Even at 3 mg/kg, a dose ensuring complete saturation of the receptor for more than a month, the percentage of IPH2101+ cells did not vary significantly after treatment (supplemental Figure 2), showing that the mAb did not induce significant expansion of the targeted population.

We investigated a variety of major cytokines, including: TNF-α, IL-1β, IL-6, IFN-γ, and MIP-1β. A modest, transient increase of IL-1β, IL-6, and IFN-γ serum levels was seen in patients at the...
higher doses (data not shown). TNF-α concentrations were increased for the majority of the patients (18 of 23) 24 hours after treatment. MIP-1β was also increased in 5 of 9 patients on dose levels 0.3, 1, and 3 mg/kg. CD69 was overexpressed 24 hours after therapy on NK cells (but not on T cells) in most patients at doses above 0.3 mg/kg (Figure 3A). A correlation among TNF-α, MIP-1β, and CD69 expression was found (Figure 3B).

**Clinical efficacy**

Twenty evaluable patients have relapsed. Median PFS, RFS, and OS were, respectively: 7.7 months (95% confidence interval [CI], 1.8-9.5); 10.8 months (95% CI, 8.8-14.4); and 12.7 months (95% CI, 10.9-24.2). Interestingly, the 6 patients treated at dose levels 0.3, 1, and 3 mg/kg showed a significantly improved OS compared with the 16 patients on the previous dose levels (median OS: 11.8 months). For the remaining dose levels, OS were, respectively: 7.7 months (95% CI, 1.8-9.5), 10.8 months (95% CI, 8.8-14.4), and 12.7 months (95% CI, 10.9-24.2). RFS, although not significant (see supplemental Table 7), were also increased for the majority of the patients (18 of 23) 24 hours after treatment. MIP-1β was also increased in 5 of 9 patients on dose levels 0.3, 1, and 3 mg/kg. CD69 was overexpressed 24 hours after therapy on NK cells (but not on T cells) in most patients at doses above 0.3 mg/kg (Figure 3A). A correlation among TNF-α, MIP-1β, and CD69 expression was found (Figure 3B).

**Discussion**

We report herein the first in human study of an anti-KIR mAb. Results show that IPH2101 treatment resulted in prolonged, full blockade of inhibitory KIR without significant adverse clinical and biologic side effects in elderly patients with AML in first CR.

IPH2101 half-life increased with dose, with a median of 16 days at the highest dose levels, in the range of IgG half-life in humans (mean, 20 days). One patient had neither detectable circulating Ab nor KIR saturation (no explanation was found and a dosing error could not be excluded). A clear relationship between exposure and KIR occupancy with small interpatient variability was observed, except at the 1 mg/kg dose level, which might have been related to the variable percentage of NK cells able to bind IPH2101 in the 3 patients (25%, 15%, and 52%). Full KIR saturation for more than 4 weeks was achieved at 3 mg/kg.

A major a priori concern was that blockade of molecules that inhibit NK cells might lower the activation threshold against normal cells expressing activation ligands or by the direct triggering of KIR2DL1/S1 and KIR2DL3/S2 on NK cells, which may represent a safety issue. However, treatment was well tolerated, the maximum tolerated dose was not reached, and no autoimmunity was observed. Major side effects were mild and infusion related. These were associated with a modest increase in serum levels of IL1-β, IL-6, and TNF-α at the highest dose levels, and skin reactions were seen at all dose levels. No effect was seen on hematologic parameters, lymphocyte subsets, or expression of NK receptors.

Interestingly, most patients treated at the higher doses showed increased levels of TNF-α and MIP-1β, with increased NK cell expression of CD69 24 hours after IPH2101 administration. These data suggest that the higher doses of IPH2101 were associated with transient activation of NK cells, although how this occurs is unclear. By blocking inhibitory KIR, we hypothesize that IPH2101 alters the balance of activating and inhibitory signals received by NK cells. Normal tissues do not usually express significant levels of activating ligands for NK cells, and this is reflected by the absence of autoimmunity seen in the present study. Signs of activation of IPH2101-bound NK cells may come from the encounter of minimal levels of activating ligands on normal cells or residual AML blasts displaying those activating ligands. Alternatively, IPH2101 also binds the activating KIR2S1/S2, which may have led to increased CD69 expression and cytokine production. However, we do not favor this interpretation because it was demonstrated that this IgG4 Ab acts as a blocking mAb both in vitro and in preclinical mice models, and therefore does not seem to cross-link either activating or inhibitory receptors. The relevance of these biomarkers will be further characterized in phase 2 trials.

Although designed as a phase 1 safety and tolerability trial, OS and RFS in the present study compared favorably with reports in comparable patient populations. Interestingly, the 6 patients treated at dose levels leading to sustained full KIR...
saturation for 2 weeks showed significantly improved OS ($P = .03$) compared with patients treated at lower dose levels, with trends toward improved RFS ($P = .07$) and PFS ($P = .07$). Although limited by the small sample size and patient heterogeneity, this observation suggests the clinical utility of anti-KIR treatment and a dose-response effect. Indeed, in the context of patients treated while in remission from AML and therefore not evaluable for response, only assessment of survival end points compared with the control group can provide confirmation regarding clinical activity.

Several issues remain to be addressed. First, the median percentage of NK cells expressing the IPH2101 mAb receptor was 35.1% (range, 8.1%-54.1%), and it is unknown whether this would affect treatment activity. Second, at the 2 highest dose levels, continuous KIR blockade was achieved. The maintenance of an activated NK cell state should be of interest. However, prolonged KIR inhibition could conversely affect NK cell education, because functional acquisition in both mice and humans relies on interactions between KIR (or their equivalent in mice) and cognate ligands. Generating robust functional data with patients treated at different dose levels cannot be achieved in the escalating part of this trial. A follow-up trial involving patients treated with 2 dose levels will assess in greater detail (ie, gating on the IPH2101 population with CD107 functional assessment against class I positive targets) any functional differences between intermittent and complete KIR blockade.

In conclusion, the results of the present study show that prolonged KIR blockade using IPH2101 is safe and well tolerated in elderly patients with AML. We have identified the 1 and 3 mg/kg doses as being able to produce full KIR occupancy without deleterious clinical, hematologic, or immunologic effects, thus
compared with patients receiving doses
Serum levels of TNF-α/H9251
ment with anti-KIR mAbs alone or in combination for these
cancers, 22 and melanoma, 23 which provides rationale for treat-

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Figure 3. Investigation of NK activation during IPH2101 treatment. (A) Activation of NK as measured by CD69 expression after IPH2101 treatment. The expression of the cell-surface activation marker CD69 was performed on NK and T cells before and 24 hours after IPH2101 infusion. The 2 representative patients included received either 0.003 or 3 mg/kg doses. (B) Increased expression of CD69 on NK cells and serum levels of TNF-α and MIP-1β in patients who received IPH2101 infusions of 0.3, 1, and 3 mg/kg compared with patients receiving doses < 0.3 mg/kg. The activation marker CD69 was analyzed by flow cytometry on NK cells before and 24 hours after IPH2101 infusion. Serum levels of TNF-α and MIP-1β were determined by ELISA before and 24 hours after IPH2101 infusion.

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Authorship
Contribution: N.V. designed and performed the research, analyzed the data, and wrote the manuscript; J.-H.B. designed and performed the research; N.B., D.B., T.P., A.C., A.E., and H.D. performed the research; P.A., F.R., and D.O. performed the research, analyzed the data, and wrote the manuscript; and D.B. wrote the manuscript.

Conflict-of-interest disclosure: N.V. received honoraria from and F.R. and P.A. are employees of Innate Pharma. The remaining authors declare no competing financial interests.

Correspondence: Norbert Vey, MD, Institut Paoli-Calmettes, 232, Blvd Sainte Marguerite, 13009 Marseille, France; e-mail: veyn@ipc.unicancer.fr.

References


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